Improvement of therapy for amblyopia

Sjoukje Elizabeth Loudon

The research project was initiated by the Department of Ophthalmology, Erasmus MC University Medical Center Rotterdam, the Netherlands. The work described in this thesis was financially supported by the Health Research and Development Council of the Netherlands (project number 2300.0020). Financial support for the printing of this thesis was received from the Prof.dr. Henkes Stichting, Orthopad, 3M Opticlude, the Rotterdamse Vereniging Blindenbelangen and the Erasmus Universiteit Rotterdam.

ISBN 978-90-8559-268-2

Layout and printing: Optima Grafische Communicatie, Rotterdam, The Netherlands
Cover design: VOF Vingerling & De Bruyne

Improvement of Therapy for Amblyopia

Verbeteren van de Behandeling voor Amblyopie

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof.dr. S.W.J. Lamberts

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 21 februari 2007 om 15:45 uur

door

Sjoukje Elizabeth Loudon
geboren te Huddersfield, Groot-Brittannië

PROMOTIECOMMISSIE

Promotoren	Prof.dr. G. van Rij
	Prof.dr. H.J. Simonsz
Overige leden	Prof.dr. P.J. van der Maas
	Prof.dr. J. Passchier
	Dr. M. Fronius
	Dr. M.J. Moseley

To my parents

CONTENTS

Publications and manuscripts on which this thesis is based

Chapter 2 S.E. Loudon, H.J. Simonsz *The history of the treatment of amblyopia.* Strabismus 2005 Jun;13(2):93-106

Chapter 3 S.E. Loudon, J.R. Polling, B. Simonsz, H.J. Simonsz *Objective survey of the prescription of occlusion therapy for amblyopia*. Graefes Arch Clin Exp Ophthalmol 2004 Sep;242(9):736-40

Chapter 4 B. Simonsz-Tóth, S.E. Loudon, H. van Kempen-du Saar, E.S. van de Graaf, J.H. Groenewoud, H.J. Simonsz *Visusevaluierung in einer historischen Kohorte von 137 okkludierten Patienten, 30-35 Jahre nach Ende der Okklusionsbehandlung / Evaluation of visual acuity in a historic cohort of 137 patients treated for amblyopia by occlusion 30-35 years ago.* Accepted for publication Klin Monatsbl Augenheilkd 2006

Chapter 5 Y. Chopovska, S.E. Loudon, L. Cirina, A. Zubcov, H.J. Simonsz, M. Luchtenberg, M. Fronius *Electronic recording of occlusion treatment for amblyopia: potential of the new technology*. Graefes Arch Clin Exp Ophthalmol 2005 Jun;243(6):539-44

Chapter 6 S.E. Loudon, J.R. Polling, H.J. Simonsz *Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase.* Graefes Arch Clin Exp Ophthalmol 2003 Mar;241(3):176-80

Chapter 7 S.E. Loudon, M. Fronius, C.W.N. Looman, M. Awan, B. Simonsz, P.J. van der Maas, H.J. Simonsz *Predictors and a remedy for non-compliance with amblyopia therapy in children measured with the Occlusion Dose Monitor.* Invest Ophthalmol Vis Science 2006 Oct;47(10):4393-400

Chapter 8 S.E. Loudon, L. Chaker, S. de Vos, M. Fronius, J. Passchier, R.A. Harrad, C.W.N. Looman, B. Simonsz, H.J. Simonsz *Effect of an educational programme on attitudes and behaviour with occlusion therapy and reasons for total non-compliance.* (submitted)

Chapter 9 S.E. Loudon, A.W. Wypekma, C.W.N. Looman, M. Fronius, B. Simonsz, H.J. Simonsz *Physiological properties of the eye patch and influence on compliance with occlusion therapy.* (submitted)

Chapter 1

General introduction

INTRODUCTION

Definition

The term 'amblyopia' originates from the Greek language and literally means dimness or dullness of vision. In time, the condition has been defined in a variety of ways, very much depending on the prevailing patho-physiological concept about its etiology. In general, amblyopia can be defined as a unilateral or bilateral decrease in visual acuity for which no organic cause can be found on physical examination of the eye. It is caused by a refractive error (one foveal image is more blurred than the other); strabismus (ocular misalignment causing each eye to have a different image on the fovea) or, more rarely, deprivation of a clear retinal image (physical obstruction, e.g. infantile cataract, ptosis) (von Noorden 1967; 1985; von Noorden and Campos 2002). Amblyopia usually presents itself during the ophthalmological examination by the ophthalmologist or the orthoptist as a reduced visual acuity in one or both eyes, in the presence of a refractive error and/or strabismus or a deprivation. This reduced visual acuity persists after optimum correction of any refractive error (i.e. a pair of spectacles) and it cannot be explained by another ocular abnormality (e.g. retinopathy).

Epidemiology & screening

Amblyopia is the most common cause of monocular vision loss in children, accounting for over 90% of the visits of children to ophthalmologists and orthoptists (Attebo, et al. 1998; Moseley, et al. 1997; Sjöstrand and Abrahamsson 1997). The general estimate of the prevalence of amblyopia is approximately 3.5%, but varies considerably in the literature (0.5-5.3%) due to differences in study design, population and the examination methods used (Attebo, et al. 1998; Cole 1959; Helveston 1965; von Noorden and Campos 2002; Simons 1996; Theodore, et al. 1946; Vinding, et al. 1991). In The Netherlands, the incidence is approximately 6500 amblyopic children each year. The national screening programme checks for the presence of strabismus after birth, and, periodically examines visual acuity from the age of three. The referral procedures in the Netherlands are currently studied by the Rotterdam AMblyopia Screening Effectiveness Study (RAMSES) (Juttmann, et al. 2001). This is a 7 year follow-up study, which evaluates the effectiveness and the efficiency of screening. Apparently, one third of all children with a positive screening test result (i.e. reduced visual acuity) are not conclusively evaluated at an ophthalmological centre and consequently fail to profit from an early detection and treatment. Whether this could be attributed to the many intermediate steps between the referral and the orthoptist (parents have to make an appointment with their general practitioner, are then referred to the ophthalmologist and finally to the orthoptist), or the lack of understanding of the necessity of the referral by the parents is still unclear. When a positive referral leads to a visit to the orthoptist and the reduced visual acuity is confirmed they will be prescribed treatment, which may continue for several months up to several years.

Treatment

Treatment of amblyopia involves complete or incomplete exclusion of the better eye from visual activity; hence, the use of the amblyopic eye is stimulated. The purpose of amblyopia treatment is equal acuity in both eyes and, consequently, preventing any future disability (e.g. choice of profession, quality of life). Early treatment, i.e. during the sensitive period of visual development lasting up to the age of 7 years, can reduce or completely reverse the effects of abnormal visual experiences, whereas treatment later in the critical period becomes less effective (Birch, et al. 1990; Crawford, et al. 1983; Epelbaum, et al. 1993; Mintz-Hittner, et al. 2000; Mitchell 1991).
The mainstay treatment has been occlusion of the better eye using an opaque patch. However, as there is little consensus amongst orthoptists concerning the necessary number of occlusion hours, occlusion regimens may vary from occluding the better eye a few minutes per day to all waking hours (Tan, et al. 2003). More recently optical penalisation (selectively fogging the image of the non-amblyopic eye by glasses) or pharmaceutical penalisation (cycloplegia by the daily instillation of drops into the fornix of the non-amblyopic eye) was described. Several studies have demonstrated that atropine was as effective as occlusion therapy, but occlusion therapy caused a more rapid response, while atropine had a somewhat higher acceptability by the families (Cole 2001; PEDIG 2002; 2003; 2004; 2005).

Despite screening and treatment, approximately a third of the affected children who have been prescribed occlusion therapy do not reach visual acuity of 6/12 in the amblyopic eye and are unable to read with the amblyopic eye. This excludes them from any future tasks that require equal good vision (Jensen and Goldschmidt 1986; Vinding, et al. 1991). Matters worsen when an amblyopic child - in one study the proportion was estimated at 0.175% (Tommila and Tarkkanen 1981) - will loose the function of the better eye later in life, because of trauma or, for example, macular degeneration. This will result in bilateral visual impairment causing job losses, an increased morbidity and social isolation (Chua and Mitchell 2004; Fronius, et al. 2005; Rahi, et al. 2002). A decrease in quality of life in adulthood has also been described (van de Graaf, et al. 2004). In people aged 20-70, amblyopia is the most common cause of monocular loss of vision (Buch, et al. 2001).

The effectiveness of occlusion therapy was questioned in a report published by Snowdon & Stewart-Brown in 1997, who conducted a systematic review of the literature (Snowdon and Stewart-Brown 1997). They concluded that occlusion therapy has not yet been subjected to formal controlled trials and that much of the improvement in visual acuity could be spontaneous and unrelated to the therapy. However, they may have overlooked the possibility that the lack of evidence for the efficacy of occlusion could be due to low compliance rather than to ineffectiveness of the treatment. Their report contributed to the set-up of five randomised

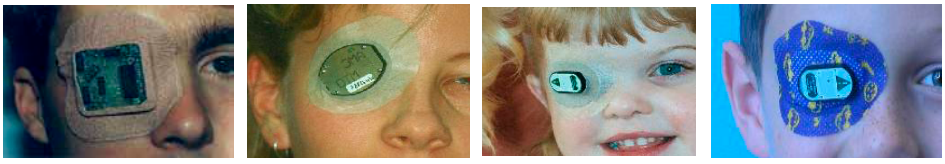
controlled trials (RCTs) that produced evidence for the effectiveness of occlusion therapy (Awan, et al. 2005; Clarke, et al. 2003; PEDIG 2002; 2004; 2005; Stewart, et al. 2004; 2005). The percentage of successfully treated amblyopes spans a broad range: 19-93% success rates. Factors that influence the outcome of treatment include age (Massie 1965; Stewart, et al. 2004; 2005), visual acuity at start of treatment (Cobb, et al. 2002; Hiscox, et al. 1992; Lithander and Sjöstrand 1991; Smith, et al. 1995, Stewart, et al. 2004; 2005) and type of amblyopia (Cobb, et al. 2002). The factor most frequently quoted, however, was the degree of compliance: the better eye is not patched according to the orthoptists' prescription (Awan, et al. 2005; Dorey, et al. 2001; Lithander and Sjöstrand 1991; Simmers, et al. 1999; Simons and Preslan 1999; Smith, et al. 1995; Stewart, et al. 2004; 2005).

Compliance

In recent years, 'compliance studies' are receiving increased attention now that it can be measured electronically (Kass, et al. 1986a; 1986b; 1987; Urquhart, 1992; 1999), with the first conference addressing the issue of patient compliance organised in 1974. Compliance is referred to as the degree of correspondence between the recommendations from the health care provider and the patients' actual dosage. The first devices that measured compliance electronically were developed to monitor the administration of pilocarpine eye drops in the treatment of glaucoma (Kass, et al. 1986a; 1986b; Norell, et al. 1980). The results showed that only 76% of the pilocarpine drops were taken as prescribed, while 6% took less than one quarter and 15% took less than half of the prescribed dosage. However, the patients' diaries reported to have taken 97% of their medication. Poor compliance decreases the effectiveness of treatment and increases costs to the health care system (Cleemput and Kesteloot 2002). In children, the issue of non-compliance is especially challenging as the relationship is compound: the orthoptist deals with non-compliant parents, the parents deal with a non-compliant child. In addition, non-compliance in a parent is regarded as a more serious fault by society than non-compliance in an adult patient and may therefore cause feelings of insufficiency and shame. Compliance with any treatment for children is largely dependent on the ability of the parents or guardian to understand and follow through with recommended treatment. Only few groups have studied compliance electronically in children. Milgrom, et al. (1996) found 58% use of prescribed inhaled corticosteroids in asthma in children electronically, whereas the diaries kept by the patients or their parents reported 95% use. More than 90% of the patients exaggerated their use of inhaled steroids, and even the least compliant reported high levels of adherence to prescribed therapy. The authors concluded that most of the hospital admissions for asthma were caused by non-compliance.

Since the development of the Occlusion Dose Monitor (ODM) by Fielder and Moseley (Fielder, et al. 1994) compliance with occlusion therapy for amblyopia can be measured electronically and therefore objectively. They developed an ODM that measured skin conductance at the

border of the patch. In 1997, the department of Medical Technical Development at the Academical Medical Center, Amsterdam modified the Fielder-ODM design and made it smaller. It now measures 24x12x3.6 mm and weighs 1.8 g. It is taped to the outside of a standard eye patch and measures the temperature difference between the front and the back of the ODM every 2 minutes, instead of skin conductance (Figure 1). In previous pilot studies with the ODM in patients from the Sophia Children's Hospital Rotterdam, it was found that compliance with occlusion therapy was low and the patterns of non-compliance remained the same for one child and were apparently case specific (Simonsz and Polling 2001). In a second pilot study the ODM was distributed by the orthoptist in the clinic to patients whose compliance was thought to be low. Parents, however, interpreted the ODM as a 'lie-detector', resulting in a breakdown in the relationship between them and the orthoptist (Simonsz, et al. 1999).



1a 1b 1c 1d

Figure 1. a the first model of the ODM developed by Prof. Alistair Fielder and Dr. Merrick Moseley in London, United Kingdom **b**: in 1997 the department of Medical Technical Development at the Academic Medical Center Amsterdam modified the design and made it smaller: it now measures temperature difference between the front and the back **c & d** the ODM as used in the study in The Hague: it weighs 1.8 g and measures 24 x 12 x 3.6 mm.

To date, several studies have demonstrated by means of the ODM that, generally, compliance with amblyopia treatment is low and treatment success is related to the level of compliance (Awan, et al. 2005; Simonsz, et al. 1999; Stewart, et al. 2004; 2005).

OBJECTIVE AND OUTLINE OF THIS THESIS

The main objective of the research presented in this thesis is, on the one side, to determine whether compliance with occlusion therapy can be improved with an educational programme explaining, without text and no animal figures, to a 4-year-old child the reasons why the better eye must be patched, together with a calendar, reward stickers and a sheet containing general information about amblyopia and its treatment; and, on the other side, to identify certain predictors leading to non-compliance. Studied were the clinical parameters of the child, the socioeconomic and ethnic parameters and the psychometric parameters. Compliance was measured electronically by means of the Occlusion Dose Monitor.

Following this first chapter, the history of the treatment for amblyopia is given in Chapter 2. Chapter 3 presents an inventory made in order to try and identify the variation in prescriptions of occlusion hours amongst orthoptists in the Netherlands and in Germany, their consistency in prescriptions and the main determinants when prescribing a certain number of occlusion hours. In Chapter 4, the current visual acuity of 137 amblyopic patients treated for amblyopia 30 years ago, is evaluated and factors associated with a poor outcome are determined. Chapter 5 investigates whether the Occlusion Dose Monitor (ODM) that is used to objectively measure compliance, is able to differentiate between measurements on the eye and on other parts of the body. Chapter 6 presents a pilot study in which the ODM was distributed via home visits by the researcher and that determined whether children whose acuity had not improved sufficiently after six months of patching were indeed the children with low compliance. The following three chapters (number 7, 8 and 9) present studies that are carried out using data from the prospective randomised clinical trial in The Hague, the Netherlands. For 30 months all newly diagnosed amblyopic children were recruited from the four clinics in The Hague. Chapter 7 illustrates the effect of the educational cartoon story on compliance and determines the influence of clinical and socioeconomic factors on compliance. Chapter 8 presents the effect of the educational programme on attitudes and behaviour factors and reasons for total non-compliance with occlusion therapy for amblyopia. Chapter 9 investigates the physiological properties of the eye patch and its influence on compliance. Chapter 10 gives an account of the study population, causes of amblyopia and the final visual acuity.

The clinical relevance of the findings and future prospects are discussed in the eleventh and final chapter.

Chapter 2

The history of the treatment of amblyopia

INTRODUCTION

The Greek word *amblyopia* means dimness or dullness of vision (*ambly αμβλυσ* = dull and *ops ωψ* = vision) and the condition has been defined in a variety of ways in the literature. Amblyopia is a decrease in visual acuity, usually in one eye. It persists after the correction of the refractive error (i.e., acuity is not improved by glasses) or removal of any pathological obstacle to vision (i.e. cataract) and no organic cause can normally be found (Ansons 2001; von Noorden 2002).

The general estimate of the prevalence of amblyopia hovers around 3.5%. The reported prevalence in the literature varies considerably (0.5-5.3%) due to differences in study design, population and the examination methods used (Attebo, et al. 1998; Ciuffreda, et al. 1999; Cole 1959; Helveston 1965; von Noorden 2002; Simons 1996; Theodore, et al. 1946; Vinding, et al. 1991). In addition, the criteria used to diagnose amblyopia differ at the start of treatment, the end of the treatment and later in life.

This developmental anomaly is mainly monocular and caused by misalignment of the eyes (strabismus), a refractive error (anisometropia) and/or a form deprivation (for example infantile cataract) (von Noorden 1967; 1985). The critical period in visual development for the development of amblyopia is commonly thought to start approx. 6 weeks after birth up to the age of six (Daw 1998; Fawcett, et al. 2004). However, this remains a subject of discussion as it involves multiple aspects, e.g. the cause of the amblyopia, treatment efficacy, etc. Treatment involves complete or incomplete exclusion of the better eye from visual activity for the purpose of equal acuity in both eyes. Early treatment can reduce or completely reverse the effects of early abnormal visual experiences, whereas treatment later in the critical period becomes less effective (Birch, et al. 1990; Crawford, et al. 1983; Epelbaum, et al. 1993; Mintz-Hittner, et al. 2000; Mitchell 1991).

The aim of this review is to provide an historical overview of the different ways that amblyopia has been treated in the past. The history of the diagnosis and treatment of amblyopia is a remarkable one and very much influenced by the prevailing pathophysiological concepts regarding its etiology. It was not until the beginning of 1960, when Hubel and Wiesel performed their neurophysiologic experiments on cats and monkeys, that some of the basic mysteries regarding its etiology were solved (Wiesel, et al. 1963a; 1963b; 1965).

GREEK ANTIQUITY

Hippocrates

As early as approx. 480 BC, Hippocrates used the term 'amblyopia', which was then used for a diminished acuity, including presbyopia, in what appeared to be healthy eyes. Strabismus was known as a disorder of the eye position and its movements. It was not considered as an eye disease as such, but as a symptom of other bodily ailments. Treatment (for both strabismus and amblyopia) consisted of a medicine, carefully made up of oil and vinegar, water, wine, honey and minerals. In addition, certain diets, for example onions and fresh vegetables, were thought to improve the eyes, whereas lentils were seen to be harmful. Physical exercises and a regular lifestyle were also said to be beneficial (Fuchs 1895).

BYZANTINE EMPIRE

Paulus de Aegina and Thabit ibn Qurrah

During the Byzantine Empire, the surgeon and obstetrician Paulus de Aegina (Alexandria, Egypt; approx. 625-690) was the first person to treat strabismus rationally when he used a mask made from nutshells with small perforations in the centre. Strabismus was thought to be caused by a 'spastic state of the muscles that move the eye'. These shells would force the strabismic eye to look straight ahead, thereby correcting the deformed vision (Berendes 1914). Paulus lived and worked in Alexandria when the Arabs invaded the city in 642. They thought very highly of Paulus and his work and honoured him with the title 'obstetrician'. He acted as a mediator between the traditional Greek medicine and the flourishing Arabian medicine.

Blindness was a major cause of disability in Arabian countries. Islamic physicians developed a particular concern and skill in the diagnosis and treatment of eye diseases. Thabit ibn Qurrah ibn Marwan al-Harrani was born in 836 at Harran (presently in Turkey) and died in Baghdad in 901 (Figure 1). He is known for his work on mechanics, astronomy, pure mathematics, geometry and anatomy and was part of the scientific team of the great Muslim mathematician

Figure 1. Thabit ibn Qurrah ibn Marwan al-Harrani was the first to describe occlusion therapy for the better eye until the vision in the strabismic eye had returned to normal.

Muhammad Ibn Musa Ibn Shakir at Baghdad. Thabit's books on mathematics, astronomy and medicine have survived. In his book 'Vision and Perception' he described the treatment of strabismus as follows: "Strabismus should be treated by patching the normal eye. Once you do that, the visual power will go in its entirety to the deviating eye and vision in that eye will return to normal. You should not release the normal eye until the vision in the strabismic eye has completely returned to normal". This description of occlusion therapy is probably the first as found in the literature (von Noorden 2002; Wafai 1991).

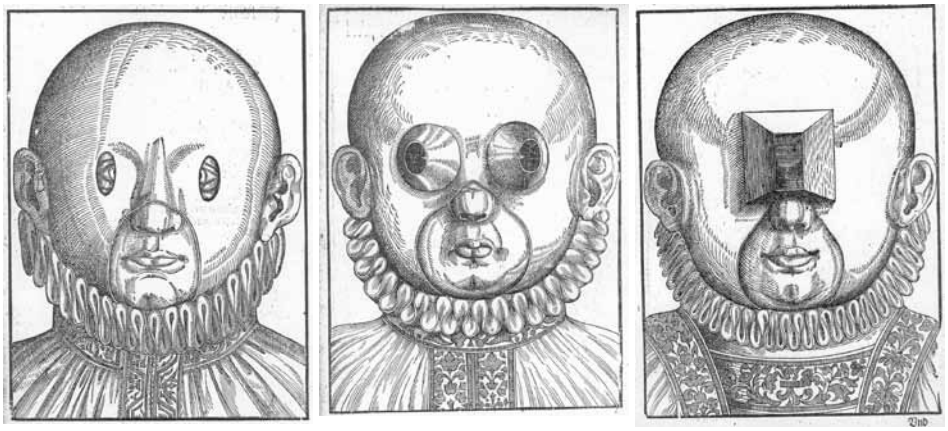
RENAISSANCE

Saint Louis IX, France and Georg Bartisch, Germany

Approximately 500 years later, during the time of the crusades, the first exclusive eye hospital was founded by Saint Louis IX in France. When he returned from his crusade in Egypt in 1254 he founded "Les Quinze-Vingts" inside his castle in the Louvre, Paris. The hospital was intended for 300 (15 x 20 beds) of his companions who had accompanied him and now suffered from trachoma. Les Quinze-Vingts was the first hospital treating patients with low vision (glaucoma, cataract, amaurosis, and trauma) and serve as an institution for the blind, inexpensive or free of charge. In 1780, prior to the French Revolution, the cardinal Louis de Rohan transferred the institute to an old and abandoned barrack, once belonging to the Black Musketeers, in the suburb Saint-Antoine to aid the local population. Despite serious protests the building was demolished in 1957, as it was deemed unfit for modern medical practice. What remains of the barracks are the main entrance, the hall and its chapel (Figure 2) (Paroisse).

After Paulus de Aegina, Georg Bartisch (1535-1607) also developed masks for the purpose of correcting the deformed vision. Bartisch was born in Gräfenhain and moved to Königsbrück when he was about 12 years old. He had an early interest in medicine, but due to financial circumstances Bartisch was unable to enrol in a scientific study. Instead, he gained his experience working with wound healers and barber surgeons. Practicing as an itinerant surgeon, he often travelled to Bohemia and Prague to gain experience and became a court oculist to the Duke of Sachsen in Dresden. Although he was not an academically educated physician, he had extensive knowledge of ancient medical practice.

Figure 2. Remains of "Hospice des Quinze-Vingts", the first institution for the blind in Paris (1254).



a b c

Figure 3. Treatment of strabismus according to Georg Bartisch (1583) for esotropia (a,b) for exotropia (c). These pictures were made available by the "Museum Boerhaave Leiden", the Netherlands.

In 1583 Bartisch published "Ophthalmodouleia/Das ist Augendienst", one of the first medical treatises to be published in the German language instead of traditional Latin. It contained several woodcuts drawn by Bartisch himself. The hoods he designed to treat strabismus covered the head entirely, with perforations corresponding with the correct position of the eyes to encourage the strabismic eye to straighten; one for an esodeviation and one for an exodeviation (Bartisch 1583) (Figure 3a, b and c). The anatomy of the head and eye is described according to Galen's ideas. Many treatments are discussed, partly displaying the mystic influences of the Middle Ages ("evils caused by magic, witchcraft and work of the devil").
His book also contained a section in which he described an orbital exenteration using a 'large spoon' with sharp edges. This operation, including an enucleation, had never been performed before. Georg Bartisch died in 1607.

In those days, ophthalmology as such was not a separate specialty. Oculists and barber surgeons performed eye surgery, as educated physicians disliked surgery. Doctors calling themselves 'ophthalmologists' were, without exceptions, general surgeons. Occasionally, a surgeon who specialised in eye diseases (mainly cataract extractions) was now called an 'oculists' (for example Bartisch and Taylor). In Paris, the first chair of ophthalmology was created in 1762, 41 years after the first chair of surgery was created. It was originally intended for Jacques Daviel, but due to his premature death it was given three years later, in 1765, to Louis Florentin Deshaies Gendron. This may be looked upon as the start of actual ophthalmology.

Charles de Saint-Yves

Charles de Saint-Yves was born in 1677 in Maubert-Fontaine, France. He started his education in general surgery when he was 17 years old. Five years later he had specialised in eye diseases at the general hospital in Paris, a hospital supported by the Countess Françoise Anthénais Montespan, the mistress of King Louis XIV. In 1711, Charles de Saint-Yves left the general hospital and opened his own Ophthalmology Clinic in Paris where he committed himself fully to eye diseases. In 1722, he wrote down his experiences in his textbook "Nouveau traité des maladies de yeux" (Figure 4). Chapter 24 deals with 'Des yeux louches' in which he wrote: "One was sometimes obliged to fully cover the non-strabismic eye, thereby straightening the strabismic eye and so as to be dependent on this eye, it will get used to looking straight ahead" (De Saint-Yves 1722). He continued: "When one closes the non-strabismic eye, the squinting eye will now look straight ahead and when opening the eye again one now finds a squint in the eye that was straight before". Based on this observation, he was one of the first to describe the cover test. Nowadays, the cover test is an important part of orthoptic practice. It includes two tests: the cover-uncover test and the alternating cover test and is the principle element in the detection and diagnosis of strabismus. To straighten the eyesight he also recommended the exercise to "sit the child in front of a mirror and that each eye looks precisely to the pupil of that eye which corresponds to him in the mirror. In addition, one must also read fine print and do handicrafts". His book is clearly written with detailed observations, including cataract


NOUVEAU TRAITÉ
DES MALADIES DES
Y E U X,
Où l'on expose leur Structure, leur usage, les Causes de leurs Maladies, leurs Symptômes, les Remedes & les Opérations de Chirurgie qui conviennent le plus à leur guérison.
AVEC
DE NOUVELLES DECOUVERTES
Sur la Structure de l'Oeil, qui prouvent l'Organe immédiat de la Vue.
Par Mr. DE SAINT-YVES,
Chirurgien Oculiste de Saint Côme.
A AMSTERDAM,
Chez FRANÇOIS L'HONORÉ.
M. DCC. XXXVI.

Figure 4. Charles de Saint-Yves was one of the first surgeons who specialised in eye diseases and wrote detailed observations about all known eye diseases in his book: "Nouveau traité des maladies des yeux" (1722).

extractions (he performed 60-80 each year). His life's work shows him to be a dedicated researcher and eye specialist. Charles de Saint-Yves died in 1736.

George Comte de Buffon

The person usually credited for the introduction of occlusion of the fixating eye for amblyopia was the French naturalist and botanist George-Louis Leclerc, Comte de Buffon (Figure 5).
He was born in Montbard (Burgundy, France) in 1707 to rich, middle class parents and inherited the title 'Comte de Buffon et Montbard' and a large sum of money when his mother died. This made him financially independent, in those days a necessity for dedicating one's life to science. He studied medicine, astronomy and botany at the Angers University. He suffered from strabismus and poor vision of his squinting eye. According to Buffon, a strabismic eye was caused by poor vision in one of the eyes, which led to a disruption in binocular vision. This was contrary to what was generally believed, i.e. that an unequal strength of the muscles or lack of concordance caused the strabismus. He also rejected the masks as he recognised they did not have the desired effect. In 1743, in his "Dissertation sur les causes du Strabisme" he described the weak eye regaining all its strength by occluding the good eye ("reprendre toutes ses forces") (De Buffon 1743). Buffon is probably better known for his "Histoire Naturelle générale et particulière (1749)", written when he was responsible for the Royal Gardens of the French King Louis XV. He played an important part in the development of biology as a science. He was an avowed opponent of Carolus Linnaeus whose taxonomy he described as artificial, which is probably the reason why Linnaeus denominated an ugly toad as a "Bufonidae". Buffon died in April 1788.

Figure 5. George-Louis Leclerc, Comte de Buffon postulated that a strabismic eye was caused by poor vision in one of the eyes causing a disruption in binocular vision, which was contrary to what was generally believed at that time (1743).

John Taylor

A new idea, to treat strabismus surgically, was introduced by John Taylor, born in Norwich (England) in approximately 1703. He started his career as a pharmacist's student in London and afterwards moved to the continent where he attended lectures on ophthalmology by Herman Boerhaave (1668-1738). He travelled around the major cities in Europe in a carriage painted with eyes, treating patients with 'incurable eye diseases'. Taylor carried out cataract operations, removed blood from inflamed conjunctiva and scars and abraded weak and paralysed eyes with the convex side of a silver tablespoon. Occasionally, Taylor would even place the concave side of the spoon over a closed eye and give it a firm push (Figure 6).
Among Taylor's patients were Johann Sebastian Bach, on whom he operated for cataract, and Georg Friedrich Händel, both of whom became blind due to complications of the operation. The most intriguing operation he performed were those on the strabismic eye. Taylor believed that strabismus was caused by an imbalance between the muscles. By cutting the nerve inner-

Figure 6. Chevalier John Taylor travelled around Europe treating 'incurable eye disease' and suggested treating strabismus with surgery. However, the technique for strabismus surgery was not developed until approximately 100 years later.

vating the strongest muscle, this balance would be restored; he therefore performed a small cut in the conjunctiva, pretending to cut the nerve and thus so straighten the strabismic eye. After the procedure he covered the operated eye to demonstrate that the other eye looked straight ahead. The next day he would cover the other eye, thereby demonstrating the strabismic eye now also looked straight ahead. When Taylor and his companions arrived in Rouen, France, Claude-Nicolas Lecat (or: Le Cat, the famous anatomist and surgeon) took his opportunity to study Taylor's work so that he might improve his own surgical techniques. Lecat was not satisfied with the result of Taylor's operations on the strabismic eye. He argued that it was unclear which nerve was to be cut in the conjunctiva. Lecat also observed that every time the better eye was closed, the strabismic eye looked straight ahead and vice versa. He regarded Taylor as a fraud, invited him to his house for dinner and served him an unexpected dessert: a human head with its eyes anatomically prepared. It was obvious there were no nerves in the conjunctiva. Taylor left Rouen the next day. All the eyes he had operated on started squinting as before (Crone 1992; Taylor 1756).

THE FIRST STRABISMUS OPERATIONS

Stromeyer, Dieffenbach and Cunier

It was not until a hundred years later doctors did what Taylor had intended to do: operate the eye muscles. The initiator was Friedrich Louis Stromeyer from Hannover, Germany. He occupied himself with orthopaedic surgery. In his book "Beiträge zur Operativen Orthopädik" (1838), he cut the Achilles tendon in the heel in order to treat (straighten) a clubfoot. The same principle could be applied to strabismus, for which he described a tenotomy of the inner eye muscle on corpses (Stromeyer 1838). Johann Friedrich Dieffenbach (1792-1847) was the first to publish his results, 10 days after operating the medial rectus muscle in Berlin (1839), when he wrote "Über die Heilung des angeborenen Schielens mittelst der Durchschneidung des inneren geraden Augenmuskels". He performed a tenotomy on a 7-year-old boy with convergent strabismus without anaesthesia (Dieffenbach 1839). Three years later, Dieffenbach had already operated 1200 patients with strabismus. Unfortunately, total tenotomies often led to an overcorrection. Meanwhile, in Brussels, Florent Cunier (1812-1852) also performed a strabismus operation claiming to be the first (Cunier/Missotten 2001). However, Dieffenbach was able to prove that he had performed the same procedure just a few days earlier.
Ludwig Boehm noticed that the visual acuity of the strabismic eye sometimes improved after the operation. He attributed this effect to the tenotomy itself and presumed that amblyopia could be cured by an operation (Boehm 1845).

DISCOVERY OF THE OPHTHALMOSCOPE AND THE START OF MODERN OPHTHALMOLOGY

Von Helmholtz, Donders and von Graefe

In 1850, Hermann Ludwig Ferdinand von Helmholtz invented the ophthalmoscope. Born in Potsdam, Germany in 1821, he was appointed professor of physiology at Königsberg at the age of 28. He was an important scientist and greatly contributed to modern ophthalmology. With the ophthalmoscope it was now possible to view the retina (Helmholtz 1851; Keeler 2002). This was revolutionary in eye care and may be considered as the start of modern ophthalmology. It was confirmed that in most cases of amblyopia the eye was structurally sound, establishing the functional character of amblyopia.

The physiologist and ophthalmologist Franciscus Cornelis Donders (1818-1889), a Dutch scientist, examined thousands of emmetropic and ametropic eyes and recorded the normal refractive error (Donders 1864). Until then, only three types of errors were known: myopia, presbyopia and astigmatism. In 1859, Donders described the hypermetropic error, and in 1861 how accommodation was linked to convergence. It was apparent that Donders already knew about the relationship between accommodation and convergence as early as 1847. In a postscript to an article written by F.W.C. Krecke on the correction of strabismus using prisms, Donders hypothesised that convergent strabismus might be related to hypermetropia (Krecke 1847). So, as a consequence, the strabismus would often improve when this refractive error was corrected. While studying in London he visited the World's Fair in 1851 and became acquainted with the German ophthalmologist Albrecht von Graefe (1828-1870, Berlin) (Figure 7).

Figure 7. Franciscus Cornelis Donders and Albrecht von Graefe, founders of the Dutch and German Ophthalmology, at the World's Fair in London, 1851.

Albrecht von Graefe was one of the founders of German ophthalmology. Inspired by each other's work, Donders and Von Graefe became friends. They readily used the Ophthalmoscope to determine the refractive error and provoked discussions about what came first: strabismus or amblyopia. This chicken-or-egg discussion (Bielschowsky, 1926) continued until 1960 (Wiesel 1963a; 1963b; 1965). Donders and Von Graefe argued that amblyopia in strabismic children could be the result of either 'not using' the eye, i.e. functional amblyopia, or of an organic visual impairment ("…wird im Folge von diesem Nichtgebrauche mit physischer Unterdrückung amblyopisch") (Donders 1864; von Graefe 1854). Instead, Carl Schweigger and Alfred Graefe advanced the theory of organic amblyopia (Graefe 1894; Schweigger 1885). In their opinion, children were born with amblyopia and this caused the strabismus. They also argued that eyes did not become amblyopic even after a long period of nonuse, for example cataract, and that the acuity became normal after removal of any obstacle to vision.

Fusion exercises

Darwin, Javal, Worth and Maddox

In England, Erasmus Darwin (1731-1802) modified Charles de Saint-Yves' cover exercises almost 50 years later (Darwin 1779). Born in Lichfield near Birmingham, he was the first to prescribe fusion exercises as a treatment for strabismus. Using a septum, he separated the two visual fields after which he presented each eye with small coloured pieces of wood to train the fixation. Once the child was able to fixate equally well with either eye, two pieces of wood were presented simultaneously to each eye and the child was asked to superimpose them. Erasmus Darwin worked in close association with other great scientists and highly skilled technicians such as Josiah Wedgwood, the porcelain manufacturer, James Watt and Joseph Priestley. His theory of evolution was elaborated on by his grandson Charles Robert Darwin.

In 1897, Louis Emile Javal (1839-1907) emphasised the use of stereoscopic exercises to treat strabismus in his "Manuel théorique et pratique du Strabisme" (Javal 1896). Born to a businessman, his parents wished him to study business and economics, hoping he would take over his father's coal-mining business. In 1865, however, he entered medical school at the University of Paris. In 1878 he became the director of the Laboratory of Ophthalmology at the University. He took a particular interest in ophthalmology, probably because his father and sister suffered from strabismus and he himself from myopic astigmatism. Javal preferred non-surgical treatments for ocular problems, hence his interest in orthoptics. Determined not to let his sister fall a victim to: "…le massacre des muscles oculaires," he trained her with his "Stéréoscope à charnière". In his manual he advised occlusion of the healthy eye, "occlusion volontaire de l'oeil meilleur," as well as the use of the stereoscope to re-establish binocular vision. Even though he suffered from progressive glaucoma he was able to finish his manual in 1897, after which he dedicated himself to the further development of Braille together with Louis Braille.

Inspired by the work of Javal, Claud Worth published his first edition of "Squint, its causes, pathology and treatment" at the turn of the century (Worth 1903). Born in 1869, he made fundamental contributions to the field of strabismus and became a member of the Ophthalmological Society of the United Kingdom in 1899. He was an advocate of occlusion therapy of the non-strabismic eye and introduced the use of atropine in mild cases of amblyopia, as an alternative to patching. He recorded the age of onset of the squint, the length of time the squint had been present before occlusion started and the final visual acuity of the deviating eye. From these results he developed a ratio: age in months when permanent turn became apparent divided by the age in months at which training/treatment began. This ratio indicated the prognosis, which improved when the ratio approached unity. Worth formulated the theory that strabismus was caused by a congenital defect of the fusion mechanism. He therefore also proposed fusion training and active stimulation of the amblyopic eye using the improved version of the 'fusion tubes' (Priestley Smith 1896), now called the 'amblyoscope'. However, the use of the amblyoscope was time consuming and results were not always satisfactory.

Ernest Edmund Maddox made use of the Worth amblyoscope in Bournemouth, England. Born in Shipton and educated at the University of Edinburgh he received his MD in 1889. He is renowned for several inventions: the double prism, the Maddox rod, the Maddox tangent scale (1898), the Maddox prism verger and the cheiroscope for orthoptic training. Near the end of his career he developed an interest in orthoptics and the Worth amblyopscope. He found that he did not have enough time to use the device properly. Instead, he taught his daughter, Mary Maddox, to use the amblyoscope. She quickly became a professional using this device and from this she turned her interest to other aspects of orthoptics. In 1929 Mary Maddox opened the first orthoptic clinic at the Royal Westminster Ophthalmic Hospital in London (Maddox 1931).

Reintroduction of occlusion therapy: Mastisolverband

Sattler

Occlusion therapy was re-introduced by C.H. Sattler when he published his experiences with the treatment of amblyopia in Leipzig in 1927 (Sattler 1927). For the treatment of strabismus related amblyopia he recommended the use of so-called 'Mastisolverband'. This occluder was glued to the skin around the eye so as to prevent the child from peeking and remained securely fastened there for at least two to three days. This was the first description of the adhesive tape patch and as such it meant the re-introduction of occlusion therapy for amblyopia. He reported that the best results were obtained in children up to the age of six. Of course, full cooperation and stimulation of the parents was essential and the acuity in the sound eye had to be checked frequently. Children in whom acuity failed to improve were considered either not to have applied the 'Mastisolverband' properly or not to have applied it at all.

Two years later, F. Weckert made use of the children's spectacles by using a spectacle 'occluder' with shields on the side to prevent light incoming from the periphery and to enable the child to blink behind the occluder more easily (Weckert 1929). The children had to wear these occluders full time. He reported good results using this type of occlusion, which, according to Weckert, was more readily accepted by the patient than Sattler's 'Mastisolverband'.

Arguments for and against occlusion therapy

Poulard, Uhthoff, Stenius, Fuchs and Gifford

At the time, there were many arguments for and against occlusion therapy. The Frenchmen Poulard shared the opinions of Alfred Graefe. He had never seen any great improvement of vision in the amblyopic eye with occlusion therapy (Poulard 1921) and could not but conclude that a deviating eye was caused by amblyopia, rather than amblyopia being caused by the deviating eye. This opinion he also shared with Uhthoff (Uhthoff 1927). Stenius, however, in 1935, reported excellent results in 2- to 6-year-olds with central fixation in their strabismic eye. He prescribed these children part-time occlusion therapy (1 or 2 hours daily) and encouraged them to read or draw pictures during the period of occlusion (Stenius 1935). The year after, Ernst Fuchs wrote in his "Aus meiner augenärztlichen Praxis" that the results he gained with occlusion therapy did not measure up to the problems parents had to endure when treating their children (Fuchs 1928). This opinion was supported by Gifford, who thought occlusion could cause a psychological trauma, leading to disorders such as stammering (Gifford 1935).
Besides these problems, complications of occlusion therapy have also been reported, e.g. occlusion amblyopia, disruption of binocularity and an increase in the angle of strabismus (Quéré, et al. 1969). An occasional occurrence of occlusion amblyopia had already been mentioned by Worth and proven to be usually reversible (Burian 1966; Hardesty 1959). Other studies did not find these adverse effects on the patched eye (Holbach, et al. 1991; Lithander and Sjöstrand 1991).

Segment Occlusion

Bangerter

Segment occlusion was introduced by Alfred Bangerter, St. Gallen, Switzerland in 1953. Self-adhesive synthetic material was applied onto the inside of the spectacles occluding only part of the glass; what part depended, for instance, on the presence of accommodative or convergent strabismus. The occlusion spectacles could also reduce the incoming light by means of a transparent foil with various densities of gratings ("Bangerter Foil") (Bangerter 1960). He also suggested the use of occluders in case of undisciplined children and in warmer weather conditions. In his book "Amblyopiebehandlung" (Bangerter 1953) Bangerter described the development of amblyopia and considered system, consequence, versatility and adjustment to be

the basic principles of his amblyopia treatment. He developed a systematic treatment of the amblyopic eye according to age, diagnosis and fixation, as well as a prophylactic treatment of amblyopia. He was a fierce opponent of occluding the better eye in the presence of an eccentric fixation. In his opinion, this was not only dangerous and futile but could also reinforce the eccentric fixation (Bangerter 1946; 1953; 1960).
Occlusion therapy would suffice to improve acuity in case of low-grade amblyopia; however, high-grade amblyopia, especially amblyopia without fixation or a paracentral fixation, needed more intensive and direct stimulating measures to achieve increased acuity (Bangerter 1953). This brings us to the pleoptic-era.

Pleoptics

Comberg and Cüppers
Pleoptic is also a Greek word and refers to *pleion*=more and *optikos*=eyesight. In Rostock in the north-east of Germany, W. Comberg described an apparatus to train central vision in children with functional amblyopia (Comberg 1936). The apparatus (1936) was designed to stimulate the area of the macula in eyes with eccentric fixation by projecting brightly illuminated objects onto the fovea.

Bangerter and later Cüppers introduced various other instruments based on these very same principles: stimulation of the fovea of the amblyopic eye to awaken central fixation.
As he was head of the department, Bangerter had the means and opportunity to pursue his ideas on how to treat amblyopia the best possible way. He invented over 20 instruments and after more than a decade of trial and modification, Bangerter constructed the "Pleoptophor" (Linksz 1961; Priestley 1961; Schlossman 1961); a device that could temporarily blind the eccentrically fixating area and stimulate the central foveal region.

Two years later, in Cologne, Conrad Cüppers gave a lecture on the pleoptic and orthoptic treatment of amblyopia and strabismus as performed at the Augenklinik Gießen (Cüppers 1956). He was a strong advocate of occlusion therapy except, like Bangerter, when an eccentric fixation was present in the amblyopic eye. Cüppers' great virtue was the development of the "Visuskop", an instrument to visualize even the smallest angles of strabismus and determine the fixation. He established that one-third of the children treated for amblyopia did not fixate with their fovea. This assumption led to the development of a different method: the creation of 'after-images' ('Nachbilder') supported by occlusion of the amblyopic eye. The after-images were created by a modified ophthalmoscope (called "Euthyskop") operated by an experienced practitioner. A circular bright light blinded the retinal periphery, while a circular spot protected the fovea. A negative after-image was thus created. Now the foveola had a momentary physiological superiority over the retinal periphery. The patient had to fixate on

the centre of the after-image, thereby regaining central fixation (Cüppers 1961). Cüppers' idea was that this technique would change the direction of the principal visual axis from eccentric to foveal. He emphasised, however, that occlusion therapy was to be preferred in younger children (he referred to the work of Sattler) and pleoptic therapy in older ones and in those with eccentric fixation. Orthoptic and pleoptic principles were to be considered as supplementary treatments and not as opposites (Cüppers 1967).

For the next decade, pleoptic treatment was a widely used and accepted way of treating amblyopia with an eccentric fixation. As pleoptic treatment was time consuming and generally limited to older and more cooperative children, so-called "Sehschulen" (Vision Schools) were set up where children received treatment for several weeks or even months on end. After the Second World War, a large number of amblyopic children were admitted.

At that time, various articles reported on the success of this treatment (Bangerter 1960; Cüppers 1967; Jablonski and Tomlinson 1979), while others were more skeptical (Koselka, et al. 1991; Schmidt and Stapp 1977) regarding the long-term effectiveness and its economic advantage over conventional occlusion therapy. Soon after, studies reported that pleoptics failed to produce a significant improvement in the linear visual acuity or a permanent cure in the majority of amblyopic patients (Fletcher, et al. 1969; von Noorden and Lipsius 1964; Parks and Friendly 1966; Richter 1960; Véronneau-Troutman, et al. 1974). It was even suggested that pleoptics might be dangerous as it could cause permanent monocular diplopia (Campos 1995). However, it should be acknowledged that pleoptics gave rise to further and greater insight into the pathophysiology of amblyopia with special emphasis on the amblyopic eye with eccentric fixation.

The idea that occlusion of the better eye would only reinforce the eccentric fixation (Bangerter 1953) has not been confirmed. Mackensen et al. demonstrated, via fundus photography, that occlusion of the better eye did not induce reinforcement of the eccentric fixation. On the contrary, they found fixation often became foveal with occlusion of the good eye (Mackensen, et al. 1965).

Penalisation

To "penalise" literally means "to punish" and the term was most probably first used by J.B. Weiss in 1968 (in previous studies it was described as "atropinisation") (Weiss and Bourrie 1968). The use of pharmacological penalisation to treat amblyopia had already been suggested by Worth in 1903 for children who did not or were too young to cooperate with conventional occlusion therapy (Worth 1903). Bangerter also used it in the first and second year of life (Bangerter 1960). Generally, it means selectively fogging the image of the non-amblyopic eye by glasses

(optical penalisation) and/or cycloplegia by the daily instillation of drops into the fornix (pharmacological penalisation). This should prevent accommodation and therefore obstruct near vision. In this way, one eye is used for distance vision and the other eye (the amblyopic eye) for near vision. Several variations of this technique have been developed (Abraham 1954; Johnson and Antuna 1965; Knapp and Capobianco 1956; Pfandl 1958; Pope 1971; 1972; Pouliquen 1964). In 1969, Quéré, Pouliquen, Lavat, Berrondo and Weiss described several techniques of penalisation (Quéré 1969).

Others who studied the effect of penalisation therapy on amblyopia reported positive results (Cibis 1974; Foley-Nolan, et al. 1997; Kaye, et al. 2002; Lowe 1965; McKenney and Byers 1975; von Noorden and Milani 1979; North and Kelly 1991; Quéré 1972; Repka and Ray 1993; Simons, et al. 1997; Swann and Hunter 1974; Timmerman 1977; Wallman, et al. 1978), either in combination with occlusion therapy, as maintenance therapy or sometimes as the main therapy. It was more readily accepted by parents and patients of all age groups and allowed a reliable assessment of compliance. Quéré observed a decrease in the angle of strabismus (Quéré 1969) and claimed that penalisation prevented the development of occlusion amblyopia (Quéré 1972). Due to the continued use of both eyes, occlusion amblyopia should be less frequent as compared to occlusion using a patch. However, occlusion amblyopia did occur and careful monitoring of the patient's sound and amblyopic eye was necessary (von Noorden and Milani 1979; North and Kelly 1991; Repka and Ray 1993; Wallman, et al. 1978; Worth 1903). Aggravation of a (latent) nystagmus, another frequent obstacle to occlusion therapy, could also be prevented by penalisation, as both eyes were open at all times. Finally, the penalised eye still received images with low spatial frequency and therefore binocular vision was less disturbed (Foley-Nolan, et al. 1997; Lowe 1965; North and Kelly 1991; Repka and Ray 1993). Other authors, however, did not find substantiated evidence to support different outcomes for monocular or binocular vision (Simons, et al. 1997) and were hesitant to prescribe penalisation in very young children as the negative effect on near vision lasted too long.

A potential disadvantage of penalisation therapy is the effect that image blur or cycloplegia may have on the development of the refractive error. Both experimental work in animals and case reports in humans have shown a myopic shift in the blurred eye leading to anisometropia (Robb 1977; Wallman, et al. 1978). A second disadvantage would be the daily use of drugs used over a long period of time. Side effects are mainly related to systemic intoxication: a case of coma has been reported (Campos, et al. 1991), hypersensitivity to atropine (Lowe 1965; Pope 1971), iris cysts (Abraham 1954; Knapp and Capobianco 1956) and dilatation of the pupil causing photophobia (Campos 1997). Moreover, the acuity of the penalised eye must be less than that of the amblyopic eye, otherwise the patient will continue to use the sound eye despite the pharmacologically or optically induced image blur. When using optical penalisation

it would also be possible for the child to peek around the glasses or remove them altogether. It seems reasonable, therefore, to limit penalisation to mild or moderate amblyopia.

Other non-conventional treatments

Brinker and Katz: Red-filter treatment

In 1963, following the controversy in treating amblyopia associated with eccentric fixation, Brinker and Katz reported on the use of a red filter treatment (Brinker and Katz 1963). Their idea was to totally occlude the non-amblyopic eye and place a red filter on the spectacle frame in front of the amblyopic eye. The red filter excluded wavelengths shorter than 640 mm (the filter most often used was Kodak Wratten gelatin red filter No. 92). The rationale for this method lay in the theory that visual cones are sensitive to stimulation by light from the red end of the spectrum and visual rods are not. The rod-populated area of the retina, which is used for eccentric fixation, is insensitive to this red light. With the non-amblyopic eye occluded and the filter in front of the amblyopic eye, the patient was encouraged to do near work. After fixation became central, the red filter was removed and conventional treatment for amblyopia with central fixation was instituted. The results from various studies reported success rates ranging from 10% to 87.5% (Cowle, et al. 1967; Malik, et al. 1966; Ratiu and Reiter 1966; Thorleifsson 1966). This range was largely due to differences in duration of treatment and response was greater when initial amblyopia was less severe. Cowle et al. suggested that in order to achieve good results, the red-filter treatment should be used for more than 7 months followed by 5 months of occlusion of the non-amblyopic eye, for a total treatment time of 12 months (Cowle, et al. 1967).

In 1998, a blue filter was suggested instead of the red filter (Metzler, et al. 1998).

Pigassou and Garipuy: Prisms

As mentioned before, the principle of pleoptic treatment stimulated further ophthalmoscopic studies of amblyopia and precipitated the concept of eccentric fixation. As one result of these further studies, the use of prisms was introduced for the treatment of amblyopia. In 1966, Pigassou and Garipuy treated amblyopia with eccentric fixation by means of occlusion of the better eye and an inverted prism in front of the amblyopic eye (Pigassou and Garipuy 1966a; 1966b; 1967). Other studies showed results that favoured the inverse prism method over conventional occlusion therapy and pleoptics (Nawratzki and Oliver 1971).

Other therapies

In 1964, Fernando Losada wrote about functional amblyopia and its treatment with occlusion therapy and surgically suturing the eyelids (Losada 1964). He especially advocated the necessity to suture the eyelid of the better eye in disobedient or uncooperative children in order to save the vision in their amblyopic eye. He was not the only person favouring this idea. As early

as 1932, F. Weckert had recommended the suturing of the eyelids in non-compliant children (Weckert 1932).
Less harmful than suturing the eyelids seemed the advice from Fralick in 1943. In very young children, he applied elbow splints made from tongue blades and adhesives, or plaster cast arm restraints during occlusion therapy (Fralick 1943; Hiles and Galket 1974). Other methods tried for the treatment of amblyopia have included eyeball massage (Darier 1904) or a diet of white wine and veal (Devaux 1912). In 1914, the removal of the adenoids was thought to be of importance (Adams 1914) and in 1958 the beneficial influence of hypnosis was asserted (Browning, et al. 1958).

Campbell: CAM Treatment (1978)
In an attempt to improve the acceptance of occlusion therapy by the parents and the child, Campbell and co-workers developed an apparatus in which high-contrast square-wave gratings were rotated slowly in front of the amblyopic eye while the child was performing a task requiring visual concentration (Banks, et al. 1978; Campbell, et al. 1978). This process took only 7 minutes during which the non-amblyopic eye was occluded. In between the weekly sessions, the non-amblyopic eye was not to be occluded. The rationale for using rotating gratings with different spatial frequencies was that it provided stimulation of the whole range of motion of the amblyopic visual system. However, there was a considerable danger of intractable diplopia in case the treatment was applied inappropriately and the use of the instrument ought therefore to be confined to hospitals and clinics. Campbell et al. reported success with this kind of minimal occlusion therapy in 73% of their patients who achieved acuities of >6/12 after three 7-minute sessions. Willshaw et all. reported the same success rate (Willshaw, et all. 1980). In spite of these encouraging results, other authors have not been able to confirm the value of the apparatus in subsequent studies (Ciuffreda, et al. 1980; Fricker, et al. 1980; Keith, et al. 1980; Mehdorn, et al. 1981; Schor, et al. 1981; Tytla and Labow-Daily 1981).

COMMENT

The history of treatment for amblyopia is a rather intriguing one. Throughout the ages, various methods of treatment have been published, with occlusion of the better eye being the very first to be described. This method, however, frequently receded into the background when other types of treatment for amblyopia were tried, e.g. pleoptophor, euthyskop, CAM-treatment, prisms and filters. These new methods became popular for a while, but were abandoned again, as they were time consuming and less effective. The fluctuations in popularity of occlusion could be explained by a limited acceptance by children and parents, resulting in low compliance. Ever since the first prescriptions were written, low compliance was already discerned as a problem affecting the outcome of treatment. It was acknowledged that occlusion

was a burden on the family life and that parents needed to be stimulated in order to achieve good results. Various other efforts to increase compliance included gluing the occluder to the skin around the eye or even suturing the eyelids in non-compliant children. Instead of implementing these radical methods it would be more effective to focus our attention on ways to increase the acceptance of occlusion therapy by children and parents. For the last decade it has been possible to measure compliance with occlusion therapy electronically, yielding exact information on the actual duration of occlusion. This enables us to study the factors that influence compliance with occlusion therapy, which should be taken into account when developing new methods for the improvement of compliance.

SEARCH STRATEGY

The selection of the literature for this review was based on the Medline database that was searched from its starting date in 1966, using key words such as amblyopia-treatment-history-penalisation-atropine-prisms-pleoptics-red filter-gratings-CAM-occlusion. Parts of the very early history were obtained from Wolfgang Münchow ("Geschichte der Augenheilkunde", 1984) and the Picarta database. Articles in any language were considered for inclusion.

ACKNOWLEDGEMENT

We thank Prof. R.A. Crone, MD PhD, Prof. G. Kolling, MD PhD and M.V. Joosse, MD PhD for their advice and contributions.

Chapter 3

Objective survey of the prescription of occlusion therapy for amblyopia

ABSTRACT

Purpose: To identify the variation within and consistency amongst orthoptists when prescribing occlusion therapy for amblyopia in an objective survey.

Methods: A questionnaire was designed with five case examples of amblyopic children and distributed at annual meetings of orthoptists in the Netherlands and Germany. It was filled out simultaneously within 15 min in complete silence to avoid any exchange of opinions between orthoptists that would reduce variability. For each case the orthoptists were asked to give their prescription of hours or days of occlusion.

Results: The questionnaire was completed by 177 Dutch orthoptists and 227 German orthoptists. Their prescriptions of occlusion therapy were classified into five main regimens: Part-Time; Part-Time Not Every Day; Full-Time; Also Occluding the Amblyopic eye; ALTernating and No Occlusion Therapy. The variation was large: the standard deviation was half the average prescribed hours of occlusion for each regimen in each of the five cases. All orthoptists were assigned a rank number for each of the five cases depending on whether their prescription was above or below average. These five rank numbers were not consistently above or consistently below average value per case.

Conclusions: The number of prescribed hours of occlusion varied widely per regimen per case. Orthoptists were not consistently strict or lenient in their prescription of occlusion therapy.

INTRODUCTION

Treatment for amblyopia with occlusion of the better eye dates back to at least the early eighteenth century. Charles de Saint-Yves first described occlusion of the dominant eye to promote use of the squinting eye in 1722 (De Saint-Yves 1722). After that, Allen in 1730 and Comte de Buffon in 1743 recommended occlusion of the good eye to straighten the squinting one (Allen 1730; De Buffon 1743). Javal in France and Worth (1901) in England advocated the use of occlusion for amblyopia (Javal 1896; Worth 1901).

Despite the fact that occlusion therapy dates back to the eighteenth century, there are still few guidelines for prescribing occlusion hours. This is in contrast to the prescription of antibiotics or other drug medication, which is done according to protocol and to scientifically derived standard measures. Age, visual acuity and to a lesser extent diagnosis seem to be the most important determinants when prescribing a number of hours of occlusion therapy. Mein and Trimble stated that the lazy eye should be occluded full-time in the case of strabismic amblyopia and part-time in case of anisometropic amblyopia followed by full-time occlusion if the acuity does not improve sufficiently (Mein, et al. 1991). According to Haase the good eye should be occluded for a number of days per week corresponding to age of the child in years, followed by one day of occlusion of the amblyopic eye (Haase 1995). Von Noorden and Campos stated that the good eye should be occluded full-time when there is a difference in visual acuity between the two eyes (Von Noorden, et al. 2002).

As there is no consensus amongst orthoptists, different orthoptists may prescribe very different hours of occlusion for the same patient. This can lead to confusion amongst parents seeking second opinions and result in non-compliance with the therapy (Tan, et al. 2003).

A questionnaire was developed with five case examples of children diagnosed with amblyopia in order to try and identify these variations in prescription of occlusion hours amongst orthoptists, their consistency and their main determinants.

METHODS

The questionnaire consisted of four example amblyopic cases and one potentially amblyopic case (Table 1). It was designed to imitate the clinical decision-making process in an orthoptist's everyday practice.

Cases 1, 2, and 5 were common amblyopic cases with a clear difference in acuity between the two eyes. Case 1 was a 3-year-old with an anisometropia and visual acuity of 5/10 and 5/5 as measured with a Children's Picture Chart. Case 2 was a 2-year-old with esotropia of the right eye first noticed 6 months earlier. Case 3 was a 5-year-old diagnosed with slight esotropia of the left eye with eccentric fixation of this eye and mild anisometropia. Case 4 was a 6-month-old baby with infantile esotropia of 30° alternating freely. Case 5 was a 3-year-old with hyper-

Table 1. The questionnaire containing the five sample amblyopic cases. The following instructions were given: Please enter below the number of hours of occlusion therapy you would prescribe in each case. Do not consider the prescription of glasses. Please do not discuss the cases with your neighbour, lest we measure less variability.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	3 years old	2 years old	5 years old	6 months old	3 years old
Diagnosis	Anisometropia	Esotropia first noticed six months earlier	Microstrabismus, untreated amblyopia	Alternating esotropia	Accommodative esotropia
Corneal reflection	Straight	20° Right esotropia	Slight left esotropia	30° Esotropia	15° Left esotropia
Cover test	Straight	Large right esotropia, no DVD / NL	Slight left esotropia	Marked esotropia, alternating, NL, DVD unclear	Large (30 cm) / moderate (5 m) left esotropia
Binocular vision	Titmus Fly +, animals ABC +	-	Titmus Fly -	-	-
Fixation RE/LE	Central / Central	Nasal / Central	Central / Eccentric nasal		Eccentric nasal
Visual acuity RE/LE	5/10 & 5/5 Pictures	Cannot maintain fixation, saccadic pursuit, some protest when occl left eye	1.0 / 0.2 E-Chart	Alternates freely	5/6 & 5/15 Pictures
Retinoscopy RE/LE	+3.5 / +2	+2 / +2	S+1.0=C-0.5axis180 / S+1.5=C-1.75axis50	+1 / +1	+4 / +4
Hours per day					
Days per week					

metropia combined with esotropia of the left eye, an eccentric fixation and a clear difference in the visual acuity between the two eyes. Case 2, 3, 4 and 5 were children with a strabismic amblyopia, case 1 was a child with an anisometropic amblyopia.

In March 2001, at the national Spring Meeting of the Union for Dutch Orthoptists in Utrecht, the questionnaire was put to Dutch orthoptists representing almost all practicing orthoptists in the Netherlands. In October 2001, at the annual meeting of the Union for German Orthoptists in Warnemünde, the questionnaire was put to the German orthoptists present. They were asked to determine their prescription of hours of occlusion (hours per day or days per week) for each of the five cases within 15 min. Additional instructions for completing the questionnaire included the statement that the prescription of glasses was not to be considered. They were not allowed to discuss or copy the cases and were under strict supervision from the four researchers present to prevent any exchange of views that might lessen variability. As a result the questionnaires were completed in silence. After 15 min the completed questionnaires were collected, also under strict supervision.

Data analysis

A database was created which consisted of four primary items; (1) the number of hours prescribed per day, (2) the number of days of occlusion per week, (3) the period of occlusion and (4) the total number of occlusion hours prescribed per week. Both eyes were itemized this way. The prescriptions given by each orthoptist were recorded on a case-by-case basis in the database. All the variations in the prescriptions of occlusion therapy could be stored into one database. From there it was possible to translate them into different regimens of prescribing occlusion therapy. For the statistical analysis of the database we used the non-parametric-tests (Mann-Whitney).

To determine whether orthoptists prescribed their hours of occlusion consistently above average or consistently below average, all orthoptists were ranked according to their number of prescribed hours of occlusion per case. From these rank numbers percentiles were derived and the standard deviation (SD) of the percentiles was calculated. Due to statistical considerations this SD of percentiles could not exceed 28.87%. If occlusion hours were completely randomly prescribed with a uniform distribution of the percentiles between 0% and 100%, the SD of the percentiles would be $\sqrt{1/12(100\%-0\%)^2} = 28.87\%$. The SD would be 0% if orthoptists prescribed consistently above or consistently below average, i.e. if the strictest orthoptist prescribed the most hours of occlusion for each of the five cases and the most lenient orthoptist prescribed the least hours of occlusion for each of the five cases.

RESULTS

Questionnaire

177 Dutch and 227 German orthoptists filled in the questionnaire. Seven (4%) Dutch orthoptists and four (2%) German orthoptists failed to complete the questionnaire properly, but in these cases only one of the five cases on the questionnaire had been left unanswered; therefore they were included in our analysis. The orthoptists wrote no negative comments on the forms regarding the sample cases.

Regimens

Variation in prescription of occlusion hours was large. In the effort to ascertain variation, consistency and determinants in the orthoptists' prescribing of occlusion, we identified certain types of regimen that were most frequently prescribed. Within the data analysis process five typical prescriptions were identified; Part-Time Occlusion (PTO), Part-Time Occlusion, Not

Table 2. Definitions of the five prescribed occlusion regimens.

PTO	Part-Time Occlusion, i.e. the non-amblyopic eye is occluded the same number of hours every day of the week
PTONED	Part-Time Occlusion Not Every Day of the week, i.e. the non-amblyopic eye is occluded for the same number of hours, followed by days of both eyes open
FTO	Full-Time Occlusion, i.e. the non-amblyopic eye is occluded for all waking hours every day of the week or the non-amblyopic occluded for all waking hours followed by days when both eyes are open
AOA	Also Occluding the Amblyopic eye, i.e. the amblyopic eye is also occluded for any period of time (either part-time or full-time) in addition to the occlusion of the non-amblyopic eye for any period of time
ALT	ALTernating occlusion therapy, i.e. both eyes are occluded alternately for the same number of hours every day, part-time as well as full-time
NOT	No Occlusion Therapy of either eye
Other	Pair of spectacles, foil, exercise, more complex regimens

Every Day of the week (PTONED), Full-Time Occlusion (FTO), Also Occluding Amblyopic eye (AOA), ALTernating occlusion (ALT), No Occlusion Therapy (NOT), (Table 2, Figure 1).

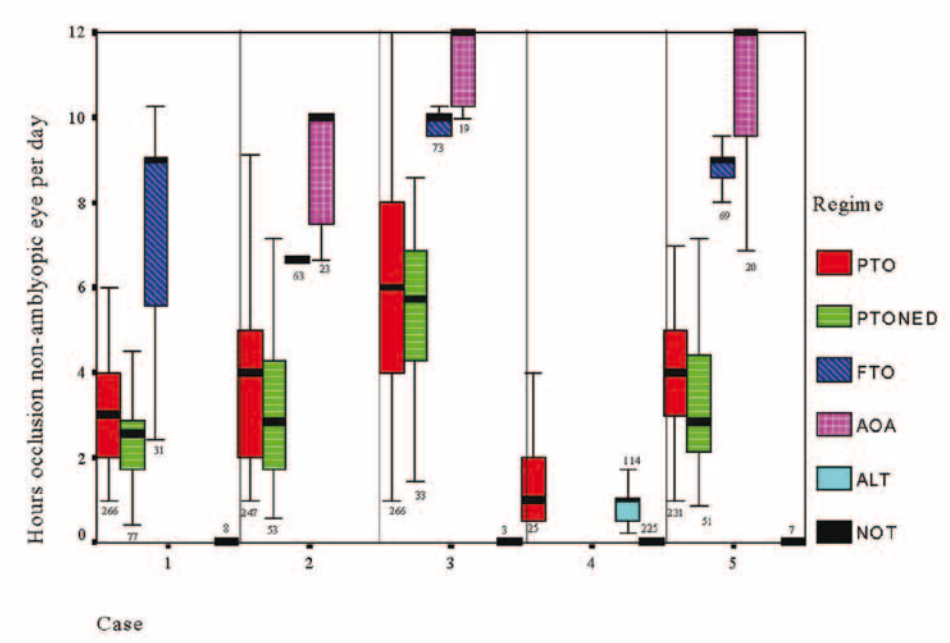


Figure 1. Median and interquartile range of the prescribed hours of occlusion per day of the non-amblyopic eye per regimen per case. The abscissa represents the five cases and the chosen regimen. The total number of orthoptists prescribing a regimen is given below each whisker. For colour figure please see 'Colour figures' on page 195.

There was an occasional prescription of a pair of spectacles, foil, inverse occlusion only or of even more complex regimens. Regimens prescribed by fewer than 12 orthoptists were excluded from analysis.

Because of the different ages of the sample cases, and in order to permit comparison of the actual hours of occlusion that had been prescribed, the time spent awake by a 6-month-old baby were estimated to be 6 h per day, a 2-year-old child, 10 h per day and a 3-year-old and 5-year-old child, 12 h per day. In this way the prescriptions of days per week were converted to hours per week.

Dutch and German orthoptists' prescribing behaviour

It became apparent that the prescribing behaviour of Dutch and German orthoptists was similar in many ways (Table 3). For both countries the preferred occlusion regime was PTO. Also, the variation in number of prescribed hours for each of the cases was as high among German orthoptists as it was among their Dutch counterparts. Differences were found in that FTO and AOA were favoured more often by the German orthoptists. However, the similarities outweighed the differences; therefore the data derived from the Dutch and German orthoptists were analysed together.The main result of this study was that for each of the five prescribed regimens the SD was half of the averaged prescribed hours of occlusion. This applied to each of the five sample amblyopic children. In addition, the following three observations were made:

(1) Orthoptists prescribed significantly more hours of occlusion when prescribing FTO than when prescribing PTO or PTONED ($P < 0.005$).

(2) In case 1, 2, 3, and 5, orthoptists who prescribed PTO prescribed significantly more hours per week than orthoptists who prescribed PTONED. This difference was significant in cases 1, 2, and 5 ($P < 0.002$).

Table 3. The median of the prescribed hours of occlusion for the non-amblyopic eye per day distributed over the five regimens per case. In brackets are the percentages of Dutch and German orthoptists prescribing that regimen.

	Case 1: Anisometropia, 3yrs		Case 2: Esotropia, 2yrs		Case 3: Microstrabismus,5yrs		Case 4: Alternating, 6mo		Case 5: Accomm. eso, 3yrs	
	Dutch	German	Dutch	German	Dutch	German	Dutch	German	Dutch	German
PTO	3 (72%)	3 (61%)	4 (81%)	4 (45%)	5 (85%)	6 (33%)	1 (7%)	2 (5%)	4 (79%)	4 (41%)
PTONED	2.1 (26%)	2.6 (14%)	2.9 (19%)	2.7 (9%)	5.7 (11%)	5.7 (6%)	0.6 (1%)	0.6 (2%)	2.9 (18%)	2.9 (8%)
FTO		9 (13%)		6.6 (28%)	12 (1%)	10 (32%)		5.1 (1%)		9 (30%)
AOA		8.6 (2%)		10 (10%)		12 (8%)		6.7 (1%)	3.4 (1%)	12 (8%)
ALT		4 (2%)				3.1 (1%)	1 (31%)	1 (26%)	3.4 (1%)	1.1 (2%)
NOT		0 (4%)			0 (1%)		0 (61%)	0 (65%)	0 (1%)	0 (2%)
Other	(2%)	(4%)		(8%)	(2%)	(20%)				(9%)

(3) In case 2 (n = 23), 3 (n = 18) and 5 (n = 19) some German orthoptists also prescribed occlusion of the amblyopic eye for a period of time. In these cases the non-amblyopic eye was occluded for significantly more hours than it was by orthoptists who prescribed PTO, PTONED or FTO ($P < 0.005$).

Consistency in prescription of occlusion hours

To calculate whether orthoptists prescribed their hours of occlusion consistently above average or consistently below average, each orthoptist was assigned a rank number according to number of prescribed hours per case. From these rank numbers the five percentiles, their average and their SD were derived. The average SD of the percentiles for all orthoptists was 21%. It would have been 28.87% if occlusion hours had been prescribed completely at random and 0% if they had been prescribed consistently above or below average (see above, Data analysis).

DISCUSSION

By distributing our questionnaire at an annual meeting for orthoptists and preventing an exchange of opinions we were able to gain an objective insight in the prescriptions of occlusion therapy for amblyopia.

Whilst analysing the data we were taken aback not only by the amount of variation in the number of prescribed hours of occlusion, but also by the diversity in the ways of prescribing occlusion therapy. The number of occlusion hours was neither normally nor log-normally distributed in any of the five example cases. However, during the analysis on a case-by-case basis it became apparent that certain ways of prescribing occlusion therapy, i.e. certain regimens, were more prevalent (Table 2). Within these regimens the SD was half of the average prescribed hours of occlusion. This applied to each of the five sample amblyopic children.

The five example amblyopic cases were chosen in order to make the difference in the prescribed hours of occlusion by orthoptists more easily transparent. Cases 1, 2 and 5 were common amblyopic cases, while cases 3 and 4 were more controversial cases. The largest variation in the prescription was found in case 3, representing a 5-year-old child with microstrabismus and untreated amblyopia. To improve visual acuity long periods of occlusion could have been thought necessary, although the outcome of the treatment was uncertain. That may have been the reason why some orthoptists decided not to occlude at all, whereas other orthoptists prescribed long periods of occlusion.

Case 4, a baby with alternating fixation, may not have required any occlusion therapy as there was no real evidence of amblyopia. However, some orthoptists prescribed ALT with a median of 1 h every day of the week. This decision to commence with alternating occlusion therapy may well have been prompted by the desire to prevent the development of an amblyopic eye. It may also have been influenced by the uncertainty of the diagnosis.

Orthoptists who prescribed FTO prescribed significantly more hours of occlusion in the same case than orthoptists who prescribed PTO and PTONED. This tendency can be partly explained by orthoptists opting for the FTO regimen when they wanted to prescribe longer periods of occlusion. Orthoptists wanting rapid success would select FTO rather than prescribing PTO or PTONED and waiting patiently. The same difference is seen between PTO and PTONED: orthoptists who chose PTO prescribed significantly more hours of occlusion in the same case than those who prescribed PTONED. It can also be partly explained by the assumption that orthoptists wanting to prescribe shorter periods of occlusion would opt for reducing the number of days per week rather than reducing the number of hours per day.
Orthoptists who prescribed an AOA regimen prescribed significantly more hours of occlusion than orthoptists who prescribed only occlusion of the non-amblyopic eye, possibly to compensate for the hours the amblyopic eye was patched.

In our questionnaire orthoptists were asked to make their prescription on the basis of the main determinants: age, visual acuity and diagnosis. Not included were further determinants that may have influenced the results, such as personal experience, the perceived domestic situation, the possible interference with homework or the waiting time for a follow-up appointment. The personal attitude of the orthoptists towards the success of the treatment was also not taken into account when designing the questionnaire.

Based on traditional and educational differences we expected a difference in occlusion prescriptions between Dutch and German orthoptists. Indeed, German orthoptists did tend to prescribe slightly longer hours of occlusion and to prescribe to FTO more often than Dutch orthoptists. However, the amount of variation in prescribed hours of occlusion was equal in the Dutch and German orthoptist (Table 3).
Neither consistently strict nor consistently lenient orthoptists of either nationality could be identified.

This study clearly emphasises the need for prospective studies investigating the relationship between prescribed occlusion hours and actual occlusion time carried out by the parents (Loudon, et al. 2003). Secondly, the relationship between the patched hours and the child's acuity increase should be established (Stewart, et al. 2002). The findings of such investigations

might lead to the development of validated guidelines or protocols for prescribing occlusion therapy.

If consensus and uniformity could be achieved among orthoptists and ophthalmologists as to the prescription of occlusion therapy, this would go a long way towards convincing the parent that a specific regimen of occlusion is the best therapy for the amblyopic eye, thus promoting compliance.

ACKNOWLEDGEMENTS

We thank the 404 orthoptists for their hospitality and filling in the questionnaire. We acknowledge René Eijkemans and Caspar Looman for their help with the statistical analysis.

Chapter 4

Visusevaluierung in einer historischen Kohorte von 137 okkludierten Patienten, 30-35 Jahre nach Ende der Okklusionsbehandlung

Evaluation of visual acuity in a historic cohort of 137 patients treated for amblyopia by occlusion 30-35 years ago

ZUSAMMENFASSUNG

Hintergrund: Der Visusverlauf des amblyopen Auges nach Ende der Okklusionsbehandlung wird unterschiedlich diskutiert. Wir untersuchten eine grosse historische Kohorte, 30-35 Jahre nach der Okklusionsbehandlung.

Material und Methode: Von 1250 Patienten, die in der Orthoptischen Abteilung des Waterland Krankenhauses in Purmerend zwischen 1968 und 1975 behandelt wurden, wurden 471 Kinder okkludiert, 5%, nach Vergleich mit den örtlichen Geburtsziffern. Wir konnten davon 203 Patienten erneut ausfindig machen, 137 wurden 2003 orthoptisch nachuntersucht. Wir korrelierten den aktuellen Visus mit der Ursache der Amblyopie (Anisometropie, Strabismus oder Kombination), dem Alter bei Beginn und Ende der Okklusion, dem Visus bei Beginn und Ende der Okklusionsbehandlung, der Fixation, dem Binokularsehen, der Refraktion und dem Refraktionsverlauf.

Ergebnisse: Die Patienten waren bei Beginn der Okklusionsbehandlung 5,4 ± 1,9 Jahre, bei Ende 7,4 ± 1,7 Jahre und bei der Nachuntersuchung 37 ± 2,7 Jahre alt. Korreliert mit dem aktuellen Visus waren ein geringer Visus des amblyopen Auges bei Beginn ($P < 0{,}0001$) und Ende der Okklusionsbehandlung *(*$P < 0{,}0001$), eine exzentrische Fixation ($P < 0{,}0001$) und die Ursache der Amblyopie ($P = 0{,}005$). Am Ende der Okklusionsbehandlung betrug der Visus der amblyopen Augen bei Patienten mit Strabismus-Amblyopie ($n = 98$) 0,29 ± 0,3 logMAR und bei der Nachuntersuchung 0,27 ± 0,3 logMAR. Bei Patienten mit Anisometropie-Amblyopie (>1 D, $n = 16$) hatte sich der Visus von 0,17 ± 0,23 logMAR auf 0,21 ± 0,23 logMAR und bei Patienten mit Anisometropie und Strabismus als Ursache der Amblyopie ($n = 23$) von 0,52 ± 0,54 logMAR auf 0,65 ± 0,54 logMAR verschlechtert. Insgesamt hatten 54 (39%) Patienten seit der Behandlung eine Visusabnahme, davon 18 um mindestens 50% in Bezug zum Visus nach Ende der Behandlung. 15 dieser 18 Patienten hatten eine Anisohyperopie, die zugenommen hatte.

Schlussfolgerung: Assoziiert mit einer langfristigen Visusabnahme nach Ende der Okklusionsbehandlung waren eine kombinierte Ursache (Anisometropie und Strabismus) der Amblyopie und eine Zunahme der Anisohyperopie.

Kurzzusammenfassung

137 Patienten aus einer historischen Kohorte, vor 30-35 Jahren wegen Amblyopie okkludiert, wurden 2003 erneut untersucht. Korreliert mit dem aktuellen Visus waren ein geringer Visus des amblyopen Auges bei Beginn und Ende der Okklusionsbehandlung, eine exzentrische Fixation und die Ursache der Amblyopie. Assoziiert mit einer Visusabnahme nach Ende der

Okklusionsbehandlung waren eine kombinierte Ursache (Anisometropie und Strabismus) der Amblyopie und eine Zunahme der Anisohyperopie.

ABSTRACT

Purpose: Opinions differ on the course of the visual acuity in the amblyopic eye after cessation of occlusion therapy. This study evaluated visual acuity in a historical cohort treated for amblyopia with occlusion therapy 30-35 years ago.

Methods: Between 1968 and 1975, 1250 patients had been treated by the orthoptist in the Waterland Hospital in Purmerend, the Netherlands. Of these, 471 received occlusion treatment for amblyopia, corresponding to 5% of the local birth rate. We were able to contact 203 of these, 137 were orthoptically re-examined in 2003. We correlated the current visual acuity with the cause of amblyopia, the age at start and end of treatment, the visual acuity at start and end of treatment, fixation, binocular vision and refractive errors.

Results: Mean age at the start of treatment was 5.4 ± 1.9 years old, 7.4 ± 1.7 years old at the end and 37 ± 2.7 years old at follow up. Current visual acuity in the amblyopic eye was correlated with a low visual acuity at the start ($P < 0.0001$) and end of occlusion therapy ($P < 0.0001$), an eccentric fixation ($P < 0.0001$), and cause of amblyopia ($P = 0.005$). At the end of the treatment, patients with a strabismic amblyopia ($n = 98$) had a visual acuity in the amblyopic eye of 0.29 ± 0.3 logMAR, and in 2003 0.27 ± 0.3 logMAR. In patients with an anisometropic amblyopia (>1 D, $n = 16$) visual acuity had decreased from 0.17 ± 0.23 logMAR to 0.21 ± 0.23 logMAR. In patients with both strabismic and anisometropic amblyopia ($n = 23$), visual acuity had decreased from 0.52 ± 0.54 logMAR to 0.65 ± 0.54 logMAR. Overall, acuity had decreased in 54 patients (39%) after cessation of treatment. Of these, 18 patients had an acuity decrease to less than 50% of their initial acuity. In 15 of these 18 patients anisohypermetropia had increased.

Conclusions: A decrease in visual acuity after cessation of occlusion therapy occurred in patients with a combined cause of amblyopia and an increase in anisohypermetropia.

For an English translation of Chapter 4, please see Appendix.

EINLEITUNG

In der Literatur wird die Prävalenz von Amblyopie mit 3,25% angegeben (Attebo, et al. 1998). Die Behandlung der Amblyopie mit Okklusion stellt seit Jahrzehnten eine etablierte Methode dar. Der Nutzen der Okklusionsbehandlung liegt vor allem in der Vermeidung von Kosten, die entstehen, wenn Patienten mit unzureichend behandelter Amblyopie im Laufe des Lebens ihr gutes Auge verlieren (Neubauer and Neubauer 2005). Der Zeitraum, den ein solcher Patient beidseitig sehbehindert (Visus beidseits >0,3 logMAR) verbringt, verlängert sich etwa von 8 auf 15 ½ Monate (van Leeuwen, et al. 2002).

Mit der Einführung des Screenings konnte Amblyopie früher erfaßt und damit erfolgreicher behandelt werden, so dass die Zahl der Patienten ohne Lesefähigkeit auf dem amblyopen Auge reduziert werden konnte. Seit Mütterberatungsstellen in den Niederlanden Kinder auf Strabismus und Amblyopie testen und den Visus im Alter von 3 sowie 3 ¾ Jahren bestimmen, ist eine zu spät entdeckte Amblyopie selten. Trotzdem misslingt bei etwa einem Drittel aller amblyoper Patienten (Jensen and Goldschmidt 1986) die Okklusionsbehandlung (Visus des amblyopen Auges > 0,3 logMAR). In der Vergangenheit wurde ein Misslingen der Okklusionsbehandlung durch zu späte Diagnosestellung (Bowman 1998) verursacht, heutzutage ist primär die Therapieuntreue (Dorey, et al. 2001; Loudon, et al. 2003) bei der Okklusionsbehandlung dafür verantwortlich.

Der Langzeiterfolg einer Okklusionsbehandlung wird in der Literatur unterschiedlich angegeben. Ein Vergleich der Studien ist schwierig aufgrund der unterschiedlichen Patientgruppen: Rekrutierung von verschiedenen Kliniken (Woodruff, et al. 1994) oder im Rahmen eines Vorschulscreenings (Bowman, et al. 1998); aufgrund der underschiedlichen Einslusskriterien: z.B. nur Patienten, die alle Kontrolltermine einhielten (Levartovsky, et al. 1995; Malik, et al. 1975); und aufgrund verschiedener Behandlungsmethoden: z.B. nur mit Vollokklusion (Scott and Dickey 1988) oder auch mit Pleoptik, Brillenokklusion oder inverser Okklusion behandelt (Schröpfer and Meinert 1975; Sparrow and Flynn 1977). Zudem variiert der Zeitpunkt der Nachuntersuchung nach Ende der Okklusionsbehandlung, Monate (Malik, et al. 1975) bis maximal zwei Jahrzehnte (Leiba, et al. 2001).
Einige Autoren berichten, dass der Visus nach Ende der Okklusionsbehandlung überwiegend unverändert blieb (Ohlsson, et al. 2002; Scott and Dickey 1988) oder besser (Leiba, et al. 2001) wurde, andere Autoren wiesen überwiegend eine geringe Visusabnahme von ein bis zwei Zeilen nach (Levartovsky, et al. 1995; Schröpfer and Meinert 1975). Negative Faktoren für das Langzeitergebnis nach abgeschlossener Okklusionsbehandlung waren ein relativ hohes Alter bei Beginn der Okklusionsbehandlung (Ham, et al. 1985; Levartovsky, et al. 1995; Meyer, et al. 1991; Stewart, et al. 2004) und ein geringer Startvisus (Meyer, et al. 1991; Scott and Dickey 1988; Sparrow and Flynn 1977; Woodruff, et al. 1994), eine exzentrische Fixation (Ham, et al.

1985; Sparrow and Flynn 1977) und eine kombinierte Ursache der Amblyopie: Strabismus und Anisometropie (Levartovsky, et al. 1995; Woodruff, et al. 1994).
Wir untersuchten den Visus sowie prognostische Faktoren für den aktuellen Visus nach Ende der Okklusionsbehandlung in einer Kohorte von 137 Patienten, die vor 30-35 Jahren in Waterland, einer ländlichen Region in Holland, wegen Amblyopie mit Okklusion behandelt wurden. Für die gesamte Region waren damals nur ein Augenarzt und eine Orthoptistin (HvK, damlas 40% Arbeitspensum) zuständig. Dieser Orthoptistin wurden von den Mütterberatungsstellen oder den Hausärzten, die die Kinder auf Amblyopie screenten, alle Amblyopieverdächtigen Kinder überwiesen. Gemeinsam mit dieser Orthoptistin wurden die Patienten 2003 erneut untersucht.

MATERIAL UND METHODEN

Hintergrund

Zum Zeitpunkt der Untersuchung stellte das Waterland Krankenhaus die medizinische Versorgung der Gemeinden Purmerend, Beemster, Waterland, Zeevang, Wormer, (einschliesslich Edam und Volendam) und Landsmeer (Anteil 50%, weil etwa die Hälfte der Einwohner nach Amsterdam-Nord überwiesen wurden) sicher. Ihre Population setzte sich aus Personen zusammen, die ursprünglich aus Purmerend oder den angrenzenden Gemeinden stammten sowie aus einzelnen Familien mit jungen Kindern, welche aus Amsterdam zugewandert waren.

Bestimmung der Daten

Es wurden alle Krankenakten von Patienten herausgesucht, die zwischen 1968 und 1975 in der Orthoptischen Abteilung des Waterland Krankenhauses in Purmerend, kurz- oder langfristig, behandelt wurden (n = 1250). Bei 471 (38%) Kindern wurde eine Okklusionsbehandlung durchgeführt. Aus den Krankenakten erhoben wir demografische Angaben der Patienten (Geschlecht, Geburtsdatum, Telefonnummer) und orthoptische Daten (Alter bei Beginn und Ende der Okklusionsbehandlung, Visus des amblyopen Auges bei Beginn und Ende der Okklusionsbehandlung, Ursache der Amblyopie).

Behandlung

Eine Amblyopie wurde damals mit Okklusion behandelt, wenn nach einer adäquaten Brillenverschreibung bei der folgenden Kontrolluntersuchung noch eine Visusdifferenz von einer Zeile bestand und amblyogene Faktoren vorhanden waren. Konnte kein Visus bestimmt werden, wurde das Führungs- und Fixationsverhalten bei Strabismus beurteilt und bei einem asymmetrischen Befund eine Okklusionsbehandlung eingeleitet.

Tabelle 1. Umrechnungstabelle Visus in Dezimalen - Visus in logMAR

Umrechnungstabelle
Visus in Dezimalen - Visus in logMAR

Visus	LogMAR
1,6	-0,2
1,25	-0,1
1,0	0,0
0,8	0,1
0,63	0,2
0,5	0,3
0,4	0,4
0,32	0,5
0,25	0,6
0,2	0,7
0,16	0,8
0,12	0,9
0,1	1,0
0,08	1,1
0,06	1,2
0,05	1,3

Damals wurde der Visus monokular bis zum vierten Lebensjahr mit Kinderbildern (Amsterdamer Bilder-Karte; Visusbereich 6/30 bis 6/5) getestet. Ab dem vierten Lebensjahr wurde der Visus mit Landoltringen und etwa ab dem siebten Lebensjahr mit Buchstaben in 6m getestet (Snellen) und in einem Dezimalwert notiert. Bei diesen zwei Tests war der Abstand zwischen den Visusstufen linear, der Sehzeichenabstand war grösser als 2,6 Bogenminuten und wurde als ‚single' beschrieben. Alle Visuswerte wurden für die Analyse in logMAR umgerechnet (Tabelle 1).

Nachuntersuchung 2003

Von 471 Patienten konnten 203 (43%) Patienten ausfindig gemacht und telefonisch kontaktiert werden. Diesen Patienten wurde ein Fragebogen zur Beurteilung der Lebensqualität bei Amblyopie und/ oder Strabismus zugesandt, der Amblyopia & Strabismus Questionnaire (A&SQ) (van de Graaf, et al. 2004). Die anderen Patienten konnten aus verschiedenen Gründen nicht kontaktiert werden: Zwei Patienten waren verstorben, bei den anderen Patienten konnte die Telefonnummer nicht ausfindig gemacht werden, oder sie waren nicht erreichbar. 174 Patienten sendeten den ausgefüllten Fragebogen zurück. Im Herbst 2003 konnten davon 137

Patienten in der Orthoptischen Abteilung des Waterland Krankenhauses in Purmerend orthoptisch und augenärztlich nachuntersucht werden. Von den 27 Patienten, die den Fragebogen zurückgesendet hatten, aber nicht nachuntersucht werden konnten, waren elf nicht erreichbar, sechs wollten nicht teilnehmen und neun konnten nicht zur Untersuchung kommen, weil sie hospitalisiert waren, im Ausland weilten oder einen langen Anfahrtsweg hatten.
Wir verfügten über Visusangaben zu drei Zeitpunkten (Beginn, Ende der Okklusionsbehandlung, sowie 2003, 30-35 Jahre nach Ende der Okklusionsbehandlung).
Folgende Untersuchungen wurden bei der Nachuntersuchung durchgeführt: Binokularsehen wurde mit dem Streifentest nach Bagolini in 6m und 0,4m getestet, Stereosehen mit Titmus-Test, Stereotest nach Lang II und TNO-Test. Der Schielwinkel wurde mittels monolateralem und alternierenden Abdecktest in 6m und 0,3m gemessen sowie eine dissoziierte Vertikaldivergenz notiert. Die Refraktion wurde mittels einer Skiaskopie ohne Zykloplegie, jedoch im abgedunkelten Raum und nachfolgendem subjektiven Abgleich geprüft. Der Visus wurde mittels Projektor (OCULUS, Medical Workshop Niederlande) mit linearen Visusstufen (Sehzeichenabstand „single") monokular in 6m Zahlen gemäss DIN EN ISO 8596 mit bestmöglicher Korrektion getestet und in Dezimalwerten notiert. Die Lesefähigkeit wurde mit einem niederländischen Lesetext bestimmt, der aus fünf Visusstufen bestand (D=0,5; D=0,8; D=1; D=1,25; D=2). D=1 entspricht Zeitungsdruckgrösse. Ferner wurde die Fixation ophthalmoskopisch geprüft. Es wurden die Vorderabschnitte und der Fundus beurteilt.

Alle Visuswerte, ausser dem Lesetext, wurden für die Analyse in logMAR umgerechnet.
Anisometropie wurde definiert als eine Differenz von mehr als 1 D sphärischem Äquivalent zwischen dem rechten und linken Auge. Eine Kombination beider Ursachen (Strabismus und Anisometropie) definierten wir als kombinierte Amblyopie.

Statistische Analyse

Wir haben eine Regressionsanalyse durchgeführt, um Parameter zu bestimmen, welche den aktuellen Visus am meisten beeinflussen. Um mögliche Störfaktoren auszuschliessen, wurde eine multivariante Analyse durchgeführt. Für die statistische Analyse wurde SPSS angewandt, Version 10.0. Als Schwelle für statistische Signifikanz wurde $P < 0,05$ bestimmt.

ERGEBNISSE

Gesamtgruppe

Die Patientengruppe bestand aus 65 Frauen und 72 Männern. Das durchschnittliche Alter bei Beginn der Okklusionsbehandlung betrug 5,4 ± 1,9 Jahre, am Ende 7,4 ± 1,7 Jahre. Zwölf (9%)

der 137 Kinder wurden bereits vor dem dritten Lebensjahr okkludiert, durchschnittlich ab 2,4 Jahren, bei ihnen bestand ein grosswinkliger Strabismus.
Der durchschnittliche Visus der amblyopen Augen bei Beginn betrug 0,6 ± 0,7 logMAR und 0,3 ± 0,5 logMAR am Ende der Okklusionsbehandlung. 98 Patienten (71%) wiesen eine Strabismus-Amblyopie auf, 16 Patienten (12%) eine Anisometropie-Amblyopie und 23 Patienten (17%) eine kombinierte Amblyopie.
Zu Beginn der Okklusionsbehandlung hatten 116 Patienten ein Visusunterschied zwischen dem Führungsauge und dem amblyopen Auge von mindestens 0,5 logMAR. 13 Patienten hatten ein Visusunterschied zwischen 0,2 und 0,5 logMAR, acht Patienten von < 0,2 logMAR. Bei fünf Patienten konnten aufgrund des Alters keine Visusangaben erhoben werden, anstatt dessen hat die Orthoptistin das Führungs- bzw. Fixationsverhalten der Patienten beschrieben. Bei allen fünf Patienten lag ein Strabismus vor: zwei Patienten hatten nur geringe Folgebewegungen bei Okklusion des Führungsauges, drei nahmen die Fixation auf, hielten diese aber nicht. Wir haben ein Visusäquivalent von 0,4 logMAR bzw. 0,2 logMAR angenommen. Der Visus bei Beginn der Okklusion wurde nur für die Korrelation des Startvisus mit dem aktuellen Visus verwendet, jedoch nicht für die prognostischen Faktoren. Diese Gleichsetzung kann man unterschiedlich interpretieren, es gilt aber zu beachten, dass es sich nur um fünf Patienten handelt.

Patienten mit Strabismus-Amblyopie wurden ab 5,1 ± 1,9 Jahren okkludiert, durchschnittlich 2,3 ± 1,3 Jahre. Patienten mit reiner Anisometropie-Amblyopie waren zu Beginn der Okklusionsbehandlung 7,2 ± 2,2 Jahre alt und wurden 1,4 ± 1,0 Jahre okkludiert. Patienten mit einer

Tabelle 2. Visus bei Beginn, Ende und 30-35 Jahre nach Okklusionsbehandlung sowie Alter bei Beginn der Behandlung, Dauer der Okklusion und Fixationsverhalten nach Ursache der Amblyopie.

Faktoren	Strabismus-Amblyopie (n = 98)	Anisometropie-Amblyopie (n = 16)	Kombinierte Amblyopie (n = 23)
Visus Beginn Okklusion (logMAR)	0,69* ± 0,5	0,53* ± 0,3	0,82* ± 0,54
Visus Ende Okklusion (logMAR)	0,29 ± 0,3	0,17 ± 0,23	0,52 ± 0,54
Visus Nachuntersuchung (logMAR)	0,27 ± 0,3	0,21 ± 0,23	0,65 ± 0,54
Alter Beginn Okklusion (Jahre)	5,1 ± 1,9	7,2 ± 2,2	5,8 ± 0,7
Dauer Okklusion (Jahre)	2,3 ± 1,3	1,4 ± 1,0	1,6 ± 1,3
Fixation			
Zentral	n = 63*	n = 16	n = 14
Exzentrisch	n = 35*	n = 0	n = 9

Sowohl bei der uni- als auch multivariaten Analyse waren der Visus des amblyopen Auges bei Beginn der Behandlung ($P < 0,0001$), die Ursache der Amblyopie ($P = 0,001$) (Strabismus, Anisometropie, kombinierte Amblyopie) sowie eine exzentrische Fixation ($P < 0,0001$) bei Strabismus signifikant in Bezug auf den aktuellen Visus in logMAR.
*Signifikante Parameter für den Visus 2003 in logMAR bei der Regressionsanalyse.

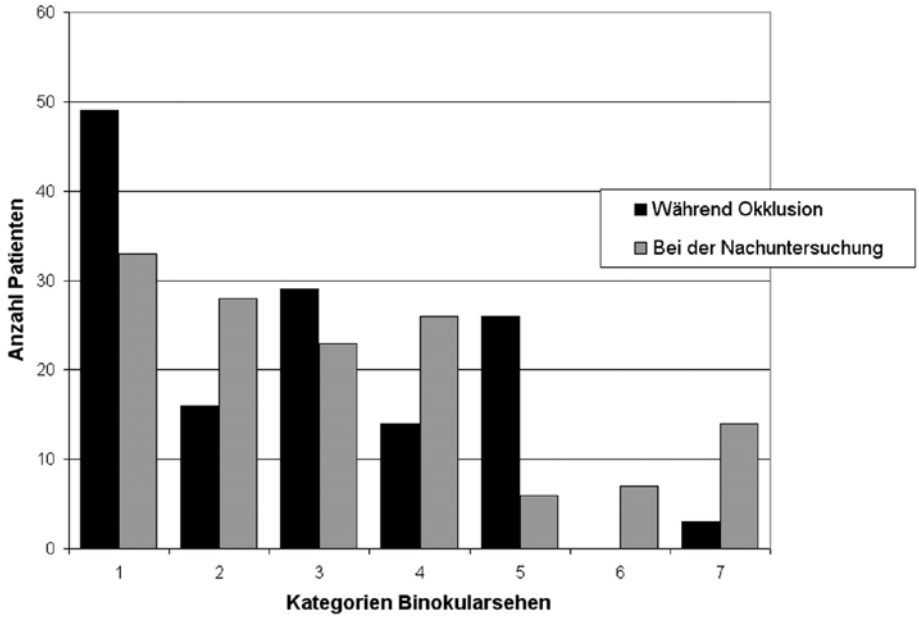


Abbildung 1. Binokularsehen der Gesamtgruppe während der Okklusionsbehandlung und bei der Nachuntersuchung 2003. Der Grad von Binokular- und Stereosehen (Abszisse) wurde in sieben Stufen eingeteilt: 1: Lichtschweiftest nach Bagolini negativ, 2: Lichtschweiftest nach Bagolini positiv, 3: Lichtschweiftest nach Bagolini und Titmus-Stereotest Fliege positiv, 4: mindestens Titmus-Stereotest Ringe 200″ bis 140″ positiv, 5: mindestens Titmus-Stereotest Ringe 100″ bis 40″ positiv, 6: Stereotest nach Lang oder mindestens TNO-Test Abbildung V (480″ & 240″) positiv, 7: TNO-Test Abbildung VI oder VII (120″ – 15″) positiv. Der schwarze Balken zeigt den Grad von Binokularsehen während der Okklusion in der Gesamtgruppe (n=137), der graue Balken bei der Nachuntersuchung 2003. Die Ordinate repräsentiert die Anzahl der Patienten.

kombinierten Amblyopie waren 5,8 ± 0,7 Jahre alt und wurden 1,6 ± 1,3 Jahre okkludiert (Tabelle 2). Das Binokularsehen verbesserte sich in der Gesamtgruppe der Patienten gering (Abbildung 1).

Visus nach Ursache der Amblyopie

Bei Patienten mit kombinierter Amblyopie hatte sich der Visus seit der Behandlung von 0,52 ± 0,54 logMAR auf 0,65 ± 0,54 logMAR und bei Patienten mit Anisometropie-Amblyopie von 0,17 ± 0,23 logMAR auf 0,21 ± 0,23 logMAR verschlechtert. Bei Patienten mit Strabismus-Amblyopie hatte sich der Visus von 0,29 ± 0,3 logMAR auf 0,27 ± 0,3 logMAR verbessert (Abbildung 2). Diese Verbesserung war signifikant ($P < 0{,}001$). Der Visus am Führungsauge dieser Patienten zeigte ebenso eine Zunahme von 0,01 ± 0,15 logMAR auf 0,05 ± 0,07 logMAR und war auch signifikant ($P = 0{,}04$).

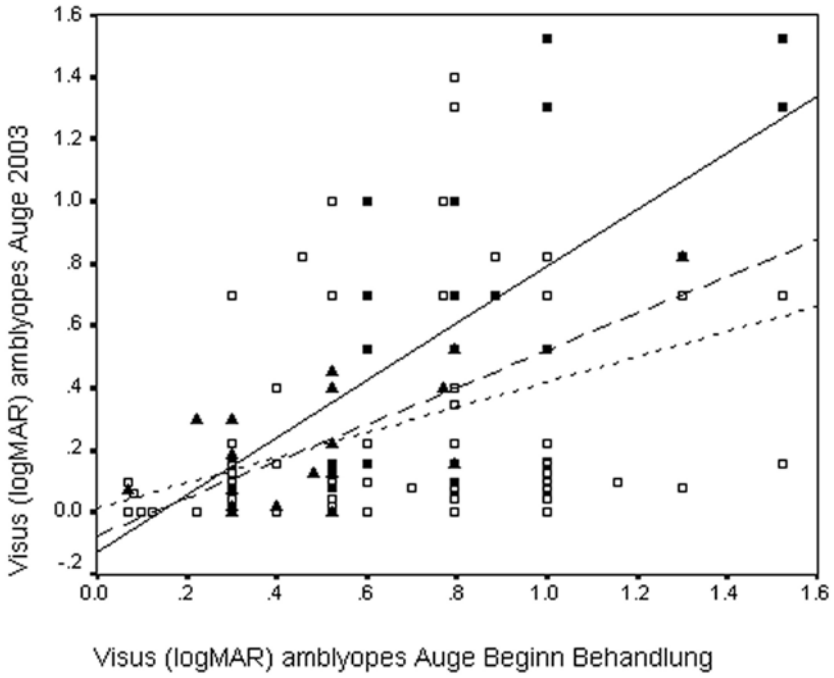


Abbildung 2. Visus des amblyopen Auges, nach Diagnose, bei Beginn der Okklusionsbehandlung und bei der Nachuntersuchung 2003.
Die Ordinate zeigt den Visus bei der Nachuntersuchung in logMAR, die Abszisse den Visus in logMAR bei Beginn der Okklusion. Patienten mit einer kombinierten Amblyopie sind dargestellt als schwarzes Viereck □, Patienten mit Anisometropie-Amblyopie als Dreieck ▲ und Patienten mit Strabismus-Amblyopie als weisses Viereck ←. Die ausgezogene Linie zeigt die Regressionslinie der kombinierten Amblyopien, die breitgestrichelte Linie die der Anisometropie-Amblyopien und die feingestrichelte Linie die der Strabismus-Amblyopien.
Sowohl Patienten mit Strabismus-Amblyopie als auch solche mit kombinierter Amblyopie hatten einen niedrigen Visus bei Beginn der Behandlung, Patienten mit Strabismus-Amblyopie erreichten bei der Nachuntersuchung, 2003, jedoch einen besseren Visus als diejenigen mit kombinierter Amblyopie.

Der Visus des amblyopen Auges zeigte sich bei 14 (10%) Patienten unverändert in Bezug zum Visus nach Ende der Okklusion. 70 (51%) Patienten wiesen eine Visusverbesserung auf. 54 (39%) Patienten hatten einen Visusabnahme, davon 18 Patienten um 50% und mehr in Bezug zum Visus des amblyopen Auges nach Ende der Okklusionsbehandlung.
47 (34%) von 137 Patienten hatten am Ende der Okklusionsbehandlung auf dem amblyopen Auge einen Fernvisus >0,3 logMAR, durchschnittlich 0,48 ± 0,6 logMAR. 55 (40,1%) von 137 Patienten hatten keine Lesefähgkeit (> D=1).

Patienten mit starker Visusabnahme

Bei 15 von 18 Patienten, die nach Ende der Okklusionsbehandlung eine Visusabnahme um mindestens 50% in Bezug zum Visus am Ende der Okklusionsbehandlung hatten, bestand eine Zunahme der Anisohyperopie. Von den 15 Patienten entwickelten neun Patienten bis zur Nachuntersuchung eine Anisohyperopie von 2,2 ± 1,7 D. Bei sechs Patienten bestand bereits während der Behandlung eine Anisohyperopie von 2,9 D, die auf 3,5 ± 1,8 D zugenommen hatte. Bei diesen 18 Patienten nahm das sphärische Äquivalent (Skiaskopiewerte) auf dem amblyopen Auge von +2,7 D auf +2,8 D zu und auf dem Führungsauge von +1,9 D auf +0,7 D ab. Nur fünf der 18 Patienten trugen bei der Nachuntersuchung eine adäquate Brille. Von diesen fünf waren drei Patienten auf dem Führungsauge myop und zwei durchschnittlich +2,75 D hyperop.

Prognostische Faktoren

Die univariate Analyse zeigte eine statistisch signifikante Korrelation zwischen dem aktuellen Visus und dem Visus bei Beginn der Okklusionsbehandlung ($P < 0{,}001$), dem Visus am Ende der Behandlung ($P < 0{,}001$), einer exzentrischen Fixation ($P < 0{,}001$) sowie der Ursache (Strabismus, Anisometropie oder kombinierte Amblyopie) der Amblyopie ($P = 0{,}005$) (Tabelle 2). Nicht signifikant waren die Dauer der Okklusion ($P = 0{,}622$) sowie das Alter bei Beginn ($P = 0{,}320$) und Ende der Okklusionsbehandlung ($P = 0{,}119$). In der korrigierten Analyse zeigte sich der Visus bei Beginn der Behandlung signifikant ($P < 0{,}001$), die Ursache der Amblyopie ($P = 0{,}018$) und die Fixation ($P = 0{,}004$). Patienten mit Anisometropie-Amblyopie hatten im Vergleich zu Patienten mit Strabismus-Amblyopie sowie mit kombinierter Amblyopie einen signifikant besseren Visus bei Beginn der Okklusionsbehandlung. Patienten mit kombinierter Amblyopie wiesen sowohl bei Beginn der Behandlung, als auch bei der Nachuntersuchung den niedrigsten Visus auf. Nur Patienten mit Strabismus-Amblyopie hatten, im Vergleich zum Visus am Ende der Behandlung, eine geringe Visusverbesserung. Die Fixation war bei Patienten mit Strabismus korreliert mit dem Visus. Es zeigte sich eine Korrelation zwischen der Visusabnahme und dem Verlust von Binokularsehen ($r = 0{,}38$).

Prävalenz der Okklusionsbehandlung

Wir wollten festzustellen, ob die historische Kohorte okkludierter Kinder für die damalige Okklusionsbehandlung repräsentativ war, bzw. ob ein Selektion Bias aufgetreten sein könnte. Die Prävalenz von Amblyopie wird mit etwa 3,25% angegeben (Attebo, et al. 1998). Wir erwarteten eher eine niedrigere Prävalenz zu finden, falls unsere historische Kohorte eine gebiaste Unterrepräsentation darstellte.

Von den 471 okkludierten Kindern waren die meisten Kinder 1965, 1966 und 1967 geboren (Abbildung 3).

Es waren 66 Kinder im Jahr 1965, 64 im Jahr 1966 und 68 Kinder im Jahr 1967 geboren. In der gesamten Region des Waterland Krankenhauses wurden in den Jahren 1965, 1966 und 1967 1286, 1328 und 1355 Geburten registriert. Dies würde, unter 1965-1967 geborenen Kindern, einer Prävalenz von okkludierten Kindern von etwa 5,0% entsprechen. Nur bei sieben der 137 Kinder, die okkludiert wurden, war die Diagnose im nachhinein diskutabel: Diese Patienten hatten einen Visusunterschied von <0,2 logMAR zwischen dem Führungsauge und dem amblyopen Auge, eine Anisometropie <1 D oder ein alternierendes Schielen, was nicht bei Anfang der Behandlung festgestellt werden konnte. Nach entsprechender Korrektion betrug die Prävalenz von okkludierten Kindern etwa 4,7%. Theoretisch wäre es möglich, dass Kinder, die ausserhalb der Region wohnten, im Waterland Krankenhaus behandelt wurden. Dies kam in unserer Gruppe aber nicht vor.

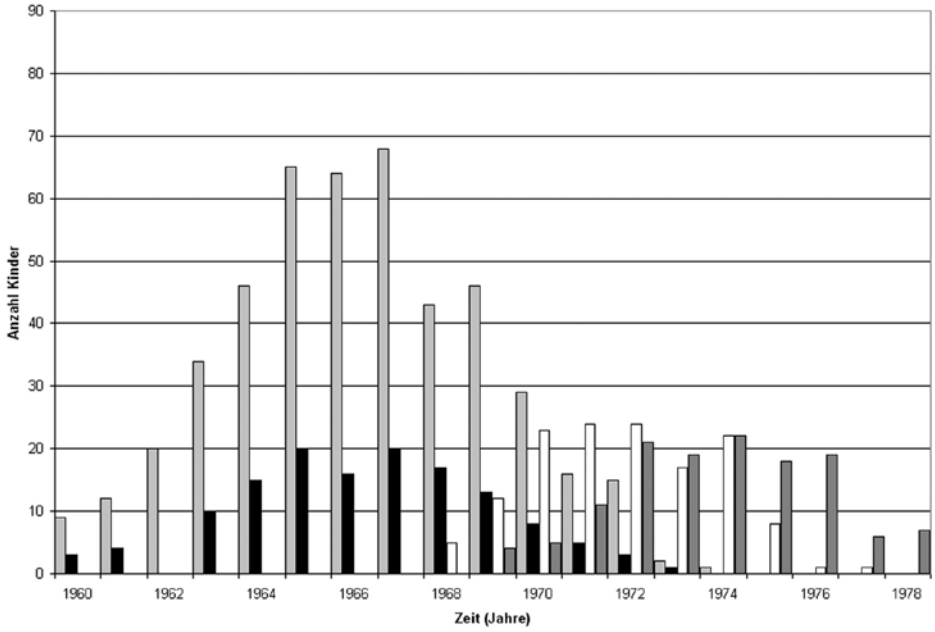


Abbildung 3. Übersicht der Patientenanzahl pro Geburtsjahr für alle im Waterland Krankenhaus okkludierten Patienten (*n* = 471, hellgrau) und für die historische Kohorte (*n* = 137, schwarz). Außerdem sind für die historische Kohorte Okklusionsbeginn (weiß) und Okklusionsende (dunkelgrau) angegeben. Von den 471 Okkludierten waren 66, 64 und 68 in den Jahren 1965, 1966 und 1967 geboren. Dies entsprach 5,0% der in der gesamten Region des Waterland Krankenhauses in diesen Jahren registrierten Geburten.

DISKUSSION

Es war uns möglich, bei 137 Patienten, länger als drei Jahrzehnte nach Ende der Okklusionsbehandlung, eine Visusevaluierung durchzuführen. Wir fanden, dass ein niedriger Visus bei Beginn der Behandlung, eine exzentrische Fixation sowie eine kombinierte Amblyopie am meisten mit dem bei der Nachuntersuchung erhobenen Visus korrelierten. Die schlechte Ausgangslage bei einem niedrigen Startvisus des amblyopen Auges und bei einer kombinierten Ursache der Amblyopie bestätigt die Beobachtung anderer Autoren, acu bei einem weitaus längeren Beobachtungszeitraum als bisher beschrieben. Eine kombinierte Ursache der Amblyopie und eine Zunahme der Anisohyperopie waren assoziiert mit einer langfristigen Visusabnahme nach Ende der Okklusionsbehandlung.

Der Visus konnte aufgrund des Schulalters der Kinder sowohl bei Beginn und bei Ende der Okklusion grösstenteils mit Landoltringen getestet werden. Der Visus bei Beginn der Okklusion, wobei die grösste Varianz zu erwarten war, wurde lediglich für die Korrelation mit dem aktuellen Visus verwendet. Bei der Bestimmung der prognostischen Faktoren haben wir Visuswerte bei Ende der Okklusionsbehandlung mit dem aktuellen Visus verglichen, der jedoch mit unterschiedlichen Visustest bestimmt wurde. Dies kann zu nicht ganz vergleichbaren Werten führen (Gräf 2004), denn Visusprüfungen mit Optotypen können nur im oberen Visusbereich gleiche Werte wie der Landoltring erzielen, im unteren Bereich tritt eine leichte Überschätzung des mit Optotypen gemessenen Visus auf (Rassow and Wang 1999). Trotzdem fanden wir eine deutliche Signifikanz.

Bei Patienten mit Strabismus-Amblyopie trat nach Ende der Okklusionsbehandlung sowohl im amblyopen Auge als auch im Führungsauge eine geringe Visusverbesserung auf. Wir vermuten daher einen natürlichen Verlauf der Visusentwicklung. Über die Entwicklung der Führungsaugen wird bisher kaum berichtet, man fand, ohne nach der Ursache der Amblyopie zu unterscheiden, eine geringe Visusverbesserung (Ohlsson, et al. 2002). Studien, die den natürlichen Verlauf bei Patienten mit unbehandelter Amblyopie untersucht haben, zeigten sowohl im Vorschulalter (Simonsz and Preslan 1999), als auch im Erwachsenenalter (Haasse and Wenzel 1996) eine Verschlechterung im amblyopen Auge auf. Hierbei ist anzumerken, dass eines der Einschlusskriterium dieser Studie ein niedriger Visus (>0,18 logMAR) war und Kinder mit nur geringer Visusminderung nicht vorkamen. Es ist daher ein Selektion Bias wahrscheinlich.

Wie andere Autoren (Levartovsky, et al. 1995; Woordruff, et al. 1994) konnten wir keine Korrelation zwischen dem Alter bei Beginn und Ende der Okklusionsbehandlung und dem 2003 erhobenen Visus des amblyopen Auges nachweisen. Man kann daraus aber nicht schliessen, dass ein Patient nicht erfolgreicher behandelt werden kann, wenn dieser Patient bereits zu einem früheren Zeitpunkt okkludiert würde.

Das Alter bei Beginn der Okklusionsbehandlung ist in unserem Krankengut relativ hoch, wahrscheinlich, weil Amblyopiescreening zum Zeitpunkt der Behandlung nicht ganz flächendeckend durchgeführt wurde. Die Mütterberatungsstellen und, ausserhalb der Stadt, die Hausärzte führten keine Visusmessung durch, so dass Amblyopie ohne auffälliges Schielen meist erst im Alter von fünf bis sieben Jahren diagnostiziert wurde. In den Niederlanden wird heutzutage von den Mütterberatungsstellen flächendeckend mit 3 sowie 3¾ Jahren ein Amblyopiescreening duchgeführt. Das Durchschnittsalter bei Beginn der Okklusionsbehandlung bei okkludierten Kindern in Den Haag lag in den Jahren 2001-2006 bei 4,6 Jahren (Loudon, et al. 2006).

Bei 15 von 18 Patienten, die nach Ende der Okklusionsbehandlung eine Visusabnahme von mindestens 50% hatten, bestand eine Zunahme der Anisohyperopie. Wichtig erscheint, dass nur fünf der 18 Patienten bei der Nachuntersuchung eine Brille trugen. Die anderen gaben an, die Brille seit ihrem 14./ 15. Lebensjahr nicht mehr zu tragen. Es ist denkbar, dass diese Patienten bereits kurze Zeit nach Erhalt der neuen Korrektion aufgrund der kontinuierlichen Zunahme der Anisometropie auf dem amblyopen Auge wieder unscharf sahen und deshalb die Brille nicht gerne tragen.
Es ist empfehlenswert, Patienten, bei denen eine Anisometropie festgestellt wurde und eine Zunahme dieser Anisometropie zeigen, häufiger zu kontrollieren und die Brille anzupassen.

In anderen Studien (Attebo, et al 1998; Leiba, et al. 2001; Levartovsky, et al. 1995; PEDIG 2002; Woodruff, et al. 1994) beträgt der Anteil reiner Anisometropie-Amblyopien im Patientengut etwa 30%, variiert aber zwischen 11% (Leiba, et al. 2001) und 50% (Attebo, et al. 1998). In unserer Studie waren nur Kinder inkludiert, die okkudiert wurden. Patienten, bei denen die Anisometropie-Amblyopie ausschliesslich mit einer Brillenkorrektion behandelt wurde, meistens nur vom Augenzarzt, kamen in unserer Studie daher nicht vor. Ob und zu welchem Zeitpunkt eine Okklusionsbehandlung, nebst der Verschreibung einer Brillenkorrektion, bei Patienten mit leichten Anisometropie-Amblyopien durchgeführt werden sollte, wird verschieden gehandhabt.

Erstaunlicherweise fanden wir eine höhere Prävalenz von okkludierten Kindern (4,7%) als die in anderen Studien genannte Prävalenz der Amblyopie (3,25%) (Attebo, et al. 1998). Wie erklärt sich diese Diskrepanz? Die Prävalenz der Amblyopie wird in den meisten Studien bei erwachsenen Patienten mit unbehandelter Amblyopie bestimmt. Aus unserer Studie geht hervor, dass der Visus nach Ende der Okklusionsbehandlung bei den meisten Patienten leicht ansteigt, bei einigen aber abnimmt. Die Orthoptistin weiss aber zu Beginn der Behandlung nicht, bei welchen Kinder, die wegen einer geringen Visusreduktion (>0,1 logMAR) von den

Mütterberatungsstellen oder Kinderärzten überweisen werden, sich der Visus spontan bessern wird und ‚überbehandelt' daher.

DANKSAGUNG

Diese Studie wurde unterstützt von der Foundation Ondersteuning Oogheelkunde 's-Gravenhage, Foundation Blindenhulp, Ooglijders Foundation.
Spezieller Dank gilt dem Waterland Krankenhaus in Purmerend für die Gastfreundschaft sowie den Orthoptisten, H.M van Minderhout und J.R. Polling.

Chapter 5

Electronic recording of occlusion treatment for amblyopia: potential of the new technology

ABSTRACT

Purpose: Approximately one third of all amblyopic eyes do not reach visual acuity of 20/40 in spite of occlusion therapy. One of the reasons is a lack of adherence to therapy, which, however could not be quantified in the past. Experience with new devices (Occlusion Dose Monitors, ODMs) for electronic recording of occlusion has recently been reported. The aim of the present study was to evaluate the potential the ODMs developed in the Netherlands. Various features were tested, including the reliability of the ODM recordings compared to diaries, two ODMs used simultaneously on one patch, the influence of the ambient temperature, and the specificity of the recording pattern for measurements on the eye.

Methods: The ODMs were taped to the outside of the standard occlusion patch and measured the temperature difference between their front and back surfaces. Members of the research group and the families of two patients kept occlusion diaries while using the ODMs. Recorded and written occlusion periods were compared. Measurements were carried out under various conditions: patch with one ODM tightly on the eye or detached (allowing peeping); ODMs taped to various parts of the body; two ODMs simultaneously on one patch; variation of room temperature.

Results: There was good correspondence between the occlusion times recorded by the ODMs and those from the diaries, as well as between the recordings of two ODMs used simultaneously on one patch. High ambient temperatures (33°C to 37°C) prevented reliable ODM measurements. Measurements on other parts of the body were misclassified with probabilities between $P = 0.099$ and $P = 0.325$ as measurements with the patch tightly on the eye.

Conclusions: In spite of some technical limitations, the ODMs provide a chance for reliable assessment of compliance and therefore objective information on dose-response function for occlusion therapy. This will lead to a more evidence based treatment for amblyopia.

The data for this chapter were collected in collaboration with the Department of Ophthalmology, J.W. Goethe University, Frankfurt am Main, Germany, and the majority of them are part of the *Dr.med* thesis of Yaroslava Chopovska.

INTRODUCTION

Amblyopia is the most common visual defect of childhood (Attebo, et al. 1998). Introduced more than 1000 years ago the accepted treatment for children with amblyopia is occlusion of the non-amblyopic eye, with prescribed regimens between a quarter of an hour and all waking hours (Loudon, et al. 2004). However, between 26% and 40% of patients do not reach 20/40 acuity in spite of occlusion therapy (Flynn, et al. 1999). One of the reasons is a lack of adherence to therapy (Dorey, et al. 2001), which could not be quantified in the past. This led to doubts about the effectiveness of occlusion and to discussions about the justification of screening for amblyopia (Clarke, et al. 2003; Snowdon and Stewart-Brown 1997; Williams, et al. 2002). Continuous objective compliance monitoring could be the key to a more evidence based treatment for amblyopia.

In 1991, Fielder et al. developed the first prototype electronic occlusion dose monitor (ODM) (Figure 1a). This prototype was changed into a modified occlusion patch with two miniature electrocardiogram electrodes attached to its undersurface (measuring patch-skin resistance) and connected with leads to the datalogger which was carried in a shoulder bag (Fielder, et al. 1995).

The design was modified in 1997 (Figure 1b) (Simonsz, et al. 1999) and again in 2001 and 2002 (Figure 1c, d). A different technical approach, measuring the temperature difference between the surface of the eye and the ambient temperature, was used. The devices were made smaller and everything including data storage was built into the ODM. All ODMs were developed in the public domain.

Although the devices are being used in large amblyopia therapy studies (Loudon, et al. 2004; Stewart, et al. 2004), details on technical features have not been made available for either of the technologies. The aim of the present study was to test the potential of the ODM types 2001 and 2002. Although it was assumed that the device might become unreliable in the summer months (Simonsz, et al. 1999), the respective temperature range is still unclear. Patients and parents might perceive the ODM to be a control and might seek ways of deceiving the system. While Fielder et al. reported their ODM to reveal episodes of peeping due to the monitoring of the patch-skin contact (Fielder, et al. 1995), this has not yet been tested for the new temperature-measuring devices.

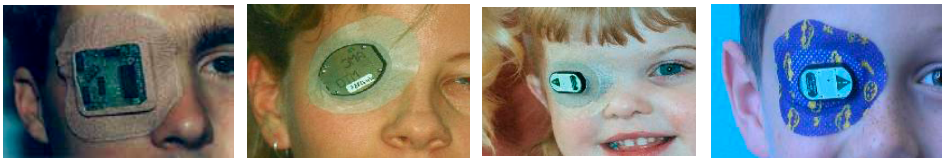
The following aspects of the new technology were tested by two members of the ERPAG study (ophthalmology departments of the universities of Frankfurt, Germany and Rotterdam, the Netherlands): reliability of the ODM recordings compared to diaries; two ODMs used simultaneously on one patch; the temperature range preventing reliable measurements; the specificity of the recording pattern for measurements on the eye.

In addition to these quantitative assessments, information was obtained from two families about the long-term use of the devices.

MATERIALS AND METHODS

Design and function of the ODMs

The ODM is composed of a microcontroller, two temperature sensors, a clock and a rechargeable battery (Simonsz, et al. 1999). It is taped to the outside of a standard eye patch using double-sided Scotch tape. When the patch with the ODM is worn on the eye, the temperature at the back of the device is higher than at the front. A microcontroller subtracts the temperature measured by the sensor at the front of the ODM from the temperature measured at the back. The temperature is sampled every 120 seconds. The sensitivity is set at 1/16°Celsius. There are no patient operated controls. After a period of recording the data are saved on a personal computer by means of the docking system.
ODM types 2001 and 2002 (Figure 1c, d) were used. The two differ mainly in size, while the features mentioned above are the same.



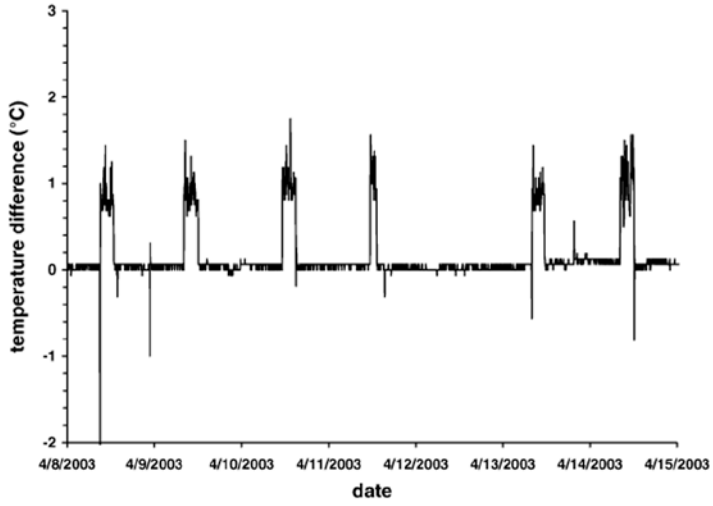
1a 1b 1c 1d

Figure 1. The development of the Occlusion Dose Monitor. **a** Year 1991: first model developed by Fielder and Moseley in Birmingham, UK (with permission of M. Moseley). The ODM was a miniature datalogger, which logs the patch-skin contact resistance every 64 s. **b** Year 1997: The Academic Medical Center Amsterdam modified the design into an ODM containing two thermistors connected to either the front or the back of the ODM (35x23x4 mm, 6 g). **c** The 2001 type used in the Netherlands (24x12x3.6 mm, 1.8 g). **d** The 2002 type used in Germany (31x15x3.5 mm, 2.3 g). For colour figures please 'Colour figures' on page 195.

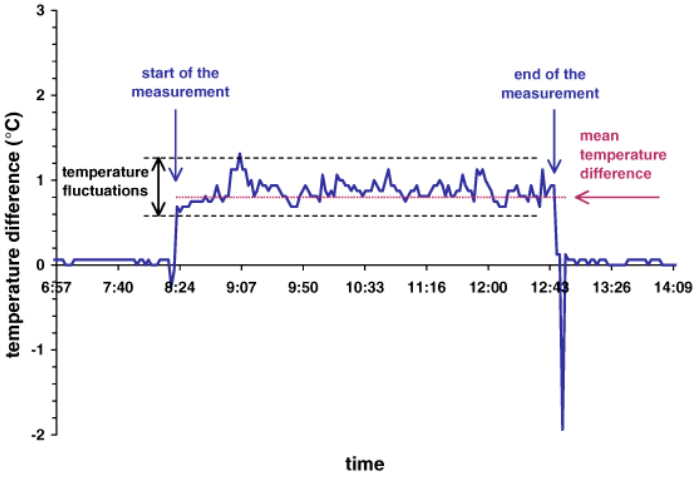
An example for a week's recording is shown in Figure 2a. By displaying a day's recording with better temporal resolution, the exact starting and ending times of occlusion may be determined (Figure 2b).

Methods of evaluation of the ODM features

Reliability of time recordings
Members of the research groups and the families of amblyopic patients from Frankfurt kept occlusion diaries while using the ODMs. Recordings of two compliant families were selected for the purpose of testing the equipment. One child had was prescribed 4 h and the second 12 h of occlusion daily. The diaries and the ODM recordings were evaluated and compared. Prior to participation, written consent was obtained from the parents after the nature of the tests



2a



2b

Figure 2. Examples of recordings with the ODM, with measured temperature difference on the ordinates. **a** A week's recording. *Abscissa*: date of the recording. The temperature difference was about "0" (0; 0.0625) while the child was not patched (baseline value) and higher during the periods of occlusion. The child's eye was occluded every day except one (12.04.03) for several hours. **b** A day's recording. *Abscissa*: time. The measured temperature difference increased at the beginning of the occlusion and dropped at the end, thus showing the duration of the measurement. Specific features of every measurement are the "mean temperature difference" and the "standard deviation", which describes the dimension of the temperature fluctuations .

was explained fully. All procedures followed the guidelines of the Declaration of Helsinki and were approved by the medical ethical committee of the University Clinic Frankfurt.

Comparison of recordings with two ODMs used simultaneously
Both groups performed tests placing two ODMs of the same type on one patch together and sticking the latter to different parts of the body. The mean temperature difference and the standard deviation of all temperature differences (Figure 2) sampled during each period of occlusion with both ODMs were compared by means of the Passing-Bablok regression. The duration of the occlusion periods was compared.

Influence of the ambient temperature
The investigators carried out measurements with ODM 2002 on the eye varying the room temperature from 18°C to 38°C to determine the temperature range preventing reliable measurements. The relationship between the measured mean temperature difference and the ambient temperature was evaluated by means of the Pearson regression test.

Specificity of pattern of measurements on the eye
We tested several possible ways of deceiving the system. Measurements were carried out with ODM 2002 while the patch was tightly on the eye, detached on the eye (peeping), on the forehead, on the arm covered with a sleeve, on the arm uncovered and in the pocket of the trousers. Room temperature was between 18°C and 23°C. Parameters "mean temperature difference" and "standard deviation" were compared by means of the Hotelling's-T^2 test (method of multivariate analysis) and the discriminant analysis.

RESULTS

Reliability of the ODMs compared to diaries

Correspondence between the occlusion times recorded by the ODMs and those from the diaries was about 99%, not only for measurements of short duration, but also for those lasting more than 11 h. The mean time difference between ODM records and the researchers' diary was about -0.5 min in both groups. This was due to the sampling rate of the ODM of 2 min. Only one fifth of the data differed by more than 2 min (maximum 5 min). In both children the mean time difference between ODM records and the occlusion diary was about -3.5 min, probably because parents kept less precise records than the researchers.

Comparison of recordings with two ODMs used simultaneously

The difference in data between two ODMs on one patch was minimal. Passing-Bablok regression revealed highly significant agreement both between the mean temperature differences ($r = 0.93$; $P < 0.01$) and between the standard deviations ($r = 0.624$; $P < 0.01$). The mean time difference between two ODMs on one patch was 0 min (SD = 1.6 min).

Influence of the ambient temperature on the measurements

The ambient temperature had a significant influence on the temperature difference measured by the ODM: $y = -0.0556x + 1.98$; $P < 0.01$; $r = -0.966$ (Figure 3a).
As expected, the measured temperature difference was "0" when the ambient temperature approached the temperature 36°C and became negative when the temperature increased further. High ambient temperatures (33°C to 37°C) prevented reliable ODM measurements (see Figure 3b for an example).

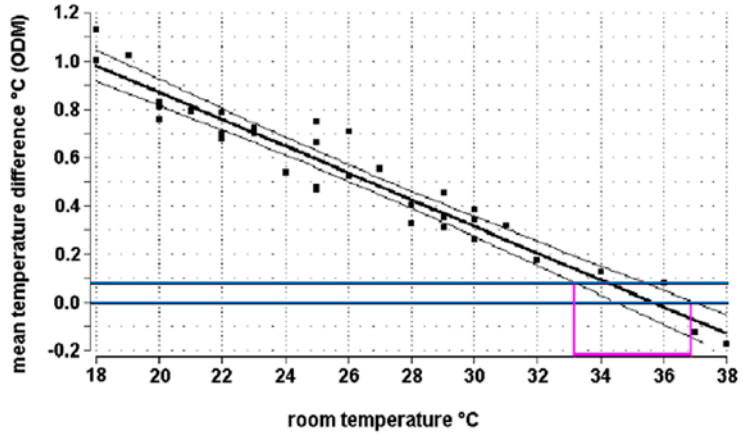
Is there a specific pattern for the measurement on the eye?

Figure 4 shows an example of the results of the discriminant analysis comparing measurements with the patch tightly on the eye with those when the patch was partly detached. The probability of false classification was $P = 0.154$. The mean temperature difference tended to be higher for the measurements with the patch tightly on the eye ($P < 0.01$, *t*-test), while the standard deviation was similar for both data groups ($P = 0.885$, *t*-test).
Table 1 summarises the results of all the situations tested.

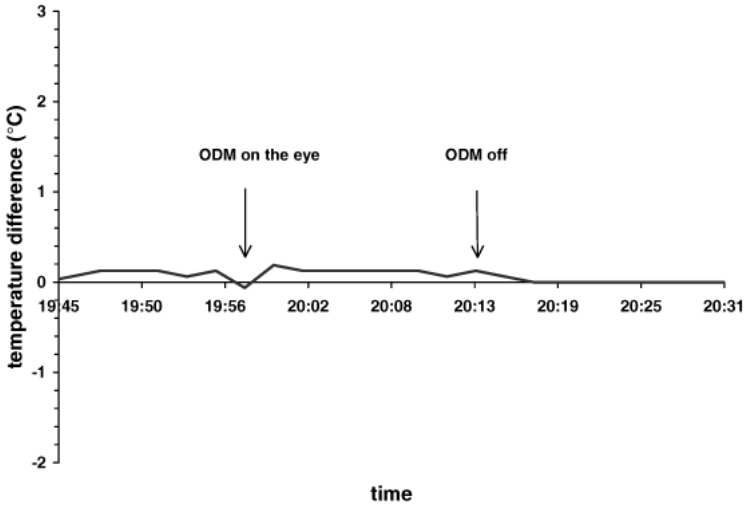
The rate of misclassification increased from the ODM placed in the trouser pocket ($P = 0.099$) to the ODM worn on an uncovered arm ($P = 0.325$). The researchers were able to discern when

Table 1. Confidence intervals (*CI*) of the mean temperature differences (*TD*) and of the standard deviations of temperature differences measured by the ODM on different locations; results of the discriminant analysis (rate of false classification) and Hotelling's-T^2 test for the comparison between measurements with the patch put tightly on the eye and measurements made elsewhere.

	eye (patch tight)	eye (patch detached)	forehead	arm covered	arm uncovered	trouser pocket
Number of tests	38	23	31	26	25	30
CI of mean TD (°C)	0.679-1.130	0.345-1.020	0.750-1.369	0.479-1.154	0.530-1.128	0.350-0.919
CI of SD of the TD (°C)	0.039-0.199	0.044-0.197	0.051-0.248	0.034-0.240	0.045-0.270	0.039-0.457
Discriminant analysis: rate of false classification	--------	P = 0.154	P = 0.242	P = 0.212	P = 0.325	P = 0.099
Hotelling's-T^2 test	--------	P < 0.01	P < 0.01	P < 0.01	P < 0.01	P < 0.01



3a



3b

Figure 3. Influence of ambient temperature on ODM measurement. **a** *Abscissa*: room temperature; *ordinate*: mean temperature differences measured by the ODMs. The regression line is shown together with the confidence interval (95%). *Horizontal lines* indicate the range of baseline fluctuations. Temperatures between 33°C and 37°C (*see vertical line*) prevented reliable ODM measurements. **b** Example of a measurement at 35°C. *Abscissa*: time; *ordinate*: temperature difference measured by the ODM. According to the occlusion diary, measurement on the eye started at 19:58 hours and ended at 20:14 hours. It is not possible to distinguish the measurement on the eye from the baseline fluctuations.

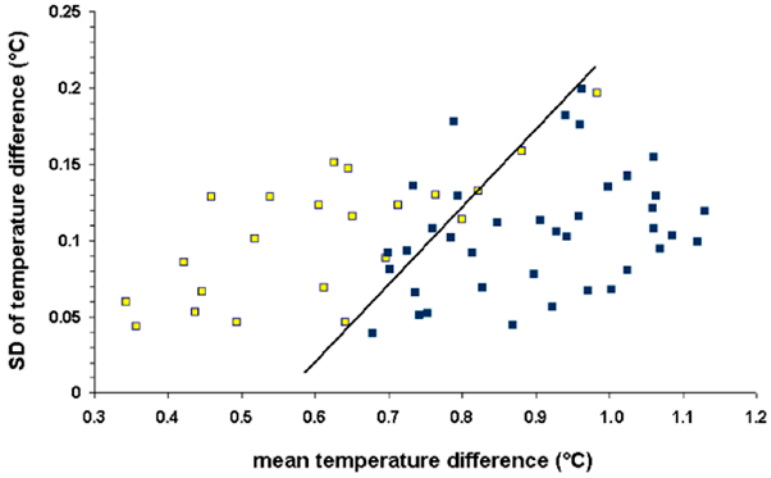


Figure 4. Discriminant analysis of patch tightly on the eye against patch detached on the eye, allowing peeping. *Abscissa*: mean temperature difference measured by the ODM; *ordinate*: SD of temperature differences measured by the ODM. *Dark squares* represent the recordings performed with the patch tightly on the eye, *lighter squares* those with the patch detached on the eye. The *line* represents the optimal separation of the data as calculated by the discriminant analysis. The recordings classified by discriminant analysis as those being tightly on the eye are to the right of the line, as those being detached on the eye to its left.

parents put the device into their pocket after occluding the child's eye.

Hotelling's-T^2 test (comparing the averages of the variables) yielded significant differences between the measurements with the patch tightly on the eye and the other situations (Table 1). This is not a contradiction to the results of the discriminant analysis, which explores whether a specific measurement was on the eye or not.

DISCUSSION

Our tests proved that the ODM measures the duration of patching with high certainty. Parents' diaries were in excellent agreement with the objective records. This was not unexpected, as compliant families were selected.

The correspondence with diaries was as good for the measurements with long duration as for the shorter ones. Longer duration of the measurement was not a cause for data loss, which was different from experiences reported with the first ODMs (Fielder, et al. 1995). A different source of data loss with the ODMs measuring temperature difference was occasional battery failure.

We showed the ODM recordings to be reproducible, since the correspondence in data between two ODMs on one patch was highly significant.
We confirmed that the device might become unreliable in summer, showing that temperatures between 33°C and 37°C prevent reliable measurements. However, such temperatures are rare in our climate, and it is hard to imagine that children would choose to spend a lot of time in conditions that were hardly bearable for the researchers. During very warm periods in summer both patches and ODMs occasionally came off, which could be another source of data loss.
Episodes of peeping could be discerned especially well with the devices monitoring patch-skin contact (Fielder, et al. 1995), but in most cases also with the ODMs measuring temperature difference. While the probability of misclassification was low for the ODM carried in the trouser pockets, it was higher when placed on the arm or forehead. The recognition of cheating could be improved if not only the information about the temperature difference, but also about the ambient temperature (Figure 3) would be stored. While ODMs measuring temperature difference often allow differentiation of whether the patch was on the eye or not, the devices recording patch-skin contact only provide the information whether the patch was detached. Obviously neither device is able to detect patching of wrong eye. Hence the ODM helps to recognise many deceptions but it cannot be used as a lie detector. Cooperation of patients and parents remains important. However, it is easier for parents to say that the child does not like the patch than to stick the ODM for weeks somewhere else than to their child's eye (Fielder, et al. 1995).

Apart from some technical limitations, ODMs provide objective information on dose-response function for occlusion therapy and compliance (Loudon, et al. 2004; Stewart, et al. 2004). Low acuity increase of the amblyopic eye has been shown to be caused by the lack of adherence to prescribed therapy (Loudon, et al. 2003). Recent studies monitoring occlusion revealed average compliance of 50-60% (Loudon, et al. 2004; Stewart, et al. 2002). This raised concerns (Fleck, et al. 2003) about the reliability of the occlusion treatment trials without electronic compliance monitoring. The ATS (Holmes, et al. 2003) and ROTAS (Stewart, et al. 2004) studies both found that 6 h and 12 h of prescribed occlusion led to similar visual outcomes. However, electronic monitoring revealed significantly more visual improvement in children receiving the higher occlusion dose (Stewart, et al. 2004).

Using the ODMs was convenient for the parents. They found the documentation of the occlusion duration more bothersome and sometimes forgot it. Carrying the patch with the device on it was no more inconvenient for children than the patch alone, because the patch itself was the bothering factor. However, the long-term use of the ODMs was time-intensive for the researches: to achieve a continuous registration of occlusion, families had to be visited every week because the capacity of the battery and the memory of the device were limited. Evalu-

ation of the record for 1 week took about 30 min. A programmeme for quick and convenient data evaluation has just been completed (Kosowski, Chopovska, manuscript in preparation). Higher capacity of the battery and memory would enable use the ODMs on a larger scale.
It would be an important advance if patients could be offered amblyopia therapy that considers established and evidence-based factors influencing the outcome. The ODM may be an important contribution.

ACKNOWLEDGEMENTS

We gratefully acknowledge the Albert von Metzler and Edith von Heyden Foundations and the association "Augenstern e. V." for financial support of this study. Thanks are due to Prof. Ohrloff for continuous support of our research, to Dr. Ackermann from the Biomathematics Department of the University of Frankfurt for help with statistics and to Valeria Petkova for research assistance.

Chapter 6

Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase

ABSTRACT

Purpose: We set out to determine whether the children who have low compliance (measured electronically) with occlusion therapy for amblyopia are those with insufficient increase of visual acuity.

Methods*:* In 14 newly identified amblyopic children (mean age 4.3 ± 1.9 years), compliance was measured electronically over a period of 1 week, 6 months after the start of occlusion therapy. Compliance was measured with an Occlusion Dose Monitor (ODM). The measurements took place during planned domiciliary visits. The children were diagnosed with anisometropia ($n = 5$), strabismus ($n = 4$) and anisometropia and strabismus ($n = 5$). Compliance was expressed in percentages of the electronically registered time compared with the prescribed occlusion time. Satisfactory acuity increase following 6 months of occlusion therapy was defined on reaching any of the following criteria: acuity increase expressed as a ratio between acuity of the amblyopic eye and acuity of the good eye more than 0.75, acuity of the amblyopic eye exceeding 0.5 as measured on the E-Chart or Landolt-C, or three logMAR lines of acuity increase.

Results: Measured compliance averaged 80% in the eight children who had a satisfactory acuity increase and 34% in the six children who had an unsatisfactory visual acuity increase. Children with low acuity increase had statistically significant lower compliance ($P = 0.038$).

Conclusions: The general assumption among orthoptists, that compliance with occlusion therapy for amblyopia is low in children with insufficient acuity increase, has been validated by electronic, objective means.

INTRODUCTION

Amblyopia is a reduction in best corrected visual acuity without any evidence of an organic eye disease. It affects up to 3.25% of the children and is the most common eye disorder in childhood, accounting for over 90% of the visits of children to ophthalmologists and orthoptists (Moseley, et al. 1997; Sjöstrand and Abrahamsson 1997; Attebo, et al. 1998). As Child Health Care Centres in The Netherlands check for the presence of strabismus from birth and measure visual acuity at the age of 3 years, it is rare for amblyopia to go undetected (Lantau, et al. 1999). The primary treatment for children with amblyopia is to occlude the better eye, with regimens ranging from a few hours of occlusion per day to all waking hours. Approximately a third of the children diagnosed do not attain visual acuity of 0.5 and are therefore unable to read with the amblyopic eye (Jensen and Goldschmidt 1986). Some amblyopic children - in one study the proportion was estimated at 0.175% (Tommila and Tarkkanen 1981) - will loose the function of the better eye later in life. Low acuity increase of the amblyopic eye is frequently caused by lack of compliance with prescribed therapy. This was confirmed in a recent study by Dorey et al., which indicated that when offering occlusion on an in-patient supervised basis for a period of five days to patients with low compliance, an acuity increase of three lines could be measured in the amblyopic eye during these five days (Dorey, et al. 2001).

In 1991 Fielder and Moseley developed an Occlusion Dose Monitor (ODM), enabling the electronic measurement of compliance with the prescribed occlusion regime for the treatment of amblyopia (Fielder, et al. 1994; 1995). Stewart et al. are currently investigating the relationship between prescribed hours of occlusion and the increase in visual acuity (dose-response relationship) with the ODM. They concluded that occlusion therapy was most effective in the first few weeks of treatment. Moreover, the acuity increase is positively related to the actual hours of occlusion and age of the patient; children younger than five years showed a greater improvement (Moseley, et al. 2001; Stewart, et al. 2002).

In 1996 and 1997 we were able to reduce the ODM to the size of a coin (Simonsz, et al. 1997) and it was used in a first pilot study. In that study compliance was found to be moderate in many cases. In some children compliance was measured four to seven times over a 2-year period. Interestingly, the patterns of non-compliance remained the same for one child and were apparently case specific (Simonsz and Polling 2001). In 1999 a second pilot study was conducted to determine whether the ODM could be used in a clinical setting. In the clinic of the Sophia Children's Hospital Rotterdam the orthoptists distributed the ODM to patients whose compliance was thought to be low. Parents, however, interpreted the ODM as a 'lie-detector', resulting in a breakdown in the relationship between them and orthoptist (Simonsz, et al. 1999).

In this present study, compliance was measured in all newly identified amblyopic children over a period of 1 week, 6 months after the start of occlusion therapy. The purpose was to

determine whether the children whose acuity had not improved sufficiently after six months of patching were indeed the children with low compliance.

METHODS AND MATERIALS

Subjects

For the period July to December 2000 all newly identified amblyopic children visiting the Sophia Children's Hospital in Rotterdam were registered. On their first visit to the clinic, age, diagnosis, acuity, ocular alignment, binocular vision, fixation, cycloplegic refraction and therapy were documented. Acuity was measured every 3-4 months using the Amsterdam Picture Chart (APK) and, in older children, the E-Chart or the Landolt-C. Compliance was measured electronically over a time period of 1 week, 6 months after the start of occlusion therapy. Parents were first contacted by telephone and were asked to give full oral informed consent during a subsequent domiciliary visit. The parents were provided with information on the exact purpose of the study, how the device worked and were shown exactly how to apply the patch with the ODM on the eye. Any questions put forward by the parents were answered. The ODM was collected after 1 week. In total, 19 children were recruited. However, the ODM failed

Table 1. Characteristics of 14 patients in whom compliance was measured: in particular, the acuity in the amblyopic eye before and after 6 months of occlusion therapy and the method used to measure visual acuity (APK=Amsterdam Picture Chart).

No	Age (yrs)	Diagnosis	Prescribed occl per day	Percentage compliance	Acuity ambl eye before occl	Acuity ambl eye after 6 mo.	Method
1	5.5	anisometropia & strabismus	1 h	100%	0.5	1.25	Landolt-C
2	5.3	anisometropia & strabismus	30 min	87%	0.25	1	E-Chart
3	4.5	anisometropia	4.5 h	98%	0.1	1	APK
4	5	anisometropia	1 h	81%	0.63	1	APK
5	2	strabismus	30 min	83%	0.5	0.9	APK
6	6.7	anisometropia & strabismus	3 days/week	51%	0.32	0.63	APK
7	2.5	strabismus	1 h	84%	0.5	0.7	APK
8	1.5	strabismus	1 h	100%	0.1	0.8	APK
9	4.9	anisometropia	2 h	5%	0.63	1.25	APK
10	5	anisometropia & strabismus	4 h	2%	0.15	0.5	E-Chart
11	2	strabismus	15 min	41%	0.7	0.7	APK
12	6.7	anisometropia	1 h	9%	0.03	0.17	APK
13	6.4	anisometropia	1 h	80%	0.78	1.25	Landolt-C
14	1.9	anisometropia & strabismus	1 day/week	19%	0.3	0.5	APK

in two cases due to technical difficulties and in two other children reliable visual acuity could not be obtained. Also, one parent experienced problems with occluding her child's eye due to the child's other difficulties (Down syndrome). Thus, 14 reliable recordings were obtained. These fourteen children (mean age 4.3 ± 1.9 years) had diagnoses of anisometropia (n = 5), strabismus (n = 4) and anisometropia and strabismus (n = 5). Prescribed occlusion time varied from 15 min per day to 3 full days of occlusion per week (Table 1). The children were assigned a number corresponding to their date of entry into the study.

Occlusion Dose Monitor (ODM)

Compliance was determined by means of the ODM. The ODM measured 35x23x4 mm and weighed 6 g. The back of the ODM was fixed to the front of the patch with double-sided adhesive tape. At 3-min intervals the ODM registered the temperature difference between the front and back of the device. Applying the patch with the ODM to the child's eye resulted in a typical temperature difference for as long as the patch remained on the eye; the difference was zero the rest of the time. After 1 week the ODM was collected and the computerised read-out provided information on when and for how long the child had worn the patch.

Outcome variables

Compliance was defined as the number of hours of patch wear per week (as measured by the ODM) divided by the number of hours prescribed by the orthoptist. In this way compliance could be expressed as a percentage.
Sufficient acuity increase after 6 months of occlusion therapy was defined as attainment of any one of the following criteria: a ratio between acuity of the amblyopic eye and acuity of the good eye of more than 0.75 using the APK, acuity of the amblyopic eye exceeding 0.5 as measured on the E-Chart or Landolt-C or three LogMAR lines of increase in acuity. If the acuity increase of the child fulfilled any of these criteria, he/she was categorized as having sufficient acuity increase.

RESULTS

Three cases selected arbitrarily from our study serve to illustrate our method.

Case 3
A 4.5-year-old patient with anisometropia was prescribed 4.5 h of occlusion every day. The patient had an acuity increase in the amblyopic eye from 0.1 to 1.0 at 6 months after the start of occlusion therapy, measured with the APK. Acuity in the good eye was 1.0. His recordings

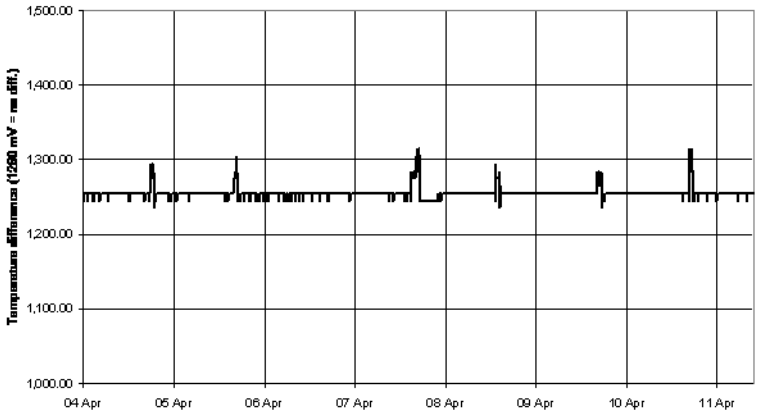


Figure 1. One-and-a-half-year-old patient with Cohen Syndrome, craniosynostosis, infantile esotropia; 1h of occlusion every day. The ordinate represents the temperature difference between the front and back of the ODM. The ODM is set at 1260 mV, meaning no temperature difference between the front and back of the ODM. The abscissa represents the corresponding days; vertical lines indicate midnight. The child wore the patch every day (rectangular peaks), except for one, so she wore a patch for 2 h the following day.

showed that occlusion was carried out for 4.4 h per day on average, resulting in a compliance of 98%.

Case 6

A 6.7-year-old girl with anisometropia and strabismus was prescribed 3 days of occlusion per week. Acuity in the amblyopic eye improved from 0.32 to 0.63. Recordings showed only 1.5 days of occlusion was managed, compliance averaging 51%.

Case 8

A 1.5-year-old patient with strabismus was prescribed 1 h of occlusion daily. Figure 1 illustrates the occlusion routine as measured by the ODM.

From the recordings compliance was 100%; the patient wore the patch every day late in the afternoon for 1 h, except for one day. To compensate for this the mother had her child wear the patch for 2 h the next day. The flutter in the ODM reading was caused by minimal temperature fluctuations around the threshold value. The acuity in the patient's amblyopic eye had improved from 0.1 to 0.8 at 6 months after commencing the occlusion therapy.

In the 14 children in the study acuity was measured at each visit to the orthoptist. The acuity increase was assessed according to the given criteria. Based on these criteria the children were divided into two groups, those with satisfactory and those with unsatisfactory acuity increase after 6 months of occlusion therapy. These criteria were based upon our clinical experience and may be arbitrarily chosen.

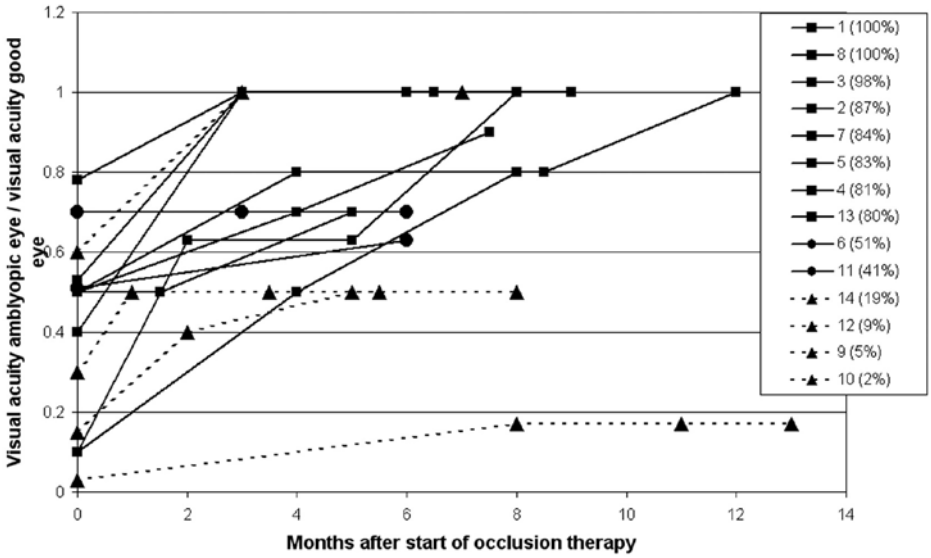


Figure 2. Graphic representation of the relationship between acuity increase during treatment and electronically measured compliance. The ordinate represents the ratio between visual acuity in the amblyopic eye and the acuity in the good eye. The abscissa represents the months after the start of occlusion therapy. On the right: patient number corresponding to the actually measured compliance in percentages in parenthesis. Squares represent patients with high compliance; circles moderate compliance; triangles represent low compliance, corresponding to the visual acuity increase after 6 months of occlusion therapy. For colour figure please see ' Colour figures' on page 196.

The electronically measured compliance was compared in the two groups. In the children who achieved satisfactory acuity increase after 6 months of occlusion ($n = 8$), average compliance was found to be 80% (SD 32%). In the children who did not attain a satisfactory acuity increase after 6 months of patching ($n = 6$), average compliance was found to be 34% (SD 31%), (Figure 2).

Compliance was significantly lower in those children who did not reach a sufficient acuity increase according to the criteria than in those who did reach a sufficient acuity increase (Mann-Whitney; $P = 0.038$).

During this study we came upon several factors influencing the outcome, which will be considered further in the discussion section. However, one confounding factor was a 5-year-old patient with anisometropia, whose compliance was 5% yet achieved an improvement of acuity in the amblyopic eye 0.63 to 1.25. He was prescribed 2 h of occlusion therapy every day and, simultaneously, a pair of spectacles. This was the only patient with no prior adaptation to the prescribed spectacles. If this patient were omitted from the analysis the significance of the relationship between acuity increase and compliance would increase to $P < 0.01$.

In contrast to the general assumption, children with low acuity at the start of the occlusion therapy did not necessarily have low compliance. Of the seven children whose acuity was less than

0.5 at the start of occlusion therapy, three attained a sufficient acuity increase - their compliance ranged from 87% to 100%. In the other four children with low acuity at the start of the occlusion therapy compliance ranged from 2% to 51% and the acuity increase was insufficient.

DISCUSSION

This study has demonstrated that there is a statistically significant relationship between acuity increase and compliance measured by objective means. Children with insufficient improvement in the acuity of the amblyopic eye were indeed the children who hardly ever wore their patch or not at all. Although our study population was relatively small we were able to identify several factors, either confounding or otherwise affecting compliance, that influenced this relationship.

Firstly, an outlier in the data was a patient with anisometropia (case number 9), with a compliance rate of 5%, yet an acuity increase from 0.63 to 1.25 as measured with the APK. This patient had been prescribed a pair of spectacles, however, in addition to 2 h of occlusion therapy per day. This supports Fielder's argument that first the spectacles should be prescribed, followed by occlusion therapy 3-4 months later, if still necessary (Moseley, et al. 1997). In this study this patient was the only patient who had been prescribed occlusion without prior adaptation to the prescribed spectacles.
Secondly, patient number 10 visited four orthoptists in different hospitals and received four different prescriptions for occlusion tine. After the last of these four visits, to the orthoptist in our hospital, she was prescribed 4 h of occlusion every day. Compliance in this case was 2%. Apparently, inconsistent prescription of occlusion hours is not conducive for compliance.
Thirdly, in two cases full days of occlusion were prescribed: in case number 6, 3 days of occlusion per week and in case number 14, 1 day. Here compliance was found to be relatively low: 51% and 19%, respectively. This low compliance may, of course, be coincidental, but could also be the result of the lack of a daily routine with the occlusion therapy.
A fourth parameter influencing the outcome was age and acuity of the patient at the start of therapy. The acuity increase was slightly higher in younger patients and was also higher in the children who started with very low acuity. This finding was confirmed by Stewart et al. (Moseley, et al. 2001; Stewart, et al. 2002).
Finally, it became apparent that the prescription of occlusion, even in similar cases, varies considerably among orthoptists and may have varied among the orthoptists treating the children in this study. In order to identify the variation, and the determining factors in the prescribing of occlusion therapy, a questionnaire was presented to 177 Dutch and 227 German orthoptists. This questionnaire comprised the cases of five sample amblyopic children. The orthoptists were asked to decide their prescribed hours of occlusion for the five cases within

10 min simultaneously. They were not allowed to discuss the cases with each other. The survey showed a wide variation in prescribed hours of occlusion in each of the five cases (Loudon, et al. 2002). As a result there is difficulty in expressing compliance in the form of percentages, because there is no standardisation of prescription for occlusion therapy.

All the parents were aware that a recording of the occlusion was being made. This could influence compliance, in a sense that compliance would be better in the week of electronic measurement. This argument is not confirmed by the data, however; compliance was moderate in many cases, despite the fact that the parents were fully informed. It seems that the child's presumably unvarying dislike of the patch plays an important part.

Compliance was measured for only 1 week because of the considerable risk of losing the rather expensive ODM device at the home or outside in the playground: in one case the device ended up in the washing machine and tumble dryer. The final outcome of visual acuity of the amblyopic eye was not likely to be influenced by 1 week of better compliance out of 13 weeks of treatment, however.

Recently the effectiveness of occlusion therapy for amblyopia has been questioned by Snowdon & Stewart-Brown (Snowdon and Stewart-Brown 1997). They maintain that occlusion therapy has not yet been subjected to formal controlled trials and that much of the improvement in acuity could be spontaneous and unrelated to the therapy. However, they may have overlooked the possibility that the lack of evidence for the efficacy of occlusion is due to low compliance rather than to ineffectiveness of the treatment.

Currently we are performing a randomised controlled trial in The Hague among 200 newly identified amblyopic children to investigate ways of enhancing compliance cost-effectively and identifying certain predictors for non-compliance.

ACKNOWLEDGEMENTS

We thank Ir. M.J.C. Eijkemans and Prof.Dr. T. Stijnen for their help with the statistical analysis. We acknowledge A. Fielder and M. Moseley, Academic Unit of Ophthalmology, University of Birmingham Medical School, United Kingdom, for their advice and help with the development of the Occlusion Dose Monitor in 1996. The Occlusion Dose Monitor was developed in the public domain by C. Romijn, J. van Leeuwen, P. Heeman and R. Voorn in 1996 and 1997 in the Academical Medical Center, Amsterdam, The Netherlands (Simonsz, et al. 1997).

Chapter 7

Predictors and a remedy for non-compliance with amblyopia therapy in children measured with the Occlusion Dose Monitor

ABSTRACT

Purpose: Non-compliance is one of the limiting factors in the success of occlusion therapy for amblyopia. Electronic monitoring was used to investigate predictors of non-compliance and, in a prospective randomised clinical trial, determined the effectiveness of an educational programme.

Methods: Compliance was measured electronically during one week every three months in 310 newly diagnosed amblyopic children. The family's demographic parameters and the child's clinical parameters were assessed for their influence on the level of compliance. In addition to standard orthoptic care, children were randomised to receive an educational cartoon story, reward stickers, and an information sheet for the parents (intervention group), or a picture to colour (reference group). These and the electronic device were distributed during home visits by researchers. The primary outcome measure was the percentage of compliance (actual/prescribed occlusion time) in the two groups. The secondary outcome measure was the influence of demographic and clinical factors on compliance.

Results: Compliance was associated with parental fluency in the national language, country of origin, level of education, and initial visual acuity of the child. During the first one-week measurement period children in the intervention group had better compliance than the reference group had (78% ± 32% vs. 57% ± 40%; $P < 0.0001$), and fewer children were not occluded at all (3 vs. 23 in the reference group; $P < 0.0001$). This difference remained throughout the study period.

Conclusions: Poor parental fluency in the national language, a low level of education and were predictors for low compliance. Education, primarily aimed at the child, improved poor acuity at the start of treatment were predictors for low compliance. Education, primarily aimed at the child, improved compliance and reduced the number of children who did not comply with occlusion at all.

Additional data for this chapter were collected at the Department of Ophthalmology, J.W.Goethe University, Frankfurt am Main, Germany as part of the *Dr.med* thesis of Larisa Pepler and at the Department of Ophthalmolgy of the University of Leicester, Great Britain by Musarat Awan.

INTRODUCTION

Amblyopia, with a prevalence of 3.5% (Attebo, et al. 1998; Brown, et al. 2000; Vinding, et al. 1991), is loss of visual function, usually unilaterally, caused by strabismus, anisometropia and/or visual deprivation. It is commonly treated with patching of the non-amblyopic eye, preferably before the age of 6. Approximately one third of the affected children do not reach visual acuity of 6/12 in the amblyopic eye (Jensen and Goldschmidt 1986; Vinding, et al. 1991), thereby increasing the risk of bilateral visual impairment due to loss of vision in the nonamblyopic eye (Chua and Mitchell 2004; Fronius, et al. 2005; Rahi, et al. 2002) and decreasing quality of life in adulthood (van de Graaf, et al. 2004). Treatment effectiveness was questioned in a report published by Snowdon and Stewart-Brown in 1997 (Snowdon and Stewart-Brown 1997) that contributed to the setup of five randomised controlled trials (RCTs) (Awan, et al. 2005; Clarke, et al. 2003; PEDIG 2002; 2003a; 2003b). These produced evidence of treatment effectiveness. Many other studies have suggested that one of the factors influencing outcome with treatment is the level of compliance (Dorey, et al. 2001; Fielder, et al. 1994; Flynn and Cassady 1978; Lithander and Sjöstrand 1991; Simmers, et al. 1999; Simons and Preslan 1999; Simonsz, et al. 1999; Smith, et al. 1995; Stewart, et al. 2004; 2005; Woodruff 1995). Low compliance was found to be associated with social deprivation (Smith, et al. 1995) and lower attendance rates were reported among amblyopic patients from more deprived areas (Bowman, et al. 1996).

In general, compliance is referred to as the degree of correspondence between the recommendations from the healthcare provider and the patients' actual dosage (Urquhart 1992). Poor compliance decreases the effectiveness of treatment and increases costs to the healthcare system (Cleemput and Kesteloot 2002). Especially in pediatric patients, low levels of compliance have been found across a range of treatments and are an important obstacle to providing effective healthcare in long-term treatments (Dunbar 1983; Farley, et al. 2003; Milgrom, et al. 1996; Parrish 1986).

Reported rates of compliance depend on the mode of measurement: pill count, patients' report, appointment-keeping behavior, blood tracers or electronic measurements, for example (Cramer, et al. 1989; Kass, et al. 1986; de Klerk and van der Linden 1996; Urquhart and de Klerk 1998). Since the development of the Occlusion Dose Monitor (ODM) by Fielder and Moseley (Fielder, et al. 1994), compliance with occlusion therapy for amblyopia can be measured electronically. By means of the ODM, it has been demonstrated that, generally, compliance with amblyopia treatment is low and treatment success is related to the level of compliance (Awan, et al. 2005; Loudon, et al. 2003; Simonsz, et al. 1999; Stewart, et al. 2004; 2005). Therefore, programmes designed to improve compliance are being distributed, and it has been concluded that increasing parents' understanding of the disease may contribute to improved compliance (Goransson, et al. 1998; Newsham 2002). However, no study has provided evidence of whether compliance can be improved in concurrence with the electronic monitoring of that compliance. The primary purpose of this study was, by means of electronic monitoring, to assess the

effectiveness of a newly developed educational cartoon story explaining to the child, without text, the rationale for treatment, combined with reward stickers and an information sheet for the parents. As a secondary purpose, it identified demographic and clinical factors determining compliance.

METHODS

Patient selection

Children were recruited from four clinics by six treating orthoptists in The Hague between July 2001 and December 2003. The study area consisted of The Hague (approximately 442,000 inhabitants), the third largest city in The Netherlands. It is a very ethnically and culturally diverse city with 58% of the population having Dutch nationality, 10% of Surinam, 6% of Turkish, and 5% of Moroccan nationality; and 21% of other nationalities. Additional children were recruited in Frankfurt am Main (Germany) and in Leicester (United Kingdom).

Included were all children with newly diagnosed amblyopia (i.e., never treated for amblyopia) with an interocular difference in visual acuity of at least 0.2 logMAR (logarithm of the minimum angle of resolution) that persisted after 6 weeks of spectacle correction, strabismus and/or anisometropia (>1.0 D), or a deprivation in the absence of additional ocular or neurological diseases.

Exclusion criteria were previous treatment for amblyopia, a neurological disorder, other eye disorders, and diminished acuity due to medication, brain damage or trauma. The Ethics Committee of Erasmus University Rotterdam and the boards of the participating clinics approved the protocol and informed consent forms. Written informed consent by the parents or guardian was a prerequisite for participation. The research adhered to the tenets of the Declaration of Helsinki.

Standard orthoptic care

Eligible children received a routine ophthalmic examination and explanation of diagnosis and treatment by the treating orthoptist. Binocular vision, ocular motility, cycloplegic refraction, and visual acuity were assessed. For this study, the charts used to assess visual acuity depended on the age: children aged 2.5 to 4 years: Amsterdam Picture Chart (uncrowded, linear optotypes; Medical Workshop, Oculus, Groningen, The Netherlands); children aged 4 to 5 years: E-chart (uncrowded, linear optotypes; Medical Workshop, Oculus); children aged 5 and older: Landolt-C (uncrowded; linear; Medical Workshop, Oculus). In children younger than 2.5 years, or otherwise unable to cooperate with the visual acuity tests, decimal equivalences were used for the following categories: far eccentric fixation and no pursuit when looking monocularly,

fierce protest when covering the better eye, 0.1; eccentric fixation and hardly any pursuit when looking monocularly, considerable protest when covering the better eye, 0.3; cannot maintain fixation and saccadic pursuit when looking monocularly, some protest when covering the better eye, 0.5; prefers fixation with the other eye and almost smooth pursuit when looking monocularly, 0.7; alternating freely and smooth pursuit when looking monocularly, no dominance found in 4-PD base-out tests; 0.9.
The severity of amblyopia was expressed as the ratio (in decimals) between the acuity in the amblyopic eye and the better eye, to minimize the influence of possible differences in testing conditions. The acuity data were expressed as decimal scores.

Anisometropic amblyopia was defined as an amblyopia in the presence of anisometropia >1.0D of spherical equivalent or >1.5D difference in astigmatism in any meridian, with no measurable heterotropia at distance or near fixation. Spectacles were prescribed in case of anisometropia >1.0D, astigmatism >1.5D, hypermetropia (spheric equivalent) >1.5D. Occlusion therapy commenced after a minimum of 6 weeks' adaptation to the spectacles.

Few guidelines exist when prescribing a certain number of occlusion hours; therefore, in this study, the duration of occlusion (number of hours per day) for the first prescription was standardized in a focus group consisting of the treating orthoptists, as experts in the field. They were given example cases of persons in whom diagnosis, visual acuity, and age varied and were asked to prescribe the number of occlusion hours per day. Diagnosis proved to be of little importance and the relationship between the two other parameters (visual acuity and age) could be represented by: -6.63 * ratio acuity amblyopic eye/acuity better eye + 0.5 * age (years) + 4.97. For example, for a 3-year-old child with an acuity ratio of 0.6, the number of hours would then be: -6.63 * 0.6 + 0.5 * 3 + 4.97, which equals ≈ 2.5 hours of occlusion per day. A table was then developed from which the orthoptists could directly read off the daily number of occlusion hours to be prescribed. It was not possible to standardize subsequent prescriptions of occlusion therapy, as the treating orthoptists wished to proceed on an individual basis, dependent on treatment success. All children were seen by the treating orthoptist for routine assessment every 3 to 4 months. This schedule continued independently of the electronic recordings of compliance. After each examination, the treating orthoptist completed and forwarded a standard examination form to the research center. Occlusion therapy was terminated when the interocular difference in visual acuity was one logMAR line or less on two consecutive visits to the orthoptist.

The researchers visited the participating orthoptists at their clinic 10 times over a 1-year period (January 2002-January 2003). The total time spent on taking patient history, examining the child, and explaining the diagnosis and treatment was recorded per child. A distinction was made between children who visited the orthoptist for the first time and follow-up visits.

Randomisation

After the first visit to the treating orthoptist, parents of children with newly diagnosed amblyopia were contacted by telephone by the researchers to obtain verbal consent and an appointment for a home visit. Before the home visit, each patient was randomised to either the intervention group or the reference group, using permuted blocks of length six. That is, when six children were randomised, three were allocated to the intervention group and three to the reference group, in a random order. Children in the intervention group received the educational programme; children in the reference group received a picture to colour. During the home visit, the researcher explained the nature and possible consequences of the study and use of the ODM, and full written informed consent was obtained.
Compliance was measured with the ODM, in all children during an entire week every 3 months. It was attached to the front of the occlusion patch with double-sided adhesive tape and measured the temperature difference between the front and back of the ODM every 2 minutes. The device has been extensively tested, including the ability to differentiate between measurements on the eye and on other parts of the body, and has been found satisfactorily reliable (Chopovska, et al. 2005). In case of an unsuccessful recording due to battery failure (no data at all or less than 7 days of data), a broken or lost ODM, the one-week-measurement with the ODM was repeated the subsequent week.

The study was designed as a prospective, single blind, randomised clinical trial. The researcher who made the home visits was aware of randomization. The treating orthoptist, however, was blind to group assignment, and randomization took place after the first visit to the orthoptist. Time spent on each home visit was approximately equal for children in both groups – that is, 45 minutes for a first home visit and 10 minutes for a following visit, and all parents were given the same explanation. The distribution of the ODM via home visits minimized the number of withdrawals from the study: home visits continued even when the parents failed to attend their clinic appointments.

Assessment of demographic and clinical factors affecting compliance

The socioeconomic and ethnic background of the families was assessed via a 23-item questionnaire registering the highest level of education of either parent (scores from 1 to 5, with 1 representing "no education" and 5 "university"); the mother's native country; material factors including housing and employment status; religion; family structure; age of the parents; and the parents' marital status. The highest level of education of either parent indicated the socioeconomic status. This questionnaire was filled in during the first home visit. The mothers' fluency in the national language was rated by the researchers (scores from 1 to 5, with 1 repre-

senting "not speaking the national language [Dutch, German, or English] at all"; 3, "moderate fluency"; and 5, "excellent fluency" [see also legend Table 1]).
The clinical factors studied included age at start of treatment, cause of amblyopia, visual acuity at start of treatment, binocular vision, and sex.

Intervention protocol

Intervention group
Children received the educational cartoon story, a calendar with reward stickers, and a one-page information sheet for the parents.
The cartoon story was designed for this study by two artists specializing in art for sick children (José Vingerling and Gerard de Bruyne) together with two specialists from the Municipal Health Service, The Hague (Karen Bree and Nicole Goedee). The educational programme was developed considering the most efficient way to transmit the message and whether to target the parent or the child. It was designed as a cartoon story, without text, as most of the children treated for amblyopia are too young to read. The cartoon depicts the orthoptic examination of a preschool child, subsequent patching therapy, and the reasons for therapy seen from the perspective of the child. As no animal figures were included, the children were more able to identify themselves with the child depicted in the story. The cartoons could not be linked to a certain ethnic or cultural group. A sheet containing general information about amblyopia and its treatment for the parents was made in eight languages and distributed with the cartoon story only during the first home visit.

Reference group
Children were given a picture to colour (e.g., Mickey Mouse or Winnie the Pooh) that was also considered a reward, but did not contain the educational message.
At the three monthly home visits, the ODM was delivered and children were given the next episode of the cartoon story (intervention) or a different picture to colour (reference). No specific instructions were given for the use of the cartoon story, the calendar with stickers, and the information sheet or, in case of the reference group, the picture to colour. To determine whether the material was used, parents were asked to fill out a short questionnaire assessing duration and frequency of usage of the cartoon story and the picture to colour during the intervening period.

Outcome measures and statistical analysis

Calculation of the sample size was based upon previous compliance studies of other diseases that used electronic monitoring to measure compliance (Cramer, et al. 1989; Kass et al. 1986; de Klerk and van der Linden 1996; Urquhart and de Klerk 1998). These results showed

a normally distributed relationship between the number of patients and the percentage of compliance with a maximum at approximately 80%-90%, an average of 68% and a SD of 22%. To reach an effect size of 3%, 2 x 150 was necessary.

The main outcome was the level of compliance in the two treatment groups, defined as the actual occlusion time measured with the ODM divided by the prescribed occlusion time and expressed as a percentage. This calculation was made for each child separately for each week of measurement with the ODM. The recruitment of patients continued for 30 months. On average, a child received three electronic measurements (ranging from one to a maximum of seven measurements) during, on average, 8 months of treatment. The effect of the educational programme on compliance was determined in a multilevel analysis in which all available weeks of ODM monitoring were used, corrected for the differences in the number of observations during follow-up. This analysis was used to estimate compliance of all included children throughout the treatment. The difference in percentages of compliance in the two treatment groups was assessed with least-squares regression analysis. Testing for an unequal distribution of baseline characteristics between the randomization groups was performed with logistic regression (Wald test).

The second research question was the influence of demographic and clinical factors on the level of compliance. We used least-squares regression analysis on the data from the first entire one-week measurement with the ODM only, because it was certain that at this moment the number of occlusion hours had been prescribed according to protocol and that the orthoptist was unaware of randomization. The results of the univariate analysis are presented first; the influence of potential confounding is corrected for in the multivariate analysis. $P < 0.05$ indicated statistical significance. The percentage of the variation in compliance that could be ascribed to the different factors involved was defined as the ratio of the percentage of the variance explained by the model, with and without the factor in question.

It would have been desirable to have final visual acuity as an outcome measure; however, the statistical noise between compliance and visual acuity increase, as measured in current orthoptic practice, would have led to the treatment groups' becoming excessively large. Therefore, the primary outcome measure was restricted to electronically measured compliance.

Children were included in the analysis when they had received at least one entire one-week measurement. When parents refused further participation in the study after the first one-week-measurement, they were asked their consent as to whether the previous ODM measurement(s) and their child's baseline characteristics could be used for analysis. Only the data of the children, whose parents agreed remained in the study ($n = 6$; intervention group; $n = 5$; reference group). Children who moved out of the area and consequently received no further ODM measurements were included in the analysis.

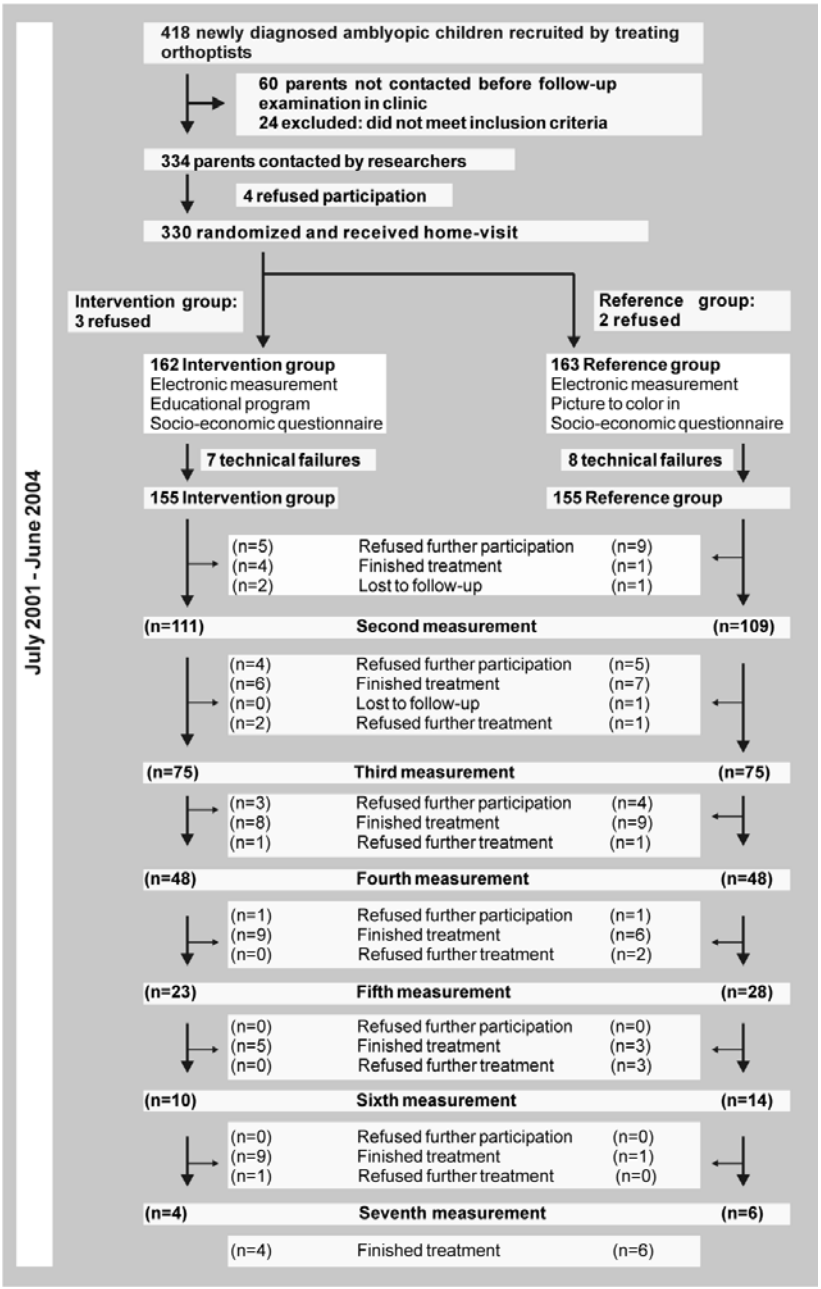


Figure 1. The study design. Recruitment of children continued for 30 months (July 2001-December 2003), and compliance was monitored 1 week every 3 months. The 6-month follow-up with the ODM finished in June 2004. It follows that the first children included received most measurements; on average, a child received 3 one-week measurements.

Table 1. Baseline characteristics of the included children.

		Number of children (%)		Mean compliance %		
Characteristic		Intervention group	Reference group	Intervention group	Reference group	Total (N=310)
Overall compliance				78	57	68
Gender						
	Male	77 (50)	93 (60)	72	57	64
	Female	78 (50)	62 (40)	83	58	72
Age - years						
	<4	62 (40)	60 (39)	80	63	72
	4-<6	71 (46)	56 (36)	77	52	66
	6>	22 (14)	39 (25)	74	55	62
Age §		4.5 ± 1.6	4.8 ± 2.3			
Cause of amblyopia						
	Anisometropia	76 (49)	64 (41)	76	57	67
	Strabismus	41 (27)	47 (30)	86	63	74
	Strabismus & Anisometropia	19 (12)	27 (18)	67	52	58
	Deprivation	3 (2)	2 (1)	80	49	72
	Other	16 (10)	15 (10)	77	57	63
Number of occlusion hours per day §						
		3:22 ± 1:36	3:00 ± 1:38			
Visual acuity ratio † **						
	0-<0.25	22 (14)	15 (10)	65	45	58

	0.25-<0.5	51 (33)	36 (23)	75	58	68
	0.5-<0.75	40 (26)	56 (36)	75	50	70
	0.75-1.0	42 (27)	48 (31)	88	72	79
Country of origin **						
	Natives	77 (50)	67 (44)	79	64	72
	Turkey	11 (7)	25 (16)	59	45	50
	Morocco	19 (12)	14 (9)	83	48	68
	Surinam	10 (7)	13 (8)	85	71	77
	Other	38 (25)	36 (23)	80	53	67
Fluency national language ~ *						
	Excellent	85 (55)	74 (48)	78	64	72
	Good	17 (11)	16 (10)	81	71	76
	Moderate	17 (11)	17 (11)	87	52	70
	Poor	10 (6)	17 (11)	69	48	56
	None	26 (17)	31 (20)	71	43	56
Highest level of education *						
	University	30 (19)	20 (13)	78	65	73
	Higher education	44 (28)	43 (28)	80	62	71
	Secondary education	49 (32)	53 (34)	80	51	64
	Primary education	26 (17)	35 (22)	76	62	67
	None	6 (4)	4 (3)	78	34	60

§ Plus-minus values are means ± SD.

† Degree of amblyopia was expressed as the ratio (in decimals) between the visual acuity in the amblyopic eye and the better eye.

~ Fluency in the national language subjectively assessed by a researcher. 'Excellent' equals a native speaker. 'Good' was non-native, but fluent. 'Moderate' equals understandable and able to engage in conversation. 'Poor' equals scarcely fluent, and 'none' equals the national language was not spoken at all.

* Characteristics significantly affecting compliance after univariate analysis ($P < 0.05$).

** Characteristics significantly affecting compliance after multivariate analysis ($P < 0.05$).

RESULTS

Study population

Of the 418 recruited children, 310 (74%) were eligible for analysis (Figure 1). Of these, 20 children were recruited in Frankfurt (18 participated) and 4 in Leicester. There was no difference in frequency of withdrawal of participants between the clinics. Throughout the study, 12 children from the intervention group no longer attended their appointments in the clinic; of those, 5 also refused further study participation. In all, parents of 13 children refused further study participation. In the reference group, 17 children no longer attended their appointments in the clinic; of those, 8 also refused further study participation. In all, parents of 19 children refused further study participation. During the study, four children (two from either group) were lost to follow-up (moved out of the area).
The birth rate in The Hague was approximately 5,071 children in the year during which most of the children in the study were born (i.e., 1997). In this study, 394 were registered for a period of 2.5 years, indicating that 3.1% of the children born were included in this study.
In case the ODM was lost or broken or the recording failed, the one-week-measurement was repeated the subsequent week. During the study period, 13 parents lost the ODM and 11 broke it (e.g., tore it apart when removing the double-sided adhesive tape), and in 29 cases, the ODM had incomplete data. Because of measurement failure, 15 parents refused further participation, but 40 children received a measurement the subsequent week.

Table 1 depicts the baseline characteristics of the included children according to their randomization; both randomization groups were comparable for the baseline characteristics, including the number of prescribed occlusion hours per day by the orthoptist. The mean age of the included children was 4.6 ± 2.0 years; 56% were boys. Amblyopia was associated with anisometropia in 140 children (mean age, 5.3 ± 1.9), with strabismus in 88 (mean age, 3.5 ± 1.9) and with both anisometropia and strabismus in 46 children (mean age, 4.7 ± 1.9). Five children had deprivation amblyopia (mean age, 3.9 ± 1.7). In 31 children, a difference in visual acuity of only 0.2 logMAR at baseline was found: the treating orthoptist had commenced occlusion therapy, although anisometropia was mild (≤1D), and there was no strabismus in these cases (mean age, 4.9 ± 1.2).

Study Outcome

Predictors of compliance
This analysis was performed on the entire study population using the data obtained from the first one-week-measurement, as the two treatment groups were comparable for the different baseline characteristics (Wald test for logistic regression).

Fluency in the national language by the mother was a significant predictor of the level of compliance ($P = 0.018$). Mean compliance ranged from 56% in the group who did not speak the national language at all to 72% in the group who spoke it excellently (Table 1, right-hand column). Univariate analysis also demonstrated the country of origin of the mother to be significant ($P = 0.018$). The highest level of education attained by either parent was also significant ($P = 0.021$). Mean compliance ranged from 60% in the group with no education to 73% in the group with an academic education.

The child's visual acuity at the start of treatment was the only significant clinical factor ($P = 0.033$). Mean compliance ranged from 58% in children with the lowest visual acuity to 79% in children with the highest visual acuity. Compliance was not significantly related to the degree of binocular vision ($P = 0.667$), the type of amblyopia ($P = 0.219$), gender ($P = 0.057$) and age at start of treatment (although the latter was borderline significant: $P = 0.050$).

After multivariate analysis the child's visual acuity ($P = 0.031$) and country of origin remained significant ($P = 0.035$), level of education and fluency in the national language were not selected. However, the correlation between country of origin and fluency in the national language was too strong to be able to separate the effects of either variable ($P < 0.001$). Adjusted analysis for the country of origin demonstrated that per 10% visual acuity increase or de-

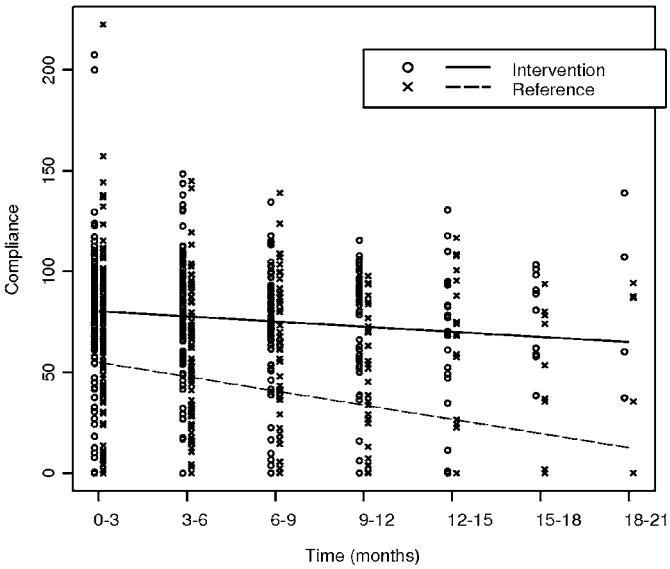


Figure 2. Mean compliance (%) throughout the study for the intervention group and the reference group. The ordinate represents compliance (%), and the abscissa is the time after start of treatment. *Solid regression line*: compliance in the intervention group (expressed as $y = b + a * x$: compliance [%] = 80 – 0.85 * treatment duration); *dashed line*: compliance in the reference group (compliance [%] = 55 – 2.35 * treatment duration). Symbols represent individual children. There was considerable superimposition of data, especially at the 0 compliance level.

crease, compliance would increase or decrease with 2%. Adjusted analysis for visual acuity (at a median level of 0.6) demonstrated levels of compliance to be 75%, 51%, 71%, 77%, for Native, Turkish, Moroccan or Surinam children, respectively, and 65% for children from other countries.

After correction for the intervention applied, 12% of the variation in compliance could be explained by the demographic and clinical factors investigated in this study.

Effect of the educational programme on compliance

During the first one-week-measurement, mean overall compliance in the intervention group was 78% ± 32% compared with 57% ± 40% in the reference group ($P < 0.0001$; Table 1). Compliance decreased over the 2-year study period on each subsequent ODM measurement, more so in the reference group than in the intervention group ($P = 0.003$; see Figure 2).

There was no difference in the number of prescribed occlusion hours per day, neither for the first nor for the subsequent measurements. Figure 2 shows the relationship between mean compliance (measured with the ODM) and the period of treatment (in months) for the children in the two treatment groups. Mean compliance in the intervention group and the reference group at a certain time point could be calculated using the formulas shown in the legend for Figure 2. There was no modification in the effect of the educational programme for visual

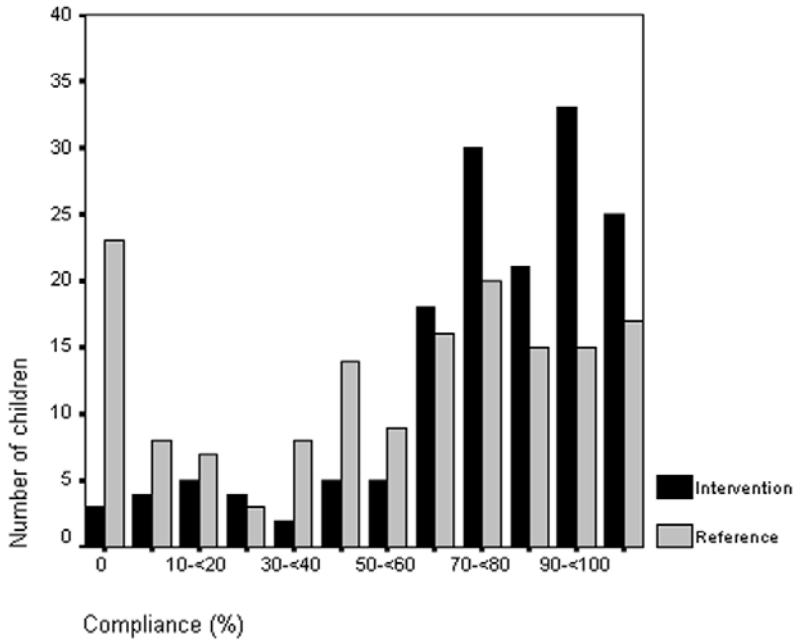


Figure 3. Compliance (%) during the first electronic measurement for the intervention group (black columns) and the reference group (grey columns). A high number of children were not occluded at all in the reference group ($n = 23$), when compared with the intervention group ($n = 3$; $P < 0.0001$).

acuity of the child ($P = 0.59$), country of origin ($P = 0.57$) or fluency in the national language ($P = 0.48$).

There was considerable variation in the level of compliance between the children and within each child, as indicated by the ODM measurements. The SD of mean compliance during the first one-week-measurement of all children ($n = 310$) was 37%. The mean of all the standard deviations of mean compliance in each child during that week was 28%.

In the intervention group, three children (2%) were not occluded at all during the first ODM measurement (mean age, 4.3 ± 0.8) compared with 23 (15%; mean age 4.6 ± 2.0) in the reference group ($P < 0.0001$, χ^2; Figure 3). Children who were not occluded at all and children who did were comparable for clinical parameters. However, there were differences in the level of parental education, country of origin and fluency in the national language.

The questionnaire designed to estimate the usage of the educational programme or the picture to colour showed that the cartoon story was used by 87% of the families. Mean time was 25 minutes per week (range, 5-180; number of observations, 123). The calendar and stickers were used by 80% of the families. Mean time was 10 minutes (range, 2-15; number of observations, 123). The information sheet was read by 67% of the parents. Mean time was 6 minutes (range, 2-10; number of observations, 123).
In the reference group the colouring picture was coloured by 71% of the children. Mean time was 12 minutes (range, 5-20; number of observations, 131).

In 28 patients, the researchers recorded time spent on explaining the diagnosis and treatment during the first visit to the orthoptist. It averaged 234 seconds in non-native patients, and 416 seconds in native patients. During follow-up visits to the orthoptist these averages were 116 seconds and 233 seconds, respectively (62 patients).

DISCUSSION

This study identified the following demographic parameters as primary predictors for non-compliance: parental fluency in the national language, level of education and the country of origin. Although country of origin was selected in the multivariate model to be most significant, we cannot exclude the possibility that fluency in the national language and level of education (being significantly correlated with the country of origin) may be the causal factors. The most important clinical parameter was the initial visual acuity of the amblyopic eye. The educational programme featuring the cartoon story that explained without words the rationale for treatment to the child significantly improved compliance throughout the study, limit-

ing in particular the number of children who were not occluded at all (3 in the intervention group vs. 23 in the reference group). The electronic monitoring performed by the researchers, who were working independently from the treating orthoptists as they distributed the ODMs during home visits, enabled us to detect these striking differences between the two treatment groups.

The study was designed as a single-blind, randomised clinical trial. The treating orthoptists were unaware of randomization, but the researcher distributing the educational programme or the picture to colour was not. Efforts were made to ensure that time spent explaining the study was equal in both groups. Randomization took place after the first visit to the orthoptist. Main results of this study were based on the data obtained from the first ODM measurement, thereby excluding any possible biases of a treating orthoptist later on in the study.

As compliance was measured in the week after the home visit, it would be reasonable to expect that compliance would be higher in the week it was monitored, and we cannot exclude that the ODM itself acted as an intervention. This bias applied to children in both groups. The study found that compliance was moderate despite the fact that parents knew that compliance was being monitored. This finding was also made in one of the previous pilot studies, in which compliance was monitored for longer periods (Simonsz, et al. 2001). For this reason, it was decided that compliance would be measured on a regular basis: 1 week every 3 months, also making the study more feasible for both parents and the researchers. Mean compliance in our reference group during the measurements was similar to that reported by the MOTAS (Monitored Occlusion Treatment of Amblyopia Study) Cooperative, who objectively monitored occlusion for a longer consecutive period (Stewart, et al. 2004).

Visual acuity at the start of treatment was the clinical parameter most significantly correlated with compliance. This finding is in agreement with other studies (Flynn and Cassady 1978; Lithander and Sjöstrand 1991; Smith, et al. 1995; Stewart, et al. 2004; 2005) and is explained by the fact that the acceptance of the patch is less when acuity is low.
The decrease in compliance during treatment, as found in our study, is partly due to a selection bias: children with low visual acuity at the start of treatment were less compliant, therefore wore the patches for a longer period, and consequently were recorded more often. The influence of treatment age on compliance has been a point of debate (Flynn and Cassady 1978; Stewart, et al. 2004; 2005); our study found the treatment age to be borderline significant, with younger children tending to have better compliance.

Having established this large study group of more than 300 children, the research group intends to proceed to an analysis of their visual acuity outcome. For this, the children's final

acuity will be assessed in a standardized fashion by the research orthoptist after the children have completed their patching treatment.

Apparently, native parents received more lengthy explanations at diagnosis and treatment than non-native parents did. Several factors may have contributed to this observation (e.g., cultural background, language skills, confidence, assertiveness, education, interests). Also, in The Netherlands, the time an orthoptist can spend on a patient varies and is sometimes limited to 15 minutes for a new patient.

Although occlusion therapy for amblyopia has been the primary treatment for centuries (Loudon, et al. 2005; von Noorden and Campos 2002) and clinically is an effective treatment, its success is limited, by, among other factors, non-compliance (Awan, et al. 2005; Dorey, et al. 2001; Loudon, et al. 2004; Stewart, et al. 2004; 2005). In this study, we confirmed, using electronic monitoring, that lack of understanding of the disease and treatment in pediatric medicine are obstacles that can be remedied by an educational programme: the cartoon story, reward stickers and an information sheet. Important demographic predictors for low compliance included poor parental fluency in the national language, country of origin and a low level of education. Education, primarily aimed at the child, improved compliance and reduced the number of children who did not comply with occlusion at all.

ACKNOWLEDGMENTS

The authors thank Bregje van Dijk, Ellen van Minderhout, Marleen Vermeulen, Roberta Delle Site, Janine van Zon, Eline Deelstra, Jorrien Bouma, Maurits Joosse, Hans Büller, Larisa Pepler, Yaroslava Chopovska, Iris Bachert, Angelika Cordey, Regine Neukam, Heike Bartz, Birgit Hermann, Marlies Murtro, Dr. Marc Lüchtenberg, Prof. Alina Zubcov, Dr. Claudia Kuhli, Dr. Richard Harrad, Dr. David Newsham and Prof. Irene Gottlob for their advice, help with data collection and efforts in recruiting the children.
The Occlusion Dose Monitor was developed at the department for Medical Technical Development at the Academical Medical Center, Amsterdam, the Netherlands in 1996-1997 as a public domain project.

Chapter 8

The influence of parental attitudes and behaviour on compliance with amblyopia therapy and the effect of an educational programme

ABSTRACT

Purpose: In the context of a randomised clinical trial, in which the effect of an educational programme on compliance with occlusion therapy was determined, this study focussed on the psychological reasons for failure to comply after 6 months of therapy.

Methods: In 310 children with newly diagnosed amblyopia compliance was measured electronically during one week, every three months. Children were randomly allocated to receive an educational programme (intervention group), or a picture to colour (reference group). After 6-9 months of treatment, during the third measurement, parents completed a 72-item questionnaire based on the Protection Motivation Theory to assess their beliefs about amblyopia and occlusion treatment. Parents with compliance less than 20%, received a separate semi-structured interview with in-depth questions that was based on differences in answers from the 72-item questionnaire between the group with compliance <20% and the compliant group. The measures were distributed via home-visits by researchers.

Results: 150 parents had reached the third measurement and 149 completed the questionnaire. A high degree of distress was most predictive for poor compliance ($P < 0.001$), followed by increased vulnerability ($P = 0.014$), increased stigma ($P = 0.017$) and poor logistics of treatment ($P = 0.044$). Twenty-eight (64%) parents who patched less than 20% cooperated with a semi-structured interview. This showed lack of knowledge, family distress and logistical problems to be the primary reasons for non-compliance. The educational programme positively influenced the level of distress ($P = 0.038$), logistics of treatment ($P = 0.016$) and parental knowledge ($P = 0.015$).

Conclusions: Distress, poor parental knowledge and difficulties implementing the treatment into the daily routine seem to be the predominant causes for non-compliance with occlusion therapy for amblyopia, part of which were obviated by the educational programme.

INTRODUCTION

Amblyopia is the most frequent cause of visual deficit in childhood (Attebo, et al. 1998; Brown, et al. 2000). The condition is usually unilateral and caused by strabismus, anisometropia and/or visual deprivation. It is commonly treated with patching of the fellow eye preferably before the age of six. Adults with insufficiently treated amblyopia are at an increased risk of bilateral visual impairment due to loss of vision in the fellow eye (trauma or other eye diseases), and a decreased quality of life in adulthood (Chua, et al. 2004; Fronius, et al. 2005; van de Graaf, et al. 2004; Rahi, et al. 2002). The factor most frequently quoted to influence the visual acuity is degree of compliance (Cobb, et al. 2002; Dorey, et al. 2001; Lithander and Sjöstrand 1991; Loudon, et al. 2003; Simmers, et al. 1999; Simons and Preslan 1999; Smith, et al. 1995; Stewart, et al. 2004; 2005). The development of the Occlusion Dose Monitor (ODM) in 1991 enabled objective monitoring of compliance (Fielder, et al. 1994) and it was found that the degree of compliance averaged 50-60% (Loudon, et al. 2006; Simonsz, et al. 1999; Stewart, et al. 2004; 2005), which is also found in studies that investigated compliance with prescriptions of medicine (Wright 1993). Since it has been shown that treatment is effective (Awan, et al. 2005; Clarke, et al. 2003; PEDIG 2002; 2003a; 2003b; Stewart, et al. 2004; 2005), efforts are underway to identify determinants of poor compliance and ways to improve it (Dixon-Woods, et al. 2006; Goransson, et al. 1998; Loudon, et al. 2006; Newsham 2002; Smith, et al. 1995; Tripathi, et al. 2002). The emotional impact of occlusion therapy (Dixon-Woods, et al. 2006; Hrisos, et al. 2004; Packwood, et al. 1999; PEDIG 2003) and poor parental understanding (Newsham 2002) were factors that affect parental implementation of occlusion therapy.

A model employed by Searle et al. based on Protection Motivation Theory (PMT) proved to be useful to understand psychosocial factors involved with non-compliance with occlusion therapy (Norman, et al. 2003; Searle, et al. 2000; 2002). PMT is based on two behavioural adaptations that occur when an individual faces a health threat. The first is threat appraisal, which focuses on the source of the threat: the individual's perception of the severity and vulnerability to the threat. The second is coping appraisal, which evaluates one's ability to address the threatened danger: that the individual is able to successfully perform an action (self-efficacy) and that this action is effective (response efficacy), both increasing the probability of an adaptive response (compliance with treatment). Both appraisal pathways contribute to protective motivation, followed by a decision to take action or not: protective behaviour. PMT has provided a coherent framework for exploring the impact and determinants of patching and it was concluded that PMT was predictive of compliance intentions and behaviour (Rogers 1975).

In a large randomised clinical trial, the ERPAG study, we previously found that poor parental fluency in the national language, a low level of education and poor acuity at start of treatment were predictors for low compliance, and, also that the educational programme, which

explained the reasons for therapy to the child, was very effective in improving compliance and reducing the number of children who were not occluded at all (Loudon, et al. 2006).
Herein, we provide reasons for failure or success to comply with occlusion therapy evaluated after 6-9 months of receiving treatment, using a questionnaire based on PMT with additional domains on knowledge and logistics of treatment, and give further insight into circumstances leading to non-compliance. In addition, the effect of the educational programme on the reasons for failure to comply with therapy was investigated.

METHODS

The design of this prospective randomised clinical trial and CONSORT statement has been reported in detail in a prior publication (Loudon, et al. 2006) and is summarised as follows: between July 2001 and December 2003, children were recruited from four clinics by six treating orthoptists in The Hague; additional children were recruited in Frankfurt (Germany). All children with newly diagnosed amblyopia, with an interocular difference in visual acuity of at least 0.2 logMAR, strabismus and/or anisometropia (>1.0 Dioptres (D)), or a deprivation in the absence of additional ocular or neurological diseases, were eligible. The severity of amblyopia was expressed as the ratio (in decimals) between the acuity in the amblyopic eye and the better eye and expressed as decimal scores. Compliance was measured electronically in all children during an entire week, every three months, using the Occlusion Dose Monitor (ODM) (Chopovska, et al. 2005; Fronius, et al. 2006).
Included children were randomised to either the intervention group or the reference group. Children in the intervention group received the educational programme: a cartoon story without text, depicting the orthoptic examination of a pre-school child, subsequent patching therapy and the reasons for therapy seen from the perspective of the child, designed to improve compliance. Folded in the back of the cartoon story was a sheet containing general information about amblyopia, its treatment and certain guidelines for the parents, available in eight languages. Children in the reference group received a picture to colour (e.g. Winnie the Pooh) that was also considered a reward, but did not contain the educational message. All parents were visited at their home by the researchers to explain nature and possible consequences of the study and to distribute the ODM with either the educational programme or the picture to colour. All children received standard orthoptic care. Occlusion was prescribed according to a standardised protocol developed for this study and representative of current orthoptic practice (Loudon, et al. 2006). The family's socio-economic status was ascertained using a 23-item questionnaire.
The Ethical Committee of Erasmus University Rotterdam and the boards of the participating clinics approved the protocol and informed consent forms. Written informed consent by the

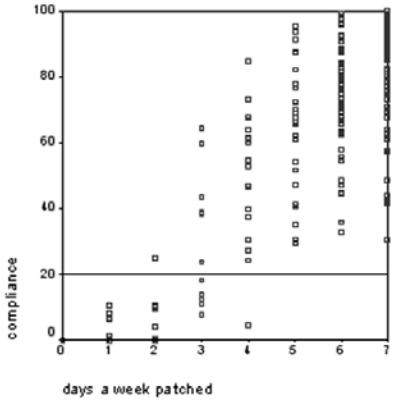
parents or guardian was a prerequisite for participation. The research adhered to the tenets of the Declaration of Helsinki.

Patching Success Questionnaire

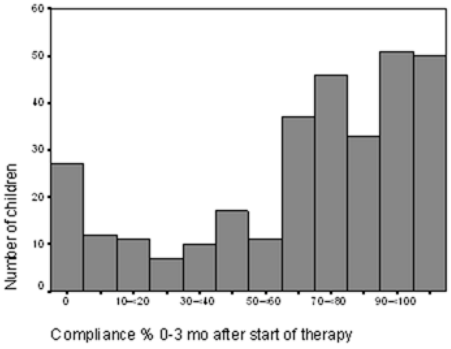
To identify reasons for failure to comply with occlusion therapy, an inventory was made using a 72-item questionnaire ('Patching Success Questionnaire' – PSQ), which was based on components of the PMT, 6-9 months after the start of treatment, during the third home-visit.
The PMT items were scored on a 5-point response domain (strongly disagree/strongly agree). Reliable measures were identified through factor analyses and internal reliability analyses: Cronbach's α (Norman, et al. 2003; Searle, et al. 2000; 2002). Measures of the variables were constructed by averaging responses to individual items such that high scores indicated high degrees on the variable of interest. Protection Motivation was assessed using three items (α=0.86). Perceived severity of the disease was assessed using six items (α=0.89). Perceived vulnerability was assessed using six items (α=0.86). Response efficacy was assessed using five items (α=0.83). Self-efficacy was assessed using four items (α=0.88). The perceived distress experienced by parents when patching their child was assessed using eight items (α=0.90), the extent to which patching may interfere or prohibit the child from engaging in every day activities was assessed using five items (α=0.62) and the stigma attached to wearing a patch was assessed using five items (α=0.78). In addition to the PMT items, information was collected on parental knowledge of disease (3 items, all on a 5-point scale; e.g. 'In general, a lazy eye is an eye that sees less clearly than the other') and treatment (2 items on a 4-point scale; e.g. 'The aim of patching therapy would be: equal vision - sufficient vision to read a book - decrease in the squint - not to wear glasses later in life') and logistic of treatment (4 items on a 5-point scale; e.g. 'I find it difficult fitting patching into my daily routine'). The questionnaire also contained 10 questions about the families' experience with the eye patch (e.g. 'after removing the eye patch my child's skin is red and/or painful').

Identification of non-compliers

To define the group of non-compliers, data of the first one-week ODM measurement were analysed. A cut-off point at compliance of 20% was chosen, which included not only the non-patchers, but also the low-frequency-patchers (i.e. the eye was occluded less than twice a week). As expected, a strong association between compliance and frequency of patching was found (Figure 1a & 1b): when compliance was less than 20%, the frequency of patching was less than three times a week (sensitivity 0.84, specificity 1.00).
Parents from the non-compliant group were contacted by phone and an appointment for an interview during a separate home visit was made. In case of poor fluency in the national language by the parents, an interpreter was present.



1a



1b

Figure 1a. A scatter plot displaying the relationship between the frequency of patching per week and electronically measured compliance during the first ODM measurement, the black line indicating the chosen cut-off point of 20% compliance. **1b.** A histogram presenting compliance during the first ODM measurement, with 10% intervals.

Statistical analysis

Descriptive statistics and crosstabs were used to calculate the means, standard deviations and inter-correlations of each domain of the questionnaire. These results were then compared to the results of the questionnaire reported by Norman et al. (2003). Linear regression analysis was used to predict protection motivation and compliance (both as dependent, continuous variables). The independent variables were: severity, vulnerability, response efficacy, distress, prohibition, stigma, self-efficacy, knowledge, logistics and protection motivation (scored as continuous variables).

The non-parametric Mann-Whitney test was used to determine the effect of the educational programme on the domains of the 'Patching Success Questionnaire'. F-values and β-values were calculated. The F-value is a test statistic that tests for differences in the variance between two groups; F=1 indicates no difference in variance between two groups. The percentage of the variation in compliance and motivation to patch their child that could be ascribed to the different factors involved was defined as the ratio of the percentage of the variance explained by the model with, and the model without the factor in question. Analysis was both Univariate and Multivariate. Descriptive statistics were applied to analyse the completed semi-structured interviews. $P < 0.05$ was considered statistically significant.

RESULTS

The study design was prospective, recruiting children for a period of 30 months. On average a child received three electronic measurements during, on average, 8 months of treatment. Therefore, not all children had reached the moment of the third measurement, the moment the questionnaire was distributed. After 6-9 months of treatment, the 150 patients who received the third measurement were asked to complete the questionnaire, 75 in the intervention group and 75 in the reference group (Figure 2). The PSQ was completed for 149 parents during the third home-visit. Mean age was 4.6 years (SD 1.9) and 53% were boys; the clinical and demographic characteristics were similar to those reported for the full study cohort (*n* = 310) (Loudon, et al. 2006).

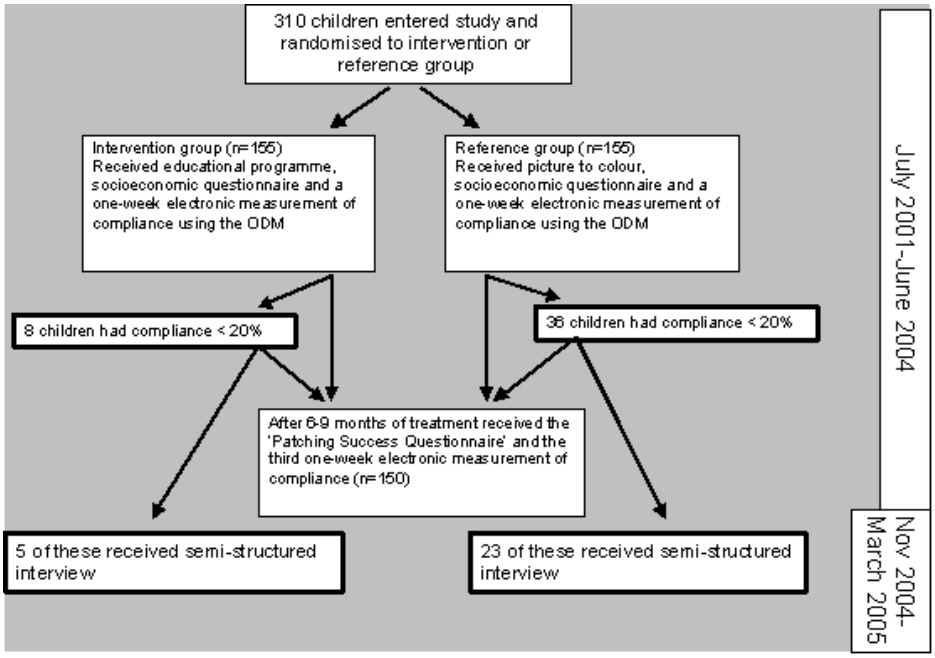


Figure 2. Flowchart illustrating the study design. After the first one-week measurement, children who patched less than 20% were identified as non-compliant. Between November 2004 and March 2005, the non-compliant group received a separate semi-structured interview with more in-depth questions that was based on differences in answers from the Patching Success Questionnaire between the compliant and the non-compliant group.

Patching Success Questionnaire

The mean scores and standard deviations per PMT domain as observed in this study differed from the scores found by Norman et al., for the domains: protection motivation, severity, vulnerability, degree of distress and stigma barrier (Table 1). The inter-correlations between the domains of the PMT, however, were comparable to those reported by Norman et al. (2003).
Stepwise backward selection demonstrated that the motivation to patch their child (PM) was high when self-efficacy ($\beta = 0.51$; $P < 0.001$), response efficacy ($\beta = 0.30$; $P < 0.001$) and severity ($\beta = 0.08$; $P = 0.048$) were also high, all three domains explaining 54% of the variation in protection motivation (adj. R^2). Stepwise backward selection showed that compliance increased when parents were well capable of implementing the occlusion therapy into their daily routine (logistics; $\beta = 6.1$; $P = 0.044$) and when they replied that their child's eye sight would get worse if left untreated ($\beta = 9.3$; $P = 0.014$). Compliance decreased when the two barriers distress and stigma increased ($\beta = -22$; $P < 0.001$ and $\beta = -6.0$; $P = 0.017$, respectively). The four domains explained 22% of the variation in compliance (adj. R^2).

Visual acuity was significantly and negatively correlated with the domains severity ($r = -0.37$; $P < 0.001$) and the degree of distress ($r = -0.17$; $P = 0.007$). Age of the children and cause of amblyopia were not correlated with any of the domains, neither was gender.
Poor fluency in the national language was positively related to stigma ($r = 0.37$; $P < 0.001$), a higher degree of distress ($r = 0.45$; $P < 0.001$) and severity ($r = 0.5$; $P < 0.001$); and negatively related to knowledge ($r = -0.22$; $P = 0.009$) and self-efficacy ($r = -0.18$; $P = 0.03$). Level of education was positively correlated with knowledge ($r = 0.20$; $P = 0.018$); and negatively correlated with the domains severity ($r = -0.23$; $P = 0.005$); degree of distress ($r = -0.29$; $P < 0.001$); and stigma ($r = -0.21$; $P = 0.009$).
The clinical and socioeconomic variables studied, explained 11% of the variance in protection motivation and 12% of the variation in compliance.

Relationship between Patching Success Questionnaire and compliance, and the effect of the educational programme

Univariate analysis of the variance demonstrated that an increased degree of distress caused by occlusion therapy negatively infl uenced compliance. However, a clear effect of the educational programme was found ($F = 4.15$; $P = 0.038$), in a sense that children and their parents who received the programme suffered less distress than the reference group (Table 2).
Compliance increased when parents found it easier to implement occlusion therapy into their daily routine (logistics). The implementation was significantly better in parents who had received the educational programme ($F = 5.97$; $P = 0.016$). Parental scores on the domain 'knowledge about treatment' were significantly higher when they had received the educational pro-

Table 1. Mean scores and standard deviation per domain for the study population in The Hague and Bristol; * *P*-value indicating a significant difference in mean scores.

Scales	The Hague (*n* =149)	Bristol (*n* =151)	*P* -value
PM	4.25 ± 0.68	4.5 ± 0.85	*<0.001
Severity	3.02 ± 0.93	3.57 ± 0.82	*<0.001
Vulnerability	3.2 ± 0.74	3.49 ± 1.00	*<0.001
Response efficacy	4.36 ± 0.5	4.33 ± 0.78	0.252
Distress barrier	2.19 ± 0.84	2.75 ± 1.04	*<0.001
Prohibit barrier	2.07 ± 0.95	1.94 ± 1.05	0.101
Stigma barrier	2.48 ± 0.83	2.85 ± 0.95	*0.001
Self-efficacy	4.04 ± 0.86	3.86 ± 1.2	0.767

gramme (F = 6.1; *P* = 0.015). This, however, did not affect compliance. Compliance increased significantly when parents were highly motivated to patch their child, when they thought their child's eye sight would be vulnerable when left untreated, when parents were able to adhere to the prescription given by the orthoptist, and decreased when their child was prohibited in his activities by the patch. The educational programme showed no demonstrable effect on these domains.

Group of non-compliers

After the first one-week ODM measurement 44 children had electronically measured compliance below 20% (8 intervention group; 36 reference group), of whom 33 could be contacted, while 11 (25%) could not be contacted with the available address or telephone numbers. 28 (64%) were interviewed at their home (5 intervention group; 23 reference group), 5 (11%) would no longer cooperate. The interviews were undertaken by two interviewers (LC and SdV) who wrote extensive reports of each visit. The time spent on these home-visits was approximately 30 minutes (range 20-45 min).

The compliant and non-compliant group were compared concerning the clinical and socio-economic factors and the answers given to the 'Patching Success Questionnaire'. The following significant differences using ANOVA were found: visual acuity at onset (F = 3.78; *P* = 0.049), fluency in the national language (F = 6.64; *P* = 0.01), country of origin (F = 3.85; *P* = 0.047), perceived distress (F = 12.51; *P* = 0.001), self-efficacy (F = 9.32; *P* = 0.003), protection motivation (F = 12.12; *P* = 0.001), logistics of treatment (F = 15.1; *P* = 0.001) and knowledge about amblyopia and its treatment (F = 8.13; *P* = 0.005). The differences found were in favour of the compliant group. These differences were used to develop a semi-structured interview with 33 additional focussed questions based on these domains, including 6 questions specifically for the child. Since compliance was related to fluency in the national language and as communication is an

Table 2. β-, F- and *P*-values of a univariate analysis of the effect of the PSQ domains on compliance.
* Indicates a significant influence.

Scales	β	F	*P* -value
PM	16.4	14.1	*<0.001
Severity	-3.1	0.8	0.358
Vulnerability	10.9	6.9	*0.009
Response efficacy	5.7	0.6	0.364
Distress barrier	-17	24.2	*<0.001
Prohibit barrier	-8.4	6.8	*0.01
Stigma barrier	-5.9	2.5	0.116
Self-efficacy	12.8	13.4	*<0.001
Knowledge disease	0	0	0.998
Knowledge treatment	2	0.4	0.546
Logistics of treatment	11.1	13.9	*<0.001

important part in compliance (Loudon, et al. 2006), questions regarding communication and relationship with the therapist in general were also included.

The semi-structured nature of the interview made it possible to thoroughly question the parents about amblyopia and its treatment. The reports were objectified by scoring them for gauging criteria done by the two researchers separately. These criteria were compiled through analyses of the survey. Based on the literature (DiMatteo 2004) and the results of the questionnaire, three main parties involved in the occlusion treatment could be distinguished: i.e. child, carer and therapist. Conclusively, 12 gauging criteria were drawn up, 4 for each party involved (Figure 3). These criteria refer to reasons for total non-compliance.
The analysis of the interviews was then conducted by scoring each report of the interview on the above-mentioned 12 criteria. This was done on a scale from 1 (not present) to 5 (dominantly present or behaviour defining). The two independent scores were analysed with the weighed kappa-test to test if the two scores differed significantly.
All parents interviewed were under the impression they had sufficient knowledge regarding the treatment, however, objectively, only 14% had sufficient knowledge. Also, a high degree of distress and logistical problems were prevalent. Parents did not regard occlusion therapy to be an effective treatment. Interviewed children replied they were often teased by their peers whilst wearing the patch (43%, of whom 29% suffered severe teasing), which decreased their self-esteem. A third of the parents answered they had received incomplete information from the treating orthoptist and that there was little time during the visit to discuss their problems. 18% of the parents thought that the orthoptist did not sufficiently address the child when explaining the eye condition and its treatment.
The following significant correlations (using Pearson's chi-square) were found: time and attention spent by therapists to problems regarding the occlusion therapy were correlated with

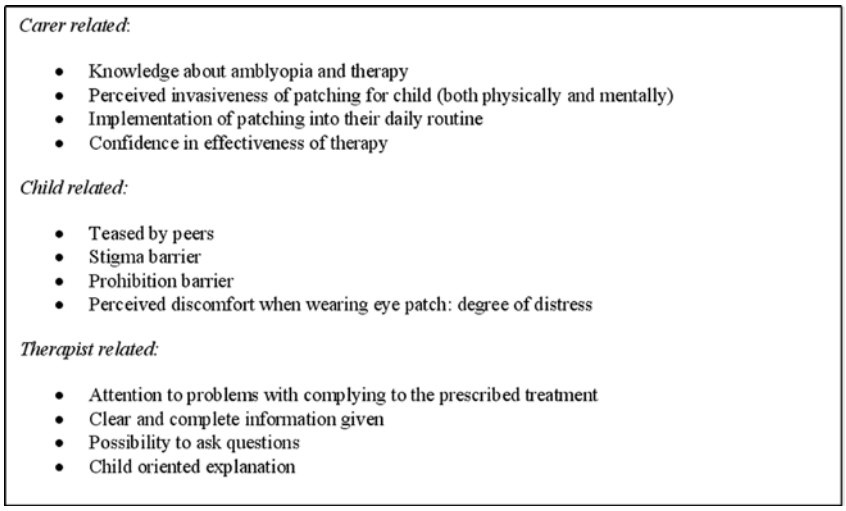


Figure 3. 12 criteria subdivided into the carer, the child and the therapist.

clarity of information, possibility to ask questions and child-orientation of the visits. Parental knowledge about amblyopia and its treatment and the perceived feeling of invasiveness of therapy were correlated to response efficacy. Confidence in the response efficacy was correlated with time and attention paid by therapists to problems encountered during patching, clarity of information given and possibility to ask questions.

DISCUSSION

In the context of a prospective, randomised, clinical trial in which the effect of an educational programme on compliance was investigated, this study provided reasons for failure to comply with occlusion therapy after 6-9 months of treatment. We used a 72-item questionnaire based on the PMT components with added domains on knowledge and logistics of treatment and separately interviewed parents who did not occlude at all. In addition, the effect of the educational programme on the domains of the questionnaire was determined.

In concordance with Searle, et al.(2002) and Norman, et al.(2003) the degrees of response efficacy and protection motivation were high, indicating that most parents thought eye patching to be an effective treatment for their child's amblyopic eye and were motivated to patch their child as prescribed by the orthoptist. More than 50% of the variation in protection motivation could be ascribed to the following three domains: self-efficacy, response efficacy and severity; thus parents' motivation to patch their child increased when they thought patching to be an effective treatment, when they were able to patch their child as recommended by the orthoptist and when they thought their child's eye condition to be severe. This finding was also

found in other studies which applied PMT in relation to compliance with therapy in amblyopia and other conditions (Abraham, et al. 1994; Flynn, et al. 1995; Fruin, et al. 1991; Norman, et al. 2003; Rippertoe and Rogers 1987; Rudman, et al. 1999; Searle, et al. 2002; van der Velde and van der Pligt 1991). As the parents in The Hague were given the same questionnaire as the parents in Bristol, it would be interesting to compare their mean scores. For several domains the parents in The Hague scored lower, probably explained by the difference in population and country.

Univariate analysis demonstrated that compliance was influenced by protection motivation, vulnerability, distress and prohibition barrier, self-efficacy and logistics of treatment. However, when corrected for potentially confounding factors no effect of protection motivation on compliance could be found: though parents may be motivated to patch their child, this did not influence compliance. Compliance decreased most drastically when parents reported a high degree of distress. This was also found in other studies (Hrisos, et al. 2004; Norman, et al. 2003; Packwood, et al. 1999; PEDIG 2003; Parkes 2001; Searle, et al. 2002). However, families who were given the educational programme that explained the occlusion therapy to the child, suffered less distress and had better compliance. The educational programme had a similar positive effect on parental knowledge of treatment and logistics of treatment. This finding is in agreement with Newsham's (Newsham 2002). Somewhat surprisingly, knowledge of the disease itself was not affected by the educational programme; perhaps it was still unclear for the parents, or they found amblyopia itself not interesting or serious enough.

The age of the child, depth of amblyopia, gender and cause of amblyopia showed little relationship with the overall scores. Poor visual acuity at treatment onset caused parents to consider the amblyopia as a serious eye condition and increased the degree of distress.

Parents who spoke the native language excellently, had better knowledge about the treatment, were confident in their ability to patch their child and were of the opinion that amblyopia was a serious eye condition; they also suffered less distress and stigma.

The questionnaire and interview were carried out on one occasion. It might have been interesting to, in a prospective design, also have distributed the questionnaire and conducted the interview immediately after the first visit to the orthoptist for prediction and to compare outcomes and any changes in opinions.

When analysing the group who did not occlude at all, it was apparent that there was a clear discrepancy of subjective knowledge and the measured knowledge. This indicated that many parents were ignorant of their lack of knowledge, therefore could not give feedback or put forward any questions, thus leaving the orthoptist unaware of the parents' problem. For a small group of parents the orthoptist was felt as the main reason for failing to patch: when there was no attention paid to problems encountered during patching, no possibility to ask questions, insufficient or unclear information supplied, parents were most likely to become steadfast non-compliers. A number of parents indicated that visits to the orthoptist should be more child-focused. Children were poorly involved in the communication between parent

and orthoptist and consequently did not understand the reason they had to be patched. The interviews were taken at their home, to overcome the problem of dropouts who no longer visited the clinic. The interview was open framed, rather than with multiple-choice questions. This open framework allowed a focused, conversational, two-way communication.
This study demonstrated that occlusion therapy for amblyopia is difficult to implement, is accompanied by a high degree of distress and is hampered by poor knowledge and understanding by the parents and therapist. If knowledge and understanding is improved, this might diminish the effect of the other determinants found in this study. The educational programme, a cartoon story explaining without text the reasons for therapy to a 4-year old and the information sheet for the parents, partly reduced the influence of these determinants and increased the acceptance of occlusion therapy.

ACKNOWLEDGMENTS

The authors thank Bregje van Dijk, Ellen van Minderhout, Marleen Vermeulen, Roberta Delle Site, Janine van Zon, Eline Deelstra, Jorrien Bouma, Maurits Joosse, Hans Büller, Larisa Pepler, Yaroslava Chopovska, Iris Bachert, Angelika Cordey, Regine Neukam, Heike Bartz, Birgit Herrmann, Marlies Murtro, Dr. Marc Lüchtenberg, Prof. Alina Zubcov and Dr. Claudia Kuhli for their advice, help with data collection and efforts in recruiting the children.
The Occlusion Dose Monitor was developed at the department for Medical Technical Development at the Academical Medical Center, Amsterdam, the Netherlands in 1996-1997 as a public domain project.

Chapter 9

Physiological and mechanical properties of the eye patch: influence on compliance and parental satisfaction

ABSTRACT

Purpose: To evaluate the physiological and mechanical properties of the eye patch and their influence on compliance as part of the prospective randomised clinical trial identifying risk factors for non-compliance with occlusion therapy for amblyopia.

Methods: For a period of 30 months all children with newly diagnosed amblyopia in The Hague were registered. Compliance was measured during 1 week every 3 months with the Occlusion Dose Monitor (ODM) that was distributed during home-visits. All children received standard orthoptic care by the treating orthoptist. After 6 months of treatment, parents completed a questionnaire evaluating comfort, size and adhesion of the patch. In the study, four brands of patches were used: Opticlude, Orthopad, Pro-Ophta and Beiersdorf. On one occasion the following physiological and mechanical properties were measured: breathing capability at 23°C (73°F) and 33°C (91°F), resistance to water penetration, opacity and strength of adhesion to the skin.

Results: 149 Parents completed the questionnaire, of whom 62% used Opticlude, 24% Orthopad, 11% Pro-Ophta and 3% used Beiersdorf. The brand of patch prescribed was correlated to the orthoptist only ($P = 0.005$). Compliance was neither related to the brand ($P = 0.179$), nor to the use of different colours or designs of patches ($P = 0.639$). It was, however, related to the use of stickers ($P = 0.028$). Parental satisfaction was moderate. Answers given by the parents matched the measured physiological and mechanical properties of the eye patch. There were large differences in the properties of the eye patch, especially in opacity and strength of adhesion to the skin. In all brands of patches the breathing capability was minimal.

Conclusions: When prescribing a certain brand the orthoptist needs to consider the wide variety in physiological and mechanical properties of the patch. Further study into these properties is necessary; especially water permeability and opacity of the eye patch require improvement since children often wear them for a longer period of time. This could contribute to increasing parental satisfaction and consequently may improve compliance.

INTRODUCTION

Amblyopia is the commonest visual defect in children with a prevalence of approximately 3.5% (Attebo, et al. 1998). The condition may be partially or completely treated preferably before the age of 6. Traditionally, treatment involves occlusion of the non-amblyopic eye with an adhesive patch applied directly to the skin around the eye, thereby forcing the use of the amblyopic eye. Occlusion therapy has been the mainstay of treatment for centuries. However, it frequently receded into the background when other types of treatment for amblyopia were tried. In 1927 it was re-introduced by C.H. Sattler in Leipzig (Sattler 1927). His occluder, called "Mastisolverband", was attached to the skin around the eye with strong adhesive tape and remained securely fastened for at least two or three days. Acceptance of this patch was poor as it caused localised skin irritation in almost all children. Nowadays, a wide selection in brand of patches is available, with patches varying in size, colour, elasticity, and gadgets or gifts distributed by the manufacturers. Whether or not a patch remains glued to the skin depends on a number of factors, e.g., skin type, the child's activities while wearing the patch and adhesive strength of the patch. The eye patches are mostly made of non-woven materials. Some manufactures assert their brand of patch is hypo-allergen, indicating special glue was used to reduce the occurrence of allergies and itching. Nevertheless, it has been reported that parents dislike the cosmetic appearance of their child wearing an eye patch. They argue that wearing the eye patch is uncomfortable, causes irritation to the skin and leads to considerable distress for the child, sometimes even outweighing any benefits from improvement in vision (Hsiros, et al. 2004; Norman, et al. 2003; Packwood, et al. 1999; Parkes 2001; PEDIG 2003; Snowdon and Stewart-Brown 1997). To date, no study has investigated the physiological and mechanical properties of various brands of eye patches and their effect on compliance. Therefore, as part of a randomised clinical trial designed to investigate a method to improve compliance and to identify certain risk factors for non-compliance, this study investigated the properties of the eye patches, focussed on the orthoptists' choice in prescribing a particular brand, the correlation with compliance and parental satisfaction.

METHODS

The design of this prospective trial has been reported in detail in a prior publication and is summarised as follows (Loudon, et al. 2006): between July 2001 and December 2003, all children with newly diagnosed amblyopia in The Hague were recruited from four clinics by six treating orthoptists; additional children were recruited in Frankfurt (Germany). Eligible children received a routine orthoptic examination and explanation of diagnosis and treatment after which a standard examination form was completed and forwarded to the research centre. The duration of occlusion (number of hours per day) for the first prescription had been

Table 1. The 10-item questionnaire as given to the parents. Each item had 5 response choices, except for questions 7 and 9, which had 2 response choices. n.a.= not applicable: at the time of the study Pro-Ophta and Beiersdorf did not have coloured patches available. * The *P*-value indicates a significant difference in answers.

Questions:	Opticlude (N=92)	Orthopad (N=35)	Pro-Ophta (N=17)	Beiersdorf (N=5)	*P*-value *
	N (%)	N (%)	N (%)	N (%)	
The patch on my child's eye is					0.44
much too big	3 (3)	0	1 (6)	0	
too big	1 (1)	2 (6)	2 (12)	0	
about right	87 (95)	33 (34)	13 (76)	5 (100)	
too small	1 (1)	0	1 (6)	0	
much too small	0	0	0	0	
The patch stays on my child's eye					***0.027**
strongly agree	19 (21)	5 (14)	3 (18)	3 (60)	
agree somewhat	55 (60)	23 (66)	9 (53)	2 (40)	
neither agree or disagree	12 (13)	5 (14)	2 (12)	0	
disagree somewhat	5 (5)	2 (6)	2 (12)	0	
strongly disagree	1 (1)	0	1 (6)	0	
The patch sticks to my child's skin					0.685
much too well	4 (4)	3 (9)	1 (6)	1 (20)	
too well	25 (27)	5 (14)	4 (23)	3 (60)	
about right	59 (65)	26 (74)	9 (53)	1 (20)	
not strongly enough	4 (4)	1 (3)	2 (12)	0	
not at all	0	0	1 (6)	0	
After removing the patch my child's skin is red and/or painful					0.162
never	17 (18.5)	11 (31)	8 (46)	0	
occasionally	23 (25)	10 (29)	3 (18)	0	
sometimes	34 (37)	8 (23)	3 (18)	3 (60)	
quite often	13 (14)	4 (11)	3 (18)	1 (20)	
almost always	5 (5.5)	2 (6)	0	1 (20)	

To what extend did the patch remain on the eye					0.216
The patch remained on the eye	72 (78)	28 (80)	10 (59)	3 (60)	
The ends of the patch have become loose	18 (20)	5 (14)	6 (35)	2 (40)	
The patch remained on the eye only just	2 (2)	2 (6)	1 (6)	0	
The patch fell off	0	0	0	0	
I was involved in the decision about the type of patch					0.058
strongly agree	8 (9)	3 (9)	1 (6)	1 (20)	
agree somewhat	18 (20)	13 (36.5)	3 (18)	1 (20)	
neither agree or disagree	22 (24)	13 (36.5)	6 (35)	3 (60)	
disagree somewhat	29 (31)	3 (9)	5 (29)	0	
strongly disagree	15 (16)	3 (9)	2 (12)	0	
What colour patch did you use					
skin coloured, skip next question	42 (46)	11 (31)	17 (100)	5 (100)	
coloured patches	50 (54)	24 (69)	0	0	
Because of the different colours, patching my child became easier					
strongly agree	9 (17)	5 (21)	n.a.	n.a.	
agree somewhat	28 (52)	14 (58)			
neither agree or disagree	10 (5)	2 (8)			
disagree somewhat	3 (6)	3 (13)			
strongly disagree	0	0			
Did you use pictures and/or stickers when patching your child					0.319
no, skip next question	26 (28)	15 (43)	5 (29)	2 (40)	
yes	66 (72)	20 (57)	12 (71)	3 (60)	
Because of the pictures and/or stickers, patching my child became easier					0.733
strongly agree	13 (20)	5 (25)	5 (42)	1 (20)	
agree somewhat	31 (47)	9 (45)	4 (33)	3 (60)	
neither agree or disagree	18 (27)	2 (10)	2 (17)	1 (20)	
disagree somewhat	3 (5)	4 (20)	1 (8)	0	
strongly disagree	1 (1)	0	0	0	

standardised and prescribed according to the protocol representative of current orthoptic practice (i.e., -6.63 * ratio acuity amblyopic eye/acuity better eye + 0.5 * age (years) + 4.97).
After the first visit to the orthoptist, parents were contacted by the independent researchers who explained the nature and possible consequences of participating in the study and use of the Occlusion Dose Monitor (ODM) (Fielder, et al. 1994) during a home-visit. Full written informed consent was obtained. Compliance was measured with the ODM in all children during a period of 1 week, every 3 months (Chopovska, et al. 2005; Fronius, et al. 2006).
In the Netherlands four brands of patches are available: 3M Opticlude™, Orthopad Master-aid® (Regular and Simpathy), Pro-Ophta® or Beiersdorf® (Elastopad and Coverlet-S), all of which had also been prescribed in the study. The orthoptists were free in their choice to decide what brand of patch they prescribed. After completing the study, in December 2005, the treating orthoptists received a semi-structured interview by the researcher. During the open part they were asked to motivate their choice for prescribing a particular brand of patch. During the structured part they were asked if their choice was influenced by the age of the children, the number of prescribed occlusion hours, their idea of compliance with treatment, and by gadgets or gifts distributed by the manufacturers. In addition, the pharmacies in The Hague were contacted by telephone to document if all patches were in stock, and if not, which brand they did have in stock.

Questionnaire

Parental experience with the eye patch was evaluated via a 10-item questionnaire; each item had 4 or 5 response choices (Table 1, left-hand column). The questions were developed together with the Consumers' Organisation, the Netherlands who published a report on all available brands of plaster (July 2001) (Consumers' Organisation the Netherlands 2001). The parents completed this questionnaire during the third home-visit after approximately 6-9 months of treatment.

Physiological and mechanical properties of the patch

Firstly, breathing capability was tested at 23°C (73°F) and 33°C (91°F): the patches were glued on top of small plastic pots, each containing 20 grams of water. The pots were completely sealed off by the patch; the only way of ventilation was through the patch. They were left on a rocking table in a stove. The various patches were tested simultaneously at a temperature of 23°C (73°F) and a humidity of 30%. The same procedure was followed at a temperature of 33°C (91°F) and a humidity of 22%. To make sure these conditions were constant; a separate digital thermometer was used to measure the temperature and humidity. After 24 hours the amount of water left in the plastic pot was measured. The breathing capability, or 'water vapour resistance' (Ret), was calculated using: $m^2 * Pa / W$ ($m = \pi * r^2 *$ time (seconds); Pa = saturated

(water) vapour pressure, depending on temperature and humidity; W=difference in amount of water (grams) after a certain time, with 1 gram of water equalling 2430 Joule). The Ret is classified as follows: an Ret > 40: 'uncomfortable', e.g. raincoat and has a restricted wearing time; 20 < Ret ≤ 40: 'somewhat comfortable'; or Ret ≤ 20, which equals 'comfortable'.
Secondly, the resistance to water penetration was tested: 1 drop of water was placed on the centre of the patch and time necessary for the drop to be absorbed was measured with a stopwatch. Material is labelled water-resistant when the drop of water is not absorbed within 1 minute.
Thirdly, the opacity of the patches was tested. All patches were glued to a fluorescent lamp of 18 Watt. We measured the amount of light transmitted through the centre and at the side of the patch. 100% light transmission equals 'no patch present'.
Finally, the strength of adhesion of the patch to the skin was tested using the 'maximum force grab method'. The patches were stuck to the skin and the force necessary to remove the patch was measured (expressed in Newton).
The breathing capability was tested at the laboratory of the ErasmusMC University Medical Center Rotterdam; the other tests were performed at the Netherlands Organisation for Applied Scientific Research (TNO), Textile Industry Enschede. All tests were performed by the researcher (SL) under supervision of co-author AW.
In addition to the tests, the elasticity of the eye patches, hygiene, available sizes and distributed gifts per brand, was noted.

Statistical analysis

Chi-square test (Pearson Chi-square in crosstabs) was used to determine the influence of age, gender, number of prescribed occlusion hours, cause of amblyopia and socioeconomic status on the orthoptists' choice in prescribing a brand of patch.
Compliance was measured during 1 week, every 3 months. It was defined as the actual occlusion time measured with the ODM divided by the prescribed occlusion time and expressed as a percentage. Differences in compliance between the four groups of patches was assessed using least-squares regression analysis, with compliance as the dependent (continuous) variable and the brand of patch as the independent (categorical) variable, using data obtained during the first ODM measurement.
To calculate differences in answers to the questionnaire between the four groups, the answers were first transformed into rank numbers and then imported in the linear regression analysis with the rank number as the dependent variable and the brand of patch as the independent variable.
Whether the answers influenced compliance was also assessed with linear regression analysis. $P < 0.05$ indicated statistical significance.

Table 2. Gender, mean age, prescribed occlusion hours and compliance (%) of the 310 children in our study, according to the eye patch used by the parents.

		Opticlude n = 165	Orthopad n = 100	Pro-Ophta n = 26	Beiersdorf n = 19
Characteristic					
Gender					
	Male (%)	61	53	44	39
	Female (%)	39	47	56	61
Mean age - years		4.7	4.5	4.1	5.5
Mean prescribed hours of occlusion per day		2:57	3:23	2:51	3:41
Overall compliance (%)		71	62	75	73

RESULTS

In the randomised clinical trial, 310 children were eligible for analysis, mean age was 4.6 years (SD 2.0), and 56% were boys. At the start of the study 165 children used Opticlude (53.2%), 100 children used Orthopad (32.3%), 26 children used Pro-Ophta (8.5%), and 19 children used Beiersdorf (6%), (Table 2). An 8% deviation from a random prescription was found.

Overall mean compliance, as measured during the first ODM measurement, was 68% (range 0-100%; SD 38%). Compliance was not significantly influenced by the brand of patch (P = 0.179). However, the highly skewed distribution of the prescribed brand of patches prevented a reliable statistical analysis.

Questionnaire

After 6 months of treatment 150 children participated in the study, of whom 149 parents completed the questionnaire. At that time in the study, 92 children used Opticlude (62%), 35 children used Orthopad (24%), 17 children used Pro-Ophta (11%), and 5 children used Beiersdorf (3%). Results from the questionnaire are shown in Table 1. The one question to which parents responded significantly different was: "The patch stays on my child's eye: strongly agree – strongly disagree" (P = 0.027). To calculate whether the answers given by the parents were predictors for compliance we used linear regression analysis; only when the parents responded positively to the use of stickers, their compliance was significantly better (P = 0.028; r = 0.22).

Table 3. Physiological and mechanical properties, flexibility, hygiene, sizes, and distributed gadgets or gifts of the 4 eye patches.

Brand/Type	*1) Breathing capability (Ret)		*2) Opacity centre of patch	*3) Water-resistant	Max. Force to remove patch from skin (N)	Flexibility/ Elasticity	Packed a piece	Size availability	Gifts
	23°C	33°C							
3M Opticlude					3.2	broadwise only, very limited	no	mini, midi, maxi	Sponge Bob
skin coloured	64.1	34.9	89%	> 1 min					
blue			79%	> 1 min					
red			82%	> 1 min					
green			78%	> 1 min					
Orthopad					5.9	broadwise only	yes	mini, maxi	Gift voucher
Regular - skin	21.8	15.2	49%	10-15 sec					
Regular - white			54%	> 1 min					
Simpathy - red			42%	< 1 sec					
Simpathy - black/ white			51%	black: 10 sec; white: > 1 min					
Simpathy - blue			43%						
Pro-Ophta	30.1	14.5	62%	> 1 min	2.6	lengthways only	no	1 size	-
Beiersdorf					8.8		yes	mini, maxi	Disney DVD or Video
Elastopad	53.9	29.7	19%	> 1 min		broadwise only			
Elastopad -lite	39.9	21.8	29%	> 1 min		broadwise only			
Coverlet - S	55.7	33.3		> 1 min		very flexible in all directions			
Coverlet - S with sticker	70.8	37.8							

*1) Ret: water vapour resistance and classified as follows: Ret > 40 = uncomfortable (e.g. raincoat) and has a restricted wearing time 20 < Ret < 40 somewhat comfortable
Ret < 20 = comfortable to wear
*2) Opacity: 100% equals 'no patch present'
*3) Material is labelled water-resistant when the drop of water is not absorbed within 1 minute

Physiological and mechanical properties of the patch

The results of the water vapour resistance (expressed as Ret) test showed that none of the

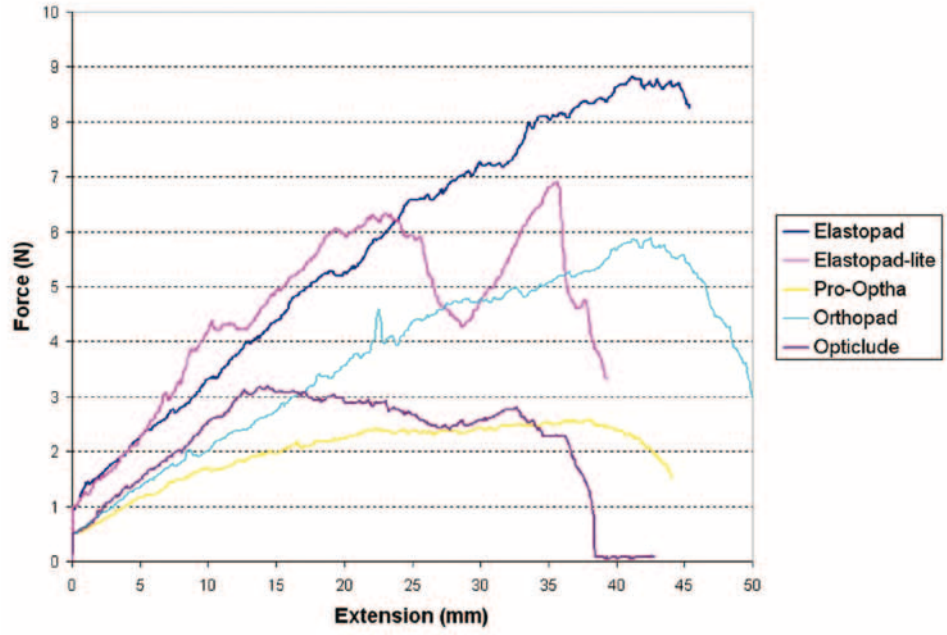


Figure 1. To remove the patches from the skin an average maximum force of 8.8 Newton (Beiersdorf), 5.9 N (Orthopad), 3.2 N (Opticlude) and 2.6 N (Pro-Ophta) was needed. For colour figures please see 'Colour figures' on page 197.

various brands of patches were 'comfortable' to wear at a temperature of 23˚C (73ºF) (= Ret < 20; Table 3). Beiersdorf and Opticlude were actually 'very uncomfortable' to wear (Ret > 40). At a temperature of 33ºC (91ºF) and a humidity of 22%, Pro-Ophta and Orthopad were 'comfortable' to wear and Beiersdorf and Opticlude were 'somewhat comfortable'.
All brands, except Orthopad, were water-resistant.
Only one brand was able to eliminate more that 70% of the light transmitted by a fluorescent lamp (Beiersdorf), whereas other brands eliminated 50% (Orthopad), 48% (Pro-Ophta) and 20% (Opticlude) of the light.

To remove the patches from the skin an average maximum force of 8.8 Newton (Beiersdorf), 5.9 N (Orthopad), 3.2 N (Opticlude) and 2.6 N (Pro-Ophta) was needed (Figure 1).
The measured physiological and mechanical properties matched the answers given by the parents on the questionnaire, e.g. Beiersdorf patches were the most difficult to remove from the skin (using the maximum force grab method), in correspondence with all parents (strongly) agreeing to the question that the patch remained on their child's eye.

The brand of patch prescribed was not significantly influenced by the age ($P = 0.428$), gender ($P = 0.147$) or the socioeconomic status ($P = 0.072$) of the children, the cause of amblyopia ($P =$

0.093) of the number of prescribed hours of occlusion ($P = 0.923$). It was, however, significantly related to the prescribing orthoptist ($P = 0.005$). Reasons for the six orthoptists to prescribe a particular brand included: (1) parent and child preference for the various motifs and coloured patches ($n = 6$); (2) Opticlude was the only brand that had a medium size available ($n = 3$); (3) personal experience ($n = 2$); and (4) out of habit ($n = 1$). Opticlude, Orthopad and Beiersdorf distributed gifts for the children when they handed in 2 or 3 barcodes from the box of patches.

The survey conducted of the pharmacies, showed 10% had all brands in stock, 5% had none, 29% Opticlude, 33% Opticlude and Orthopad and 14% had three brands in stock. In case children had been prescribed a patch that was not in stock, 19% of the pharmacies changed the orthoptists' prescription into the prescription of a patch they did have in stock.

DISCUSSION

This study evaluated the physiological and mechanical properties of the eye patch and the influence on compliance and parental satisfaction. In addition, reasons for prescribing a certain brand of patch by the orthoptist were recorded. The tests performed on the eye patches demonstrated large differences in these properties between the four brands. The breathing property of all patches was minimal at room temperatures; some patches could be compared to wearing a raincoat in the sun and would therefore clearly be more suited only when occluding for shorter periods of time. There was also considerable difference in strength necessary to remove the patch from the skin. As a consequence, when prescribing occlusion for a longer period of time, one might consider to prescribe the patch that was the most difficult to remove from the skin. No patch was able to eliminate 100% of the light, however, it is unclear whether the patch must exclude all light and form, or that it is sufficient to exclude form, but allow the passage of some light. The differences in properties did not seem to influence the orthoptists' choice in prescription. There was a clear preference to prescribe Opticlude patches, though when testing them they were not of a higher quality. The orthoptists alleged that overall they left it to the parent and child to decide and because Opticlude had the largest assortment this would thus increase the change of choosing an Opticlude patch. Moreover, differences in publicity and Public Relations of the patch manufacturers might also influence the decision to prescribe a particular brand of patch.

Consequently, the high prevalence of Opticlude patches in our study population made it difficult to statistically analyse differences in answers given by the parents. No correlation could be found between the electronically measured compliance and the brand of patch or the use of the different coloured patches. In addition, the answers given by the parents were comparable to the measured physiological and mechanical properties of the patch. Parents were moderately satisfied with the eye patches. Therefore, as children often wear the eye patches

for longer periods of time, it seems reasonable to expect orthoptists to take comfort of wear into consideration when prescribing a certain brand of patch and for manufacturers to spend more time and effort on improving the properties of their patches.

ACKNOWLEDGEMENTS

The authors thank Bregje van Dijk, Ellen van Minderhout, Marleen Vermeulen, Roberta Delle Site, Janine van Zon, Eline Deelstra, Jorrien Bouma, Hans Büller, Larisa Pepler, Yaroslava Chopovska, Iris Bachert, Angelika Cordey, Regine Neukam, Heike Bartz, Birgit Herrmann, Marlies Murtro, Dr. Marc Lüchtenberg, Prof. Alina Zubcov and Dr. Claudia Kuhli for their help with data collection and efforts in recruiting the children.
The Occlusion Dose Monitor was developed at the department for Medical Technical Development at the Academical Medical Center, Amsterdam, The Netherlands in 1996-1997 as a public domain project.

Chapter 10

Account of the study population in The Hague: prevalence of occluded children, causes of amblyopia and final visual acuity

ACCOUNT OF THE STUDY POPULATION IN THE HAGUE: PREVALENCE OF OCCLUDED CHILDREN, CAUSES OF AMBLYOPIA AND FINAL VISUAL ACUITY

This chapter gives an account of three aspects of our study population in The Hague area. First of all, we determined the prevalence of occluded children in The Hague and we considered to what extent our study group represented a true coverage of the amblyopic children. Secondly, the diagnoses given to the children and the causes of amblyopia in our study group are analysed. Finally, the visual outcome of the children in our study group is evaluated and the possibility of having visual acuity as primary outcome measure instead of compliance is discussed.

Prevalence of occluded children

Estimates of amblyopia's prevalence in the literature have ranged from 0.5% to 5.3%. This broad range is caused by differences in the approach to studying the prevalence. Studies have differed in terms of study population (e.g. pre-school children, 6-year old children, and military recruits), the applied examination methods and the visual acuity criterion used to diagnose amblyopia. In addition, these criteria are different at the start of occlusion treatment, the end of the occlusion treatment and in adulthood. This study defined amblyopia at the start of occlusion treatment as follows:
- A difference of visual acuity between the sound eye and the amblyopic eye of >2 logMAR lines or acuity <20/40 in the amblyopic eye.
- Strabismic amblyopia: Amblyopia in the presence of a heterotropia at distance and/or near fixation, with anisometropia of 1.00 D or less of spherical equivalent.
- Anisometropic amblyopia was defined as an amblyopia in the presence of anisometropia >1.0D, with no measurable heterotropia at distance or near fixation.
- Combined mechanism amblyopia: Amblyopia in the presence of any heterotropia at distance and/or near fixation and anisometropia >1.00 D spherical equivalent or >2D difference in astigmatism in any meridian, which persists after at least 4 weeks of spectacle correction.

Our study population encompassed all children with newly diagnosed amblyopia in the municipality of The Hague (with the exception of the areas Voorburg, Leidschendam, Wassenaar, Nootdorp, Ypenburg and Rijswijk). The Hague, being the third largest city in the Netherlands, harbours four main ophthalmology clinics with six treating orthoptists. Between July 2001 and December 2003, the six treating orthoptists recruited children who had been diagnosed with amblyopia, using the above mentioned criteria, and had consequently been prescribed occlusion therapy. In this study 361 children with newly diagnosed amblyopia were registered for a period of 2.5 years, which equals 144 children per year. Also included in this number are

the families who refused study participation and those who could not be contacted before the second visit to the orthoptist and were therefore excluded from the analysis.
The birth rate in the defined area of The Hague averaged 4,262 children / year in the years during which most of the children in the study were born (i.e. 1997, 1998 and 1999). Thus, the prevalence of occluded children in The Hague would be 144 / 4,262, which equals 3.38%. However, in 25 children the cause of amblyopia was undetermined. When correcting for these children, the prevalence of occluded children would be 3.15%.
We analysed the coverage of the eligible children in our defined area of The Hague, and it became apparent that not all orthoptists had recruited the same number of children per working hour. In some cases this could be explained by the fact that in one clinic several children had already been prescribed occlusion therapy by an ophthalmologist, therefore, these children could not be included in the study. We calculated an estimate of the eligible number of children, based on the number of children recruited, divided by the number of working hours per recruiting orthoptist. This estimate recruitment ratio was 10 newly diagnosed amblyopic children per 4 working hours per orthoptist per year, resulting in a total estimate of 230 eligible children per year in our defined study area of The Hague. In our study 144 children had been included, implying 63% coverage. Based on the 230 eligible children per year, the prevalence of occluded children in our defined study area of The Hague would be 230 / 4,262, which equals 5.4%. As discussed in Chapter 4, the prevalence of occluded children in the population is higher than the prevalence of amblyopia in adulthood (defined as acuity >0.3 logMAR). This is possibly caused by over-treatment of amblyopia in childhood, because after cessation of occlusion therapy (at the age of app. 8) the visual acuity may increase or decrease until adulthood. The orthoptist is unaware in which child the visual acuity will increase or decrease and will therefore treat all children that have any chance of reaching an acuity of 0.5 or less in adulthood.

Cause of amblyopia

Of the 361 occluded children in The Hague, the diagnoses were marked on the standard examination form by the treating orthoptists. In our study 35 possible diagnoses could be given. The cause of amblyopia was assessed after cessation of occlusion therapy by the researchers. We thought it important to register for each patient all the diagnoses of the amblyopia; therefore a distinction between the diagnoses and the cause of amblyopia was made.
The cause of amblyopia in the 361 occluded children was assessed as anisometropia in 132 children (37%), strabismus in 81 (22%), both strabismus and anisometropia in 42 (12%), hypermetropia in 12 (3%), both strabismus and hypermetropia in 18 (5%), both anisometropia and hypermetropia in 8 (2%), astigmatism in 27 (7%), both strabismus and astigmatism in 9 (3%), and deprivation in 7 (2%). The cause of amblyopia in 25 children (7%) was undetermined.

In the 361 children the orthoptists marked a diagnosis a total of 701 times, varying from 132 children who had only one diagnosis marked, to one child who had six different diagnoses.
The three most frequent diagnoses in our study population were anisometropia > 1D (*n* = 156; 22%), hypermetropia > 3D (*n* = 145; 21%) and astigmatism (*n* = 135; 19%). Infantile esotropia was diagnosed in 21 children (3%), accommodative esotropia in 35 children (5%) and micro-strabismus in 64 children (9%).
On further analysis of the children with the diagnosis hypermetropia, 33 children were also diagnosed with a micro-strabismus, 20 with an accommodative esotropia and 10 with an infantile esotropia. In 42 children with anisometropia, strabismus was also present, mainly micro-strabismus (*n* = 27). This also applies to the children with astigmatism: in a quarter of these children (*n* = 36) strabismus was present, mainly micro-strabismus (*n* = 23).
When analysing the children with the diagnoses micro-strabismus, half of these children also had hypermetropia (*n* = 34), 27 an eccentric fixation, 27 an anisometropia, 23 astigmatism and 4 a latent nystagmus. In half of the children with an infantile esotropia, hypermetropia was present (*n* = 10), 6 children also had astigmatism, 5 a latent nystagmus and 4 had anisometropia.

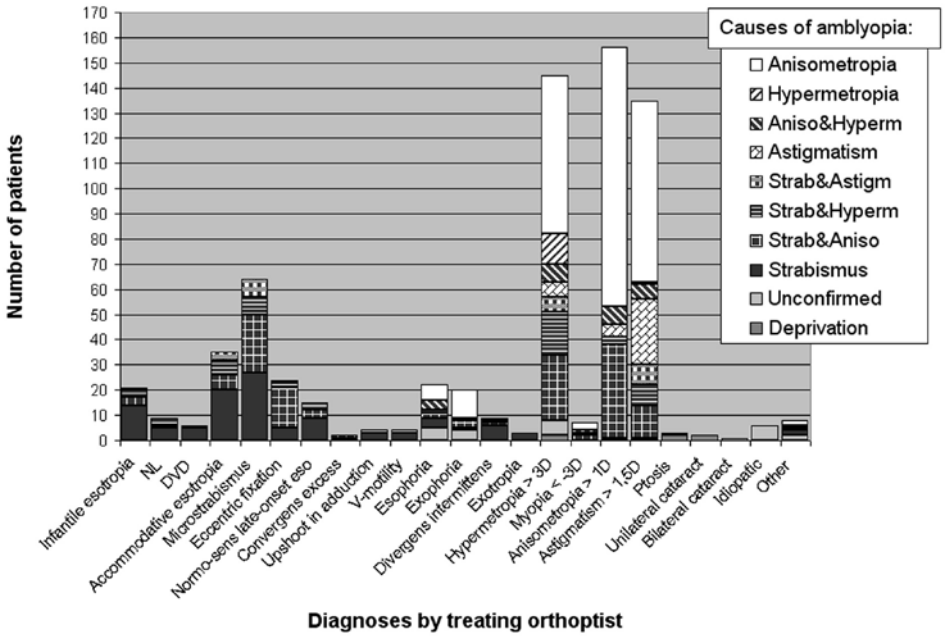


Figure 1.a. The distribution of the 10 possible causes of amblyopia per diagnose. Each bar represents a diagnosis. In our study population 23 diagnoses were given by the treating orthoptist and more than one diagnosis may be given to one child. Each bar was subdivided into the cause of amblyopia (assessed by the researchers), e.g. the diagnosis 'late-onset esotropia' was present in the following three causes of amblyopia: strabismus, strabismus & anisometropia and strabismus & hypermetropia. For colour figure please see 'Colour figures' on page 198.

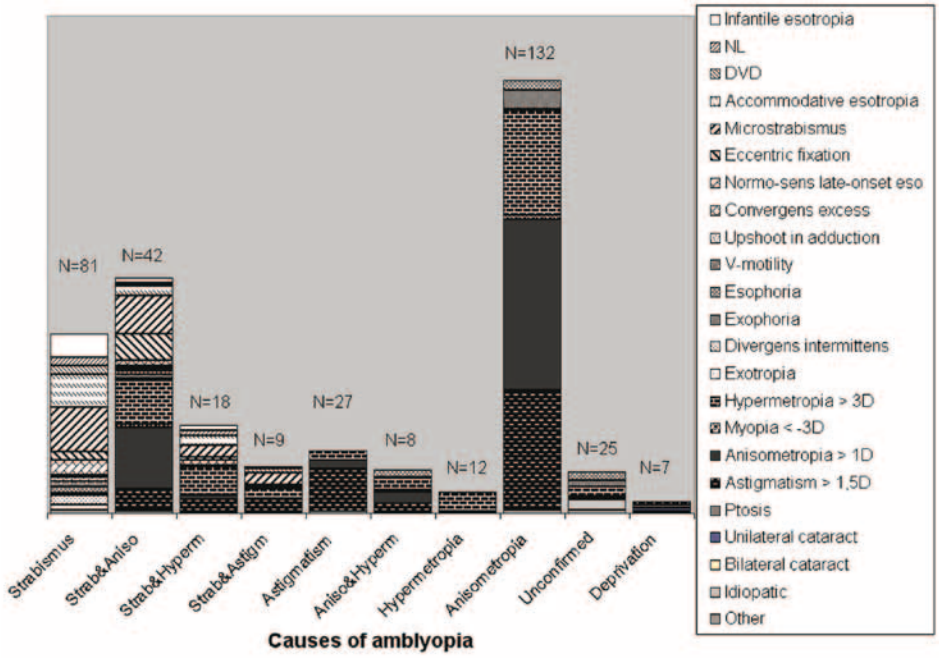


Figure 1.b. The distribution of the 23 diagnoses in our study population per cause of amblyopia. Each bar represents 1 of the 10 causes of amblyopia, which was subdivided in the diagnoses given in our study population. One child may have more than one diagnosis, but only one cause of amblyopia. For example, anisometropia was assessed as the cause of amblyopia in 132 children; however, 6 children with anisometropic amblyopia also had the diagnosis 'esophoria' and 11 'exophoria'. These diagnoses were not the main cause of amblyopia. The number above the bar corresponds with the number of children whose cause of amblyopia is represented in that bar. For colour figure please see 'Colour figures' on page 199.

Figure 1a shows the distribution of the 10 causes of amblyopia per diagnosis, of the 361 occluded children in The Hague. In our study population 23 out of the possible 35 diagnoses were given by the treating orthoptist. The diagnoses given by the treating orthoptist may not necessarily be the only cause of amblyopia. For example, of the 21 children who were given the diagnosis 'infantile esotropia' (Figure 1a, bar on the left-hand side), only in 14 of those, the infantile esotropia, i.e., strabismus was indeed the cause of amblyopia. In 3 out of those 23 children, a combined anisometropia and strabismus was the cause of amblyopia; in 3 children the cause of amblyopia was strabismus and hypermetropia and one child had diagnosis 'infantile esotropia', but had amblyopia caused by both strabismus and astigmatism.
Figure 1b shows the distribution of the 23 diagnoses given to the children in our study population per cause of amblyopia. As mentioned before, a child may have more than one diagnosis. For example, in the 81 children in whom the amblyopia was caused by strabismus, 108 diagnoses were given: see bar on the left-hand side. In 42 children the amblyopia was caused

by strabismus and anisometropia; in this group a diagnoses was given 142 times to these children.
This manner of visualisation was chosen to facilitate a comparison with other studies that investigated causes of amblyopia.

Visual acuity as treatment outcome

When designing the study it was intended to have the visual acuity of the children as primary outcome measure. However, the referees objected to this outcome measure because of the statistical noise between compliance and visual acuity increase, as measured in current orthoptic practice. When measuring visual acuity in young children the testability and co-operation is often limited. Consequently, when having visual acuity as the primary outcome measure, the treatment groups would need to be excessively large. Therefore, the primary outcome measure was restricted to electronically measured compliance. Now, we contemplated whether visual acuity could have been used as primary outcome measure as we have included almost three times the primary target (which was 110 patients).
Visual acuity was assessed in children whose occlusion treatment was either 'completed' by the orthoptists or 'terminated' by the parents, and in children who had reached the age of six, using standard protocols (n = 203). The independent research orthoptist tested the best corrected visual acuity using Landolt-C chart 2.6'. At least 3 out of 5 optotypes had to be answered correctly per line. The luminance was measured during the tests. This ranged from 160 cd/m^2 to 320 cd/m^2, which is in accordance with the norm. To correct for a difference in testing distance, a correction factor was applied (e.g. when the distance to the chart was 5.7m, a correction factor of 1.14 was applied).
Figure 2 shows the relationship between visual acuity of the amblyopic eye (logMAR) at the start of treatment, at the end of treatment (both measured by the treating orthoptist) and the moment the acuity was assessed in a standardised fashion (measured by the treating orthoptist), per category compliance. Visual acuity as measured by the orthoptists at the end of treatment was comparable to that measured by the research orthoptist in a standardised fashion at follow-up. There was no significant difference in age of the children between the four categories of compliance. The graph illustrates that children with poor visual acuity in their amblyopic eye at treatment onset have low compliance. Despite their low compliance, visual acuity improves to an average of 0.7 (= 0.21 logMAR). This supports the idea that visual acuity improves with little patching, but could also be due to the natural course of visual acuity development.

In general, having established this large study group of over 300 children, it was possible to provide an evaluation of visual acuity outcome, despite the critical note of the referees. However, we feel that testability and co-operation of young children in the current everyday

orthoptic practise may be too unreliable a variable and unsuitable as primary outcome measure for our study design. Nevertheless, when applying standard protocols, e.g. one very experienced orthoptist using only one acuity test (all logMAR scale) for all children in the same consultation room with sufficient testing time available, to measure visual acuity at treatment onset, during treatment and at end of treatment, visual acuity could be used as primary outcome measure.

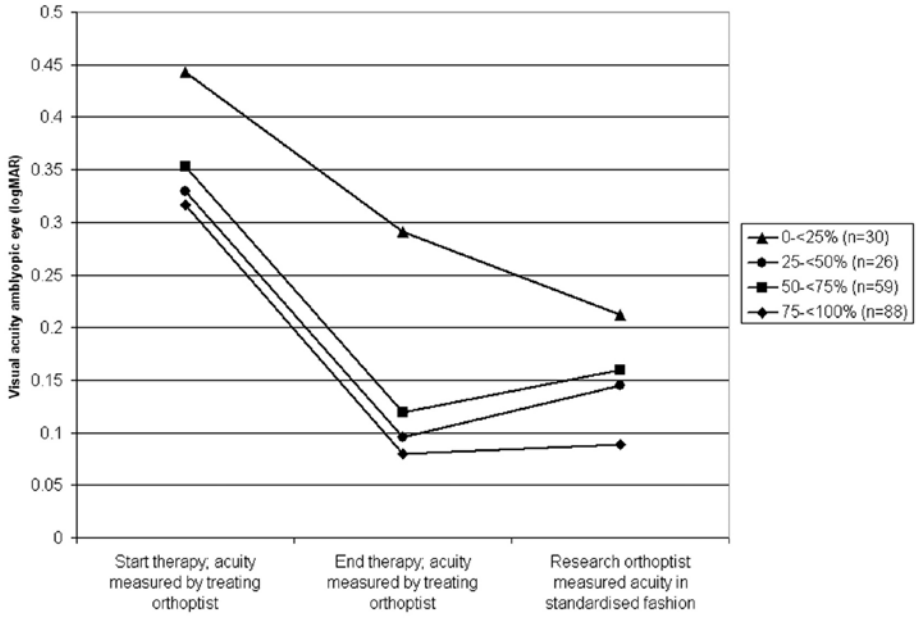


Figure 2. The relationship between visual acuity of the amblyopic eye (logMAR) at the start of treatment as measured by the treating orthoptist, at the end of treatment and the moment the acuity was assessed in a standardised fashion by the research orthoptist, per category compliance. The red line represents patients with poor compliance, the green line with high compliance. The graph illustrates that despite a low level of compliance, visual acuity improves.

Chapter 11

General discussion and future prospects

GENERAL DISCUSSION AND FUTURE PROSPECTS

Amblyopia (a lazy eye) is the most common eye disorder in children. It is usually treated with patching of the non-amblyopic eye preferably before the age of 6. Since Child Health Care Centres in the Netherlands check for strabismus in infants and measure visual acuity at age 3, untreated amblyopia has become a rarity. Nevertheless, one third of the affected children do not reach visual acuity of 6/12 in their amblyopic eye (acuity necessary to read) primarily caused by non-compliance: children and/or their parents do not patch the non-amblyopic eye as prescribed by the orthoptist. This increases the risk of bilateral visual impairment due to loss of vision in the non-amblyopic eye and decreases their quality of life in adulthood.
To date, no study has provided information on which factors influence compliance and whether compliance with occlusion therapy can be improved, in concurrence with the electronic monitoring of that compliance. Therefore, all children with newly diagnosed amblyopia in The Hague were registered in order to determine the effect of clinical, socioeconomic and psychometric factors on compliance. To investigate whether compliance could be improved, an educational programme was developed: included children were randomised to receive either the educational programme (intervention group) or a picture to colour (reference group). The main findings of our research will be discussed and the clinical relevance and future prospects will be considered.

Occlusion therapy

Occlusion therapy for amblyopia has been the mainstay treatment for centuries (Chapter 2). In current orthoptic practice, prescribed occlusion hours range from 15 minutes per day to all waking hours (Tan, et al. 2003). Nevertheless, few guidelines for the prescription exist. Different orthoptists prescribe very different regimens of prescriptions for the same patient and no consistently strict or consistently lenient orthoptists could be identified (Chapter 3). Our study in The Hague found a borderline significant relationship between the number of occlusion hours prescribed by the orthoptist and the actual hours patched by the parents: when the number of prescribed hours increased, compliance decreased and the variation in compliance was larger ($P = 0.058$; $r = 0.512$) (Loudon, et al. 2004). On average, when 6 hours/day had been prescribed, the actual dose received was 3 hours/day. These findings were confirmed by Awan et al. (Awan, et al. 2005). The relationship between the actual hours of patching and the visual acuity improvement was objectively documented by Stewart et al. (Stewart, et al. 2004). They found that 82% of the improvement was achieved during the first 6 weeks of treatment, and 2 hours/day had a similar effect as 6 hours/day, although the children with a higher number of occlusion hours attained a successful outcome level more rapidly. The authors suggested that occlusion regimens of 1 hour/day would have a similar effect on the visual acuity outcome as 2 hours/day or more (Stewart, et al. 2005); a result also found by the recent Amblyopia Treat-

ment Study who compared the visual acuity outcome of 2 hours/day with 6 hours/day (PEDIG 2003). In addition, it seems as though the dose-response appears to be saturated at a level of 100 cumulative hours of occlusion (Stewart, et al. 2005). These findings all emphasise the idea that when compliance is poor, or is expected to be poor, a more flexible approach towards treatment and less intensive patching regimens could offer a solution.

Group at risk for non-compliance

Several studies have provided evidence that the initial visual acuity of the amblyopic eye is a prognostic factor of outcome of treatment (Hiscox, et al. 1992; Lithander and Sjöstrand 1991; Smith, et al. 1995; Stewart, et al. 2005). Children with severe amblyopia have significantly greater residual amblyopia at the end of the treatment than children with mild or moderate amblyopia. This is not unexpected, since we found the initial visual acuity of the amblyopic eye to be the most important clinical parameter for compliance: poor visual acuity caused poor compliance with treatment, explained by the fact that the acceptance of the patch is less when acuity is low (Chapter 7).
In our study population in The Hague the following socioeconomic parameters as predictors for non-compliance were identified: poor parental fluency in the national language, a low level of education and the country of origin. Although country of origin was selected in the multivariate model to be most significant, we cannot exclude the possibility that fluency in the national language and level of education may be the causal factors (both being strongly correlated with the country of origin). Nonetheless, we were able to conclude that families from Surinam, who were either native speakers or otherwise fluent in the Dutch language, showed the same level of compliance as the Dutch families. Therefore, in practice, the fluency in the national language appeared to be the most important factor. In concordance, time spent on explaining the diagnosis and treatment was shorter in patients who were scarcely fluent or did not speak the national language at all, compared to patients who were native or good speakers of the national language. Several factors may have contributed to this observation, e.g. language skills, confidence, assertiveness, education, interests, etc. Patients who lack the confidence to converse in the national language might be inhibited to ask questions, assuming they understand the care givers' explanation of disorder and treatment. Also, in the Netherlands, the time an orthoptist can give a patient varies and is sometimes limited to 15 minutes for a new patient, allowing the orthoptist very little extra time for those less fluent in the native language.

Another common theme of studies into factors affecting compliance with occlusion therapy is that eye patching causes considerable distress for both the family and the child, sometimes with adverse psychological impact on the child. However, outcomes of behavioural measure did not suggest any adverse effect on the child's general well-being either during or after

cessation of treatment (Hrisos, et al. 2004; Parkes 2001). A model employed by Searle et al. based on Protection Motivation Theory (PMT) by Rogers in 1983 proved useful to understand psychosocial factors involved with non-compliance (Norman, et al. 2003; Rogers 1975, 1983; Searle, et al. 2000; 2002). They concluded that many parents experienced distress related to patching therapy and also, that past compliance behaviour was predictive for future compliance behaviour. In our study in The Hague we used this PMT questionnaire to identify the most important psychometric factors influencing compliance. We found the prohibition barriers 'degree of distress' and 'stigma' to negatively influence compliance: when the child cried, got upset or was teased while wearing the patch, parents were afraid this might have a negative influence on their relationship with their child and consequently the patch would come off. An increased ability to 'implement the occlusion therapy into their daily routine' positively influenced compliance, and finally, the 'vulnerability' of their child's eye condition also influenced compliance: when parents were of the opinion that if the eye was left untreated it would affect their child's abilities later in life, compliance increased (Chapter 8). Dixon-Woods et al. interviewed 25 parents whose child was being treated with occlusion therapy for the amblyopic eye (Dixon-Woods, et al. 2006). They described many parents experiencing tensions due to the treatment and were likely to non-comply when no or insufficient improvement in acuity was found. Therefore, they recommended that interventions applied to improve compliance should focus on strategies that parents often already applied themselves.

Improving compliance

Current compliance enhancing programs, aimed at the parents, have been proven to be effective in increasing their understanding of the disease (Goransson, et al. 1998; Newsham 2002). The existing programs aimed at the children contain animal figures that wear eye patches and have exciting adventures. José Vingerling, an artist specialised in art for sick children, thought it was necessary to develop a fully self-explanatory cartoon written from the perspective of a child. The child follows the same course of events as children do in real life: the ophthalmologic examination and the subsequent occlusion therapy. Hence, this made it easier for them to identify themselves with the child in the cartoon. The programme was intended for children from all ethnic, social and cultural backgrounds and was not gender specific. Furthermore, it had no text, as most of the children treated for amblyopia are too young to read. Objective monitoring of compliance in the amblyopic children in The Hague revealed mean compliance to be 78% in the group who received our educational programme as compared to 57% in the group who did not (reference group). Compliance decreased over the 2-year study period on each subsequent electronic measurement, more so in the reference group than in the intervention group, partly due to a selection bias: children with low visual acuity at the start of treatment were less compliant, were therefore patched for a longer period of time and, consequently, were monitored more often. There was considerable variation within and between

the children; we found past compliance behaviour to be an unreliable predictor for future compliance behaviour. The most striking finding of our study was the number of children who did not occlude at all: 3 in the intervention group as compared to 23 in the reference group (Chapter 7). At present, these children are expensive in terms of diagnoses and treatment and in the future, in case the vision in their better eye is lost or decreases. Children who were not occluded at all and children who were, were comparable for clinical parameters. However, there were differences in the level of parental education, country of origin and fluency in the national language. On further examination of the children in whom compliance was less than 20%, it was apparent that there was a clear discrepancy of objective knowledge and the measured knowledge of the parents. This indicated that parents were unaware of their lack of knowledge, therefore could not give feedback or put forward any questions, thus leaving the orthoptist oblivious to the parents' problem. For a small group of parents that what happened at the orthoptists' was the main reason for failing to patch: when no attention could be paid to problems encountered during patching, no questions could be asked or answered and only poor information was supplied, parents were most likely to become non-compliers. A number of parents indicated that visits should be more child-focused. Children were poorly involved in the communication between parent and orthoptist and consequently did not understand the reason they had to be patched. However, the children and families who received the educational programme had better knowledge of the treatment, suffered less distress, and were more able to implement the treatment into their daily routine (Chapter 8).
Therefore, we suggested that the educational programme, explaining reasons for therapy to the child, partially obviated the poor communication between parent and orthoptist.

Future prospects

The research described in this thesis focussed on a method to improve compliance with occlusion therapy for amblyopia and to identify certain risk-factors for non-compliance. We aimed to treat the included children according to standard orthoptic care in The Netherlands. However, performing house-visits and measuring compliance with an ODM the child had to wear on the eye patch during one week, every three months, are not part of standard orthoptic care. Our method had the advantage of the researchers being seen as working independently from the treating orthoptists and, also, that children who no longer visited the clinic remained in the study, but naturally may have affected compliance. For future studies it would be desirable to have visual acuity as primary outcome measure. This would also preclude the problem that in our study compliance was measured only one week out of a possible 12.
The educational programme employed in this study and the risk-factors identified should be made widely available. Future research should therefore focus on the implementation and distribution of the educational programme in the current orthoptic practice. Furthermore, the

orthoptists should be made aware of, and be able to identify the group most at risk for non-compliance and take the appropriate action.

Since the most significant factors that affect compliance were not disease specific (i.e. compliance was found only to be influenced by the initial visual acuity of the amblyopic eye), it seems validated that subsequent research should focus on the development of an educational programme for other enduring treatments for young children, based on the same principles as the programme used in this thesis.

In this thesis the influence of clinical, socioeconomic and psychometric factors on compliance was calculated. The analysis demonstrated that 12% of the variation in compliance could be explained by the socioeconomic and clinical factors. Another 22% of the variation in compliance was explained by the psychological variables. These present results suggest that additional factors need to be included in further studies into compliance behaviour models. Eventually, we aim to proceed to the development of a structural model, exploring the relationships between the factors influencing compliance and the final visual acuity outcome.

References

REFERENCES

Abraham CS, Sheeran P, Abrams D, Spears R. 1994. Exploring teenagers adaptive and maladaptive thinking in relation to the threat of HIV infection. Psychology and Health 9:253-72.

Abraham SV. 1954. Intra-epithelial cysts of the iris. Am J Ophthalmol 37:327-31.

Adams CF. 1914. Adenoids as a factor in amblyopia. Ophthalmol Chicago. 10:264-7.

Allen J. 1730. Synopsis Universae Medicinae Practicae. Westenius Amsterdam.

Ansons AM, Davis H. 2001. Diagnosis and management of ocular motility disorders. Amblyopia.3rd Edition Blackwell Science Ltd, p 213.

Attebo K, Mitchell P, Cumming R, Smith W, Jolly N, Sparkes R. 1998. Prevalence and causes of amblyopia in an adult population. Ophthalmol 105:154-9.

Awan M, Proudlock FA, Gottlob I. 2005. A randomized controlled trial of unilateral strabismic and mixed amblyopia using occlusion dose monitors to record compliance. Invest Ophthalmol Vis Sci 46:1435-9.

Bangerter A. 1946. Behandlung der Amblyopie. Ophthalmologica. 111:220.

Bangerter A. 1953. Amblyopiebehandlung 1 Aufl. Karger, Basel.

Bangerter A. 1960. Die Okklusion in der Pleoptik und Orthoptik. Klin Monatsbl Augenheilkd. 136:305-31.

Banks RV, Campbell FW, Hood C. 1978. A neurophysiological approach to the treatment of amblyopia. J Physiol. 275: 16P.

Bartisch G. 1583. Ophthalmodouleia/Das ist Augendienst. Stoeckel, Dresden.

Bielschowsky A. 1926. Zur Frage der Amblyopia ex anopsia. Klin Monatsbl Augenheilkd 77:302-14.

Birch EE, Stager DR, Berry P, Everett ME. 1990. Prospective assessment of acuity and stereopsis in amblyopic infantile esotropes following early surgery. Invest Ophthalmol Vis Sci 31:758-65.

Boehm L. 1845. Das Schielen und der Sehnenschnitt in seinen Wirkungen auf Stellung und Sehkraft der Augen. Duncker & Hamblot, Berlin.

Bowman RJC, Williamson TH, Andrews RG, Aitchison TC, Dutton GN. 1998. An inner city preschool visual screening programme: long term visual results. Br J Ophthalmol 82:543-8.

Bowman RJC, Bennett HGB, Houston CA, Aitchinson TC, Dutton GN. 1996. Waiting times for and attendance at paediatric ophthalmology outpatient appointments. BMJ 313:1244-6.

Brinker WR, Katz SL. 1963. New and practical treatment of eccentric fixation. Am J Ophthalmol 55:1033-5.

Brown SA, Weih LM, Fu CL, Dimitrov P, Taylor HR, McCarty CA. 2000. Prevalence of amblyopia and associated refractive errors in an adult population in Victoria, Australia. Ophthalmic Epidemiol 7:249-58.

Browning CW, Quinn LH, Crasilneck HG: 1958. The use of hypnosis in suppression amblyopia of children. Am J Ophthalmol 46:53-67.

Buch H, Vinding T, La Cour M, Nielsen NV. 2001. The prevalence and causes of bilateral and unilateral blindness in an elderly urban Danish population. The Copenhagen City Eye Study. Acta Ophthalmol Scand 79:441-9.

Buffon de. 1743. Dissertation sur la cause de strabisme on des yeux louches. Memoires de l'academie royale des sciences Paris.

Burian HM. 1966. Occlusion amblyopia and the development of eccentric fixation in the occluded eyes. Am J Ophthalmol 62:853-7.

Campbell FW, Hess RF, Watson PG, Banks R. 1978. Preliminary results of a physiologically based treatment of amblyopia. Br J Ophthalmol 62:748-55.

Campos E. 1995. Amblyopia: Major Review. Surv Ophthalmol 40:23-39.

Campos EC, Chiesi C, Rozzi N. 1991. Intossicazione da atropina in corso di terapia antiambliopica. G It Ortotte Tec Strum Oft 8:185-8.

Campos EC. 1997. Future directions in the treatment of amblyopia. The Lancet 349:1190.

Ching FC, Parks MM, Friendly DS. 1986. Practical management of amblyopia. J Pediatr Ophthalmol 23: 12-6.

Chopovska Y, Loudon SE, Cirina L, Zubcov A, Simonsz HJ, Lüchtenberg M, Fronius M. 2005. Electronic recording of occlusion treatment for amblyopia: potential of the new technology. Graefes Arch Clin Exp Ophthalmol 243:539-44.

Chua B, Mitchell P. 2004. Consequences of amblyopia on education, occupation, and long term vision loss. Br J Ophthalmol 88:1119-21.

Cibis L. 1974. Penalization, treatment of ARC and amblyopia. Am Orthopt J 25:79-84.

Ciuffreda KJ, Goldner K, Connelly R. 1980. Lack of positive results of a physiologically based treatment of amblyopia. Br J Ophthalmol. 64:607-12.

Ciuffreda KJ, Levi D, Selenow A. 1999. Amblyopia: basic and clinical aspects. Oxford: Butterworth-Heinemann.

Clarke MP, Wright CM, Hrisos S, Anderson JD, Henderson J, Richardson SR. 2003. Randomised controlled trial of treatment of unilateral visual impairment detected at preschool vision screening. BMJ 327:1251-6.

Cleemput I, Kesteloot K. 2002. Economic implications of noncompliance in health care. The Lancet 359:2129-30.

Cobb CJ, Russell K, Cox A, MacEwen CJ. 2002. Factors influencing visual outcome in anisometropic amblyopes. Br J Ophthalmol 86:1278-81.

Cole RBW. 1959. The problems of unilateral amblyopia. A preliminary study of 10,000 national health patients. BMJ. 1:202.

Cole SR, Beck RE, Moke PS, Celano MP, Drews CD, Repka MX, Holmes JM, Birch EE, Kraker RT, Kip KE; Pediatric Eye Disease Investigator Group. 2001. The amblyopia treatment index. J AAPOS 5:250-4.

Comberg W. 1936. Ein Gerät zur Unbung des zentralen Sehens bei funktioneller Schwachsichtigkeit. Zentralbl Ophthalmol 36:369.

Consumers' Organisation the Netherlands. July 2001. Pleisters. 49:66-8.

Corpus Hippokratikum. 1895. Sämmtliche Werke, Hrsg. R. Fuchs, 3Bd. Verlag, Lüneburg, München.

Cowle JB, Kunst JH, Philpotts AM. 1967. Trial with red-filter in the treatment of eccentric fixation. Br J Ophthalmol 51:165.

Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. 1989. How often is medication taken as prescribed? A novel assessment technique. JAMA 261:3273-7.

Crawford MLJ, Noorden GK von, Meharg LS, Rhodes JW, Harwerth RS, Smith EL 3rd, Miller DD. 1983. Binocular neurons and binocular functions in monkeys and children. Invest Ophthalmol Vis Sci 24:491-5.

Crone RA. 1992. Licht, kleur, ruimte: de leer van het zien in historisch perspectief. Bohn Stafleu Van Lochum 103-125.

Cunier F. 2001. Sur la myotomie appliquée au traitement du strabisme. Translated by L Missotten. Strabismus 9;179-95.

Cüppers C. 1956. Moderne Schielbehandlung. Klin Monatsbl Augenheilkd 129:579-604.

Cüppers C. 1961. Grenzen und Möglichkeiten der pleoptischen Therapie. In Hollwich F ed, volume 38: 1-68

Cüppers C. 1967. Ergebnisse der pleoptischen Therapie unter besonderer Berücksichtigung der Dauerresultate. Doc Ophthalmol 23:249-547.

Darier. 1904. Amblyopie aus Nichtgebrauch durch Massage von 1/50 auf 1/3 gebessert. Klin Monatsbl Augenheilkd 42:100-2.

Darwin E. 1779. A new case in squinting. Philos Transact Roy Soc London 68,I,86.

Daw NW. 1998. Critical periods and amblyopia. Arch Ophthalmol 116:502-5.

de Klerk E, van der Linden SJ. 1996. Compliance monitoring of NSAID drug-therapy in ankylosing spondylitis, experiences with an electronic monitoring device. Br J Rheumatol 35:60-5.

Devaux. 1912. Un cas d'amblyopie gueri par le régime de la viande et du vin blanc. J Ophthalmol Provinc 9.

Dieffenbach JF. 1839. Über die Heilung des angeborenen Schielens mittelst Durchschneidung des innern geraden Augenmuskels. Med Zeit Verein Heilk Preussen 8, 227.

DiMatteo RM. 2004. Review. The role of effective communication with children and their families in fostering adherence to pediatric regimens. Patient Educ Couns 55:339-44.

Dixon-Woods M, Awan M, Gottlob I. 2006. Why is compliance with occlusion therapy for amblyopia so hard? A qualitative study. Arch Dis Child 91:491-4.

Donders FC. 1864. On the anomalies of accommodation and refraction of the eye. London: The new Sydenham society. Vol.22.

Dorey SE, Adams GGW, Lee JP, Sloper JJ. 2001. Intensive occlusion therapy for amblyopia. Br J Ophthalmol 85:310-3.

Dunbar JM. 1983. Compliance in pediatric populations: a review. Pediatric and adolescent behavioral medicine. McGrath PJ and Taylor CB, editors. New York: Spectrum; 3:115-45.

Epelbaum M, Milleret C, Buisseret P, Dufier JL. 1993. The sensitive period for strabismic amblyopia in humans. Ophthalmol 100:323-7.

Farley J, Hines S, Musk A, Ferrus S, Tepper V. 2003. Assessment of adherence to antiviral therapy in HIV-infected children using the Medication Event Monitoring System, pharmacy refill, provider assessment, caregiver self-report, and appointment keeping. J Acquir Immune Defic Syndr 33:211-18.

Fawcett SL, Wang YZ, Birch EE. 2004. The critical period for susceptibility of human stereopsis. Invest Ophthalmol Vis Sci 46:521-5.

Fielder AR, Irwin M, Auld R, Cocker KD, Jones HS, Moseley MJ. 1994. Compliance monitoring in amblyopia therapy. The Lancet 343:547.

Fielder AR, Irwin M, Auld R, Cocker KD, Jones HS, Moseley MJ. 1995. Compliance in amblyopia therapy: objective monitoring of occlusion. Br J Ophthalmol 79:585-9.

Fleck BW. 2003. Amblyopia therapy. Br J Ophthalmol 87:255-6.

Fletcher MC, Silverman SJ, Boyd J, Callaway M. 1969. Biostatistical Studies: Comparison of the Management of Suppression Amblyopia by Conventional patching, Intensive Hospital Pleoptics and Intermittent Office Pleoptics. Am Orthopt J 19:40-7.

Flynn JT, Cassady JC. 1978. Current trends in amblyopia therapy. Ophthalmol 85:428-50.

Flynn JT, Woodruff G, Thompson JR, Hiscox F, Feuer W, Schiffman J, Corona A, Smith LK. 1999. The therapy of amblyopia: an analysis comparing the results of amblyopia therapy utilizing two pooled data sets. Trans Am Ophthalmol Soc 97:373-90.

Flynn ME, Lyman RD, Prentice-Dunn S. 1995. Protection motivation theory and adherence to medical treatment regimens for muscular dystrophy. J of Soc and Clin Psychol 14:61-75.

Foley-Nolan A, McCann A, O'Keefe M: 1997. Atropine penalisation versus occlusion as the primary treatment for amblyopia. Br J Ophthalmol. 81:54-7.

Fralick FB. 1943. The treatment of amblyopia. Am J Ophthalmol 26:1195-8.

Fricker SJ, Kuperwaser MC, Stromberg AE, Goldman SG. 1980. A study of a modified "stripe therapy" for amblyopia. Invest Ophthalmol Vis Sci 19 (ARVO abstracts): 143.

Fronius M, Chopovska Y, Nolden J, Loudon SE, Luchtenberg M, Zubcov A, Pepler L. 2006. Occlusion treatment for amblyopia: assessing the performance of the electronic occlusion dose monitor. Strabismus 14:65-70.

Fronius M, Cirina L, Cordey A, Ohrloff C. 2005. Visual improvement during psychophysical training in an adult amblyopic eye following visual loss in the contralateral eye. Graefes Arch Clin Exp Ophthalmol 243:278-80.

Fruin DJ, Pratt C, Owen N. 1991. Protection motivation theory and adolescents' perceptions of exercise. J of Appl Soc Psychol 22:55-69.

Fuchs E. 1928. Aus meiner augenärtzlichen Praxis. Festschrift der Univ-Augenklinik in Zagreb.

Gifford SR. 1935. Some notes on the treatment of strabismus. Br J Ophthalmol 19:148-151.

Goransson A, Dahlgren LO, Lennerstrand G. 1998. Changes in conceptions of meaning, effects and treatment of amblyopia. A phenomenographic analysis of interview data from parents of amblyopic children. Patient Educ Couns 34:213-25.

Graaf van de ES, Sterre van der GW, Polling JR, Kempen van H, Simonsz B, Simonsz HJ. 2004. Amblyopia & Strabismus Questionnaire: design and initial validation. Strabismus 12:181-93.

Graefe A v. 1854. Beiträge zur Physiologie und Pathologie der schiefen Augenmuskuln. Arch. Ophthalmol (Graefe) 1,I,1.

Graefe A. 1854. Schwachsichtigkeit bei Schielenden und Behandelung des Schielens mittels stereoskop. Übungen Graefe-Saemisch Hb ges Augenheilkd, vol 6. Leipzig, Engelmann: 110-115; 142.

Gräf M. 2004. Strategien der Visusbestimmung. Klin Monatsbl Augenheilkd 221:557-65.

Haase W, Wenzel F. 1996. The natural course of untreated functional amblyopia: Does it progress between childhood and adulthood? Binoc Vis Strab Quart 12:17-24.

Haase W. 1995. Amblyopie. In Kaufmann H., ed. Strabismus, 2nd ed. Stuttgart: Ferdinand Enke Verlag, 283-395.

Ham O, Claramunt M, Diasz T. 1985. Strabismic amblyopia final results of occlusion treatment in 205 cases. Binocular Vision 1:195-9.

Hardesty HH. 1959. Occlusion amblyopia. Report of a case. Arch Ophthalmol 63:314.

Helmholtz H. 1851. Beschreibung eines Augenspiegels zur Untersuchung der Netzhaut im lebenden Auge. Jean Renaud, Berlin.

Helveston EM. 1963. The incidence of amblyopia ex anopsia in young adult males in Minnesota in 1962-1963. Am J Ophthalmol 60:75-82.

Hiles DA, Galket RJ. 1974. Plaster cast arm restrains and amblyopia therapy. J Ped Ophthalmol 11:151-2.

Hiscox FN, Strong N, Thompson JR, Minshull C, Woodruff G. 1992. Occlusion for amblyopia: a comprehensive survey of outcome. Eye 6:300-4.

Holbach HT, Noorden GK von, Avilla CW. 1991. Changes in esotropia after occlusion therapy in patients with strabismic amblyopia. J Pediatr Ophthalmol Strabismus 28:6-12.

Holmes JM, Kraker RT, Beck RW, Birch EE, Cotter SA, Everett DF, Hertle RW, Quinn GE, Repka MX, Scheiman MM, Wallace DK; Pediatric Eye Disease Investigator Group. 2003. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmol 110:2075-87.

Hsiros S, Clarke MP, Wright CM. 2004. The emotional impact of amblyopia treatment in preschool children. Ophthalmol 111:1550-6.

Jablonski M, Tomlinson E. 1979. A new look at pleoptics. Ophthalmol 86:2112-4.

Javal E. 1896. Manuel théoretique et practique du strabisme. Paris, Masson, 91-97.

Jensen H, Goldschmidt E. 1986. Visual Acuity in Danish schoolchildren. Acta Ophthalmol 64:187-91.

Johnson DS, Antuna J. 1965. Atropine and miotics for treatment of amblyopia. Am J Ophthalmol 60:889-91.

Juttmann RE. 2001. The Rotterdam AMblyopia Screening Effectiveness Study (RAMSES): compliance and predictive value in the first 2 years. Br J Ophthalmol 85:1332-5.

Kass MA, Gordon M, Meltzer DW. 1986. Can ophthalmologists correctly identify patients defaulting from pilocarpine therapy? Am J Ophthalmol 101:524-30.

Kass MA, Gordon M, Morley RE, Meltzer DW, Goldberg JJ. 1987. Compliance with topical timolol treatment. Am J Ophthalmol 103:188-93.

Kass MA, Meltzer D, Gordon M, Cooper D, Goldberg J. 1986. Compliance with topical pilocarpine treatment. Am J Ophthalmol 101:515-23.

Kaye SB, Chen SI, Price G, Kaye LC, Noonan C, Tripathi A, Ashwin P, Cota N, Clark D, Butcher J. 2002. Combined optical and atropine penalization for the treatment of strabismic and anisometropic amblyopia. J AAPOS 6:289-93.

Keeler CK. 2002. The ophthalmoscope in the lifetime of Hermann von Helmholtz. Arch Ophthalmol 120:194-201.

Keith CG, Howell ER, Mitchell DE, Smith S. 1980. Clinical trial of the use of rotating grating patterns in the treatment of amblyopia. Br J Ophthalmol 64:597-606.

Knapp P, Capobianco NM. 1956. Use of miotics in esotropia. Am Orthopt J 6:40-6.

Koselka PU, Mikkola T, Laatikainen L. 1991. Permanent results of pleoptic treatment. Acta Ophthalmol Scand 69:39-44.

Krecke FWC. 1847. Over eene nieuwe soort van brillen voor scheelzienden. Nederlandsch Lancet 227-45.

Lantau VK, Juttmann RE, van der Maas PJ. 1991. State of the Rotterdam Amblyopia Screening Evaluation Study (RAMSES). Trans IX Orthoptic Cong, Stockholm, p39-41.

Leeuwen van R. 2002. Altersabhängige Prävalenz von bilateralen Sehbehinderungen bei unbehandelten Amblyopen aufgrund einer prospektiven Bevölkerungs-Kohortstudie. Poster, 9. Meeting Bielschowsky-Gesellschaft für Schielforschung, Heidelberg.

Leiba H, Shimshoni M, Oliver M, Gottesman N, Levartovsky S. 2001. Long-term follow-up of occlusion therapy in amblyopia. Ophthalmol 108:1552-5.

Levartovsky S, Oliver M, Gottesman N, Shimshoni M. 1995. Factors affecting long term results of successfully treated amblyopia: initial visual acuity and type of amblyopia. Br J Ophthalmol 225–8.

Linksz A. 1961. Theory of pleoptics. Int Ophthalmol Clin 1. 747-85.

Lithander J, Sjöstrand J. 1991. Anisometropic and strabismic amblyopia in the age group 2 years and above: a prospective study of the results of treatment. Br J Ophthalmol 75:111-6.

Losada F. 1964. Consideaciones sobre la amblyopia funcional y su tratamiento por la oclusion o la blefarorrafia. Arch Soc Hisp Am 24:568-86.

Loudon SE, Fronius M, Looman CWN, Awan M, Simonsz B, van der Maas PJ, Simonsz HJ. 2006. Predictors and a remedy for non-compliance with amblyopia therapy in children measured with the Occlusion Dose Monitor. Invest Ophthalmol Vis Sci 47:4393-400.

Loudon SE, Polling JR, Simonsz B, Simonsz HJ. 2004. Objective survey of the prescriptions of occlusion therapy for amblyopia. Graefes Arch Clin Exp Ophthalmol 242:736-40.

Loudon SE, Polling JR, Simonsz HJ. 2003. Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase. Graefes Arch Clin Exp Ophthalmol 241: 176-80.

Loudon SE, Simonsz B, Joosse MV, Fronius M, Awan M, Newsham D, Harrad RA, Simonsz HJ. 2004. Electronic Recording of Patching for Amblyopia Study: predictors for non-compliance. Ann Meet Abstr Progr Planner (www.arvo.org) Ass Res Vision & Ophthalmol. E-Abstract 4991.

Loudon SE, Simonsz HJ. The history of the treatment of amblyopia. Strabismus 2005;13(2):93-106.

Loudon SE, Verhoef BL. Polling JR, Simonsz HJ. 2002. Amblyopic children with low compliance measured electronically have insufficient acuity increase. Ann Meet Abstr Progr Planner (www.arvo.org) Ass Res Vision & Ophthalmol. E-Abstract 4696.

Lowe RF. 1965. Atropine treatment for amblyopia ex anopsia. Br Orthopt J 22:35-42.

Mackensen G, Kröner B, Postic G. 1965. Zur Änderung der exzentrischen Fixation unter der Okklusionsbehandlung. Klin Monatsbl Augenheilkd 147:213-30.

Maddox M. 1931. The orthoptic treatment of strabismus. Trans Ophthal Soc UK 51:296-307.

Malik SR, Virdi PS, Goel BK. 1975. Follow-up results of occlusion and pleoptic treatment. Acta Ophthalmol (Copenh) 53:620-6.

Malik SRK, Gupta AK, Choudry S. 1966. The red-filter treatment of eccentric fixation. Am J Ophthalmol 67:586-90.

Massie H. 1965. Fixing eye for occlusion: survey of 1,000 cases of patients receiving occlusion of the fixing eye. Trans Ophthalmol Soc Aust 24:39-46.

McKenney S, Byers M. 1975. Aspects and results of penalization treatment. Am Orthopt J 25:85-9.

Mehdorn E, Mattheus S, Schuppe A, Klein U, Kommerell G. 1981. Treatment for amblyopia with rotating gratings and subsequent occlusion therapy: a controlled study. Int Ophthalmol 3:161-6.

Mein J, Trimble R. 1991. Diagnosis and management of ocular motility disorders. 2nd ed. Oxford: Blackwell Scientific.

Metzler U, Ham O, Flores V, Claramunt M, Sepulveda C, Casanova D. 1998. Blue filter amblyopia treatment protocol for strabismic amblyopia: a prospective comparative study of 50 cases. Binocul Vis Strabismus Q 13:241-8.

Meyer E, Mizrahi E, Perlman I. 1991. Amblyopia success index – a new method of quantitative assessment of treatment efficiency, application in a study of 473 anisometropic amblyopic patients. Binocular Vision Quarterly 6:83-90.

Milgrom H, Bender B, Ackerson L, Bowry P, Smith B, Rand C. 1996. Noncompliance and treatment failure in children with asthma. J Allergy Clin Immunol 98:1051-7.

Mintz-Hittner HA, Fernandez KM. 2000. Successful amblyopia therapy initiated after age 7 years. Arch Ophthalmol 118:1535-41.

Mitchell DE. 1991. The long-term effectiveness of different regimes of occlusion on recovery from early monocular deprivation in kittens. Philosophical Trans R Soc Lond Series 333:51-79.

Moseley MJ, Fielder AR. Irwin M, Jones HS, Auld RJ. 1997. Effectiveness of occlusion therapy in ametropic amblyopia: a pilot study. Br J Ophthalmol 81:956-61.

Moseley MJ, Fielder AR, Stewart CE, Stephens DA, The MOTAS Cooperative. 2001. Design of the Monitored Occlusion Treatment for Amblyopia Study (MOTAS) Invest Ophthalmol Vis Sci 42:S399.

Nawratzki I, Oliver M. 1971. Eccentric fixation managed with inverse prism. Am J Ophthalmol 71:549-52.

Neubauer AS, Neubauer S. 2005. Kosteneffektivität von Screening auf Amblyopie. Klin Monatsbl Augenheilkd 222:110-6.

Newsham D. 2002. A randomised controlled trial of written information: the effect on parental non-concordance with occlusion therapy. Br J Ophthalmol 86:0-4.

Noorden GK von, Campos EC. 2002. Binocular Vision and Ocular Motility, 6th Edition. Mosby Inc. St. Louis Chapter 14:247-97.

Noorden GK von, Lipsius RMC. 1964. Experiences with pleoptics in 58 patients with strabismic amblyopia. Am J Ophthalmol 58:41-51.

Noorden GK von, Milani JB. 1979. Penalization in the treatment of amblyopia. Am J Ophthalmol 88:511-8.

Noorden GK von. 1967. Classification of Amblyopia. Am J Ophthalmol 63:238.

Noorden GK von. 1985. Amblyopia: A multidisciplinary approach (Proctor Lecture). Invest Ophthalmol Vis Sci 26:1704-16.

Noorden von GK, Campos EC. 2002. Binocular Vision and Ocular Motility, 6th Edtion. Mosby Inc. St. Louis. Chapter 24:537-58.

Noorden von GK, Campos EC. 2002. Principles of Nonsurgical Treatment, 6th ed. St. Louis: CV Mosby, Inc, 537-58.

Norell SE, Granstrom PA. 1980. Self-medication with pilocarpine among outpatients in a glaucoma clinic. Br J Ophthalmol 64:137-41.

Norman P, Searle A, Harrad RA, Vedhara K. 2003. Predicting adherence to eye patching in children with amblyopia: An application of protection motivation theory. Br J Health Psychology 8:67-82.

North RV, Kelly ME. 1991. Atropine occlusion in the treatment of strabismic amblyopia and its effect on the non-amblyopic eye. Ophthalmic Physiol Opt 11:113-7.

Ohlsson J, Baumann M, Sjostrand J, Abrahamsson M. 2002. Long term visual outcome in amblyopia treatment. Br J Ophthalmol 86:1148-51.

Packwood EA, Cruz OA, Rychwalski PJ, Keech RV. 1999. The Psychosocial Effects of Amblyopia Study. J AAPOS 3:15-7.

Parkes LC. 2001. An investigation of the impact of occlusion therapy on children with amblyopia, its effect on their families, and compliance with treatment. Br Orthopt J 58:30-7.

Parks MM, DS Friendly. 1966. Treatment of eccentric fixation in children under four years of age. Am J Ophthalmol 61:395-8.

Paroisse Saint Antoine des Quinze-Vingts. Histoire. http://perso.wanadoo.fr/saqv/hop_histoire.htm

Parrish JM. 1986. Parent compliance with medical and behavioral recommendations. Child health behavior: A behavioral pediatrics perspective. Krasnegor NA, Arasteh JD, Cataldo MF, editors. New York: Wiley 453-501.

Paulos von Aegina. 1914. Des besten Arztes. Sieben Bücher. Translated and edited by I. Berendes. Verlagsbuchhandlung vormals E.J. Brill. Leiden.

Pfandl E. 1958. Ein neuer Weg zur Verhinderung der Ausbildung einer anomalen retinalen Korrespondenz bei Strabismus convergens concomitans. Acta XVIII Concilium Ophthalmologicum Belgica. 1:82-5.

Pigassou R, Garipuy J. 1966. Essai d'Interprétation du Mécanisme d'Action du Traitement de la fixation excentrique par le prisme calibré et l'occlusion totale. Ann. Oculist (Paris) 201:270-8.

Pigassou R, Garipuy J. 1966. Traitement Excentrique de la Fixation Strabique par le Port d'un Prisme et l'Occlusion. Bull. Mém. St'é Française Ophth 79:367-82.

Pigassou R, Garipuy J. 1967. Treatment of Eccentric Fixation. J Ped Ophthalmol 4:35-42.

Pope LJ. 1971. Treatment of eccentric fixation without occlusion. Br Orthoptic J 28:77-82.

Poulard M. 1921. Amblyopie par strabisme. Ann Ocul 158:95-100.

Pouliquen P. 1964. Sur correction optique et angle strabique. Bull Soc Ophthalmol Fr 64:742-5.

Pouliquen P. 1972. Zum Problem der Penalisation. Klin Monatsbl Augenheilkd 161:130-9.

Priestley BS. 1961. Pleoptic instruments and methods. Int Ophthalmol Clin 1. 787-801.

Quéré MA, Rossazza C, Delplace MP. 1969. Les techniques de pénalisation à la période pré-orthoptique du strabisme convergent. Bull Soc Ophthalmol Fr 69:365-9.

Quéré MA. 1972. Die Methoden der Penalisation in der Behandlung des Strabismus convergens. Klin Monatsbl Augenheilkd 161:140-6.

Rahi JS, Logan S, Timms C, Russell-Eggitt I, Taylor D. 2002. Risk, causes, and outcomes of visual impairment after loss of vision in the non-amblyopic eye: a population-based study. The Lancet 360:597-601.

Rassow B, Wang Y. 1999. Anschluß von Buchstaben-Optotypen an den Landolt-Ring für verschiedene Bereiche der Sehschärfe. Klin Monatbl Augenheilkd 215:119-126.

Ratiu E, Reiter E. 1966. Results obtained with the red filter method in the treatment of amblyopia with eccentrische fixation. J Ped Ophthalmol 3:28-30.

Repka MX, Ray JM. 1993. The efficacy of optical and pharmacological penalization. Ophthalmol 100:769-75.

Richter S. 1960. Erfahrungsbericht über pleoptische und orthoptische Behandlungsergebnisse. Klin Monatsbl Augenheilkd 137:155-60.

Rippertoe PA, Rogers RW. 1987. Effects of components of protection motivation theory on adaptive and maladaptive coping with a health threat. J of Personality and Social Psychology 52:596-604.

Robb RM. 1977. Refractive errors associated with hemangiomas of the eyelids and orbit in infancy. Am J Ophthalmol 83:52-8.

Rogers RW. 1975. A protection motivation theory of fear appeals and attitude change. J of Psychology 91:93-114.

Rogers RW. 1983. Cognitive and psychological processes in fear appeals and attitude change: A revised theory of protection motivation. In B.L. Cacioppo, L.L. Petty & D. Shapiro (Eds), Social Psychophysiology: A Sourcebook. London: Guilford Press.

Rudman LA, Gonzales MH, Borgida E. 1999. Mishandling the gift of life: Non-compliance in renal transplant patients. J of Soc and Appl Psychol 29:834-51.

Saint-Yves de C. 1722. Des yeux louches. Noveau traité des maladies des yeux. Paris: Pierre-Augustin le Mercier 118-123.

Sattler CH. 1927. Erfahrungen über die Beseitigung der Amblyopie und die Wiederherstellung des binokularen Sehakts bei Schielenden. Z Augenheilkund 63:19-37.

Schlossman A. 1961. Prognosis, management and results of pleoptic treatment. Int Ophthalmol Clin 1. 829-40.

Schmidt D, Stapp M. 1977. Uber die Wirkung der Euthyskop und Okklusionsbehandlung beim Konvergenzschielen. Klin Monatsbl Augenheilkd 171:105-16.

Schor C, Gibson J, Hsu M, Mah M. 1981. The use of rotating grating patterns for the treatment of amblyopia: a clinical trial. Am J Optom Physiol Opt 58:930-8.

Schröpfer H-D, Meinert K. 1975. Spätergebnisse in der Amblyopiebehandlung. Klin Monatsbl Augenhkd 166:315-20.

Schweigger C. 1885. Amblyopie und Amaurose. Handbook der Augenheilkd, ed. 5. Berlin, Hirschwald 508-27.

Scott WE, Dickey CF. 1988. Stability of visual acuity in amblyopic patients after maturity. Graefe's Arch Clin Exp Ophthalmol 226:154-7.

Searle A, Norman P, Harrad RA, Vedhara K. 2002. Psychosocial and clinical determinants of compliance with occlusion therapy for amblyopic children. Eye 16:155-5.

Searle A, Vedhara K, Norman P, et al. 2000. Compliance with eye patching in children and its psychosocial effects: A quantative application of protection motivation theory. Psychology, Health and Medicine 43-54.

Simmers AJ, Gray LS, McGraw PV, Winn B. 1999. Functional visual acuity loss in amblyopia and the effect of occlusion therapy. Invest Ophthalmol Vis Sci 40:2859-71.

Simons K, Gotzler KC, Vitale S. 1997. Penalization versus part-time occlusion and binocular outcome in treatment of strabismic amblyopia. Ophthalmol 104:2156-60.

Simons K, Preslan M. 1999. Natural history of amblyopia untreated owing to lack of compliance. Br J Ophthalmol 83:582-7.

Simons K. 1996. Preschool vision screening: rationale, methodology and outcome. Surv Ophthalmol 41:3-30.

Simonsz HJ, Polling JR, Voorn R, van Leeuwen J, Meester H, Romijn C, Dijkstra BG. 1999. Electronic monitoring of treatment compliance in patching for amblyopia. Strabismus 7:123-33.

Simonsz HJ, Polling JR. 2001. Clinical use of electronic monitoring of patch wearing in amblyopia. Ann Meet Abstr Progr Planner (www.arvo.org) Ass Res Vision & Ophthalmol. E-Abstract 399.

Simonsz HJ. 2001. Call for collaborators on compliance measurements in amblyopia patching.

Sjöstrand J, Abrahamsson M. 1997. Prevention of amblyopia and the concept of cure. Eur J Ophthalmol 7:121-9.

Smith LK, Thompson JR, Woodruff G, Hiscox F. 1995. Factors affecting treatment compliance in amblyopia. J Pediatr Ophthalmol Strabismus 32:98-101.

Snowdon SK, Stewart-Brown SL. 1997. Preschool Vision Screening: Results of a Systematic Review. York Publishing Services Ltd.: University of York. NHS Centre for Reviews and Dissemination.

Sparrow JC, Flynn JT. 1977. Amblyopia: a long-term follow-up. J Pediatr Ophthalmol 14:333-6.

Stenius S. 1935. Sehübungen bei Schielamblyopie und ihre Ergebnisse. Zentralbl Ophthalmol 33:683.

Stewart CE, Fielder AR, Moseley MJ, Stephens DA, MOTAS Cooperative. 2002. Dose-response relationship for occlusion therapy for the treatment of amblyopia: initial results from the MOTAS Study. Ann Meet Abstr Progr Planner (www.arvo.org). Ass Res Vision & Ophthalmol. E-Abstract 2939.

Stewart CE, Fielder AR, Stephens DA, Moseley MJ. 2002. Design of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Br J Ophthalmol 86:915-9.

Stewart CE, Fielder AR, Stephens DA, Moseley MJ. 2005. Treatment of unilateral amblyopia: factors influencing visual outcome. Invest Ophthalmol Vis Sci 46:3152-60.

Stewart CE, Moseley MJ, Fielder AR, Stephens DA, ROTAS Cooperative. 2004. Optimisation of the dose-response of occlusion therapy for amblyopia: the ROTAS study. 2002 Ann Meet Progr Planner (www.arvo.org). Assoc Res Vision Ophthalmol. E-Abstract 2579.

Stewart CE, Moseley MJ, Stephens DA, Fielder AR, MOTAS Cooperative. 2004. Treatment dose-response in amblyopia therapy: The Monitored Occlusion Treatment of Amblyopia Study (MOTAS). Invest Ophthalmol Vis Sci 45:3048-54.

Stromeyer GFL. 1838. Beiträge zur Operativen Orthopädik. Helwing, Hannover.

Swann AP, Hunter CD. 1974. A survey of amblyopia treated by atropine occlusion. Br Orthopt J 31:65-9.

Tan JHY, Thompson JR, Gottlob I. 2003. Differences in the management of amblyopia between European countries. Br J Ophthalmol 87:291-6.

Taylor J. 1756. Dissertazione sopra l'arte di ristabilire la sana posizione degli occhi, prodotta da un vizio conosciuto sotto nome di strabismo. Malatesta, Mailand.

Thabit Ibn Qurrah. 1991. Vision and perception. Translated by MZ Wafai. Riyadh, Saudi-Arabia. Obiekan Publishing House.

The Pediatric Eye Disease Investigator Group. 2002. A randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. Arch Ophthalmol 120:268-78.

The Pediatric Eye Disease Investigator Group. 2002. The clinical profile of moderate amblyopia in children younger than 7 years. Arch Ophthalmol 120:281-7.

The Pediatric Eye Disease Investigator Group. 2003. A randomized trial of patching regimens for treatment of moderate amblyopia in children. Arch Ophthalmol 121:603-11.

The Pediatric Eye Disease Investigator Group. 2003. A randomized trial of prescribed patching regimens for treatment of severe amblyopia in children. Ophthalmol 110:2075-87.

The Pediatric Eye Disease Investigator Group. 2003. Impact of patching and atropine treatment on the child and family in the Amblyopia Treatment Study. Arch Ophthalmol 121:1625-32.

The Pediatric Eye Disease Investigator Group. 2004. A randomized trial of atropine regimens for treatment of moderate amblyopia in children. Ophthalmol 111:2076-85.

The Pediatric Eye Disease Investigator Group. 2005. Two-year follow-up of a 6-months randomized trial of atropine vs. patching for treatment of moderate amblyopia in children. Arch Ophthalmol 123:149-57.

Theodore FH, Johnson RM, Miles NE, Bonser WH. 1946. Causes of impaired vision in recently inducted soldiers. Arch Ophthalmol 31:309-12.

Thorleifsson H. 1966. Red filter in the treatment of eccentric fixation. Acta Ophthal 44:57.

Timmerman GJMEN. 1977. The results of penalization. Doc Ophthalmol 42:385-9.

Tommila V, Tarkkanen A. 1981. Incidence of loss of vision in amblyopia after loss of the good eye. Br J Ophthalmol 65:525-7.

Tripathi A, O'Donnell N, Holden R, Kaye L, Kaye SB. 2002. Occlusion therapy for the treatment of amblyopia: Letting the parents decide. Ophthalmologica 216:426-9.

Tytla ME, Labow-Daily LS. 1981. Evaluation of the CAM treatment for amblyopia: a controlled study. Invest Ophthalmol Vis Sci 20:400-6.

Uhthof W. 1927. Zur "Schiel-amblyopie". Klin Monatsbl Augenheilkd 78:453-60.

Urquhart J, Klerk de E. 1998. Contending paradigms for the interpretation of data on patient compliance with therapeutic drug regimens. Stat Med 17:251-67.

Urquhart J. 1992. Ascertaining how much compliance is enough with outpatient antibiotic regimens. Postgrad Med J 68 Suppl 3:S49-S59.

Urquhart J. 2002. The odds of the three nons when an aptly prescribed medicine isn't working: non-compliance, non-absorption, non-response.Br J Pharmacol 54:212-20.

Velde van der FW, Pligt van der LS. 1991. Aids-related health-behaviour: Coping, protection motivation and previous behaviour. J of Behavioural Medicine 14:429-51.

Véronneau-Troutman S, Schudel Dayanoff S, Stohler T, Clahane AC. 1974. Conventional occlusion vs. pleoptics in the treatment of amblyopia. Am J Ophthalmol 78:117-120.

Vinding T, Gregersen E, Jensen A, Rindziunski E. 1991. Prevalence of amblyopia in old people without previous screening and treatment. Acta Ophthalmol 69:796-8.

Wallman J, Turkel J, Trachtman J. 1978. Extreme myopia produced by modest change in early visual experience. Science 201:1249-50.

Weckert F. 1929. Zur Bekampfung der Schielamblyopie. Klin Monatsbl Augenheilkd 82:240-241.

Weckert F. 1932. Neue Wege zur Bekämpfung der Schielamblyopie. Klin Monatsbl Augenheilkd 88:818-9.

Weiss JB, Bourrie F. 1968. Pénalisation de l'œil dominant. Ann Ocul 201:827-31.

Wiesel TN, Hubel DH. 1963. Effects of visual deprivation on morphology and physiology of cells in the cat's lateral geniculate body. J Neurophysiol 26:978-93.

Wiesel TN, Hubel DH. 1963. Single-cell responses in striate cortex of kittens deprived of vision in one eye. J Neurophysiol 1002-17.

Wiesel TN, Hubel DH. 1965. Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. J Neurophysiol 28:1029-40.

Williams C, Northstone K, Harrad RA, Sparrow JM, Harvey I, ALSPAC Study Team. 2002. Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial. BMJ 324:1549-51.

Willshaw HE, Malmheden A, Clarke J, Williams A, Dean L. 1980. Experience with the CAM vision stimulator: preliminary report. Br J Ophthalmol 64:339-41.

Woodruff G, Hiscox F, Thompson JR, Smith LK. 1994. Factors affecting the outcome of children treated for amblyopia. Eye 8:627-31.

Woodruff G. 1995. Amblyopia: could we do better? BMJ 310:1153-54.

Worth C. 1901. Squint: its causes, pathology and treatment. London: John Bale, Sons & Danielsson.

Worth CA. 1903. Squint: its causes, pathology and treatment. 1st Edition John Bale, Sons&Danielsson.

Wright EC. 1993. Non-compliance-or how many aunts has Mathilda? The Lancet 342:909-13.

Summary / Samenvatting

SUMMARY

In this thesis the following questions concerning the occlusion treatment for amblyopia using an eye patch, were addressed: guidelines for prescribing a certain number of occlusion hours, the course of visual acuity after cessation of occlusion therapy, and the relationship between compliance and visual acuity increase. Then it was determined which factors influenced compliance with occlusion therapy for amblyopia and whether compliance could be improved.

Compliance is an important factor for treatment success. It is generally referred to as the degree of correspondence between the patients' dosage or behaviour and recommendations from the health care provider. Poor compliance decreases the effectiveness of treatment and increases costs to the health care system. Amblyopia (a lazy eye, prevalence 3.25%) is defined as a diminished acuity in one eye. It is caused by strabismus, anisometropia and/or visual deprivation. By occluding the non-amblyopic eye for several hours per day, preferably before the age of six, a permanent deterioration in the acuity of the amblyopic eye can be prevented. Despite screening at the Child Health Care Centres and an effective treatment by the orthoptist, the amblyopia persists in approximately a third of the affected children, primarily caused by non-compliance.
Since the development of the Occlusion Dose Monitor (ODM) by Fielder and Moseley in 1991, compliance with occlusion therapy for amblyopia can be measured electronically and therefore objectively. The design of the Fielder-ODM was modified by the Medical Technical Department of the Academic Medical Center Amsterdam. It measures the temperature difference between the front and the back of the ODM every two minutes and is attached to the front of the patch on the eye by double sided tape.

In the introduction, **chapter 1,** the objective of this thesis is discussed and special attention is given to previous studies of other (eye) diseases that used electronic monitoring to measure compliance.

Chapter 2 provides an historical overview of the discussion, which has continued for the past three centuries, as to the optimal treatment for amblyopia. The first treatment described for amblyopia, as found in the literature, was the eye patch. This was described by Charles de Saint-Yves in Paris in 1722, and not by the person usually credited for the introduction of occlusion therapy: George Comte de Buffon (1743). Besides the eye patch, various other treatment methods have been ventured (i.e. atropine treatment).

Few guidelines exist when prescribing a certain number of occlusion hours and the treatment is more or less 'practice based'. Consequently, for a child with a given age and acuity, the prescribed occlusion hours may vary from a few minutes per day to all waking hours. An

inventory of the variation in the prescription of occlusion therapy is described in **chapter 3**. A questionnaire was designed with five case examples of amblyopic children. It was completed by 404 orthoptists simultaneously and in complete silence during two national orthoptic meetings in the Netherlands and Germany. The variation in the number of prescribed hours of occlusion was large. In addition, the orthoptists were not consistently strict or lenient in their prescription of occlusion therapy.

There is a world-wide discussion on the subject of the course of the visual acuity after cessation of occlusion therapy at the age of approximately eight years. **Chapter 4** describes a historical cohort of 137 patients who were treated for their amblyopia 30 years ago and were orthoptically re-examined in 2003. In general, in most patients the acuity in the amblyopic eye had increased after cessation of occlusion therapy. However, when the amblyopia was caused by both strabismus and anisometropia, or when the anisohypermetropia had increased during the years, acuity in the amblyopic eye had decreased.

Chapter 5 considers the reliability and limitations of the ODM. The ODM was found satisfactorily reliable to be able to differentiate between measurements on the eye and on other parts of the body. However, the ODM placed elsewhere on the head (i.e. the forehead) and a high ambient temperature (> 33°C) prevented a reliable ODM measurement.

Chapter 6 describes a pilot study that preceded the study in The Hague. This study confirmed the assumption that a higher level of compliance was correlated with a better improvement in visual acuity.

Chapters 7 to 10 describe the main study of this thesis, in which risk factors for non-compliance are analysed and the effect of a newly developed educational programme is assessed. The study was designed as a prospective randomised clinical trial. For 30 months all children with newly diagnosed amblyopia were registered in The Hague, with additional children from Frankfurt and Leicester. Compliance was measured electronically with the ODM. The ODM was distributed by means of home visits by the researchers after the child had been randomised to either the intervention or control group. Children in the intervention group received the newly developed educational programme designed to improve compliance. It was developed by two artists who are specialised in art for sick children: José Vingerling and Gerard de Bruyne. The programme consisted of a cartoon story without text that explained to the child why it should patch, a calendar with stickers and an information sheet for the parents. Children in the control group received a picture to colour that was also considered a reward, but did not contain the educational message. Because of the home visits and not distributing the ODM in the out-patient clinic, the researchers were seen as working independently from the treating

orthoptist. Therefore, the ODM was less likely to be interpreted as a lie detector and, also, that non-compliant patients or patients who no longer visited the clinic remained in the study.
All parents, in both groups, completed the socio-economic questionnaire. After six months of treatment they completed a second questionnaire assessing possible reasons for failure or success of treatment.

Chapter 7 evaluates which clinical and socio-economic factors influence compliance and the effect of the educational programme on compliance. The most important socio-economic factors included parental fluency in the national language, country of origin and the level of education. However, the correlation between country of origin and fluency in the national language was too strong to be able to detect the effect of either variable. Nonetheless, it was found that children from mothers born in Surinam, who were either native speakers or otherwise fluent in the Dutch language, showed the same or even higher levels of compliance as the children from mothers born in the Netherlands. Therefore, the fluency in the national language appeared to be the most important factor. The most important clinical factor was the initial visual acuity of the child: children with low visual acuity were less compliant.
Children who received the educational programme had better compliance than the control group had (78% vs. 57%), and fewer children were not occluded at all (3 vs. 23 in the control group). The educational programme, explaining reasons for therapy to the child, partially obviated the main risk factors for non-compliance with occlusion therapy for amblyopia.

In **chapter 8** the most important reasons for failure or success of occlusion therapy are assessed by means of a questionnaire. It was concluded that a high level of distress caused by occlusion therapy, poor parental knowledge about disease and treatment and difficulties implementing the treatment into the daily routine were strongly correlated with non-compliance.

In the study in The Hague, four brands of patches were used: Opticlude, Orthopad, Pro-Ophta and Beiersdorf. **Chapter 9** describes a study into the properties of the eye patch, parental satisfaction and the influence of the different patches on compliance. There were large differences in the properties of the eye patch, especially in opacity and strength of adhesion to the skin. In all brands of patches the breathing capability was minimal. These differences however, did not influence the orthoptists' choice in prescribing a certain brand of patch; one orthoptist mainly prescribed one brand of patch, without taking into account, for example, the occlusion duration or skin type. Compliance was not influenced by the brand of patch. In general, parental satisfaction was moderate.

Chapter 10 gives an account of to what extent the study group represented a true coverage of the amblyopic children in The Hague and describes the diagnoses given to the children and

the causes of amblyopia. Finally, the possibility of having visual acuity as primary outcome measure instead of electronically measured compliance is discussed. The visual outcome of the children was evaluated. This analysis demonstrated that children who patched less than a quarter of the prescribed occlusion time showed practically no improvement in visual acuity in the amblyopic eye.

SAMENVATTING

In dit proefschrift worden de volgende punten ten aanzien van de behandeling van het luie oog met de afplakpleister aan de orde gesteld: richtlijnen voor het voorschrijven van de duur van het afplakken, het verloop van de gezichtsscherpte na het beëindigen van het afplakken, en de relatie tussen de therapietrouw en verbetering van de gezichtsscherpte. Vervolgens wordt de vraag gesteld welke factoren van invloed zijn op de therapietrouw bij de afplakbehandeling en wordt er gekeken of de therapietrouw verbeterd kan worden.

Therapietrouw is één van de belangrijkste factoren voor een succesvolle behandeling. Over het algemeen wordt therapietrouw gedefinieerd als de mate waarin de patiënt zich houdt aan de voorgeschreven dosering of gedragsregels van een zorgverlener. Therapieontrouw leidt niet alleen tot een verminderde effectiviteit van de behandeling, maar ook tot een verhoging van de kosten ervan. Amblyopie (lui oog, prevalentie 3,25%) is een verminderde gezichtsscherpte in één van beide ogen, wat ontstaat door een onderbreking van de normale visuele ontwikkeling. De belangrijkste oorzaken zijn scheelzien, een refractie afwijking (ongelijke plussterkte in de bril) of, meer zeldzaam, aangeboren staar. Door het goede oog enkele uren per dag vóór de leeftijd van zes jaar af te plakken door middel van een oogpleister kan een permanente achteruitgang in de gezichtsscherpte van het luie oog voorkomen worden. Ondanks het screenen op een lui oog op het Consultatiebureau en een effectieve behandeling ingezet door de orthoptist, blijft ongeveer één derde van deze kinderen een lui oog houden, waarvan de hoofdoorzaak therapieontrouw is.
Sinds de introductie van de Occlusion Dose Monitor (ODM) door Fielder en Moseley in 1991 kan de therapietrouw bij de afplakbehandeling van kinderen met een lui oog elektronisch gemeten worden. De ODM is door de afdeling Medisch Technisch Onderzoek van het Academisch Medisch Centrum aangepast en kleiner gemaakt. Het meet iedere twee minuten het temperatuurverschil tussen de voorkant en de achterkant en wordt met dubbelzijdig plakband aan de buitenkant van de oogpleister mee op het oog geplakt.

In de inleiding, **hoofdstuk 1**, wordt de vraagstelling behandeld en wordt nader ingegaan op eerdere studies die elektronisch de therapietrouw bij de behandeling van andere (oog)aandoeningen onderzocht hebben.

In **hoofdstuk 2** wordt een historisch overzicht gegeven van een al meer dan drie eeuwen durende discussie over de beste behandelmethode van een lui oog. De eerst beschreven behandeling voor het luie oog was de afplakpleister. Deze werd voor het eerst beschreven door Charles de Saint-Yves in Parijs in 1722 en niet, zoals door velen wordt gedacht door de George Comte de Buffon (1743). Tal van andere behandelmethoden worden besproken waarbij de pleister niet gedragen hoeft te worden (bijv. Atropine behandeling).

Er zijn nauwelijks richtlijnen voor het voorschrijven van het aantal uren per dag dat een kind afgeplakt moet worden gegeven een bepaalde gezichtsscherpte en leeftijd. Voor paramedische behandelingen bestaan over het algemeen nauwelijks richtlijnen en is de behandeling vaak 'practice based'. In **hoofdstuk 3** wordt een studie beschreven waarin deze variatie in het voorschrift van de orthoptist werd geïnventariseerd. Tijdens twee nationale orthoptisten vergaderingen, in Nederland en in Duitsland, werd een enquête met vijf standaard amblyope kinderen door alle 404 aanwezige orthoptisten tegelijkertijd en in stilzwijgen ingevuld. De variabiliteit in het plakvoorschrift was enorm. Bovendien waren er geen orthoptisten die consequent streng voorschreven en orthoptisten die consequent niet-streng voorschreven.

Wereldwijd is het al jaren een punt van discussie wat het verloop is van de gezichtsscherpte na het beëindigen van de afplakbehandeling rond ongeveer het achtste levensjaar. In **hoofdstuk 4** wordt een historisch cohort beschreven wat 30 jaar geleden de afplakbehandeling heeft ondergaan en in 2003 opnieuw orthoptisch onderzocht is. Over het algemeen was de gezichtsscherpte in het luie oog bij de meeste mensen na het stoppen van de behandeling toegenomen. Echter, als het luie oog veroorzaakt werd door zowel scheelzien als een ongelijke brilsterkte of als er gedurende de jaren een toename was van het verschil tussen de brillenglazen, was er juist een daling van de gezichtsscherpte in het luie oog.

In **hoofdstuk 5** worden de betrouwbaarheid en de beperkingen van de ODM, het elektronische apparaatje, uiteengezet. De ODM werd voldoende betrouwbaar gevonden om onderscheid te kunnen maken tussen de locatie op het oog of elders op het lichaam. Alleen wanneer de ODM ergens anders op het hoofd werd geplakt (bijv. voorhoofd) en er sprake was van een hoge omgevingstemperatuur (> 33°C) was een betrouwbare meting vrijwel onmogelijk.

In **hoofdstuk 6** wordt een pilot-studie beschreven, die vooraf ging aan het onderzoek in Den Haag, waarin bevestigd werd dat een betere therapietrouw gecorreleerd was met een snellere stijging van de gezichtsscherpte.

Hoofdstuk 7 tot en met 10 zijn gewijd aan de hoofdstudie van dit onderzoek, waarbij risicofactoren voor therapieontrouw zijn geanalyseerd en het effect van een nieuw ontwikkeld educatief programma is onderzocht. Het was een prospectief, gerandomiseerde studie waarbij gedurende 30 maanden alle kinderen in Den Haag, inclusief enkele kinderen in Frankfurt en Leicester, die voor het eerst een afplakbehandeling ondergingen meededen. De therapietrouw werd elektronisch gemeten met de ODM. Deze werd rondgebracht door middel van huisbezoeken door de onderzoeker, nadat het kind was ingedeeld in de interventie groep of de controle groep. Kinderen in de interventie groep kregen het speciaal, door twee kunstenaren gespecialiseerd in kunst voor het zieke kind (José Vingerling en Gerard de Bruyne) voor de studie ontwikkelde educatieve programma, bedoeld om de therapietrouw te verbeteren. Het

programma bestond uit een tekstloos stripverhaal, zonder dierfiguren, gericht op het kind, dat aan het kind uitlegt waarom er geplakt moest worden. Daarnaast kregen de kinderen een kalender met stickers en de ouders een informatiefolder, beschikbaar in zes talen, over de aandoening en de behandeling. De kinderen in de controle groep kregen een kleurplaat die volledig los stond van de behandeling, maar wel door de kinderen werd ervaren als een beloning. De onderzoekers werden door de ouders en kinderen als onafhankelijk van de behandelende orthoptist gezien. Dit kwam mede doordat de onderzoekers via huisbezoeken de metingen verricht hebben en niet in het ziekenhuis op de polikliniek. Hierdoor werd de ODM niet door de ouders als een leugendetector gezien en bleven ook therapieontrouwe mensen en de mensen die niet meer op controle in het ziekenhuis kwamen toch in de studie.
Alle ouders, zowel in de interventie als in de controle groep, vulden tijdens het eerste huisbezoek een sociaal-economische enquête in. Na zes maanden behandeling werd een tweede enquête ingevuld waarin redenen voor het falen of succesvol zijn van de behandeling werden geïnventariseerd.

Hoofdstuk 7 beschrijft welke klinische en sociaal-economische factoren van invloed waren op de therapietrouw en het effect van het educatieve programma op de therapietrouw. De belangrijkste factoren voor therapieontrouw waren de vaardigheid van de ouders in de Nederlandse taal, het land van herkomst en de hoogst genoten opleiding van een van beide ouders. Echter, de correlatie tussen het land van herkomst en de vaardigheid in de Nederlandse taal was te sterk om het aparte effect van één van beide parameters te bepalen. Wel werd er gevonden dat kinderen van moeders geboren in Suriname, met een goede beheersing van de Nederlandse taal, net zo een goede therapietrouw hadden of zelfs beter, dan de kinderen van moeders geboren in Nederland. Dit lijkt de indruk te bevestigen dat de vaardigheid in de Nederlandse taal de belangrijkste rol speelt. De belangrijkste klinische factor voor de therapietrouw was de gezichtsscherpte in het luie oog van het kind bij het begin van de behandeling: hoe slechter de gezichtsscherpte hoe slechter er geplakt werd.
De kinderen die het educatieve programma met het stripverhaal kregen hadden een betere therapietrouw dan de kinderen in de controle groep (respectievelijk 78% en 57%). Het meest opvallende verschil was het aantal kinderen dat helemaal niet afplakte: 3 in de interventie groep en 23 in de controle groep.
Het educatieve programma, wat aan het kind uitlegt waarom hij of zij geplakt moet worden, lijkt de belangrijkste redenen voor therapieontrouw te ondervangen.

In **hoofdstuk 8** is achteraf, door middel van een vragenlijst, gekeken wat de belangrijkste redenen zijn waarom de afplakbehandeling wel of niet succesvol verlopen is. Hieruit bleek dat een hoge mate van stress in het gezin, gebrek aan kennis over de aandoening en behandeling en moeite met de dagelijkse implementatie van de afplakbehandeling sterk gecorreleerd waren met de therapieontrouw.

In de studie in Den Haag werd gebruik gemaakt van vier merken afplakpleister: Opticlude, Orthopad, Pro-Ophta en Beiersdorf. In **hoofdstuk 9** wordt een onderzoek beschreven waarin aandacht is besteed aan de kwaliteit van de afplakpleister, de tevredenheid van de ouders erover en de invloed van de pleistersoort op de therapietrouw. Er werden grote verschillen gevonden tussen de pleistermerken wat betreft de eigenschappen. Vooral in lichtdoorlaatbaarheid en plakkracht waren de verschillen aanzienlijk. In alle pleisters was het ademende vermogen minimaal. Deze verschillen in eigenschappen lieten zich echter niet vertalen in het voorschrift van de orthoptist; een orthoptist schreef voornamelijk één merk voor zonder rekening te houden met bijvoorbeeld de duur van het afplakken of het huidtype.
Er kon niet aangetoond worden dat de therapietrouw gecorreleerd was met een merk pleister. Over het algemeen waren de ouders matig tevreden over de door hen gebruikte pleister.

In **hoofdstuk 10** wordt een verantwoording gegeven van in hoeverre de studie populatie in Den Haag representatief is voor de kinderen in Den Haag met een lui oog en worden de resultaten van de verschillende oorzaken van het luie oog (scheelzien, verschil in brilsterkte, etc.) weergegeven. Tot slot wordt besproken of, achteraf gezien, ook de stijging in gezichtsscherpte van de kinderen als uitkomstmaat voor de studie gebruikt had kunnen worden, in plaats van elektronisch gemeten therapietrouw. Uit deze analyse kon geconcludeerd worden dat kinderen die minder dan een kwart van de voorgeschreven uren hadden afgeplakt, vrijwel geen stijging hadden in de gezichtsscherpte van het luie oog.

Dankwoord

Onderzoek doen is boeiend, verrijkend en leuk. Toch is een woord van dank zeker nodig, want promotieonderzoek doe je nooit alleen en hoewel alleen mijn eigen naam op de voorkant van dit proefschrift staat, hebben veel mensen aan het onderzoek bijgedragen. De interesse en betrokkenheid van iedereen heeft mij altijd goed gedaan, daarvoor mijn hartelijke dank. In het bijzonder wil ik graag de volgende mensen bedanken.

Mijn promotor en begeleider, Prof. dr. H.J. Simonsz. Beste Huib, je vroeg of ik kon borduren en of ik al een richting voor verdere specialisatie had gekozen. Vervolgens leerde jij mij zodanig naar ogen kijken waardoor ik zeker wist dat ik in die richting verder wilde. Je gedrevenheid, passie voor het vak en voor onderzoek waren voor mij reden genoeg om na een bespreking weer met goede moed verder te gaan. Waar ook ter wereld en op welk tijdstip dan ook, ik mocht je altijd bellen: "*The sky is the limit*". Zeer veel dank voor dit alles! Ook je hulp bij het opzetten van een onderzoek in Boston waardeer ik zeer.

Prof.dr. G. van Rij, mijn andere promotor, hartelijk bedankt voor de mogelijkheid die ik gekregen heb om deel te nemen aan het onderzoek, uw interesse daarin en begeleiding daarbij. Voor de juiste woorden op die zo cruciale momenten. Daarnaast wil ik u bedanken om na het onderzoek de opleiding tot oogarts te mogen volgen.

De leden van de kleine commissie, Prof.dr. Passchier en Prof.dr. van der Maas, hartelijk bedankt voor het beoordelen van het manuscript en de discussies die op vele plaatsen terug te vinden zijn. Dr. Merrick Moseley, thank you very much for critically reading the manuscript and the pleasant discussions we had during the sunny conferences.
Ich möchte mich auch bei Frau Dr. Fronius bedanken für Ihre Gastfreundlichkeit während meines Aufenthaltes im Goethe Institut Frankfurt, Deutschland und für die konstruktive Zusammenarbeit. Vielen Dank für die kritische Beurteilung des Manuskriptes.

De mensen van de afdeling Medisch Technisch Onderzoek van het AMC in Amsterdam, in het bijzonder Ruud Voorn en Hugo Molenaar; dankzij jullie technisch vernuft en doorzettingsvermogen hebben we als één van de eersten de therapietrouw op een zo grote schaal elektronisch kunnen meten. Zeer hartelijk dank daarvoor.
Ik zou geen resultaten hebben kunnen verzamelen zonder ook de grote inzet van de orthoptisten in Den Haag: Ellen van Minderhout, Marleen Vermeulen, Roberta Delle Site, Janine van Zon, Eline Deelstra en Jorrien Bouma-van Wondergem. Hartelijk bedankt voor al jullie hulp,

jullie rekrutering was overweldigend! Dr.Maurits Joosse, de oogarts, bedankt voor je hulp en je relativerende vermogen als het even niet liep zoals gepland.
Grote dank gaat uit naar alle kinderen en hun familieleden in Den Haag die aan het onderzoek hebben meegewerkt.
Gerard de Bruyne en José Vingerling, jullie originele ideeën en creativiteit mondde uit in het stripverhaal met stickers en mede daardoor is deze studie een succes geworden. Hartelijk dank daarvoor. De omslag van het proefschrift is prachtig.

Bregje van Dijk-Verhoef, mijn fiets-maatje in Den Haag. Mede dankzij jouw grote inspanningen hebben we het onderzoek in Den Haag kunnen opzetten. Het memorabele fietstochtje naar Stompwijk zal mij altijd bijblijven.
Brigitte Simonsz-Tóth, mijn auto-maatje in Den Haag. Herzlichen Dank voor het voortzetten van het onderzoek in Den Haag en je orthoptische expertise bij de analyse van de database. Dank ook voor de gezelligheid bij jullie thuis met Annika en het goede eten, kortom: het Zwitserleven gevoel!

Caspar Looman, ik kon altijd even bij je binnenlopen voor een statistische vraag. Hartelijk bedankt voor je input en correcties, de manuscripten zijn er significant beter door geworden!

Graag wil ik mijn directe collega's van "de 16e" bedanken voor de collegialiteit en de prettige, ontspannen sfeer op de afdeling. Het afwisselen van de co-schappen met het onderzoek en vice versa was niet altijd even gemakkelijk, maar dankzij jullie kon ik altijd snel mijn draai weer vinden. Emine, samen AiO zijn schept een band! Dat was super! Walter, onze figuur deskundige en grootste afnemer van het legal-addictive-stimulant-apparaat: Douwe Egbert' s Senseo! Het succesvol afronden van je promotie moet nu zeker lukken! Michael, we hebben ongeveer even lang op de 16e mogen bivakkeren, bedankt voor je gezelligheid en je traktatie op de swirl ijsjes. Jan Roelof, bedankt voor je swingende bijdrage op de donderdagochtenden. Elizabeth, de woensdag begon pas echt als jij er ook was, there was never a dull moment. Hartelijk bedankt voor je interesse en het lezen van mijn abstracts. Angela, ik ben erg blij dat jij met de behaalde resultaten een nieuw project gaat uitvoeren. Heel veel succes daarmee, samen met Elizabet, *go for it girl!* Hanneke en Jolanda veel succes met het oogmelanomenonderzoek. Dominiek (ook een beetje van de 16e), heel veel succes met je onderzoek en ik kijk er naar uit om je als collega beneden te kunnen begroeten.

Sander Schutte, *mister sjoette*, je technische blik op het arts-zijn opende voor mij een tot nu toe onbekende wereld. Ik respecteer je ongedwongenheid en openheid over tal van zaken. Je gezelligheid en hulp bij de voorbereidingen voor congressen en op de congressen zelf maakte alles een stuk leuker. Heel veel succes met je promotie, en ik hoop dat ik later je uitvindingen in de praktijk kan brengen.

De (oud-)assistenten en stafleden van de oogheelkunde, bedankt voor jullie interesse en kritische vragen tijdens alle besprekingen. Joan Boller en Nicole van Basten, bedankt voor jullie snelle reactie, hulp en organisatorische talenten als ik weer eens hulpeloos over de gang struinde.
Jacqueline Willemse, bedankt voor het wijzen van de goede weg als ik dan weer op een zijspoor beland was.

Ylian Liem. Lieve Yls, je enthousiasme, betrouwbaarheid, systematiek en betrokkenheid heb ik vanaf de eerste dag dat ik je leerde kennen altijd bewonderd. Mensen als jij zijn schaars en moeten gekoesterd worden. Veel succes met je onderzoek en de opleiding, en de opmerking: "So you're not a statistician then?" houden we in gedachten!

Mijn paranimfen, Jan Roelof Polling en Emine Kiliç. Jan Roelof, jij was het die mij introduceerde in 'de wereld van de orthoptie' en 'de wereld van de wintersport'. Je was van het begin af aan betrokken bij het onderzoek. Niet alleen bij de uitvoering ervan, maar ook voor de mentale ondersteuning kon ik altijd op je rekenen. Je mening en hulp zijn voor het tot een succesvol einde brengen van het onderzoek absoluut onontbeerlijk geweest. Heel veel dank daarvoor. Emine, zowel op de 16e, als op congressen, als thuis voor de buis of achter de laptop, was het altijd goed toeven met jou! Je optimisme, kritische en nuchtere kijk op de zaken hebben zeker ook aan mijn ontwikkeling een positieve bijdrage geleverd. Ik verheug me op de dag dat ik samen met jou arts-assistent mag zijn en ik hoop nog lang met je te mogen samenwerken.

Mijn vrienden, dichtbij en ver weg, bedankt voor de momenten van ontspanning en jullie interesse in de vorderingen van het onderzoek. Ik kom nu weer uit mijn grot.

Mum & Dad, thank you for giving me roots and wings! You deserve a whole thesis of thanks and respect. The never ceasing support, encouragement and love have played a very central part in who I am and what I have accomplished. This book is for you, I hope you like it!
Stephanie & Oliver, mijn zus en broer, bij jullie kon ik altijd gewoon mijn verhaal kwijt. Dank jullie wel daarvoor!
Allerliefste Gerard, I am always on the lookout for a way to tell you how special you are!
Oneindig veel dank voor al je hulp, je geduld, je humor en bovenal je liefde.
Next stop: Boston!

About the author

Sjoukje Loudon was born in Huddersfield in the United Kingdom on the 30th October 1978. In 1982 she moved with her family to the Netherlands. She graduated from the "Professor Zeeman" Secondary School in 1997 and started her medical study at the ErasmusMC University Medical Center Rotterdam that same year. In her third year she spent a one-month clinical exchange at the First Internal Medicine Department in Kurume University Hospital in Japan. During her studies she participated in arranging the international clinical exchanges and was president of the local committee of the International Federation of Medical Students' Associations (IFMSA). In 2003 she was secretary of the Organising Committee of the IFMSA Conference "Medical Ethics" and August Meeting 2003. After obtaining her master's degree in July 2001, she started the research described in this thesis at the Department of Ophthalmology; supervisors were Prof. dr. G. van Rij and Prof. dr. H.J. Simonsz. In 2005 she received the 'Jonkers Prize' for the most innovative research leading to important new insights in the field of orthoptics. In February 2007, she will become a medical doctor.

After this PhD research she will participate in a research project at the Department of Ophthalmology, Children's Hospital Boston, USA, supervised by Prof. dr. D.G. Hunter.

In January 2008 she will start her training as an ophthalmologist at the Department of Ophthalmology ErasmusMC University Medical Center Rotterdam (head Prof. dr. G. van Rij).

List of publications

S.E. Loudon, J.R. Polling, H.J. Simonsz *Electronically measured compliance with occlusion therapy for amblyopia is related to visual acuity increase.* Graefes Arch Clin Exp Ophthalmol 2003 Mar;241(3):176-80

S.E. Loudon, J.R. Polling, B. Simonsz, H.J. Simonsz *Objective survey of the prescription of occlusion therapy for amblyopia*. Graefes Arch Clin Exp Ophthalmol 2004 Sep;242(9):736-40

S.E. Loudon, H.J. Simonsz *The history of the treatment of amblyopia.*
Strabismus 2005 Jun;13(2):93-106

Y. Chopovska, S.E. Loudon, L. Cirina, A. Zubcov, H.J. Simonsz, M. Luchtenberg, M. Fronius *Electronic recording of occlusion treatment for amblyopia: potential of the new technology*. Graefes Arch Clin Exp Ophthalmol 2005 Jun;243(6):539-44

S.E. Loudon, M. Fronius, C.W.N. Looman, M. Awan, B. Simonsz, P.J. van der Maas, H.J. Simonsz *Predictors and a remedy for non-compliance with amblyopia therapy in children measured with the Occlusion Dose Monitor.* Invest Ophthalmol Vis Science 2006 Oct;47(10):4393-400

B. Simonsz-Tóth, S.E. Loudon, H. van Kempen-du Saar, E.S. van de Graaf, J.H. Groenewoud, H.J. Simonsz *Visusevaluierung in einer historischen Kohorte von 137 okkludierten Patienten, 30-35 Jahre nach Ende der Okklusionsbehandlung / Evaluation of visual acuity in a historic cohort of 137 patients treated for amblyopia by occlusion 30-35 years ago.* Accepted for publication in Klin Monatsbl Augenheilkd 2006

S.E. Loudon, L. Chaker, S. de Vos, M. Fronius, J. Passchier, R.A. Harrad, C.W.N. Looman, B. Simonsz, H.J. Simonsz *Effect of an educational programme on attitudes and behaviour with occlusion therapy and reasons for total non-compliance.* (submitted)

S.E. Loudon, A.W. Wypekma, C.W.N. Looman, M. Fronius, B. Simonsz, H.J. Simonsz *Physiological properties of the eye patch and influence on compliance with occlusion therapy.* (submitted)

S.E. Loudon, J.R. Polling, H.J. Simonsz *A preliminary report about the relation between visual acuity increase and compliance in patching therapy for amblyopia*. Strabismus 2002 Jun;10(2):79-82

S.E. Loudon *Charles de Saint-Yves (1677-1736)*. Strabismus 2005 Sep;13(3):143-4

M. Fronius, Y. Chopovska, J. Nolden, S.E. Loudon, M. Luchtenberg, A. Zubcov, L. Pepler *Occlusion treatment for amblyopia: assessing the performance of the electronic occlusion dose monitor*. Strabismus 2006 Jun;14(2):65-70

Appendix / Colour figures

Evaluation of visual acuity in a historic cohort of 137 patients treated for amblyopia by occlusion 30-35 years ago

(English translation Chapter 4)

INTRODUCTION

Treatment of amblyopia with occlusion therapy has been a long established method of treatment. The value of occlusion therapy can be found mainly in the prevention of costs which may arise when patients with insufficiently treated amblyopia lose their dominant eye later in life (Neubauer and Neubauer 2005).
The time such a patient spends with a diminished visual acuity in both eyes (acuity both eyes >0.3 logMAR) increases from 8 months to 15.5 months (van Leeuwen, et al. 2002).

With the introduction of screening, amblyopia could be detected at an earlier age, making treatment more effective, so that the number of patients who were unable to read with the amblyopic eye could be reduced. Since health centres in the Netherlands test children for strabismus and amblyopia and measure the acuity at the age of 3 and 3 years and 9 months an undetected amblyopia rarely happens.
In spite of this, the occlusion therapy fails in almost one third of all patients with amblyopia (acuity in the amblyopic eye >0.3 logMAR) (Jensen and Goldschmidt 1986).

The literature quotes a prevalence of amblyopia of 3.25% (Attebo, et al. 1998). Formerly, failure of the occlusion therapy was thought to be due to a late diagnose (Bowman 1998), nowadays non-compliance with occlusion therapy (Dorey, et al. 2001; Loudon, et al. 2003) is held primarily responsible. The long-term success of occlusion therapy varies according to literature. Most studies include groups of patients with varying inclusion criteria: recruitment of patients from different clinics (Woodruff, et al. 1994) or in the context of pre-school screening (Bowman, et al. 1998), only patients who attended all check up appointments (Levartovsky, et al. 1995; Malik, et al. 1975), who had total occlusion treatment only (Scott and Dickey 1988) or were also treated with pleoptics, spectacle occlusion or inverse occlusion (Schröpfer and Meinert 1975; Sparrow and Flynn 1977). In addition, the moment for the follow-up examination after cessation of the occlusion therapy varies from a couple of months (Malik, et al. 1975) up to a maximum of twenty years (Leiba, et al. 2001).
Some authors suggested that the acuity more or less stayed the same after cessation of the occlusion therapy (Ohlsson, et al. 2002; Scott and Dickey 1988), or improved (Leiba, et al. 2001), whilst other authors demonstrated a slight decrease in acuity of one to two lines (Levartovsky, et al. 1995; Schröpfer and Meinert 1975).
Factors negatively influencing the course of visual acuity after cessation of therapy, included a relatively high age (Ham, et al. 1985; Levartovsky, et al. 1995; Meyer, et al. 1991; Stewart, et al. 2004) and a low start acuity (Meyer, et al. 1991; Scott and Dickey 1988; Sparrow and Flynn 1977; Woodruff, et al. 1994), an eccentric fixation (Ham, et al. 1985; Sparrow and Flynn 1977) and a combined cause, strabismus and anisometropia, for the amblyopia (Levartovsky, et al. 1995; Woodruff, et al. 1994).

We examined the current visual acuity and analysed the influence of certain factors on the current acuity after cessation of occlusion therapy in a total of 137 patients, who, 30-35 years ago, were treated for amblyopia with occlusion therapy in Waterland, a rural region in Holland. At that time only one ophthalmologist and one orthoptist (less than 0.5 Fte) provided for that region. All children suspected of amblyopia were referred to this orthoptist (HvK) by health care centres and general practitioners who screened the children for amblyopia. Together with this orthoptist these patients were examined once more in 2003.

MATERIAL AND METHODS

Background

At the time of the research the Waterland hospital took care of the medical service to the townships of Purmerend, Waterland, Zeevang, Wormer, Edam and Volendam. The population consisted of people originating from these areas and families with young children who had come to live there from Amsterdam.

Data

All files from patients who had been treated in the orthoptic department of the Waterland hospital in Purmerend, short term or long term, between 1968 and 1975 were analysed (n = 1250). 471 (38%) of these children received occlusion therapy. From the files we derived the demographic data of the patients (sex, date of birth, telephone number) and orthoptic data (age at start and end of occlusion therapy, acuity at start and end of occlusion therapy and cause of the amblyopia, fixation, binocular vision, ocular motility and cycloplegic refraction).

Treatment 30 years ago

Amblyopia was treated with occlusion therapy when, after an adequate spectacle prescription, an acuity difference of one line together with other amblyogenic factors, was present.
Up to the age of four, acuity was tested monocularly with pictures (Amsterdam Picture Chart; acuity range 6/30 to 6/5). From the age of four, acuity was tested with Landolt-C and from about the age of seven Letters (Snellen) were used and noted down in decimals.
In both these tests the distance between the lines of the chart was linear; the distance between the optotypes was larger than 2.6"and was described as 'single'. All visual acuity outcomes were converted into logMAR (Table 1).

Table 1 . Table of conversion: acuity in decimals to acuity in logMAR.

Conversion table
acuity in decimals - acuity in logMAR

Visus	LogMAR
1.6	-0.2
1.25	-0.1
1.0	0.0
0.8	0.1
0.63	0.2
0.5	0.3
0.4	0.4
0.32	0.5
0.25	0.6
0.2	0.7
0.16	0.8
0.12	0.9
0.1	1.0
0.08	1.1
0.06	1.2
0.05	1.3

Follow- up re-examination in 2003

Of the 471 patients, 203 (42%) could be traced and contacted by telephone. These patients were sent a questionnaire to establish their quality of life with amblyopia and/or strabismus; the amblyopia & strabismus questionnaire (A&SQ) (van de Graaf, et al. 2004). The other patients could, for different reasons, not be reached: two patients had died, of the other patients telephone numbers could not be traced or they could not be contacted. 174 patients returned the completed questionnaire.

In the autumn of 2003, 137 of them could be re-examined by the orthoptist and the ophthalmologist at the orthoptic department of the Waterland hospital in Purmerend.

Of the 174 patients who had returned the questionnaire, 27 patients could not be re-examined, 11 could not be contacted, six refused participation and nine could not attend as they were in hospital, abroad or had a long way to travel.

We now had acuity measurements taken at three different moments in time (at the start of occlusion therapy, end of occlusion therapy and in 2003, 30-35 years after cessation of the occlusion therapy).

The following parameters were determined at the follow-up examination: binocular vision was tested using the Bagolini at 6m and 0.4m distance, stereo vision using the Titmus-Fly

test, the stereo-test from Lang II and TNO-Test. The angle of the strabismus was measured by means of the cover-uncover and alternating cover test at 6m and 0.3m distance.
Cycloplegic refraction was tested by means of retinoscopy without atropine. It was tested, however, in a darkened room and according to subjective equations.
Visual acuity was tested by means of a projector (OCULUS, Medical Workshop, the Netherlands) with linear acuity lines monocularly at 6m numbers analogue DIN EN ISO 8596 with the best possible spectacle correction and noted in decimals.
The reading ability was determined by means of a Dutch reading text that consisted of five acuity gradations (D=0.5; D=0.8; D=1; D=1.25; D=2) D=1 is similar to newspaper print size.
In addition fixation was tested. The macula and front segment were assessed.

All acuity outcomes, the reading text test excepted, were converted into logMAR for the analysis. Anisometropia was defined as a difference of more than 1D spherical equivalent between the right eye and the left. A combination of both causes (strabismus and anisometropia) was defined as combined amblyopia.

Statistical analysis

We applied a regression analysis to determine the influence of the measured parameters on current visual acuity. The influence of potential confounding is corrected for in the multivariate analysis. SPSS, version 10.0 was used for the statistical analysis. $P < 0.05$ indicated statistical significance.

RESULTS

Study population

Of the 137 patients, 65 were female. Mean age at start of occlusion therapy was 5.4 ± 1.9 years and 7.4 ± 1.7 years at the end of treatment. Of the 137 children twelve (9%) were occluded before the age of three (mean age 2.4 years); all had amblyopia caused by strabismus.

Amblyopia was associated with strabismus in 98 patients (71%), with anisometropia in 16 patients (12%) and with both anisometropia and strabismus in 23 patients (17%).
Mean acuity in the amblyopic eye at start of treatment was 0.6 ± 0.7 logMAR and 0.3 ± 0.5 logMAR at the end of treatment.

At the start of occlusion therapy, 116 patients had an acuity difference of at least 0.5 logMAR between the dominant and the amblyopic eye. 13 patients had an acuity difference of 0.2-0.5

logMAR, 8 patients of < 0.2 logMAR. Five patients were too young to be able to cooperate with the visual acuity tests. Therefore, the orthoptist recorded the pursuit and fixation behaviour. In all five patients amblyopia was caused by strabismus: two patients had hardly any pursuit when looking monocularly, three preferred fixation with the dominant eye. The following decimal equivalences were used: 0.4 logMAR and 0.2 logMAR, respectively. In these cases, the acuity at start of treatment was used only to determine the correlation between the acuity at treatment onset and the current acuity, however not for the prognostic factors. This decimal equivalence could be interpreted in different ways. However, it should be noted that it only concerned five patients and that nevertheless, the acuity at treatment onset was strongly correlated to the current visual acuity.

Patients with amblyopia caused by strabismus were occluded from the mean age of 5.1 ± 1.9 years; for an average of 2.3 ± 1.3 years.
Patients with clear anisometropic amblyopia were on average 7.2 ± 2.2 years of age at the start of treatment and were occluded for an average of 1.4 ± 1.0 years.
Patients with amblyopia caused by strabismus and anisometropia were occluded from the mean age of 5.8 ± 0.7 years, for an average of 1.6 ± 1.3 years (see also Table 2).
Binocular vision improved slightly in the total study population (Figure 1).

Table 2. Acuity at treatment onset, cessation and 30-35 years after cessation of occlusion therapy, the age at start of treatment, duration of occlusion and fixation for each cause of amblyopia.

Parameters	strabismus-amblyopia (*n* = 98)	anisometropic-amblyopia (*n* = 16)	combined amblyopia (*n* = 23)
acuity start occlusion (logMAR)	0.69* ± 0.5	0.53* ± 0.3	0.82* ± 0.54
acuity end occlusion (logMAR)	0.29 ± 0.3	0.17 ± 0.23	0.52 ± 0.54
acuity at follow-up (logMAR)	0.27 ± 0.3	0.21 ± 0.23	0.65 ± 0.54
age start occlusion (years)	5.1 ± 1.9	7.2 ± 2.2	5.8 ± 0.7
time of occlusion (years)	2.3 ± 1.3	1.4 ± 1.0	1.6 ± 1.3
Fixation			
central	n=63*	n=16	n=14
eccentric	n=35*	n=0	n=9

In both the univariate and multivariate analysis, acuity in the amblyopic eye at start of treatment ($P < 0.0001$), the cause of the amblyopia ($P = 0.001$) (strabismus, anisometropia, combined amblyopia) and an eccentric fixation ($P < 0.0001$) with strabismus, were significantly correlated with the current visual acuity in 2003.
*Significant parameter for the acuity in 2003 in logMAR in the regression-analysis.

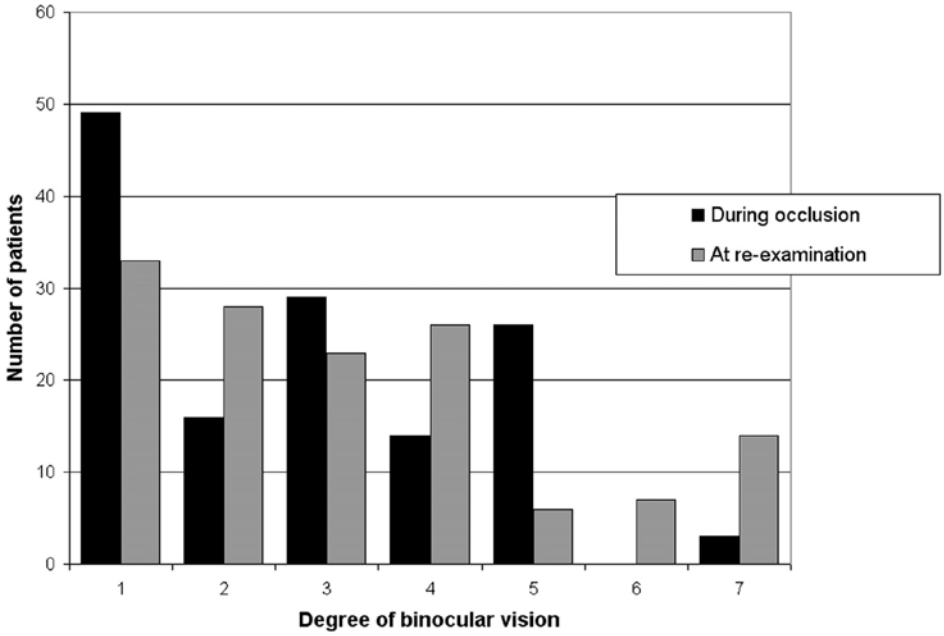


Figure 1. Binocular vision of the total study population during occlusion treatment and at the time of the follow-up re-examination in 2003.
The degree of binocular vision (abscissa) was arranged into seven categories
1: Bagolini negative, 2: Bagolini positive, 3: Bagolini and Titmus-Stereotest Fly positive, 4: lowest Titmus-Stereotest circle 200″-140″ positive, 5: lowest Titmus-Stereotest circle 100″-40″ positive, 6: Stereotest from Lang or lowest TNO-Test figure V (480″ & 240″) positive, 7: TNO-Test figure VI or VII (120″-15″) positive. The black bars show the degree of binocular vision during the occlusion treatment (n=137), the grey bars at the time of the follow-up re-examination. The ordinate represents the number of patients.

Relationship between visual acuity and the cause of amblyopia

Since the cessation of occlusion therapy visual acuity had deteriorated from a mean of 0.52 ± 0.54 to 0.65 ± 0.54 logMAR in patients with a combined cause of amblyopia and from a mean of 0.17 ± 0.23 to 0.21 ± 0.23 logMAR in patients with an anisometropic amblyopia.
Visual acuity had improved from 0.29 ± 0.3 to 0.27 ± 0.3 logMAR in patients with strabismic amblyopia (Figure 2). This improvement was significant ($P < 0.001$). The acuity of the dominant eye of these patients had also improved from 0.01 ± 0.15 to 0.05 ± 0.07 logMAR, this was also significant ($P = 0.04$).
In general, in 14 patients (10%) the acuity in the amblyopic eye was unchanged. In 70 patients (51%) acuity had improved. In 54 patients (39%) acuity had deteriorated, of which 18 patients had an acuity loss of >50% compared to acuity at the end of treatment.
Of the 137 patients, 47 (34%) had an acuity in the amblyopic eye at distance (6m) of > 0.3 log-MAR lines at the end of treatment, on average 0.48 ± 0.6 logMAR.

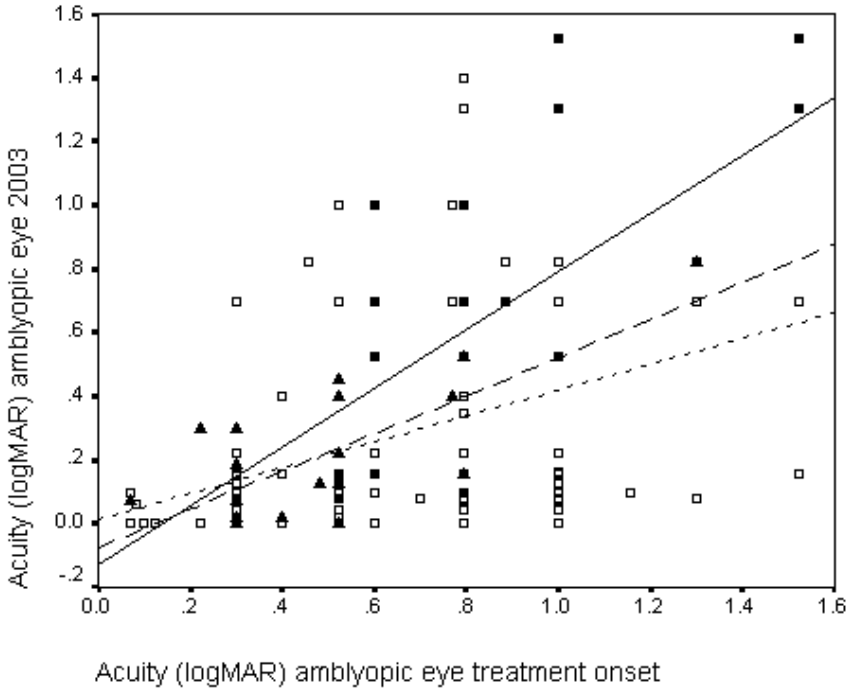


Figure 2. Acuity in the amblyopic eye at treatment onset and at follow-up re-examination in 2003, for each cause of amblyopia.
The ordinate shows the acuity at the time of the follow-up re-examination in logMAR lines, the abscissa shows the acuity in logMAR lines at treatment onset. Patients with a combined amblyopia are represented by a black square ←, patients with anisometropic-amblyopia by a triangle ▲ and patients with strabismic-amblyopia by a white square □. The solid regression line represents the combined amblyopias, the dashed regression line those of the anisometropic-amblyopias and the dotted line those of the strabismic-amblyopias.
Both patients with strabismic-amblyopia and those with combined amblyopia had a poor acuity at treatment onset, patients with strabismic-amblyopia, however, had a better acuity at the follow-up re-examination in 2003.

Of the 137 patients, 55 (40%) were unable to read with the amblyopic eye (>D=1).

Patients with profound deterioration in visual acuity

18 Patients had an acuity loss >50% compared to acuity at the end of treatment. Of these, 15 showed an increase of anisohypermetropia. Of these 15 patients, nine had developed an anisohypermetropia of 2.2 ± 1.7D. In six patients, an anisohypermetropia had already been present (mean was 2.9D), which had increased to 3.5 ± 1.8D.

In the 18 patients the spherical equivalent of the amblyopic eye had increased from +2.7D to +2.8D. The spherical equivalent had decreased from +1.9D to +0.7D in the dominant eye. Only five of the 18 patients wore adequate spectacles at the time of the follow-up re-examination. Three of these five patients were myopic in the dominant eye, and two were on average +2.75D hyperopic.

Correlations

The univariate analysis showed a statistically significant correlation between the current visual acuity and the acuity at the start of the occlusion therapy (P <0.001), an eccentric fixation (P <0.001) and the cause of the amblyopia (strabismus, anisometropia or combined cause), (P = 0.005) (see also table 2). No significant influence could be found for the duration of occlusion therapy (P = 0.622), the age at start of occlusion treatment (P = 0.320) and at the end of occlusion treatment (P = 0.119).
When correcting for potentially confounding factors in the multivariate analysis, the visual acuity at the start of treatment, the cause of the amblyopia and the fixation remained significant (P < 0.001; P = 0.018; P = 0.004, respectively).

Prognostic factors

Patients with anisometropic amblyopia had, compared to patients with strabismic amblyopia and patients with combined amblyopia, a significantly better visual acuity at the start of the occlusion therapy. Patients with combined amblyopia had the poorest acuity at the start of treatment and also at the follow-up re-examination. Only patients with strabismic amblyopia showed a slight acuity improvement, compared to acuity at the end of the treatment.
In patients with strabismus, the fixation was correlated with the acuity. A correlation could be found between the decrease in acuity and the loss of binocular vision (r = 0.38).

Prevalence of occlusion therapy

We aimed to establish whether the historical cohort was representative of the number of children receiving occlusion therapy at that time; i.e. if any selection bias had occurred. The prevalence of amblyopia has been quoted to be approximately 3.25% (Attebo, et al. 1998). It was expected to find a lower prevalence rate, as our historical cohort was comprised of a biased under-representation. Of the 471 occluded children, 66, 64 and 68 children were born in 1965, 1966 and 1967, respectively (Figure 3). In the whole of the Waterland hospital region 1286, 1328 and 1355 births were registered in 1965, 1966 and 1967, respectively. This would concur with a prevalence of 5.0% occluded children.

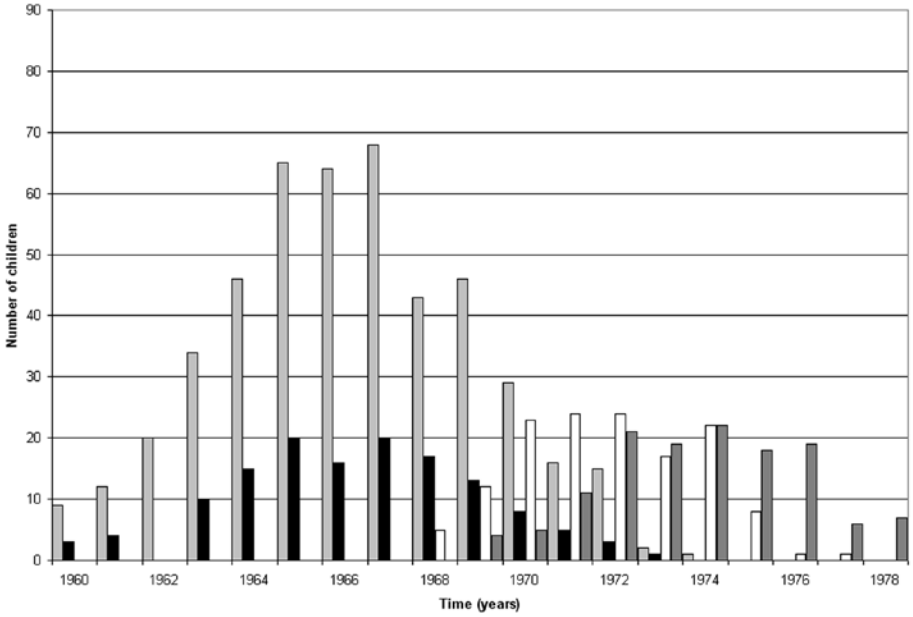


Figure 3. Overview of the total number of patients for their year of birth: all patients occluded in the Waterland hospital (n=471, light grey) and of the historical cohort (n=137, black). Also for the historical cohort start of occlusion (white) and cessation of occlusion (dark grey) has been given. Of the 471 occluded children 66, 64 and 68 were born in 1965, 1966 and 1967, respectively. This corresponded to 5.0% of the registered births in the total region of the Waterland hospital in those years.

In hindsight, the amblyopia could not be confirmed in seven of the 137 children. These patients had an acuity difference of <0.2 logMAR lines between the dominant and the amblyopic eye, an anisometropia <1D, and/or an alternating strabismus.
After the necessary correction, the prevalence of occluded children was approximately 4.7%. Theoretically, it could be possible that children living outside the region were also treated in the Waterland hospital. This, however, was not the case in our group.

DISCUSSION

For this study we were able to establish an evaluation of the visual acuity in 137 patients more than thirty years after the cessation of occlusion therapy. We found that a poor acuity in the amblyopic eye at the start of treatment, an eccentric fixation and a combined cause of amblyopia were correlated with the current visual acuity measured at the follow-up re-examination. That a poor visual acuity in the amblyopic eye at start of treatment and the cause of amblyopia were predictors for a poor outcome has also been described by other authors, even when a lengthier period of observation time was examined. A combined cause of amblyopia and an

increase of the anisohypermetropia were, after 30 years, associated with a decrease in visual acuity after the end of the occlusion therapy.

In most of the children, due to the school age, acuity could be tested using the Landolt-C chart, both at the start and the end of treatment. The acuity at treatment onset, in which the largest variation was to be expected, was merely used in the analysis of the correlation with the current acuity. When analysing the prognostic factors the acuity at the end of treatment was used. The acuity was determined with different acuity charts. This could cause the outcomes to be not entirely comparable (Gräf 2004), as acuity tests with optotypes can only score similar outcomes as when using Landolt-C, when acuity is higher. When acuity is poor, a slight overrating of the acuity will occur when it is measured using optotypes (Rassow and Wang 1999). Nevertheless, we found a strong significance that could be even stronger, when acuity is tested in equal testing conditions.

After cessation of occlusion therapy a slight improvement of the acuity was found in both the amblyopic eye and the dominant eye in patients with strabismic amblyopia. We presumed this to be the natural development of the acuity. Information is scarce concerning the development of the acuity in the dominant eye. In general, when not taking into account the cause of amblyopia, a slight improvement of the acuity was found (Ohlsson, et al. 2002). Studies of the natural course of the acuity in patients with untreated amblyopia, showed a worsening of the acuity in the amblyopic eye both at pre-school age (Simonsz and Preslan 1999) and in adulthood (Haasse and Wenzel 1996).
It should be taken into account, however, that an inclusion criteria for the study was poor acuity (>0.18 logMAR lines; n = 18) and that children with a slight decrease in acuity were excluded, making a selection bias probable.

In agreement with other studies (Levartovsky, et al. 1995; Woordruff, et al. 1994) we were unable to demonstrate a correlation between the age at treatment onset, the age at the end of treatment and the current visual acuity in 2003. However, it could not be concluded that a patient may not be treated more successfully if occlusion in this patient had started at an earlier age.

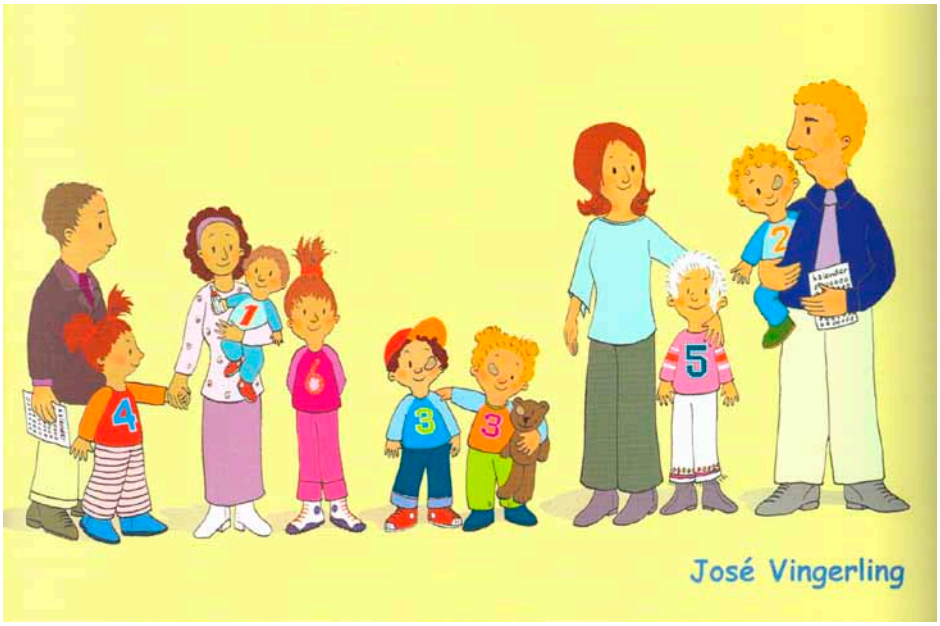
In our study group the age at the start of the occlusion therapy was relatively high, probably caused by the fact that, at that time, screening for amblyopia had not altogether been properly introduced. With the exception of the cities, health centres and general practitioners did not carry out acuity measurements, causing amblyopia without a notable strabismus to be first diagnosed at the age of 5-7 years. Nowadays, in the Netherlands, the Child Health Care Centres screen for the presence of strabismus and measure visual acuity at the age of three. The current mean age at treatment onset is 4.6 years (Loudon, et al. 2006).

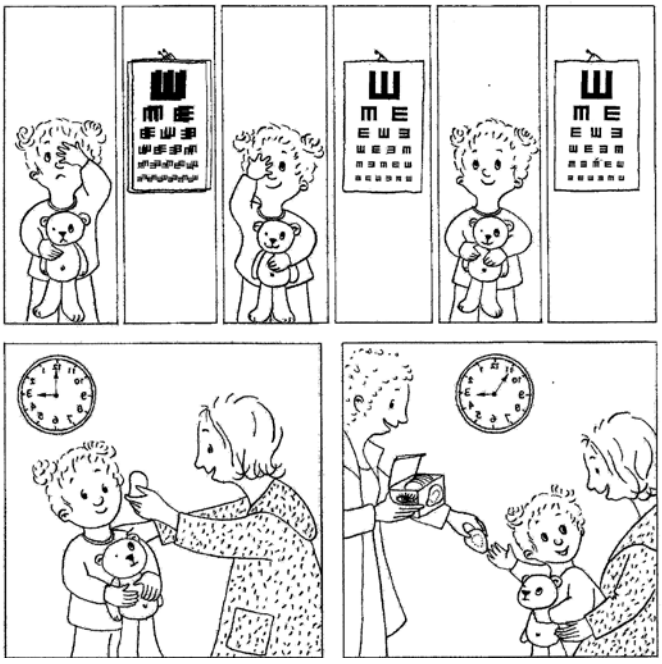
Fifteen of the 18 patients, in whom acuity had decreased >50% after the cessation of the occlusion therapy, had an increase of the anisohypermetropia. At the time of the follow-up re-examination it seemed important to remark that only five of these were wearing spectacles or contact lenses. They indicated they stopped wearing the spectacles from the age of 14/15. It may be possible that, after the latest spectacle correction, these patients started to see out of focus again with their amblyopic eye, because of the increase in anisometropia and, for that reason, did not like to wear the spectacles.
It is therefore recommendable to check patients that had anisometropic amblyopia and show an increase of the anisometropia more often and to adjust the spectacles accordingly.

In other studies (Attebo, et al 1998; Leiba, et al. 2001; Levartovsky, et al. 1995; PEDIG 2002; Woodruff, et al. 1994), amblyopia caused by a pure anisometropia is approximately 30%, varying, however, between 11% (Leiba, et al. 2001) and 50% (Attebo, et al. 1998). In our study, only the children who received occlusion therapy for their amblyopic eye were included. Therefore, children who had been treated for their anisometropic amblyopia using a spectacle correction were not included.

Surprisingly, we found the prevalence of occluded children (4.7%) to be higher than the prevalence's of amblyopia mentioned in other studies (3.25%), (Attebo, et al. 1998). How could this discrepancy be explained? The prevalence of amblyopia in most studies is determined among adult patients with untreated amblyopia. Our study demonstrated that in most patients the acuity after the cessation of the occlusion therapy improves slightly; in only few it deteriorates. At the start of occlusion therapy the orthoptist is unaware which children, who have been referred by health centres or paediatricians because of a slight reduction in acuity (>0.1 logMAR), will have a spontaneous improvement of acuity and may therefore, over-treat.

Appendix 2: educational cartoon programme

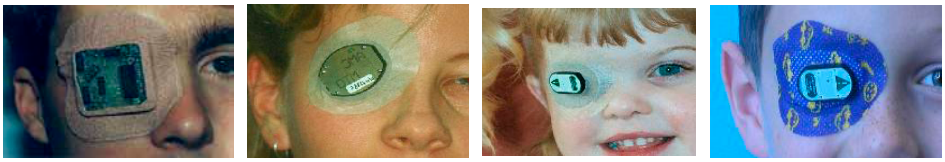




The educational programme, developed by José Vingerling and Gerard de Bruyne, to improve compliance with occlusion therapy for amblyopia. It consisted of a cartoon story without words, explaining to the child why he or she should patch. There were no animal figures included, making it easier for the child to identify him or herself with the child in the story. It was bolstered by an immediate reward system (calendar and stickers). © Vingerling & De Bruyne.

Colour figures

CHAPTER 1



1a 1b 1c 1d

Figure 1. a the first model of the ODM developed by Prof. Alistair Fielder and Dr. Merrick Moseley in London, United Kingdom **b**: in 1997 the department of Medical Technical Development at the Academic Medical Center Amsterdam modified the design and made it smaller: it now measures temperature difference between the front and the back **c & d** the ODM as used in the study in The Hague: it weighs 1.8 g and measures 24 x 12 x 3.6 mm.

CHAPTER 3

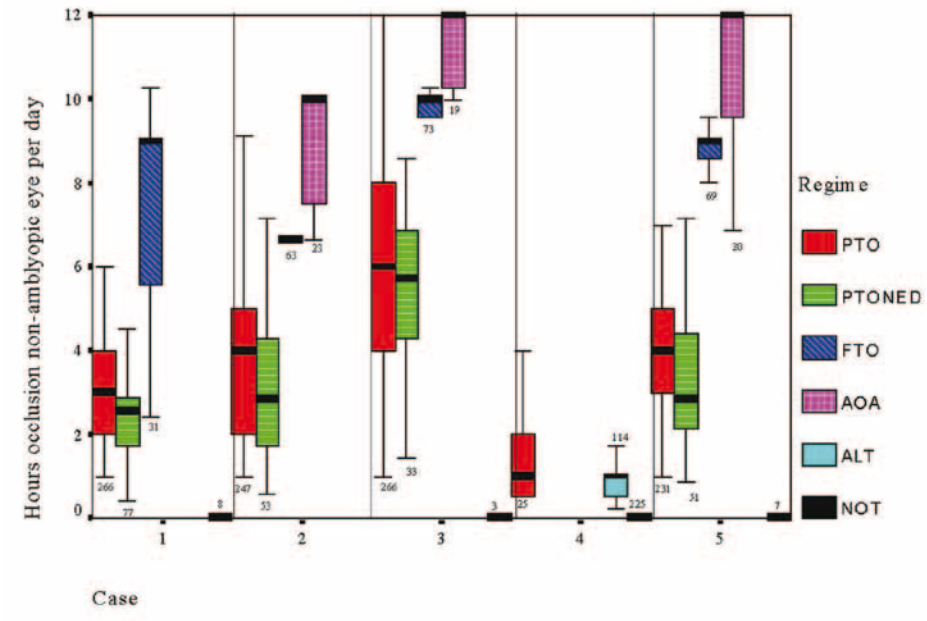


Figure 1. Median and interquartile range of the prescribed hours of occlusion per day of the non-amblyopic eye per regimen per case. The abscissa represents the five cases and the chosen regimen. The total number of orthoptists prescribing a regimen is given below each whisker.

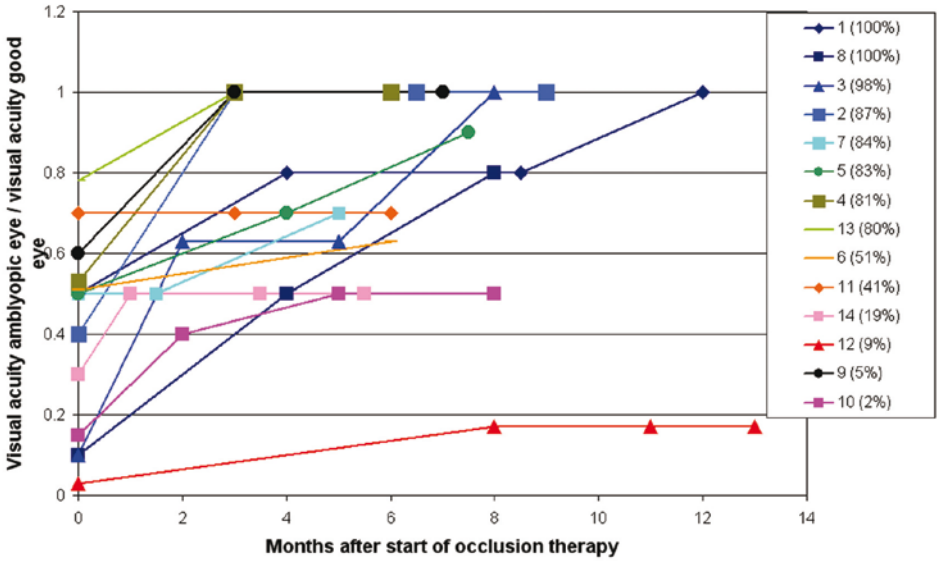


Figure 2. Graphic representation of the relationship between acuity increase during treatment and electronically measured compliance. The ordinate represents the ratio between visual acuity in the amblyopic eye and the acuity in the good eye. The abscissa represents the months after the start of occlusion therapy. On the right: patient number corresponding to the actually measured compliance in percentages in parenthesis. Blue lines represent patients with high compliance; red lines represent low compliance, corresponding to the visual acuity increase after 6 months of occlusion therapy.

CHAPTER 9

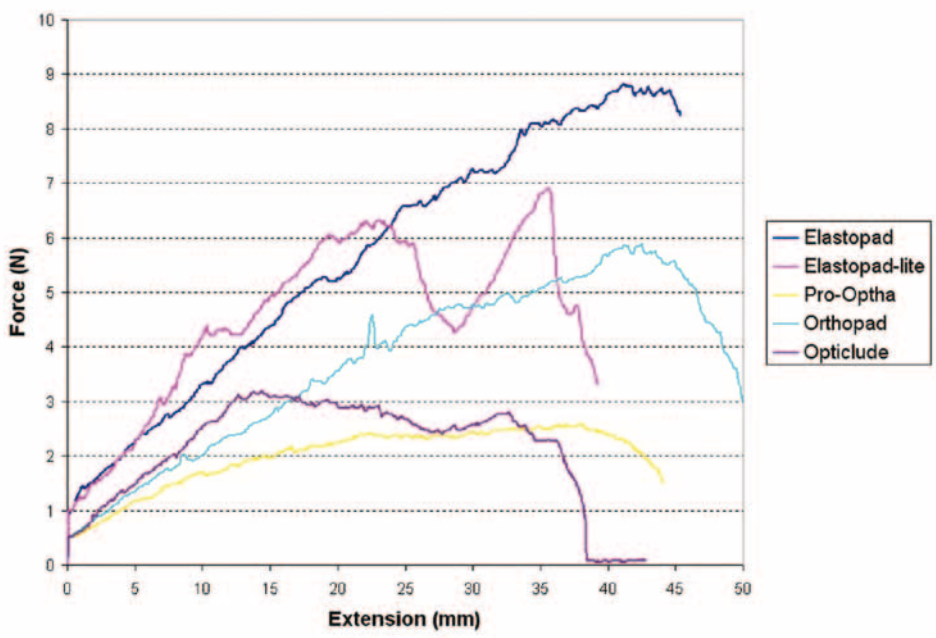


Figure 1. To remove the patches from the skin an average maximum force of 8.8 Newton (Beiersdorf), 5.9 N (Orthopad), 3.2 N (Opticlude) and 2.6 N (Pro-Ophta) was needed.

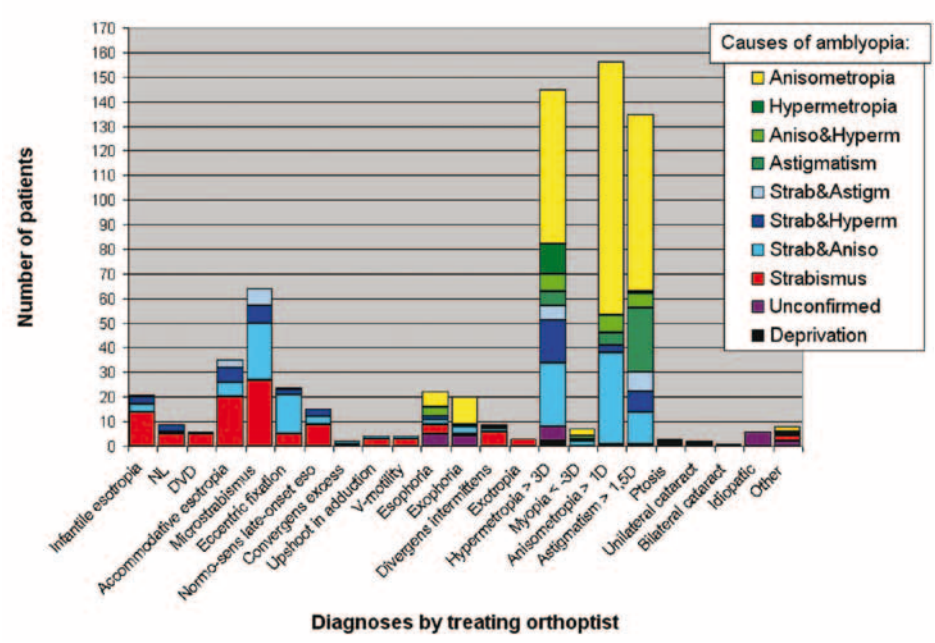


Figure 1.a. The distribution of the 10 possible causes of amblyopia per diagnose. Each bar represents a diagnosis. In our study population 23 diagnoses were given by the treating orthoptist and more than one diagnosis may be given to one child. Each bar was subdivided into the cause of amblyopia (assessed by the researchers), e.g. the diagnosis 'late-onset esotropia' was present in the following three causes of amblyopia: strabismus, strabismus & anisometropia and strabismus & hypermetropia.

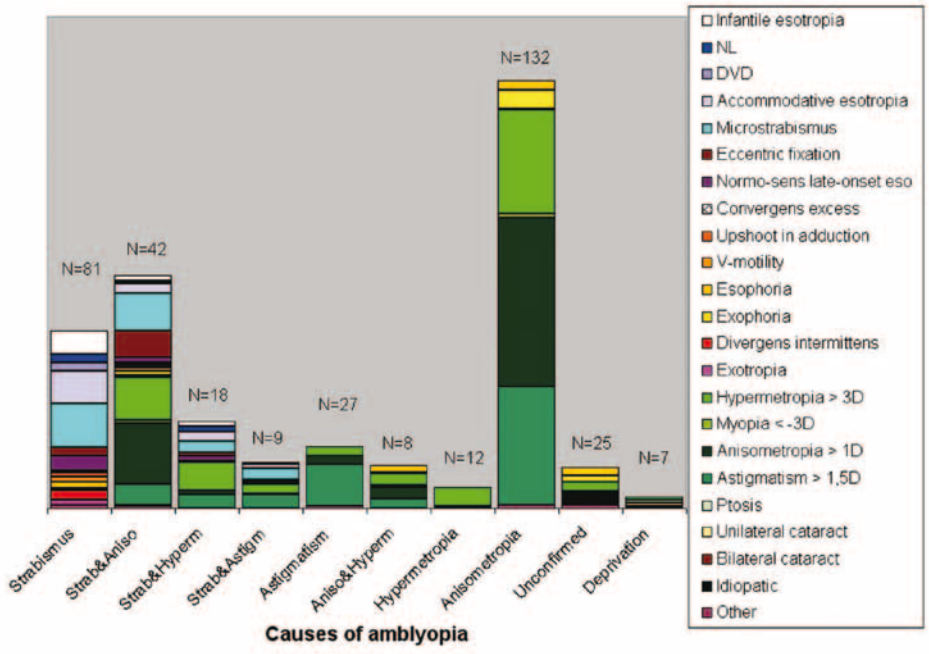


Figure 1.b. The distribution of the 23 diagnoses in our study population per cause of amblyopia. Each bar represents 1 of the 10 causes of amblyopia, which was subdivided in the diagnoses given in our study population. One child may have more than one diagnosis, but only one cause of amblyopia. For example, anisometropia was assessed as the cause of amblyopia in 132 children; however, 6 children with anisometropic amblyopia also had the diagnosis 'esophoria' and 11 'exophoria'. These diagnoses were not the main cause of amblyopia. The number above the bar corresponds with the number of children whose cause of amblyopia is represented in that bar.