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The Fourth Monitoring Report of the Early vs. Late Infantile Strabismus Surgery Study

The Early vs. Late Infantile Strabismus Surgery Study Group

Abstract The Early vs. Late Infantile Strabismus Surgery Study Group is a group of strabismologists and orthoptists from 58 clinics in 11 European countries. They investigate whether early or late surgery is preferable in infantile strabismus, in a non-randomized, prospective, multi-center trial.[1] Infants between 6 and 18 months of age receive a standardized entry examination and are then operated either before their second anniversary in clinics A, or between their 32nd and 60th month of age in clinics B. The children are evaluated at age six. After completion of the study, the two groups can then be compared regarding degree of binocular vision, angle of strabismus and visual acuity of the worse eye relative to the better. The current status of the study is reported here.

Up to December 13, 1996, 58 clinics have entered a total of 532 patients. Currently, 232 children have been entered in the early surgery group and 300 in the late surgery group. Completeness of data and forms are excellent. Thirty-eight patients have definitively dropped out. There is no evidence for inhomogeneities between the two therapy groups concerning the distribution of the four most important prognostic factors: spherical equivalents, horizontal angle of squint, degree of amblyopia and limitation of abduction.

Keywords Infantile strabismus; visual acuity; binocular vision; surgery

Preliminary remark All registration and other forms that reached the study center before December 13th were included in the analysis. Throughout the report we use the designation '*entered*' to characterize patients that have been included in the study, monitored and evaluated at age 6. For all children with infantile, convergent strabismus age 6 to 18 months referred to a participating clinic for the first time, an Entry Examination form and an Examination form were filled out, even if any of these children were further excluded from the study for any reason. Data on children that might have taken part but did not do so, for any reason, were obtained to get an impression of what is ex- and what is included in each participating clinic. Accordingly, the designation '*excluded*' is used throughout this report to indicate all patients that were excluded and not entered into the study thereafter. All entered and excluded children are '*registered*'.

Participants Originally, 84 clinics from 14 countries sent a letter of intent to participate in the study. Forty-one of these elected to take part in the

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TABLE 1. Listing of active participants per country. For each country, the country coordinating clinic with the country coordinator is listed first (marked with "CC"), followed by the other clinics in alphabetical order. Each entry consists of the clinic's name, the name of the clinic coordinator, and the assigned therapy group.

early surgery group and 43 in the late surgery group. They have been listed in the 1994 monitoring report.[2] Fifty-eight of these (33 in the late and 25 in the early surgery group) have become active, i.e. have registered children at the study center. These active participants are listed in Table 1.

Patient enrollment

PLANNED AND ACTUAL PATIENT RECRUITMENT The recruitment period ended on October 31st, 1996. The current recruitment numbers of 232 children in the early surgery group and 300 in the late surgery group reflect the

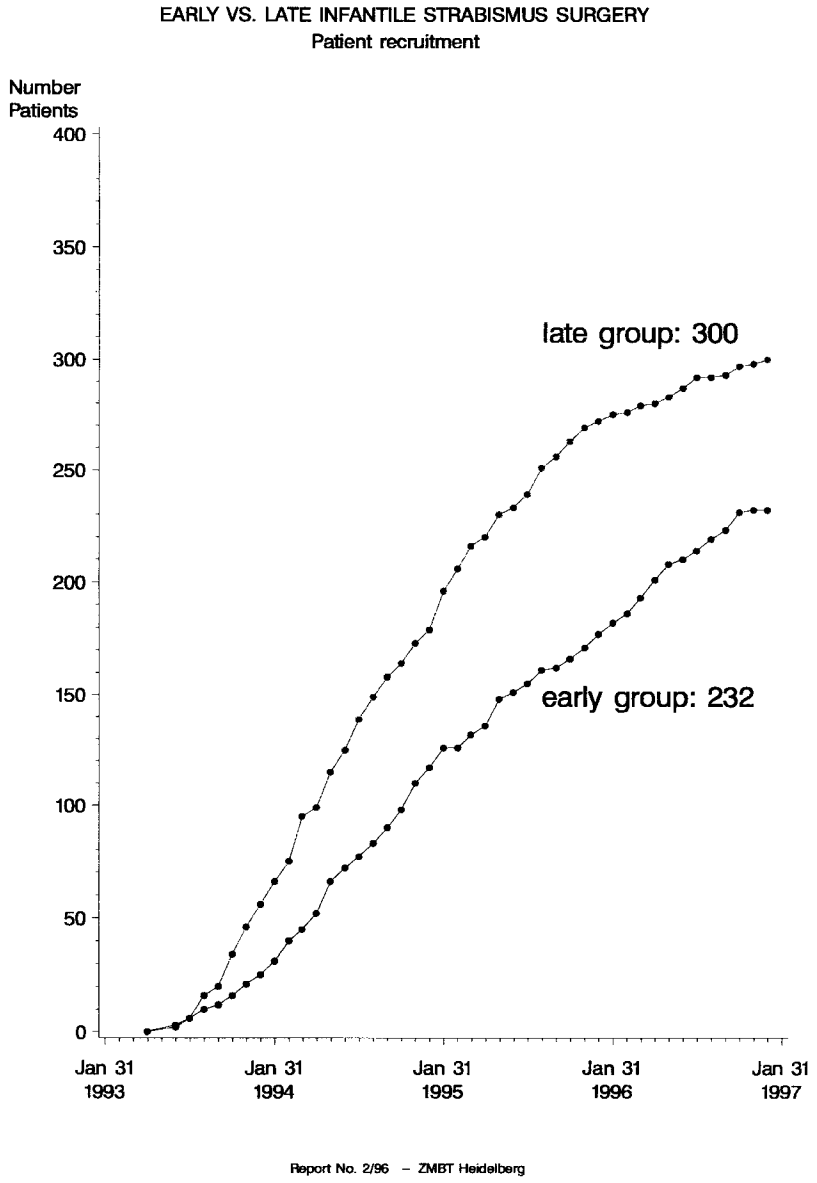
AU — Austria		
St. Pölten	Dr. Hildegard Gruber-Luka (CC)	late
Graz	Dr. Andrea Langmann	late
Linz	Ass. Dr. Andreas Hajek	late
Salzburg	OAe Dr. Helga Thaller-Antlanger	late
Vienna: Hanusch-Krh.	Univ. Doz. Dr. S. Harrer	late
Vienna: II. Univ-Augenklinik	Prof. Dr. Arnulf Thaler	early
Vienna: Wilhelminenspital	Prof. Dr. Arnulf Thaler	early
Vienna: Wiener Neustadt	Dr. Rudolf Pelz	late
B — Belgium		
Brussels	Prof. M. Spiritus (CC)	early
Edegem	Dr. Evens	early
CH — Switzerland		
Lausanne	Dr. Giorgio Klainguti (CC)	early
Zurich	Dr. Klara Landau	early
D — Germany		
Halle	Dr. R. Weidlich (CC)	late
Heidelberg	Prof. Dr. Gerald Kolling (CC)	late
Berlin Steglitz	Dr. Jandeck	late
Berlin Virchow	Dr. Ebba-Ch. Schwarz	early
Dresden	PD Dr. Erika Sommer	late
Erlangen	Dr. G. Gusek	late
Frankfurt/M. Univ	Dr. A. Zubcov	early
Freiburg Univ	Prof. Dr. Kommerell	late
Hamburg Univ	Prof. Dr. Elisabeth Schulz	late
Homburg/Saar	Dr. B. Kaesmann	late
Cologne Univ	Dr. F. Kaszli	late
Munich TU	PD Dr. T. Schmidt	late
Munich Univ	Prof. Dr. Boergen	late
Regensburg Univ	Prof. Dr. Lorenz	late
F — France		
Lyon	Dr. Bourron-Madignier (CC)	early
GB — Great Britain		
Dundee	Dr. C.J. McEwen	early
Liverpool	Dr Ian Marsh	early
London H. f. Sick Children	Dr. Chris Timms	early

I — Italy		
Florence	Prof. Dr. Riccardo Frosini (CC)	late
Sassari	Prof. Dr. Francesco Carta	late
N — Norway		
Bergen	Dr. Olav H. Haugen (CC)	early
Aalesund	Dr. Geir Hanken	late
Forde Sentralsjukehuset	Dr. Leif Steene Eriksen	late
Haugesund	Dr. John Bore	early
Lillehammer	Dr. Tore Bulie	late
Tonsberg	Dr. Hans Petter Brinck	late
NL–Netherlands		
Amsterdam	Dr. L. Wenniger-Prick (CC)	early
Goes	Dr. A.G. Tjiam	early
Rotterdam Univ. Hosp.	PD Dr. H.J. Simonsz	late
Rotterdam Eye Hosp.	Dr. Jan-Tjeerd de Faber	early
S — Sweden		
Huddinge	Drs. Holmström / Lennerstrand (CC)	late
Boras	Dr. Gunnar Ladenvall	late
Danderyd	Dr. Agneta Wallin	late
Eskilstuna	Dr. Peter Furuskog	early
Jönköping	Dr. Birgitta Sunnqvist	early
Linköping	Dr. Peter Jakobsson	early
Sundsvall	Dr. Marlene Lindberg	late
Umea	Dr. Kent Johansson	early
Växjö	Dr. Ingvar Axelsson	late
T — Turkey		
Istanbul Beyoglu	Dr. Birsen Acar (CC)	late
Adana	Dr. Gülhanim Haciyakupoglu	late
Ankara Hacettepe Univ.	Prof. Dr. Ali Sefik Sanac	early
Ankara Saglik Bakanligi	Dr. Saniye Demirci	early
Ankara Univ.	Dr. Necile Erkam	early
Edirne Trakya Univ.	Prof. Dr. Nazan Erda	late
Izmir 9 Eyül Univ.	Dr. Ayse Tulin Berk	early

definitive numbers (apart from a rare child that may have been registered between December 13th and 31st). Patient recruitment rates have been lower than expected originally (Fig. 1). Possible consequences for analysis have to be decided upon at the end of the follow-up period, when the definitive number of children available for analysis is fixed. It is theoretically possible that not all three questions of the study but only the first two will be able to be answered.

PATIENTS ENTERED AND PATIENTS EXCLUDED PER CLINIC Table 2 gives an overview of the patients entered and excluded per clinic. The columns contain the number of patients entered into the study and the number of patients excluded, for early and late surgery, respectively. The ratio of entered to excluded children varies considerably per clinic. This may be due in part to differing patient populations (for instance, university clinics will

Fig. 1. Patient recruitment.



have more excluded children because their patients are more affected by neurological and developmental disorders) and in part to failure to register these children. For both groups of clinics, however, the ratio is similar with 232:183 for the early and 300:272 for the late surgery group.

When Table 2 is compared with the results from last year's report, the ratio of entered to excluded children is similar. However, the proportion of excluded children in the early surgery group has decreased. Most clinics contributed patients with entry rates similar to the past, but a few clinics have been dramatically less active than before.

LISTING OF EXCLUSION CRITERIA EMPLOYED The reasons that excluded patients did not enter the study are listed in Table 3 (multiple reasons are possible).

Clinic	entered early surgery	entered late surgery	excluded early surgery	excluded late surgery
AU – Austria				
Graz	0	9	0	1
Linz	0	2	0	8
Salzburg	0	3	0	2
St. Pölten	0	22	0	21
Vienna: Hanusch-Krh.	0	16	0	21
Vienna: II Univ-Augenklinik	17	0	22	0
Vienna: Wilhelminenspital	13	0	17	0
Vienna: Wiener Neustadt	0	21	0	13
	30	**73**	**39**	**66**
B – Belgium				
Brussels	34	0	16	0
Edegem	5	0	3	0
	39	**0**	**19**	**0**
CH – Switzerland				
Lausanne	23	0	15	0
Zurich	2	0	6	0
	25	**0**	**21**	**0**
D – Germany				
Berlin Steglitz	0	3	0	4
Berlin Virchow	18	0	14	0
Dresden	0	10	0	22
Erlangen	0	28	0	23
Frankfurt/M. Univ	15	0	19	0
Freiburg Univ	0	37	0	24
Halle	0	1	0	0
Hamburg	0	23	0	5
Heidelberg	0	26	0	15
Homburg/Saar	0	3	0	39
Cologne	0	6	0	3
Munich TU	0	5	0	0
Munich Univ	0	18	0	3
Regensburg Univ	0	17	0	4
	33	**177**	**33**	**142**
F – France				
Lyon	24	0	11	0
GB – Great Britain				
Dundee	1	0	2	0
Liverpool	3	0	1	0
London H. f. Sick Children	1	0	0	0
	5	**0**	**3**	**0**
I – Italy				
Florence	0	3	0	9
Sassari	0	2	0	0
	0	**5**	**0**	**9**

TABLE 2. Entered and excluded children per clinic.

DELAY BETWEEN ENTRY EXAMINATION AND PATIENT REGISTRATION

The median delay between the entry examination and receipt of the patient registration form at the study center was 11 days. 75% of all forms were received within 4 weeks as compared to 73% in the last report.

N–Norway				
Aalesund	0	0	0	1
Bergen	14	0	1	0
Forde Sentralsjukehuset	0	3	0	2
Haugesund	5	0	2	0
Lillehammer	0	2	0	0
Tonsberg	0	5	0	10
	19	**10**	**3**	**13**
NL–Netherlands				
Amsterdam	3	0	1	0
Goes	3	0	2	0
Rotterdam Univ. Hosp.	0	7	0	11
Rotterdam Eye Hosp.	0	0	22	0
	6	**7**	**25**	**11**
S–Sweden				
Boras	0	0	0	4
Danderyd	0	8	0	0
Eskilstuna	5	0	1	0
Huddinge	0	1	0	0
Jönköping	11	0	5	0
Linköping	8	0	4	0
Sundsvall	0	5	0	1
Umea	5	0	0	0
Växjö	0	4	0	0
	29	**18**	**10**	**5**
T–Turkey				
Adana	0	1	0	1
Ankara Hacettepe Univ.	2	0	6	0
Ankara Saglik Bakanligi	2	0	0	0
Ankara Univ	14	0	11	0
Edirne Trakya Univ.	0	9	0	23
Istanbul Beyoglu	0	0	0	2
Izmir 9 Eyül Univ.	4	0	2	0
	22	**10**	**19**	**26**
All Clinics	**232**	**300**	**183**	**272**

TABLE 3. Listing of exclusion criteria employed.

Reason	*Frequency*
Age limit	23
Onset of strabismus after the age of 4 months	126
Prematurity	32
Congenital nystagmus	49
Cerebral palsy or other neurological deficit	101
Angle of strabismus <5°	25
Angle of strabismus >30°	72
Divergent strabismus	11
No exclusion criteria apply but parents declined to participate	7
Other medical reasons (e.g. tachycardia)	14
Organizational reasons (e.g. language problems)	6
Formal reasons (e.g. application after surgery)	97

QUALITY OF THE DOCUMENTATION Tables 4 and 5 summarize the completeness of the documentation forms and of the data for all entered patients. The plausibility of the data is permanently monitored by the study center.

TABLE 4. State of the documentation forms per clinic.

Country and Clinic	complete	returned for ≤ 4 weeks	due for ≤ 4 weeks	returned for > 4 weeks	due for > 4 weeks
AU–Austria					
Graz	46			5	10
Linz	12				2
Salzburg	16			2	3
St. Pölten	123				2
Vienna: Hanusch-Krh.	73		2	1	19
Vienna: II. Univ-Augenklinik	93			1	5
Vienna: Wilhelminenspital	99			2	13
Vienna: Wiener Neustadt	120				4
	582	**0**	**2**	**11**	**58**
B–Belgium					
Brussels	204	1	2		16
Edegem	19			3	2
	223	**1**	**2**	**3**	**18**
CH–Switzerland					
Lausanne	129	1	2	1	9
Zurich	15				1
	144	**1**	**2**	**1**	**10**
D–Germany					
Berlin Steglitz	10		1		1
Berlin Virchow	83		2	1	16
Dresden	56	1			4
Erlangen	117		2		61
Frankfurt/M. Univ	102			3	4
Freiburg Univ	210		4		3
Halle	3				
Hamburg	106		2	3	1
Heidelberg	130	3	1	2	28
Homburg/Saar	16				2
Cologne	20			1	8
Munich TU	25		1		6
Munich Univ	110	2	2		11
Regensburg Univ	81		1	1	24
	1069	**6**	**16**	**11**	**169**
F–France					
Lyon	136	3	5		15
GB–Great Britain					
Dundee	6				
Liverpool	12		1		2
London H. f. Sick Children					7
	18	**0**	**1**	**0**	**9**
I–Italy					
Florence	2		2	4	16
Sassari	6			1	
	8	**0**	**2**	**5**	**16**

N–Norway					
Bergen	105		3	4	20
Forde Sentralsjukehuset	19			1	4
Haugesund	36			3	7
Lillehammer	3			1	8
Tonsberg	31		1	2	4
	194	**0**	**4**	**11**	**43**
NL–Netherlands					
Amsterdam	20			1	3
Goes	22			2	2
Rotterdam Univ. Hosp.	33	1		1	
	75	**1**	**0**	**4**	**5**
S–Sweden					
Danderyd	44		2	2	8
Eskilstuna	22				3
Huddinge	6				2
Jönköping	74	1	2		3
Linköping	67			3	3
Sundsvall	30	2		1	5
Umea	39		1		1
Växjö	25			2	7
	307	**3**	**5**	**8**	**32**
T–Turkey					
Adana				3	1
Ankara Hacettepe Univ.	6				2
Ankara Saglik Bakanligi	7				3
Ankara Univ.	29		2		20
Edirne Trakya Univ.	30				16
Izmir 9 Eyül Univ.	6		1	3	17
	78	**0**	**3**	**6**	**59**
All Clinics	**2834**	**15**	**42**	**60**	**434**

Table 4 lists all documentation forms in one of five categories. 'Complete' means that the forms are without error. 'Due' means that the forms should become available to the study center shortly. There can be various reasons for this: for instance, a delay in the examination procedure or an internal organizational problem. 'Returned' means that the forms have been returned for completion or for correction of plausibility errors. The number of forms per clinic in each category is listed in the table.

The completeness rates of the forms were good. However, the proportion of forms due for more than 4 weeks has increased from 10% (last year) to 12%.

Table 5 shows the percentage of completeness of the required data among all documentation forms of entered patients. All forms that were available to the study center were included in this part of the analysis, regardless of whether they were 'complete' or 'returned'. Interdependencies in the data are taken into account: for instance, patterns of previous occlusion therapy can only be given when the question 'previous occlusion therapy?' has been answered affirmatively.

Country and Clinic	Entry Examination Form	Examination Form	Surgery Form
AU–Austria			
Graz	100	99	100
Linz	100	100	
Salzburg	100	98	100
St. Pölten	100	100	96
Vienna: Hanusch-Krh.	100	98	100
Vienna: II. Univ-Augenklinik	100	97	100
Vienna: Wilhelminenspital	100	97	100
Vienna: Wiener Neustadt	100	100	100
B–Belgium			
Brussels	100	99	98
Edegem	100	98	93
CH–Switzerland			
Lausanne	100	95	100
Zurich	100	100	100
D–Germany			
Berlin Steglitz	100	100	
Berlin Virchow	99	98	100
Dresden	100	100	100
Erlangen	100	100	100
Frankfurt/M. Univ	100	98	96
Freiburg Univ	99	99	100
Halle	100	100	
Hamburg	99	99	100
Heidelberg	100	100	
Homburg/Saar	100	99	
Cologne	98	98	
Munich Tu	100	98	100
Munich Univ	100	99	100
Regensburg Univ	99	99	100
F–France			
Lyon	100	97	99
GB–Great Britain			
Dundee	100	98	92
Liverpool	100	89	100
I–Italy			
Florence	92	89	
Sassari	100	99	
N–Norway			
Bergen	100	98	100
Forde Sentralsjukehuset	100	100	100
Haugesund	100	99	100
Lillehammer	100	98	
Tonsberg	97	96	100
NL–Netherlands			
Amsterdam	100	96	100
Goes	96	94	100
Rotterdam Univ. Hosp.	100	96	97

TABLE 5. Percentage of completeness of required data per clinic.

Country and Clinic	Entry Examination Form	Examination Form	Surgery Form
S–Sweden			
Danderyd	99	99	
Eskilstuna	100	97	100
Huddinge	100	97	
Jönköping	99	99	98
Linköping	95	93	94
Sundsvall	100	95	
Umea	100	98	100
Växjö	97	90	100
T–Turkey			
Adana	91	63	
Ankara Hacettepe Univ.	100	100	100
Ankara Saglik Bakanligi	100	97	86
Ankara Univ.	100	98	
Edirne Trakya Univ.	100	98	
Izmir 9 Eyül Univ.	97	100	100
All Clinics	**100**	**98**	**99**

Dropouts and deviations of therapy

DROPOUTS In total, 38 children have been lost to follow-up, 18 in the early and 20 in the late operating group. In 12 cases the child and parents had moved, in 14 cases the parents were no longer compliant, in one case the treatment had to be continued in another clinic because of a health insurance problem and in another case the patient suffered from a psychomotor retardation. In 10 cases the parents were not contacted and the reason for the dropout remains unknown.

SURGERY SCHEDULE Surgery should be performed before the child's second birthday in the early operating group, and after its 32nd month in the late group.

In the early group, 140 children have been operated in accordance with the study protocol.[1] For 35 children, no surgery has been documented although they are already two years old; 14 children were definitely operated too late. Among these 49 children, 3 cases could not be operated as scheduled because the child was ill, in 6 other cases the childrens' parents opted for late surgery. For 7 patients surgery was cancelled because of a small angle of strabismus, and 10 children were dropouts. In 22 cases the reason is not known to the study center.

In the late group, 43 children have been operated up to now. Six of them had not completed their 32nd month of life at the time of surgery for the following reasons: The parents wished an early surgery in two cases, two patients suffered from torticollis, one child often fell when walking, and in one case occlusion was not tolerated.

EXAMINATION INTERVALS Intermediate examinations should be performed every 6 months with a maximum delay of 4 weeks. 1274 out of 1439 documented intermediate examinations have been performed accordingly.

The two longest examination intervals were 21 and 28 months. Intermediate examinations should also be performed within 2 weeks after surgery, with a tolerance of two weeks. This has been achieved in 166 of 212 cases of surgery (including 18 cases of re-operation). Furthermore, 24 examinations were done within the second month after surgery. Thirteen cases with a delay of 3 to 9 months after surgery are considered as regular intermediate examinations instead of postoperative examinations. In 9 cases, no postoperative examination is documented at the study center.

Prognostic factors To ensure the internal validity of the study's results, prognostic factors should be distributed homogeneously in the early and late surgery groups. With respect to external validity it is, in addition, desirable that the distribution be the same among entered children as in the

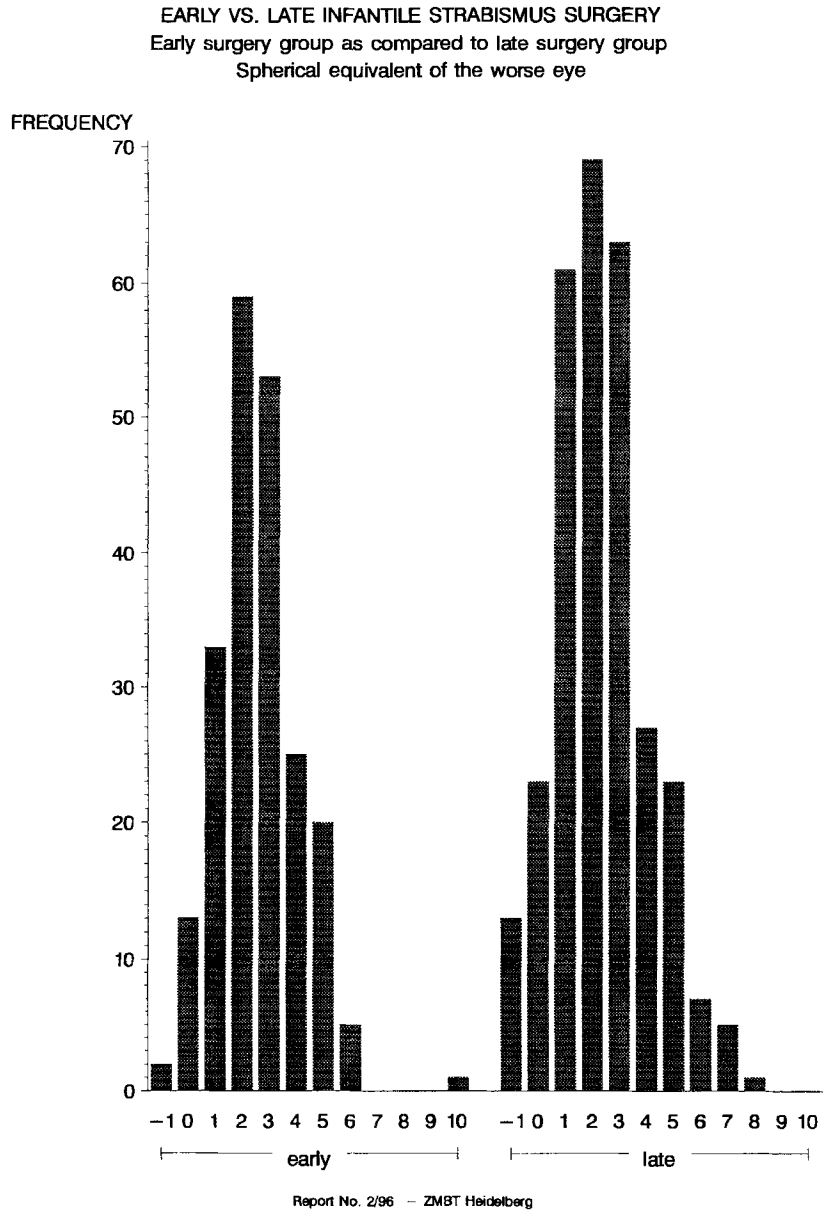


Fig. 2. Distribution of retinoscopy values among the two groups.

entire population. Therefore, excluded children are also documented. Details on important prognostic factors are reported below.

RETINOSCOPY VALUES The spherical equivalents of the worse eye in the early and the late group followed a unimodal distribution, both with a median of Sph. +2.3 (Fig. 2). Values ranged from −1.5 to 10 in the early group and from −1.5 to 7.5 in the late group. Excluded children also have a unimodal distribution with a median of Sph. +2, and with values ranging from −11 to 30.

HORIZONTAL ANGLE OF SQUINT The range of entered children is limited by the exclusion criteria from 5 to 30 degrees (Fig. 3). The median values were 22 degrees in the early and 20 degrees in the late surgery group. Ex-

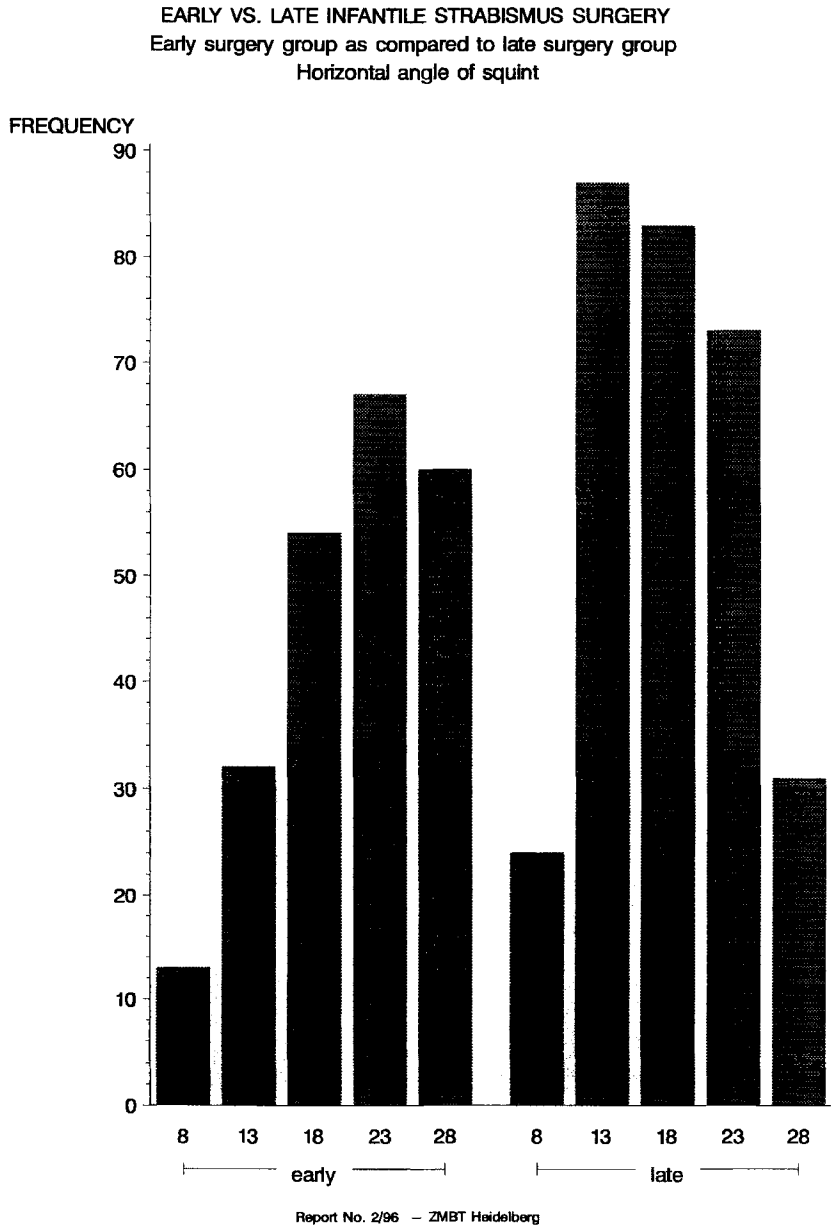


Fig. 3. Distribution of horizontal angle of squint among the two groups.

cluded children had a median of 17 degrees with extreme values of -40 and 50 degrees.

DEGREE OF AMBLYOPIA OF THE WORSE EYE The distributions were similar for all groups (Fig. 4). The most frequent category was 2 (alternating but preference of fixation); 39% of the early surgery and 47% of late surgery children as well as 37% of excluded children fell into this category. The proportion of children within categories 1 to 3 was 94% in the early and 96% in the late group as compared to 85% in the excluded group (categories 1 to 3 are prognostically better than 4 and 5).

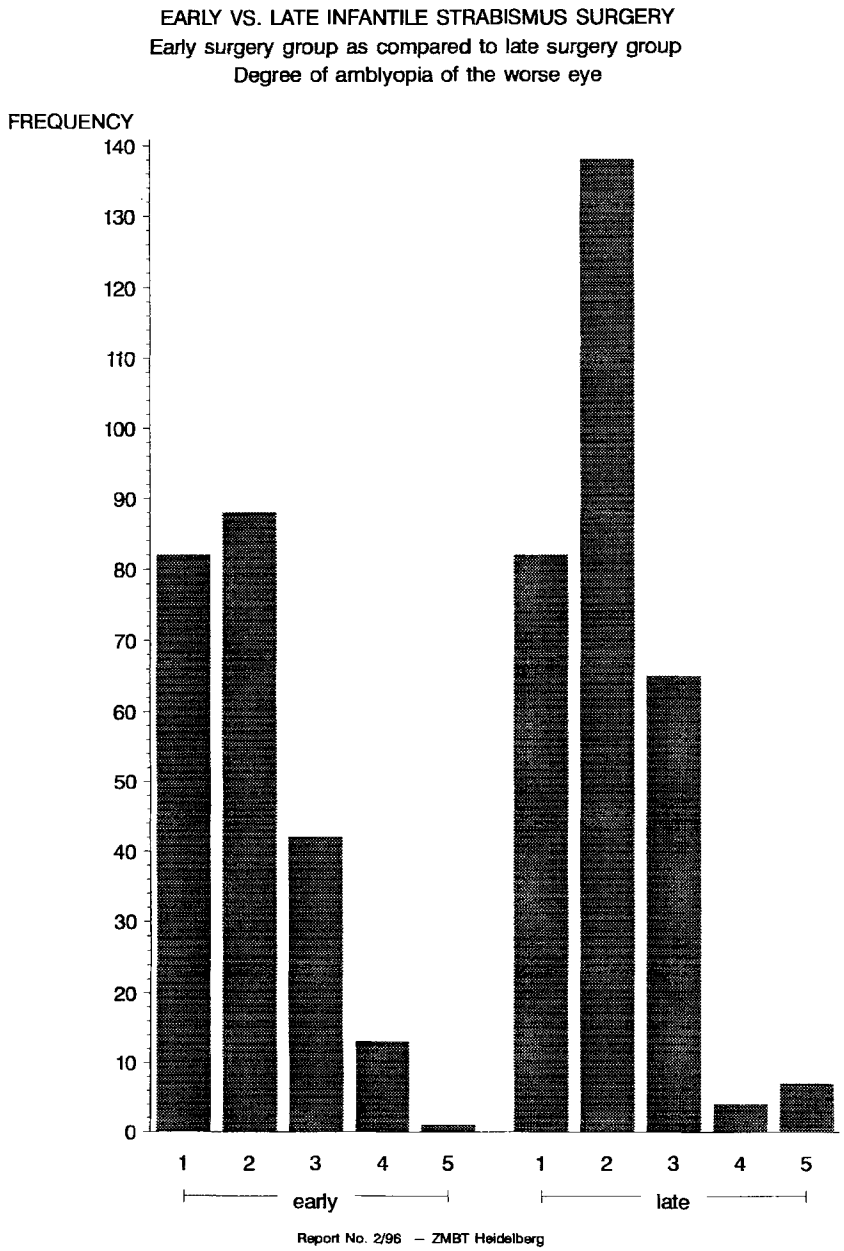


Fig. 4. Distribution of degree of amblyopia of the worse eye among the two groups.

RESTRICTION OF ABDUCTION OF THE WORSE EYE Distributions were similar (Fig. 5). The most frequent category was 1 (free, using pursuit movements), the second was 3 (passing midline but not free, using any method). Categories 1 and 2 applied to 63%, 57% and 61% for early, late and excluded children, respectively.

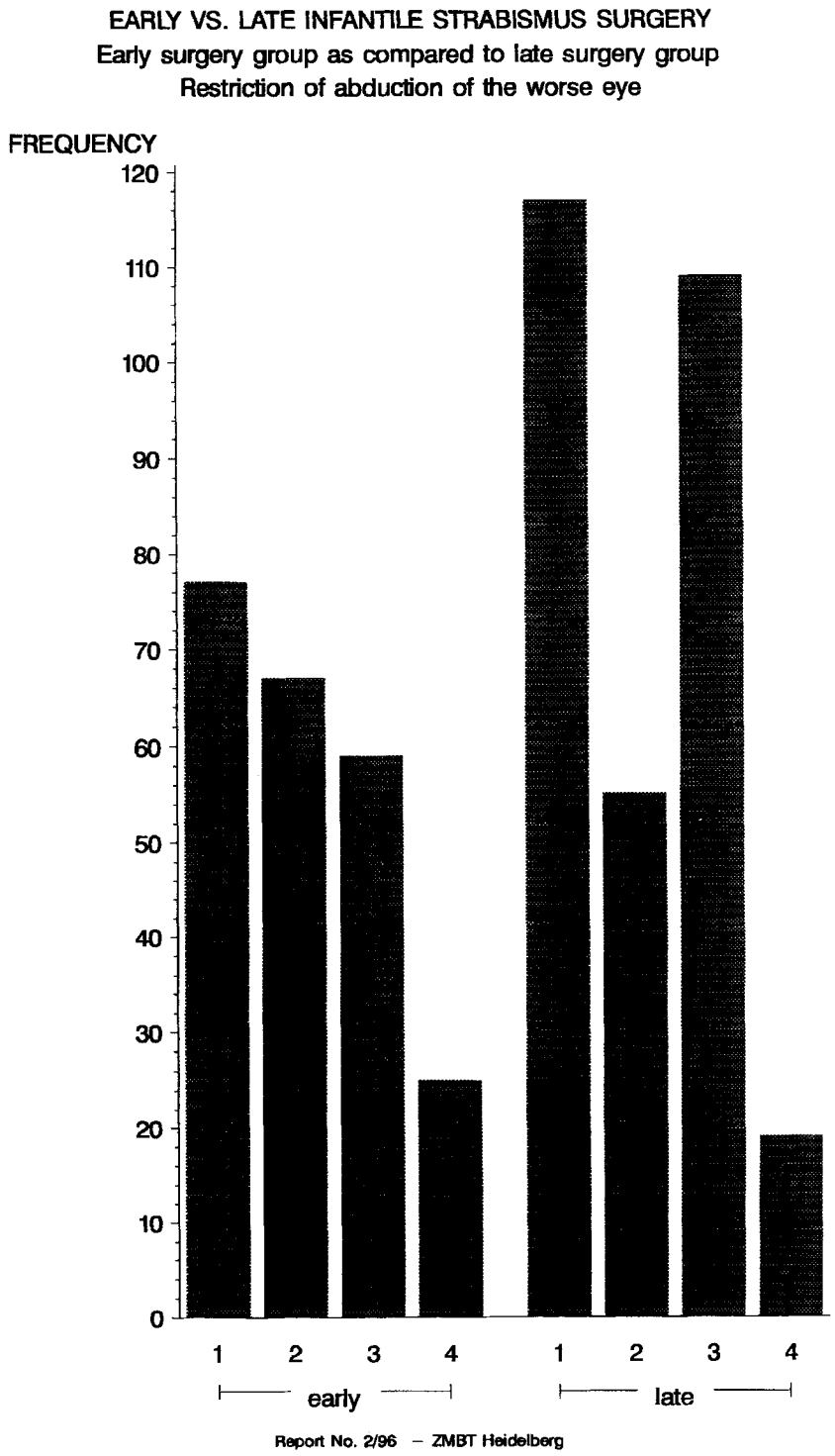


Fig. 5. Distribution of restriction of abduction of the worse eye among the two groups.

Variable	early surgery	late surgery
Mean of occlusion pretreatment in months	2.0	2.3
Median of occlusion pretreatment in months	0	0
Third quartile of occlusion pretreatment	3	4
Mean age in days at the time of the entry examination	338	333
Rate of previously prescribed glasses	19%	24%
Rate of previously prescribed atropine	3%	2%
Rate of permanent occlusion tolerance	81%	81%
Rate of vertical deviation in primary position	10%	16%
Rate of vertical deviation in left or right gaze	17%	32%
Rate of V-pattern >5 degrees	3%	9%
Rate of A-pattern	0.4%	2.4%
Rate of latent nystagmus	16%	33%
Rate of torticollis	11%	19%
Rate of DVD	8%	14%

TABLE 6. Summary of variables.

OTHER VARIABLES A summary of the distribution of other variables is presented in Table 6. Amazingly, all of these symptoms were more often found in the late than in the early group. Age of the child at the entry examination was not the cause, because the average age was similar in the two groups. It may have to do with the large regional variations in orthoptist- and ophthalmologist-density that we face in Europe. Most of the late children were recruited in Germany by centers employing more orthoptists than elsewhere in Europe.

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