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The Early vs. Late Infantile Strabismus Surgery Study: Monitoring Report

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 who investigate whether early or late surgery is preferable in infantile strabismus, in a non-randomized, prospective, multi-center trial. Infants between six and 18 months of age will receive a standardized entry examination and then be operated either before their second anniversary, in clinics A, or between 32nd and 60th month of age in clinics B. The children will be 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 one. This is the second monitoring report of the study.

Key words Strabismus; surgery

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Preliminary remark The analysis for this monitoring report was performed in April 1995. All Registration and other forms that reached the study before April 11th were included in the analysis.

Please note: Throughout the report we use the designation *entered* to characterize patients who are included into the study, monitored and evaluated at age six.

For all children with infantile, convergent strabismus age six to 18 months referred to a participating clinic for the first time, an Entry Examination form and an Examination form must be filled out, even if any of these children is further excluded from the study for any reason. Data on children who might have taken part but did not do so for any reason, must be obtained to get an impression of what is excluded and what is included in each participating clinic. Accordingly, the designation *excluded* is used throughout this report to indicate all patients who were excluded and not entered into the study thereafter. All entered and excluded children are *registered.*

1 Participants Originally, 84 clinics from 14 countries did send a letter of intent to participate in the study. Forty-one of these elected to take part in the early surgery group and 43 in the late surgery group. They have been listed in the last year's monitoring report (The Early vs. Late Infantile Strabismus Surgery Study Group, 1994). Unfortunately, only 55 of these (33 in the late and 22 in the early surgery group) have become active, *i.e.*, did register children at the study center.

TABLE I. Listing of active participants per country.

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

TABLE 1, *continued*

NL – Netherlands		
Amsterdam	Dr. L. Wenniger-Prick (CC)	early
Goes	Dr. A.G. Tjiam	early
Rotterdam Akademisch Z.	PD Dr. H.J. Simonsz	late
Rotterdam Oogziekenhuis	Dr. Jonathan de Faber	early
S – Sweden		
Huddinge	Drs. Holmstroem/Lennerstrand (CC)	late
Boras	Dr. Gunnar Ladenvall	late
Danderyd	Dr. Agneta Wallin	late
Eskilstuna	Dr. Peter Furuskog	early
Jönköping	Dr. Brigitta Sunnqvist	early
Linköping	Dr. Peter Jakobsson	early
Sundsvall	Dr. Marlene Lindberg	late
Umeå	Dr. Kent Johansson	early
Vaexjö	Dr. Invar Axelsson	late
T – Turkey		
Istanbul Beyoglu	Dr. Birsen Acar (CC)	late
Adana	Dr. Guelhanim Haciyakupoglu	late
Ankara Hacettepe Univ.	Prof. Dr. Ali Sefik Sanac	early
Ankara Saglik Bakanligi	Dr. Saniye Demirci	early
Edirna Trakya Univ.	Dr. Nazan Erda	late
Izmir 9 Eyuel Univ.	Dr. Ayse Tulin Berk	early

The active participants are listed in Table 1, including one clinic with preliminary registrations only. For each country, the country coordinating clinic with 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.

2 Patient enrolment

2.1 PLANNED AND ACTUAL PATIENT RECRUITMENT According to the revised schedule, 380 patients must be recruited per group on December 31st, 1995. However, until 15th of April only 223 children have been recruited in the late and 141 in the early surgery group (see Fig. 1). The proportion of 223 to 141 children fits exactly the proportion of 33 to 22 active clinics. In addition there are 11 preliminarily registered children who still await definite entry to the study.

Until December 31st, 1995, in all likelihood, there will at least be recruited 200 children in the early and 300 children in the late group. This will be sufficient to reach the main goal of the study: to assess in a confirmatory analysis whether early or late surgery is preferable concerning binocular vision. Whether the study will be able to answer this question in regard to angle of strabismus and amblyopia remains uncertain, however.

Details will be discussed during the next meeting of the Study Committee in Cambridge, in September 1995, during the ESA conference, to which all Country Coordinators, their representatives or other participants are invited. Possible actions could be (1) extending the recruitment period, (2) concen-

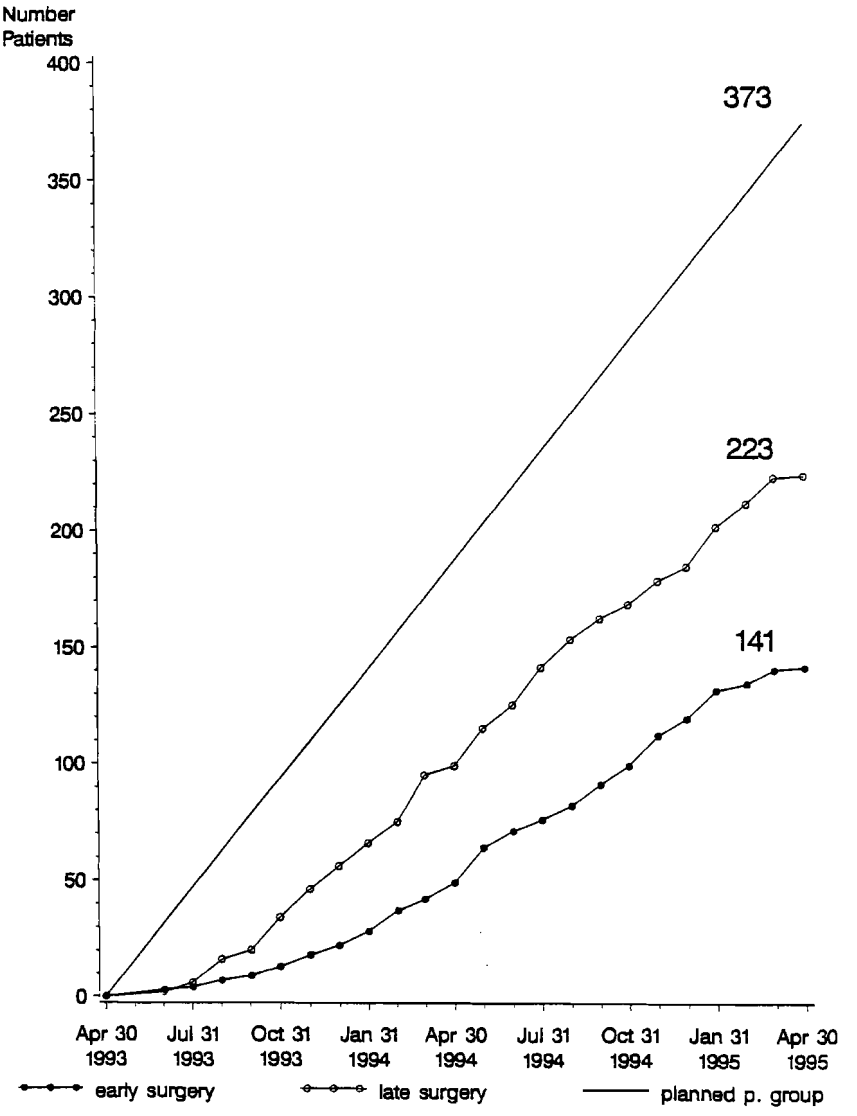

Fig. 1. Planned and actual patient recruitment. The number of 373 planned patients per group was determined according to the original schedule.

trating on binocular vision as the main criterion of the study while angle of strabismus and amblyopia are examined in an exploratory analysis only and (3) no action, accepting the loss in power associated with a lower sample size than intended.

2.2 PATIENTS ENTERED AND PATIENTS EXCLUDED PER CLINIC Table 2 gives an overview of 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.

As in last year's report, the ratio of entered to excluded children varies considerably per clinic. For all clinics, however, the ratio is very similar with 141:115 for the early and 223:178 for the late surgery group.

2.3 LISTING OF EXCLUSION CRITERIA EMPLOYED Excluded patients did not enter the study for the reasons listed in Table 3 (multiple reasons possible).

TABLE 2. Entered and excluded children per clinic.

Clinic	*Entered early surgery*	*Entered late surgery*	*Excluded early surgery*	*Excluded late surgery*
AU – Austria				
Graz	0	6	0	1
Linz	0	3	0	6
Salzburg	0	3	0	2
St. Pölten	0	15	0	13
Wien Hanusch-Krh.	0	15	0	17
Wien II. Uni-Augenklinik	9	0	19	0
Wien Wilhelminenspital	9	0	14	0
Wiener Neustadt	0	14	0	8
	18	**56**	**33**	**47**
B – Belgium				
Bruxelles	27	0	8	0
Edegem	1	0	2	0
	28	**0**	**10**	**0**
CH – Switzerland				
Lausanne	10	0	12	0
Zürich	2	0	3	0
	12	**0**	**15**	**0**
D – Germany				
Berlin Charité	5	0	9	0
Berlin Steglitz	0	2	0	3
Dresden	0	7	0	16
Erlangen	0	22	0	13
Frankfurt/M. Uni	13	0	12	0
Freiburg Uni	0	25	0	14
Halle	0	1	0	0
Hamburg	0	11	0	4
Heidelberg	0	19	0	9
Homburg/Saar	0	4	0	21
Köln	0	5	0	2
München TU	0	2	0	0
München Uni	0	13	0	3
Regensburg Uni	0	12	0	1
	18	**123**	**21**	**86**
F – France				
Lyon	20	0	7	0
GB – Great Britain				
Liverpool	0	0	1	0
London H.F. Sick Children	1	0	0	0
	1	**0**	**1**	**0**
I – Italy				
Firenze	0	3	0	9
Sassari	0	2	0	0
	0	**5**	**0**	**9**
N – Norway				
Aalesund	0	0	0	1
Bergen	11	0	1	0
Forde Sentralsjukehuset	0	3	0	0
Haugesund	5	0	0	0
Lillehammer	0	2	0	0
Tonsberg	0	5	0	8
	16	**10**	**1**	**9**

Table 2 continued p. 136

TABLE 2, *continued*

Clinic	*Entered early surgery*	*Entered late surgery*	*Excluded early surgery*	*Excluded late surgery*
NL – Netherlands				
Amsterdam	2	0	1	0
Rotterdam Akademisch Z.	0	2	0	9
Rotterdam Oogziekenhuis	4	0	16	0
	6	**2**	**17**	**9**
S – Sweden				
Boras	0	1	0	2
Danderyd	0	6	0	0
Eskilstuna	1	0	1	0
Huddinge	0	1	0	0
Jönköping	6	0	2	0
Linkoeping	6	0	2	0
Sundsvall	0	5	0	1
Umeå	3	0	0	0
Vaexjö	0	4	0	0
	16	**17**	**5**	**3**
T – Turkey				
Adana	0	2	0	0
Anakara Hacettepe Univ.	1	0	4	0
Ankara Saglik Bakanligi	2	0	0	0
Edirne Trakya Univ.	0	8	0	13
Istanbul Beyoglu	0	0	0	2
Izmir 9 Eyuel Univ.	3	0	1	0
	6	**10**	**5**	**15**
All Clinics	**141**	**223**	**115**	**178**

2.4 DELAY BETWEEN ENTRY EXAMINATION AND PATIENT REGISTRATION Last year, we reported on the problem of long delays between entry examination and registration of the patient. The situation has improved since. 40% (23% last year) of all children are registered within a

TABLE 3. Listing of exclusion criteria employed

Reason	*Frequency*
Age limit	15
Onset of strabismus after the age of four months	90
Prematurity	17
Congenital nystagmus	28
Cerebral palsy or other neurological deficit	58
Angle of strabismus <5°	19
Angle of strabismus >30°	40
Divergent strabismus	4
No exclusion criteria apply but parents declined to participate	4
Other medical reasons (e.g., tachycardia)	8
Organizational reasons (e.g., language problems)	4
Formal reasons (e.g., application after surgery)	70

TABLE 4. State of documentation form per clinic

Clinic	*Complete*	*Returned for ≤ 4 weeks*	*Due for for ≤ 4 weeks*	*Returned for > 4 weeks*	*Due for > 4 weeks*
AU – Austria					
Graz	17		1	3	3
Linz	9				
Salzburg	7			1	
St. Pölten	56				
Wien Hanusch-Krh.	38				
Wien II. Uni-Augenklinik	39			1	2
Wien Wilhelminenspital	48	1			1
Wiener Neustadt	48				
	262	**1**	**1**	**5**	**6**
B – Belgium					
Bruxelles	87		7		12
Edegem	2			1	
	89	**0**	**7**	**1**	**12**
CH – Switzerland					
Lausanne	38				
Zürich	6		1		
	44	**0**	**1**	**0**	**0**
D – Germany					
Berlin Charité	21	1			1
Berlin Steglitz	5				1
Dresden	21	1			
Erlangen	62		3		17
Frankfurt/M. Uni	56		2		
Freiburg Uni	82				1
Halle	3				1
Hamburg	28	1		1	
Heidelberg	56		3		11
Homburg/Saar	10				
Köln	11	1	1		
München TU	5				
München Uni	51	1			3
Regensburg Uni	41				3
	452	**5**	**9**	**1**	**38**
F – France					
Lyon	57	1	3		
GB – Great Britain					
Liverpool					3
London H. F. Sick Children					
I – Italy					
Firenze	2		1	4	6
Sassari	4				
	6	**0**	**1**	**4**	**6**
N – Norway					
Aalesund					
Bergen	32		5	1	11
Forde Sentralsjukehuset	9		1	1	
Haugesund	21			3	1
Lillehammer	3				3
Tonsberg	16	1		1	1
	81	**1**	**6**	**6**	**16**

TABLE 4, *continued p. 138*

TABLE 4, *continued*

Clinic	*Complete*	*Returned for ≤ 4 weeks*	*Due for for ≤ 4 weeks*	*Returned for < 4 weeks*	*Due for < 4 weeks*
NL – Netherlands					
Amsterdam	3			1	
Rotterdam Akademisch Z.	9		1		
Rotterdam Oogziekenhuis	2				7
	14	**0**	**1**	**1**	**7**
S – Sweden					
Boras	2				1
Danderyd	14		1	1	5
Eskilstuna	5				
Huddinge	3			1	
Jönköping	28	2			1
Linköping	20	1	1		2
Sundsvall	15		2	1	1
Umeå	14		1		
Vaexjö	11	1		1	4
	112	**4**	**5**	**4**	**14**
T – Turkey					
Adana	1	1	1	1	2
Ankara Hacettepe Univ.				2	2
Ankara Sglik Bakanligi	5				1
Edirne Trakya Univ.	18				2
Istanbul					
Izmir 9 Eyuel Univ.	3			3	4
	27	**1**	**1**	**6**	**11**
All Clinics	**1144**	**13**	**35**	**28**	**113**

week and 77% (45% last year) within four weeks after the entry examination, which is still in accordance with the protocol (The Early vs. Late Infantile Strabismus Surgery Study Group, 1993).

3 Quality of the documentation Tables 4 and 5 summarize the completeness of the documentation forms and of the data. The plausibility is permanently monitored by the study center.

Table 4 lists all documentation forms into 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 to happen, 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.

Table 5 displays the percentage of completeness of the required data among all documentation forms. All forms that are 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, occlusion patterns should only be noted in the form if the question 'previous occlusion therapy?' has been answered affirmatively.

TABLE 5. Percentage of completeness of required data per clinic

Country Clinic	*Entry examination form*	*Examination form*	*Surgery form*
AU – Austria			
Graz	100	99	
Linz	100	99	
Salzburg	100	98	
St. Pölten	100	100	
Wien Hanusch-Krh.	100	100	
Wien II. Uni Augenklinik	100	94	100
Wien Wilhelminenspital	100	97	100
Wiener Neustadt	100	100	
B – Belgium			
Bruxelles	100	100	95
Edegem	100	100	80
CH – Switzerland			
Lausanne	100	99	100
Zürich	100	100	100
D – Germany			
Berlin Charité	98	100	100
Berlin Steglitz	100	100	
Dresden	100	99	
Erlangen	100	100	
Frankfurt/M. Uni	100	98	94
Freiburg Uni	99	100	
Halle	100	100	
Hamburg	100	97	
Heidelberg	100	100	
Homburg/Saar	100	100	
Köln	98	99	
München TU	100	100	
München Uni	100	100	100
Regensburg Uni	98	99	
F – France			
Lyon	100	99	96
GB – Great Britain			
Liverpool			
London H. F. Sick Children			
I – Italy			
Firenze	92	90	
Sassari	100	100	
N – Norway			
Aalesund			
Bergen	100	99	100
Forde Sentralsjukehuset	100	99	
Haugesund	100	99	100
Lillehammer	100	100	
Tonsberg	95	98	

TABLE 5, *continued p. 140*

TABLE 5, *continued*

Country Clinic	*Entry examination form*	*Examination form*	*Surgery form*
NL – Netherlands			
Amsterdam	100	96	
Rotterdam Akademisch Z.	100	100	
Rotterdam Oogziekenhuis	100	100	
S – Sweden			
Boras	100	100	
Danderyd	98	99	
Eskilstuna	100	100	100
Huddinge	100	94	
Jönköping	98	100	100
Linköping	100	99	100
Sundsvall	100	95	
Umeå	100	99	100
Vaexjö	97	93	
T – Turkey			
Adana	95	58	
Ankara Hacettepe Univ.	100	100	
Ankara Saglik Bakanligi	100	100	
Edirne Trakya Univ.	100	100	
Istanbul			
9 Eyuel Univ.	96	100	
All Clinics	**99**	**99**	**98**

4 Dropouts and deviations of therapy

4.1 DROPOUTS In total eight children have been lost to follow-up, three in the early and five in the late operating group. In one case the child and parents had moved, in seven cases the parents were no longer compliant.

4.2 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, 54 children have been operated in accordance with the study protocol. For 13 children, no surgery is documented although they are already two years old. Four children have definitively been operated too late. Among these 17 children, two could not be operated as scheduled because the child was ill, in three other cases the childrens' parents opted for late surgery.

In the late group, one child has been operated up to now. It did not complete its 32nd month of life, however.

4.3 EXAMINATION INTERVALS Intermediate examinations should be performed every six months with a maximum delay of four weeks. 328 out of 356 documented examinations have been performed accordingly. The longest delays were 11 or 12 months in three cases. Intermediate examinations should also be performed within two weeks after surgery, with a tolerance of two weeks. This has been achieved in 51 of 63 cases of surgery (including four cases of re-operation). Furthermore, five examinations were done

TABLE 6. Summary of variables.

Variable	*Early surgery*	*Late surgery*
Mean of occlusion pretreatment in months	2.2	1.9
Median of occlusion pretreatment in months	0	0
Third quartile of occlusion pretreatment	4	3
Mean age in days at the moment of the entry examinaton	346	328
Rate of previously prescribed glasses	21%	23%
Rate of previously prescribed atropine	2%	3%
Rate of permanent occlusion tolerance	79%	78%
Rate of vertical deviation in primary position	6%	15%
Rate of vertical deviation in left or right gaze	25%	34%
Rate of V-pattern > 5 degrees	2%	8%
Rate of A-pattern	1%	2%
Rate of latent nystagmus	11%	33%
Rate of torticollis	8%	19%
Rate of DVD	6%	15%

within the second month after surgery. In seven cases, no postoperative examination is documented at the study center.

5 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 also desired that the distribution of the samples (entered children) is the same as in the population. Therefore, excluded children are also documented. Details about 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. Values ranged from −0.5 to 6 in the early group and from −4.5 to 7 in the late group. The wider range in the late group is not alarming since there are more patients in this group. Excluded children also have a unimodal distribution with the same median of Sph. +2, but with values ranging from −11 to 30.

HORIZONTAL ANGLE OF SQUINT The range is limited by the exclusion criteria from 5 to 30 degrees. The median values were 21 degrees in the early and 20 degrees in the late surgery group. Excluded children had a median of 17 degrees with extreme values of −25 and 50 degrees.

DEGREE OF AMBLYOPIA OF THE WORSE EYE The distributions were similiar for all groups. The most frequent category was 2 (alternating but preference of fixation). Forty-five percent of the early surgery and 49% of late surgery children, as well as 36% of excluded children fell into this category. The proportion of children within categories 1 to 3 was 91% in the early and 97% in the late group as compared to 83% in the excluded group (categories 1 to 3 are prognostically better than 4 and 5).

RESTRICTION OF ABDUCTION OF THE WORSE EYE Distributions were similar. The most frequent category was 1 (free, using pursuit movements), the second was 3 (passing midline but not free, using any method). Catego-

ries 1 and 2 applied to 62%, 56% and 60% for early, late and excluded children, respectively.

A summary of the distribution of other variables is presented in Table 6.

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