The Critical Period for Surgical Treatment of Dense Congenital Unilateral Cataract

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Purpose. Early treatment of dense congenital unilateral cataract is associated with better acuity outcomes. It is unclear whether there is a gradual worsening of prognosis with delay of treatment from the time of birth (*linear model*) or whether there exists an early window of time during which treatment is maximally effective, followed by declining success (*bilinear model*). The aim of the current study was to determine which model better describes the response to treatment.

Methods. A maximum likelihood procedure that permits statistical comparison between linear and bilinear models was applied to acuity outcomes from a group of 45 children 5 to 8 years of age with a history of dense congenital unilateral cataract diagnosed at 1 to 10 days of age. Contrast sensitivity and vernier acuity data from a subset of these children were evaluated with nonparametric statistical methods.

Results. The bilinear model provided a significantly better fit to the acuity outcome data. The line fitted to the initial portion of the function had a shallow slope that was not significantly different from 0.0. The intersection of the two linear functions occurred at 5.6 weeks and was followed by a steep decline in visual acuity outcomes. Contrast sensitivity and vernier outcome measures over a range of spatiotemporal conditions showed better outcomes were obtained with early treatment.

Conclusions. Intervention before 6 weeks of age may minimize the effects of congenital unilateral deprivation on the developing visual system and provide for optimal rehabilitation of visual acuity. Invest Ophthalmol Vis Sci. 1996;37:1532–1538.

The surgical treatment of adults with cataracts is one of the most common and most successful of procedures, with 93% of adult patients achieving 20/40 or better acuity.[1] In contrast, outcome after surgical treatment of infants with dense congenital unilateral cataracts historically has been dismal, with few patients treated before 1980 achieving 20/200 and most achieving only light perception.[2,3] Despite routinely excellent surgical outcomes and the availability of infant aphakic contact lenses, the unilateral visual deprivation experienced by these infants during the first months of life resulted in a severe abnormality in visual development that was often resistant to any late efforts toward visual rehabilitation. However, data from animal models of unilateral visual deprivation suggested that there may exist an early critical period during which the effects of visual deprivation are, at least to some extent, reversible.[4–10]

Consistent with data from animal models, recent reports have provided evidence that good acuity outcomes can be attained with early treatment.[e.g.,11–13] Although there is considerable variability in the literature, most studies conducted since 1980 used a criterion of 20/80 or better as an operational definition of a "good" acuity outcome and of approximately 4 months of age as an operational definition for the latest age for "early" surgery. Using these criteria to review the literature since 1980, approximately 40% of infants with early surgery achieved good acuity outcomes.[14]

Our initial studies[12,15] found good visual acuity

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outcomes in patients who had surgery by 2 months of age and excellent compliance with occlusion therapy; 85% achieved 20/80 or better acuity at age 5 years. In comparison, those who had surgery after 2 months of age had poorer outcomes (ranging from 20/160 to Hand Motion) and were less likely to comply with occlusion therapy. More recently, we reported that, in addition to better visual acuity outcomes, children who had early surgery also achieved better contrast sensitivity, better grating acuity, and better vernier acuity than children who were treated after 2 months of age.[14,16]

Thus, it is clear from the existing literature that earlier treatment is associated with better acuity outcomes. It is unclear whether there is a gradual worsening of prognosis with delay of treatment from the time of birth or whether there exists an early window of time after birth during which treatment is maximally effective, followed by declining success. The aim of the current study was to determine which of the alternatives better describes the response to treatment and, if an early window of time exists, to define the time period during which treatment is maximally effective.

METHODS

Participants

Forty-five children 5 to 8 years of age participated in the study. All children initially were diagnosed and treated during 1985 to 1990. Each had a history of dense congenital unilateral cataract noted by an ophthalmologist at 1 to 10 days of age, with the fundus not visible on indirect ophthalmoscopy. All children had been treated with a combination of surgery, aphakic contact lens correction, and occlusion therapy.[14] In addition, 82.2% of the children have had one or more surgeries for the treatment of strabismus. None of the patients had congenital malformations or infections, ocular abnormalities unrelated to the cataract, persistent hyperplastic primary vitreous, or neurologic dysfunction. To control for the potentially intervening variable of compliance, only patients with good (>75% of prescribed number of hours) to excellent (>95% of prescribed number of hours) compliance with contact lenses, bifocal and/or multifocal spectacles, and occlusion therapy were included in the analysis. All the children provided Snellen acuity data. A subset of children who were willing to return for two additional visits provided contrast sensitivity ($n = 19$) and vernier acuity ($n = 15$) data.

Informed consent was obtained from one or both parents before the child's participation. This research protocol observed the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the University of Texas Southwestern Medical Center.

Characteristics of the Population of Patients With Congenital Unilateral Cataract Available for Study

The 45 children who participated in the study were a selected sample (65.2%) from a larger population of 69 children with a history of dense congenital unilateral cataract who are currently at least 5 years of age and are active participants in our research program. The remaining 24 children were not recruited for the current study because (in order of exclusion priority) the presence of a dense cataract was not confirmed by an ophthalmologist by day 10 of life (12 children, 17.4%), the child had poor compliance with contact lens wear and/or occlusion therapy (7 children, 10.1%), glaucoma developed after surgery (1 child, 1.4%), or there were problems in scheduling visits (4 children, 5.8%). One unusual aspect of the population deserves further comment; few participants have poor compliance with contact lens wear and occlusion therapy. Because the research program is conducted with a group of patients whose families are willing to attend a series of research appointments at an independent research center remote from clinical services, these families generally are highly motivated to pursue rehabilitation efforts.

Treatment Protocol

Surgery. The treatment protocol has been described in detail elsewhere.[14] Briefly, surgical management consisted of lens aspiration with posterior capsulotomy and anterior central vitrectomy. Mydriatrics and steroids were administered for 4 to 6 weeks after surgery. Strabismus surgery was performed when indicated.

Optical Correction. At approximately 1 week after surgery, aphakic eyes were fitted with pediatric aphakic lenses for near vision; optical correction was adjusted at 1-month intervals during the first year, at 3-month intervals during the second year, and at 6- to 12-month intervals thereafter. At 2 to 4 years of age, children were fitted with contact lenses for distance vision and bifocal spectacles for near vision. At 5 to 8 years of age, progressive bifocals were prescribed as a permanent replacement for standard bifocals.

Occlusion Therapy. Occlusion therapy was initiated at the time of lens fitting. For all patients, 6 to 8 hours per day was prescribed. Because the number of hours spent in sleep and waking vary with age, this regimen corresponds to approximately 90% of waking hours during the first months of life, with a gradual decline to 50% of waking hours by age 2 or 3 years. Typically, occlusion therapy was continued through at least 6

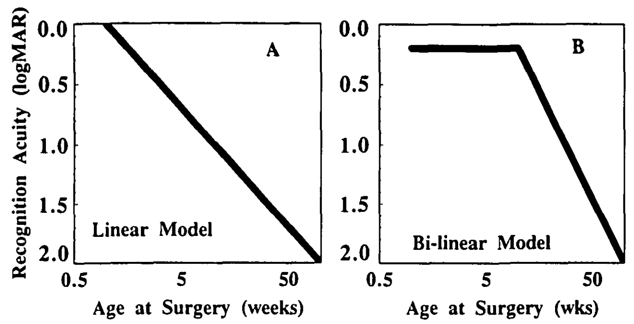

FIGURE 1. Examples of linear (A) and bilinear (B) models of treatment effectiveness. In the linear model, the logMAR recognition acuity outcome is proportional to the age at surgery (in log weeks). In the bilinear model, there exists an early window of time during which treatment is equally effective, followed by a range of later treatment ages during which logMAR recognition acuity outcome is proportional to the age at surgery (in log weeks). Note that, although the slope of the initial portion of the bilinear model in this example is 0.0, the slope was a parameter estimated by the maximum likelihood fitting procedure.

years of age. Regardless of the acuity outcome, occlusion therapy was terminated at 9 years of age.

Compliance with occlusion therapy was evaluated as excellent (≥95% of prescribed number of hours), good (≥75% of prescribed number of hours), or poor (<75% of prescribed number of hours) on the basis of interviews with the parents conducted periodically in three separate locations: by the orthoptist and physician at the site of ongoing medical care, by the physician and ophthalmic technician who provided contact lens services, and by the research scientist and orthoptist conducting this study. These interviews included specific questions about the number of patches used per day or week, whether the prescribed number of hours of occlusion was achieved as a single period of time or as an accumulation of several briefer periods of occlusion, and direct observation of the child's tolerance of occlusion during examinations. Consistent responses about compliance, both within and among settings, were required to assign a compliance score. When there were inconsistencies among answers, the lowest compliance category reported was used. As noted above, only those children with good to excellent compliance were included in the current study. Children with good compliance comprised 20% of those who had surgery by 6 weeks of age and 13% of those who had surgery after 6 weeks of age.

Visual Acuity

Visual acuity at distance was measured in a mirrored lane with linear arrangements of Sloan letters on a B-VAT II BVS video system. Letter size progresses logarithmically on this chart, with an equal number of proportionally spaced letters for each size. The criterion for passing a line was that the majority of letters could be read. Acuities were recorded on a logMAR scale. If acuity was measured on more than one occasion during the 5- to 8-year age range, acuity from the most recent examination was entered into the analysis.

Contrast Sensitivity and Vernier Acuity

Contrast thresholds at three spatial frequencies (0.38, 1.5, and 6 cyc/deg) were measured at each of two temporal frequencies (2 Hz and 8 Hz sinusoidal counterphase modulation) using D6 grating patches. A spatial, two-alternative, forced-choice, interleaved staircase protocol was used.[14] Briefly, the child moved a joystick to indicate whether a D6 grating patch appeared on either the right side or the left side of the display. Vernier acuities were obtained as a function of contrast (100%, 40%, 16%, 4%) in four interleaved staircases, using a 1.5 cyc/deg D6 grating patch (with the center third of a grating patch displaced to the left or to the right) and the same test protocol as for contrast sensitivity. All log sensitivity and log acuity thresholds were determined by performing maximum likelihood estimation on the staircase data sets using a three-parameter model of the psychometric function.[17]

Nonparametric analyses of differences in contrast sensitivity and vernier acuity between treatment groups were conducted because some children were unable to respond consistently even to the highest contrast or largest vernier offset in some spatiotemporal conditions. In these cases they were assigned a default threshold of 0.0 log sensitivity (the minimum measurable contrast sensitivity) or 3.0 log sec arc for vernier (the maximum measurable offset).

Linear and Bilinear Models

Two alternative models of treatment effectiveness were compared; these are presented schematically in

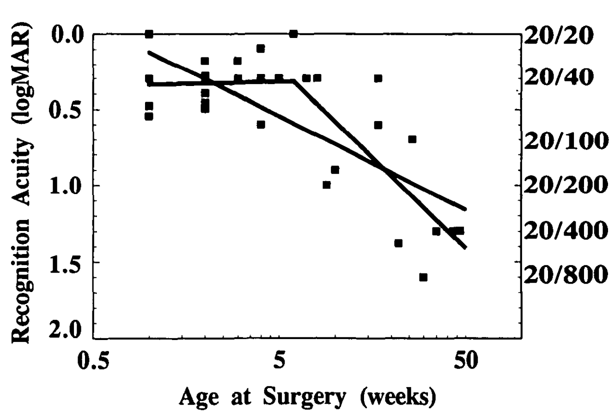

FIGURE 2. Recognition acuity outcome data and the best fit linear and bilinear functions determined by maximum likelihood estimation. Parameters of the best fit functions and statistical comparison of the fits are summarized in Table 1.

TABLE 1. Parameters of the Best-Fit Linear and Bilinear Models

	Slope	*Intercept (logMAR)*	*Critical Age (log weeks)*	r^2	χ^2	*P*
Linear	0.614	0.12		0.53		
Bilinear			0.75	0.65		
line 1	−0.024	0.34				
line 2	1.145	−0.54				
Linear versus bilinear					9.38	0.009

Figure 1. A linear model was used to represent the hypothesis that the earlier the treatment is initiated, the better the outcome. A bilinear model was used to represent the hypothesis that there exists an early window of time, beginning at birth, during which an optimal outcome can be attained. The appropriateness of these models in describing the data was evaluated using a statistical procedure developed by Owsley et al[18] to evaluate the effects of senescence on the visual system. Briefly, the bilinear model is recast into a four-parameter nonlinear model by means of B-splines with only a single nonlinear parameter; thus, only a one-dimensional nonlinear optimization is required. The same approach is used to construct the linear model with the constraint that the slopes of both halves of the single straight line are equal. To test the hypothesis that the data are better described by a bilinear model than by a linear model, a likelihood ratio test was constructed under the assumption that the errors are distributed normally. Under this assumption, the least-square estimate equals the maximum likelihood estimate and $\chi^2 = -2 \times \log(\text{likelihood ratio})$ with 2 degrees of freedom. This model has been used successfully to evaluate the effects of aging various visual functions.[18–20] All fits were computed on a log scale; i.e., log visual acuity in minutes, log contrast sensitivity, or log vernier acuity in seconds versus log age in weeks.

RESULTS

Acuity Outcome at ≥5 years

Aphakic eye acuity outcomes ranged from 0.0 (20/20) to Count Fingers among the 45 children. Because acuity outcomes poorer than 20/800 could not be quantified, the models were evaluated only over the range of treatment ages within which all children had measurable acuities, i.e., for the 35 children who were treated between 1 and 52 weeks of age. Figure 2 shows the best linear and bilinear fits to this data set; Table 1 summarizes the model parameters and statistical test outcomes. For children treated during the first year of life, the bilinear model provided a significantly better fit to the data. The line fitted to the initial portion of the function has a shallow slope that is not significantly different from 0.0. Note that the average logMAR acuity outcome for children treated during the first 6 weeks of life was 0.33 logMAR (20/45). The intersection of the two linear functions occurs at 5.6 weeks and is followed by a steep decline. Over this declining portion, each doubling of age (e.g., 10 ver-

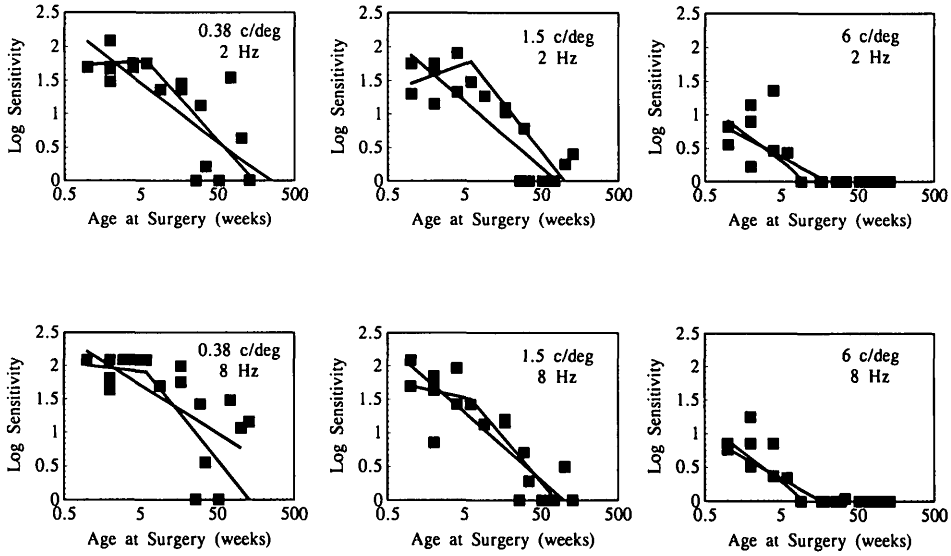

FIGURE 3. Contrast sensitivity outcomes for each of 6 spatiotemporal conditions. Because many children were unable to see even 100% contrast in each of the conditions, maximum likelihood estimation could not be used to determine linear and bilinear fits. Instead, bilinear functions were fit by eye to illustrate trends in the data. Nonparametric statistical comparison of the early and late treatment groups is summarized in Table 2.

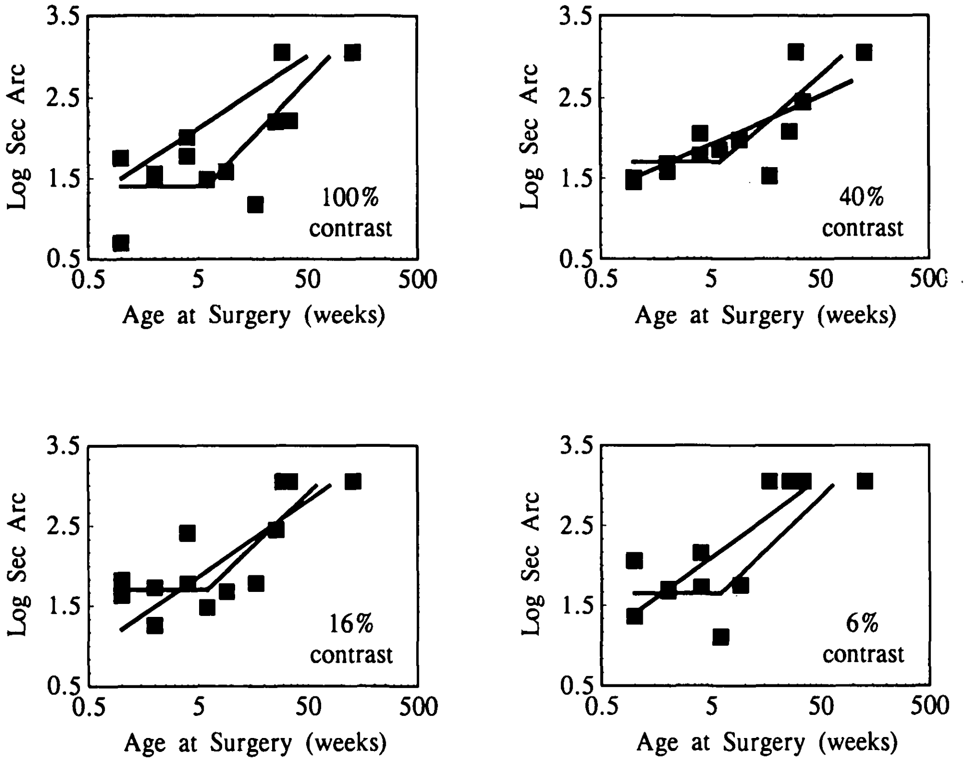

FIGURE 4. Vernier acuity outcomes for each of four contrast conditions. Because many children were unable to see even the largest vernier offsets (1024 sec arc) in each of the conditions, maximum likelihood estimation could not be used to determine linear and bilinear fits. Instead, bilinear functions were fit by eye to illustrate trends in the data. Nonparametric statistical comparison of the early and late treatment groups is summarized in Table 3.

sus 20 weeks) is accompanied by an approximate doubling of the Snellen denominator (e.g., 20/80 versus 20/160).

Contrast Sensitivity and Vernier Acuity Outcomes at ≥5 Years

The linear and bilinear models could not be evaluated statistically for these outcome measures because of the large number of children who had surgery at late ages and failed to detect reliably even the most salient stimuli. However, the data for contrast sensitivity and vernier acuity are presented in Figures 3 and 4 to illustrate the qualitative similarity to the acuity outcome data. Linear and bilinear functions were fit by eye for purposes of comparison with the acuity outcome data; the intersection in the bilinear fit was arbitrarily placed at 6 weeks based on the acuity data.

In all spatiotemporal conditions, both the contrast sensitivity and vernier outcome measures showed that treatment was more effective when surgery was conducted earlier. At least some of the contrast sensitivity and vernier functions show a trend toward an early window of time after birth during which treatment is maximally effective, followed by declining success (e.g., contrast sensitivity at 0.38 cyc/deg, vernier acuity at 16% contrast). Overall, however, it is not possible to determine with confidence whether the outcomes are a linear or a bilinear function of age at treatment nor whether 6 weeks represents the optimal placement of the intersection for the bilinear fit.

Based on the acuity outcome finding that the first 6 weeks offers a period of equally effective treatment, nonparametric comparisons of the median log contrast sensitivities and vernier acuities for children who had surgery by 6 weeks of age versus those who had surgery after 6 weeks of age was conducted (Tables 2 and 3). Although this represents a somewhat arbitrary division of the treatment ages, it does offer initial insights into the comparative effectiveness of early versus later treatment.[14,16,21] For all six spatiotemporal conditions, children with surgery by 6 weeks of age had significantly better contrast sensitivity. For vernier acuity at 40%, 16%, and 6% contrast, children with surgery by 6 weeks of age had significantly better vernier acuity. At 100% contrast, a similar trend was observed, but it failed to reach statistical significance at $\alpha = 0.05$.

DISCUSSION

The statistical analysis of Snellen acuity outcome data supports a bilinear model of treatment effectiveness. That is, there exists a 6-week window of time, beginning at birth, during which treatment of dense congenital unilateral cataract is maximally effective. If treatment is initiated during this period and the child is compliant with contact lens wear and occlusion therapy, excellent visual acuity outcomes frequently are obtained. In addition, better contrast sensitivity and vernier acuity outcomes are obtained with early treatment. Early treatment with good compliance also is

TABLE 2. Mann–Whitney Rank Sum Tests Comparing Log Contrast Sensitivity for Patients With Surgery Before 6 Weeks of Age ($n = 9$) and Patients With Surgery After 6 Weeks of Age ($n = 10$)

Spatiotemporal Condition	*<6-Week Median (log sensitivity)**	*>6-Week Median (log sensitivity)**	*T*	P
0.38 cyc/deg 2 Hz	1.69	0.88	134	<0.001
1.5 cyc/deg 2 Hz	1.66	0.33	134	<0.001
6 cyc/deg 2 Hz	0.64	0.00	130	<0.01
0.38 cyc/deg 8 Hz	2.08	1.29	131	<0.001
1.5 cyc/deg 8 Hz	1.69	0.39	132	<0.001
6 cyc/deg 8 Hz	0.76	0.00	129	<0.01

* A default log sensitivity value of 0.0 was assigned when the child was unable to respond reliably to 100% contrast, and a default value of 2.0 was assigned when the child was able to respond reliably to 1% contrast.

associated with a lower prevalence of strabismus[14,21,22] and a higher prevalence of fusion and stereopsis.[14,22]

After the initial 6-week period of visual development, the effectiveness of treatment in achieving excellent acuity outcomes rapidly diminishes. Although estimates of the slopes for contrast sensitivity and vernier acuity outcomes as a function of age at treatment could not be obtained, the preliminary data suggest that a rapid decline in outcome results from delay in treatment.

The statistical analysis used to determine whether the linear model or the bilinear model provides a better fit to the acuity outcome data has been shown to be relatively immune to missing regions of the age continuum if the underlying distribution is truly linear.[18] Moreover, when the underlying distribution is truly bilinear, missing regions of the age continuum bias the analysis toward rejection of the bilinear model. Thus, any sparseness or inhomogeneity of sampling along the age continuum would have biased the analysis toward the linear model. The bilinear model provides a good empirical fit to the data, accounting for 67% of the variance. It is possible that other, nonlinear models may provide a better fit to the data, particularly during the period of decline beyond 6 weeks. Nonetheless, the analysis presented here is sufficient to establish that the first 6 weeks after birth represent a period during which treatment is optimally effective.

The location of the intersection of the two lines at 6 weeks is consistent with other data that suggest the first 6 weeks of life may represent a precortical stage in visual development.[23-25] That is, intervention before the development of cortical control of visual function may minimize the effects of unilateral deprivation on the developing visual system. Taken together, these results support the hypothesis that treatment initiated before 6 weeks of age is optimal for promoting visual acuity development of a congenitally cataractous eye.

Key Words

acuity, amblyopia,congenital cataract

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TABLE 3. Mann–Whitney Rank Sum Tests Comparing Vernier Acuity for Patients With Surgery Before 6 Weeks of Age ($n = 7$) and Patients With Surgery After 6 Weeks of Age ($n = 6$)

Contrast (%)	*<6-Week Median (log sec arc)**	*>6-Week Median (log sec arc)**	*T*	P
100	1.55	2.21	54	0.10
40	1.67	2.26	57	<0.05
16	1.73	2.75	57	<0.05
6	1.70	3.05	61	<0.005

* A default vernier acuity of 3.0 was assigned when the child was unable to respond reliably to the largest offset (1024 seconds).

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