Timing of surgery in essential infantile esotropia – What more do we know since the turn of the century?

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This review summarizes the results and interpretations of studies pertaining to the long-standing debate regarding the timing of surgery in infantile esotropia, more recently referred to as essential infantile esotropia. A systematic search of studies from the year 2000 onward pertaining to the timing of surgery in infantile esotropia as listed in PubMed, Google Scholar, and the Cochrane database was performed. Appropriate cross-references from the articles were also included. Data collected included demographics, presentation, time of surgery, complications, and outcomes. Very early surgery, that is, within 6 months of the onset of infantile esotropia, offers significant advantages in terms of the quality of stereopsis and binocular vision as well as promoting the development of cortical visual processing, thereby benefiting cortical development in human infants. However, the postoperative alignment was not found to be significantly different in the very early, early, or late surgery groups. The reduction in the incidence of manifest dissociated vertical deviation postoperatively in the very early surgery group also showed measurable benefits. The results of this recent literature review demonstrated that very early surgery, within 6 months of misalignment, showed demonstrable benefits in essential infantile esotropia.

Key words: Essential infantile esotropia, infantile esotropia, stereopsis, timing of surgery

Over the last 50 years, strabismologists have debated the timing of surgery in infantile esotropia based on their individual experiences and outcomes. Essential infantile esotropia (EIE), or synonymously referred to as infantile esotropia (and previously referred to as congenital esotropia), is a constant large-angle esotropia defined as onset within the first six months of age.[1-3]

The characteristics described in EIE include a constant large-angle esotropia of more than 30 prism diopters (Δ), age-appropriate refraction, and often features cross-fixation with the background of a normal systemic and neurological examination. Associations include abnormal stereopsis, latent nystagmus, dissociated strabismus complex such as dissociated vertical deviation (DVA), inferior oblique overaction, naso-temporal asymmetry of monocular smooth pursuit OKN, and abnormal motion visual evoked potentials (mVEPs).[4-6] A recent theory hypothesizes that essential infantile esotropia is caused by perturbing the development of binocularity in the striate cortex. This leads to the subcortical immature motor pathways (accessory optic system) to decompensate nasalward in the direction of innate or convergent biases.[7,8]

A Cochrane review that partly addressed the question of the timing of surgery concluded that there is a general agreement that any intervention should be earlier rather than later, although gross stereopsis is still possible with late surgery.[9] Other major reviews have also concluded that early surgery is better for sensory and motor outcomes.[10-15] The literature from the turn of the century pertaining to the timing of surgery in EIE and ascertaining whether the recent evidence favors early or late surgery has been reviewed.

Methods

A PubMed and Google Scholar search of all articles on infantile esotropia and essential infantile esotropia was carried out. Terms used for this search included “essential,” “infantile,” “esotropia,” “pediatric,” “squint,” “strabismus,” “time,” “timing,” “surgery,” “outcomes,” and “complications.” All articles pertaining to the timing of surgery in infantile esotropia from the year 2000 onwards and those published in English were included in the study. Specific search was narrowed down to treatment in infantile esotropia and the timing of treatment. The terms “infantile esotropia” and “essential infantile esotropia” have been used synonymously in some of the articles. Cross-references from all these articles were further assessed for inclusion in the study. None were RCTs and none of the articles were duplicated. Data analyzed included type of study, demographic details of the cohort, results based on the timing of surgery, and individual outcomes for both the prospective and retrospective studies.

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Results

Brief background

Surgery remains the mainstay of treatment in essential infantile esotropia (EIE), whereas botulinum toxin has been used as the initial primary treatment or as augmentative in cases of residual esotropia. Based on the angle of deviation, two-muscle surgery (i.e., binomial recessions) or adding a third muscle in the form of a lateral rectus resection is performed. The controversy about the optimal age for surgery in infantile esotropia commenced in 1939 when Chavasse stated that most infants with congenital squint were capable of developing fusion if the deviation could be fully corrected before the age of 2 years.[10] A study by the Pediatric Eye Disease Investigator Group (PEDIG) confirmed that infantile esotropia ≥ 40 prism diopters (Δ) without significant hyperopia, noted by 2–4 months of age, rarely resolves spontaneously.[17] In their cohort from two locations studied prospectively, 0/45 and 0/21 patients showed resolution. The Congenital Esotropia Observational Study (CEOS) defined a clinical profile wherein an esotropia of 40 Δ or more on at least two visits 2.5 months apart would sufficiently account for the persistence of esotropia for early surgical correction to be considered.[18]

Both prospective nonrandomized and retrospective studies have evaluated the outcomes with regard to the timing of surgery. However, there are no randomized prospective trials evaluating early or late surgery in infantile esotropia. The current review will address the prospective and retrospective studies separately to provide the readers with clear views based on the level of evidence.

Historical studies

In the 20th century, many studies highlighted the advantages of early surgery in infantile esotropia; by the end of the century, it was established that early surgery (defined as earlier than 2 years of age) was beneficial.[10,17,19] Traditionally, age at initial surgery rather than the duration of misalignment was used to draw conclusions for early surgery (age at alignment) and is still considered in some studies. According to these studies, early surgical alignment was instrumental in the resultant monofixation syndrome, which included an alignment within 8Δ and suboptimal binocularity.[20] Ing et al.[19] in their series of 16 patients operated between the ages of 3 months and 11.8 months, achieved within 10 D of orthotropia in 12 out of the 16 patients and reported no significant difference in binocularity between the age groups of 3, 6, and 12 months. Wright et al.[21] advocated very early surgery (i.e., less than 6 months of age) to achieve high-grade stereopsis, which he reported in a cohort of seven children who underwent surgery between 13 and 19 weeks of age. This advocacy was considered premature in an editorial by Repka.[22] In a study to prospectively assess the Randot stereacuity following the successful surgical correction of infantile esotropia, Birch et al. concluded in their prospective study of 73 patients that the prevalence of stereacuity was higher (42.9%; n = 32 in 5–8-month-old children, 55.6%; n = 19 in 9–12-month-old children, and 0%; n = 22 in 13–16-month-old children) in those aligned before 12 months or within 12 months of the onset of infantile esotropia.[23] The controversy regarding the benefit of very early surgery has subsequently continued.

Prospective studies [Table 1A and B]

There were a total of 11 studies since the year 2000 with varying number of patients. Table 1A and 1B give an overview of the demographics and outcomes of the prospective studies.

A. Prospective Animal Studies – A series of animal studies on infant macaques were performed to ascertain specific advantages of early correction in infantile esotropia. These infant macaques were either fitted with prism goggles or the ones with esotropia were subjected to early or delayed surgery. The conclusion from these studies was that the critical periods of functional recovery were noted to occur between the first 3–12 months postnatally, with early correction preventing maldevelopment of eye movements, whereas a standard or delayed correction resulted in deficits associated with infantile esotropia.[24,25] Studies have also postulated that early strabismus correction may be beneficial for brain development in human infants.[25,26] In addition, the duration of infantile esotropia longer than 6 months showed a greater deficit of binocular connections and correlated with a more severe misalignment as opposed to those macaques fitted with prisms for a 3-week duration.[27,28]

B. Prospective Human Studies – At the turn of the century, Birch et al. and Stager et al. studied the role of early surgery and the duration of misalignment in promoting improved stereopsis outcomes on 129 consecutive patients. According to their study, successful early surgical alignment yields better stereopsis (alignment at 6 months: 100% stereopsis; alignment after 1 year: 8% stereopsis).[29] A follow-up study by the same group subsequently stated that early alignment and a short period of misalignment are important in developing binocular function. Duration of misalignment of 3 months or less is significantly associated with stereacuity as compared to misalignment of more than 3 months.[30]

One of the largest series was by the Early vs. Late Infantile Strabismus Study (ELISS) group, which was conducted over 58 clinic locations in Europe assessing the effect of early vs. late surgery in infantile esotropia on stereopsis.[31] According to their results, early surgery, less than 24 months, is warranted as a large number of patients achieved binocular single vision and stereopsis in that group. [Table 1B] The reported stereopsis with the Titmus fly test at 6 years of age was significantly better (13.5%) in the early group as compared to the late group (3.9%). No significant difference between the angle of strabismus post-surgery was noted in the two groups, and amblyopia in both the groups was comparable.

To report on constitutes an early surgery, Birch and Stager evaluated the long-term motor and sensory outcomes after early surgery for infantile esotropia by prospectively studying a cohort divided into two groups, early surgery by 6 months of age (n = 50) and surgery at 7–12 months of age (n = 78). Based on the 5-years follow-up data, they concluded that surgery by 6 months of age achieved greater fusion (77.8%) and stereopsis (14.8%) without adverse motor or sensory outcomes nor the need for additional surgery based on the 5-year follow-up data.[32] In contrast, some gross stereopsis in 38.4% of children undergoing late surgery over 3 years of age was reported by Polling et al.[33]

Another advantage of early surgery in infantile esotropia is with regard to cortical development in human infants.
Table 1A: Prospective animal studies

| Author/year | Study title | Study design | Methodology/results | Conclusion |
|-------------|-------------|--------------|---------------------|------------|
| Wong et al. 2003 | Early vs delayed repair of infantile strabismus in Macaque Monkeys I. Ocular motor effects | Prospective Animal study | Early correction group (2 experimental + 1 control) goggles for 3 weeks. Delayed correction group (3 experimental + 1 control) goggles for 3 or 6 months | Early correction - normal eye movements, binocular eye alignment and stable fixation. Delayed correction - persistent esotropia, latent fixation nystagmus, DVD, OKN asymmetry. |
| Tychsen et al. 2003 | Maldevelopment of convergence eye movements in Macaque Monkeys with small and large angle infantile esotropia | Prospective Animal study | 4 adult macaque monkeys (2 with strabismus 2 normal) Far and near distance targets used to evoke large symmetric convergence eye movements. Convergence response of large-angle esotropia monkey was asymmetric and weak. | Monkeys with small and large angle infantile esotropias have maldevelopments of binocular convergence. |
| Tychsen et al. 2004 | Early versus delayed repair of infantile strabismus in macaque monkeys: II. | Prospective Animal study | Early correction group (2 experimental + 1 control) goggles for 3 weeks. Delayed correction group (3 experimental + 1 control) goggles for 3 or 6 months. Motion VEP responses were assessed several months later. | Early repair of optical strabismus in primates restores normal development of visual motion pathways. Early strabismus repair is beneficial for brain development in infant primates. |
| Sin et al. 2007 | Early Versus Delayed Correction of Infantile Strabismus in Macaque Monkeys: Effects on Long‑Term Eye Alignment | Prospective Animal study | 6 infant macaque monkeys fitted with prisms and removed after 3 weeks, 3 months and 6 months. Longer duration of strabismus co-relates with more severe misalignment. | Longer duration of infantile strabismus is supported. |
| Richards et al. 2007 | Early Versus Delayed Correction of Infantile Strabismus in Macaque Monkeys: Effects on Horizontal Binocular Connections in the Striate Cortex. | Prospective Animal study | 6 infant macaque monkeys fitted with prisms and removed after 3 weeks, 3 months and 6 months. 3 week animals- equal number of monocular and binocular connections. 6 month animals- monocular connections three times more than binocular. | Longer duration of infantile strabismus causes greater deficit of binocular connections. Early correction of infantile strabismus is supported. |

Gerth and colleagues assessed the effects of timing of surgery for infantile esotropia in humans on cortical motion visual evoked responses.[34] Their study provides additional evidence of the benefit of early surgery (<11 months) for the cortical development in human infants because the duration of misalignment and the timely restoration of binocular image correlation in the critical early period promotes the development of cortical visual motion processing, as noted by symmetrical mVEP obtained being similar in both the early surgery and a control cohort. However, the mVEP responses were noted to be abnormal and asymmetrical in the standard surgery group (11–18 months).

Retrospective studies

There have been a total of 17 studies since 2000. Table 2 gives an overview of the retrospective studies since the turn of the century.

While Birch et al. analyzed their results prospectively addressing the duration of misalignment as an important consideration in stereopsis outcome at the turn of the century, Ing reevaluated his original series retrospectively confirming the same.[35] In his study with stereopsis testing (Titmus test), the percentage of patients achieving any stereopsis was identical (80%) for those aligned at 0–6 months or 7–12 months of misalignment. However, children with misalignment between 12 and 24 months showed 58% achieving stereopsis. The quality of stereopsis was also lower in the late study group. A subsequent study by Birch et al. considering stereopsis and long-term stability of alignment in esotropia showed that with regards to the infantile esotropia cases, very early or early surgery within 3 months of onset resulted in a higher prevalence of stereopsis and/or better stereoaucity as a long-term outcome; however, they did not directly compare early vs. late surgery.

A decision analysis by Trikalinos et al.[36] using a mathematical model that divided and analyzed three hypothetical cohorts with age at first surgery at 6, 24, and 48 months concluded that at 8 years of age, the advantage of having eyes aligned for a longer duration with better stereopsis outweighed a risk for extra operation. They recommended correcting large-angle infantile esotropia as early as possible based on their stated risk/benefit tradeoff.

The role of early surgery in infantile esotropia in motor development was studied using a parent questionnaire. The results showed that sensorimotor and gross motor development
### Table 1B: Prospective human studies

| Authors/ year | Study title | Study Design | Methodology | Results | Conclusion |
|---------------|-------------|--------------|-------------|---------|------------|
| Birch et al. 2000 | Why does early surgical alignment improve stereoacuity outcomes in Infantine esotropia | Prospective | 129 consecutive patients. F/U for 5 yrs. Age @ onset 2-6m Age at alignment=age at which 0-8 achieved and maintained | Overall 36.4% obtained some stereoacuity. 21.7% passed Randot stereotest. Those aligned at 6 months had 100% stereoacuity & 8% for alignment after 1 year | Early surgical alignment better stereoacuity - minimizes duration of misalignment results in improved random dot stereopsis and more stable long term alignment outcomes. Large sample size and long f/u. |
| O'Connor et al. 2002 | Factors influencing sensory outcomes following surgical correction of infantile esotropia | Prospective | 85 children | Of the 85, 47% had measurable stereoacuity. Duration of misalignment <3 mths associated with presence of stereoacuity (P<0.01) compared to >3 months group. (P=0.5) Age of alignment before 6 months - increase in number of children with stereoacuity. (P=0.04) | Early alignment and shorter period of misalignment are important for development of binocular function |
| ELISS study group H.J Simonsz et al. 2005 | Final report on Early vs Late infantile strabismus surgery study | Prospective Multi centre 58 clinics in Europe | n=231 recruited for early surgery (6 to 24 months), age at surgery 20 months (SD 8.4) dropout rate 26.0%. Surgeries per child 1.18 (SD 0.67) n=301 late surgery group (32-60 months), age at surgery 49.1 months (SD 12.7), dropout rate 22.3%. Surgeries per child 0.99 (SD 0.64) | At 6 years of age - Early surgery group- better stereopsis and binocular vision (13.5%) than 3.9% in late group identified Titmus fly. Angle of alignment no significant difference | Early group had better gross stereopsis at age six as compared to children in the late group. Re-surgery rate more in the early group. Dropout rate high in both groups. Despite the dropouts, this is a large multicentre prospective trial which clearly defines the benefit of early surgery with regards to stereopsis |
| Birch et al. 2006 | Long term motor and sensory outcomes after early surgery for Infantile ET | Prospective | n=50 early surgery by 6 months of age n=78 standard surgery by 7-12 months | Peripheral and central fusion better in early group 77.8% and 14.8% than standard group 61.4% and 2.3%. Alignment & need for re-surgery comparable | Surgery by 6 months of age - greater fusion and stereopsis without adverse motor or sensory outcomes |
| Polling et al. 2009 | A randomised comparison of bilateral recession versus unilateral recession-resection as surgery for infantile esotropia | Prospective study 12 university clinics | n=124 randomly assigned to bilateral recession or recess-resect. Children older than 3 years included | The angle of reduction in strabismus was comparable in both groups. Some postoperative binocular vision was noted in both groups. | 38.4% had some binocular vision postoperatively with Bagolini striated glasses. Children with binocular vision had better ocular alignment. Strength : Multicentre prospective trial with large sample size. Early strabismus repair is beneficial for cortical development in human infants. Study addresses a different perspective, the mVEP responses were symmetrical and normal in the early surgery and control groups as opposed to late surgery group with asymmetrical responses. |
| Gerth et al. 2008 | Timing of surgery for infantile esotropia in Humans: Effects on cortical motion visual evoked responses | Prospective | n=8 Early group surgery <11months n=8 Standard surgery group 11-18 months | mVEP responses in the early surgery group - normal and abnormal responses in the standard surgery group. | |
| Author/year          | Study title                                                                 | Study design | Methodology                                                                 | Results                                                                 | Conclusions                                                                 |
|---------------------|------------------------------------------------------------------------------|--------------|-----------------------------------------------------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------|
| Ing et al. 2002     | Outcome study of stereopsis in Relation to duration of misalignment in congenital esotropia | Retrospective | n=90 aligned by 2 years of age. Compared Titmus stereopsis with duration of misalignment and age at alignment | Aligned by 6 to 12 months of age or within 6-12 months misalignment=no difference in stereopsis outcome or quality of stereopsis. After 12 months misalignment decrease in percentage with stereopsis noted (P>0.05, power 0.8) and quality of stereopsis (P<0.001, power 0.8) | Test used was Titmus fly not Randot. Alignment within 1 year of age or within 12 months of misalignment favourably affects patients who develop stereopsis in treatment of IET. Quality of stereopsis is affected by duration of misalignment rather than age of alignment. Large sample size |
| Birch et al. 2004   | Stereopsis and long term stability of alignment in Esotropia                 | Retrospective | n=70 infantile ET, n=66 accommodative ET. Random dot stereacity tested within 3 months of surgery | In infantile ET group, early nil stereopsis had 3.6 times greater risk (CI 2.4-4.1) of re-surgery for recurrent ET/consecutive XT and 4.2 times greater risk (CI 3.3-4.4) for nil stereopsis at ≥5 years. | Very early or early surgery within 3 months of onset results in a higher prevalence of stereopsis and/or better stereoaucity as a long term outcome. Nil early stereopsis has greater risk of re-surgery and greater risk of nil stereopsis at ≥5 years |
| Trikalinos et al. 2005 | Decision analysis with Markow Processes supports early surgery for Large-angle Infantile Esotropia | Mathematical model | 3 hypothetical cohorts with age at surgery at 6, 24 and 48 months. | At 8 years of age, advantage of having eyes aligned for a longer duration with better stereopsis outweighs risk for an extra operation. | Recommend correcting large-angle infantile esotropia as early as possible. |
| Drover et al. 2008  | Improvement in motor development following surgery for infantile esotropia    | Retrospective | 25 item questionnaire - to assess sensorimotor & gross motor development. n=143 infants 3-10 month old and n=58 infants 6-11 month old | Before surgery a delay in sensorimotor and gross motor milestones was observed in all age groups. After surgery a greater rate of sensorimotor development than age matched controls was noted. Esotropic children caught up with normal children on both sensorimotor and gross motor skills. | Early surgery is beneficial to both visual and motor development. |
| Caputo et al. 2007  | Motor coordination in children with congenital strabismus: effects of late surgery | Retrospective | Children tested using the movement assessment battery performed 1 week before and 3 weeks after surgery | The 1 week before results found abnormal or borderline results, in more than half children with strabismus, the 3 weeks after results found no difference between study and control groups. | Surgical correction of strabismus, even if late, is effective in improving perceptual motor and motor function |
| Author/year | Study title | Study design | Methodology | Results | Conclusions |
|-------------|-------------|--------------|-------------|---------|-------------|
| Leuder et al. 2008 | Effect of preoperative stability of alignment on outcome of strabismus surgery for infantile esotropia | Retrospective | Total n=30, mean interval between first office visit and surgery=2 months Group 1 - n=15, stable angle preoperative <5 D Group 2 - n=15, change in angle of deviation >10 D | Successful outcomes 11 of 15 in each groups. Both groups had equal outcomes. | No difference in outcome between children with stable and increasing angle of deviation preoperatively. Strabismus surgery need not be delayed while waiting for angle to stabilize. Surgical correction may be advised at an earlier age. Small sample size as opposed to PEDIG study which questions need for delaying surgery till angle of deviation stabilizes. |
| PEDIG 2009 | The relationship between preoperative alignment stability and postoperative motor outcomes in children with esotropia | n=167, infantile esotropia n=68, accommodative ET n=99. Surgery age <6 yrs. F/U period 18 months. | Median 6 week and 6 month postoperative deviation similar in stable and unstable deviation group. | Postoperative alignment at 6 weeks and 6 months similar in children with stable versus unstable preoperative esotropia? Need for delaying surgery for angle to stabilize. |
| Simonsz 2010 | Predication value of age, angle and refraction on rate of reoperation and rate of spontaneous resolution in infantile esotropia | Metaanalysis | n=204 previously operated children meta-regression analysis of these and other reoperation rates. | Reoperation rates between 60% and 80% for children first operated around age 1 and 25% for children operated around age 4. A small angle at age 1 and hyperopia of approx. + 4 had increased chance of spontaneous decrease of angle into microstrabismus. | Benefit of early surgery for gross binocular vision is balanced by a higher reoperation rate. |
| Simonsz et al. 2011 | Best age for surgery in infantile esotropia | Meta-analysis | | | Consider end points. Binocular vision restored/retained by early surgery b) post-operative angle of strabismus and its long term stability c) numbers of surgery to reach its goal |
| Cerman et al. 2014 | Oldest age at which stereopsis can be achieved with excellent motor alignment | Retrospective | 38 patients 2 groups: Group 1 stereo >1000 arcsec Group 2 no stereo | Gr 1 (n=23) age <16 months at surgery - median stereo of 480 arcsec 16-38 months (n=15) - median stereo of 1000 arcsec. Optimum cut-off value of the age at surgery for predicting stereopsis was 16 months 95% CI: 0.62-0.90; P=0.0002). | Surgery before 16 months results in measurable stereopsis. Study limitation: small sample size, retrospective |

Contd...
| Author/year         | Study title                                                                 | Study design | Methodology                      | Results                                                                                                                                                                                                 | Conclusions                                                                                           |
|---------------------|------------------------------------------------------------------------------|--------------|----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Magli et al. 2017   | Post-operative sensory outcomes in EIE                                         | Retrospective| 188 patients n=69 early surgery <2 years, n=119 late surgery >2 years | Multivariate analysis -Children >2 years are 0.4% less likely to obtain BSV                                                                                                                                 | Perform surgery in infantile esotropia between 1-2 years of age                                      |
| Yagasaki et al. 2020| Relationship between stereopsis outcome and timing of surgery                 | Retrospective| 76 patients Very early group <8 month n=22, early 9-24 month n=30, late >24 months n=26 | Very early : Stereopsis 200" or better in 31.8%. Overall stereopsis significantly higher in very early (77%) than early (20%) or late group (13%) (P<0.001). Binocular response : 90-95% for very early , 57-80% early , 41-50% late group | Very early surgery at<8 months improves chance of post op stereopsis                                   |
| Muz et al. 2020     | Effects of Surgical timing on Surgical success and Long-term Motor and Sensory Outcomes of Infantile Esotropia | Retrospective| 79 patients divided in Early group n=27 (6-11 months) late group n=26 (12-17 months) very late group n=26 (18-27 months) follow up more than 60 months in 75% patients. | Surgical success (≤10 Δ) : 25.9%, 23.1% and 53.8% in early, late and very late groups whereas measureable stereoaucity was 37%, 3.8% and 3.8% in each group respectively. Amblyopia : same across groups | Later surgery increases motor success rate and early surgery improves stereopsis.                    |
| Yagasaki et al. 2011| Does timing of surgery contribute to better sensory outcomes and severity of DVD | Retrospective | 55 children Very early 0-8 months Early Surgery 9-24 months Late surgery - 25 months and older | stereopsis after treatment - 50.0% in very early and 11.1% in late surgery. DVD’s of very early group -latent, 38.9% of DVD’s late surgery group were manifest | Early surgery for infantile ET decreases the severity of DVD and lowers need for additional surgery. |
| Arshan et al. 2010  | DVD and its relationship with time and type of surgery in Infantile Esotropia | Retrospective | 144 patients n=59 early surgery (6-24 months), n=55 late surgery group | DVD seen in 37.5% cases that were surgically treated and 80.5% cases with no surgery. DVD seen in 24.1% cases treated between 6mths-2 years and in 52% cases treated after 2 years. | Comparable results of early and late surgery. Very early surgery may offer advantages                 |
| Shin et al. 2014    | Factors influencing development of DVD in infantile esotropia                | Retrospective | 3 groups - latent DVD n=18, spontaneous DVD n=34 (seen without occluding other eye) and no DVD n=38 | no DVD group had a lesser age at surgery (21.3 +/- 7.7) no DVD group had better stereopsis (84.2%). Multivariate logistic regression analysis between groups revealed that later surgery (OR=8.23; P<0.001) were associated with greater development of spontaneous DVD | Surgical correction prior to 24 months reduced incidence of spontaneous DVD                           |
| Altinsoy et al. 2016| Long term motor and sensory outcomes after surgery for infantile ET          | Retrospective | 108 children’ 3 groups Gr I <1 year Gr 2 1-2 years Gr 3 >2 years | Development rate of DVD greater (40%) in group I. Risk of additional surgical greater in patients with a younger mean age. Measureable stereopsis rate higher in group I, difference among groups is insignificant. | Limited potential for high grade stereopsis despite early surgery                                     |

ET=Esotropia, DVD=Dissociated vertical deviation
was delayed as compared to normal children, and following surgery, a greater rate of development of motor skills was noted, thus suggesting that early surgery is beneficial to visual and motor development. However, late surgery can also be effective in improving perceptual motor and motor function.

Delaying surgery in infantile esotropia was not advisable, as concluded by some of the subsequent studies, as the duration of misalignment had the greatest influence on the development of binocular vision. Although one of the reasons for delaying surgery in infantile esotropia has been to achieve a stable angle of deviation, a study by Leuder et al. concluded that strabismus surgery in infantile esotropia does not need to be delayed while waiting for the angle to stabilize. Their series included 30 children operated before 2 years of age, equally divided into two groups, one with a ≤5 Δ difference and the other with a  10 Δ increase in the deviation measured preoperatively. No difference in outcomes between the two groups was observed when followed for 2 years postoperatively. This has been substantiated by a similar observation by the PEDIG group who studied the relationship between the preoperative alignment stability and postoperative motor outcomes in esotropia patients including infantile esotropia.

A meta-regression analysis conducted by the ELISS group concluded a higher reoperation rate in their early-surgery group. The same group, in a subsequent study, conducted a year later, concluded that the endpoints to consider when contemplating surgery are binocular vision restored or retained by early surgery, the postoperative angle of strabismus and its long-term stability, and the number of surgeries required to reach its goal or chance of spontaneous resolution.

To determine the oldest age at which measurable stereopsis can be achieved with excellent motor alignment, Çerman et al. divided their cohort into two groups based on the stereopsis achieved. They recommended surgery before 16 months (median stereopsis: 48 arcsec), with a caveat of factors such as postoperative alignment within 5 Δ playing a role. While all patients with surgery less than 13 months achieved some stereopsis, none above the age of 39 months achieved any stereopsis. Despite a small sample size, their study is consistent with many other studies that show better stereopsis following early surgery. Similarly, Magli et al. conducted a study on a larger cohort and suggested performing surgery between 1 and 2 years of age.

A recent study by Yagasaki et al. demonstrated that very early surgery up to 8 months of age provided a significantly better stereopsis. They looked at the relationship between stereopsis outcome and timing of surgery and stated that early surgery (9–24 months) was associated with better binocularity and that very early surgery (<8 months) improved the chances of postoperative stereopsis. The binocular responses were again significantly better for the very early (<8 months) at 90%–95%, as opposed to the early (9–24 months) or the late groups (>24 months) at 57%–80% and 41%–50%, respectively.

Improved surgical success (≤10 Δ) with later surgery was reported by Muz and Sanac in their recent study of a cohort of 79 patients followed up for more than 60 months. They reported surgical success as 53.8% in the very late group (18–27 months), 23.1% in the late group (11–17 months), and 25.9% in the early group (6–11 months). However, the measurable stereopsis with the Titmus fly test was higher in the early group and was seen in 37% of patients as opposed to 3.8% in the late and very late groups.

The occurrence of postoperative dissociated vertical deviation (DVD) is affected by the timing of the surgery. Early surgery for infantile esotropia has shown a decrease in the severity of DVD and lowered the need for additional surgery as stated by Yagasaki et al. They also showed that all the DVD was latent in children in the very early group (up to 8 months), while 38.9% of the late group had manifest DVD. In addition to the reduced severity of DVD, a reduced incidence of DVD in early surgery was highlighted by Arslan et al. They noted that the incidence of DVD was twice that in the late surgery group compared to the early group (6–24 months). In addition, there was a significantly higher percentage of DVD in the cases that did not have surgery as compared to the surgically treated (80.5% vs. 37.5%).

It is not uncommon to encounter spontaneous DVD in infantile esotropia, although the incidence is significantly reduced when surgical correction is carried out prior to 24 months. Shin et al. showed that the group without DVD had a mean age at surgery of 21.3 ± 7.7 months. This group also had better stereopsis (84.2%) than the spontaneous (58.8%) or the latent DVD group (72.2%). While all these studies suggest surgery less than 24 months of age in EIE for a reduced incidence of DVD, the very early surgery accounts for the least likelihood of manifest DVD, obviating the need for additional vertical muscle surgery.

Another known association of infantile esotropia is inferior oblique overaction which, if present, may be managed either at the same surgery for infantile esotropia surgery or subsequently. Arslan, in his series of infantile esotropes, reported overaction of the inferior oblique muscles associated with DVD in 30 cases (43%).

| Table 3: Timing of surgery - claimed advantages and disadvantages |
|---|
| **Advantages** | **Disadvantages** |
| **Early surgery** | Better stereopsis and binocular vision |
| | Reduced incidence and severity of postoperative DVD and inferior oblique overaction. |
| | Improved psychosocial and parental bonding |
| | Minimizes delay in sensorimotor and gross motor development. |
| **Late surgery** | Better accuracy in estimating the angle of deviation |
| | Possibility of correction of vertical misalignment if any at same surgical sitting |
| | Possibility of treating amblyopia successfully. |
| | Accurate estimation of the angle of deviation is challenging. |
| | Possibility of development of accommodative esotropia as sequelae. |
| | Increased incidence and severity of DVD necessitating additional surgery. |
| | Poorer fine and gross stereopsis and binocular vision |
Contrary to the previously mentioned studies, Altinsoy et al.\(^1\) stated that the difference in stereopsis amongst the groups (<1 year, 1–2 years, and >2 years) was insignificant and that early surgery has the potential effect of development of inferior oblique overaction and DVD earlier with the possibility of an increased need for additional surgery. However, they suggested that very early surgery (<6 months) may have better results with regards to development of DVD.

**Conclusion**

The advantages and disadvantages of early and late approaches to the surgical management of infantile esotropia are summarized in Table 3. Recent evidence, which is in favor of very early surgery (within 6 months of onset of infantile esotropia), outweighs the evidence in favor of early (up to 24 months of age) and late surgery (after 24 months of age) in infantile esotropia with regards to both high-grade stereopsis in some children and the percentage of children developing any stereopsis. The specific advantages of very early surgery for infantile esotropia include the reduced severity of DVD and a reduced need for additional surgery for either DVD or inferior oblique overaction and the additional benefit of minimizing a delay in sensorimotor and gross motor development.

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**Conflicts of interest**

There are no conflicts of interest.

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