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## The Infant Aphakia Treatment Study: Further on intra- and postoperative complications in the intraocular lens group

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The Infant Aphakia Treatment Study (IATS) did not find a significant difference in visual acuity for infants with a unilateral congenital cataract <7 months of age who were corrected with a contact lens compared to an intraocular lens (IOL) after cataract surgery. However, there were significantly more intraoperative and postoperative adverse events and additional intraocular surgeries in the IOL group compared to the contact lens group. This outcome prompted the recommendation that IOL implantation be limited to infants at risk of experiencing “significant periods of uncorrected aphakia” if an IOL was not implanted. Some pediatric cataract surgeons have speculated that if the IATS protocol had been designed differently or if more experienced surgeons had performed the cataract surgeries that the high rate of adverse events in the IOL group would have been averted. Some of these critiques have been published as letters-to-the editor and others have been raised in forums, both public and private. In this report, we address these issues and, in some areas, we provide additional outcome data from the IATS to help clarify areas where there may have been misunderstandings.

### Was the intraoperative and postoperative corticosteroid regimen adequate?

The surgical and postoperative protocols for the IATS were arrived at by consensus of the IATS investigators using the best available knowledge at the time the protocols were developed. Based on this information, the IATS protocol mandated the administration of

topical prednisolone acetate 1% at least 4 times a day for at least 1 month. The protocol allowed the frequency of topical corticosteroids to be increased at the discretion of investigators and to be continued for up to six months if persistent inflammation was noted postoperatively. In fact, the majority of the IATS patients received more corticosteroids than the minimal proscribed in the protocol. The most common dosage of topical corticosteroids prescribed for both treatment groups was prednisolone acetate 6 times a day for 4 weeks; 54/57 (95%) of patients in the IOL group and 38/57 (67%) of patients in the contact lens group were prescribed topical corticosteroids >4 times a day during the early postoperative period. Given the varied doses of topical corticosteroids prescribed and the uncertainty of patient compliance, it is difficult to ascertain whether prescribing the administration of topical corticosteroids on a more frequent basis would have further reduced the incidence of inflammatory postoperative adverse events such as pupillary membranes.

Additionally, while not mandated by the protocol, subconjunctival dexamethasone was administered to 48/57 (84%) eyes in each of the treatment groups (contact lens group, mean  $2.3 \pm 1.5$  mg; IOL group, mean  $2.5 \pm 1.7$  mg). Furthermore, 2 eyes in the contact lens group and 1 eye in the IOL group received subconjunctival methylprednisolone (10-16 mg). Finally, 1 patient in the IOL group received IV methylprednisolone (1 mg/kg) intraoperatively, but no subconjunctival corticosteroids. Thus, patients in both treatment groups received similar doses of intraoperative corticosteroids.

Would there have been fewer postoperative adverse events if corticosteroids had been administered intraoperatively to every patient in both treatment groups? To answer this question, we compared the incidence of pupillary membranes between patients who received subconjunctival corticosteroids compared to those who did not. Pupillary membranes developed in 2 of 15 (13%) eyes that did not receive subconjunctival steroids compared to 16 of 99 (16%) of eyes that received subconjunctival steroids ( $p=0.99$ ). Thus, the evidence at least suggests that administering subconjunctival steroids to each patient probably would not have reduced the incidence of pupillary membranes. However, while the  $p$  values suggest that the frequency of topical corticosteroid administration did not affect the incidence of pupillary membranes, the small sample size of our study does not allow us to answer this question definitively.

## **Was the prevalence of glaucoma increased by ciliary sulcus fixation of IOLs?**

A recent multi-center meta-analysis reported a lower incidence of glaucoma in infantile eyes that underwent IOL implantation at the time of cataract surgery compared to eyes that were left aphakic. However, these eyes were not randomized to IOL implantation and a consistent definition of glaucoma was not used by the centers participating in the study. In contrast, the IATS is a randomized clinical trial and a uniform definition of glaucoma and glaucoma suspect was used at all participating sites. The IATS found a similar incidence of glaucoma for eyes in the IOL (11/57 (19%)) and contact lens (9/57 (16%)) treatment groups at age 5 years. Two of the 11 eyes in the IOL group that developed glaucoma had an IOL implanted in the ciliary sulcus. Some have speculated that the trauma associated with initially

implanting an IOL in the capsular bag and then explanting it prior to implanting an IOL in the ciliary sulcus may have resulted in a higher incidence of glaucoma in this subset of patients. The IATS protocol specified that the IOL should be implanted into the capsular bag whenever possible. Ciliary sulcus fixation was only allowed if both haptics could not be implanted into the capsular bag. Fifty-two of the 56 (93%) eyes in the IOL group had an AcrySof SN60AT IOL (Alcon Laboratories, Fort Worth, TX) implanted in the capsular bag while 4 (7%) eyes had an AcrySof MA60AC IOL implanted in the sulcus. Only one patient had an IOL initially implanted in the capsular bag that was then explanted prior to implanting an IOL in the ciliary sulcus. After a 5 year follow-up, this eye has not developed glaucoma. In the other three eyes with ciliary sulcus fixated IOLs, no attempt was made to implant an IOL into the capsular bag prior to implanting an IOL in the sulcus. One of the 3 eyes with primary ciliary sulcus fixation of the IOL developed glaucoma. However, this eye had persistent fetal vasculature (PFV) that likely increased the risk of this eye developing glaucoma independent of the IOL location.

### **Did the IATS surgeons inexperienced in infantile IOL implantation have a higher rate of postoperative adverse events?**

All of clinical sites participating in the IATS reported performing a high volume of pediatric cataract surgery prior to the initiation of the clinical trial. All of the surgeons participating in the IATS passed a certification examination prior to enrolling a patient in the study. In addition, each investigator was required to submit a video showing him/her performing a cataract operation with IOL implantation on a child <2 years of age using the IATS protocol. This video was critically reviewed by a member of the steering committee (Dr. Edward Wilson) to confirm that the surgery was performed using the IATS protocol. In addition, training in both basic and advanced techniques for pediatric cataract surgery was provided at IATS investigators' meetings by the most experienced IATS surgeons as well as outside experts. Nevertheless, we realized that there would be different levels of experience among the surgeons participating in the clinical trial. For this reason, we assigned the 12 participating clinical sites to one of three groups with 4 clinical sites in each group: Group 1) a clinical site with a steering committee member; Group 2) a clinical site that participated in the IATS pilot study without any investigators on the steering committee; and Group 3) all other clinical sites. We assumed that the surgeons in Group 1 would have had the most experience performing infantile cataract surgery, but some of the surgeons in Groups 2 and 3 may have been just as experienced as the surgeons in Group 1. It should also be noted that some clinical sites had two investigators who had differing levels of experience. Clinical sites were stratified in the randomization process so that an equal number of patients in both treatment groups would be randomized to each of the three groups, thus controlling statistically for different levels of surgeon experience. Twelve patients in the IOL group and two patients in the contact lens group had iris prolapse during surgery. Iris prolapse likely increases anterior segment inflammation in infantile eyes. Pupillary membranes developed in 4 of 12 (33%) eyes in the IOL group that experienced iris prolapse compared to 12 of 45 (27%) eyes that did not have iris prolapse ( $p=0.72$ ). Among the 57 eyes in the IOL group, surgeons in Group 1 had 3/19 (16%) cases of iris prolapse, compared to 4/18 (22%) cases in Group 2 and 5/20 (25%) cases in Group 3 ( $p=0.85$ ). Although we cannot exclude the

possibility that the incidence of pupillary membranes would have been lower in the IOL group if all the surgeries would have been performed by the most experienced surgeons, we have no evidence to support this supposition.

## Did serious vision threatening complications occur more often in aphakic eyes?

Two eyes in the contact lens group had serious vision threatening complications (one eye developed endophthalmitis and a retinal detachment and one eye developed a retinal detachment and phthisis bulbi). We discussed these complications in detail in previous publications. Endophthalmitis is a rare complication after pediatric cataract surgery with an estimated prevalence of .07%. We have reviewed the cataract surgery video, operative reports and postoperative treatment for the patient who developed *Haemophilus influenza* endophthalmitis and have not been able to identify a cause for the infection. The second patient developed a retinal detachment after a pars plana membranectomy performed by a vitreoretinal surgeon two weeks after the initial cataract surgery. Prior to the membranectomy, a B-scan ultrasound documented that the retina was attached. This patient had PFV that may have been a risk factor for developing both the pupillary membrane and retinal detachment. The percentage of patients with serious vision threatening complications was not significantly different between the two groups using the Fisher exact test (contact lens group, 2 of 57 patients [3.5%]; IOL group, 0 of 57 patients;  $p=0.50$ ).

As noted above, it is possible that the incidence of intraoperative and postoperative adverse events would have been lower if the most experienced surgeons had performed all of the cataract surgeries. However, all of the surgeons who participated in the IATS were experienced pediatric cataract surgeons and each received additional training prior to enrolling patients in the IATS. It is also our opinion that the most common adverse event in the IOL group, lens repopulation into the visual axis, is not related to surgeon experience or postoperative anti-inflammatory regimen.

In conclusion, we maintain that most children with a unilateral congenital cataract should be left aphakic and treated with a contact lens until the family and surgeon decide that secondary IOL implantation is indicated. However, when family circumstances make primary IOL implantation a better option, we recommend that these surgeries be performed by experienced infant cataract surgeons given the high rate of intraoperative and postoperative adverse events associated with this surgical procedure.

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