**Importance**  Aggressive posterior retinopathy of prematurity (AP-ROP) rapidly progresses to retinal detachment despite application of photocoagulation. Early vitreous surgery might achieve prompt regression of neovascular activity and a high incidence of retinal reattachment.

**Objective**  To evaluate visual outcomes in eyes with AP-ROP after early vitreous surgery.

**Design**  Retrospective nonrandomized study of patients who underwent early vitreous surgery with lensectomy when retinal detachment developed despite photocoagulation. Aphakic correction with spectacles or contact lenses and the use of orthoptics were continued postoperatively. The best-corrected visual acuity (VA) was measured in eyes with a total retinal reattachment using the preferential looking technique in patients ranging in age from 8 months to no more than 3 years and a VA chart with Landolt rings or pictures for older children. The VA findings were converted to Snellen lines.

**Setting**  Institutional ophthalmology practice.

**Participants**  Of the 103 eyes (57 patients) that underwent early vitreous surgery for AP-ROP, the VA was measured in 58 (32 patients) at a corrected age ranging from 8 months to 4 years.

**Interventions**  Early vitreous surgery and VA measurement using the preferential looking technique and a VA chart.

**Main Outcomes and Measures**  Postoperative VA, ROP stage, extent of fibrovascular tissue (FT) growth, and laterality of the eyes that underwent surgery.

**Results**  The VAs ranged from 20/2000 to 20/40. The VA may not be related to the preoperative ROP stage 4A or 4B but may depend on the preoperative extent of FT growth. In 39 of 58 eyes (67.2%), the FT had not reached the vitreous base preoperatively, and foveal formation occurred postoperatively with nearly age-appropriate VA (range, 20/250 to 20/40). In 17 of 58 eyes (29.3%), the FT had reached the vitreous base, and no fovea formed (VA range, 20/2000 to 20/250). Two of 58 eyes (3.4%) had deprivation amblyopia with a VA worse than 20/1600. The difference in VA between both eyes of patients who underwent bilateral vitreous surgery depended on ROP progression; patients who underwent a unilateral procedure in which the fellow eyes with ROP stabilized after photocoagulation tended to have poor vision because of deprivation amblyopia.

**Conclusions and Relevance**  Early vitreous surgery may be beneficial for AP-ROP and should be performed before the FT reaches the vitreous base to facilitate foveal formation and good VA outcomes. The roles of photocoagulation, vitreous surgery, and anti–vascular endothelial growth factor therapy in the treatment of AP-ROP should be investigated in randomized trials regarding efficacy, safety, convenience, and cost.

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With the improving survival of very small premature infants owing to progress in neonatal intensive care, the incidence of aggressive posterior retinopathy of prematurity (AP-ROP), an unusual and severe form of ROP, is increasing and threatening vision. Retinal photocoagulation, which stabilizes classic ROP, often fails to stop progression to retinal detachment in AP-ROP. Previous vitreous surgery performed to treat retinal detachment has obtained poor visual outcomes ranging from light perception to ambulatory vision despite successful retinal reattachment.

One study has proposed that patients undergo early vitreous surgery for AP-ROP, which has resulted in prompt regression of neovascular activity and a high incidence of retinal reattachment. We report here the visual outcomes after early vitreous surgery for AP-ROP.

Methods

From July 1, 2004, through December 31, 2011, 103 eyes of 57 patients (31 girls and 26 boys) with AP-ROP underwent early vitreous surgery with lensectomy. Diagnosis of AP-ROP was based on the protocol of the International Classification of Retinopathy of Prematurity, including prominent plus disease and a posteriorly located flat network of neovascularization at the deceptively featureless junction between the vascularized and nonvascularized retina. In all eyes, dense laser photocoagulation had been applied previously at our clinic or elsewhere; however, this treatment failed to stop progression of ROP. When fibrovascular tissue (FT) continued to proliferate or recurred after transient regression and progressed circumferentially for 6 or more continuous clock hours with a tractional retinal detachment that developed simultaneously (stage 4), the same surgeon (N.A.) performed early vitreous surgery as a secondary treatment. The surgical procedure has been described previously. The refractive error of aphakia was corrected postoperatively with spectacles or contact lenses, and continuous occlusion therapy was provided in cases in which a unilateral procedure was performed.

Postoperative foveal formation was evaluated by fundus photography and fluorescein angiography using a retinal camera (RetCam, Massie Research Laboratories, Inc) in all eyes. We examined the visual outcomes after vitreous surgery in eyes that achieved total retinal reattachment. Patients who were mentally challenged were excluded. The best-corrected visual acuity (VA) was measured with the preferential looking technique at a distance of 50 cm using a commercially available inspection apparatus (Awaya-Mohindra-type apparatus; Nitten Pharmaceutical Co, Ltd) in patients ranging in age from 8 months to younger than 3 years; a VA chart with Landolt rings or pictures at 5 m was used for older children. The VA findings were converted to Snellen lines. We also determined the normal curve of VA development. One eye each of 81 healthy children (40 girls and 41 boys; age range, 2 months to 3 years) who had no bilateral abnormalities detected by ocular examination and who had good visual function was evaluated by the preferential looking technique; and 72 eyes of 72 healthy children (37 girls and 35 boys; age range, 3-6 years) were evaluated using a VA chart.

Results

Gestational age at birth ranged from 22 to 30 (mean, 24) weeks. Birth weight ranged from 268 to 1676 (mean, 706) g, and the postmenstrual ages at vitreous surgery ranged from 34 to 44 (mean, 37) weeks. Because capillary hypoperfusion is present in the entire retina with AP-ROP, preoperative photocoagulation applied up to the vascularized retina may be the key to good surgical outcomes. In 89 eyes with adequate photocoagulation, total retinal reattachment was achieved in 81 (91.0%) and partial reattachment in 8 (9.0%); the fovea was well formed in 63 (70.8%). In contrast, among 14 eyes treated with inadequate photocoagulation, total retinal reattachment was achieved in 2 (14.3%), partial reattachment in 5 (35.7%), and no reattachment owing to FT regrowth in 7 (50.0%). The fovea was unformed in all 14 eyes with inadequate photocoagulation. In the eyes in which total reattachment was achieved, formation of the fovea depended on the absence (Figure 1A-E) or the presence of retinal dragging by residual FT (Figure 1F-J).

The postoperative VAs were measured in 64 eyes of 35 patients (19 girls and 16 boys; 58 eyes underwent simultaneous bilateral surgery and 6 eyes, unilateral surgery) at corrected ages ranging from 8 months to 4 years. We compared the VA in these patients with the visual development curve obtained from the controls. To compare the anatomic and functional outcomes, 2 eyes with bilateral corneal opacity due to congenital anterior segment dysgenesis and 4 eyes with bilateral small corneas and postoperative glaucoma (VA of worse than 20/200 in each eye) were excluded. Thus, 58 eyes of 32 patients (bilateral surgery, 52 eyes; unilateral surgery, 6 eyes) underwent analysis. Preoperative development of ROP reached stage 4A in 42 eyes and stage 4B in 16 eyes. All 41 eyes in which the FT preoperatively had not reached the posterior lens surface or the vitreous base achieved foveal formation postoperatively; the remaining 17 eyes in which the FT already reached the posterior lens surface or the vitreous base had no fovea. The postoperative VAs ranged from 20/2000 to 20/40. Forty eyes (69.0%) obtained VAs of 20/250 or better (Figure 2).

The VA outcomes may be unrelated to the preoperative stages of ROP: the VAs in the 42 eyes with ROP stage 4A ranged from 20/2000 to 20/40, and those in the 16 eyes with ROP stage 4B ranged from 20/2000 to 20/65. The difference in the VAs between both eyes of each patient may depend on the preoperative extent of the FT growth. Thirty-seven of the 52 eyes (71.2%) that underwent bilateral surgery when the FT had not reached the posterior lens surface or vitreous base achieved foveal formation and had VAs ranging from 20/250 to 20/40, which was nearly age appropriate (Figure 1A-E and Figure 2). In contrast, the 15 eyes (28.8%) in which the FT reached the posterior lens surface or vitreous base failed to achieve foveal formation and had VAs ranging from 20/2000 to 20/250 (Figure 1F-J and Figure 2). The fovea was absent in 15 eyes: in 11 (73%) because of progression of retinal dragging by contraction of the excessive FT and in 4 (27%) because of malformation of an immature retina despite preservation of the presumed foveal region.
Six eyes underwent unilateral vitreous surgery. Two eyes with good anatomic outcomes obtained good VA at 20/100; the fellow eyes had ROP and developed a total retinal detachment (stage 5). In contrast, 4 eyes had poor VA (worse than 20/1600) despite successful retinal reattachment, postoperative aphakic correction with a contact lens, and continuous occlusion therapy. The fellow eyes achieved ROP stabilization after photocoagulation, foveal formation, and good VA. Two eyes had retinal dragging as a result of worsening ROP, and the other 2 eyes with a nearly normal fovea may have developed deprivation amblyopia.

**Discussion**

The results of this study indicate that early vitreous surgery may provide benefits for patients with AP-ROP. The disease can stabilize in some eyes treated with only dense photocoagulation; however, when FT continues to grow and a retinal detachment develops, ROP no longer regresses spontaneously. Thus, vitreous surgery is necessary as a secondary treatment.3,10 Postoperatively, the retina reattached completely in 83 of the 103 eyes (80.6%), and the fovea formed in 63 eyes (61.2%); these results were much better (ie, 91.0% and 70.8%, respectively) when adequate photocoagulation was applied preoperatively. Of the eyes with a total retinal reattachment, postoperative VAs ranged from 20/250 to 20/40 in 68.9%, and those patients could be expected to be mainstreamed into public school systems. The VA outcomes obtained in our patients are fairly good compared with those obtained after lens-sparing vitrectomy for classic ROP11 despite the poor conditions for visual development, including retinal prematurity in association with a very early birth and postoperative aphakia. Although our study is limited by its uncontrolled retrospective case series design, it is one of the few analyses, to our knowledge, that have examined the functional outcomes of AP-ROP management after surgical procedures performed by a single surgeon.

The VA outcomes are related principally to foveal formation, which starts prenatally and continues postnatally.12 The fovea was well formed in 71.2% of the eyes in which the VA was
examined but not in the remaining 28.8% because of retinal dragging or malformation of an immature retina. Whether the foveal region is preoperatively involved in a retinal detachment (ROP stage 4B) or not (ROP stage 4A) may not be related to foveal formation and VA outcomes when the retina is promptly reattached postoperatively. Because AP-ROP rapidly progresses to severe retinal dragging and retinal detachment, prompt surgery performed when FT begins to grow and does not reach the posterior lens surface or the vitreous base is expected to facilitate foveal formation and good VA outcomes.

The difference in the VA outcomes in the fellow eyes of the patients who underwent simultaneous bilateral surgery may depend on the preoperative progression of the FT and the postoperative foveal formation. Refractive correction for aphakia using spectacles or contact lenses also helped to facilitate good visual development, although the lens was removed. The eyes that underwent unilateral surgery, the fellow eye of which was blind because of ROP progression, also achieved a good VA. In contrast, in cases of unilateral vitrectomy and/or lensectomy with a functioning fellow eye, the VA outcomes were disappointing despite good anatomic outcomes. When the fellow eye achieves a good VA after successful ROP stabilization by photocoagulation, deprivation amblyopia may develop despite aphakic correction and continuous occlusion therapy. Lens preservation is important to prevent deprivation amblyopia and promote visual development; thus, amblyopia is predictable after unilateral surgery with lens removal, which can only contribute to prevention of blindness.

Good anatomic results after lens-sparing vitrectomy for AP-ROP have been reported in cases in which the surgery was performed before or just after development of a retinal detachment, which was earlier than in our study. We cannot easily predict whether FT that circumferentially extends less than 1 quadrant will regress or progress after photocoagulation. Furthermore, FT often expands vertically and circumferentially at about 1 week after transient resolution of and sudden recurrence of plus disease. However, our experience with lens-sparing vitrectomy to treat AP-ROP in which FT progressed circumferentially for more than 2 continuous quadrants did not stop the progression of retinal detachments compared with the group in which lensectomy was performed. Vitrectomy removes the vitreous gel along which the FT grows; however, when vitrectomy is performed to spare the lens, highly active FT regrows along the residual vitreous gel in the periphery, resulting in progression of the retinal detachment. Fundus angiography showed capillary hypoperfusion throughout the nonvascularized and vascularized retina with AP-ROP; this hypoperfusion is usually restricted to the nonvascularized retina with classic ROP, indicating release of vascular endothelial growth factor (VEGF) from the wide ischemic area of capillary hypoperfusion, which was insufficiently suppressed by wide dense application of photocoagulation.

Thus, vitrectomy associated with lens removal facilitates total removal of the vitreous gel and washout of VEGF from the eye. The indication for and timing of surgery and the choice between a lens-sparing procedure or lens removal may be determined by further analysis of FT behavior and changes in VEGF concentrations in the vitreous cavity.

Intravitreal injection of anti-VEGF drugs, primarily bevacizumab (Avastin), which stabilizes neovascular formation, is thought to be useful for treating ROP. However, the efficacy of the drug as therapy for AP-ROP is not well established. Monotherapy administered to avoid photocoagulation in the treatment of ROP may not stabilize severe ROP involving the entire retina that is hypoperfused in the presence of a large amount of VEGF. Relatively good outcomes after anti-VEGF therapy combined with other surgical interventions have been reported recently, such as salvage therapy that prevents progression of retinal detachments after application of photocoagulation and an adjunctive therapy to achieve a dilatory effort before planned vitreous surgery, for which some problems remain to be addressed. Contraction of FT, an adverse drug effect that promotes retinal dragging and detachment, is critical when the FT is extensive. Because a large amount of VEGF may be released during a long period in eyes with AP-ROP, a transient effect of the drug may later result in unpredictable recurrence of the retinal detachment. Serum evaluation has shown that intravitreally injected bevacizumab can migrate from the eye into the systemic circulation and reduce the serum level of VEGF in infants with ROP. This adverse effect might disrupt organ development, including that of the central nervous system, in extremely small premature babies with AP-ROP. Thus, the roles of photocoagulation, vitreous surgery, and anti-VEGF therapy in the treatment of AP-ROP should be further investigated in randomized trials regarding efficacy, safety, convenience, and cost. However, a combination of photocoagulation and early vitreous surgery may be a good option for managing this difficult problem at the present time.

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Original Investigation Research


