Surgery for advanced pediatric vitreoretinopathies remains formidable even in the hands of experienced retinal surgeons. This is underscored by the abysmal retinal reattachment failure rate of up to 100% in cases of retinopathy of prematurity (ROP) complicated by iatrogenic full-thickness retinal breaks at the time of vitrectomy.1

The distinct anatomic and physiologic differences between pediatric and adult vitreoretinopathies pose unique challenges. The stronger vitreoretinal (VR) adhesion in children than adults precludes surgical induction of posterior vitreous detachment (PVD) during vitrectomy in most babies and young children. In proliferative vitreoretinopathies such as ROP and familial exudative vitreoretinopathy, adequate removal of epiretinal membranes enmeshed within layers of formed vitreous is crucial for retinal reattachment to occur. This article discusses the potential role of microplasmin (ThromboGenics NV, Leuven, Belgium) as a surgical adjunct to vitrectomy for pediatric vitreoretinopathies.

PLASMIN ENZYME-ASSISTED VITRECTOMY IN INFANTS AND CHILDREN

Plasmin enzyme (PE) hydrolyzes glycoproteins, such as fibronectin and laminin, and induces vitreous liquefaction with simultaneous PVD in humans.2 Evidence suggests that PE is a useful surgical adjunct in pediatric VR surgery. For example, in stage 5 ROP, or total retinal detachment, complete zone 1 reattachment of the retina is achievable in 68.8%3 to 100%4 of eyes in which autologous plasmin enzyme (APE) is used as an adjunct to vitrectomy. This is demonstrated in the following case:

A premature baby of Ukrainian descent, who was born at a gestational age of 29 weeks and a birth weight of 2.6 lbs, presented to us at postmenstrual age of approximately 50 weeks with stage 5 ROP in the right eye and stage 4B ROP in the left eye. No prior laser or cryotherapy had been performed prior to presentation. The child underwent bilateral sequential surgeries 1 week apart. Blood was drawn from the infant’s mother 3 days before surgery. In each eye, heterologous (maternal) PE was injected 30 to 60 minutes before 20-gauge lensectomy and vitrectomy via a scleral limbal approach. Extensive membrane peeling was performed. There were no iatrogenic retinal breaks. A fluid-air exchange was done at the end of each case. Six months postoperatively, following a single operation in each eye, there was bilateral retinal reattachment in zone 1 except for a residual dry retinal fold at the left macula (Figures 1 and 2).

The results of vitrectomy for stage 5 ROP with PE contrast with a macular reattachment rate of 28% in a large study of 601 patients in which vitrectomy was performed without adjunctive PE.5 In eyes with stage 5 ROP and iatrogenic retinal breaks from previous vitrectomy, retinal reattachment (partial or complete) has been shown to occur in 0% of eyes undergoing vitrectomy alone,1 compared with 53% of eyes undergoing PE-assisted vitrectomy.3

In congenital X-linked retinoschisis (CXLRS), the use of autologous PE eliminated the need for inner wall retinectomy in 82% of eyes, and 91% of eyes achieved retinal reattachment.6 The enzymatic degradation of the VR junction largely overcomes the difficulty of achieving complete mechanical PVD induction in these eyes.

In combined hamartoma of the retina and retinal pigment epithelium (RPE), PE-assisted vitrectomy can be helpful when a VR dissection plane is not visible on clinical examination or optical coherence tomography (OCT). In a series of
Figure 1. Preoperative image of right eye with stage 5 ROP (A). The image is in focus immediately posterior to the native lens with a detached retina in view. There is marked anterior hyaloidal and preretinal proliferation. At 1 week after surgery (B), stage 5 ROP remains, although the funnel is now largely open with the optic disc visible centrally. At 3 months after surgery (C), the retina in posterior zone 1 has reattached. Several months of observation may be required before the success of an operation can be judged. At 6 months after surgery (D), the area of retinal reattachment in zone 1 has remained stable. Peripheral subretinal exudates have significantly resolved.

Figure 2. Preoperative image of left eye with stage 4B ROP (A). The inferior half and anterior annulus of the retina is detached with associated anterior hyaloid and preretinal proliferation. A good red reflex in part of the superior retina is visible, which correlates with an area of attached retina noted intraoperatively. At 3 months after surgery (B), retinal reattachment has occurred in zone 1/ posterior zone 2. Subretinal exudates are present in the macular fold. At 6 months after surgery (C), the area of retinal reattachment has remained stable. The macular fold has decreased, with associated resolution of subretinal fluid and exudates (ie, dry fold).
six pediatric eyes, retinal architecture improved in all cases following APE-assisted vitrectomy and membrane stripping. Visual acuity improved in 66% of eyes and stabilized in 33%.9
In patients of mean age 10 years (range 1-15 years) with pediatric traumatic macular hole, primary anatomic closure was achieved in 92% of eyes following PE-assisted vitrectomy.8

Although these studies demonstrate that pharmacologic vitreolysis by PE facilitates posterior vitreous separation and vitreous and membrane removal, the time-sensitive and complex process required to isolate and purify plasmin has precluded its widespread use. Recombinant microplasmin is a promising alternative to APE.

CURRENT STATUS OF MICROPLASMIN
Microplasmin has been shown to be efficacious in treating symptomatic vitreomacular adhesion (VMA) in adults. Two phase 3, multicenter, randomized, placebo-controlled, double-masked clinical trials have recently been completed.9 In the TG-MV-006 and TG-MV-007 studies, 652 patients with vitreomacular traction, macular hole, or macular pucker were recruited at 90 centers in the United States and Europe. Study participants were randomly assigned to receive a single intravitreal injection of 125 mg microplasmin (n=464) or 100 mL placebo solution (n=188). The primary efficacy endpoint was the proportion of patients who achieved resolution of sVMA at day 28 by masked OCT at a central reading center. The endpoint was met, with 26.5% of microplasmin-treated patients achieving pharmacologic resolution of symptomatic VMA compared with 10.1% in the control group (P < .001). Secondary endpoints were also met. At day 28, secondary end points were met with microplasmin showing a statistically significant effect vs placebo: 40.6% of participants had pharmacologic macular hole closure, which was maintained at month 6 (P < .001), and pharmacologic induction of total PVD occurred in 13.4% of patients (P < .001). No safety concerns were highlighted in these trials, reaffirming findings from previous phase 2 clinical trials evaluating microplasmin.10-12

MICROPLASMIN-ASSISTED VIRECTOMY IN INFANTS AND CHILDREN
In light of these clinical trial results, which demonstrated, placebo-controlled, double-masked clinical trial to assess the safety and efficacy of a single dose of 175 mg microplasmin in infants and children aged 16 years or younger undergoing vitrectomy (ClinicalTrials.gov identifier: NCT00986362). The key difference between this and the adult trials is in the use of microplasmin as a surgical adjunct to vitrectomy rather than as a nonsurgical alternative therapy.

The trial rationale is that pharmacologic vitreolysis with microplasmin will induce vitreolysis and facilitate hyaloidal separation during vitrectomy. A higher dose (175 mg microplasmin) is being used to maximize the potential vitreolysis effect of the drug, although exposure time will be significantly less than in the clinical trials in adults, minimizing potential safety concerns. Twenty-four patients will be recruited and allocated in a 2:1 ratio to either microplasmin or placebo intravitreal injection 30-60 minutes before vitrectomy. Participants will be followed for 6 months. Primary efficacy endpoints are masked assessment of vitreous liquefaction at the beginning of vitrectomy, the proportion of eyes with total macular PVD at the beginning of vitrectomy or after application of suction, and retinal attachment status at follow-up. Safety will be assessed via multiple endpoints including ophthalmic and systemic adverse events, ophthalmoscopy, and fundus fluorescein angiography. Study outcomes are anticipated to be published in 2012.

TARGET CONDITIONS
If microplasmin can be demonstrated to be at least as efficacious as APE in inducing vitreolysis, it could be applicable to a wide range of pediatric vitreoretinopathies in which hyaloidal separation is crucial to surgical success. These would include, but are not be limited to, the following vasoproliferative and nonvasoproliferative diseases:

- Vasoproliferative
  - ROP retinal detachment
  - Familial exudative vitreoretinopathy retinal detachment
  - Persistent fetal vasculature syndrome
  - Combined hamartoma of the retina and RPE
  - Norrie disease
  - Incontinentia pigmenti
  - Any of the above conditions with localized or diffuse hyaloidal contraction

- Nonvasoproliferative
  - CXLRS
  - Colobomatous retinal detachment (RD)
  - Macular hole
  - Stickler syndrome
  - Traumatic RD (penetrating and nonpenetrating)
CONCLUSION

Hyaloidal separation is crucial for surgical success in a range of pediatric vitreoretinopathies. APE and heterologous (parental) plasmin enzyme have been shown to facilitate surgical success and improve clinical outcomes; however, the complexity of its preparation has impeded widespread use. Phase 2 and 3 clinical trials in adults have shown that recombinant microplasmin can induce clinically significant pharmacologic vitreolysis. If this can be translated to and optimized for pediatric vitreoretinal surgery, it would represent the first use of microplasmin as a surgical adjunct and significantly bolster our current surgical armamentarium. ■

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