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ABSTRACT
The treatment of anisometropic or ametropic amblyopia has traditionally enjoyed a high treatment success rate. Early initiation and consistent use of spectacle correction can completely resolve amblyopia in a majority of patients. For those with anisometropic amblyopia that fail to improve with glasses wear alone, patching or atropine penalisation can lead to equalisation of visual acuity. However, successful treatment requires full-time compliance with refractive correction and this can be a challenge for a patient population that often has one eye with good acuity without correction. Other barriers for a select population with high anisometropic or ametropic amblyopia include rejection of glasses for various reasons including discomfort, behavioural or sensory problems, postural issues and visually significant aniseikonia. When consistent wear of optical correction proves difficult and patching/atropine remains a major obstacle, surgical correction of refractive error has proven success in achieving vision improvement. Acting as a means to achieve spectacle independence or reducing the overall needed refractive correction, refractive surgery can offer a unique treatment option for this patient population. Laser surgery, phakic intraocular lenses and clear lens exchange are three approaches to altering the refractive state of the eye. Each has documented success in improving vision, particularly in populations where glasses wear has not been possible. Surgical correction of refractive error has a risk profile greater than that of more traditional therapies. However, its use in a specific population offers the opportunity for improving visual acuity in children who otherwise have poor outcomes with glasses and patching/atropine alone.

INTRODUCTION
A significant difference in refractive error (anisometropia) or a large degree of refractive error in both eyes (isoametropia) predisposes a child to the development of amblyopia. Anisometropia may occur in the setting of asymmetric myopia, hyperopia or astigmatic error. The amount of anisometropia that may generate amblyopia is not concrete, but the results of the Multi-Ethnic Pediatric Eye Disease Study established that 59.5% of subjects with $\geq$2 dioptries (D) spherical equivalent (SE) of anisometropia had amblyopia.1 The risk for amblyopia development is seen with relatively smaller differences in hyperopia ($\geq$1.50 D SE) or astigmatism ($\geq$2 D SE). In contrast, $<$3 D SE of anisometropia myopia does not usually cause amblyopia.2 3 Ametropia guidelines are less exact but concern is that those refractions of $\geq$4 D of hyperopia, $\geq$2.50 D of astigmatism or $\geq$6 D of myopia place a child at risk for amblyopia.2 4

Standard of care practice for refractive amblyopia includes correction of the refractive error using glasses followed by patching or atropine penalisation of the fellow eye for anisometropic amblyopia.5–8 Studies by the Pediatric Eye Disease Investigator Group (PEDIG) have carefully defined the amount, duration and options for the modification of both patching and atropine therapy.5–8 Further improvement in visual acuity occurs with addition of a plano lens in the fellow, non-amblyopic eye.9 10

Successful treatment, however, is predicated on full-time compliance with refractive correction. Anisometropic children often have one eye with good acuity without correction; therefore, they perceive little benefit from glasses and may reject them. Other barriers to spectacle compliance include intolerance for a myriad of reasons including discomfort with wear, sensory disorders and postural issues. Furthermore, higher degrees of anisometropia may cause visually significant aniseikonia. Two to three dioptres of anisometropia induces 5%–6% aniseikonia, a challenging amount of image disparity for the brain to resolve.11

High isoametropia, especially those cases of severe bilateral myopia, can cause bilateral amblyopia or reduced best-corrected visual acuity (BCVA). Amblyopia can occur whenever high refractive error exists, even in the context of compliance with spectacle correction. Object minification due to high myopic lenses limits acuity and contributes to limited BCVA.12

Contact lens correction (CTL) for the amblyopic eye in children with significant anisometropia is an acceptable alternative to spectacle correction. CTL do not induce aniseikonia for the same degree of correction and have the benefit of only nominal image minimisation for children with high myopic refractive errors. However, the barriers to CTL correction are similar to those for spectacle wear (no perceived benefit, discomfort, intolerance). Additional limitations include parents discomfort with CTL handling and placement and the lack of coverage on most insurance plans, which further dampens parent’s enthusiasm for this approach.

When optical correction cannot be consistently worn, patching/atropine remains a major obstacle, or for the small subset of patients who have excellent compliance with glasses and amblyopia treatments, yet continue to stall in visual improvement, evidence suggests surgical refractive correction is a reasonable option to combat amblyopia. The benefits of surgical correction of refractive error are manifold. It eliminates compliance with refractive
correction for any reason as a barrier to amblyopia treatment and has the same benefits as CTL without the associated perceived and real drawbacks of CTL use in the paediatric population. Furthermore, the ability to reduce anisometropia and resulting aniseikonia, even with residual spectacle dependence, is a positive—and unique—benefit to surgical correction in the treatment of amblyopia.

Laser surgery
Photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK) and laser-assisted subepithelial keratectomy (LASEK) have been used to effectively treat refractive errors in the children. The first reported use of laser-assisted refractive surgery in children was published by Singh in 1995. Since that time, numerous case reports and series have documented both the safety and efficacy of the operation in these patient cohorts. The utility of the procedures has been documented to treat high hyperopia, high myopia and large amounts of astigmatism. To date, no randomised controlled trial has documented the effectiveness of laser-assisted refractive surgery in the treatment of amblyopia.

Use of laser-assisted refractive surgery for the treatment of myopic anisometropia has been reported in over 17 case series. Yin et al described successful use of LASEK in myopic astigmatism (SE ranged from −15.8 D to −5.4 D) in 32 children. BCVA improved from 20/50 to 20/33 and the rates of stereopsis improved from 19% to 73%. Incidence of corneal haze was low (6/32) and mild. In a similarly sized study of 35 patients, Tychsen et al treated an even greater range of anisomyopia (SE ranges from −3.3 D to −24.3 D) using PRK and LASIK. Mean BCVA improved from 20/87 to 20/47. Low rates of haze were reported. Paysse et al reported a similar patient cohort with over 3 years of follow-up. This population also included myopes ranging from −21.0 D to −9.75 D. In this report, the maximum treatment dose was −11.5 D, which allowed for successful treatment of high myopes taking into consideration the need to leave a sufficient residual stromal bed. Overall, the published studies document a trend towards improvement in BCVA. Low rates of complications were reported in all studies and included minimal haze and two incidents of flap dislocation in LASKIK patients.

Treatment of anisohyperopia with corneal refractive surgery is less extensively reported. It differs from myopic treatments in the size and shape of the ablation zone, rendering it slightly more challenging and prone to regression. PK, LASEK and LASIK have shown promise in improving BCVA, binocular vision and density of amblyopia. Dvali et al studied an older population, mean age of 12.7 years, and had encouraging results. Twenty-four patients had improvement in amblyopia and twenty had it completely resolve. Reassuringly, even treatment of high hyperopes did not lead to high rates of corneal haze. Astle and colleagues reported on the results of 47 patients undergoing LASEK in 72 eyes for the treatment of bilateral hyperopia and hyperopic anisometropic amblyopia. In this cohort, the upper limit of hyperopia treated was +2.15 D. Among the children able to complete acuity testing, a 41.7% improvement in distance acuity was seen. There was also improvement in gross and fine stereopsis.

High isometropia, especially severe bilateral myopia, can cause bilateral amblyopia or reduced BCVA. Poor spectacle compliance is a primary contributing factor to the development of bilateral amblyopia. While this is often seen in the setting of developmental delay and/or neurobehaviourally impaired children who struggle with glasses wear, amblyopia can occur whenever high refractive error exists. Minification due to high myopic lenses also limits acuity. Astle also included an example of high bilateral hyperopia in a 11-year-old who, despite excellent glasses compliance, could not achieve BCVA better than 20/80. With LASEK, he improved to 20/40, although the postoperative course was complicated by 2+ corneal haze. The combined effect of additional magnification and improved uncorrected visual acuity can have impressive effects on overall function.

Laser refractive surgery for children is not yet a perfect solution for the treatment of amblyopia. Despite being well tolerated, having low rates of visually significant complications and repeatedly documented BCVA gains, there remains room for improvement. Regression occurs across all groups of preoperative refractive errors. Some surgeons advocate the application of the antimetabolite mitomycin C during treatment to reduce regression in both myopic and hyperopic treatments, but controlled studies are lacking. Most regression occurs over the first year following surgery, with smaller shifts over the following 2–3 years. Treatment for high myopia generally shows even faster rates of regression. Authors suggest anticipating this shift and overcorrecting by 1–2 D. Therefore, laser-assisted refractive surgery may not free a child from spectacle dependence. Moreover, while the assumption was that with reduced anisometropia glasses and patching compliance should improve, this was not reported to be the case.

Studies have suggested that amblyopia treatment of large refractive errors with refractive surgery should take place while younger to maximise visual rehabilitation. Astle reported successfully treated dense amblyopia from anisomyopia and anisostigmatism in children less than 1 year of age. Refractive errors were quite large in these cases and amblyopia was felt to be unresponsive to all prior forms of treatment. It follows that treatment in this age range will require general anaesthesia. The logistics of arranging for anaesthesia staff and supplies in facilities already containing excimer laser can be complicated. However, a practical framework for PK with general anaesthesia has been outlined by Paysse and colleagues.

Drawbacks linked to treatment-specific complications are as a whole quite low. Severe vision compromising complications are exceptionally rare. Instances of flap dislocations among LASIK patients are reported in the literature, but remain reassuringly infrequent. Reports of corneal haze are low and generally did not become visually significant. Most resolved with the use of topical steroids. Surgeons continue to look for ways to improve their techniques and outcomes, especially in regards to corneal clarity and refractive targets. The use of femtosecond technology, mitomycin C and more precisely selecting good refractive candidates are all the ways future refractive outcomes may continue to improve.

Phakic intraocular lenses (pIOLs)
PpIOLs are available in three models: iris-fixed anterior chamber, ciliary sulcus-supported posterior chamber and angle-supported anterior chamber. The preference currently appears to be for iris-claw anterior chamber IOLs. As noted by Cleary et al, the creation of iris-claw lenses took place in the 1970s with the original models of what currently are the Artisan and Verryse lenses. They have undergone modification in the decades since and now feature a biconvex design. Hyperopic correction ranges from +2 to +30 D and myopic correction ranges from −1.00 to −23.50 D. Toric configurations of the Artisan lens can correct up to 7.50 D of astigmatism. Use of the iris-claw lens was first
reported in children in 1997 in a series of 38 eyes of 27 aphakic children.26

High anisomyopic amblyopia has been successfully corrected using Artisan and Verisyse lenses.20–22 Pirouzian and Ip reported the successful rehabilitation of seven patients (age 5–11 years) with greater than 8 D of myopia with the use of Verisyse lenses. Each child was entered into the study with a BCVA <20/100. At follow-up 3 years later, mean BCVA was 20/40 (range 20/30–20/60). The mean SE refraction was −14.28 D preoperatively and −1.10 D 3 years postoperatively.20 In this group of neurodevelopmentally normal but non-compliant patients, all improved with spectacle wear and occlusion therapy postoperatively.

Tychsen et al reported the successful implantation of Artisan/Verisyse lenses in high myopia and hyperopia in a group of 12 children with neurobehavioural disorders.20 This group of patients with long-term, severe refractive error has been diagnosed with visual autism (a constellation of symptoms including decreased interest in the outside world, fearfulness and markedly withdrawn social interaction) by the authors.36–39 This report also referenced the successful treatment of a high hyperope (mean SE +10.3) and outlined the utility of pIOLs in the visual rehabilitation of this group of neurodevelopmentally delayed children. While not all patients were able to complete comprehensive eye examinations, documented improvement by caregivers in visual awareness, attentiveness or social interactions was reported. Using validated visual function questionnaires, scores improved after surgery by 73% in bilateral ametropes and by an average 58% in anisometropes.20

The Visian implantable collamer lens pIOL is a foldable posterior chamber pIOL designed to be placed in the posterior chamber behind the iris with the haptic zone resting on the ciliary sulcus. This has been approved for use in the correction of myopia in adults.34 Correction of anisometropic amblyopia in both myopes and hyperopes has been reported with its use. A toric form of this lens allowed for successful targeting of astigmatic anisometropia in children.35

Foremost among concerns about enclavation of pIOLs was potential damage to endothelial cells. Improvements in lens design have dramatically increased the safety profile. In adults, endothelial cell loss has been strictly monitored and remains a concern, but has not proved significant enough to deter use of the lens. Long-term follow-up of endothelial cell densities includes reports with up to 12 years of follow-up data.36 Guidelines also specify the use of pIOLs only in situations where anterior chamber depth >3.2 mm.37 Alio et al provided 5 years of follow-up on nine children implanted with iris-fixated pIOL for anisometropic amblyopia, and endothelial cell count was > 2000 cells/mm² in 80% of patients. For the remaining patients, eye rubbing and ocular trauma was implicated in endothelial cell loss.37 Dislocation, pigment dispersion or iris trauma, cataract formation and shallowing of the anterior chamber are reported rare events in adults.38

Clear lens exchange (CLE)

For extreme refractive errors (> −15.0 D) or instances of shallow anterior chambers (<3.2 mm), CLE or refractive lens exchange is a suitable solution. With increasing evidence supporting the use of IOLs in paediatric cataract surgery, many paediatric ophthalmologists feel comfortable with the skills required for CLE.39 40 Turning to CLE for ametropia or lensectomy alone for high myopes is an effective means to improve in refractive error.41 42 Tychsen and coauthors were able to improve visual acuity (VA) and correct ametropia within range of the target refraction. Average gains in VA are less than that seen in other forms of refractive surgery. The authors suggest that their cohort had poorer initial acuity and ocular comorbidities than other studies of refractive surgery, limiting potential gains.

In contrast to the regression seen after laser correction, which may average ~1 D/year, myopic regression after lens extraction appears to be less, on the order of ~0.5 D/year.37 Regression tends to be more pronounced in younger groups of patients who undergo CLE.

Highly myopic eyes make up the largest cohort of patients receiving CLE or lensectomy and are inherently at greater risk for retinal detachments. It has been established in adults that risk increases threefold following lens extraction.33 Prophylactic barrier laser remains controversial.43 In one study in children, one patient sustained a detachment following trauma months after CLE.35 Other reports include a higher than expected rate of posterior capsule opacification. Most include primary posterior capsulotomy as a routine part of their procedure, but still warn it may need to be repeated.

Summary/conclusions

Refractive surgery has demonstrated benefits for the population of children with refractive amblyopia who are non-compliant with spectacle wear or non-responsive to standard treatment in multiple case series. Evidence also suggests that correction of ametropia in children with neurobehavioural disorders that preclude spectacle correction improves not only vision but also global functioning. Clear lens extraction has shown some benefit, but not the robust gains that PRK and pIOL treatments have demonstrated. While there are no randomised controlled trials to support widespread adoption of these techniques, PEDIG is currently planning Amblyopia Treatment Study 19, which is a controlled randomised clinical trial that will compare PRK versus non-surgical treatment of anisometric amblyopia in children who have failed conventional treatment. The results from this trial may provide yet more evidence for the use of refractive surgery in the management of amblyopia.

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