Indications for and Outcomes of Deep Anterior Lamellar Keratoplasty in Mucopolysaccharidoses

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ABSTRACT

Purpose: To describe the outcome of deep anterior lamellar keratoplasty (DALK) for visually significant corneal clouding in patients with mucopolysaccharidoses (MPS).

Methods: A retrospective consecutive case series of patients with MPS and corneal clouding were analyzed at a tertiary eye hospital. A review of the English literature regarding MPS and DALK was performed. The main outcomes measures of the study were intraoperative surgical complications, change in visual acuity, and postoperative DALK-related complications.

Results: Four eyes from 2 patients with MPS I (Hurler's syndrome and Hurler-Scheie syndrome) and a history of DALK met inclusion criteria for the case series. Using the “big-bubble” technique, DALK was performed successfully in all eyes. Completed Descemet’s membrane bar-}

ing was achieved in 3 or 4 eyes and a pre-Descemet’s membrane dissection in 1 eye. The mean age at the time of DALK was 17.3 years (range: 15.4 to 19.5 years). Mean follow-up time after DALK was 16.7 months (range: 6 to 31 months). Mean visual acuity before DALK was 20/80 (0.59 ± 0.12 logMAR). Mean visual acuity at the last visit for all 4 eyes was 20/50 (0.41 ± 0.17 logMAR). Visual acuity improved in all eyes. Recurrence of MPS corneal clouding was not noted in any of the corneal grafts.

Conclusions: DALK is a beneficial and preferable intervention in appropriate patients with significant corneal clouding due to MPS I. Improvement in vision can be obtained with stable, clear corneal grafts, although other ophthalmic manifestations may limit vision.

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INTRODUCTION

The mucopolysaccharidoses (MPS) are a heterogeneous group of lysosomal storage disorders characterized by accumulation of glycosaminoglycans (GAG). These inborn metabolic syndromes are caused by functional mutations of specific catabolic lysosomal enzymes, resulting in progressive GAG accumulation in tissues and organs throughout the body. These syndromes are subdivided according to enzyme defect and systemic manifestations and include MPS IH (Hurler), MPS IS (Scheie), MPS IH/S (Hurler-Scheie), MPS II (Hunter), MPS III (Sanfilippo), MPS IV (Morquio), MPS VI (Maroteaux-Lamy), MPS VII (Sly), and MPS IX (Natowicz).

The MPS disorders vary in their clinical manifestations based on the specific enzyme deficiency.

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and characteristics. These include short stature, atypical facies, skeletal deformities, hepatosplenomegaly, cardiac and respiratory compromise, neurologic decline, and ophthalmologic abnormalities. Common ocular manifestations include ptosis, significant progressive corneal opacification, acute and chronic angle-closure and open-angle glaucoma, optic nerve atrophy, and papilledema secondary to hydrocephalus (Table 1). Corneal clouding is a common cause of visual disability in Hurler, Hurler-Scheie (MPS I), Morquio (MPS IV), and Maroteaux-Lamy (MPS VI) syndromes. Without treatment for these conditions, diffuse corneal clouding is typically progressive, ranging from mild to severe, with corresponding visual disability and marked photophobia and poor night vision.

This disease affects all layers of the cornea to some extent. In particular, corneal epithelial cells and stromal keratocyte lysosomes have numerous vacuoles containing GAG. Epithelial basement membrane shows frequent breaks and peg-like undulations. Bowman’s layer is markedly attenuated. Anterior stromal scarring occurs in the middle and posterior stroma with abnormal morphology of keratocytes. Descemet’s membrane can display thickening and excrecent abnormalities. Corneal endothelial cells have normal morphology, but they may contain vacuolated lysosomal inclusions.

Historically, penetrating keratoplasty (PKP) has been the principal method to treat corneal opacity of patients with MPS. Recently, deep anterior lamellar keratoplasty (DALK) has been used to address these patients. Limited data on DALK outcomes in MPS are available. We describe 4 eyes of 2 patients with MPS type I who underwent DALK with review of the peer-reviewed published English literature.

### PATIENTS AND METHODS

After institutional review board waiver, two patients (4 eyes) with MPS I who underwent DALK at the Massachusetts Eye and Ear Infirmary between April 2010 and September 2012 were identified. All surgeries were performed by a single surgeon (RP). The following data were collected: ophthalmic and medical history, Snellen best-corrected (spectacle) monocular visual acuity with logMAR equivalent, slit-lamp biomicroscopic examination of the anterior segment, and dilated funduscopic examination with indirect ophthalmoscopy. Baseline visual acuity measurements were obtained from the preoperative ocular examination.

<table>
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<tr>
<th>Finding</th>
<th>MPS IH (Hunter)</th>
<th>MPS IH/S (Hurler-Scheie)</th>
<th>MPS IH/S (Sanfilippo A-D)</th>
<th>MPS II (Morquio)</th>
<th>MPS IV (Morquio)</th>
<th>MPS IV (Morquio)</th>
<th>MPS VI (Maroteaux-Lamy)</th>
<th>MPS VII (Sly)</th>
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*Data from Ashworth et al.*

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Subsequent comparisons were made after DALK. The end point of visual acuity was chosen to be the last recorded ophthalmologic evaluation.

We searched the PubMed database using combinations of the following search terms: “mucopolysaccharidoses,” “Hurler syndrome,” “Hurler-Scheie syndrome,” “Scheie syndrome,” “MPS,” and “deep anterior lamellar keratoplasty.” Titles and abstracts of the identified English articles were reviewed and retrieved if they described cases of DALK performed in patients with MPS I. Data collected included surgical technique, number of eyes, age, sex, intraoperative/postoperative complications, preoperative and postoperative visual acuity, and follow-up duration.

Intraoperative DALK Technique

The Anwar “big-bubble” DALK technique was used in eyes 1, 2, and 4. A corneal marker was used to mark the cornea, allowing centration. Trephination was performed using the Barron–Hessburg vacuum trephine (Katena, Denville, NJ); the number of turns was made so as to reach 75% of total corneal depth without penetration. The anterior corneal stromal button was partially removed with a disposable crescent knife prior to generation of the “big bubble” using a Fogla dissector and cannula (Bausch & Lomb, Rochester, NY). In the pre-Descemet DALK case (eye 1) careful manual dissection was needed to bare Descemet’s membrane without anterior chamber penetration. In all cases, the donor button was trephined 0.25 mm larger than the host trephine, and Descemet’s membrane was stripped from the donor cornea using trypan blue. The donor button was then sutured using either sixteen 10-0 nylon sutures into the host bed (eye 2) or eight 10-0 nylon interrupted sutures and 1 eight-bite running suture (eyes 1, 3 and 4). Subconjunctival antibiotic and steroid were given at the end of the procedure, and a small air bubble was left in the anterior chamber.

The pachy-bubble DALK technique was performed in case 3. The technique has been recently described. In brief, a Hessburg-Barron suction trephine (Katena) was used to perform superficial trephination to approximately 60% to 70% of corneal thickness, usually six to seven quarter turns on the trephine (approximately 400 mm). Intraoperative corneal thickness measurements using ultrasound pachymetry (AccuPach VI; Accutome, Malvern, PA) were taken 1.0 mm internally from the trephination groove in the the 11- to 1-o’clock positions. In this area, a 2-mm incision was made, parallel to the groove, with a micrometer diamond knife (Mastel, Rapid City, SD), calibrated to 90% depth of the thinnest measurement. A Fogla dissector and 27-gauge cannula were used to generate the “big bubble.” Due to the thickness of the cornea, it was removed in two layers. The “big-bubble” was entered with a 15 degree blade and the corneal stroma flaps removed exposing Descemet’s membrane.

Postoperative Care

Standard topical steroid and antibiotic drops were used eight times and four times a day, respectively, for the first week, and then the steroid drops were reduced monthly. The indication for early suture removal was any sign of loose sutures, scarring, or vascularization at the suture entry points within the donor button.

RESULTS

Four eyes of 2 patients with MPS I underwent DALK. One patient had Hurler’s syndrome and the other had Hurler-Scheie syndrome. The outcomes and comparative literature review are summarized in Table 2. Using the big-bubble technique, DALK was performed successfully in all eyes with MPS in both our cases and those reported in the literature. Complete Descemet’s baring was achieved in 3 of 4 eyes and pre-Descemet’s membrane dissection in 1 eye. No intraoperative or postoperative complications were observed, except partial attachment of Descemet’s membrane in case 1 on the first postoperative day that resolved spontaneously by 1 week.

The mean age at the time of graft procedure was 17.3 years (range: 15.4 to 19.5 years). Mean follow-up time after DALK was 16.7 months (range: 6 to 31 months). Mean visual acuity before DALK was 20/80 (0.59 ± 0.12 logMAR). Mean visual acuity at the last visit for all 4 eyes was 20/50 (0.41 ± 0.17 logMAR), ranging from 0.18 to 0.54 logMAR (20/70 to 20/25). Visual acuity improved in all eyes. Recurrence of MPS opacification was not noted in any of the corneal grafts and peripheral host corneal clearing was clinically evident in eyes receiving DALK more than 1 year after surgery (Figure 1).

Case Reports

Case 1. A 15-year-old boy was seen complaining of blurry vision, photophobia, and ocular red-
ness in both eyes. He had Hurler’s syndrome diagnosed at 9 months of age. He underwent a bone marrow transplant at 1 year old, which included chemotherapy and total body radiation. His best corrected visual acuity (BCVA) was 20/100 in both eyes. External ocular examination was normal. On slit-lamp biomicroscopy, there was severe bilateral diffuse ground-glass stromal opacity. Pachymetry values were 721 µm in the right eye and 686 µm in the left eye. Clinical examination revealed moderate to dense posterior subcapsular cataracts and raised intraocular pressure in both eyes (20/22 mm Hg). Dilated fundus examination was unremarkable. DALK was performed for visual rehabilitation. Fifteen months after surgery of the left eye (case 1), the corneal graft was clear and BCVA was 20/70 (correction: -4.50/-3.50 diopters × 115). Six months after surgery of the right eye (case 2), the corneal graft was clear and BCVA was 20/70 (correction: +0.25/-1.00 diopters × 77) with vision limited by posterior subcapsular cataracts in each eye.

Case 2. An 18-year-old man was seen complaining of blurry vision. He had a previous diagnosis of Hurler-Scheie syndrome and had been receiving intravenous enzyme replacement therapy for many years. A 1-year trial of topical ocular application of l-alpha-uronidase resulted in no change in the corneal clouding. His BCVA remained 20/60 in both eyes. External ocular examination was normal. On slit-lamp biomicroscopy, there was significant bilateral diffuse ground-glass stromal opacity. Intraocular pressure and dilated fundus examination was normal in both eyes. Pachymetry values were 764 in the right eye and 738 µm in the left eye. DALK was performed in both eyes for visual rehabilitation. Two years and 7 months after surgery in the right eye (case 3), the corneal graft was clear and BCVA was 20/25 (correction: plano -1.00 diopters × 070). Fifteen months after surgery in the left eye (case 4), the corneal graft was clear and BCVA was 20/25 (correction: -2.25 -2.00 × 090).

**DISCUSSION**

New treatments resulting in a longer lifespan and better intellectual function for many patients with MPS have made the long-term ocular management of these patients crucial for optimum quality of life. Current methods of corneal transplantation include PKP and DALK. DALK in MPS is a surgical technique that preserves the endothelium, thus
avoiding the risk of endothelial rejection associated with PKP.

PKP has been reported to provide good results in MPS when the visual loss is thought to be primarily related to corneal clouding of the visual axis. Some authors prefer this technique because signs of degeneration and decompensation could develop in the endothelium over the course of disease. However, replacement of all layers of the cornea may not be needed in these cases, where the disease is mostly limited to stromal and epithelial layers.

Table 2 shows 11 cases (including our cases) of patients with DALK and MPS I. Ten of 11 eyes had successful “big-bubble” technique. Seven of 11 DALK procedures were done for eyes with MPS I (Hurler-Scheie). All 11 corneal grafts were reportedly clear during a mean follow-up of 36.9 months (range: 9 to 90 months). Visual acuity was reported as superior than 20/40 in 6 of 11 eyes. Complications described were Descemet’s membrane rupture (1), Urretz-Zavalia syndrome (1), and increased intraocular pressure (1). Our case results were good and consistent with the literature. Based on these results, we believe DALK should be considered preferable to PKP in cases of MPS I.

The advantages of DALK over PKP include the elimination of endothelial rejection and more rapid restoration of postoperative visual acuity, avoidance of most complications associated with open-sky surgery, reduced chance of postoperative complications such as anterior synechiae of iris or secondary glaucoma, and easier postoperative management. Moreover, patients who are predisposed to the risk of glaucoma and the long-term use of steroids after PKP may further aggravate this problem. DALK also preserves globe integrity against blunt ocular trauma, which is of importance for patients who may not regularly attend follow-up examinations and are more likely to experience ocular trauma because of intellectual impairment. Another advantage of DALK in MPS is when the opacity recurs in the transplanted cornea. As graft opacity becomes severe enough to affect vision, retransplantation may be required and DALK can potentially be repeated.

DALK is usually more difficult to perform in younger patients because Descemet’s membrane...
does not separate as easily. The combination of MPS disease and bone marrow transplant or enzyme replacement therapy may have been important in the successful “big-bubble” in these patients. The accumulation of GAG in the cornea associated with this condition leads to a more rigid cornea, making the passage of air or viscoelastic into the corneal lamellae virtually impossible if the opacity is dense. In these cases, the DALK technique in MPS can be modified with manual dissection of the cornea from Descemet’s membrane.

The effect of MPS I on endothelial cells is controversial. Corneal endothelial cells have normal morphology, but they may contain vacuolated lysosomal inclusions. However, there are no studies reporting endothelial decapensation caused by MPS. It seems endothelial cells are the last part of the cornea that might be affected by this disease, especially in advanced stages. It remains to be seen whether the signs of degeneration and decompenation will develop in the endothelium over the course of the disease following surgical intervention in these cases.

DALK is an acceptable alternative to PKP for replacing opaque stroma in MPS I despite apparent secondary involvement of the endothelium. More cases with longer follow-up are needed to judge the long-term outcomes of DALK in these patients. However, based on our experience and review of the literature, it appears DALK is a better choice in patients with MPS I for visual rehabilitation, although other ocular manifestations may limit visual potential.

REFERENCES