Title: **Corneal Endothelial Cell Changes after Ahmed Valve and Molteno Glaucoma implants**

Running Head: **Corneal Endothelial Cell Changes in Glaucoma Implants**

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ABSTRACT

PURPOSE: To evaluate the changes in corneal endothelial cell (CEC) indices in Ahmed valve and single-plate Molteno implants after 24 months of follow-up.

SETTING: Imam Hossein Medical Center, Negah Eye Hospital and Vanak Eye Surgery Center, Tehran, IRAN

METHODS: A historical cohort study was conducted. The records of patients who had Ahmed valve (*n*=29) or single-plate Molteno (*n*=28) implants and completed a 24-month period of the trial were reviewed and postoperative CEC indices were measured. Preoperative central CEC indices, performed for a then-ongoing trial, were compared with postoperative measurements of the last follow-up. The main outcome measure was endothelial cell count.

RESULTS: There was no difference between the two operations in improving visual acuity and decreasing the number of anti-glaucoma medications required. However, Molteno group showed significantly better postoperative IOP control ($P<0.001$). There were 11.52% and 12.37% reduction in CEC density (cells/mm^2) and 3.78 and 2.48 increase in CEC area (mm^2) after 24 months in Ahmed valve and Molteno groups, respectively. There was no significant between-group difference in CEC density and area as well as corneal thickness, postoperatively. Both univariate and multivariate analyses did not show any significant difference between central CEC loss and patients' pre- and postoperative factors.

CONCLUSION: There were statistically significant quantitative (cell density) and minor qualitative (cell area) changes in central CEC parameters in both groups after 24 months of follow-up. Both groups appear to cause similar CEC damage after 2 years.

INTRODUCTION

The corneal endothelium is metabolically active and ensures that the corneal stroma maintains its usual dehydrated state, which requires a water content of 70%. This degree of dehydration is required for corneal clarity and optical transparency.[1] Corneal endothelial damage diminishes corneal endothelial cell (CEC) density, increases the mean CEC size, and alters the normal morphometric endothelial pattern[2] while cell division capacity remains low even after corneal damages.[3] Endothelial cell damage has been reported to occur after different glaucoma treatments including of antiglaucoma medications,[4] previous laser therapy[5,6,7] or filtering surgeries,[8-11] and the use of antifibrotic agents.[10, 12-15] Previously in 1993, McDermott et al.[16] studied endotheilial cell changes after Molteno implants in 19 patients who were followed for 1 year after the surgery. It was concluded that there is no clinically significant endothelial cell loss after Molteno implants. Recently, studies suggest that endothelial cell density progressively decreased after Ahmed glaucoma valve implantation and this decrease remains at least for 2 years.[17,18]

In this study, we aimed to report endothelial cell changes in our previous study[19] comparing the efficacy and safety of Ahmed valve and Molteno implants.

METHODS AND MATERIALS

Study Subjects

A historical cohort study was conducted, and the records of patients (n = 101) enrolled in a comparative study[19] conducted in three medical centers, namely, Imam Hossein Medical Center, Negah Eye Hospital, Vanak Eye Surgery Center, Tehran, Iran, between 2003–2005 and operated by a single surgeon (Nader N.) were reviewed. The study aimed to assess the efficacy and safety of Ahmed glaucoma valve and single-plate Molteno implants in treatment of refractory glaucoma during 24 months of follow-up. The inclusion and exclusion criteria as well as method of sampling were completely explained elsewhere.[19] For the purpose of the current study, enrolled patients of the trial (Ahmed group: 46 eyes; Molteno group: 46 eyes) who completed the 24-months of follow-up (Ahmed group: 29 eyes; Molteno group: 28 eyes) were analyzed for central corneal endothelial cell (CEC) indices at month 24. Completion of the trial was considered as those without follow-up loss and failure (defined as persistent IOP of more than 21 mm Hg on maximally tolerated medications or IOP less than 6 mm Hg on 2 consecutive visits, phthisis bulbi, reduction of vision to no light perception, removal of the shunt implant, reoperation for glaucoma, or any devastating intraoperative or postoperative complication.).[19] Central CEC indices had been among the preoperative but not postoperative assessments of the trial. Within the study, those who completed the trial were assessed for central CEC indices at month 24.

Pre- and Postoperation Assessments

Presurgical assessment of the trial had included registration of glaucoma type, biomicroscopic examination, fundoscopy, visual acuity (VA), baseline intraocular (IOP, mm Hg), the number of antiglaucoma medications, visual filed (VF), central CEC indices (CEC density, CEC area, and hexagonality), and corneal thickness. Postoperative measures for the purpose of the current study (24 month) included VA, IOP, number of antiglaucoma medications, VF, central CEC indices, and corneal thickness.

The best-corrected visual acuity was measured using a Snellen chart (CP-690; Nidek Co, Ltd, Gamagori Aichi, Japan) calibrated for a 20-foot (approximately 6 m) distance by the line assignment method within the month before the surgery; the figures were converted to logarithm of the minimal angle of resolution notation by the standard conversion table. IOP was measured using a Goldman applanation tonometer (AT-900; Haag-Streit AG, Koniz, Switzerland) mounted on a slit lamp; if required, gonioscopy (Haag-Streit AG) also was performed. Use of glaucoma medication was reported as the number of drugs (topical or systemic) taken, with no differentiation as to the type or frequency of medications. The routine applied medications were timolol, trusopt, and dorzolamide. The corneal thickness was measured by pachymetry (UP-1000 Nidek; Nidek Co, Tokyo, Japan). Central CEC indices (CEC density, CEC area, and hexagonality) were measured using a noncontact specular microscope (SP-3000P; Topcon, Tokyo, Japan). The first good-quality specular photograph was used for CEC analysis. It has been reported that between 50 and 100 CECs are needed to be analyzed to calculate the CEC density to minimize the sampling error.[20] To have equal measurements for all patients and as a standard practice in our surgery center, whenever possible, one hundred CECs in the cell center, as identified on the specular photograph, was required for CEC counting. However, if this was not possible, a minimum of 50 CECs was required to make the measurement reliable.

Procedure

The tube shunts used were either the valved 184-mm2 surface area Ahmed Glaucoma Valve (Model FP7; New World Medical, Inc, Rancho Cucamonga, California, USA) or the 134-mm2 surface area single-plate Molteno implant (Molteno Ophthalmic Limited, Dunedin, New

Zealand). The surgical techniques as well as postoperative management was completely explained elsewhere.[19]

Statistical analysis

The between-group comparisons of the continuous variables were performed using the nonparametric Mann–Whitney U test. The Wilcoxon signed-ranks test was used to evaluate the within-group differences in pre- and postoperative measures. To evaluate the significance of difference between qualitative variables, chi-square or Fisher exact tests were used, as appropriate. Moreover, to determine where the significant differences lie, the stringent Scheffe post hoc test was administered.[21] The significance of Pearson correlation coefficient was checked to understand the correlation between each pair of continuous variables. To elucidate the factors independently associated with CEC indices, multivariate analyses of selected variables were performed using linear regression models with stepwise method. Statistical significance for all comparisons was set at $P < 0.05$.

RESULTS

The pre- and postoperative measures of 28 eyes in Molteno group and 29 eyes in Ahmed valve group who completed the trial [19] were analyzed. Overall, the 2 groups had similar demographic characteristics and disease history (Table 1). The Molteno group, compared with the Ahmed group, achieved significantly ($p<0.001$) lower IOP 24 months after surgery while the mean number of antiglaucoma medications were comparable in both groups ($p=0.778$).Visual acuity deteriorated in both groups after 2-year follow-up and there were no significant between-group differences at the end of the trial (Table 2).

In both groups, there were significant increase in CEC area expansion ($p<0.001$) and CEC loss ($p<0.001$) at 24 month compared to preoperative measures (Table 2).We did not find any marked difference in hexagonality in both groups, before and after the surgery.

On both univariate and multivariate analyses, CEC loss was not significantly different between patients categorized by age; gender; the side of the involved eye; glaucoma subtype; lens status; history of trabeculectomy or penetrating iridectomy; the presence of bilateral glaucoma, hypertension, and diabetes mellitus; preoperative CEC density, CEC area, corneal thickness, IOP, number of medications, VA.

There was no intraoperative complication and the frequency and management of postoperative complication were completely explained elsewhere.[19]

DISUCSSION

In this historical cohort study, the changes in central CEC indices after Ahmed valve and Molteno implants were reported. In this study, we did not have any case in which tube–corneal touch had developed. After 2-years of follow-up, Ahmed vale and Molteno groups showed 11.52% and 12.37 % reduction in CEC density, respectively. This was less than the report by Lee et al.[18] where the reduction in central CEC density was 15.4% after 24-month follow-up. They also reported that these changes in CEC density differed according to the specific area measured and the time after surgery. The greatest decrease was reported to be in the superior cornea at 1 month and in the supratemporal area at all subsequent time points. The smallest decrease was in the central area at all time points. They also demonstrated that there was no significant changes in CEC morphologic indices either polymegathism (coefficient of variation in cell area) or pleomorphism (hexagonality of the cells). We similarly did not find any marked difference in hexagonality in both groups, before and after the surgery; however, we have seen 2.48% and 3.78 % expansion of CEC area after 2-year follow-up in Ahmed valve and Molteno groups, respectively.

Kim at al.[17] in a prospective study reported 6.5% reduction in central CEC after 12 months following Ahmed glaucoma valve implantation. They reported that the superotemporal area, which was closest to the tube, showed the greatest decrease in endothelial cell density at 1 year after surgery, while the central cornea showed the least decrease. Regarding endothelial cell morphology, they mentioned that the polymegathism and pleomorphism increased in the early postoperative periods, and then gradually approached the preoperative status by 6 months after surgery. Using Heidelberg cornea tomograph II, Mendrinos et al.[22] reported that over a 6-month period, mean corneal endothelial loss was 7.9% in the central and 7.5% in the peripheral cornea following Ahmed glaucoma valve implant. They also mentioned that there was no correlation between central or peripheral corneal endothelial cell loss and the tube-cornea and tube-iris distances, or the intracameral length of the drainage tube.

Previously, McDermott et al.[16] reported changes in the CEC density after Molteno implant and they reported no clinically significant change at 10 months after surgery in 19 patients. However, because they did not determine the CEC density before surgery so that they could not evaluate the change in density over time after surgery compared with the density before surgery.

In our study, CEC loss of more than 80% was not detected in any of the patients (maximum detected CEC loss was 19.7%). This amount of CEC loss may result in a CEC density of less than 500 cells/mm2, which has been reported as the threshold for endothelial decompensation.[23]

The exact mechanism causing damage to the corneal endothelium is still unclear. Lee et al.[18] summarized the proposed theories in this regard as follows: McDermott et al. proposed the jet flow around the tube end caused by the heartbeat, inflammation in the chamber, intermittent tube–corneal touch, tube–uveal touch, and a foreign body reaction to the silicone tube as possible mechanisms of corneal endothelial damage.[16] Setälä suggested that high IOP and long duration of elevated IOP before surgery may affect the endothelium directly or may cause hypoxic damage indirectly.[24] Fiore et al.[25] proposed that the mechanism of corneal endothelial damage may involve the toxicity of the preservatives in eye drops, the duration of surgery, shallowing of the anterior chamber during or after surgery, or changes in the composition of the aqueous humor attributable to the direct connection with the sub-Tenon space. In this study, there was no case with flat anterior chamber or hypotony. In addition, there was no case with tube–corneal touch and in all cases the tube was far away to directly touch the cornea.

This study had some limitations. We only measured endothelial parameters of the central cornea and did not measure those of the periphery; thus, potentially significant regional differences could not be assessed. Furthermore, CEC density was used as an indicator of corneal endothelial injury, although analyses of CEC shape and pattern rather than CEC density alone have been reported to be more sensitive indicators of endothelial damage.[26]

In conclusion, there were statistically significant quantitative (cell density) and minor qualitative (cell area) changes in central CEC parameters in the operated eye 24 months after both Ahmed valve and Molteno glaucoma implant surgeries. These findings can imply that particular care should be taken during intraoperative and postoperative management of glaucoma shunt implantation especially in those with higher risk factor for corneal injury in order to minimize damage to the endothelium. Further prospective studies involving a larger multi-centric cohort of patients with longer follow-ups measuring the CEC indices in the entire cornea are warranted.

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