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COMPARISON OF CHANGES IN ENDOTHELIAL CELL DENSITY AND MORPHOLOGY AFTER MANUAL SMALL INCISION CATARACT SURGERY IN DIABETICS VS. NON-DIABETICS – A PROSPECTIVE STUDY

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ABSTRACT **Purpose:** To compare the changes in endothelial cell density (ECD) and morphology after manual small incision cataract surgery (MSICS) in diabetics vs. non-diabetics **Methods:** All consecutive consenting adults with age related cataract < grade 2 nuclear sclerosis undergoing MSICS were recruited. Specular microscopy was done to document the ECD, coefficient of variation (CoV) and percentage of hexagonality in all eyes before and 1 month after MSICS. The primary outcome measure was the difference in ECD between diabetics and non-diabetics at 1 month compared to baseline. **Results:** One hundred eyes of 100 patients were recruited in the diabetic (n=50) and non-diabetic (n=50) groups and completed 1 month follow up. There were no differences at baseline, though non-diabetics had marginally higher counts (p=0.07). The mean ECD decreased significantly in both groups (p<0.001 for both) but this drop was significantly more in diabetics (566 + 137cells/mm3, 95% CI= 527 to 604) compared to non-diabetics (347 + 94cells/mm3, 95% CI= 320 to 373) (p<0.001). The percentage hexagonality decreased slightly after MSICS in both, although by the same magnitude (-6.4 + 3.7 in diabetics vs. -5.2 + 3.9%, p=0.09) where as the CoV changed more (-5.8 + 5.5 in non-diabetics vs. 2.9 + 2.6, p<0.001) in the diabetic group. **Conclusions:** Eyes with softer cataracts in diabetics undergoing MSICS experience much greater endothelial cell loss at 1 month, though changes in the morphology such as percentage hexagonality and CoV are not as marked.

KEYWORDS : manual small incision cataract surgery, diabetes, endothelial cell count, soft cataract, specular microscopy.

INTRODUCTION

Manual small incision cataract surgery (MSICS) is a well established alternative to phacoemulsification in treating all forms of cataract.—(15) Its cost effectiveness, efficiency in low resource settings, relative ease in advanced cataracts, good visual recovery and comparable complication rates has meant that MSICS has been adopted widely across the developing world.(6,7) It has also been shown to reduce the carbon footprint by reducing use and allowing reuse of consumables.(8)

Some amount of endothelial cell loss is inevitable following cataract surgery, including during MSICS.—(911) This loss in endothelial cell count after MSICS has been shown to be comparable to phacoemulsification.(10,12) The common belief that MSICS may cause more mechanical damage to the corneal endothelium due to anterior chamber manoeuvres closer to the endothelium have not been substantiated by large studies as well as meta-analyses.(7,13)

In addition to cataract surgery and age, several other factors influence the endothelial cell counts, especially disease states like diabetes mellitus– –(1416) and corneal endothelial diseases like Fuch's endothelial dystrophy.(12) In fact, diabetes is known to affect all layers of the cornea including diabetic keratopathy(17) and endothelial cell dysfunction via various mechanisms. (16,18) It has been previously shown that diabetics experience greater endothelial cell loss after routine phacoemulsification as compared to age-matched individuals with similar degrees of cataract.(14,19)

However, the change in endothelial cell count and function following MSICS in patients with diabetes has been less commonly studied. Mathews et al reported greater percentage loss of endothelial cells in diabetics compared to non – diabetics.(20) More recently, Kudva et al have shown similar trends with greater endothelial cell loss in diabetic eyes.(21) However, most comparisons have been made in eyes with relatively advanced cataracts (white, brown, black) where greater endothelial cell loss is expected in any case.(22) To address this issue, we enrolled eyes with softer cataracts and compared endothelial cell counts and morphology in diabetic vs. non diabetic eyes undergoing MSICS.

METHODS

This was a prospective observational study carried out at a tertiary government facility in north India and was approved by the institutional review board of the parent institution. Informed consent was taken from all patients before enrolment and the study was carried out as per the tenets of declaration of Helsinki. The manuscript has been prepared in compliance of the STROBE guidelines.(23)

Participants

All consecutive adults with age related cataract scheduled to undergo manual small incision cataract surgery at our institution were invited to participate in this study and those consenting and willing to follow up for a minimum of 1 month after surgery were enrolled. Eyes with corneal guttae or other signs of Fuch's endothelial dystrophy, cataract > nuclear sclerosis grade III and an ECD of <1000 cells/mm^3 at baseline were excluded. Similarly, eyes with coexistent ocular morbidities such as corneal or retinal diseases, pupil <5mm, pseudoexfoliation, zonular dehiscence, post traumatic cataract and similar conditions expected to interfere with surgical manoeuvres or outcomes were excluded.

Clinical assessment

At baseline, after recording basic demographics and diabetic status, all patients underwent a comprehensive ophthalmic examination including visual acuity assessment, anterior segment evaluation for gross endothelial dysfunction and cataract density and dilated fundus evaluation to rule out coexistent pathologies. The ECD was measured using a non-contact specular microscope (Topcon, Japan) by an experienced examiner, masked to the diabetic status of the patient. The examiner focussed the specular microscope on the central corneal endothelium and used the auto – capture mode on the machine to obtain images. After manually inspecting the visible endothelial cells on the image, the endothelial cell density (ECD), coefficient of variation and percentage of hexagonal cells was recorded as displayed on the machine console. The measurements were done three times, at 5 minutes intervals on the same eye, and a mean value for all parameters was derived for a particular visit. The central corneal thickness was also measured at each visit using ultrasound pachymetry (Nidek , Japan).

All surgeries were performed under peribulbar anesthesia as per standardized techniques of MSICS described previously.(1,5) All eyes were prescribed topical steroids in a tapering fashion for 1 month along with topical antibiotics for 7days. Patients were reviewed on postoperative day 1, 7 and then at 1 month. At each visit, in addition to visual acuity and slit lamp evaluation, they underwent specular microscopy and ultrasound pachymetry using the same techniques mentioned above.

Outcome measure:

The change in ECD from baseline to 1 month, defined as ECD at 1 month – ECD at baseline, in eyes with and without diabetes was assessed. The changes in percentage of hexagonality, coefficient of variation and CCT were secondary outcome measures.

Statistical analysis

Sample size was based on the assumption of a 10±5% greater loss of ECD in the diabetic group vs. the non-diabetic group at 1-month follow up with an alpha error of 0.05 and a beta error of 0.80, which yielded a requirement of 47 eyes in each group. To account for a 15% loss to follow up, we recruited 109 eyes overall.

All continuous variables were expressed as means with standard deviations or median with interquartile range and were represented using a box and whisker plot or a line diagram showing means with standard deviations. Group differences were assessed using the student t test or Wilcoxon ranksum test for variables with non-parametric distributions and means, standard deviations and 95% confidence intervals (CI) were reported. Similarly, categorical variables were expressed as proportions (n, %) and group differences were analysed using the chi square or Fischer's exact test. Changes in variables before and after surgery were analysed using the paired t test with the Bonferroni adjustments. Univariate and multivariable linear regression analysis was used to determine factors influencing the ECD at 1-month and the change in the ECD using covariates of age, ECD at baseline and diabetic status. Outcomes were expressed as beta coefficients with 95% confidence intervals.

All data were entered in Microsoft Excel and analysed using STATA 12.1 I/c (STATA Corp, Fort Worth, Texas, USA). All p values less than 0.05 were considered statistically significant.

RESULTS:

Of the 109 patients included in the study, 100 eyes of 100 patients (n=50 eyes each in the diabetic and non-diabetic groups) who followed up for the 1-month period were included in the analysis. The mean age of participants was 63.6 ± 6.8 years and there was no difference in age in diabetics (63.4 ± 6.2 years) and non-diabetics (63.9 ± 7.4 years) (p=0.69). At baseline, the mean ECD was slightly lower in the diabetic eyes but this difference was not statistically significant (table 1). A comparison of the absolute ECD (Figure 1A, B) and change in the ECD at various time points across the study is shown in table 1. There was a significant decrement in the ECD at every time point in both diabetic and non-diabetic eyes compared to baseline, however the magnitude of this drop was significantly greater in the diabetic group (Figure 2). In terms of percentage drop, diabetic eyes experienced 9.5% decrement from baseline (vs. 5.5% in non-diabetics) on day 1, 16% decrement (vs. 9.8% in non-diabetics) at 1 week and 22% decrement (vs. 13% in non-diabetic eyes) at 1 month follow up (p<0.001 for all). At 1 month, the drop in ECD varied from 320 to 373 cells/mm^3 in 95% participants in the non diabetic group while this ranged from 527 to 604 cells/mm^3 in 95% diabetics The percentage of hexagonal cells reduced in both groups on day 1 and at 1 week postoperatively, and later stabilized (table 2). The reduction in percentage of hexagonality was similar in diabetics and non-diabetics. Similarly, the coefficient of variation in endothelial cells showed significant changes at each time point in both intra and inter-group comparisons (table 3). The central corneal thickness showed a significant increment with maximum increase at day 1 after surgery (figure 3), followed by reduction towards baseline levels at 1 week and 1 month time point.

Univariate and multivariable linear regression analysis showed that the change in endothelial cell count was mainly influenced by the diabetic status (236 cells/mm^3 greater loss in diabetics vs. non-diabetics, 95% CI= 190 – 281 cells/mm^3, p<0.001). The baseline endothelial count also influenced the magnitude of endothelial loss with eyes having higher ECD at baseline experiencing slightly more cell loss (18 cells/mm^3 greater loss for every 100 cell/mm^3 increment at baseline, 95%CI=8-28 cells/mm^3 loss, p=0.03). However influence was much smaller than the influence of diabetes status, even in multivariable models. Age did not vary much in our population and therefore did not show any influence on the ECD.

DISCUSSION

We found a significant reduction in ECD eyes with relatively softer cataracts undergoing MSICS with and without diabetes, though the magnitude of cell loss was significantly greater in diabetics. Additionally, we also found evidence of pleomorphism and polymegathism in terms of percentage of hexagonality and coefficient of variation. The central corneal thickness increased immediately after surgery and returned back to baseline levels on expected time lines. Diabetic status was the main driver of the ECD loss at 1 month, though baseline ECD cell count could also predict this, but to a lesser extent.

A trend of progressive endothelial cell loss at different time points after cataract surgery has been shown in many previous studies.(10,19) This may occur due to the use of ultrasonic energy in eyes undergoing phacoemulsification, where as larger incisions and harder cataracts may lead to some mechanical trauma and endothelial cell loss after MSICS. The fact that diabetic eyes experienced significantly more cell loss may be explained by various theories of corneal endothelial affection in diabetics, including intracellular mitochondrial dysfunction,(18) delayed cell recovery from trauma, defective endothelial cell pump, and loss of cell junctional integrity. (16) Our results in the diabetic group compare well with cell loss rates published by Mathews et al a decade age.(20) However, since then, there have been significant improvements and iterations of MSICS and newer visco-surgical devices with better endothelial cell protection. Our rates are much lower than those recently published by Kudva et al,(21) who report much lower ECD (well below 2000 cells/mm3) in both diabetics and non-diabetics. We believe that this difference may be due to relatively softer cataracts in our cohort, exclusion of eyes with poor mydriasis in our series leading to lesser surgical manipulations, and potentially due to differences in use of viscoelastics and surgical expertise.

We also found that presence of diabetes was the main driver of the degree of ECD loss, with greater than 200 cells lost in diabetics compared to non – diabetics, while baseline ECD came a distant second in terms of predictive ability to determine the magnitude of cell loss. This shows that all diabetics planning to undergo MSICS should be carefully evaluated using a specular microscopy before surgery, even if no guttae or other clinical signs of endothelial dysfunction are not noted. Additionally, it may be beneficial to use an endothelial – protective visco-surgical device during the surgery, make sufficiently large scleral tunnels with good pockets allowing effortless nucleus delivery and minimize anterior chamber manipulations in diabetics.

The major drawbacks of this study are its short follow up duration. The merits of this study are the calculated sample size enrolled to answer the study question, use of masking to eliminate observer bias and standardized use of the specular microscopy to obtain more accurate at every visit.

In conclusion, diabetic eyes with softer cataracts undergoing MSICS experience much greater endothelial cell loss starting from day1, up till day 30 of follow up. It will be important to follow these patients longitudinally and report on the endothelial counts at 1 and 2 years follow up.

Table 1: Comparison of endothelial cell density across time points in diabetics vs. non-diabetics.

Time point	Non diabetic (n=50)	Diabetic (n=50)	Overall	P value
Baseline	2630 + 185	2535 + 256	2582 + 228	0.07
Day 1	2486 + 176**	2294 + 250**	2390 + 236**	0.001
day 1 from baseline	-144 + 37	-240 + 39	-192 + 61	<0.001
CI for day 1	-133 to -154	-251 to -229	-204 to -180	---
1 week	2370 + 181**	2132 + 239**	2251 + 242**	<0.001
1 week from baseline	-259 + 70	-402 + 88	-331 + 106	<0.001
CI for day 7	-280 to -239	-427 to -377	-352 to -309	---
1 month	2238 + 190**	1969 + 235**	2126 + 265**	<0.001
1 month from baseline	-347 + 94	-566 + 137	-456 + 160	<0.001
CI for 1 month	-373 to -320	-604 to -527	-488 to -424	---

Table 2: Comparison of endothelial cell "coefficient of variation" across time points in diabetics vs. non-diabetics.

Time point	Non diabetic (n=50)	Diabetic (n=50)	Overall	P value
Baseline	38.1 + 4.2	38.4 + 4.1	38.2 + 4.2	0.39
Day 1	35.9 + 5.1**	42.3 + 3.6**	39.1 + 5.4*	<0.001

day 1 from baseline	-2.1 + 4.2	3.9 + 2.7	0.9 + 0.5	<0.001
1 week	34.1 + 5.1**	40.4 + 3.6**	37.2 + 5.5**	<0.001
1 week from baseline	-4.0 + 5.2	1.9 + 2.6	-1.1 + 5.7	<0.001
1 month	32.1 + 5.3**	41.4 + 3.6**	36.7 + 6.5*	<0.001
1 month from baseline	-5.8 + 5.5	2.9 + 2.6	-1.1 + 5.7	<0.001

Comparison from previous time point *P<0.1, **p<0.05

Table 3: Comparison of endothelial cell "hexagonality (%)" across time points in diabetics vs. non-diabetics.

Time point	Non diabetic (n=50)	Diabetic (n=50)	Overall	P value
Baseline	43.2 + 4.1	42.8 + 6.3	43.1 + 5.3	0.49
Day 1	38.5 + 4.7**	38.4 + 5.8**	38.4 + 5.3**	0.82
day 1 from baseline	-4.7 + 2.8	-4.4 + 3.7	-4.6 + 3.3	0.67
1 week	36.4 + 4.7**	35.4 + 5.8**	35.9 + 5.3**	0.32
1 week from baseline	-6.7 + 2.8	-7.4 + 3.7	-7.1 + 3.3	0.29
1 month	38.2 + 5.2*	36.3 + 5.8*	37.2 + 5.6*	0.14
1 month from baseline	-5.2 + 3.9	-6.4 + 3.7	-6.1 + 3.3	0.09

Comparison from previous time point *P<0.1, **p<0.05

Table 4: Comparison of central corneal thickness across time points in diabetics vs. non-diabetics.

Time point	Non diabetic (n=50)	Diabetic (n=50)	Overall	P value
Baseline	505 + 36	514 + 36	509 + 36	0.23
Day 1	516 + 42**	540 + 36**	528 + 40**	0.03
day 1 from baseline	11.3 + 2.7	26.1 + 4.7	18.6 + 5.7	<0.001
1 week	505 + 39**	531 + 37**	518 + 40**	0.001
1 week from baseline	0.06 + 2.31	17.1 + 4.0	8.5 + 3.9	<0.001
1 month	497 + 36**	522 + 37**	509 + 38**	<0.001
1 month from baseline	-7.8 + 2.7	8.5 + 4.5	0.35 + 2.1	<0.001

Comparison from previous time point *P<0.1, **p<0.05

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