Medico Research Chronicles

ISSN No. 2394-3971

Original Research Article

CORNEAL ENDOTHELIAL CELL LOSS AFTER SMALL INCISION CATARACT SURGERY IN DIABETIC VERSES NON DIABETIC PATIENTS.

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Submitted on: February 2016
Accepted on: February 2016
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Abstract:

Rationale : This study was undertaken to assess the postoperative endothelial cell loss, change in endothelial cell morphology and central corneal thickness in patients with type II diabetes undergoing manual SICS and to compare them with age-matched normal individuals. **Method:** The present study is a prospective, comparative study carried out at a tertiary care hospital which aims to assess and compare the endothelial cell loss and changes in central corneal thickness after manual small incision cataract surgery in patients with type II diabetes versus age-matched normal individuals. **Result:** A total of 100 eyes of 100 individuals with type II diabetes and 100 eyes of 100 age matched normal individuals in the age group of 50-80 years were studied The endothelial cell loss at 3 months in cases was 22.01 ± 10.49% and in controls was 16.64 ± 6.72% with a significant difference indicating increased vulnerability of corneal endothelium in diabetics to intraocular surgical stress.

- Coefficient of variation of cell size and percentage of hexagonal cells, being indicators of repair after cataract surgery were not found to be significantly different in cases and controls.
- Central corneal thickness was maximum at the first follow up at 2 weeks in both the groups, and then gradually decreased. CCT was significantly raised in diabetics in all the follow-ups indicating a slower resolution of postoperative corneal edema in diabetics.

Conclusion: Postoperatively, there was a significant endothelial cell loss between cases and controls at 3 months. Therefore, in spite of a good glycemic control and no corneal abnormalities before surgery, the endothelium in diabetic subjects was found to be more vulnerable to surgical trauma and also having a lower capability in the process of repair. This suggests that eyes of diabetic patients are under metabolic stress and have corneal endothelium with lower reserve ability than non diabetic eyes. Therefore, surgery should be planned with appropriate precautions in diabetic patients. **Key words:** diabetes, corneal endothelium, endothelial cell loss, small incision cataract surgery, specular microscopy.

Introduction:

Corneal endothelial cells are largely hexagonal cells, responsible for maintaining the desiccation of the stroma by actively removing water and thus play a pivotal role in maintaining the clarity of the cornea. These cells have limited mitotic capacity, and a disturbance in the endothelial homeostasis might therefore have a profound effect on the clarity of the cornea. Changes in corneal epithelial and endothelial, structure and function are commonly seen in diabetes mellitus. Diabetes mellitus can cause, among other things, morphological changes in epithelial cells; they may also have a low endothelial reserve, making the endothelium more prone to stress-related injuries like ocular surgeries, despite a normal endothelial count.

Cataract surgery is one of the well-known factors that cause endothelial cell loss and corneal decomposition. All surgical procedures that involve entry into the anterior chamber damage a proportion of the endothelial cells as a result of intraoperative corneal manipulations.

In India, where the prevalence of cataract among the rural population is high, socioeconomic issues favor manual SICS, which is more economical than the phacoemulsification technique. There is a paucity of data from India on the effect of SICS on the corneal endothelium. This study was undertaken to assess the postoperative endothelial cell loss, change in endothelial cell morphology and central corneal thickness in patients with type II diabetes undergoing manual SICS and to compare them with age-matched normal individuals.

Aim and Objectives

- To compare endothelial cell parameters preoperatively in patients with type II diabetes and age-matched normal individuals. The parameters studied are:
  - Endothelial cell density
  - Percentage of hexagonal cells
  - Coefficient of variation of cell size
- To compare central corneal thickness preoperatively in patients with type II diabetes and age-matched normal individuals.
- To compare endothelial cell parameters postoperatively after manual small incision cataract surgery at different follow-ups in patients with type II diabetes versus age-matched normal individuals. The parameters studied are:
  - Endothelial cell loss
  - Percentage of hexagonal cells
  - Coefficient of variation of cell size
- To compare central corneal thickness after manual small incision cataract surgery at different follow-ups in patients with type II diabetes versus age-matched normal individuals.

Methodology

The present study, which is a prospective, comparative study,

Inclusion Criteria:

- Age group: 50-80 years.
- Patients operated by uneventful manual SICS.
- Preoperative cataract grading by LOCS III classification done and nucleus sclerosis grades 1-4, all cortical cataract grades and all posterior subcapsular grades included.

Exclusion criteria:

- Age of patient < 50 years and >80 years.
- Traumatic cataract / a history of trauma.
- Complicated cataract.
- Corneal endothelial dystrophies or any other corneal diseases affecting endothelial cell function.
- Uveitis.
- Glaucoma.
- Pseudoexfoliation syndrome.
- Patients with previous intraocular surgeries.

- Poorly controlled or uncontrolled type II diabetes mellitus i.e. HBA1c > 7 %.
- Nucleus sclerosis grading 5, 6 by LOCS III classification.
- Preoperative endothelial cell count of <1500 cells/mm^2
- Small pupil diameter after a full dilatation of less than 4 mm.
- Patients with intra-operative complications like PC rent, dislocated IOL and iridodialysis.

Sampling Size Estimation

A total of 100 eyes of 100 individuals with type II diabetes and 100 eyes of 100 normal individuals were studied. Patients with type II diabetes mellitus in the age group of 50–80 years and age-matched patients without diabetes undergoing manual small incision cataract surgery by a single experienced surgeon

The various endothelial cell morphological parameters that can be quantified are:

- Cell size which is measured as : Mean cell area (μm^2) or Endothelial cell density (ECD) in cells/mm^2
- Polymegathism i.e. variation of cell size which is measured as: Coefficient of variation of mean cell size (CV)

  $CV = \frac{\text{Standard deviation of cell area}}{\text{Mean cell area}}$
- Pleomorphism i.e. variation of cell shape which is measured as : Percentage of hexagonal cells (6A) in %
- Parameters examined in this study included endothelial cell density (ECD), coefficient of variation of cell size (CV) and percentage of hexagonal cells (6A).
- Normal values:
  - ECD: From the second to eighth decades of life, the cell density declines from approximately 3000–4000 cells/mm^2 to around 2600 cells/mm^2.
  - CV: 0.27-0.28 in young adults. It increases with age.
  - 6A: 70-80 % in young adults. It decreases with age.
- A clinical semi automated noncontact specular microscope was used by the principal investigator to study endothelial cell details. Images were taken with low flash intensity in automatic mode using the fixed frame analysis method to analyze central corneal endothelial cell density, coefficient of variation of cell size and percentage of hexagonal cells. Two separate readings were taken, with patient taking the chin off the chinrest, blinking once and returning to the examining position. The average value was recorded as the measurement. The number of cells counted ranged minimum from 70 to 100 to increase the validity of the readings.
- Preoperative central corneal thickness (CCT) was measured using noncontact pachymeter incorporated in the specular microscope. An average of 3 readings to the nearest of 10 µm was taken.
- Postoperatively, the patients were reviewed three times: at 2 weeks, 6 weeks and 3 months. At each visit, they had a complete ophthalmic examination, which included the best-corrected visual acuity, slit lamp examination, specular microscopy and pachymetry.
- Endothelial cell loss (ECL) was calculated at each follow up by the formula:
- $\frac{\text{Change in endothelial cell density at that follow up from preoperative value}}{\text{Preoperative value of endothelial cell density}} \times 100$

Statistical Analysis

Continuous variables (age, FBS, HbA1c, endothelial cell density, endothelial cell loss, coefficient of variation of cell size, percentage of hexagonal cells and central corneal thickness) were presented as mean ± SD. Categorical variables (sex) were

expressed in actual numbers. Baseline values (preoperative) of endothelial cell density, coefficient of variation of cell size, percentage of hexagonal cells and central corneal thickness between cases and controls were compared by unpaired t test. Endothelial cell density was compared at different follow-ups in cases and controls group by performing one way repeated measure ANOVA. Endothelial cell loss was compared at different follow-ups in cases and controls group by multiple comparison test i.e. Bonferroni test. Coefficient of variation of cell size, percentage of hexagonal cells and central corneal thickness were compared at different follow-ups between cases and controls by paired t test. $P < 0.05$ was considered as statistically significant. Statistical software STATA version 13.1 was used for data analysis.

Observation

Age range was 50-80 years with minimum age being 50 years and maximum age being 78 years. In cases, mean age was found to be 61.74 ± 8.52 years and mean age in controls group was 61 ± 3.81 years. Cases and controls were age matched.

Table 1: Age Distribution

Age (in years)	No. of Cases	No. of Controls
50 – 59	46	43
60 – 69	34	51
70 – 79	20	6
Total	100	100
Mean Age	61.74 ± 8.52 (50 – 78)	61 ± 3.81 (50 – 78)
p-value	0.4732,NS	

Distribution of males and females in both cases and controls was equal. Both groups had 42 male patients and 58 female patients.

Table 2: Sex Distribution

SEX	Cases (n=100)	Controls (n=100)
Male	42	42
Female	58	58
Total	100	100

Table 3: Comparison of baseline values (preoperative) of endothelial cell density (ECD), coefficient of variation of cell size(CV), percentage of hexagonal cells (6A) and central corneal thickness (CCT) in cases and controls.

	Cases (n=100)	Control (n=100)	p-value
ECD in cells/ mm^2	2718.88 ± 244.86	2721.87 ± 163.63	0.9190,NS
CV	0.34 ± 0.15	0.32 ± 0.13	0.2308,NS
6A in %	57.37 ± 6.33	58.86 ± 4.54	0.0585,NS
CCT in µm	511.46 ±14.85	502.7 ± 14.66	<0.0001,HS

Preoperatively, the endothelial cell density, coefficient of variation of cell size and percentage of hexagonal cells were not significantly different in cases and controls.

But there was a significant difference in preoperative central corneal thickness between the two with 511.46 ± 14.85 µm being in cases and 502.7 ± 14.66 µm being in controls in spite of good metabolic control.

Table 4: Endothelial cell density in cases and controls at different follow-ups.

FOLLOW UPS	ECD in Cases (n=100)	ECD in Controls (n=100)
Pre op	2718.88 ± 244.85	2721.87±163.63
2 week	2530.65 ± 226.07	2575.3 ± 155.40
6 week	2474.12 ± 235.63	2449 ± 137.8
3 month	2102.12 ± 195.96	2269.00 ± 155.44
F-value	119.43	132.21
p-value	< 0.0001, HS	< 0.0001, HS

In both cases and controls, the endothelial cell density gradually decreased from preoperative values.

Table 5: Comparison of endothelial cell loss in cases and controls at different follow-ups.

	ECL in Cases (n=100)	ECL in Controls (n=100)	p-value
2 week	6.67 ± 6.44	5.38 ± 5.50	0.0884,NS
6 week	8.65 ± 8.04	10.02 ± 6.52	0.2815,NS
3 month	22.01 ± 10.49	16.64 ± 6.72	<0.0001,HS

The endothelial cell density at each follow up was compared to the preoperative values and endothelial cell loss in % was determined.

The endothelial cell loss in cases and controls was not significant at 2 and 6 weeks but at 3 months, endothelial cell loss was 22.01 ± 10.49% in cases and 16.64 ± 6.72% in controls. And it was highly significant.

Table 6: Comparison of mean values of percentage of hexagonal cells (6a) in cases and controls at different follow-ups.

	6A in Cases (n=100)	6A in Controls (n=100)	p value
Pre op	57.37 ± 6.33	58.85 ± 4.54	0.0585,NS
2 week	55.72 ± 6.32	57.18 ± 5.18	0.0759,NS
6 week	55.62 ± 6.16	57.07 ± 4.69	0.0618,NS
3 month	55.35 ± 5.73	56.68 ± 4.45	0.0646,NS

The percentage of hexagonal cells being an indicator of repair process after endothelial cell loss was found to have steadily decreased postoperatively in both the groups but at every follow up, it was non-significant.

Table 7: Comparison of mean values of coefficient of variation of cell size (CV) in cases and controls at different follow-ups.

	CV in Cases (n=100)	CV in Controls (n=100)	p value
Pre op	0.34 ± 0.15	0.32 ± 0.13	0.2308,NS
2 week	0.35 ± 0.13	0.34 ± 0.15	0.7134,NS
6 week	0.38 ± 0.12	0.37 ± 0.12	0.9013,NS
3 month	0.38 ± 0.11	0.37 ± 0.12	0.3218,NS

The coefficient of variation of cell size, also being an indicator of repair process after endothelial loss, was found to have increased postoperatively in both the groups but without statistical significance. It has stabilized after 6 weeks in both the groups.

Table 8: Comparison of mean values of central corneal thickness (CCT) in cases and controls at different follow-ups.

	CCT in Cases (n=100)	CCT in Controls (n=100)	p value
Pre op	511.45 ± 14.84	502.7 ± 14.65	< 0.0001 , HS
2 week	549.70 ± 15.08	528.83 ± 16.47	<0.0001, HS
6 week	542.40 ± 14.20	525.96 ± 12.75	<0.001,HS
3 month	527.64 ± 14.34	523.13 ± 15.36	0.0326,S

The CCT i.e. central corneal thickness, was maximum at the first follow up at 2 weeks in both the groups, and then gradually decreased. CCT was significantly higher in diabetic patients in all three follow-ups.

Discussion

After every type of cataract surgery, with or without IOL implantation, the corneal endothelial cell count is diminished. Several studies have indicated an increased corneal vulnerability in diabetic subjects to intraocular surgical stress. [3, 81, 82] It is likely that this phenomenon occurs because of chronic metabolic changes on the cellular level that primarily seem to affect the monolayer of corneal endothelial cells.

Therefore, this study which is a comparative, prospective study aims to assess and compare the endothelial cell loss and changes in central corneal thickness after manual small incision cataract surgery in patients with type II diabetes versus age-matched normal individuals not support this speculation. So, increased dry weight of cornea could be the cause. This finding is also supported by Busted N *et al* [108] who stated that augmented corneal thickness due to increased dry weight of cornea may be one of the earliest detectable changes of the diabetic eye.

Comparison of baseline values (preoperative) of endothelial cell density, coefficient of variation of cell size, percentage of hexagonal cells and central corneal thickness in cases and controls.

It was observed that the preoperative endothelial cell, coefficient of variation of cell, percentage of hexagonal cells there was no significant difference between the two. But there was a significant difference in the preoperative central corneal thickness between the two with 511.46 ± 14.85 µm being in cases and 502.7 ± 14.66 µm being in controls despite of good metabolic control. The cornea has been reported to be thicker in eyes of diabetic patients than in eyes of non-diabetic subjects by some authors.

A study by Priya Thomas Mathew *et al* [98], in their study on endothelial cell loss and central corneal thickness in patients with and without diabetes after manual small incision cataract surgery showed similar results as this with no significant differences between ECD, CV and 6A but a significantly higher CCT in diabetics.

The increased corneal thickness in diabetic patients may be due to either increased water content or an increased dry weight content of the cornea or both.

If the increased corneal thickness of the diabetics is due to an increased hydration of the cornea, an abnormal function of the corneal endothelium might be postulated as a cause. In our study, the endothelial cell parameters are not significantly different in diabetics from non-diabetics and thus, do

Endothelial cell density in cases and controls at different follow-ups:

In both cases and controls, the endothelial cell density decreased from preoperative values. Similar results were also found in studies done by Priya Thomas Mathew *et al* [98] , Mikkel Hugod *et al* [78] and Soichi Morikubo *et al*. [3]

Comparison of endothelial cell loss in cases and controls at different follow-ups.

The endothelial cell density at each follow up was compared to the preoperative values and endothelial cell loss in percentage was determined.

Similar to our study, Mikkel Hugod *et al* [78] found a significantly greater corneal endothelial cell loss in diabetic subjects as compared with non-diabetic subjects 3 months after cataract surgery with intraocular lens implantation.

Priya Thomas Mathew *et al* [98] said that the endothelial cell density was found to steadily decrease after manual SICS in both the groups, with a significant difference in the percentage of endothelial cell loss between 6 weeks and 3 months, which was much more in patients with diabetes.

Significant difference in endothelial cell loss was found at 3 months because by this time the endothelial cell loss stabilizes.

Significant endothelial cell loss between cases and controls may suggest increased susceptibility of endothelial cells to intraocular surgical stress in diabetes as compared to controls.

Comparison of percentage of hexagonal cells in cases and controls at different follow-ups

The 6A i.e. percentage of hexagonal cells also being an indicator of repair process after endothelial cell loss, was found to have steadily decreased postoperatively in both the groups.

The corneal endothelium, once decreased, does not proliferate, and the defects are covered by stretching, extension, and transfer of the residual corneal endothelium.[109] Therefore, there is a decrease in percentage of hexagonal cells and an increased variability of cell size i.e. coefficient of variation of cell size. But because the repair process is delayed in diabetics, in spite of the significantly decreased endothelial cell loss, percentage of hexagonal cells is not significantly decreasing.

Similar results were concluded by Soichi Morikubo *et al* [3] in their study where percentage of hexagonal cells between cases and controls was found to be insignificant.

Comparison of coefficient of variation of cell size in cases and controls at different follow-ups.

The coefficient of variation of cell size, also being an indicator of repair process after endothelial cell loss, was found to have increased postoperatively in both the groups.

In endothelial repair process, there is a short term increase in the cell size. When the endothelium stabilizes after a period of rearrangement, the coefficient of variation of cell size comes back to preoperative values. [23, 30] In our study, coefficient of variation of cell size has stabilized after 6 weeks in both the groups.

In studies done by Priya Thomas Mathew *et al* [98] and Mikkel Hugod *et al* [78] ,coefficient of variation of cell size values at 3 months was insignificant in cases and controls.

Comparison of central corneal thickness in cases and controls at different follow-ups.

The CCT i.e. central corneal thickness, was maximum at the first follow up at 2 weeks, and then gradually decreased in both cases and controls but never returned to its preoperative values.

Priya Thomas Mathew *et al* [98] got a significantly high CCT in diabetics at 6th week postoperatively while Soichi Morikubo *et al* [3] studied change in CCT from preoperative value and found a significant increase at 1 month in diabetics.

In our study, in all three follow-ups, CCT is significantly more in diabetics. This indicates that it will take more time for postoperative corneal edema in diabetics to resolve as the repair process is slow.

Therefore, we have concluded that, the decrease in endothelial cell density which reflects the surgical trauma itself is more in diabetes type II than normal individuals. Also, the change in morphology which is more closely associated with the process of repair is deranged in diabetic patients in spite of having a good glycemic control.

Conclusion

- Preoperatively, endothelial cell parameters were found to be similar in cases and controls except central corneal thickness which was more in cases in spite of a good glycemic control.
- Postoperatively, there was a significant endothelial cell loss between cases and controls at 3 months. Therefore, in spite of a good glycemic control and no corneal abnormalities before surgery, the

endothelium in diabetic subjects was found to be more vulnerable to surgical trauma and also having a lower capability in the process of repair. This suggests that eyes of diabetic patients are under metabolic stress and have corneal endothelium with lower reserve ability than non diabetic eyes. Therefore, surgery should be planned with appropriate precautions in diabetic patients.

- In diabetic patients, there is a delay in the postoperative recovery of corneal edema as compared with non diabetic eyes.
- Because of advances in small-incision cataract surgery, severe corneal edema rarely develops, but the protection of the corneal endothelium is important for long-term corneal function after intraocular surgery in eyes of diabetic patients.
- Considering these findings, specular microscopy should be done in every patient having type II diabetes before planning cataract surgery.

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