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ORIGINAL PAPER

BKC and CME: Is benzalkonium chloride hindering our efforts to achieve the desired postoperative visual acuity?

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Abstract

Purpose To evaluate and compare the change in postoperative central macular thickness in patients receiving benzalkonium chloride (BKC)-preserved and BKC-free medications after uneventful phacoemulsification.

Setting V.M.M.C & Safdarjung Hospital, New Delhi (a tertiary health care hospital).

Study design Prospective randomized comparative observational study.

Materials and methods Once patients were selected, the baseline standard ophthalmic examination was done. Sample size: 140 eyes were enrolled and randomly divided into two groups. (a) Group I: receive BKC-preserved topical medications and (b) Group II: receive BKC-free topical medications of same constituents postoperatively. Group I patients received topical BKC-preserved moxifloxacin 0.5% + dexamethasone 0.1% eye drops six times a day, timolol maleate 0.5% twice daily, tropicamide 0.8% + phenylephrine 5% once a day for 6 weeks, and Group II received same BKC-free topical eye drops for 6 weeks. Postoperatively, the patients were reviewed at day 1, week 1, week 6 for same parameters.

Statistics Quantitative variables: paired and unpaired t test. p value < 0.05 was considered statistically significant.

Results The mean CMT in μm at 1 week in Group I was 269.39 ± 14.56 and in Group II was 270.04 ± 6.56. The mean CMT in μm at 6 weeks in Group I was 270.39 ± 17.18 and in Group II was 270.90 ± 7.00.

Conclusion Neither do BKC-preserved topical medications have any independent role in increasing the central macular thickness after uneventful surgery nor do they have any role in causing pseudophakic CME.

Keywords BKC · CME · Phacoemulsification

Introduction

Cataract extraction is the most commonly performed ophthalmic surgical procedure in the developed world, and the most common cataract extraction procedure performed is phacoemulsification.

In 1953, Irvine described cystoid macular edema (CME) that specifically arose after cataract surgery [1]. Gass and Norton subsequently studied the characteristics of the new disease entity with fluorescein angiography [2]. Pseudophakic cystoid macular edema, also known as Irvine–Gass syndrome, is one

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of the most common causes of incomplete visual recovery after cataract surgery [3]. The pathogenesis of pseudophakic CME is thought to be multifactorial. Miyake et al. demonstrated in several clinical trials and cellular studies that preoperative and postoperative topical glaucoma medications specifically latanoprost and timolol may increase the incidence of pseudophakic CME [4]. It appears that a commonly used preservative, benzalkonium chloride (BKC), is cytotoxic and stimulates inflammatory responses [4].

BKC is a detergent and quaternary ammonium compound with a broad range of antimicrobial activity [5]. It is the most frequently used preservative in ophthalmic solutions today, and its concentrations in ocular formulations range from 0.004 to 0.02% [6]. While the efficacy of BKC is well known, there is a multitude of published studies that document the detrimental effect of BKC [7–9]. Much less is known about the potential effect of BKC on the deeper structures of the eye in vivo. As many topical medications containing BKC are used in postoperative period following cataract surgery, it is of utmost importance to know their deleterious effects.

To validate this hypothesis that postoperative medications containing BKC can have effect on deeper structures, we have chosen to investigate the potential inflammatory effect of BKC, by means of measuring the central macular thickness before and after uncomplicated phacoemulsification surgical procedure.

Materials and methods

Study design

Comparative randomized observational study.

Center

Ophthalmology Department, Tertiary Eye Care Centre (VMMC & Safdarjung Hospital).

Duration

The study was conducted over a period of 18 months.

Sample size

Hundred and forty eyes were enrolled and randomly divided into two groups of 70 each using table of random numbers. All patients gave informed consent.

Subjects

Inclusion criteria:

(a) Age > 40 years
(b) Immature senile cataract cases in which CMT measurement is possible with OCT.

Exclusion criteria:

(a) H/O previous intra-ocular inflammation
(b) Any corneal or macular pathology
(c) Patients suffering from all those diseases which can effect CMT like trauma, vascular retinopathy (anemia, diabetes and hypertension.), vascular occlusions and previous ocular surgery
(d) Any intra-operative or postoperative complications which may affect the central macular thickness.

Procedure and data collection

Ethical clearance was obtained from the ethical clearance committee, IRB, VMMC & Safdarjung Hospital. Patients fulfilling the above-mentioned criteria were enrolled in the study after explaining pertinent details of the study and obtaining valid consent for the same.

Once patients were selected, the baseline assessment included standard ophthalmic examination including

(c) Best-corrected visual acuity
(d) Anterior segment evaluation with slit-lamp biomicroscopy
(e) Dilated fundus examination by direct and indirect ophthalmoscopy
(f) Schirmer test and tear film break-up time (TBUT)
(g) Central macular thickness (CMT) by spectral domain OCT.

Assuming the effect size to be 0.6, power of study 90%, level of significance 5%, using software G power

3.1.7, the sample size for study was 140 patients (140 eyes of 140 patients) who were divided into two groups. All surgeries were performed by the same surgeon under topical anesthesia under the same settings. Having thus obtained baseline parameters, patients were randomly allocated (using table of random numbers) into:

Group I: Receive BKC-preserved topical medications

Group II: Receive BKC-free topical medications of same constituents postoperatively

Group I patients received topical BKC-preserved moxifloxacin 0.5% + dexamethasone 0.1% eye drops six times a day, timolol maleate 0.5% twice daily, tropicamide 0.8% + phenylephrine 5% once a day for 6 weeks, and Group II received same BKC-free topical eye drops for 6 weeks.

Patients who required any other medication after surgery apart from the above medications were excluded from the study.

The patients were asked to come for follow-up at post-op 1 day, 1 week and 6 weeks. On each of their visits, the same above parameters were noted.

Statistical analysis

- Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then nonparametric test was used.
- The data were entered in MS EXCEL spreadsheet, and analysis was performed using Statistical Package for Social Sciences (SPSS) version 21.0
- Data were analyzed using paired *t* test for intra-group change and Student's *t* test for inter-group change in central macular thickness as compared to baseline.
- *p* value $\leq$ 0.05 was considered significant.

Table 1 Age-wise distribution of population

Age	Group I	Group II	Total
41–50 years	9 (12.9%)	3 (4.3%)	12 (8.6%)
51–60 years	12 (17.1%)	26 (37.1%)	38 (27.1%)
61–70 years	24 (34.3%)	29 (41.4%)	53 (37.9%)
> 70 years	25 (35.7%)	12 (17.1%)	37 (26.4%)
Total	70 (100%)	70 (100%)	140 (100%)

Table 2 Sex-wise distribution of population

Sex	Group I	Group II	Total
Male	32 (45.7%)	35 (50%)	67 (47.9%)
Female	38 (54.3%)	35 (50%)	73 (52.1%)
Total	70 (100%)	70 (100%)	140 (100%)

Results

Age- and sex-wise distribution

Tables 1 and 2 show the age- and sex-wise distribution of the sample population.

Mean age in Group I was 65 years, while mean age in Group II was 63 years.

Maximum patients in Group I were more than 70 years and in Group II were between 61 and 70 years of age.

Mean age was not significantly different between the two groups $p = 0.147$.

Schirmer test comparisons at various time intervals

In Group I, the preoperative baseline Schirmer test value in mm was 13.79 ± 0.81. Postoperative week 1 and week 6 values were 9.94 ± 0.66 and 9.76 ± 0.62, respectively. Statistically significant change (p value < 0.05) was seen in preoperative and postoperative values (Fig. 1).

In Group II, the preoperative baseline Schirmer test value in mm was 13.83 ± 0.87. Postoperative week 1 and week 6 values were 13.71 ± 0.92 and 13.59 ± 1.12, respectively. Statistically insignificant change (p value = 0.896 at week 1 and p value = 0.830 at week 6) was seen in preoperative and postoperative values.

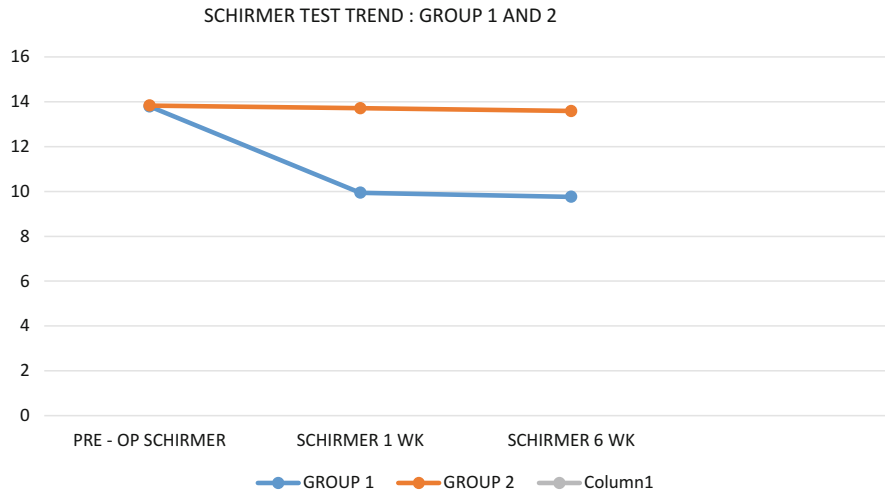

Fig. 1 Schirmer test comparisons at various time intervals in Group I and Group II

TBUT test comparisons at various time intervals

In Group I, the preoperative baseline TBUT test value in mm was 13.03 ± 0.74. Postoperative week 1 and week 6 values were 9.90 ± 0.68 and 9.60 ± 0.67, respectively. Statistically significant change (p value < 0.05) was seen in preoperative and postoperative values (Fig. 2).

In Group II, the preoperative baseline TBUT test value in mm was 13.07 ± 0.75. Postoperative week 1 and week 6 values were 13.10 ± 0.92 and 13.04 ± 0.95, respectively. Statistically insignificant change (p value = 0.974 at week 1 and p value = 0.975 at week 6) was seen in preoperative and postoperative values.

Comparison of central macular thickness between the two groups

The mean CMT in µm before the procedure in Group I was 262.91 ± 17.2 and in Group II was 264.00 ± 6.57. No statistical difference was found between CMT in both groups before the procedure.

The mean CMT in µm at 1 week in Group I was 269.39 ± 14.56 and in Group II was 270.04 ± 6.56. No statistical difference was found between CMT in both groups at 1 week.

Table 3 shows the CMT comparison between the two groups at 6 weeks.

The mean CMT in µm at 6 weeks in Group I was 270.39 ± 17.18 and in Group II was 270.90 ± 7.00.

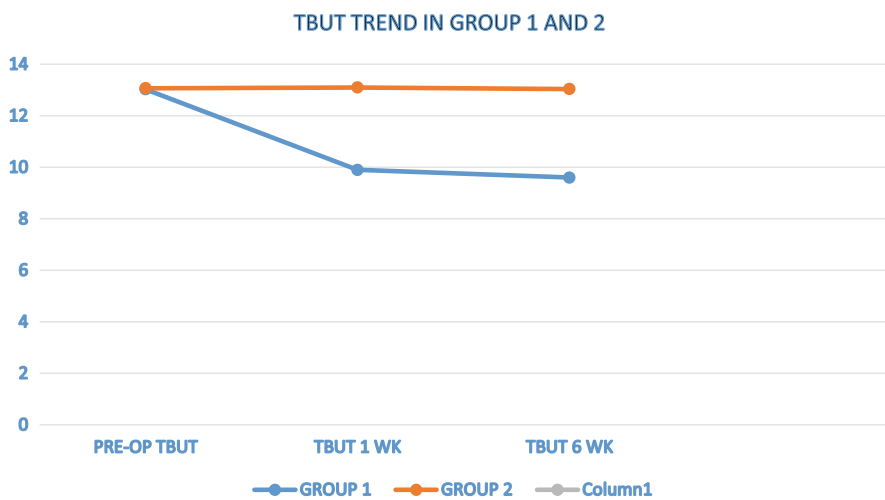

Fig. 2 TBUT test comparisons at various time intervals in Group I and Group II

Table 3 Comparison of CMT trend in Groups I and II

	Group I	Group II	*p* value
Mean CMT change at week 1	6.4714	6.0429	0.651
Mean CMT change at week 6	7.4714	6.9000	0.223

No statistical difference was found between CMT in both groups at 6 weeks.

There is a significant change in mean CMT of patients in Group I from the preoperative measurement with respect to postoperative CMT at week 1 and week 6.

There is a significant change in mean CMT of patients in Group II from the preoperative measurement with respect to postoperative CMT at week 1 and week 6.

Table 3 shows an inter-group comparison of the trend in CMT change.

There is no significant change in variation of mean CMT at week 1 and week 6 when both Group I and Group II are compared (Fig. 3).

Discussion

Our study was undertaken to assess the effect of the preservative benzalkonium chloride (BKC) on the central macular thickness as well as its probable role in causing pseudophakic cystoid macular edema (CME) after an uncomplicated phacoemulsification surgery in the postoperative period up to 6 weeks. The central macular thickness was assessed with optical coherence tomography preoperatively, at week 1, at week 6 postoperatively, and a comparison was made between the measurements of the two study groups.

The standard ETDRS subfields divide the macula into central fovea, inner macula and outer macula, comprising of nine subfields [10]. The central subfield is 1 mm in diameter and the inner and outer subfields have the diameters of 3 mm and 6 mm, respectively. The central macular thickness used for comparison among the study subjects in our study corresponded to the mean thickness of all points in the central subfield of 1 mm diameter (1000 μm) of the ETDRS macular subfields.

In our study, none of the patients developed clinical macular edema on optical coherence tomography (OCT). Thus our study demonstrated that after an uneventful phacoemulsification surgery, topical medications containing BKC as preservative did not have any independent role in influencing the change in central macular thickness when compared to topical medications which are BKC free.

Cataract surgery is one of the most commonly performed surgeries. Although this procedure is generally safe, the most common adverse event leading to postoperative vision loss is the development of pseudophakic cystoid macular edema (PCME) [11]. The incidence of clinically significant acute PCME (vision loss greater than 20/40 from an expected 20/20 or equivalent) ranges from 0.6 to 3.6% with a peak

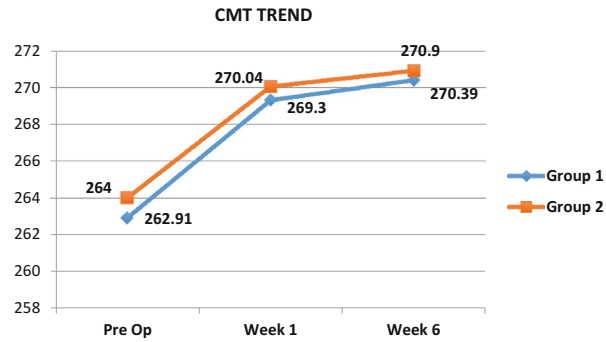

Fig. 3 Comparison of CMT trends in Groups I and II

incidence at around 5 weeks after uncomplicated cataract surgery [11–13]. The majority of PCME cases resolve spontaneously with vision returning to normal [11, 12]. Clinically significant PCME includes ophthalmic and angiographic findings with vision loss. A visual acuity of 20/40 best-corrected visual acuity (BCVA) or less has been considered clinically significant by most studies [14]. The gold standard for identifying PCME has been with fluorescein angiography and has yielded prevalences as high as 9.1 to 25.5% [12]. Findings of angiographic PCME do not correlate well with vision loss. However, measurement of macular thickness with optical coherence tomography (OCT) does correlate well with visual impairment and final best-corrected visual acuity [15, 16].

Various studies by Perente et al. [17], Cagini et al. [18], Sourdille et al. [19], Yoo et al. [20], Wang et al. [21], Neto et al. [22], Hwang et al. [23], Arora et al. [24] and Von Jagow et al. [14] measured the macular thickness by OCT in a healthy population before as well as between 1 and 6 months postoperatively after an uncomplicated phacoemulsification surgery. They concluded that the onset of clinically significant CME is rare after uncomplicated phacoemulsification cataract surgery. But with respect to preoperative values, there was an asymptomatic increase in macular thickness and volume in 12 weeks. The clinical and subclinical thickness changes without breakdown of blood–aqueous barrier can be detected after cataract surgery. Most of these changes resolve spontaneously, but their mean and long-term significance is unknown.

Postoperative inflammation seems to be a major cause of PCME. This impact on the healthy retina even after an uncomplicated phacoemulsification surgery can be attributed to factors such as intra-operative photo-stress due to microscope light, intra-operative changes of the ocular pressure caused by surge or to the ultrasound energy delivered. Vitreous tractions following removal of the lens could also contribute [24]. It is postulated that surgical manipulation within the anterior chamber may lead to the release of arachidonic acid from uveal tissue, with the production of either leukotrienes via the lipoxygenase pathway or prostaglandins (PGs) via the cyclooxygenase (COX) pathway [25]. Subsequently, inflammatory mediators diffuse posteriorly into the vitreous and disrupt the blood–retinal barrier. This disruption results in increased permeability of the perifoveal capillaries and fluid accumulation within the retina [26]. It is not clear why the fluid leaking from the perifoveal capillaries accumulates within the macula, despite the massive production and distribution of inflammatory cytokines throughout the retina. The reduced fluid reabsorption within the macula may be explained, at least in part, by the absence of blood vessels within the avascular zone combined with the high metabolic activity of the fovea [27]. Patients with marked postoperative inflammation tend to develop PCME more frequently than others do [28]. This observation implies that the degree of inflammation determines the severity of PCME, which can range from very mild to clinically significant forms. As postoperative inflammation is inseparably linked to each cataract surgery procedure, noncomplicated cases also induce an increase in subclinical central macular thickness (CMT).

Although Miyake et al. [29] found a higher incidence of CME in eyes receiving BKC-preserved solutions ($p < 0.01$), we were not able to detect macular edema with OCT nor did we find any statistically significant BKC-induced changes in macular thickness measurements. However, according to one study, the sensitivity of fluorescein angiography as a detection tool for disturbances in the blood–retinal barrier function may be better than OCT, because it permits the study of vascular leakage from the retina and choroid. Furthermore, posterior capsular rupture, a well-known risk factor for the development of CME, was excluded from our study.

Abe et al. [30] did a prospective randomized comparative study of 44 healthy eyes of 44 pseudophakic volunteers. They were randomly assigned preservative-free artificial tears (Group I) and BKC-preserved artificial tears (Group II). They observed no statistically significant change in macular thickness measurements at day 15 and 30 in either group ($p > 0.05$) compared with baseline. They also did not find any evidence of CME in their eyes. Although in our study, we observed an increase in central macular thickness compared to preoperative baseline values, which can be attributed to the fact that our study was conducted on newly pseudophakic eyes where inflammatory mediators play a role in causing change in macular thickness, but yet both studies are consistent with the finding that BKC does not play any role in causing changes in macular thickness.

In our study, we could appreciate substantial ocular surface changes following BKC-preserved topical medication administration. Chhabra et al. [31] did a comparative crossover study of benzalkonium chloride-free latanoprost versus benzalkonium chloride-preserved latanoprost on ocular surface health in patients of primary open-angle glaucoma. Their Schirmer test and tear film break-up time (TBUT) were recorded at the baseline. The findings of this study are consistent with our observations and give an indication toward ocular surface changes caused by BKC-preserved topical medications.

Conclusively, although we did not find any role of BKC in causing changes in central macular thickness and pseudophakic CME, we observe ocular surface changes caused by BKC-preserved topical medications. Due to this fact, we would like to recommend caution while using BKC-preserved medications for prolonged use.

Conclusion

There can be an asymptomatic increase in CMT compared to the preoperative baseline value even after an uncomplicated phacoemulsification surgery. The comparison of mean CMT increases from preoperative baseline values of both the groups (those receiving BKC-preserved topical medications and BKC-free topical medications) which is statistically insignificant. Therefore, neither BKC-preserved topical medications do have any independent role in increasing the central macular thickness after uneventful surgery nor do they have any role in causing pseudophakic CME. BKC-preserved topical medications play a role in causing ocular surface changes indicated by reduced Schirmer test value and tear break-up time (TBUT).

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with animals performed by any of the authors. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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