

Research Article

Current Trends in Ophthalmology

The Effect of Brimonidine 0.15% on the Development of Bulbar Redness Following Femtosecond Laser Assisted Cataract Surgery

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Abstract

Purpose: To assess the effect of brimonidine tartrate 0.15% on reducing bulbar redness, measured with a bulbar redness score, following femtosecond laser assisted cataract surgery (FLACS).

Patients and methods: A prospective, masked randomized controlled study was done using single-blinded simple randomization. All FLACS cases completed between June and August 2019 were included except that on anticoagulation or with prior conjunctival surgery. All operated eyes received usual preoperative eye drops, while Study group received added brimonidine. Exclusion criteria included >1 vacuum attempt during FLACS and any intraoperative complications. All subjects received Bulbar Redness (BR) Score and Analyzed Area (AA) imaging by Oculus 5M Keratograph preoperatively and postoperatively. AA including non-conjunctival structures, <25mm², or postoperative AA values >10% different from preoperative values were excluded from final analysis. Absolute values and differences between mean postoperative and preoperative BR and AA were compared using Student's *t*-test.

Results: 62 eyes (Study group=25, Control group=37) of 56 patients were randomized and included for analysis. Baseline demographic comparison between the two groups was similar. Preoperative BR score in the Study group trended higher (1.62) than Control (1.40, *p*=0.07), while postoperative BR score remained similar between groups (*p*=0.70). Difference in postoperative and preoperative BR score was significantly larger in the study group (-0.21±0.56) than controls (+0.06±0.43, *p*=0.036).

Conclusions: The use of preoperative brimonidine in FLACS reduces the amount of postoperative bulbar redness following FLACS. Oculus 5M BR scoring has potential to be used as an objective method of quantifying bulbar redness after ophthalmic surgeries and procedures.

Keywords: Cataract surgery, Brimonidine tartrate, Brimonidine, Bulbar redness, Femtosecond laser-assisted cataract surgery

Abbreviations: AA: Analyzed Area; BR: Bulbar Redness; FLACS: Femtosecond Laser Assisted Cataract Surgery

Introduction

Femtosecond laser assisted cataract surgery (FLACS) surgery given its improved refractive outcomes and is becoming an increasingly common form of cataract efficiency compared to traditional cataract surgery [1,2].

Complications of FLACS include incomplete capsulotomy, anterior capsulotomy tag, anterior capsular tear and, subconjunctival haemorrhage [3]. Subconjunctival hemorrhage occurs following suction ring application during FLACS [4]. Although subconjunctival hemorrhage is a self-limiting complication, it impacts recovery time and cosmetic appearance for patients which has clinical relevance when considering FLACS as a refractive procedure.

Brimonidine-tartrate is a selective α_2 -adrenergic agonist that vasoconstricts and lowers intraocular pressure (IOP), commonly used to treat glaucoma [5]. While the IOP lowering effect of brimonidine is well-known, the vasoconstrictive effect in the context of reducing subconjunctival hemorrhage during ophthalmic surgery and procedures has not been as extensively studied. Preoperative use of brimonidine to reduce subconjunctival hemorrhage has been investigated in the context of laser in situ keratomileusis (LASIK), intravitreal injections, strabismus surgery, pterygium surgery, and cataract surgery via manual corneal incision [6-13]. However, none of these studies used objective methods to quantify postoperative subconjunctival hemorrhage or bulbar redness, making it difficult to validate the results and conclusions of these studies.

Bulbar redness is a broad measure of ocular surface redness which may be attributed to a combination of subconjunctival hemorrhage, vasodilation, and increased vascularization. We utilize an objective method of quantifying bulbar redness using the Oculus 5M Keratograph. To our knowledge, this is the first study to evaluate the preoperative use of brimonidine to reduce bulbar redness following FLACS.

Methods

This study adhered to the tenets of the Declaration of Helsinki and was approved by the William Osler Health System Research Ethics Board (REB file #19-0024) prior to commencement of the study. All consecutive patients undergoing FLACS at an ambulatory surgical centre in Ontario, Canada between June and August 2019 were enrolled. Patients were excluded if they were on anticoagulation therapy or who had prior conjunctival surgery. After informed consent was obtained, patients were randomized to either the study group or control group using simple randomization. If a patient required bilateral FLACS, the patient was randomized again prior to the second surgery and that eye was counted as an independent entity. A minimum of two weeks was required between surgeries.

All subjects underwent baseline preoperative imaging with the Oculus 5M Keratograph (Oculus Optikgeräte, GmbH, Wetzlar, Germany), recording Bulbar Redness (BR) score (or "R-Scan") and Analyzed Area (AA). The AA is an automatic analysis of the exposed scleral area of the captured image. The absolute AA is given in mm^2 . BR score is an automated feature of the Oculus 5M which quantifies the amount of redness captured in the AA, by evaluating the sclera-to-blood ratio to determine the degree of redness. BR severity is then graded on a scale of 0 to 4.

Subjects in both groups then received the usual preoperative eye drops in the operated eye, including moxifloxacin 0.5%, cyclopentolate 1%, mydracyl 1%, and phenylephrine 10%, with a 1-minute wait between each drop. 5 minutes later, subjects in the study group received an additional drop of brimonidine-tartrate 0.15%.

Subjects then underwent FLACS (J&J Catalys Precision Laser System + J&J Whitestar Signature Pro, Abbott Medical Optics Inc.) completed by one of three surgeons (E.T., H.C., or S.S.). All operated eyes of subjects from both control and study group had topical tetracaine approximately 10 minutes prior to the start of FLACS. They also received 0.5mg midazolam IV at the start of the intraocular portion of the surgery. All operated eyes in both study and control groups had a drop of 5% povidone iodine as part of the routine preparation prior to the intraocular portion of the surgery. The operated eye was engaged to the liquid optics interface, and a vacuum was applied. A standard capsulotomy, lens fragmentation, and corneal incisions were completed. Phacoemulsification and intraocular lens implantation then followed. Within 15 minutes following surgery, imaging with the Oculus 5M Keratograph was repeated.

The number of attempts to achieve adequate vacuum and duration of surgery were recorded. Procedures requiring more than one vacuum attempt during the FLACS procedure and those who had any intraoperative complications were excluded from the analysis.

To ensure only comparable preoperative and postoperative images of subject eyes were used for data analysis, we further excluded all subjects where AAs included structures other than conjunctiva (e.g. palpebrae), were $<25\text{mm}^2$ in size, and had $>10\%$ size difference between preoperative and postoperative images which could not provide accurate comparisons (Figure 1). These values were determined through our piloting phase where we found that AA $<25\text{mm}^2$ in size did not allow for accurate

BR assessment, and images that had >10% difference in AA led to certain sections of the sclera being excluded. An example of images that met inclusion criteria are also provided in Figure 1.

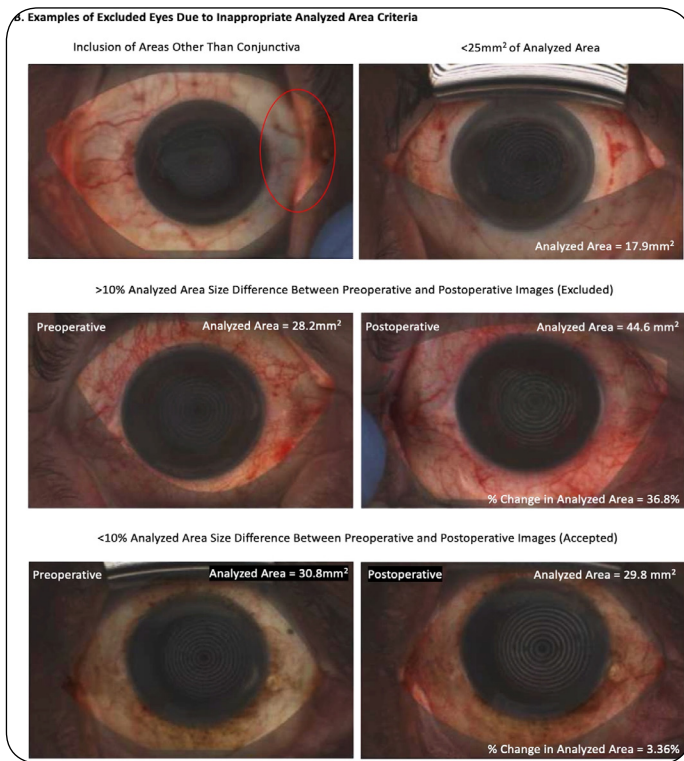


Figure 1: Examples of excluded images due to inappropriate analyzed area (i.e. inclusion of areas other than conjunctiva, <25mm² AA, or >10% AA size difference between preoperative and postoperative images). An example of included preoperative and postoperative images with appropriate AA is provided.

Statistical analysis

The preoperative and postoperative mean BR score and mean AA were calculated for the study and control groups. The change between individual preoperative and postoperative mean BR scores and percent change between preoperative and postoperative mean AA were calculated. Values were analyzed between study and control groups using two-tailed unpaired *t*-test.

Results

241 eyes were recruited to the study with 120 eyes randomized to the study group and 121 eyes randomized to the control group. After further exclusion to ensure AA comparable AAs 62 eyes (25 in the study group, 37 in the control group) of 56 patients met all inclusion and exclusion criteria for data analysis. The bilateral eyes of six patients were included in which case two patients had both eyes randomized to control, and four patients had

one eye randomized to control and one to brimonidine arm (Figure 2).

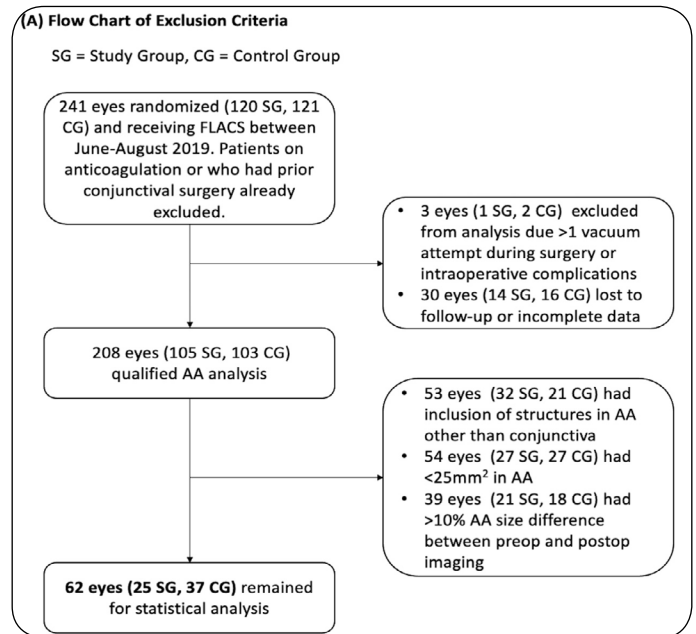


Figure 2: Flow chart indicating number of excluded patients based on exclusion criteria. SG = Study group receiving brimonidine, CG = control group, BR = Bulbar redness score, AA = analyzed area.

There was no significant difference in demographics between the two groups (Table 1).

Preoperative mean BR score trended higher in the study group (1.62 ± 0.52) as compared to the control group (1.40 ± 0.34) but was not statistically significant ($p=0.07$). Similarly, the difference in postoperative BR score between the study (1.42 ± 0.44) and control group (1.46 ± 0.43) was not statistically significant ($p=0.70$) (Figure 3). Mean AA was similar between both groups preoperatively ($p=0.28$) and postoperatively ($p=0.46$).

When the change in mean BR score from preoperative to postoperative levels were compared, a statistically significant difference was found between the study and control groups (-0.21 ± 0.56 and $+0.06 \pm 0.43$ respectively, $p=0.036$) (Figure 4). The preoperative to postoperative percent change in mean AA remained similar between the study and control groups respectively ($0.40\% \pm 3.60\%$ vs. $1.40\% \pm 4.30\%$, $p=0.33$).

Table 1: Baseline Characteristics Between Study and Control Group.

Characteristics	Brimonidine	Control	P-value
	(n = 25)	(n = 37)	
Age (years)			
Mean ± SD	66.64 ± 9.25	69.19 ± 8.16	0.27
Range	47-81	53-85	
Gender (n, %)			
Male	12 (48%)	12 (32%)	0.23
Female	13 (52%)	25 (68%)	
Medical Conditions (n, %)			
Hypertension	12 (48%)	17 (46%)	0.88
Diabetes	6 (24%)	8 (22%)	0.7

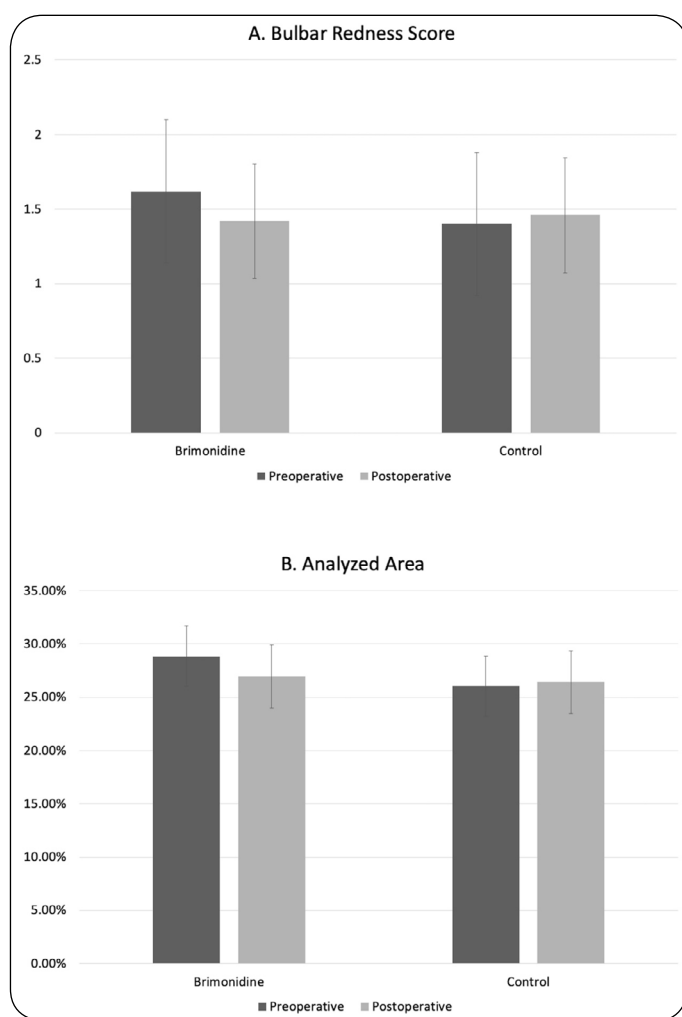


Figure 3: (A) Mean preoperative and postoperative bulbar redness scores between study and control groups. Standard deviation is depicted. (B) Mean preoperative and postoperative analyzed area between study and control groups. Standard deviation is depicted.

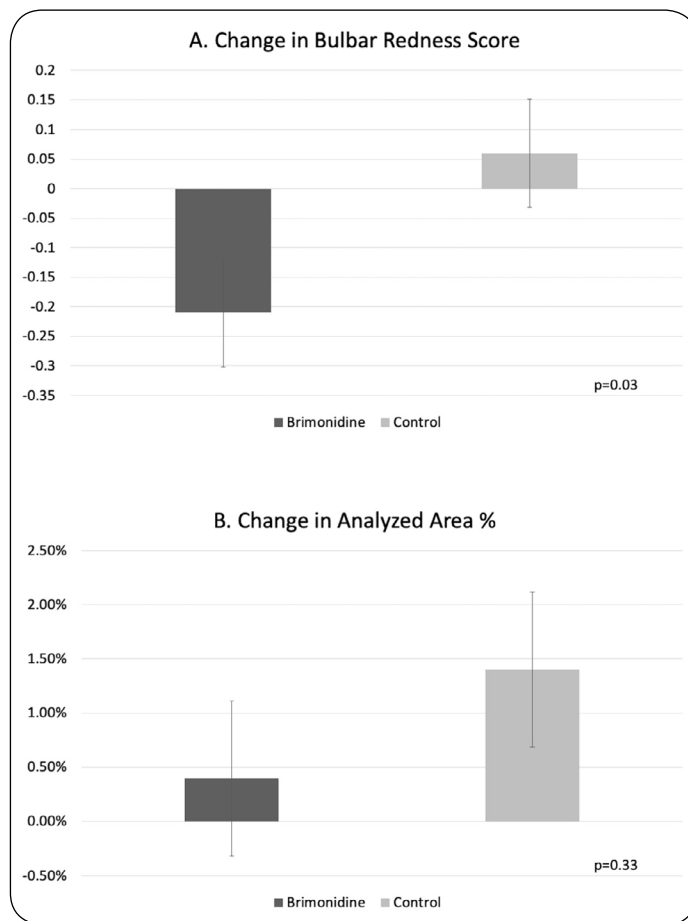


Figure 4: (A) Mean difference between postoperative and preoperative bulbar redness score between study and control groups. Standard error is depicted. (B) Mean difference between postoperative and preoperative analyzed area between study and control groups. Standard error is depicted.

Discussion

Given that the goal of cataract surgery is to improve visual function and mitigate use of visual aids, technologies such as FLACS addresses patient demand for not only excellent vision recovery and flawless surgical outcomes, but also expedient return to normal appearance and daily function. Suction ring application during FLACS is known to cause subconjunctival haemorrhage [4]. While subconjunctival hemorrhage is self-limiting and does not cause pain or affect vision recovery, the increased bulbar redness may cause anxiety related to early perceived surgical outcomes for patients.

We demonstrate that the use of preoperative brimonidine-tartrate 0.15% decreased bulbar redness after FLACS. The change between postoperative and preoperative mean BR scores was significantly larger in the brimonidine group compared to the control group. This finding that

brimonidine has additive vasoconstrictive effects being beneficial to ophthalmic surgery procedures and outcomes are consistent with other studies in the literature. A study by Desco et al. found preoperative brimonidine to decrease rates of subconjunctival hemorrhage after cataract surgery with manual corneal incision [13]. Similar results of decreased subconjunctival hemorrhage following ophthalmic procedures with prophylactic brimonidine were reported for intravitreal injections, strabismus surgery, and LASIK [6-11]. However, a common limitation of these studies is their subjective method of quantifying subconjunctival hemorrhage.

To our knowledge, previous studies in the literature used subjective methods of grading postoperative subconjunctival hemorrhage. Grading was based on the number of quadrants involved, and sometimes combined with an additional grade for the size of the haemorrhage [6,7,11,13]. Subjective methods do not allow for consistent reproducibility, comparison between studies, or validation of study conclusions. To overcome the limitations of subjective scoring, we utilized Oculus 5M BR score as an objective and standardized method of quantifying bulbar redness, which includes subconjunctival hemorrhage, and vasodilation, after ophthalmic procedures. The automated BR scoring by Oculus 5M has been well-validated [14-16]. Oculus BR scoring was found to have similar or better intra-observer variability than other methods of BR quantification such as Red-value, Institute Eye Research (IER), Validated Bulbar Redness scale (VBR), and Efron grading scale [14,15,17].

One limitation of this study is that bulbar redness is the cumulative effect of subconjunctival hemorrhage, vasodilation, and injection due to increased vascularity, and therefore may not truly delineate the impact of brimonidine-tartrate 0.15% on the reduction of subconjunctival hemorrhage. Patients with ocular surface disease and dry eyes were not excluded and may have potentially confounded BR score. A further potential limitation is that the AA of imaging for BR scoring is automatically processed and cannot be adjusted manually leading to inconsistencies in surface areas measured and possible inclusion of non-conjunctival areas. For this study, these challenges were overcome by implementing stringent exclusion criteria which limited our sample size. In practical clinical use and future studies, further development of programs allowing for manual adjustment of AA may allow for more accuracy and increased consistency. Another limitation is the possible confounding effect of preoperative phenylephrine 10% and 5% povidone-iodine used prior to surgery. However, this impact was mitigated as it was

a standard application in both groups. Furthermore, the objective of this study was to examine whether brimonidine could cause further vasoconstriction and lead to improved bulbar redness above and beyond the typical dilating drops used preoperatively. For future studies, repeat imaging 2-3 hours after surgery would help to delineate the true BR after the drugs wear off. We suspect the small sample size coupled with phenylephrine vasoconstriction may have likely blunted the brimonidine effect, and this supports the need for larger studies in this area.

Conclusion

The use of preoperative brimonidine 0.15% in FLACS reduces the amount of post-operative bulbar redness. Oculus BR scoring has potential to objectively quantify bulbar redness after ophthalmic surgeries and procedures, despite challenges associated with image capturing.

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