

Prophylactic Effect of Brimonidine To Minimize The Incidence of Subconjunctival Hemorrhage after 23G Pars Plana Vitrectomy

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Abstract

Background

Several studies have already investigated the prophylactic effect of brimonidine drops in preventing subconjunctival hemorrhage in some microincisional ophthalmic surgeries. The aim of the current study was to determine if subconjunctival hemorrhage after 23G pars plana vitrectomy (PPV) could be prevented with the use of prophylactic topical brimonidine.

Main text

It was a phase III, prospective, interventional, randomized, controlled single-center clinical trial with a follow-up of 2 weeks. A total of 77 eyes (mean age: 68.4 ± 10.7 years) undergoing 23G PPV were included and randomized into 2 groups: group 1 including 41 patients receiving prophylactic preoperative treatment with brimonidine, and Group 2 (control group) including 36 patients not receiving this prophylactic treatment. Differences in terms of number of conjunctival quadrants affected with subconjunctival hemorrhage were evaluated in each of the follow-up visits. The presence of subconjunctival hemorrhage was similar in both groups the first days after surgery ($p > 0.05$). At the last visit, this condition was significantly more frequent in control group where there was a significant difference, being more frequent in the control group (7.3% vs. 28.6%, $p = 0.022$). The number of conjunctival quadrants affected was also similar in both groups, except for the last visit in which most of patients treated with brimonidine (92.7%) showed no bleeding compared to 71.4% in control group. No effect on the efficacy of brimonidine treatment of the presence of blood hypertension, diabetes and antiplatelet or anticoagulant treatment was observed.

Conclusions

Brimonidine seems to be a useful option to decrease subconjunctival hemorrhage after micro-incisional vitreoretinal surgery or improve its resolution during the first postoperative week. This finding should be mainly due to the vasoconstrictor effect of brimonidine.

Trial registration

EudraCT, 2012-002895-15. Registered 19 December 2012, <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2012-002895-15>

Background

Brimonidine tartrate is a selective alpha 2 adrenergic receptor agonist that is used for the treatment of ocular hypertension. It binds to alpha 2 adrenergic receptors located in the ciliary body and iris, reducing the production of aqueous humor and increasing uveoscleral drainage [1]. Brimonidine has been approved by the American Food and Drug Administration (FDA) as a 0.15% and 0.2% ophthalmic solution that reduces intraocular pressure in patients with open angle glaucoma or ocular hypertension [2]. It is

also available as a 0.33% topical ointment for treating non-transient facial erythema in adults with rosacea [3]. Additionally, it has shown its vasoconstrictor efficacy at low doses (0.025 to 0.2%), with the potential of reducing bleeding during ophthalmic surgery [4–6] or intravitreal injections [7], and consequently promoting a conjunctival whitening [8] prior to any eye surgery. Brimonidine’s cosmetic eye whitening effect has also been recently approved by the FDA [9].

Several studies have already investigated the prophylactic effect of brimonidine drops in preventing subconjunctival hemorrhage in some microincisional ophthalmic surgeries, such as intravitreal injections, cataract surgery, laser in situ keratomileusis (LASIK) or strabismus surgery [4–7]. To this date, there are no studies reported investigating this prophylactic effect after 23G microincisional vitreoretinal surgery. It should be considered that a decrease in the incidence of subconjunctival hemorrhage or postoperative hyperemia after this surgical procedure may significantly improve the postoperative discomfort and the esthetic result of this surgery. The hypothesis of the current research is that, given the vasoconstriction effect of this drug, its use may be beneficial to diminish the risk of conjunctival vascular damage during surgery, reducing the intra and postoperative bleeding.

Main Text

Patients

This study was a single-center, interventional, randomized (1:1), double blinded, controlled, prospective cohort, phase III clinical trial (EudraCT Eprobri: 2012-002895-15). A total of 77 eyes undergoing 23G micro-incisional vitreoretinal surgery were included and randomly assigned to one of two groups: group 1 including patients treated with brimonidine drops (2 mg/ml) (2 drops administered 15 minutes and 5 minutes before surgery) and group 2 (control group) including patients who underwent surgery without previous medication with brimonidine. Inclusion criteria for the clinical trial were men or women older than 18 years, who were going to receive 23G pars plana vitrectomy (PPV). Exclusion criteria included other surgeries such as conjunctival incision, known allergy to brimonidine, and subconjunctival hemorrhage in the study eye immediately before surgery. The sample of 77 eyes was recruited during a period of 52 months, from February 2013 until December 2016. All patients were informed about the nature of the study before their participation, only including those giving written informed consent. This clinical trial was conducted following the current Spanish and European legislation, respecting the standards of good clinical practice and according to the tenets of the Declaration of Helsinki. It was approved by the ethics committee of the Hospital.

Clinical protocol

The current clinical trial included a total of 4 visits:

- Visit 1: Inclusion visit (0–15 days before surgery). Patients were evaluated to confirm the fulfillment of the inclusion/exclusion criteria.

- Visit 2: Surgery day. Randomization was performed 30 minutes before surgery and pretreatment with brimonidine was prescribed in Group 1. After surgery, the surgeon performed the first postoperative external evaluation to detect the presence of subconjunctival hemorrhage. The analysis was performed in the 4 different quadrants and the area of extension of the hemorrhage was measured if it was present.
- Visit 3: Follow-up 1–3 days after surgery. A biomicroscopic analysis was performed in the 4 different quadrants and the area of extension of the hemorrhage was measured if it was present.
- Visit 4: Follow-up 10–14 days after surgery. The same analysis as in visit 3 was conducted.

The principal variable was the number of quadrants affected by subconjunctival hemorrhage in each of the follow-up visits. Measurements of the hemorrhage area were performed with a surgical caliper in visit 2 and using the slit lamp biomicroscope in visits 3 and 4. Secondary variables included presence of blood hypertension, diabetes mellitus, or antiplatelet or anticoagulant treatment.

Data analysis

The primary objective of the current clinical trial was to determine if subconjunctival hemorrhage after 23G PPV could be prevented or if its extension could be reduced with the preoperative use of brimonidine. The secondary objective was to determine if individual previous conditions (diabetes mellitus, blood hypertension, antiplatelet or anticoagulant treatment) could affect this potentially prophylactic effect.

Descriptive and inferential statistical analysis was performed using the SPSS software (IBM Corporation, Armonk, NY, USA). Chi-square independence test was used to evaluate the association between the presence of hemorrhage in each group and in each time-point. The Mann-Whitney test was used to assess the homogeneity in the distribution of the number of affected quadrants and maximum size in each time-point of the follow-up. Differences between treatment and control groups considering demographic and clinical factors were evaluated with the Pearson's Chi-square, Fisher's exact and Student t tests.

Results

The sample evaluated included 77 eyes from 77 patients, with a balanced distribution in terms of gender (male/female, 50.6%/49.4%). Age of patients recruited ranged from 28 to 86 years, with a mean value of 68.4 ± 10.7 years. A total of 41 patients were included in Group 1 (patients receiving prophylactic treatment with brimonidine) and 36 patients in Group 2 (control group). Both groups were homogeneous in terms of age ($p = 0.117$), gender ($p = 0.915$), treatment with antiplatelet ($p = 0.962$) or anticoagulant drugs ($p = 0.699$), and presence of blood hypertension ($p = 0.206$) and diabetes mellitus type I ($p = 0.679$) and II ($p = 0.735$).

Regarding the presence of subconjunctival hemorrhage, the rate of eyes affected in the first visit was similar in both groups ($p > 0.05$), with a minimal trend of a higher percentage of this condition in the group of untreated patients. In visit 4, a significant difference in the incidence of subconjunctival

hemorrhage was found between groups 1 and 2 ($p = 0.022$), with only 7.3% of eyes showing this condition in group 1 and 28.6% of eyes in group 2 (Fig. 1). The number of conjunctival quadrants affected by subconjunctival hemorrhage only differed significantly during the follow-up in the last visit ($p = 0.018$). Most patients treated with brimonidine (92.7%) did not show subconjunctival hemorrhage at the end of the follow-up, whereas this percentage was 71.4% in the control group or Group 2 (Fig. 2). In terms of severity, 8.6% of eyes of Group 2 had 2 or more quadrants affected compared to 4.9% of eyes in Group 1 (Fig. 2). The maximum diameter of the largest hemorrhage detected in each visit of the study was also measured, but differences between groups did not reach statistical significance (visit 2, $p = 0.587$; visit 3, $p = 0.685$; visit 4, $p = 0.876$).

Regarding the effect of antiplatelet and anticoagulant treatments, only 6 patients in Group 2 and 7 in Group 1 referred to take antiplatelet drugs, whereas anticoagulant treatments were prescribed in 4 patients in Group 2 and 3 in Group 1. Although there was a trend to a better hemorrhagic result in eyes in Group 1, differences between groups as a function of this type of treatments did not reach statistical significance ($p = 0.235$). The presence of high blood pressure or diabetes mellitus did not produce any relevant effect on the presence and extent of subconjunctival hemorrhage in both groups ($p \geq 0.065$).

No adverse effects or serious adverse effects were recorded throughout the clinical trial.

Discussion

This is the first study evaluating the potential benefit of the prophylactic use of brimonidine preoperatively in terms of decreasing the risk of conjunctival vascular damage during and after vitreoretinal surgery. Therefore, our results cannot be compared with any previous study. However, some previous research has demonstrated the preventive effect of brimonidine to avoid the occurrence of subconjunctival hemorrhage in other ophthalmic surgeries, such as laser in situ keratomileusis (LASIK), intravitreal injections, strabismus surgery and phacoemulsification cataract surgery [4–7]. In any case, it should be noted that vitreoretinal surgery is longer in duration and includes more manipulation of the ocular (conjunctiva-sclera-choroid) tissues, especially when introducing microcannulas, than other micro-incisional surgeries. In a case series study conducted in patients that underwent PPV for epiretinal membrane peeling or macular hole repair, ophthalmic brimonidine tartrate 0.1% (topical solution) was prescribed to be applied twice a day for a week before the surgery [10]. At the time of the surgery, most patients had a vitreous brimonidine concentration greater than 2 nM, and brimonidine at these concentrations is known to activate alpha 2 receptors in animal retinas, playing a neuroprotective role. In addition, the affinity of brimonidine for alpha 2 versus alpha 1 receptor is 790 times greater which allows for a greater and faster vasoconstrictor effect [4, 7].

Desco et al [5] studied the effect of brimonidine in terms of reducing the incidence of subconjunctival hemorrhage after cataract surgery. These authors concluded that the preoperative use of brimonidine could significantly reduce the incidence of this condition in subjects undergoing this surgical procedure. A case-control study was also conducted to evaluate the efficacy of brimonidine to reduce the level of

conjunctival and episcleral hyperemia, and postoperative bleeding after pterygium surgery [6]. This clinical research concluded that brimonidine reduced the level of postoperative bleeding in at least 50% of patients using this prophylactic treatment compared to a control group. Therefore, our results are consistent with those confirming the potential of brimonidine as a preventive treatment of subconjunctival hemorrhage in other types of ocular surgery. A recent metaanalysis from 4 clinical trials evaluating the efficacy and safety of 0.025% brimonidine tartrate as a topical vasoconstrictor for eye redness concluded that this pharmacological agent is effective reducing eye redness with a good safety and tolerance profile and without tachyphylaxis or rebound eye redness [11].

The level of anxiety in patients requiring vitreoretinal surgery is often high due to the severity of their pathology and the concern about surgery itself [12]. Vitrectomy surgery with the use of microcannulas has shortened the duration of the postoperative period, avoiding the need to use stitches, which has also reduced postoperative discomfort. Postoperative subconjunctival hemorrhage is very striking and is usually a cause of concern in patients and family members. In addition, a subconjunctival blood collection may worsen the ocular surface discomfort associated with this surgery [4]. Therefore, a simple maneuver, with less adverse effects, such as brimonidine instilling, can provide some benefits to patients undergoing vitreoretinal surgery. In the current study, no difference in the prophylactic effect of brimonidine was found between patients taking antiplatelet drugs and those with no medication (control group), as in a previous study evaluating the preventive after another type of ocular surgical intervention [5]. In any case, it should be noted that only 6 patients in the control group and 7 in the treatment group took antiplatelet drugs in the current series.

Conclusions

In conclusion, the prophylactic use of brimonidine before micro-incisional vitreoretinal surgery seems to be useful to decrease the incidence of subconjunctival hemorrhage postoperatively and to accelerate its resolution in the first postoperative week, minimizing patient discomfort and aesthetic discomfort. This finding is mainly due to the vasoconstrictor effect of brimonidine. Future studies with larger sample sizes are needed to corroborate these findings.

Abbreviations

FDA
Food and Drug Administration
LASIK
laser in situ keratomileusis
PPV
pars plana vitrectomy

Declarations

Ethics approval and consent to participate

This study was approved by the ethics committee of FISABIO Valencia (EudraCT Eprobri: 2012-002895-15). All patients were informed about the study prior to their inclusion and signed a written informed consent before being examined.

Consent for publication

Not applicable.

Competing interests

No competing interests of any of the authors participating in the study

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Authors' contributions

M Carmen Desco (concept, data analysis, data gathering, writing of the manuscript, supervision), Julio Cesar Molina Martín (concept, data gathering, critical revision of the manuscript, supervision), Jorge Mataix-Boronat (data gathering, critical revision of the manuscript, supervision), Isabel Pascual-Camps (data gathering, critical revision of the manuscript, supervision), Elena Palacios-Pozo (data gathering, critical revision of the manuscript, supervision), Marisa Barón-García (data gathering, critical revision of the manuscript, supervision), David P Piñero (concept, data analysis, critical revision of the manuscript, supervision), Amparo Navea-Tejerina (concept, data analysis, data gathering, writing of the manuscript, supervision, coordination). All authors read and approved the final manuscript.

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Not applicable.

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Figures

Incidence of subconjunctival hemorrhage

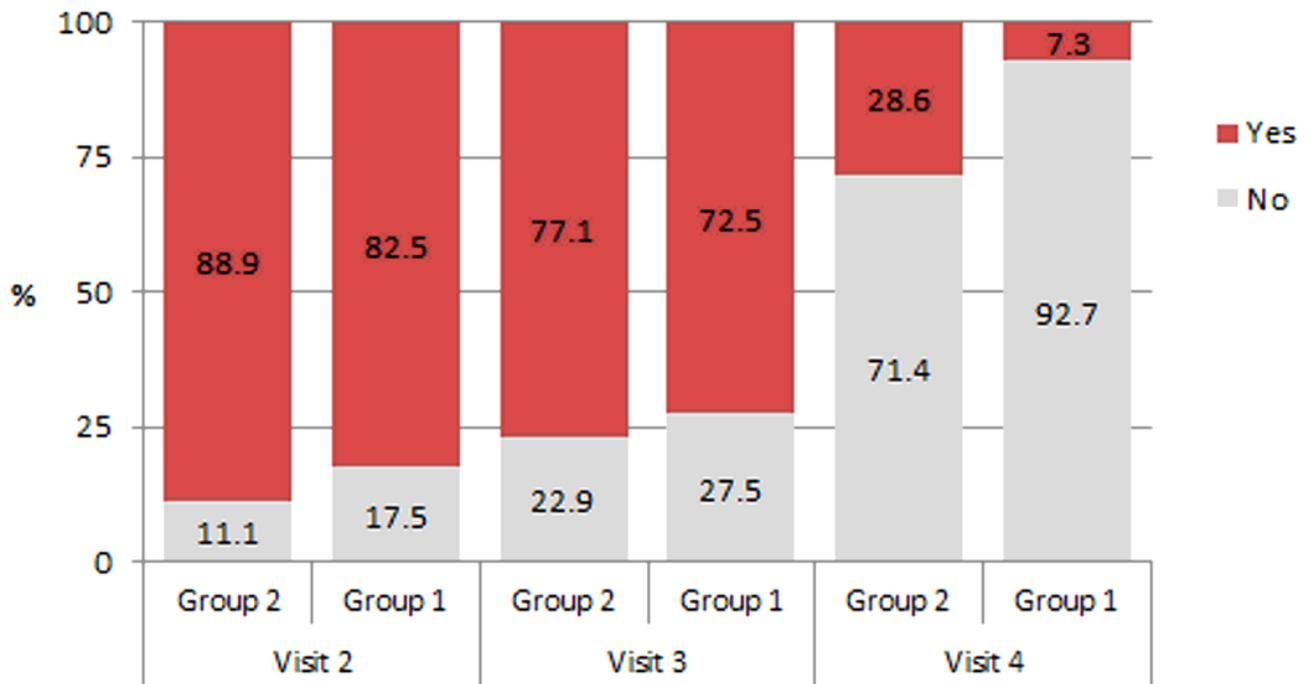


Figure 1

Incidence of subconjunctival hemorrhage in groups 1 (brimonidine group) and 2 (control group) of the current study during the follow-up.

Number of conjunctival quadrants affected by subconjunctival hemorrhage

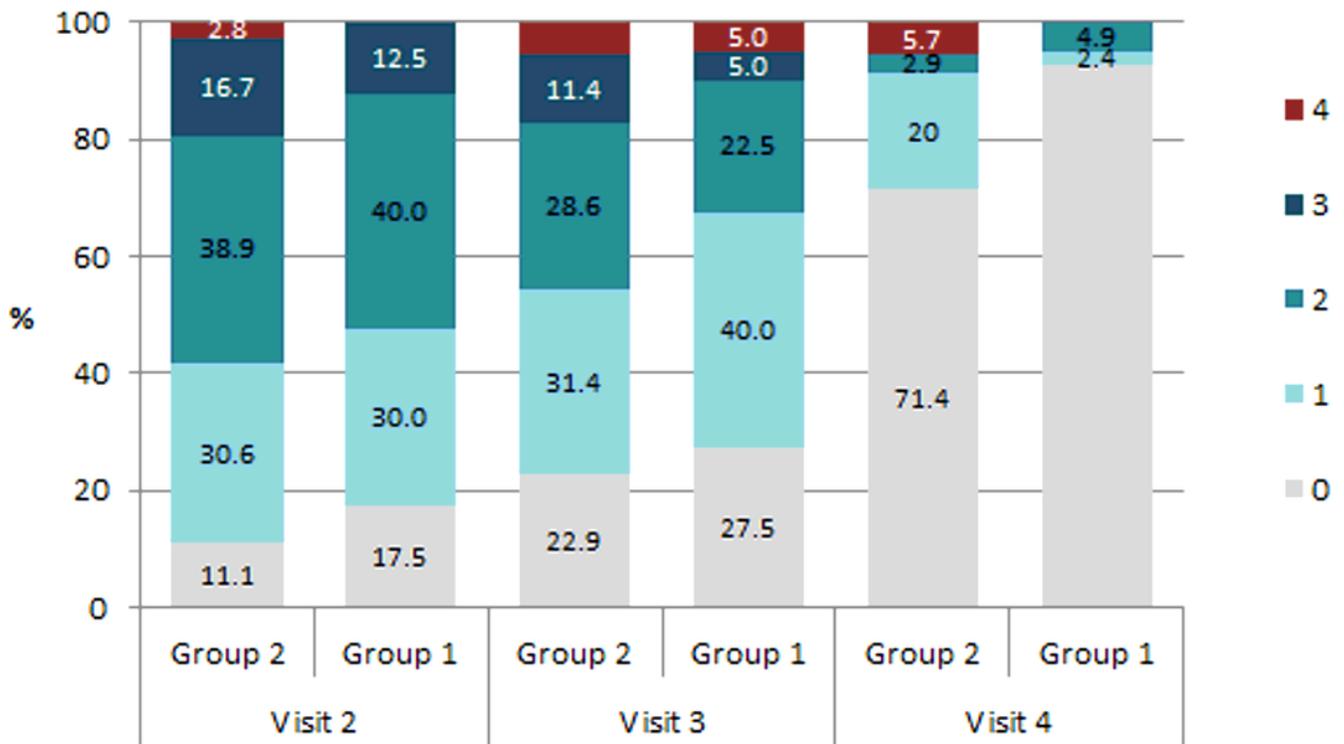


Figure 2

Number of conjunctival quadrants affected by subconjunctival hemorrhage in groups 1 (brimonidine group) and 2 (control group) of the current study during the follow-up.