Effectiveness of apraclonidine 1% in preventing intraocular pressure rise following macular hole surgery

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Abstract

Aim—To determine the efficacy of apraclonidine hydrochloride 1% in preventing intraocular pressure (IOP) spikes following idiopathic macular hole (IMH) surgery with platelet adjunct and intraocular gas tamponade.

Methods—This is a prospective, double masked, randomised study to compare apraclonidine hydrochloride 1%, an α2 agonist, with a placebo in the prevention of IOP rises following macular hole surgery. Each patient was randomly selected to receive either the study drug or the placebo; one drop was instilled in the conjunctival sac 2 hours preoperatively and on completion of the procedure. IOP was measured at baseline and at 1, 3, 6, 24, 48 hours, and 2 weeks postoperatively. Blood pressure and heart rate were also recorded at baseline and at 3 and 24 hours postoperatively. Macular hole repair surgery was performed as standardised in the unit with a vitrectomy, platelet concentrate, and complete fill of the vitreous cavity with perfluoropropane gas (C3F8) at a concentration of 16%.

Results—25 patients (26 eyes) were enrolled. 12 eyes received apraclonidine hydrochloride 1% (mean age 70.7; range 62–78 years) and 14 eyes received the placebo (mean age 70.0; range 57–81 years). At baseline evaluation the mean IOP was 15.6 mm Hg for the study group and 14.3 mm Hg for the placebo group. The mean postoperative IOP at 1 hour, 3 hours, 6 hours, and 24 hours was 10.6, 9.6, 8.2, and 14.0 mm Hg in the apraclonidine group. In the control group at the same time intervals the mean IOP was 23.4, 17.5, 19.2, and 24.7 mm Hg. These readings were statistically significant different: 1 hour (p=0.0001); 3 hours (p=0.0015); 6 hours (p<0.0001); and 24 hours (p=0.019), the readings at 48 hours and 2 weeks were not statistically significant different (p=0.15 and p=0.59). Only one of the patients in the study group had an IOP above 25 mm Hg at any time. In the control group an IOP above 25 mm Hg was found in seven patients (50%) at the 1 hour postoperative measurement. At 2 weeks the IOP was recorded below 25 mm Hg in all patients. No statistically significant difference was noted between the two groups regarding the systolic or diastolic blood pressure values and the heart rate records. No local or systemic adverse reactions were observed.

Conclusions—Apraclonidine hydrochloride 1% appears to be an efficacious and safe drug in the prophylaxis of early postoperative IOP elevations in patients undergoing macular hole surgery.

Macular hole surgery has become increasingly successful since it was first described.1 Protocols are varied, depending on the use of different types and concentrations of tamponading agents or the use of adjuvant substances in promoting healing (recombinant or bovine transforming growth factor β, (TGFβ)), autologous platelet concentrate, or tissue glue).2–4 Specific complications related to this procedure have been reported, including visual field defects and sustained intraocular pressure (IOP) elevation.5–7 Raised IOP is even more pronounced when adjuvants are used.4 The incidence of raised IOP (more than 30 mm Hg) varies between 15% and 22% of patients in the first 24 postoperative hours.7 In a significant number of patients this transient rise can last up to 2 weeks.8–11 The complication of raised postoperative IOP is potentially preventable with prophylactic pharmacological treatment. Apraclonidine hydrochloride 1% is successful in the prevention of IOP rises following YAG capsulotomy, argon laser trabeculoplasty, cyclopedia, and cataract extraction.10–11

We conducted a prospective, randomised, double masked study to determine the efficacy of apraclonidine hydrochloride 1% to control these IOP spikes following surgery for macular hole repair.

Patients and methods

The study was designed accordingly to the Declaration of Helsinki standards. Local ethics committee and the Medicine Control Agency approval for the study was obtained. Exclusion criteria were: history of glaucoma, ocular hypertension, previous ocular surgery, or ocular laser treatment, active ocular inflammation, uniconular patients, patients affected by cardiovascular, pulmonary, or renal disease with the exception of medically controlled systemic hypertension. Patients were also excluded if they were taking systemic sympathomimetics, monoamine oxidase inhibitors, or tricylic antidepressants, and if they were known to have had hypersensitivity reactions to clonidine derivatives.
Twenty five consecutive patients affected by idiopathic macular hole (IMH) meeting these entry criteria were enrolled in the study. Patients were then counselled preoperatively on the purpose of the study and written informed consent was obtained to participate.

All eligible patients underwent full preoperative ophthalmological examination, including best corrected visual acuity for near and distance, slit lamp biomicroscopy of the anterior segment, and dilated funduscopy, and also electrocardiogram and blood glucose analysis. Baseline evaluation of the main outcome measurement, IOP, was recorded with a Goldmann applanation tonometer. Blood pressure and heart rate were also recorded. Patients were then randomly assigned to the study or placebo group. The randomisation code was obtained from computer generated random number table; this assigned a random number to each identical Minims for each sequential patient before commencement of the study. All Minims sachets were identical apart from the identification number to ensure absolute masking of the study at the time of instilling drops and also when the IOP was measured. One drop (approximately 30 μl) of the study drug (apraclonidine hydrochloride 1%) or placebo (sodium chloride 0.9%) was instilled in the conjunctival sac 2 hours preoperatively.

Pupil dilatation was started 1 hour before surgery with one drop each of phenylephrine 10% and cyclopentolate 1%. This was repeated after 15 and 30 minutes. Patients received also one drop of diclofenac 4% at the same timings.

Local anaesthesia was obtained by a peribulbar block technique. Between 7 and 10 ml of a mixture of 50% of bupivacaine 0.5% and lignocaine 2%, with the addition of 300 IU of Hylase, were injected inferotemporally (70%) and medially (30%).

A single experienced vitreoretinal surgeon (AGC) carried out the surgical procedure as follows: three port pars plana vitrectomy with self sealing sclerotomies, removal of the posterior cortical hyaloid, and careful epiretinal membrane dissection if judged clinically significant. Air-fluid exchange was repeated after 5 minutes, and 0.1 ml of autologous platelet concentrate was used as adjuvant.17 Perfluoropropane gas (C3F8) at a concentration of 16% was exchanged to achieve a complete fill of the vitreous cavity.

On completion of surgery patients received a subconjunctival injection of cefuroxime 125 mg and betamethasone 2 mg diluted in 2 ml of sterile water. One drop of the study drug or the placebo, depending on randomisation, was instilled in the conjunctival sac. The eye was then covered with Jelonet, a double pad, and a shield. No other systemic or topical IOP lowering agents other than apraclonidine hydrochloride 1%, where applicable, were administered at the time of surgery.

Strict supine position was maintained for the first 24 hours. At 1 hour, 3 hours, and 6 hours postoperatively the IOP was measured with a calibrated Perkins applanation tonometer by the same clinician (AS), who also recorded all subsequent IOPs at 24 and 48 hours and at 2 weeks. To ensure reliability between the Perkins and Goldmann tonometer these were cross checked at the beginning of the study. At 24 hours patients were examined on the slit lamp and the IOP was measured with a Goldmann tonometer. Blood pressure and heart rate were taken at 3 hours and 24 hours postoperatively by a trained nurse.

Patients were then commenced on dexamethasone 0.1% and neomycin 0.5% ointment twice a day and instructed to posture prone or maintain a face down position for the following 2 weeks. The subsequent IOP recordings at 48 hours and 2 weeks were obtained again with a Goldmann tonometer. All patients were examined postoperatively to assess the gas bubble size as part of a full ophthalmic examination.

Based on a power of 90% and an α of 0.05, and assuming an effectiveness of 25% for the placebo (π2) and of 80% for the study drug (π1), the calculated sample size was of 12 eyes in each group. Considering the eventuality of dropouts for various reasons we recruited a slightly larger number of patients. Only at the end was the code broken and the data collected analysed. A statistician performed the statistical analysis with the software package STATA. We used two sample Student’s t-test with equal variance to calculated significance and also determined the 95% confidence intervals for each postoperative measurement.

Results

After randomisation, 12 eyes were assigned to the study group and 14 eyes to the placebo group; all patients completed the trial. The demographic data of the two groups are presented in Table 1. In the study group 11 eyes were diagnosed with a stage III IMH and one with stage IV. In the placebo group 10 eyes were affected by a stage III and four eyes by a stage II IMH. Mean symptoms duration was 6 (SD 3.05) months in the study group and 5.35 (3.70) months in the placebo group.

All surgical procedures were eventful and, in particular, none required lens extraction or cryotherapy for intraoperative complications.

INTRAOCULAR PRESSURE

The mean preoperative IOP was 15.6 (2.6) mm Hg in the study group and 14.3 (2.0) mm Hg in the control group.

The mean IOP at 1 hour was 10.6 (7.0) mm Hg in the apraclonidine group and 23.4 (6.4) mm Hg in the placebo group with a difference of 12.7 mm Hg (95% confidence intervals 18.2 to 7.2, p=0.0001). At 3 hours means were 9.6 (4.2) mm Hg and 17.5 (6.5) mm Hg in the apraclonidine and the study group respectively, with a difference of 7.9 mm Hg (95% confidence intervals 12.4 to 3.3, p=0.0015). At 6 hours the respective values as above were 8.2 (3.7) mm Hg and 19.2 (6.8) mm Hg, with a difference of 11.0 mm Hg (95% confidence intervals 15.6 to 6.4, p<0.001). For the 24 hours measurement, again the respective values were 14.0 (5.7) mm Hg and 24.7 (13.8) mm Hg, with a difference of 10.7 mm Hg.
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that the difference could be related to the adjuvant used.

There are several mechanisms that could explain IOP spikes following macular hole surgery. In our view the most plausible reasons, which are strictly related to this particular type of vitreoretinal surgery, are the presence of intraocular gas, an inflammatory reaction caused by the surgery and the adjuvant (platelets aggregate). These can affect both the ciliary body and the trabecular meshwork function. Another interesting mechanism proposed by Massicotte and Shuman is the obstruction of aqueous outflow by the residual anterior hyaloid. This could theoretically explain the transient IOP rise in our patients since they were all phakic and none required intraoperative lens extraction. However, we did not notice a shallow anterior chamber in any of our patients. We could speculate that in our case series the IOP was not sufficiently high to make this process irreversible as occurred in Massicotte’s patients.

There is clear evidence that apraclonidine hydrochloride 1% is the drug of choice in the management of short term IOP spikes. Clinical studies have demonstrated the efficacy of apraclonidine hydrochloride 1% in reducing the aqueous flow rate up to 35–45% at 3 hours, and also to increase the trabecular outflow facility. This effect is more pronounced when apraclonidine acts on an uninflamed ciliary body.

With this concept in mind it appears logical to pretreat eyes with an agent such as apraclonidine hydrochloride 1% to allow maximum effect on the ciliary body before the iatrogenic inflammatory reaction is induced. Apraclonidine hydrochloride 1%, unlike clonidine, does not cross the blood–brain barrier, and has been proved to be relatively safe and effective in avoiding complications such as systemic hypotension and bradycardia.

The question whether a short spike of the IOP might have a harmful effect on the ocular tissues, and specifically on the optic nerve head axons might be debatable. It is known from experimental models that an elevated IOP compromises the optic nerve head blood flow, which in turn could affect axonal transport. This vascular theory of axonal damage is probably less important in this mechanism compared to the mechanical one. Anderson and Hendrickson first demonstrated the impairment of the rapid component of the orthogonal axonal transport in owl monkey eyes during transient IOP elevations as short as 6–8 hours. Discrete accumulations of the radioactive isotope leucine, injected intravitreally, were observed in the lamina cribrosa and also as far as in the lateral geniculate nucleus. Minkler likewise found accumulations of granular material in the monkey optic nerve head after only 4 hours following an IOP elevation between 30 and 50 mm Hg. It is presumed that these granular accumulations are an expression of axonal blockage, and are first observed in the posterior lamina cribrosa when the IOP is kept at 30 mm Hg. The same author proved that the orthogonal axonal transport is equally affected by modest elevations of the IOP, at levels of 25 mm Hg, even if the partial arterial oxygen tension was kept at levels of 100 mm Hg.

It is also true that it remains to be verified at what time point such processes become irreversible. Quigley and Anderson showed that it is possible to reverse the axonal blockage if the IOP returns to normal levels within 4 hours.

With this evidence it reasonable to argue that it would be advantageous to maintain an IOP below 30 mm Hg to avoid axonal damage at the optic nerve head.

In conclusion, our results demonstrate that apraclonidine hydrochloride 1% is effective in controlling IOP spikes in the immediate postoperative period. This drug is demonstrated to be safe in the short term and we would thus recommend the use of prophylactic apraclonidine hydrochloride 1% for patients undergoing macular hole surgery with adjuvants to prevent IOP elevations.

Presented at the Association for Research in Vision and Ophthalmology meeting on the 13 May 1998.

The authors have no financial interest in any of the products mentioned.


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Br J Ophthalmol 2001 85: 164-168
doi: 10.1136/bjo.85.2.164

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