THE USE OF TOPICAL AQUEOUS SUPPRESSANTS IN THE PREVENTION OF POSTOPERATIVE INTRAOCULAR PRESSURE ELEVATION FOLLOWING PARS PLANA VITRECTOMY WITH LONG-ACTING GAS TAMPONADE*

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ABSTRACT

Purpose: To determine if topical aqueous suppressant therapy applied after pars plana vitrectomy (PPV) with gas tamponade successfully prevents postoperative elevation of intraocular pressure (IOP).

Methods: A prospective, controlled study was performed on patients who met inclusion criteria and underwent PPV with gas tamponade (SF_6 18%-20% or C_3F_8 12%-16%) over a 1-year period. Treatment eyes received topical aqueous suppressants at the end of surgery. Postoperative IOP checks were performed at 4 to 6 hours, 1 day, and 1 week.

Results: Twenty-one control (C) and 20 treatment (T) eyes met the inclusion criteria. The IOP (in mm Hg) measured at 4 to 6 hours (23.05 [C], 14.73 [T]) and 1 day (23.24 [C], 17.28 [T]) postoperatively showed a statistically significant difference between the groups (P =.0038) at 4 to 6 hours, and a trend toward significance (P =.057) at 1 day. Eleven control and 3 treatment eyes had an IOP spike above 25 mm Hg at 4 to 6 hours or 1 day postoperatively (P =.02), and 6 control and 1 treatment eye had a

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postoperative IOP above 30 mm Hg. A pressure rise above 40 mm Hg was seen in 2 control eyes and no treatment eyes.

Conclusions: Use of topical aqueous suppressants following PPV with long-acting gas tamponade is effective in preventing significant postoperative IOP elevation in a majority of cases.

INTRODUCTION

Pars plana vitrectomy (PPV) combined with the instillation of a long-acting gas tamponade, even in nonexpansile concentrations, can cause elevated intraocular pressures (IOP) in the early postoperative period.[1-3] Surgeons at many institutions regularly perform postoperative IOP checks during the time of maximal gas expansion (4 to 8 hours following injection), while others forego this measurement, potentially risking visual loss if the IOP is markedly elevated.[4] Still others will prophylactically give intravenous or oral acetazolamide at the end of the surgical procedure, even though it is unknown whether this therapy is effective.[5]

We undertook a prospective, controlled study to determine (1) the incidence of significant IOP elevations after PPV with long-acting gas tamponade, (2) whether therapy with topical aqueous suppressants applied at the end of surgery would prevent significant IOP elevation, and (3) whether this prophylactic measure would negate the need for a postoperative IOP check (in 2 to 6 hours). We chose topical therapy because of the high incidence of sulfa allergy in the general population, which precludes the use of oral or intravenous acetazolamide in many cases. Acetazolamide also causes a postoperative diuresis, which can be problematic in patients who need to maintain a face-down position and in those who may have difficulty ambulating after surgery owing to decreased vision.

METHODS

A prospective, controlled study was performed on all consecutive patients who met inclusion criteria and underwent PPV with instillation of a long-acting gas (SF_6 or C_3F_8) at the Medical College of Wisconsin Eye Institute Vitreoretinal Service, Milwaukee, from November 1996 through November 1997. Patients with a history of glaucoma or uveitis were excluded. Also excluded were those who underwent procedures in which a viscoelastic was injected intraocularly for concurrent cataract extraction or to coat the posterior surface of an intraocular lens to enhance visualization during an air-fluid exchange. The first 20 consecutive patients who met inclusion criteria were assigned to the control group, and the next 20

patients were selected for the treatment group. The next 4 consecutive patients were assigned to the control group because 3 patients in the first set of controls did not meet all of the exclusion criteria.

A standard three-port vitrectomy was performed on all patients with placement of an inferotemporal infusion cannula and two superior sclerotomies for bimanual surgery. After completion of an air-fluid exchange and closure of one of the superior sclerotomies, a mixture of long-acting gas was injected through the infusion port while the remaining sclerotomy was held open. About 45 cc of the gas mixture was instilled by this method, ensuring a complete exchange of gas for air. The surgeon personally diluted the gas mixture with sterile air prior to injection into the eye in each case. Only nonexpansile or minimally expansile concentrations of gas were used (SF_6 18%-20% or C_3F_8 12%-16%). If general anesthesia was used for the procedure, no nitrous oxide was administered. No growth factors were used for macular hole surgeries.

The intraocular pressure was measured in each case after closure of the three sclerotomies and before conjuctival closure using a Tonopen (Mentor O and O, Norwell, Mass). The Tonopen was calibrated prior to each use, and only measurements with less than 5% error were used. Only those eyes with an IOP at the end of the case between 10 and 23 mm Hg were included in the study.

Treatment eyes then received 1 drop of 3 of the following topical aqueous suppressants in multidose vials stored in the recovery room of the Eye Institute: timolol maleate 0.5%, apraclonidine hydrochloride 0.5%, dorzolamide hydrochloride 2%, or brimonidine tartrate 0.2%. Three different medications were used because pilot data suggested that the problem of postoperative IOP increase in this surgical setting was severe and that 1 or 2 topical aqueous suppressants may not be sufficient to produce a dramatic treatment effect. Drops were administered one at a time and 5 to 10 minutes apart. The eyes were patched in between administration of drops. Patients with a history of heart or lung disease did not receive timolol, and patients with a sulfa allergy did not receive dorzolamide.

Postoperative IOP checks were performed at 4 to 6 hours, 1 day, and 1 week postoperatively. All measurements were performed with the Tonopen after calibration of the instrument. As stated, only measurements with less than 5% error were recorded. If the IOP was elevated during the postoperative period studied, one of the following regimens was used for treatment: For IOP of 26 to 30 mm Hg, observation or repeated administration of 1 or 2 of the topical aqueous suppressants. For IOP of 31 to 40 mm Hg, repeated administration of 3 of the topical medications. For IOP greater than 40 mm Hg, repeated administration of 3 of the topical medications, oral or intravenous acetazolamide (500 mg), and if no effect on IOP was noted, an anterior chamber paracentesis performed via a 30-

gauge needle at the limbus without removing any of the intraocular gas. A slit-lamp examination was performed on postoperative day 1 and the anterior chamber cell and flare was recorded using a standard scale of 1 through 4 , with 1 representing minimal and 4 maximal inflammation. The anterior chamber depth, both peripheral and central, was also carefully examined with a fine slit beam. The presence of fibrin or hemorrhage in the anterior chamber was noted as well.

Data recorded for each patient included (1) preoperative diagnosis, (2) type of surgery performed, (3) phakic, pseudophakic, or aphakic status at end of surgery, (4) prior surgical procedures performed, if any, (5) IOP at end of case and at 4 to 6 hrs, 1 day, and 1 week postoperatively, and (6) the anterior segment examination on postoperative day 1. The data were analyzed using repeated measures ANOVA for continuous measurements, Fisher's exact test for count data, and the paired Student's t test for paired data.

RESULTS

A total of 21 control eyes and 20 treatment eyes met the inclusion criteria and had complete follow-up data. There was an overall treatment effect when comparing all measurements from the control and treatment groups using a repeated measures ANOVA test (P =.0006), and this effect varied with respect to different time points postoperatively (P =.0002). The IOP measured at the end of surgery was not significantly different between the 2 groups (mean 15.33 mm Hg for the controls [C] and 14.18 mm Hg for the treatment group [T]). The IOP measured at 4 to 6 hours (mean 23.05 C, 14.73 T) and at 1 day postoperatively (mean 23.24 C, 17.28 T), however, showed a difference between the groups, with the treatment eyes demonstrating a much lower average IOP (Table I). A repeated measures ANOVA test comparing differences between the 2 groups back to IOP at the end of the case showed a statistically significant difference at 4 to 6 hours (P =.0038) and a trend toward significance at 1 day (P =.0567) (Table I). At the 1-week postoperative time point, the IOP measured for both groups (mean 17.90 C, 16.75 T) again showed no appreciable difference.

TABLE I: ANALYSIS OF TREATMENT EFFECT OVER TIME

TIME OF MEASUREMENT	IOP IN CONTROL EYES, MM HG (SD)	IOP IN TREATMENT EYES, MM HG (SD)	*P* VALUE
End of case	15.33 (3.28)	14.18 (3.29)	
4-6 hours	23.05 (7.75)	14.73 (6.42)	.0038
1 day	23.24 (7.62)	17.28 (6.64)	.0567
1 week	17.90 (6.13)	16.75 (5.48)	.9986

TABLE II: COMPARISON OF IOP RISE IN EARLY POSTOPERATIVE PERIOD BETWEEN CONTROL AND TREATMENT EYES

	IOP AT END OF CASE, MM HG	IOP AT 4-6 HR, MM HG	*P* VALUE*: END OF CASE VERSUS 4-6 HRS.	IOP AT 1 DAY, MM HG	*P* VALUE*: END OF CASE VERSUS 1 DAY
Control eyes	15.33	23.05	0.00008	23.24	0.00009
Treatment eyes	14.18	14.73	0.4	17.28	0.05

*Paired *t*-test.

When the control group's baseline IOP was compared to the IOP at 4 to 6 hours and 1 day, a statistically significant rise in pressure in this early postoperative period was noted (Table II). Evaluation for an IOP spike greater than 25 mm Hg during the early postoperative period (4 to 6 hours or 1 day postoperatively) showed that 11 control eyes and 3 treatment eyes had an IOP above this level, a difference that was statistically significant using the Fisher's exact test ($P = .02$). Seven control eyes and only 1 treatment eye had an IOP greater than 25 mm Hg at the 4- to 6-hour time point. Evaluation for an IOP spike above 30 mm Hg showed 6 control eyes and 1 treatment eye achieving a pressure above this level in the early postoperative period ($P = .09$ with Fisher's exact test). A pressure rise above 40 mm Hg was seen in 2 control eyes and no treatment eyes. Eight eyes received treatment for an elevated IOP in the early postoperative period in the control group, while 3 eyes underwent therapy in the treatment group. Both eyes that had a pressure spike above 40 mm Hg in the control group required an anterior chamber paracentesis for IOP control. The IOP was 25 mm Hg or greater at 1 week postoperatively in 4 control and 2 treatment eyes. Both of the eyes in the treatment group that spiked at 1 week did not exhibit a pressure rise above 25 mm Hg in the early postoperative period.

Comparison of the diagnosis, type of surgery, and prior surgery data revealed differences between the control and treatment groups. Control group diagnoses included 6 retinal detachments with a recent or remote history of trauma, 5 macular holes, 4 diabetic traction or combined traction/rhegmatogenous retinal detachments, 3 retinal detachments with proliferative vitreoretinopathy (PVR), 2 rhegmatogenous retinal detachments (RRDs) without diabetic changes or PVR, and 1 subretinal hemorrhage. Treatment group diagnoses included 8 diabetic traction or combined traction/rhegmatogenous retinal detachments, 4 macular holes, 2 retinal detachments with PVR, 2 RRDs, 2 subretinal hemorrhages, 1 retinal detachment with a history of trauma, and 1 choroidal neovascular membrane. Pars plana lensectomy was performed in 4 control eyes and 2 treat-

ment eyes. A scleral buckle was placed in 11 control eyes (6 in eyes with a prior history of trauma) and 4 treatment eyes. Intraoperative laser with over 1,000 spots placed was performed in 4 control eyes and 2 treatment eyes. Finally, prior intraocular surgery was performed in 12 control eyes (5 trauma eyes) and 6 treatment eyes. Given these differences, a multiple regression analysis adjusting for lensectomy, scleral buckle, and trauma differences between the 2 groups was performed, but no statistically significant relationships between these variables and IOP were found.

The 2 groups did not differ significantly with respect to preoperative presence of a scleral buckle, lens status after surgery, or anterior-segment inflammation after surgery. The control group had 3 eyes and the treatment group 2 eyes that had had a scleral buckle placed in a previous surgery. The lens status at the end of surgery for the control group included 4 eyes pseudophakic, 5 eyes aphakic, and 12 eyes phakic, while the treatment group had 2 eyes pseudophakic, 3 eyes aphakic, and 15 eyes phakic. There were no significant differences between the grade of cell and flare on postoperative day 1 for the control and treatment eyes, but 2 treatment eyes did have a fibrin reaction, and 1 treatment eye had a small amount of hemorrhage.

DISCUSSION

In 2 recent retrospective series, the incidence of postoperative IOP elevation following PPV with long-acting gas tamponade was reported. Chen and Thompson[3] demonstrated a 43% incidence of IOP elevation above 25 mm Hg, and Chen[1] demonstrated a 52% IOP rise above 30 mm Hg. Clearly, IOP can be a significant problem in the early postoperative period in these patients and can potentially cause visual impairment if sustained. This is the basis for the 4- to 6-hour postoperative IOP check at our institution. The control group in our study had a similar incidence of IOP elevation as in these studies, with 52% achieving an IOP above 25 mm Hg and 29% above 30 mm Hg. The treatment group, however, which received 3 topical aqueous suppressant drops immediately after surgery, had a significant decrease in IOP spikes postoperatively, with 15% achieving an IOP above 25 mm Hg and 5% above 30 mm Hg.

As has previously been shown, a number of factors are associated with a postvitrectomy IOP elevation[2] These include the concurrent placement of a scleral buckle, extensive photocoagulation, performance of a lensectomy during the procedure, and postoperative fibrin membranes. For this reason, the control and treatment groups were carefully analyzed, and an increased number of scleral buckle procedures were noted in the control group. There was also a higher number of patients with a recent or remote history of prior trauma in the control group, which could potentially cause

a predisposition for elevated IOP postoperatively. To determine if these differences had influenced our IOP outcomes, we reanalyzed the data using a multiple regression analysis adjusting for differences in lensectomy, scleral buckle, and trauma rates between the control and treatment groups and found that there was no statistically significant relationship between these variables and IOP in this study.

The Tonopen is a pressure-measuring device that has a number of advantages over other methods of IOP measurement in postvitrectomy patients.[6] Applanation of the tip of the Tonopen, which is covered by a single latex cover, results in the activation of a strain gauge that converts the IOP into an electrical signal. Several readings are averaged automatically, and a final digital reading with a coefficient of variance is displayed. The unit is hand-held, is easily portable, and can be used without accessory instruments. Furthermore, the tips used with the device can be ethyleneoxide sterilized.[7] Most important for postvitrectomy patients, the instrument is accurate, even with an irregular or absent corneal epithelium.

The Tonopen is generally thought to be nearly as accurate as the Goldmann tonometer for measuring IOP in the normal range when tested on normal and glaucomatous eyes.[6,8] Controversy exists, however, regarding its accuracy for extremely low or high pressures. Some investigators have shown that it underestimates pressures of more than 30 mm Hg and overestimates pressures of less than 9 mm Hg, while others claim that it is more accurate for IOP of more than 24 mm Hg.[8]

Accurate pressure measurement in a gas-filled eye is difficult because the presence of a compressible gas results in an underestimation of the IOP by indentation tonometry. Studies comparing the Schiotz tonometer, Perkins (hand-held Goldmann) tonometer, and pneumotonometer have shown that the Schiotz is extremely unreliable in gas-filled eyes, while the pneumatic and Perkins tonometers show a small to moderate underestimation of the IOP.[9,10] The Perkins tonometer is the most accurate of the three but requires an intact corneal epithelium for optimal use. Hines and associates[11] compared the Tonopen and pneumotonometer to the Goldmann in a large clinical study and found that the Tonopen was more accurate for eyes with an IOP greater than 25 mm Hg. The Tonopen underestimated the IOP only 8% of the time, while the pneumotonometer underestimated it 51% of the time. The pneumotonometer was especially inaccurate for IOPs in the 30- to 40-mm Hg range in this study. A follow-up clinical and manometric study by Lim and colleagues[12] in 1990, however, did not show any significant differences between the pneumotonometer and Tonopen. Both methods in this study underestimated the IOP to a similar extent, especially when the IOP was greater than 30 mm Hg.

Badrinath and coworkers[7] in 1993 developed a calibration curve for the

Tonopen for use with air-filled vitrectomized eyes by studying the intraocular pressure measured with the Tonopen and comparing it with the manometric pressure. In their model a Tonopen pressure of 20 corresponded to an actual IOP of 24.78, 25 =30.77, and 30 = 36.73 (all measurements in mm Hg). Taking into account all of the available information, we felt that the Tonopen was as reliable as any other method for measuring the IOP in postvitrectomy gas-filled eyes. Realizing that the IOPs obtained with the Tonopen were probably not as high as the actual pressure inside the eye, we chose to designate a spike above 25 mm Hg as significant. Our study shows that postoperative topical aqueous suppressant therapy is able to effectively decrease the incidence of significant IOP elevations, as defined above, for pars plana vitrectomy surgery with long-acting gas tamponade.

Long-acting gas concentrations thought to be "nonexpansile" were used in this study. While there is controversy regarding an exact nonexpansile concentration for both SF_6 and C_3F_8, the amounts used were similar to those described in other experimental and clinical studies as "nonexpansile."[13] It has previously been shown that there is no significant difference in postoperative IOP between eyes receiving 12% or 20% C_3F_8, and therefore the small differences in gas concentrations used after vitrectomy in this study are not likely to play a major role in early postoperative IOP elevation.[14] We chose to check the pressure postoperatively at 4 to 6 hours because if any small expansion of the gas does occur, it will be maximal at this time.

We found that instillation of topical aqueous suppressants significantly lowered the IOP at 4 to 6 hours and at 1 day postoperatively when compared with the end-of-case measurement. Furthermore, this decrease was in direct contrast to control eyes, which had a significant increase in IOP during this same period (average, 8-mm Hg increase). Most important, our study shows that use of postoperative aqueous suppressants is able to reduce the percentage of eyes with IOP spikes above 25 mm Hg (52% of control eyes, 15% of treatment eyes) and 30 mm Hg (29% of control eyes, 5% of treatment eyes) in the early postoperative period, thus potentially decreasing the risk of visual loss from elevated IOP. The medications can be easily administered to patients before they go home after the operation. Since multidose vials of these medications can be used, the overall cost per patient is less than that of intravenous or oral acetazolamide.

With the significant effects seen with topical aqueous suppression, one may question the need for a postoperative IOP check at 4 to 6 hours. At this time, we still recommend that patients who have a history of glaucoma or whose vitreous surgery involved viscoelastic material have their pressure checked after surgery when a long-acting gas

tamponade is used, because our study excluded patients with these conditions. Further study is under way to determine if 1 or 2 topical aqueous suppressants are sufficient to achieve the same treatment effect seen in this study.

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DISCUSSION

DR GEORGE W. WEINSTEIN. The study by Dr Mittra and colleagues investigates an important topic involving patients who undergo pars plana vitrectomy together with gas tamponade: the elevation of intraocular pres-

sure (IOP) soon after the surgical procedure.

The authors noted that such IOP changes often occur early after the surgery, within a few hours following the conclusion of the operation. Many vitrectomy surgeons do not check the IOP soon after the end of the procedure, which potentially can lead to pain and even irreversible vision loss. Therefore, the authors decided to conduct a study using topical medications for controlling IOP, to determine if this would be effective in managing the IOP, thereby avoiding vision damage.

The IOP was measured with the Tonopen, an instrument that may be inaccurate when the IOP is higher or lower than the usual pressure range. However, their study shows that it is more accurate than the Schiotz tonometer, Perkins tonometer, and pneumotonometer.

The history of intraocular gases was described by Chang in volume 3 of the series entitled *Retina,* edited by Ryan. Intraocular gas was first used by Olm of Germany in 1911. Later, Rosengren followed this approach to ensure contact of the retina to the pigment epithelium. In the 1960s, Norton utilized air to tamponade the flap of giant retinal tears. He then considered the potential benefit of an expandable gas. Lincoff in New York followed Norton's approach and introduced the use of straight-chain perfluorocarbon expandable gases, which have expansile activity and intraocular longevity. Chang also describes the complications of gas use, including elevated IOP and glaucoma. Chang states that elevated IOP can be controlled medically and should be monitored.

In *Ophthalmic Surgery Complications,* edited by Charlton and myself, the chapter on complicatons of vitreoretinal surgery, written by Lehmer and Lewis, includes reference to the possibility of increased IOP by as much as 42 mm Hg. This can occur with the use of either perfluoropropane or sulfur hexafluoride.

The chapter on glaucoma associated with retinal disorders and retinal surgery by Campo and Reiss in *Duane's Clinical Ophthalmology*, currently edited by Tasman and Jaeger, also refers to elevation of IOP, mentioning that this typically occurs 6 to 12 hours after injection. The book *Ophthalmic Surgery: Principles & Practice,* edited by Spaeth, contains a chapter on retinal detachment by Benson. It also mentions elevated IOP related to intraocular gas.

While the study by Dr Mittra and colleagues is not very large, it does provide a good comparison between the control and the treatment eyes, indicating that the topical medications are clearly helpful in minimizing IOP elevation, especially elevation to high levels, such as pressure rises over 30 mm Hg, and especially over 40 mm Hg.

Accordingly, the study strongly supports the use of topical aqueous suppressants following pars plana vitrectomy combined with long-acting gas tamponade. I believe that it would be beneficial for confirmation of

these findings by an even more extensive study. I commend the authors for having devised an important approach to patients in need of this procedure.

PAUL R. LICHTER, MD. I would like to ask the authors whether they have tried oral carbonic anhydrous inhibitors instead of the topical agents which they mentioned. In cataract patients with glaucoma, there is commonly a substantial pressure risk during the first day following cataract surgery. For instance, it is not uncommon on the first postoperative day for the intraocular pressure to be 40 to 50 millimeters of mercury. Therefore, to avoid these major pressure elevations, I have for years routinely given oral Diamox Sequels to my glaucoma patients who have just undergone cataract surgery.

Specifically, I give them a Diamox Sequel at the end of the surgery, again the same evening, and another one the next morning. Almost always, this routine will avoid any marked pressure elevation. I think that this regimen could be helpful in the surgical situation described by the authors. It may be more effective than the topical agents they have used.

PAUL TORNAMBE, MD. I think that patients that are placed in a prone position after retinal surgery may be predisposed to pressure rises. The pupil is dilated, debris can settle in the trobecular meshwork. It is a type of prone provocative test. I think we also have to consider the expense of prophylactic glaucoma drops and the compliance with the use of these drops. Many of these patients have swollen sore lids, particularly after scleral buckling procedures; they may not use their drops as prescribed.

MICHAEL ELMAN, MD. I would like to congratulate the authors on an excellent paper. Since I have converted to outpatient vitrectomy and scleral buckling surgery 3 or 4 years ago, I have used intravenous acetazolamide during surgery and follow this in all patients with oral acteazolamide. Using this regimen, I have had only 1 patient with a pressure over 40 on the first postoperative day. The reason we control the pressure is to avoid central retinal artery closure and also to increase the patient's comfort. My question is whether the authors used any other therapy? Did you do the same thing in every case? Did you give them all atropine, steroids, or oral steroids? If so, did you see any relationship to these other agents? Why did you choose to use the topical agents rather than the oral agents? Since you did use topical agents, why did you just give the patient a single dose and not give drops to use on their own following surgery?

WILLIAM MIELER, MD. We chose topical medications to avoid or limit complications associated with systemic glaucoma medications. Our study

excluded patients with glaucoma or uveitis, conditions that can predispose to pressure rise after surgery. Regarding postoperative face down positioning, I cannot say what role it had in affecting the intraocular pressure.

In terms of expenses, we utilized medications in our recovery room from a single bottle of each agent. The medications were administered by the physicians to avoid contamination, and to avoid having the patient be charged for a single drop of medication. In addition to the study medications, all patients were placed on topical cycloplegics and corticosteroids.