Effects of Crystalloid *versus* Colloid and the α-2 Agonist Brimonidine *versus* Placebo on Intraocular Pressure during Prone Spine Surgery

A Factorial Randomized Trial

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ABSTRACT

Background: Volume replacement with colloid solution and topical α-2 agonists may each moderate the progressive increase in intraocular pressure (IOP) during prone surgery. The authors tested the hypotheses that during prolonged prone surgery, IOP increases less with goal-directed intravenous administration of 5% albumin than with goal-directed administration of lactated Ringer's solution, and with topical α-2 agonist brimonidine than with placebo eye drops.

Methods: Patients having complex prone spine surgery were factorially randomized to albumin and topical placebo (n = 15); albumin and topical brimonidine (n = 16); lactated Ringer's solution and topical placebo (n = 13); and lactated Ringer's solution and topical brimonidine (n = 16). IOP was measured with a pneumotonometer. The primary outcome was time-weighted average intraoperative IOP.

Results: Prone positioning increased IOP a mean ± SD of 12 ± 6 mmHg. IOP increased to 38 ± 10 mmHg at the end of anesthesia (approximately 5.5 h). Time- weighted average intraoperative IOP in the brimonidine group was 4 (95% CI: 1, 8) mmHg lower than in the placebo group ($P = 0.023$), but no different in the crystalloid and albumin groups (mean difference (95% CI) of −2 (−5, 2) mmHg ($P = 0.34$). There was no interaction between the two randomized factors.

Conclusions: Brimonidine slightly reduced the primary outcome of intraoperative time-weighted average IOP, whereas there was no significant difference between goal-directed albumin or crystalloid administration. Brimonidine thus helps reduce IOP during spine surgery, but maintaining adequate blood pressure might play a more important role.

What We Already Know about This Topic

- Increased intraocular pressure may contribute to the pathogenesis of postoperative visual complications in prone spine surgery patients
- Using a factorial randomization, topical brominidine (an α-2 adrenergic agonist) *versus* placebo and albumin *versus* crystalloid fluid administration were tested for their abilities to lessen the increase in intraocular pressure during prone spine surgery

What This Article Tells Us That Is New

- Brominidine blunted the increase in intraocular pressure during prolonged prone spine surgery whereas albumin administration did not

POSTOPERATIVE vision loss after spine surgery is a rare but devastating problem. The incidence of postoperative vision loss was 3.09/10,000 after spinal fusion in the United States Nationwide Inpatient Sample.[1] Among the causes of postoperative vision loss after spine surgery are central retinal artery occlusion and ischemic optic neuropathy. Central retinal artery occlusion is generally due to unrecog-

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nized compression of the eye, whereas perioperative ischemic optic neuropathy remains a poorly understood disorder. Intraocular pressure (IOP) usually increases over time in the prone position. Previous studies[1,2] report that IOP can reach up to 40 mmHg after 6 h in the prone position.

Increased IOP might be related to positive intraoperative fluid balance. In healthy volunteers, for example, acute water loading (14 ml/kg) increases IOP by 3 mmHg,[3] whereas exercise-induced dehydration reduced IOP.[4] Optimal fluid management and avoidance of hypotension are difficult to achieve in patients undergoing major spine surgery. Increased IOP reduces ocular perfusion pressure, which is approximated by the difference between mean arterial pressure and IOP.

Goal-directed fluid therapy is probably the best way to optimize individual fluid administration. Goal-directed fluid therapy improves patient outcomes and reduces the duration of hospitalization in several types of surgical procedures.[5–8] It is possible that the use of plasma expanders, specifically human albumin, which largely remain in the intravascular space, provokes less volume shift from the vascular bed into interstitial tissues than crystalloids.[9] The American Society of Anesthesiologists Practice Advisory on Perioperative Blindness recommended the use of colloids with crystalloids in patients undergoing lengthy spine surgery.[10] Previous studies have shown that IOP increases less during cardiopulmonary bypass when the bypass pump is primed with colloid rather than crystalloid.[11] It remains unknown whether colloid administration similarly moderates the usual time-dependent increase in IOP and consequent reduction in ocular perfusion pressure during extensive spine surgery.

One cause of increased IOP during prone position is increased episcleral venous pressure.[12] α-2 agonists decrease IOP by decreasing aqueous production as well as increasing uveoscleral outflow.[13] As might thus be expected, the topical α-2 agonist brimonidine has been used successfully as monotherapy for glaucoma.[13] Systemically administered α-2 agonists also have a neuroprotective effect on retinal ganglion cells.[14] We therefore tested the hypotheses that during prolonged prone surgery, IOP increases less with goal-directed intravenous administration of 5% albumin than with goal-directed administration of lactated Ringer's solution; and IOP increases less with ocular administration of the α-2 agonist brimonidine than with placebo eye drops.

Materials and Methods

After Cleveland Clinic Institutional Review Board (Cleveland, OH) approval and written informed consent, patients scheduled for complex spine surgery (single segment with instrumentation or multiple-segment laminectomies with or without instrumentation) in prone position were factorially randomized into four groups: 5% albumin and topical placebo; 5% albumin and topical brimonidine; lactated Ringer's solution and topical placebo; and lactated Ringer's solution and topical brimonidine. Brimonidine 2% or placebo was administered, one drop in each eye in the preoperative area, approximately 1 h before the induction of anesthesia and then every 8 h for 24 h. Randomization was based on computer-generated codes with a random block design and no stratification. Allocations were concealed in sequentially numbered opaque envelopes that were opened shortly before induction of anesthesia. The eye drops were prepared by the Cleveland Clinic Research pharmacy so that clinicians and investigators were fully double-blinded. We selected albumin because it can be given in large quantities without potentially impairing coagulation or renal function (fig. 1).

Anesthesia was induced with propofol (2–3 mg/kg) and fentanyl (up to 1 μg/kg), and maintained with sevoflurane titrated to an end-tidal concentration between 1.5–2.5% in 80% oxygen and 20% air. A sufentanil infusion was titrated between 0.007–0.01 μg/kg/min per clinical routine to maintain mean arterial pressure within 20% of preoperative values. End-tidal pressure of carbon dioxide was maintained near 35 mmHg. Arterial catheters were used in all patients, as was a Foley bladder catheter; however, central venous catheters were inserted according to the anesthesiologist's preference.

As is our routine for this type of lengthy surgery in our institution, the patient's head was maintained in skull pins that allowed free access to the eyes and avoided any pressure to the eye globe. The patient's head was elevated five degrees to decrease IOP. All patients were positioned on a Jackson frame for surgery.

All the patients were given 5–7 ml/kg lactated Ringer's solution in the immediate preoperative period, which was followed by 6–7 ml/kg/h lactated Ringer's solution for maintenance. In patients assigned to supplemental crystalloid, additional lactated Ringer's solution was given as guided by esophageal Doppler. In patients assigned to supplemental colloid, 5% human albumin was given as guided by esophageal Doppler to supplement maintenance crystalloid. Anesthesia providers were not blinded to fluid allocation. Erythrocyte transfusions were given as necessary to keep the hematocrit $\geq$30%. A hematocrit of 30% was chosen on clinical grounds because there is not a single randomized intraoperative trial suggesting that one transfusion trigger is better than another.

Supplemental fluid (above the maintenance lactated Ringer's infusion) was guided by esophageal Doppler, using a 6-mm-diameter esophageal Doppler ultrasound probe (EDM; Deltex Medical, Inc, Irving, TX) that was positioned in the midesophagus. The probe was secured in position once satisfactory blood flow signals were achieved, and readjusted as necessary to maintain a good signal. The Doppler monitor displays blood flow within the descending thoracic aorta. A nomogram incorporated in the monitor estimates the aortic cross-sectional area, enabling calculation of the left ventricular stoke volume from the area of the velocity–time wave-

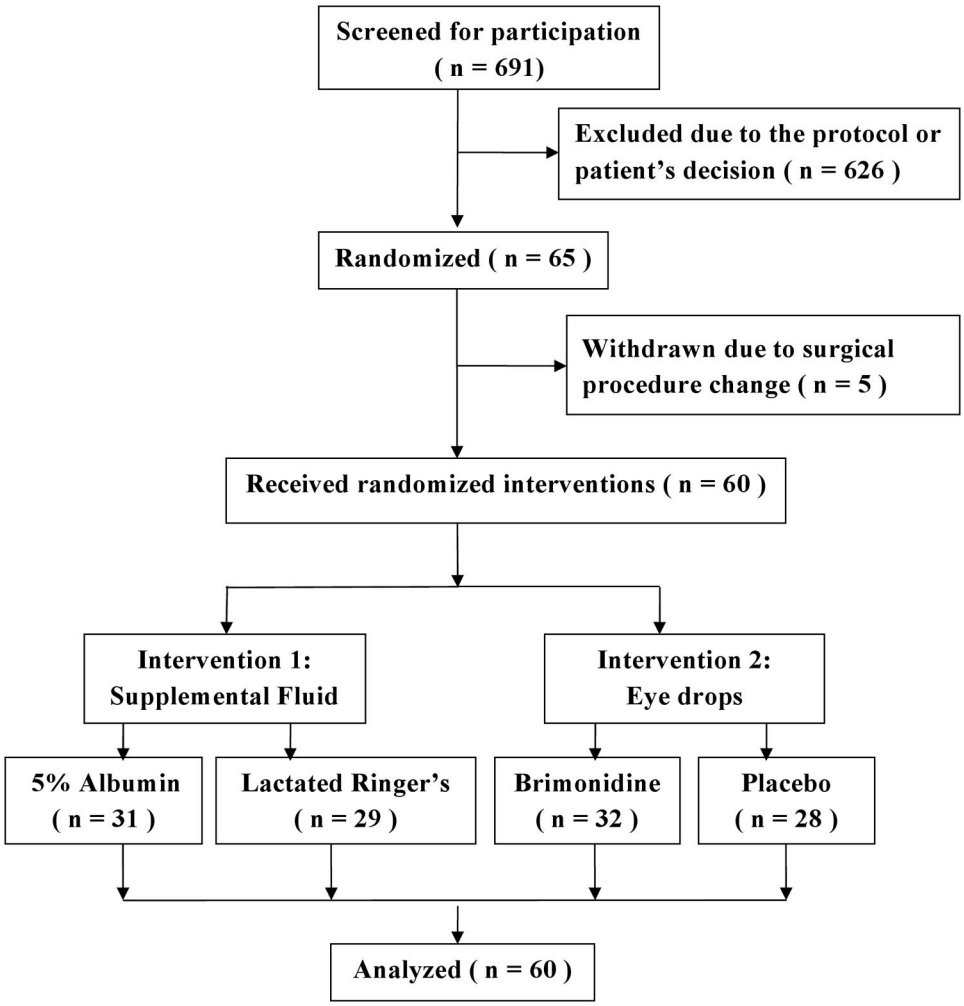

Fig. 1. Flowchart of the study groups.

form. This nomogram includes the patient's height, weight, and age.

The designated fluid was given under esophageal Doppler guidance to maintain a corrected aortic flow time of approximately 0.35 s or an increase in stroke volume of 10%.[5–8] Intravenous bolus doses of phenylephrine (or infusion) or ephedrine were given as necessary to keep mean arterial blood pressure 20% of preoperative baseline. If the patients were randomized to crystalloids, clinicians were given the option of slightly modifying the fluid management protocol by giving boluses of colloids when they failed to keep the blood pressure within the target value despite reaching stroke volume and corrected flow time target values measured using esophageal Doppler guidance and using vasoactive drugs.

If IOP reached 50 mmHg, attempts were made to reduce IOP by hyperventilating (arterial carbon dioxide tension [$Paco_2$] = 30 mmHg), and giving diuretics (10–20 mg furosemide) to increase urine output. Mean arterial pressure was also increased by 10% to improve ocular perfusion pressure.

The sufentanil infusion was discontinued 45 min before the anticipated end of the surgery. When surgery was complete, anesthesia was discontinued; patients were extubated in the operating room and transferred to the postanesthesia care unit.

Measurements

Demographic characteristics, number of surgical spinal segments, and duration of surgery were recorded. In addition, we recorded corrected aortic flow time, cardiac index, and stroke volume before and after each fluid challenge. Mean arterial pressure, heart rate, saturation, and end-tidal pressure of carbon dioxide, along with anesthetic data, were recorded at 15-min intervals throughout surgery. Blood loss, fluid administration, vasopressor use, and urinary output were recorded at the end of surgery.

Intraoperative IOP was recorded preoperatively as a baseline measurement. Subsequently, a single IOP measurement was recorded after induction of anesthesia and after assuming a prone position at every 30-min interval. However, if IOP measurements reached 50 mmHg, we double-checked the measurement and averaged the two measurements. IOP was measured at hourly intervals postoperatively for 4 h. IOP measurements were performed with a Model 30 Classic Tm

pulse mode pneumotonometer, which records 40 readings per second (Eichert, Depew, NY).

The severity of facial edema was graded on a scale of 1–4, with 1 being mild and 4 being severe. Facial edema was evaluated by a blinded investigator upon arrival to the postanesthesia care unit (PACU), and on postoperative days 1 and 2.

The time from assuming the supine position at the end of surgery to extubation was measured in each group. The time spent in the PACU was measured, along with a modified Aldrete recovery score[15] upon admission to the recovery unit and hourly thereafter. The duration of hospitalization was also recorded.

Statistical Analysis

Balance on baseline variables across treatments for each of the fluid and eye drop randomized interventions was assessed descriptively using standard summary statistics and the standardized difference (difference in means or proportions divided by pooled SD). Imbalance was defined as absolute value of the standardized difference, $\geq 1.96 \times \sqrt{2/\text{N per group}}$.[16] Our main analysis for both the primary and secondary outcomes was intent-to-treat, for which we included all randomized patients. Transformations of data were made to meet model assumptions, as appropriate.

Our primary outcome of time-weighted average (TWA) IOP was calculated for each patient using all available IOP measurements from start of the procedure (first IOP in prone position) until the end of surgery. The main effects of the fluid and eye drop interventions and their interaction on IOP-related outcomes were assessed using linear regression, except for duration of intraoperative IOP more than 40 mmHg (Wilcoxon rank sum test). We adjusted for preoperative IOP as a covariate for the primary outcome of TWA IOP and secondary outcomes of IOP in the prone position, IOP at the end of anesthesia, and TWA PACU IOP. We adjusted for preoperative perfusion pressure (mean arterial pressure minus IOP) when comparing randomized groups on intraoperative TWA perfusion pressure but not when TWA percent decrease from baseline was the outcome.

The intervention effects on whether IOP reached 50 mmHg, whether perfusion pressure was less than 40 mmHg during surgery, and whether the IOP had returned to baseline ± 3 mmHg after 1 h in PACU were assessed using logistic regression, whereas Poisson regression was used for number of fluid challenges.

Linear regression models were used to evaluate the effects of the fluid interventions on additional surgical outcomes including amount of crystalloids, amount of colloids, amount of urine output during surgery, amount of blood loss during surgery, TWA arterial pressure during surgery, phenylephrine dose, TWA stroke volume, TWA cardiac index, and cardiac index at incision and end of anesthesia.

Fluid effect on mean Aldrete score over time was assessed using repeated measures analyses to adjust for within-subject correlation (unstructured covariance structure). Proportional odds models were used to evaluate the effect of the fluid intervention on the ordinal edema score. Logistic regression was used to assess treatment effects on additional binary outcomes, whereas time-to-event outcomes (length of hospital stay, duration of recovery, and time to extubation) were assessed using Kaplan–Meier time-to-event curves and Cox proportional hazards models.

In the presence of a significant interaction between the fluid and eye drop interventions ($P < 0.10$), the effects of each factor were assessed within the levels of the other factor, and a Bonferroni correction for multiple comparisons was applied ($P < 0.025$ significance criterion). Otherwise, main effects were assessed collapsing over the other randomized factor. For repeated measures analyses, three-way interactions were also considered (two randomized factors and time).

A linear mixed-effects model assuming smaller correlation for times farther apart (*i.e.*, a spatial ('power') covariance structure) was used to estimate the mean slope of IOP during surgery for all patients combined and to assess differences between each intervention and control, adjusting for preoperative IOP. All IOP measurements used to calculate a patient's TWA IOP were used for this analysis.

Cheng *et al.*[1] observed an IOP mean ± SD of 40 ± 7 mmHg for patients in the prone position over a mean duration of 5 h. We thus assumed similar variability. With 60 total patients, our study was designed to have 90% power at the 0.05 significance level to detect differences of 8 mmHg or more between randomized groups, assuming no interaction between the two randomized factors and a SD of 8 for TWA IOP. If an interaction between the two factors occurred, we also had 65% power to detect similar differences within levels of the other factor.

The significance level for each hypothesis was 0.05; all tests were two-sided. A Bonferroni correction for multiple comparisons within a hypothesis was implemented where applicable. SAS statistical software (Cary, NC) was used for all analyses. Data are reported as mean ± SD, mean (SE), median [first, third quartiles], or percent, as appropriate.

Results

Sixty-five patients were randomized at the Cleveland Clinic from April 2008 to December 2009. Five patients could not be given the assigned treatments due to a last-minute change in the surgical procedure. Our intention-to-treat analysis thus included 60 patients in whom the planned surgery was performed. Baseline factors were reasonably balanced for each randomized factor (table 1); none of the absolute standardized differences exceeded 0.51, our criterion for balance. The average number of IOP measurements per patient throughout the study period was 9 ± 3. Overall, IOP in-

Table 1. Baseline and Surgical Characteristics for Each Intervention

Factor	Supplemental Fluid			Eye Drops		
	5% Albumin (No. = 31)	Lactated Ringer's Solution (No. = 29)	STD*	Brimonidine (No. = 32)	Placebo (No. = 28)	STD*
Female — %	58	52	0.13	50	61	−0.22
White race — %	94	90	0.14	91	93	−0.08
ASA physical status III (*vs.* II) — %	45	41	0.08	41	46	−0.12
No. of spinal segments — %	3 [2, 3]	2 [2, 3]	0.26	2 [2, 3]	3 [2, 4]	−0.43
1	16	24		22	18	—
2	32	41		44	29	—
3	32	14		25	21	—
4+	19	21		9	32	—
Age (year)	60 ± 8	57 ± 15	0.28	57 ± 13	60 ± 11	−0.30
Body mass index (kg/m^2)	30 ± 6	29 ± 6	0.03	30 ± 6	29 ± 5	0.31
Surgery duration (min)	5.7 ± 2.2	5.7 ± 1.9	0.02	5.8 ± 2.4	5.6 ± 1.6	0.06
Time first to last intraoperative IOP (h)	4.6 [3.8, 5.1]	4.5 [3, 5.5]	0.07	4.6 [3.3, 5.5]	4.6 [3.3, 5.2]	0.09
Preoperative MAP (mmHg)	87 ± 10	84 ± 9	0.33	86 ± 10	85 ± 10	0.09
Preoperative perfusion pressure (mmHg)	71 ± 10	68 ± 10	0.27	70 ± 10	70 ± 10	0.004

Results presented as percent, means ± SDs, or median [first quartile, third quartile].

* STD = standardized difference; was considered as imbalanced if any variable with absolute STD $\geq 1.96 \times \sqrt{2/\text{N per group}} = 0.51$.

ASA = American Society of Anesthesiologists; IOP = intraocular pressure; MAP = mean arterial pressure.

creased 12 ± 6 (SD) mmHg from the last supine to first prone measurement. The mean duration of anesthesia time was 5.7 h, with median [quartiles] of 5.5 [4.5, 6.9] and maximum of 12.3 h. Surgery exceeded 8 h for 8 patients, who thus received intraoperative eye drops.

For the primary outcome of TWA IOP, no interaction between the fluids and eye drops interventions was found ($P = 0.50$). Similarly, no significant interaction was found between the interventions for any of the IOP-related variables in table 2 (all interaction P values were more than 0.30, except $P = 0.16$ for whether IOP reached 50 mmHg during surgery). Therefore, the main effects of the fluid and eye drop interventions were assessed marginally in the next paragraphs (*i.e.*, by collapsing over the alternate factor).

No difference in mean TWA IOP was found between the 5% albumin and lactated Ringer's solution groups, with an estimated mean (95% confidence interval [CI]) difference of −2 (−5, 2) mmHg ($P = 0.34$, fig. 2A and B, table 2). Figure 3A shows the intraoperative increases in mean IOP in patients assigned to each fluid.

Brimonidine lowered mean intraoperative TWA IOP by 4 [95% CI: 1, 8] mmHg compared with placebo ($P = 0.023$). In secondary analyses, mean IOP at the end of surgery was also significantly lower (table 2). Figure 3B shows the intraoperative increases in mean IOP in patients assigned to brimonidine or placebo eye drops.

No significant effects of either 5% albumin or brimonidine were found for the proportion of patients reaching an IOP of 50 mmHg during surgery, variability (SD) of intraoperative IOP, or duration of intraoperative IOP more than 40 mmHg. Furthermore, no difference for either randomized factor was found for TWA perfusion pressure or the proportion of patients having a perfusion pressure less than 40 mmHg sometime during surgery (table 2). Body mass index was not significantly correlated with intraoperative TWA IOP level (Pearson correlation coefficient 0.10 (95% CI: −0.16, 0.34) ($P = 0.45$). In addition, no difference was found between those with a body mass index ≥35 (18% of patients) *versus* <35 (kg/m^2) on either preoperative IOP (multivariable $P = 0.28$) or intraoperative TWA IOP (multivariable $P = 0.10$).

IOP increased at a mean (SE) rate of 2.0 (0.4) mmHg/h in the albumin group, which was significantly slower than in the patients receiving crystalloid [3.1 (0.4) mmHg/h, $P = 0.03$]. Consequently, final prone IOP was significantly greater in the patients receiving crystalloid (41 ± 10 mmHg) than in those receiving albumin (36 ± 9 mmHg, $P = 0.03$). In contrast, there was no difference between brimonidine and placebo in the increase over time ($P = 0.81$, table 2). Among the 12 patients (approximately 20%) who reached ≥50 mmHg during surgery, 7 were responsive to protocol interventions such that IOP returned to less than 50 mmHg before they were turned supine. Among treated patients, three of four patients randomized to albumin and brimonidine responded, two of two given albumin and placebo responded, two of two given lactated Ringer's solution and brimonidine responded, and zero of four given lactated Ringer's solution and placebo responded.

Mean TWA prone ocular perfusion pressures were low (approximately 47 mmHg) and were not significantly affected by the interventions. Approximately 70–80% of the patients in each group experienced at least one ocular perfusion pressure less than 40 mmHg at some point while prone.

Table 2. IOP-related Outcomes for Supplemental Fluid and Eye Drop Interventions: Main Effect Results

Outcome	Supplemental Fluid				Eye Drops			
	5% Albumin (No. = 31)	Lactated Ringer's (No. = 29)	Difference (95% CI)†	*P* Value*	Brimonidine (No. = 32)	Placebo (No. = 28)	Difference (95% CI)*	*P* Value*
Primary outcome: TWA IOP (mmHg)†	34.3 ± 8	35.2 ± 8	−1.66 (−5.12, 1.80)	0.34	33.4 ± 7	36.2 ± 8	−4.09 (−7.58, −0.59)	0.023
Secondary outcomes	—	—	—	—	—	—	—	—
IOP preoperative supine (mmHg)	16 ± 2	16 ± 3	0.48 (−0.91, 1.86)	0.49	16 ± 3	15 ± 3	0.88 (−0.51, 2.26)	0.21
First IOP in prone position (mmHg)†	28 ± 7	28 ± 6	0.83 (−3.91, 2.24)	0.59	27 ± 7	29 ± 6	−3.22 (−6.32, −0.11)	0.043
IOP change: supine to prone (mmHg)†	11 ± 6	12 ± 6	−0.75 (−3.79, 2.29)	0.62	10 ± 6	13 ± 5	−3.09 (−6.14, −0.05)	0.047
IOP slope,** mean (SE) (mmHg/h)	2.0 (0.36)	3.1 (0.40)	−1.0 (−1.91, −0.09)	0.031	2.3 (0.36)	3.1 (0.40)	−0.11 (−1.02, 0.80)	0.81
IOP at end of anesthesia (mmHg)†	36 ± 9	41 ± 10	−5.02 (−9.56, −0.47)	0.03	37 ± 9	41 ± 10	−5.45 (−10.06, −0.86)	0.021
Duration of intraoperative IOP >40 mmHg (min)‖	0 [0, 173]	43 [0, 120]	0 (−36.9, 1.0)††	0.42	4 [0, 61]	46 [0, 183]	−5.64 (−85.5, 0.01)††	0.17
IOP reached 50 in surgery (% yes)‡	19	21	0.91 (0.26, 3.25)‡‡	0.89	19	21	0.84 (0.24, 3.00)‡‡	0.79
TWA PACU IOP (mmHg)†	19 ± 5	20 ± 7	0.99 (0.81, 1.02)§§	0.11	19 ± 5	21 ± 7	0.88 (0.78, 0.98)§§	0.025
TWA intraoperative ocular perfusion pressure (mmHg)§	48 ± 11	46 ± 9	1.98 (−3.22, 7.18)	0.44	48 ± 11	47 ± 9	0.96 (−4.20, 6.12)	0.71
Perfusion pressure <40 mmHg (% yes)‡	68	79	0.54 (0.17, 1.76)‡‡	0.31	72	75	0.83 (0.26, 2.66)‡‡	0.76
TWA mean arterial pressure (mmHg)#	82 ± 5	81 ± 6	0.06 (−2.58, 2.69)	0.97	81 ± 5	82 ± 6	−1.81 (−4.41, 0.80)	0.17

Data presented as percent, means ± SDs, or median [first quartile, third quartile]; for IOP in the prone position, n = 1 missing for each group.

* All regression models include both fluid and eye drop factors (linear regression unless noted): † adjusting for baseline IOP; ‡ logistic regression; § adjusting for baseline perfusion pressure; ‖ Wilcoxon rank sum test; # adjusting for baseline mean arterial pressure. ** slope: IOP increase per hour, beginning with first intraoperative prone measurement; †† median difference; ‡‡ odds ratio; §§ the ratio of means. All interaction *P* values between the two interventions > 0.1 (nonsignificant).

IOP = intraocular pressure; PACU = post anesthesia care unit; TWA = time-weighted average.

Per protocol, patients assigned to lactated Ringer's solution received significantly more crystalloid than patients assigned to receive albumin ($P < 0.001$). The mean ± SD number of fluid challenges were 6 ± 4 in the albumin group and 7 ± 6 in the lactated Ringer's solution group ($P = 0.16$). Urinary output, estimated surgical blood loss, TWA mean arterial pressure, variability (SD) of mean arterial pressure, TWA stroke volume, TWA cardiac index, cardiac index at incision and end of anesthesia, and hemodynamics throughout surgery were not different between the two fluid management groups. Furthermore, comparable amounts of vasopressors were used in both groups (table 3).

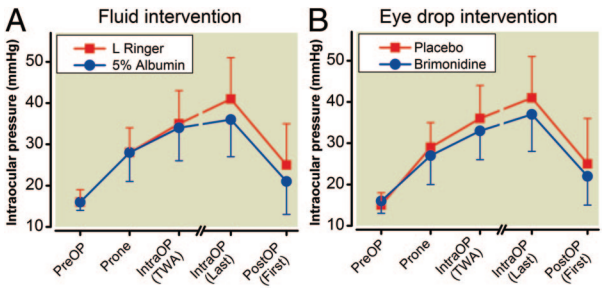

Fig. 2. Pattern of intraocular pressure (IOP) in each intervention. IntraOP values are based on all intraoperative measurements. TWA = time-weighted average. Results presented as means ± SDs. Mean IOP increased for all groups during surgery. Adjusting for preoperative IOP, 5% albumin was no different from lactated Ringer's solution. ($P = 0.34$, *A*), but brimonidine had lower mean intraoperative TWA IOP than placebo ($P = 0.023$, *B*). IntraOP = all intraoperative data; PostOP = postoperative data; PreOP = postoperative data.

Patients assigned to albumin had less facial edema in the PACU than those given lactated Ringer's solution [$P = 0.003$, odds ratio (95% CI) for worse edema score of 0.2 (0.1, 0.6); that is, patients assigned to albumin was 79% more likely to have better edema scores]. No fluid effects on facial edema were found for postoperative days 1 ($P = 0.32$) or 2 ($P = 0.08$), although on postoperative day 1 the 5% albumin appeared to reduce edema for the placebo eye drop group ($P = 0.038$) but not the brimonidine group ($P = 0.43$, interaction $P = 0.037$, table 4).

The mean and SE of the average of the PACU admission and 1-h Aldrete scores were similar in the albumin [8.2 (0.2)] and lactated Ringer's solution [7.9 (0.2)] groups ($P = 0.54$). Five percent albumin did not significantly affect the duration of recovery (6 [5, 9] *vs.* 5 [4, 6] h, multivariable $P = 0.064$) or the duration of hospitalization (5 [4, 7] *vs.* 5 [4, 6] days,

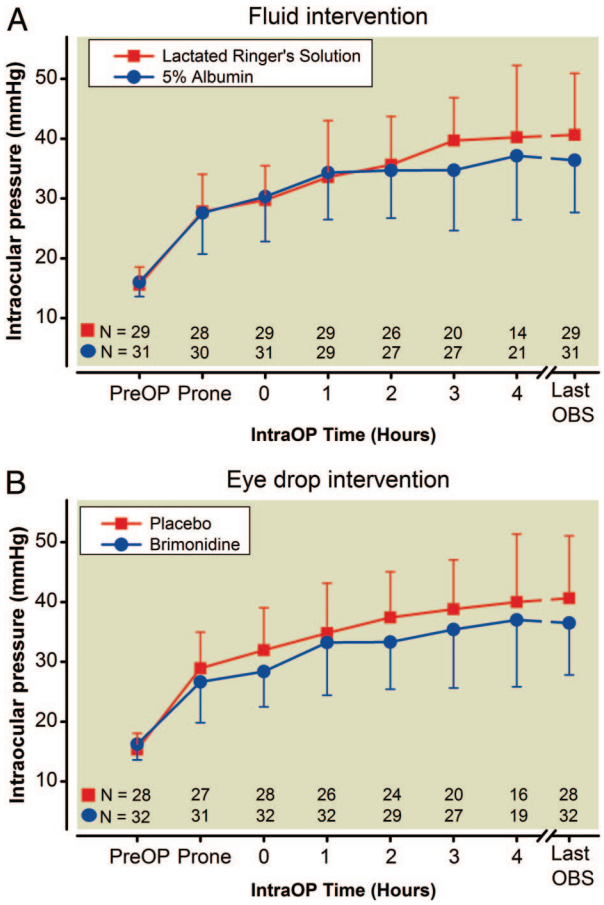

Fig. 3. Intraocular pressure (IOP) over time during surgery for the supplemental fluid (*A*) and eye drop (*B*) interventions. Half error bars are means ± SDs. Albumin did not reduce time-weighted average (TWA) IOP [$P = 0.34$ for TWA IOP and $P = 0.09$ for mean IOP collapsing over time (*A*)]. However, brimonidine reduced both TWA IOP ($P = 0.023$) and the mean IOP collapsing over time (*B*, $P = 0.003$). Rate of IOP increase was slower for patients receiving albumin than those receiving crystalloid ($P = 0.031$), but no different between brimonidine and placebo ($P = 0.81$). Both interventions reduced IOP by end of surgery. IntraOP = all intraoperative data. OBS = observation. PreOP = preoperative data.

multivariable $P = 0.30$). None of our patients experienced clinically apparent visual defects.

Discussion

IOP increased significantly by 12 ± 6 mmHg when patients were turned prone, a finding that is consistent with previous reports.[1] We also observed an increase over time of approximately 2 mmHg/h in the albumin group and 3.1 mmHg/h in the lactated Ringer's solution group.

TWA prone IOP, our primary outcome, did not differ significantly between the patients receiving albumin and crystalloid, nor did the precentage of patients (approximately 20%) who experienced IOP more than 50 mmHg. Nonetheless, the mean rate of IOP increase in the prone position was significantly greater in the patients receiving crystalloid than those receiving albumin (3.1 *vs.* 2.0 mmHg/h); consequently, mean prone IOP at the end of surgery was significantly greater by approximately 5 mmHg in the patients receiving crystalloid. The clinical importance of this observation remains unclear: the difference in IOP at the end of surgery was relatively small. Despite the difference in IOP at the end of surgery, TWA perfusion pressure and the fraction of perfusion pressures less than 40 mmHg did not differ significantly between the fluid groups.

Maintenance of blood pressure appears to be the more significant factor resulting in maintenance of calculated ocular perfusion pressure in this study, despite use of maneuvers to decrease IOP. We aggressively treated hypotension, and thus maintained a time-weighted mean arterial pressure near 80 mmHg, although surgery lasted an average of approximately 5.5 h and blood loss averaged 700 ml.

Hemodynamic stability, such as normal mean arterial pressure and cardiac output, were maintained by using esophageal Doppler guidance to optimize fluid administration. All patients received a baseline crystalloid infusion of 6–7 ml/kg/h with supplemental fluid replacement being guided by stroke volume as determined using esophageal Doppler guidance. Consequently, hemodynamic parameters such as stroke volume, cardiac output, and mean arterial pressure were similar in both groups. Our study is unique as we randomized patients to receive either crystalloid or colloid fluid boluses guided by esophageal Doppler. Previous research showing improved outcomes with goal-directed fluid management used colloid supplementation in goal- directed patients and compared that to patients receiving standard of care fluid management (*i.e.*, not directed by esophageal Doppler).[5,7,17,18] The importance of using esophageal Doppler guidance is that it allowed us to titrate two very different fluids to comparable physiologic effect. It might very well be that guiding fluid management to physiologic parameters might be more important in maintaining hemodynamic stability and thus optimizing ocular perfusion pressure than the different fluids used.

The α-2 agonist brimonidine significantly reduced IOP by approximately 3 mmHg (on average) right from the first measurement. IOP subsequently increased over time in both the brimonidine and placebo patients, but the rates of increase were comparable. Brimonidine thus proved effective, and our study is the first to demonstrate that it decreases IOP in the prone position.

Our factorial design allowed us to simultaneously assess the effects of albumin and brimonidine on TWA IOP and other variables. Because the interaction between the two factors was highly nonsignificant, we were able to assess the effects of each factor while collapsing over the other, thus taking advantage of the full power of the factorial design. The nonsignificant interactions meant that the effects of the two factors were additive, and a simple sum of the main effects would give the estimated combined effect of albumin and brimonidine. For example, the estimated combined effects of the two interventions on mean TWA IOP if patients would

Table 3. Effects of Supplemental Fluid Intervention on Secondary Outcomes

Outcome	5% Albumin (No. = 31)	Lactated Ringer's Solution (No. = 29)	Ratio of Means (95% CI)*	*P* Value*
Crystalloid (l)	3.4 [2.4, 4.8]	5 [3.8, 6.5]	0.7 (0.6, 0.8)	<0.001
Colloid (l)	1.2 [1, 2]	0.5 [0, 0.5]	61 (16, 236)	<0.001
Urine output (ml)	1,000 [490, 1,360]	725 [505, 1,470]	1.2 (0.8, 1.7)	0.45
Estimated blood loss (ml)	700 [450, 1,400]	700 [450, 1,000]	1.1 (0.7, 1.7)	0.71
Number of fluid challenges	6.1 ± 3.7‡	6.8 ± 6.3§	0.9 (0.7, 1.1)†	0.16†
			Difference in Means (95% CI)*	
Phenylephrine dose (mg)	4.5 ± 4.2‖	4.6 ± 4.7‡	−0.05 (−2.4, 2.3)	0.97
Time-weighted average stroke volume (ml)	66 ± 18‖	69 ± 18	−3.2 (−12.7, 6.3)	0.50
Time-weighted average cardiac index (l/min)	2.5 ± 0.9‖	2.4 ± 0.6	0.1 (−0.3, 0.5)	0.61
Cardiac index at incision (l/min/m^2)	2.4 ± 0.9‖	2.3 ± 0.7	0.1 (−0.3, 0.5)	0.64
Cardiac index at end of anesthesia (l/min/m^2)	2.6 ± 1.2‖	2.5 ± 0.8	0.1 (−0.4, 0.7)	0.68

Data presented as means ± SDs or median [first quartile, third quartile].

* Models include both fluid and eye drop factors (all interaction *P* values for two factors >0.1); linear regression unless noted. † Poisson regression. ‡, §, ‖ n = 3, 2, and 1 missing data.

receive both treatments would be a reduction of 4 mmHg for brimonidine (*vs.* placebo) and 2 mmHg for colloids (*vs.* crystalloids), for a total of 6 mmHg. In fact, this is what we observed in the subset of patients who received both treatments. Our study is thus unique in simultaneously evaluating the effects of albumin and brimonidine on IOP pressure, and assessing whether the effects are additive.

Despite the fact that TWA IOP did not differ in patients assigned to crystalloid and albumin, patients given supplemental crystalloid had considerably worse facial edema in the postanesthesia care unit. By the next morning, most edema had resolved in both groups and the amount no longer differed significantly. Although visual loss has been attributed to facial edema in a small case series,[19] our results suggest that facial edema *per se* is a poor clinical indicator of IOP.

Previous studies have identified substantial differences in extubation times, recovery duration, and hospital stay when comparing goal-directed colloid administration to routine fluid management with (mostly) crystalloids. Our study differs in that supplemental albumin and lactated Ringer's solution were both given under esophageal Doppler guidance. Perhaps as a consequence, extubation time, recovery duration, and hospital stay were all comparable among the randomized fluid types. In terms of these outcomes, using guided management to determine the optimal volume and timing of administration may be more important than the choice of fluid *per se*. Although no patients experienced clinically apparent visual defects, our study was far too small to detect this rare complication.

In summary, prone positioning increased IOP 12 ± 6 mmHg. IOP further increased to 38 ± 10 mmHg at the end of anesthesia (approximately 5.5 h); 12 of 60 patients had IOPs ≥50 mmHg during surgery (no group differences). Brimonidine alone reduced intraoperative TWA IOP (our primary outcome) and reduced IOP at the end of surgery (*post hoc* secondary outcome). Five percent albumin alone had little effect on TWA IOP, but reduced IOP at the end of surgery by 0–10 mmHg. Much larger studies will be needed to determine whether maintaining appropriate ocular perfu-

Table 4. Effect of Fluid Intervention on Facial Edema Scores

Time	None\Mild\Moderate\Severe			
	5% Albumin (No. = 31)*	Lactated Ringer's Solution (No. = 29)	Odds Ratio† (95% CI)	*P* Value‡
PACU–frequency	7\13\9\2	0\9\15\5	0.21 (0.08, 0.58)	0.0027
Postoperative day 1	22\7\0\0	19\8\2\0	0.56 (0.18, 1.74)	0.32
Eye drop: brimonidine (No. = 32)	10\5\0\0	13\2\1\0	1.94 (0.38, 9.96)	0.43§
Eye drop: placebo (No. = 28)	12\2\0\0	6\6\1\0	0.14 (0.02, 0.89)	0.038§
Postoperative day 2	29\0\0\0	26\3\0\0	N/A‖	0.081‖

Edema presented as the number of patients with none/mild/moderate/severe scores.

* n = 2 missing edema scores at postoperative day 1 and 2. † Odds ratio of having a worse edema score using 5% albumin compared with lactated Ringer's solution. ‡ Proportional odds model, unless noted. § 5% albumin effect also analyzed within eye drop levels due to colloid-eye drop interaction for postoperative day 1 (*P* = 0.037); within-level significance criterion is 0.025. ‖ Wilcoxon rank sum test used due to few distinct edema levels.

PACU = postanesthesia care unit.

sion pressure reduces the risk of visual injury during complex spine surgeries.

References

1. Cheng MA, Todorov A, Tempelhoff R, McHugh T, Crowder CM, Lauryssen C: The effect of prone positioning on intraocular pressure in anesthetized patients. ANESTHESIOLOGY 2001; 95:1351–5
2. Hunt K, Bajekal R, Calder I, Meacher R, Eliahoo J, Acheson JF: Changes in intraocular pressure in anesthetized prone patients. J Neurosurg Anesthesiol 2004; 16:287–90
3. Brucculeri M, Hammel T, Harris A, Malinovsky V, Martin B: Regulation of intraocular pressure after water drinking. J Glaucoma 1999; 8:111–6
4. Martin B, Harris A, Hammel T, Malinovsky V: Mechanism of exercise-induced ocular hypotension. Invest Ophthalmol Vis Sci 1999; 40:1011–5
5. Sinclair S, James S, Singer M: Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: Randomised controlled trial. BMJ 1997; 315:909–12
6. Singer M, Allen MJ, Webb AR, Bennett ED: Effects of alterations in left ventricular filling, contractility, and systemic vascular resistance on the ascending aortic blood velocity waveform of normal subjects. Crit Care Med 1991; 19: 1138–45
7. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS: Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. ANESTHESIOLOGY 2002; 97:820–6
8. Noblett SE, Snowden CP, Shenton BK, Horgan AF: Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. Br J Surg 2006; 93:1069–76
9. Jacob M, Bruegger D, Rehm M, Welsch U, Conzen P, Becker BF: Contrasting effects of colloid and crystalloid resuscitation fluids on cardiac vascular permeability. ANESTHESIOLOGY 2006; 104:1223–31
10. American Society of Anesthesiologists Task Force on Perioperative Blindness: Practice advisory for perioperative visual loss associated with spine surgery: A report by the American Society of Anesthesiologists Task Force on Perioperative Blindness. ANESTHESIOLOGY 2006; 104:1319–28
11. Abbott MA, McLaren AD, Algie T: Intra-ocular pressure during cardiopulmonary bypass–a comparison of crystalloid and colloid priming solutions. Anaesthesia 1994; 49:343–6
12. Lam AK, Phil M, Douthwaite WA: Does the change of anterior chamber depth or/and episcleral venous pressure cause intraocular pressure change in postural variation? Optom Vis Sci 1997; 74:664–7
13. Cantor LB: The evolving pharmacotherapeutic profile of brimonidine, an alpha 2-adrenergic agonist, after four years of continuous use. Expert Opin Pharmacother 2000; 1:815–34
14. Donello JE, Padillo EU, Webster ML, Wheeler LA, Gil DW: alpha(2)-Adrenoceptor agonists inhibit vitreal glutamate and aspartate accumulation and preserve retinal function after transient ischemia. J Pharmacol Exp Ther 2001; 296:216–23
15. Aldrete JA: The post-anesthesia recovery score revisited. J Clin Anesth 1995; 7:89–91
16. Austin PC: Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009; 28:3083–107
17. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C: Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. Anaesthesia 2002; 57:845–9
18. Giglio MT, Marucci M, Testini M, Brienza N: Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: A meta-analysis of randomized controlled trials. Br J Anaesth 2009; 103:637–46
19. Dunker S, Hsu HY, Sebag J, Sadun AA: Perioperative risk factors for posterior ischemic optic neuropathy. J Am Coll Surg 2002; 194:705–10