Risk Factors Associated with Ischemic Optic Neuropathy after Spinal Fusion Surgery

The Postoperative Visual Loss Study Group*

ABSTRACT

Background: Perioperative visual loss, a rare but dreaded complication of spinal fusion surgery, is most commonly caused by ischemic optic neuropathy (ION). The authors sought to determine risk factors for ION in this setting.

Methods: Using a multicenter case-control design, the authors compared 80 adult patients with ION from the American Society of Anesthesiologists Postoperative Visual Loss Registry with 315 adult control subjects without ION after spinal fusion surgery, randomly selected from 17 institutions, and matched by year of surgery. Preexisting medical conditions and perioperative factors were compared between patients and control subjects using stepwise multivariate analysis to assess factors that might predict ION.

Results: After multivariate analysis, risk factors for ION after spinal fusion surgery included male sex (odds ratio [OR] 2.53, 95% CI 1.35–4.91, $P = 0.005$), obesity (OR 2.83, 95% CI 1.52–5.39, $P = 0.001$), Wilson frame use (OR 4.30, 95% CI 2.13–8.75, $P < 0.001$), anesthesia duration (OR per 1 h = 1.39, 95% CI 1.22–1.58, $P < 0.001$), estimated blood loss (OR per 1 l = 1.34, 95% CI 1.13–1.61, $P = 0.001$), and colloid as percent of nonblood replacement (OR per 5% = 0.67, 95% CI 0.52–0.82, $P < 0.001$). After cross-validation, area under the curve = 0.85, sensitivity = 0.79, and specificity = 0.82.

Conclusions: This is the first study to assess ION risk factors in a large, multicenter case-control fashion with detailed perioperative data. Obesity, male sex, Wilson frame use, lon-

What We Already Know about This Topic

- Visual loss after spinal fusion surgery is a devastating complication most commonly caused by ischemic optic neuropathy (ION)
- The risk factors for ION after spinal fusion surgery have not been systematically evaluated with detailed perioperative data

What This Article Tells Us That Is New

- In a case-control examination of 80 patients with ION compared with 315 matched control subjects, independent risk factors were male sex, obesity, Wilson frame use, longer anesthetic duration, greater estimated blood loss, and lower percent colloid administration

* Members of The Postoperative Visual Loss Study Group are listed in the appendix.

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ger anesthetic duration, greater estimated blood loss, and decreased percent colloid administration were significantly and independently associated with ION after spinal fusion surgery.

ALTHOUGH many patients have improved quality of life and function with instrumented spinal fusion surgery, the procedure is often associated with large blood loss, long operative duration, and other complications.[1,2] One of the most devastating complications is postoperative visual loss (POVL), frequently caused by ischemic optic neuropathy (ION).[3] Visual deficits range from blurred vision to complete blindness, usually without significant recovery.[4] Estimates of ION after prone spinal fusion surgery from multicenter or national databases range from 0.017% to 0.1% (direct or derived estimates[5–7]), and the condition can occur in healthy individuals of all ages. Suggested factors associated with ION include anemia, hypotension, blood loss, large fluid shifts, venous congestion of the orbits, and coexisting diseases such as atherosclerotic vascular disease, diabetes, obesity, and hypertension.[3] These factors are also common in patients who have undergone spinal fusion and who do not develop ION, and hence it has not been possible to determine whether they have a causative role in this complication.

Prior studies of ION after spine surgery have been hindered either by small numbers of similar patients with ION from single institutions, or by lack of detailed perioperative data from national inpatient databases.[5–8] The American Society of Anesthesiologists (ASA) POVL Registry database contains the largest collection to date of ION cases associated with spine surgery with detailed anesthetic and postoperative data.[4] Anesthetic records provide frequent intraoperative values for physiologic parameters, fluid and blood product transfusion management, and timing of events. An analysis of the initial 83 ION cases reported to the ASA POVL Registry demonstrated that these cases were characterized by prolonged duration in the prone position and large blood loss; however, the lack of a control group prevented identification of risk factors.[4] We used the ION cases associated with prone spine surgery from the ASA POVL Registry in a multiinstitutional case-control study to identify risk factors for this devastating perioperative complication.

Materials and Methods

Study Design

The study design was multiinstitutional case control, in which preexisting conditions and perioperative factors of patients with ION after spinal fusion from the ASA POVL Registry (n = 80) were compared with control subjects who did not develop ION (n = 315). Institutional review board approval was obtained from the University of Washington and from all participating centers. ION cases from the ASA POVL Registry were collected by voluntary submission using a detailed data collection form.[4]† For the purpose of this analysis, inclusion criteria for ION cases from the ASA POVL Registry were: age ≥18 yr, spine fusion as the first or only spine surgery on index admission, surgery date between 1991 and 2006, prone position for a portion of the procedure, anesthetic duration ≥4 h, and surgical site that included any of the interspaces T1 through S5. Exclusion criteria were any history of perioperative cardiopulmonary resuscitation or cerebrovascular stroke; multiple (staged) spine procedures preceding ION on the index admission, and inadequate/incomplete data. A total of 80 ION cases from the ASA POVL Registry met inclusion and exclusion criteria.

Control subjects were selected from 17 academic medical centers that perform a large volume of spine fusion surgery using the following Current Procedural Terminology codes:[9] 22610 (arthrodesis, posterior or posterolateral, single level; thoracic), 22612 (arthrodesis, posterior or posterolateral, single level; lumbar), 22614 (arthrodesis, posterior or posterolateral, single level; each additional vertebral segment), 22630 [arthrodesis, posterior or interbody technique, including laminectomy or diskectomy, to prepare interspace (other than for decompression) single interspace; lumbar], 22632 [arthrodesis, posterior or interbody technique, including laminectomy or diskectomy, to prepare interspace (other than for decompression), each additional interspace], 22800 (arthrodesis, posterior, for spinal deformity, with or without cast; up to 6 vertebral segments), 22802 (arthrodesis, posterior, for spinal deformity, with or without cast; 7–12 vertebral segments), 22804 (arthrodesis, posterior, for spinal deformity, with or without cast; 13 or more vertebral segments), 22842 (posterior segmental instrumentation; 3–6 vertebral segments), 22843 (posterior segmental instrumentation; 7–12 vertebral segments), 22844 (posterior segmental instrumentation; 13 or more vertebral segments), 22848 [pelvic fixation (attachment of caudal end of instrumentation to pelvic bony structures) other than sacrum], 22849 (reinsertion of spinal fixation device), 22850 (removal of posterior nonsegmental instrumentation, *e.g.*, Harrington rod), and 22852 (removal of posterior segmental instrumentation). A total of 43,410 control subjects were identified with eligible Current Procedural Terminology codes for the control database. Four control subjects per ION case were randomly selected from this control database and matched by year of surgery to the eligible cases. (Matching by year of surgery was not used in the analysis but was conducted for sample selection to mirror possible practice changes in spinal fusion surgery that may have occurred during the study period). After selection, medical records of control subjects were checked for the same inclusion/exclusion criteria as ION cases. In addition, control subjects were excluded for any new perioperative complaint of visual disturbance (excepting isolated corneal abrasion).

† http://depts.washington.edu/asaccp/eye/providers/packet.pdf. Accessed August 28, 2011.

For each control subject designated to be drawn from a center, an additional seven replacements were randomly selected from the same center from the pool of control subjects matched to the case. Replacement control subjects were selected sequentially by each center if the initial control subject did not meet all study criteria, so that the next randomly selected control subject would be included. In the event all replacements were exhausted at a center without meeting study criteria, replacement control subjects were randomly selected from the entire control database, matched by year of surgery to the ION case. A total of 160 control records (50% of the randomly selected control subjects) met all inclusion/exclusion criteria on the first match; the remainder were abstracted from replacements. The most commonly encountered inclusion criteria not met by the first matches were surgical procedure criteria such as surgical site, prone position, duration, and age. The most common exclusion criteria necessitating replacement selection were missing records and staged procedures. Five of 320 control subjects submitted were excluded from the study for failure to meet study criteria during final assessment, leaving 315 control subjects for comparison.

To prevent any one or two centers from dominating the control group, each center was limited to contributing up to 50% more than or 10 patients more than (whichever was larger) its expected total contribution based on caseload for all years combined. Similarly, to avoid random exclusion of centers, each center was required to contribute a minimum of half its expected proportion based on caseload, or a minimum of one control case, whichever was smaller. The centers provided an electronic roster of eligible control subjects along with the required matching data (year of surgery). We randomly selected four control subjects (and seven potential replacements randomly selected from the same center) for each case from the pool of control subjects matched to the case. We compared the percentage distribution of the selected control subjects with the corresponding percentage distribution of eligible control subjects per year and center in the electronic roster to verify similarity of the distributions. If any center had a disproportionate excess or deficit of control subjects, then the sampling process was repeated until an acceptable distribution of controls was obtained.

A subset of patient and perioperative factors from the data available from the ASA POVL Registry was compared between ION cases and control subjects. These factors were hypothesized to be possibly associated with ION. Patient preexisting conditions included age, sex, and the following comorbidities: hypertension, diabetes, smoking, atherosclerosis (any coronary artery disease/myocardial infarction, or cerebrovascular disease), and obesity (defined by either clinical assessment or body mass index $\geq$30). Other patient factors examined included fusion location (lumbar *vs.* nonlumbar), indication for surgery (tumor, trauma, or other), and clinic blood pressure. Predetermined procedural factors included type of surgical frame, number of levels of fusion, and the headrest type. Potentially modifiable intraoperative procedural factors included anesthetic duration and estimated blood loss (EBL). Potentially modifiable intraoperative management factors included decrease in blood pressure (measured as reduction for a minimum of 30 consecutive or nonconsecutive min in the following ranges: 0–20% below baseline; 21–40% below baseline; and >40% below clinic baseline for either systolic blood pressure or mean arterial pressure), lowest hematocrit, fluid management variables (total volume replacement [all blood products, crystalloid, and colloid], total nonblood product replacement [crystalloid and colloid], total volume replacement:EBL ratio, and colloid [hydroxyethyl starch or albumin] as percent of total nonblood replacement), and use of vasopressors.

Data from the ION cases from the ASA POVL Registry with a high proportion of missing values such as increased cholesterol/lipids, tilt of surgical table, facial swelling, airway edema, and other factors, or undefined variables such as deliberate hypotension with wide interpretation were not included in this analysis. Similarly, factors such as cardiopulmonary bypass, use of cyclosporine, and primary anesthetic technique (general, regional, or monitored anesthesia care) that were not relevant for major spinal surgery were not included in this analysis. Factors with very low incidence (less than 5%) in patients and control subjects such as glaucoma, cataracts, macular degeneration, hypothermia, and seizures were also not included in this analysis.

Statistical Analysis

Univariate analysis of the association between patient and perioperative factors and the risk of developing ION was carried out using logistic regression (table 1). The effect of each factor is presented as the odds ratio (OR) from the logistic regression with the corresponding 95% CI and P value. A cutoff of $P < 0.2$ was used as a filter for determining appropriate factors for the multivariate analysis.

For the multivariate analysis, preexisting conditions and perioperative factors were grouped into stages according to their modifiability and role in the surgery (table 1). The stages form a sequence, starting with preexisting conditions (stage 1); predetermined procedural factors (stage 2), potentially modifiable intraoperative procedural factors (stage 3), and potentially modifiable intraoperative management factors (stage 4). Correlation coefficients were determined between potentially interrelated perioperative factors (table 2). The multivariate model was built using the four stages of variables in sequence (table 3). Initially, stage 1 variables with $P < 0.2$ in the univariate analysis were considered for inclusion. Next, additional variables with $P < 0.2$ were selected from stage 2, then sequentially from stages 3 and 4. Variables were selected using the forward stepwise selection technique with $P < 0.05$ for inclusion in the model. Variables selected in previous stages were retained in the model. At the end of each stage, we assessed two-way interactions among all vari-

Table 1. Univariate Analysis of Coexisting Conditions and Perioperative Factors

Stage*	No. Controls/ Cases	Controls Mean ± SD or n (%) Positive	Cases Mean ± SD or n (%) Positive	OR (95% CI)	*P* Value
Stage 1: Preexisting Conditions					
Age (yr), OR per 10 yr	315/80	51.6 ± 17.0	51.3 ± 13.2	1.00 (0.98–1.01)	0.9
ASA 1 and 2 *vs.* 3 and 4	314/78	115 (37%)	25 (32%)	0.82 (0.48–1.37)	0.5
Male	315/80	145 (46%)	55 (69%)	2.58 (1.55–4.41)	<0.001
Obesity	309/80	108 (35%)	43 (54%)	2.16 (1.32–3.57)	0.002
Diabetes	309/80	25 (8%)	13 (16%)	2.20 (1.04–4.47)	0.03
Smoking	310/79	161 (52%)	39 (49%)	0.90 (0.55–1.48)	0.7
Hypertension	314/80	114 (36%)	38 (48%)	1.59 (0.97–2.61)	0.07
Atherosclerosis	311/79	41 (13%)	6 (8%)	0.54 (0.20–1.24)	0.2
Clinic systolic BP (mm), OR per 20 mm	314/79	132 ± 19	136 ± 17	1.27 (0.97–1.66)	0.08
Clinic MAP (mm), OR per 20 mm	314/79	95 ± 13	97 ± 10	1.36 (0.90–2.04)	0.14
Lumbar location (Yes/No)	315/77	281 (89%)	70 (91%)	1.21 (0.54–3.08)	0.7
Year of surgery, OR per yr	315/80	2,000 (3)	2,000 (3)	1.00 (0.92–1.09)	0.99
Stage 2: Predetermined Procedural Factors					
No. of fusions, OR per three fusions	310/76	3.2 ± 2.6	3.6 ± 3.1	1.18 (0.91–1.52)	0.2
Frame	—	—	—	—	<0.001
Jackson	315/80	141 (45%)	23 (29%)	Reference	—
Wilson	315/80	43 (14%)	31 (39%)	4.42 (3.25–8.45)	<0.001
Neither Jackson nor Wilson	315/80	131 (42%)	26 (32%)	1.22 (0.66–2.25)	0.5
Mayfield pins or Gardner-Wells Tongs	315/80	44 (14%)	15 (19%)	1.42 (0.75–2.71)	0.3
Stage 3: Potentially Modifiable Intraoperative Procedural Factors					
Anesthesia duration (h), OR per 1 h	315/80	7.1 ± 2.4	9.6 ± 3.0	1.37 (1.25–1.51)	<0.001
Estimated blood loss (l), OR per 1 l	313/80	1.4 ± 1.4	3.1 ± 3.5	1.43 (1.27–1.65)	<0.001
Stage 4: Potentially Modifiable Intraoperative Management Factors					
BP >40% below baseline 30 min	314/79	56 (18%)	23 (29%)	1.93 (1.09–3.38)	0.02
Lowest intraoperative HCT (%), OR per 5%	231/58	29.2 ± 5.6	27.3 ± 4.6	0.72 (0.54–0.95)	0.02
Vasopressors during maintenance	315/80	114 (36%)	26 (32%)	0.85 (0.50–1.42)	0.5
Total volume replacement (l), OR per 1 l	315/79	6.0 ± 3.3	11.6 ± 6.5	1.30 (1.22–1.40)	<0.001
Total volume replacement/EBL ratio	313/79	6.5 ± 4.3	6.8 ± 8.4	1.01 (0.96–1.05)	0.7
Crystalloid as % of total volume replacement, OR per 10%	315/79	84.6 ± 15.8	84.3 ± 12.0	0.99 (0.84–1.17)	0.9
Total nonblood replacement (l), OR per 1 l	315/79	5.3 ± 2.5	9.7 ± 4.5	1.49 (1.36–1.65)	<0.001
Colloid as % of nonblood replacement, OR per 5%	315/79	8 ± 12	4 ± 6	0.78 (0.65–0.92)	0.005

Blood pressure (BP) >40% below baseline 30 min denotes 40% reduction below baseline BP, for either systolic BP or MAP, for ≥30 min. Total volume replacement is defined as all blood products, crystalloid and colloid administered. Total nonblood replacement is defined as the sum of crystalloid, hydroxyethyl starch, and albumin administered. Colloid is defined as the sum of hydroxyethyl starch and albumin administered. Atherosclerosis is defined as any history of myocardial infarction/cardiovascular or cerebrovascular disease.

* The four groups of variables correspond to the four stages described in the text.

ASA = American Society of Anesthesiologists Physical Status 1–6, a physical status classification based on condition of the patient independent of the planned operation, where ASA 1 is a normal healthy patient; ASA 2, a patient with mild systemic disease that results in no functional limitation; ASA 3, a patient with severe systemic disease that results in physical limitation, ASA 4, a patient with severe systemic disease that is a constant threat to life; ASA 5, a moribund patient who is not expected to survive without the operation; ASA 6, a declared brain-dead patient for organ donation; EBL = estimated blood loss; HCT = hematocrit; MAP = mean arterial pressure; OR = odds ratio.

ables already in the model and added any interactions with $P < 0.01$ to the model.

Alternative multivariate models were constructed by repeating the four-stage variables selection process, but at each stage we used backward elimination variable selection technique ($P > 0.05$ for exclusion) instead of forward stepwise selection. We calculated area under the receiver operating characteristic curve (AUC), and sensitivity and specificity for the model completed after each stage. A sensitivity and specificity combination was selected to maximize the sum of sensitivity and specificity. Two tenfold cross-validations, one for the forward stepwise and one for the backward elimination variable selection technique, were conducted to validate the model-building process. AUC, sensitivity, specificity, and frequency of variable selection in the cross-validation were calculated. Unless noted otherwise, AUC, sensitivity, and specificity are from the cross-validation.

The ORs from the final multivariate model and the ION rates of 0.017% and 0.1% from the literature were used as a basis to estimate a range of absolute ION rates for patients with a specified risk factor profile.[5,7] In calculating the absolute ION rates, our control group was assumed to be representative of the population to which the absolute rate of 0.017% (or 0.1%) applied. Using the multivariate model, an absolute rate of ION can be calculated corresponding to the risk factor profile for each patient in the control group. We multiplied all these rates by a common factor to force the average rate in the control group to be equal to either 0.017% or 0.1%.

The value $P < 0.05$ was used to denote statistical significance. Calculations were carried out in R version 2.12.0

Table 2. Pearson Correlation Coefficients among Intraoperative Variables

Variables Compared	No.Controls/ Cases	Correlation	*P* Value
Obesity and diabetes	303/80	0.19	<0.001
Total volume replacement and anesthesia duration	315/79	0.70	<0.001
Total volume replacement and EBL	313/79	0.75	<0.001
Total nonblood replacement and anesthesia duration	315/79	0.71	<0.001
Total nonblood replacement and EBL	313/79	0.63	<0.001
Total blood replacement and EBL	313/79	0.80	<0.001
Colloid as % of nonblood replacement and anesthesia duration	315/79	0.08	0.13
Colloid as % of nonblood replacement and EBL	313/79	0.14	0.008
Anesthesia duration and EBL	313/80	0.50	<0.001
Lowest HCT and EBL	229/58	−0.36	<0.001
Lowest HCT and anesthesia duration	231/58	−0.33	<0.001
Lowest HCT and total volume replacement	231/57	−0.42	<0.001
Lowest HCT and total nonblood replacement	231/57	−0.37	<0.001
BP >40% below baseline 30 min and anesthesia duration	315/78	0.07	0.14
BP >40% below baseline 30 min and EBL	313/78	0.20	<0.001

Blood pressure (BP) >40% below baseline 30 min denotes 40% reduction below baseline BP for either systolic BP or mean arterial pressure, for ≥30 min. Correlation coefficients of potentially interrelated perioperative variables. Because of the high correlation of total nonblood volume and total volume replacement variables with anesthesia duration or estimated blood loss (EBL), colloid as percent of nonblood replacement was chosen as the volume variable considered in stage 4 of the multivariate analysis.
HCT = hematocrit.

(Vienna, Austria). The sample size was selected to provide 80% power at $P < 0.05$ with two-sided tests to detect an OR of 1.4 (or larger), corresponding to a 1 SD increase in the covariate for continuous variables.

Results

Univariate Analysis

In the univariate analysis, male sex, obesity, diabetes, use of the Wilson frame, anesthesia duration, EBL, and blood pressure more than 40% below baseline values for ≥30 min were associated with a significantly increased risk of ION (table 1). There were no statistically significant associations of case/control status with age, ASA physical status, other preexisting conditions, type of headrest, number of levels fused (table 1), or with indication for surgery (tumor, trauma, or other diagnosis; results not shown).

Higher nadir hematocrit was associated with a decreased risk of developing ION (table 1). This comparison excludes approximately 100 surgeries with unavailable hematocrit data, but there was no statistically significant difference in the risk of ION between those with and those without hematocrit data ($P = 0.9$). Higher total volume replacement and total nonblood replacement conferred an increased risk of developing ION, but the percent crystalloid in the total volume replacement and the total volume replacement to EBL ratio had no statistically significant effect (table 1). The colloid as percent of total nonblood volume replacement was associated with a reduced risk of developing ION (table 1), although most (more than 93%) of control subjects did not exceed 1,500 ml colloid.

Colloid as percent of total nonblood replacement was only weakly correlated with anesthesia duration and EBL, whereas total volume and total nonblood volume variables were highly correlated with these variables (table 2).

Multivariate Regression Model

The final multivariate model after the four stages of the stepwise selection contained the risk factors of male sex (OR 2.53, 95% CI 1.35–4.91, $P = 0.005$), obesity (OR 2.83, 95% CI 1.52–5.39, $P = 0.001$), Wilson frame (OR 4.30, 95% CI 2.13–8.75, $P < 0.001$), anesthetic duration (OR 1.39 per 1 h, 95% CI 1.22–1.58, $P < 0.001$), EBL (OR 1.34 per 1 l, 95% CI 1.13–1.61, $P = 0.001$), and colloid as percent of total nonblood replacement (OR 0.67 per 5% colloid, 95% CI 0.52–0.82, $P < 0.001$) (table 3 cross-validated AUC = 0.85, and fig. 1). During cross-validation analysis, the number of fusions came into every model in stage 2; however, it became a nonsignificant predictor ($P = 0.7–1.0$) when anesthetic duration and EBL were added later in stage 3. Number of fusions appears to be a surrogate marker for anesthesia duration and EBL, which are the significant predictors in the model. Two alternative multivariate models were considered, using alternative fluid replacement variables and an interaction factor for variables in stage 4 (see tables 1 and 2, Supplemental Digital Content 1, http://links.lww.com/ALN/A793, which are tables showing alternative multivariable models for predicting ION that include the total nonblood replacement variable and interaction factor for total nonblood replacement: anesthesia duration in stage 4).

Using the final multivariate forward selection stepwise model in table 3, and using an ION incidence of either 0.017% or 0.1%, the absolute and relative risk of patients developing ION was calculated based on the presence of one or more risk

Table 3. Multivariate Regression Analysis*

—	Stage 1 Model Preexisting Conditions		Stage 2 Model Predetermined Procedural Factors		Stage 3 Model Potentially Modifiable Intraoperative Procedural Factors		Stage 4 Model Potentially Modifiable Intraoperative Management Factors	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Male	2.80 (1.66–4.85)	<0.001	2.49 (1.46–4.37)	0.001	2.72 (1.47–5.18)	0.002	2.53 (1.35–4.91)	0.005
Obesity	2.38 (1.43–3.99)	<0.001	2.07 (1.22–3.53)	0.007	2.35 (1.30–4.32)	0.005	2.83 (1.52–5.39)	0.001
Wilson	—	—	3.40 (1.90–6.06)	<0.001	4.87 (2.48–9.68)	<0.001	4.30 (2.13–8.75)	<0.001
Anesthesia duration (hr), OR per 1 h	—	—	—	—	1.32 (1.18–1.50)	<0.001	1.39 (1.22–1.58)	<0.001
Estimated blood loss (l), OR per 1 l	—	—	—	—	1.31 (1.12–1.54)	<0.001	1.34 (1.13–1.61)	0.001
Colloid as % of nonblood replacement, OR per 5%	—	—	—	—	—	—	0.67 (0.52–0.82)	<0.001
AUC (all data/ cross-validation)	0.64/0.60	—	0.71/0.71	—	0.85/0.83	—	0.87/0.85	—
Sensitivity† (all data/cross-validation)	0.69/0.36	—	0.55/0.63	—	0.85/0.88	—	0.81/0.79	—
Specificity† (all data/cross-validation)	0.54/0.86	—	0.80/0.73	—	0.73/0.65	—	0.82/0.80	—

* Only variables with $P < 0.2$ in the univariate analysis (table 1) were considered. Selection criterion: $P < 0.05$. At the end of each stage, interactions were tested for variables in the model and were added if $P < 0.01$ (no interactions in this model had P values <0.01). The same model was derived using backward elimination ($P > 0.05$ for exclusion). The following variables were considered: stage 1: sex, obesity, diabetes, hypertension, atherosclerosis, clinic systolic blood pressure, clinic mean arterial blood pressure; stage 2: Wilson frame; stage 3: anesthesia duration and estimated blood loss, stage 4: lowest intraoperative hematocrit, systolic or mean arterial blood pressure >40% below baseline 30 min, and colloid as percent of nonblood replacement. Because of the high correlation with anesthesia duration, estimated blood loss, total volume replacement and total nonblood replacement variables (table 2), colloid as percent of nonblood replacement was chosen as the volume variable considered in stage 4 of the multivariate analysis (see Discussion). Alternative multivariate models including total nonblood replacement in stage 4 are shown in Supplemental Digital Content 1, tables describing these models, http://links.lww.com/ALN/A793. † This combination of sensitivity and specificity optimizes the sum of the two. Other combinations can be calculated with trade-offs between better/worse sensitivity combined with worse/better specificity, respectively.

AUC = area under the curve; OR = odds ratio.

factors (table 4). This table can be used to evaluate the increased absolute and relative risks of ION by changing one or more variables in the model such as sex, surgical frame, anesthesia duration, EBL, or colloid as % of nonblood replacement.

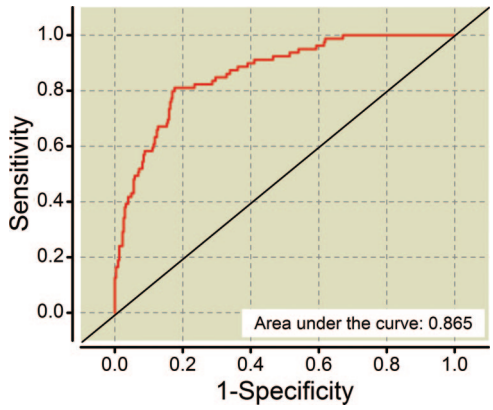

Fig. 1. Receiver operating characteristic curve for final (stage 4) multivariate model. Area under the curve = 0.87. Plot of the false negative rate (1-Specificity) *versus* the true positive rate (Sensitivity) for the final multivariate regression model in table 3. Area under the curve after cross validation = 0.85.

Discussion

This is the first multicenter study to identify risk factors for ION patients compared with patients without ION after prone spinal fusion surgery using detailed perioperative data. This study design is unique because of the large number of ION cases obtained from a national registry, the large multiinstitutional dataset of control subjects, and the detailed perioperative information in anesthetic and postoperative records. This data analysis identified novel risk factors for ION after spine surgery including male sex, Wilson frame use, longer anesthetic duration, greater EBL, and decreased percent colloid administration, and confirmed the risk factor of obesity identified in a previous study.[5] Although one previous study found that longer anesthetic duration and greater EBL were associated with POVL after spine surgery, the cases used were a heterogeneous mix of POVL diagnoses including ION, cortical blindness, and central retinal artery occlusion.[10] The predictive model identified from these data may allow clinicians to estimate the risk of ION for specific patients undergoing spine surgery.

Table 4. Risk Prediction for ION after Major Spine Surgery: Effect of Changes in Variables on ION Risk

Sex	Obesity	Wilson Frame	Anesthesia (h)	EBL (l)	Colloid (%)*	Absolute Risk of ION per 10,000 Procedures† (Based on 0.017% Overall Rate)	Absolute Risk of ION per 10,000 Procedures† (Based on 0.1% Overall Rate)	Relative Risk‡
Female	**No**	**No**	**5**	**1**	**10**	0.08	0.45	1.00§
Female	**Yes**	No	5	1	10	0.22	1.27	2.83
Female	No	**Yes**	5	1	10	0.33	1.93	4.30
Female	No	No	**7.5**	1	10	0.17	1.01	2.26
Female	No	No	**10**	1	10	0.39	2.30	5.12
Female	No	No	5	**2**	10	0.10	0.60	1.34
Female	No	No	5	**3**	10	0.14	0.80	1.78
Female	No	No	5	1	**0**	0.17	1.00	2.24
Female	**Yes**	**Yes**	**10**	**3**	**0**	18.98	111.67	249.27
Male	No	No	5	1	10	0.19	1.14	2.53
Male	**Yes**	No	5	1	10	0.55	3.21	7.17
Male	No	**Yes**	5	1	10	0.83	4.89	10.91
Male	No	No	**7.5**	1	10	0.44	2.57	5.74
Male	No	No	**10**	1	10	0.99	5.82	12.98
Male	No	No	5	**2**	10	0.26	1.52	3.39
Male	No	No	5	**3**	10	0.34	2.03	4.52
Male	No	No	5	1	**0**	0.43	2.54	5.67
Male	**Yes**	**Yes**	**10**	**3**	**0**	48.11	283.00	631.73

Variables in bold and shaded areas indicate changes in risk factors from the female reference patient with the lowest risk variables in this table (bold, first line), to demonstrate the effect on the range of absolute and relative risks of ION using examples of common clinical scenarios. For example, a male patient has an increased relative risk = 2.53 for ION compared with the reference female patient, with an absolute risk range of 0.19–1.14 per 10,000 procedures; an obese female patient has an increased relative risk = 2.83 for ION compared with the reference nonobese female patient, with an absolute risk range of 0.22–1.27 per 10,000 procedures; a female patient placed on a Wilson frame has an increased relative risk = 4.30 for ION compared with the reference female patient (non-Wilson frame), with an absolute risk range of 0.33–1.93 per 10,000 procedures; *etc*. The highest risk variables for females and males are shown in the last row of each sex group. In this table, the clinical scenario with the highest risk variables for males (obese, Wilson frame use, 10-h duration, 3 l EBL, no colloid in the total nonblood replacement) has a 631-fold increased risk of ION compared with the clinical scenario with the lowest risk variables for females (nonobese, no Wilson frame use, 5-h duration, 1 l EBL, and 10% colloid of total nonblood replacement).

* Colloid as % of total non-blood replacement, where total non-blood replacement = (crystalloid + albumin + hetastarch). † Range of low and high absolute risks of ION based on the literature from multicenter studies or national databases.[5–7] ‡ Relative risk of ION compared with the lowest risk set of patient variables in this table: first row (bold, no shading), reference value = 1 · 0. § Reference category for relative risk: female, non-obese, non-Wilson frame, 5 h anesthesia duration, 1 l EBL, and 10% colloid of non-blood replacement administered, first row (bold, no shading).

EBL = estimated blood loss; ION = ischemic optic neuropathy.

Limitations

The use of a voluntary registry with anonymous submission for obtaining ION cases has limitations. Bias and inaccuracy may be introduced by its retrospective nature and the type of cases submitted; however, the reliability of ION case data were previously found to be acceptable to excellent.[4] Cases with anterior and posterior ION occurring after major spine surgery were combined because of the lack of any significant differences between groups in the variables studied herein, similarities in ophthalmologic findings, and their occurrence after the same procedure.[4] This supposition could influence the effect of variables on the outcome. Data on control subjects were collected in a more rigorous fashion than for cases because all control entries were made by study investigators. Variables such as operative table tilt noted to have a substantial percentage of missing values in the ION cases were excluded from the study. We cannot eliminate the possibility of missing an effect of these variables or other unmeasured variables on the development of ION. Although the anesthesia time was the most accurate record of time in the operating room, it is a surrogate for operative time. We also cannot exclude the possibility that the cases come from a different mix of institutions than control subjects and that some of the effect of risk factors may be a facility effect. Due to the limited number of ION cases (n = 80) available for modeling, there was no dataset available to validate the predictive model. Due to these limitations, quantitative estimates of risk must be interpreted with caution. Although only statistically significant factors in the multivariate model ($P < 0.05$) are considered to have an independent effect on ION, the effect of other statistically significant factors from the univariate analysis cannot be excluded with absolute certainty.

Risk Factors

The higher proportion of men developing perioperative ION after spinal fusion surgery (69%) is much greater than the almost equivalent proportion of men and women under-

going spine surgery.‡ It is almost identical to the proportion of men who develop perioperative ulnar neuropathy (70%).[11] There are no known sex-related anatomic differences in the anatomy of the anterior visual pathways, but some animal studies suggest a protective effect of estrogen with specific optic nerve disease.[12] Our multivariate analysis found no statistically significant independent effect on ION of older age, hypertension, atherosclerosis, smoking, or diabetes. These data are in agreement with case reports of ION in children after major spine surgery, and with literature reviews demonstrating that most ION patients after prone spine surgery are relatively healthy.[3,13,14] These findings suggest that the etiology of ION may be more strongly influenced by intraoperative physiologic perturbations than by any known preexisting disease or vasculopathy.

Obese patients may have increased intraabdominal and central venous pressures in the prone position related to increased abdominal girth, thereby causing increased venous pressure in the head. These physiologic changes reduce systemic venous return and cardiac output, leading to reduced end organ blood flow. Similarly, the Wilson frame is a rounded, hump-shaped frame that places the patient's head much lower than the heart, and may greatly exacerbate venous congestion in the head over time. Prolonged acute elevation of venous pressure in the orbit can lead to interstitial edema formation and reduced perfusion pressure, which may also negatively affect oxygen delivery to the optic nerve.

The finding of increasing duration in the prone position and increasing EBL as risk factors for ION is consistent with case series and literature reviews.[3,4,7] This effect may have been larger if all prone spine operations had been included, instead of only those with ≥4 h anesthetic duration. Larger EBL increases fluid shifts, capillary leak, interstitial edema, and systemic inflammation. It also predisposes to periods of reduced cardiac output and end-organ blood flow. Prolonged duration allows for increased blood loss and subsequent increased fluid administration, and exposes the patient for longer periods to the physiologic perturbations predisposing to ION.

The addition of fluid replacement variables to the model did not substantially change the AUC for predicting ION because of strong correlations between total volume variables, anesthetic duration, and EBL (tables 2 and 3). Separating specific effects of these variables was not possible with this retrospective nonrandomized study design. Percent colloid of nonblood replacement was chosen as the fluid replacement variable in the multivariate model because it was only weakly correlated with anesthetic duration and EBL. Moreover, inclusion of total volume variables would conceal potentially significant differences in volume expansion and transcapillary leakage between crystalloid, colloid, and blood products. Despite its high statistically significant effect on ION, the difference in the average percent colloid of nonblood replacement between control subjects and cases was 4%, making its clinical significance less certain.

The lack of an independent effect of anemia or any blood pressure more than 40% below baseline for 30 min in the multivariate analysis demonstrates the importance of using detailed perioperative data on control subjects to assess whether or not the effect of these factors remains significant when other relevant intraoperative data such as anesthesia duration, EBL, and volume administration are analyzed. These data, uniquely available in the current study, were not available from the National Inpatient Sample database, case series, or literature reviews.[3–7]

Acute Venous Congestion

We have previously hypothesized that ION associated with prone spine surgery may be related to the acutely increased venous pressure in the head and neck,[4] because other procedures with similar physiology in the head such as bilateral radical neck operations and robotic prostatectomies in the steep head-down position are also associated with ION.[15,16] Placing a patient in the prone position increases intraabdominal, intrathoracic, and intraocular pressures.[17,18] It is theorized that the increased venous pressure in the head and neck leads to interstitial fluid accumulation from capillary leak, decreased venous outflow, and decreased perfusion of the optic nerve. After a critical period of time, damage to the optic nerve could occur *via* various mechanisms, including ischemia caused by compression of small pial arteries supplying the nerve, venous infarction from reduced venous outflow, or even direct mechanical damage from the elevated interstitial pressures. Most perioperative ION cases associated with spine surgery occur in the posterior optic nerve where there is poor collateral flow, making the nerve vulnerable to prolonged pathophysiologic changes in blood flow, both venous and arterial.[4,15,16] Almost all of the variables selected into the multivariate model in table 3 including obesity, Wilson frame, anesthetic duration, EBL, and % colloid of nonblood volume, could exacerbate these proposed pathophysiologic mechanisms.

Prevention

At this point, preventive strategies are the only option to reduce the effect of this complication, as effective treatment has not been identified. Using this model, the only preoperative factor that is practically modifiable is surgical frame selection and position. Maneuvers to keep the head at or above heart level to reduce venous congestion in the head have been recommended in the ASA practice advisory for perioperative visual loss associated with spine surgery.[19] Minimizing duration in the prone position and maximizing hemostasis may also be beneficial, although the utility of staging complex procedures would require further study to

‡ Merrill C, Elixhauser A: Hospital stays involving musculoskeletal procedures, 1997–2005, Statistical Brief #34 from the Healthcare Cost and Utilization Project and the Agency for Healthcare Research and Quality. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb34.pdf. Accessed February 3, 2011.

assess the relative risks and benefits. Theoretically, using colloid along with crystalloid, also suggested in the ASA practice advisory,[19] may reduce the edema formation, but also requires further study as colloids are associated with dose-related deleterious side effects and increased mortality in critically ill patients.[20,21] The low incidence of perioperative ION may preclude randomized controlled trials demonstrating benefit from these suggested interventions.

The prediction table for ION (table 4) uses examples of different typical values of the variables from the final multivariate model to provide an absolute risk (rate per 10,000 procedures) and relative risk assessment for patients, surgeons, and anesthesiologists. Validation of this multivariate model will require testing in a new population. Patients undergoing lengthy spine surgery in the prone position should be informed of the increased risk for ION.[22] In this era of informed and shared decision-making with patients, these data might influence patients' and surgeons' decisions between conservative management and various options for surgical treatments. Anesthesiologists could use these data to guide fluid administration.

In conclusion, this study demonstrates that obese and male patients have an increased risk of developing ION after major spinal surgery in the prone position. Avoidance of the Wilson frame and minimizing the anesthetic duration and EBL may decrease the risk of developing ION. Use of colloid along with crystalloid may decrease the risk of developing ION, but its overall risk-to-benefit profile in major spine surgery cannot be adequately evaluated using this study design. Prediction tables for ION based on this study may help inform patients, surgeons, and anesthesiologists of the absolute and relative risk for patients developing ION, and guide decision-making.

Appendix: The Postoperative Visual Loss Study Group Investigators

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