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Original Article

Preoperative anemia increases postoperative morbidity in elective cranial neurosurgery

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Abstract

Background: Preoperative anemia may affect postoperative mortality and morbidity following elective cranial operations.

Methods: The American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database was used to identify elective cranial neurosurgical cases (2006-2012). Morbidity was defined as wound infection, systemic infection, cardiac, respiratory, renal, neurologic, and thromboembolic events, and unplanned returns to the operating room. For 30-day postoperative mortality and morbidity, adjusted odds ratios (ORs) were estimated with multivariable logistic regression.

Results: Of 8015 patients who underwent elective cranial neurosurgery, 1710 patients (21.4%) were anemic. Anemic patients had an increased 30-day mortality of 4.1% versus 1.3% in non-anemic patients ($P < 0.001$) and an increased 30-day morbidity rate of 25.9% versus 14.14% in non-anemic patients ($P < 0.001$). The 30-day morbidity rates for all patients undergoing cranial procedures were stratified by diagnosis: 26.5% aneurysm, 24.7% sellar tumor, 19.7% extra-axial tumor, 14.8% intra-axial tumor, 14.4% arteriovenous malformation, and 5.6% pain. Following multivariable regression, the 30-day mortality in anemic patients was threefold higher than in non-anemic patients (4.1% vs 1.3%; OR = 2.77; 95% CI: 1.65-4.66). The odds of postoperative morbidity in anemic patients were significantly higher than in non-anemic patients (OR = 1.29; 95% CI: 1.03-1.61). There was a significant difference in postoperative morbidity event odds with a hematocrit level above (OR = 1.07; 95% CI: 0.78-1.48) and below (OR = 2.30; 95% CI: 1.55-3.42) 33% [hemoglobin (Hgb) 11 g/dl].

Conclusions: Preoperative anemia in elective cranial neurosurgery was independently associated with an increased risk of 30-day postoperative mortality and morbidity when compared to non-anemic patients. A hematocrit level below 33% (Hgb 11 g/dl) was associated with a significant increase in postoperative morbidity.

Key Words: Anemia, cranial, hematocrit, hemoglobin, National Surgical Quality Improvement Program, neurosurgery

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INTRODUCTION

Anemia has been shown to be an independent risk factor of postoperative mortality and morbidity for several surgical procedures.[4,6,9,28,32,47] Anemia is of particular concern in clinical neurosurgery due to the substantial metabolic demand of neural tissue. Compensatory mechanisms can alleviate some effects of a low hematocrit, such as autoregulatory changes in cerebral blood flow[18,19,26] and greater oxygen extraction ratios.[26] However, an optimal hematocrit value or range has yet to be established.[42]

The effect of anemia on overall short-term mortality and morbidity following cranial surgery remains uncertain. Preoperative anemia can exacerbate the clinical manifestations of significant intraoperative blood loss, which may range from 50 to 4300 ml[48] in cranial surgery.[26,40] With over 574,000 cranial neurosurgical procedures performed in the United States each year,[37] it is important to assess preoperative anemia as a risk factor for morbidity and mortality. Currently in neurosurgery, anemia is associated with worse outcomes in emergent cases for aneurysmal subarachnoid hemorrhage (SAH);[26] however, no similar association has been found in elective neurosurgical cases.

The purpose of this study was to determine the effect of preoperative anemia on overall short-term mortality and morbidity in patients undergoing elective cranial surgery. Also, tolerable hematocrit levels and postoperative morbidity profiles were explored for various neurosurgical procedures.

METHODS

Data source

The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database was used to identify patients undergoing common cranial neurosurgical procedures between 2006 and 2012. NSQIP is a nationally validated, risk-adjusted, prospectively collected database, which provides perioperative prognostic variables.[15] Over 250 hospitals, both academic and non-academic, participate in NSQIP, with over 2,000,000 patients collected to date. NSQIP has accumulated over 40,000 neurosurgical procedures to date.

Patients

We identified patients undergoing common elective cranial surgeries from 2006 to 2012 using American Medical Association Current Procedural Terminology (CPT) codes. All emergent procedures were excluded. The following CPT codes were included: 61450, 61458, 61460, 61500, 61512, 61519, 61600, 61510, 61545, 61546, 61575, 61576, 61583, 61584, 61680, 61682, 61684, 61690, 61697, 61698, 61700, and 61702. The CPT code descriptions can be found in Table 1. The six craniotomy or craniectomy procedural categories included in the study are: Pain (decompression of sensory root ganglion or cranial nerves), removal of extra-axial tumor or lesion, removal of intra-axial tumor, excision of sellar/parasellar tumors by craniofacial or orbitocranial approach, arteriovenous malformation (AVM), and aneurysm.

Definition of primary outcome and anemia

The primary outcome was 30-day overall postoperative mortality and morbidity, which was an aggregation of all available complications in the NSQIP database. These complications include wound infection, systemic infection, cardiac, respiratory, renal, neurologic, thromboembolic events, and unplanned returns to the operating room, as seen in Table 2. Anemia's influence on the primary outcome was assessed. According to the definitions from the World Health Organization,[22] anemia was defined as a preoperative hematocrit <36% [hemoglobin (Hgb) <11 g/dl] for women and <39% (Hgb <13 g/dl) for men for dichotomous analysis and <39% (Hgb <13 g/dl) for categorical analysis. Hgb values can be determined by dividing the hematocrit level by 3.

Statistical analyses

The study population was described using summary statistics. Continuous variables are displayed as their mean and standard deviation [mean (SD)], while categorical variables are displayed as the number of patients followed by the corresponding proportion with respect to the exposure group [*n* (%)]. Comparisons between groups were made using the *t*-test/Wilcoxon rank-sum test for continuous variables or the Chi-squared test for categorical variables, as appropriate. Results were considered significant if the observed $P > 0.05$.

For 30-day postoperative mortality and morbidity occurrence, adjusted odds ratios (ORs) were estimated using a multivariable logistic regression model for anemic versus non-anemic patients. Modeling was done using a forward stepwise approach, and the model was adjusted extensively for both clinically and statistically relevant confounders [Tables 3 and 4]. That is, preoperative predictors in NSQIP were tested in the univariable regression model. Statistically significant variables in the simple logistical regression were then included in the multiple logistical regression. In total, 17 variables were adjusted for in the multiple logistical regression model: Age, sex, body mass index (BMI), smoking status, operation year, work relative value units, wound classification, current wound infection, transfusion <72 h prior to surgery, cardiovascular, neurological, respiratory, and renal comorbidity, diabetic status, steroid use for chronic condition, length of operation, and history of previous operation within 30 days of the surgery. Lastly, preoperative predictors

Table 1: Descriptions of CPT codes for cranial neurosurgical procedures

CPT code number	Description
Craniotomy for pain	
61450	Craniectomy, subtemporal; for section, compression, or decompression of sensory root of gasserian ganglion
61458	Craniectomy, suboccipital; for exploration or decompression of cranial nerves
61460	Craniectomy, suboccipital; for section of one or more cranial nerves
Craniotomy for removal of extra-axial tumor or lesion	
61500	Craniectomy; with excision of tumor or other bone lesion of skull
61512	Craniectomy, trephination, bone flap craniotomy; for excision of meningioma, supratentorial
61519	Craniectomy for excision of brain tumor, infratentorial or posterior fossa; meningiomas
61600	Resection or excision of neoplastic, vascular or infectious lesion of the base of anterior cranial fossa; extradural
Craniotomy for removal of intra-axial tumor	
61510	Craniectomy, trephination, bone flap craniotomy; for excision of brain tumor, supratentorial, except meningiomas
Excision of sellar/parasellar tumors	
61545	Craniotomy with elevation of bone flap; for excision of craniopharyngioma
61546	Craniotomy for hypophysectomy or excision of pituitary tumor, intracranial approach
61575	Transoral approach to the skull base, brain stem, or upper spinal cord for biopsy, decompression or excision of lesion
61576	Transoral approach to the skull base, brain stem, or upper spinal cord for biopsy, decompression or excision of lesion; requiring splitting of tongue and/or mandible (including tracheostomy)
61583	Craniofacial approach to anterior cranial fossa; intradural, including unilateral or bifrontal craniotomy, elevation or resection of frontal lobe, osteotomy of base of anterior cranial fossa
61584	Orbitocranial approach to anterior cranial fossa; extradural, including supraorbital ridge osteotomy and elevation of frontal and/or temporal lobe (s); without orbital exenteration
Craniotomy for intracranial vascular lesion (arteriovenous malformation)	
61680	Surgery of intracranial arteriovenous malformation; supratentorial, simple
61682	Surgery of intracranial arteriovenous malformation; supratentorial, complex
61684	Surgery of intracranial arteriovenous malformation; infratentorial, simple
61690	Surgery of intracranial arteriovenous malformation; dural, simple
Craniotomy for intracranial vascular lesion (aneurysm)	
61697	Surgery of complex intracranial aneurysm, intracranial approach; carotid circulation
61698	Surgery of complex intracranial aneurysm, intracranial approach; vertebrobasilar circulation
61700	Surgery of simple intracranial aneurysm, intracranial approach; carotid circulation
61702	Surgery of simple intracranial aneurysm, intracranial approach; vertebrobasilar circulation

in NSQIP that contained over 10% missing values were not included in the multivariable regression analysis; however, these variables were not significant in the univariable logistical regression. Thus, these dropped variables would not represent unmeasured confounders in the multivariable results.

Data management and statistical analyses were done with STATA/SE 12. In accordance with Johns Hopkins guidelines (which follow the US Code of Federal Regulations for the Protection of Human Subjects), Institutional Review Board approval was not needed or sought for the present study. Data were collected as an ACS-NSQIP quality assurance endeavor and only de-identified data were received.

RESULTS

This study analyzed 8015 prospectively collected patients undergoing elective cranial neurosurgery from 2006 to 2012 in the NSQIP databases. Perioperative prognostic factors including age, sex, BMI, race, smoking status, diabetes, alcohol intake, steroid use, operative time, reoperation, and composite system morbidity variables have been included in Table 5. The mean age of patients was 56.1 years and the average BMI was 28.6. Of the total population, 1710 patients (21.4%) were anemic with a preoperative hematocrit below 39 for men and below 36 for women. Hematocrit values were collected on an average of 5.3 ± 8.6 days before surgery. The patients underwent six main procedures (craniotomy or craniectomy) for pain (5.1%), extra-axial tumor (25.8%),

Table 2: General characteristics of patients undergoing elective cranial neurosurgery by anemia status

	Non-anemic patients (*n*=6301)	Anemic patients (*n*=1710)	*P* value	All patients (*N*=8015)
General variables, n (%)				
Age, mean±SD	55.2±14.6	59.4±14.9	0.332	56.1±14.7
BMI, mean±SD	28.7±6.5	27.8±6.5	0.985	28.6±6.5
Sex (female)	3520 (55.86)	896 (52.40)	**<0.001**	4416 (55.10)
Race				
Caucasian	4465 (70.86)	1164 (68.07)	**<0.001**	5631 (70.26)
African American	358 (5.68)	172 (10.06)		530 (6.64)
Latino	1087 (17.25)	255 (14.91)		1342 (16.74)
Asian/American Indian/ Native Hawaiian Pacific Islander	178 (2.82)	55 (3.22)		234 (2.92)
Unknown	213 (3.38)	64 (3.74)		278 (3.47)
Current smoker	1371 (21.76)	360 (21.05)	0.952	1732 (21.61)
Diabetes	605 (9.60)	328 (19.18)	**<0.001**	933 (11.64)
Non-insulin	414 (6.57)	184 (10.76)		598 (7.46)
Insulin	191 (3.03)	144 (8.42)		335 (4.18)
Operation time, mean minutes±SD	212.5±126.6	207.5±123.3	0.176	211.4±125.9
Alcohol intake in previous 2 weeks†	116 (3.50) *n*=3317*	27 (3.03) *n*=890*	0.948	143 (1.78) *n*=4209*
Steroid use for chronic condition	1007 (15.98)	316 (18.48)	**0.009**	1325 (16.53)
Operation within previous 30 days	43 (1.31) *n*=3277*	34 (3.83) *n*=887*	**<0.001**	77 (1.83) *n*=4209*
Composite system morbidity variables, *n* (%)				
Composite cardiovascular morbidity	487 (7.73)	237 (13.86)	**<0.001**	724 (9.04)
Composite neurological morbidity††	1940 (30.79)	557 (32.57)	0.158	2497 (31.17)
Composite respiratory morbidity	286 (4.54)	176 (10.29)	**<0.001**	462 (5.77)
Composite hepatobiliary morbidity	0 (0.00)	5 (0.29)	**<0.001**	5 (0.06)
Composite renal morbidity	5 (0.08)	25 (1.46)	**<0.001**	30 (0.37)
Composite hemato-oncological morbidity	1032 (16.38)	543 (31.75)	**<0.001**	1575 (19.66)

Data presented as *n* (% of column total), *n*: Total number of patients; SD: Standard deviation; BMI: Body mass index; †>Two drinks per day, **n*=number of patients in alcohol and previous operation variables reduced due to missing data, ††composite neurological morbidity other than main lesion. Bold values represent statistically significant values

intra-axial tumor (57.2%), sellar tumor (2.7%), AVM (2.5%), and aneurysm (6.7%).

Medical comorbidities

In general, anemic and non-anemic cohorts had similar ages, BMIs, smoking status, operation times, and alcohol intake within the previous 2 weeks. Anemic patients were more likely to be African American, diabetic, on steroids for a chronic condition, and have had an operation within the previous 30 days [Table 5]. When stratified by procedure type, patients had the same preoperative renal and hepatobiliary morbidity. Patients undergoing craniotomy for pain had the least amount of comorbidities. Patients with aneurysms had the most preoperative cardiovascular, preoperative neurological (beside their main lesion), and respiratory morbidity. Furthermore, patients with an intra-axial tumor had the highest rate of hemato-oncological comorbidity.

Postoperative complications

Anemic patients had an overall 30-day mortality rate of 4.1% versus 1.3% in non-anemic patients ($P < 0.001$) and an overall 30-day morbidity rate of 25.9% versus 14.1% in non-anemic patients ($P < 0.001$) [Table 6]. Anemic and non-anemic patients had the same rates of superficial surgical site infection (SSI), deep incisional SSI, organ space SSI, wound dehiscence, pulmonary embolism, progressive renal insufficiency, stroke with neurological deficit, coma greater than 24 h, cardiac arrest requiring cardiopulmonary resuscitation (CPR), and unplanned return to the operating room. Anemic patients had statistically significantly increased rates of pneumonia (2.9% vs. 1.3%), unplanned intubation (3.0% vs. 1.7%), being on the ventilator >48 h (2.6% vs. 0.4%), acute renal failure (0.2% vs. 0.1%), urinary tract infection (4.4% vs. 2.5%), myocardial infarction (0.5% vs. 0.2%), graft/prosthesis failure (0.1% vs. 0.0%), deep vein thrombosis/thrombophlebitis requiring treatment (3.3% vs. 2.1%), sepsis (3.4% vs. 1.4%), and septic shock (1.2% vs. 0.5%) over non-anemic patients, respectively.

Patients undergoing craniotomy for an aneurysm had statistically significantly higher rates of pneumonia, unplanned intubation, utilization of a ventilator >48 h, urinary tract infection, stroke with neurological deficit, coma >24 h, and septic shock [Table 2]. Sellar tumor patients had the highest rate of postoperative sepsis.

Table 3: 30-day mortality and morbidity complications of patients undergoing elective cranial neurosurgery by anemia status

	Non-anemic (*n*=6301)	Anemic (*n*=1710)	*P* value
Mortality			
Deceased	82 (1.30)	70 (4.09)	**<0.001**
Overall morbidity			
Total morbidity events	1116	519	-
Total number of patients with ≥1 morbidity event	891 (14.14)	443 (25.91)	**<0.001**
Superficial surgical site infection	37 (0.59)	9 (0.53)	0.768
Deep incisional SSI	25 (0.40)	8 (0.47)	0.684
Organ space SSI	54 (0.84)	18 (1.05)	0.408
Wound dehiscence	10 (0.16)	4 (0.23)	0.509
Pneumonia	79 (1.25)	50 (2.92)	**<0.001**
Unplanned intubation	109 (1.73)	51 (2.98)	0.001
Pulmonary embolism	104 (1.65)	19 (1.11)	0.108
On ventilator >48 h	23 (0.37)	45 (2.63)	**<0.001**
Progressive renal insufficiency	5 (0.08)	3 (0.18)	0.265
Acute renal failure	3 (0.05)	4 (0.23)	0.021
Urinary tract infection	156 (2.48)	76 (4.44)	**<0.001**
CVA/stroke with neurological deficit	119 (1.89)	41 (2.40)	0.182
Coma >24 h	17 (0.27)	8 (0.47)	0.193
Cardiac arrest requiring CPR	19 (0.30)	3 (0.18)	0.377
Myocardial infarction	11 (0.17)	8 (0.47)	**0.027**
Graft/prosthesis failure	0 (0.00)	2 (0.12)	**0.007**
DVT/thrombophlebitis requiring treatment	135 (2.14)	56 (3.27)	**0.006**
Sepsis	87 (1.38)	58 (3.39)	**<0.001**
Septic shock	31 (0.49)	20 (1.17)	**0.002**
Unplanned return to operating room (*n*=2748*)	92 (4.31)	36 (5.91)	0.097

Data presented as *n* (% of column total). *Unplanned reoperations only recorded post-2011, *n*: Number of patients; SSI: Surgical site infection; CVA: Cerebrovascular accident; CPR: Cardiopulmonary resuscitation; DVT: Deep vein thrombosis Bold values represent statistically significant values. Bold values represent statistically significant values

The highest rates of unplanned reoperation occurred in patients undergoing craniotomy for sellar tumor at 10.1%. The overall 30-day morbidity rates for all patients undergoing cranial procedures stratified by diagnosis are as follows: 26.5% for aneurysm, 24.7% for sellar tumor, 19.7% for extra-axial tumor, 14.8% for intra-axial tumor, 14.4% for AVM, and 5.6% for pain. The 30-day mortality rates for each diagnosis were: 3.2% for aneurysm, 2.3% for intra-axial tumor, 1.9% for sellar tumor, 1.2% for extra-axial tumor, 0.0% for AVM, and 0.0% for pain.

Logistic regression analyses

Initial regression analyses compared all anemic patients to non-anemic patients undergoing cranial neurosurgery [Table 3]. On univariable regression analysis, anemic patients were found to have statistically significantly higher odds of postoperative mortality (OR = 3.24; 95% CI: 2.34-4.47) and morbidity (OR = 1.70; 95% CI: 1.47-1.97). After a forward selection, stepwise regression model building approach, we adjusted for preoperative general characteristics and comorbidities, which on multivariable regression analysis revealed anemic patients to have statistically significantly higher odds of postoperative morbidity when compared to their non-anemic counterparts (OR = 1.29; 95% CI: 1.03-1.61). Attempts to identify a hematocrit level at which morbidity was increased revealed no differences between anemic and non-anemic patients above the 33% hematocrit level (Hgb 11 g/dl). However, patients with a hematocrit of ≥30 (Hgb 10 g/dl) but less than 33 (Hgb 11 g/dl) had increased odds of morbidity (OR = 2.30; 95% CI: 1.55-3.42). Also, all patients with a hematocrit lower than 30 (Hgb 10 g/dl) had increased odds of morbidity (OR = 1.84; 95% CI: 1.01-3.34). Finally, 30-day mortality for anemic patients was almost threefold higher than for non-anemic patients (4.1% vs. 1.3%; OR = 2.77; 95% CI: 1.65-4.66).

When multivariable regression analyses are stratified by procedure type, each cranial procedure group demonstrated increased odds of postoperative morbidity in anemic patients, except extra-axial tumors [Table 4]. Craniotomy for intra-axial tumor (OR = 2.15; 95% CI: 1.24-3.74), sellar tumor (OR = 9.69; 95% CI: 1.04-90.20), and aneurysm (OR = 3.30; 95% CI: 1.45-7.50) all revealed increased odds of postoperative morbidity at the 30-33% hematocrit level (Hgb 10–11 g/dl). All patients undergoing craniotomy for pain with a hematocrit lower than 33% (Hgb 11 g/dl) experienced morbidity. Moreover, all patients with a hematocrit lower than 30% (Hgb 10 g/dl) in the AVM cohort experienced morbidity. These data are consistent with the overall anemic cohort demonstrating increased odds of morbidity below the 33% (Hgb 11 g/dl) hematocrit level.

DISCUSSION

While anemia has been shown to be a risk factor in other surgical fields,[4,6,9,28,32,47] the association has yet to be elucidated in neurosurgery. Anemia is generally regarded as an indicator of overall patient health status; however, it may also independently predispose patients to worse outcomes.[34] This study provides evidence that anemia is an independent risk factor for increased postoperative mortality and morbidity events following elective neurosurgical procedures. In addition, a specific level of anemia corresponding to a hematocrit below 33% (Hgb 11 g/dl) was shown to be associated with increased morbidity. When procedures were stratified into craniotomy for pain, extra-axial lesion or tumor, intra-axial tumor, sellar tumor, AVM, and aneurysm, all procedures except those for extra-axial tumor and aneurysm had increased odds of morbidity if patients were anemic. Anemia may be both a primary contributor

Table 4: 30-day mortality and morbidity complications of patients undergoing elective cranial neurosurgery by procedure

	Craniotomy for pain (*n*=411)	Craniotomy for extra-axial tumor (*n*=2064)	Craniotomy for intra-axial tumor (*n*=4584)	Craniotomy for sellar tumor (*n*=215)	Craniotomy for arteriovenous malformation (*n*=201)	Craniotomy for aneurysm (*n*=540)	*P* value
Mortality							
Deceased	0 (0.0)	25 (1.2)	106 (2.3)	4 (1.9)	0 (0.0)	17 (3.2)	**<0.001**
Overall morbidity							
Total morbidity events	24	431	864	65	35	215	-
Total number of patients with ≥1 morbidity event	23 (5.6)	407 (19.7)	679 (14.8)	53 (24.7)	29 (14.4)	143 (26.48)	**<0.001**
Superficial surgical site infection	1 (0.2)	13 (0.6)	27 (0.6)	2 (0.9)	0 (0.0)	3 (0.6)	0.767
Deep incisional SSI	1 (0.2)	10 (0.5)	18 (0.4)	3 (1.4)	0 (0.0)	1 (0.2)	0.208
Organ space SSI	3 (0.7)	16 (0.8)	48 (1.1)	3 (1.4)	0 (0.0)	1 (0.2)	0.205
Wound dehiscence	0 (0.0)	4 (0.2)	8 (0.2)	1 (0.5)	0 (0.0)	1 (0.2)	0.827
Pneumonia	3 (0.7)	37 (1.8)	50 (1.1)	5 (2.3)	6 (3.0)	28 (5.2)	**<0.001**
Unplanned intubation	2 (0.5)	39 (1.9)	83 (1.8)	8 (3.7)	2 (1.0)	26 (4.8)	**<0.001**
Pulmonary embolism	1 (0.2)	35 (1.7)	73 (1.6)	5 (2.3)	2 (1.0)	7 (1.3)	0.263
On ventilator>48 h	1 (0.2)	7 (0.3)	34 (0.7)	2 (0.9)	2 (1.0)	22 (4.07)	**<0.001**
Progressive renal insufficiency	0 (0.0)	3 (0.2)	5 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0.872
Acute renal failure	0 (0.0)	2 (0.1)	3 (0.1)	0 (0.0)	0 (0.0)	2 (0.4)	0.311
Urinary tract infection	6 (1.5)	65 (3.2)	122 (2.7)	9 (4.2)	5 (2.5)	25 (4.6)	0.041
CVA/stroke with neurological deficit	1 (0.2)	42 (2.0)	61 (1.3)	5 (2.3)	8 (4.0)	43 (8.0)	**<0.001**
Coma>24 h	0 (0.0)	8 (0.4)	7 (0.2)	0 (0.0)	0 (0.0)	10 (1.9)	**<0.001**
Cardiac arrest requiring CPR	0 (0.0)	9 (0.4)	12 (0.3)	1 (0.5)	0 (0.0)	0 (0.0)	0.363
Myocardial infarction	0 (0.0)	4 (0.2)	12 (0.3)	1 (0.5)	0 (0.0)	2 (0.4)	0.759
Graft/prosthesis failure	0 (0.0)	2 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.329
DVT/thrombophlebitis requiring treatment	2 (0.5)	53 (2.6)	118 (2.6)	5 (2.3)	2 (1.0)	11 (2.0)	0.097
Sepsis	2 (0.5)	39 (1.9)	76 (1.7)	7 (3.3)	5 (2.5)	16 (3.0)	0.037
Septic shock	0 (0.0)	11 (0.5)	29 (0.6)	1 (0.5)	1 (0.5)	9 (1.7)	0.032
Unplanned return to operating room (*n*=2748*)	1 (0.9)	32 (4.4)	78 (4.7)	7 (10.1)	2 (4.0)	8 (5.71)	0.128
Total morbidity events	24	431	864	65	35	215	-
Total number of patients with≥1 morbidity event	23 (5.6)	407 (19.7)	679 (14.8)	53 (24.7)	29 (14.4)	143 (26.48)	**<0.001**

Data presented as *n* (% of column total). *Unplanned reoperations only recorded post-2011, *n*: Number of patients; SSI: Surgical site infection; CVA: Cerebrovascular accident; CPR: Cardiopulmonary resuscitation; DVT: Deep vein thrombosis. Bold values represent statistically significant values

to post-operative complications as well as a marker for important co-morbidities.

Interpretation of results

Patients undergoing cranial neurosurgery generally have significant underlying pathophysiologic disease, which anemia may indicate.[25] This study demonstrated anemic patients to be at almost three times higher odds of mortality than non-anemic patients (4.1% vs. 1.3%) and to have almost two times the rate of postoperative complications as non-anemic patients (25.9% vs. 14.1%). Interestingly, any type of SSI was the same between the groups. However, the differences that were noteworthy consisted of increased rates of unplanned intubation, renal and respiratory complications, myocardial infarction, deep vein thrombosis, and sepsis with and without shock. These complications are severe and suggest anemia's association with medical adverse events.

Also, patients undergoing elective craniotomy for aneurysm had the highest rate of adverse events at 26.5%. Aneurysm patients had the highest rates of poor neurologic prognostic markers, such as utilization of a ventilator >48 h, stroke with neurological deficit, and coma >24 h. These data suggest patients with underlying vascular pathology might be at increased risk of postoperative mortality and morbidity compared to those with other neuropathology.

Anemia in neurosurgery

The results of our study differ markedly from those of Alan *et al*., who studied a cohort of 6576 patients undergoing cranial neurosurgery, of whom 28.4% had mild anemia and 2.7% had either moderate or severe anemia.[2] Patients with mild anemia and moderate to severe anemia had increased odds (OR: 1.5 and 1.8) of having a prolonged length of stay (LOS), respectively.

Table 5: Logistic models for 30-day mortality and morbidity complications for all patients undergoing elective cranial neurosurgery

	Univariable regression			Multivariable regression[§]		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Mortality						
Not anemic	Referent			Referent		
Anemic*	**3.24**	2.34-4.47	<0.001	**2.77**	1.65-4.66	<0.001
Overall morbidity						
Not anemic	Referent			Referent		
Anemic*	**1.70**	1.47-1.97	<0.001	**1.29**	1.03-1.61	0.028
Overall morbidity						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to <39	0.90	0.75-1.07	0.228	0.79	0.61-1.04	0.091
Hematocrit≥33 to <36	**1.41**	1.14-1.74	0.001	1.07	0.78-1.48	0.662
Hematocrit≥30 to <33	**2.71**	2.09-3.50	<0.001	**2.30**	1.55-3.42	<0.001
Hematocrit<30	**2.40**	1.70-3.38	<0.001	**1.84**	1.01-3.34	0.045

*Anemia is defined as a hematocrit<39 for men and<36 for women. §Multivariable analysis after adjusting for the following variables: (1) age, (2) sex, (3) body mass index, (4) smoking status, (5) operation year, (6) work relative value units, (7) wound classification, (8) current wound infection, (9) transfusion<72 h prior to surgery, (10) previous cardiovascular morbidity, (11) previous neurological morbidity, (12) previous respiratory morbidity, (13) previous renal morbidity, (14) diabetic status, (15) steroid use for chronic condition, (16) length of operation, and (17) history of previous operation within 30 days of surgery. Bold type indicates statistical significance

Craniotomy for malignant brain tumor surgery was analyzed as a subgroup of patients with the conclusion that anemia increased the LOS, but did not increase complication rates or mortality. They concluded that while anemia does not increase the risk of adverse outcomes, it does extend the LOS, thereby increasing resource utilization and costs. These findings differ from our conclusion for various reasons. First, our study population was inclusive of more types of patients undergoing elective cranial neurosurgery for various tumors, vascular anomalies, and nerve compressions. Second, our study has greater statistical power as we analyzed an additional 1500 patients relative to the study of Alan *et al*. Finally, we defined anemia according to the WHO definitions, classifying women with a hematocrit less than 36% and men with a hematocrit lower than 39% as anemic. Alan *et al*. defined patients as anemic if they had a hematocrit percentage of less than 38.

A systematic review by Le Roux demonstrated that preoperative anemia is associated with adverse outcomes in SAH patients.[26] They also concluded that anemia may lead to or exacerbate delayed ischemia in cerebral tissue. Other groups have shown an increase in severe disability, delayed infarction, and even death following SAH in anemic patients.[24] Other rare neurologic bleeding episodes can happen in the presence of pathologic anemia, such as in sickle cell anemia, hemorrhagic infectious diseases, coagulopathies, dural AVMs, and hemorrhagic tumors.[3,33] Anemia resulting from aneurysmal SAH increases the risk of symptomatic vasospasm[38] and is associated with poor 3-month outcomes.[44]

Anemia has also been shown to be a risk factor for postoperative complications in other neurosurgical subspecialties, including spine. Anemia is associated with postoperative ileus in lumbar fusion,[12] an increased LOS in posterior lumbar spine surgery,[2,17] postoperative delirium after lumbar surgery,[13] postoperative ischemic optic neuropathy,[7] and overall postoperative morbidity in elective spine surgery.[2] Anemia also increased the rate of SSIs following spine surgery.[1] In addition, intraoperative acute blood loss anemia has been associated with perioperative cardiac events following cervical[14] and lumbar spine surgery.[11]

Anemic correction

Our study demonstrates preoperative anemia is associated with postoperative mortality and morbidity, highlighting the question of whether the anemia should be treated prior to elective cranial surgery. Anemia may be treated with iron supplementation, erythropoietin, or transfusion of packed red blood cells, among other rare options.[29] The benefits of correcting low hemoglobin levels must be weighed against the risk of these interventions, especially transfusion therapy, which is associated with infectious agent transmission, pneumonia, impaired pulmonary function, extended ventilator support, acute lung injury, acute respiratory distress syndrome, systemic inflammatory response syndrome, organ failure, transfusion reactions, and a prolonged LOS.[5,8,10,16,20,30,31,35,36,39,41]

Guidelines for anemia correction have yet to be established within neurosurgery, but laboratory studies of both animals and healthy human participants show a hemoglobin below 7 g/dl impairs brain function and below 10 g/dl hinders recovery following traumatic brain injury.[7,42] New guidelines for acute upper gastrointestinal bleeding have suggested a more restrictive transfusion strategy for survival benefit,[43] and such a restrictive transfusion strategy is currently favored in general critical

Table 6: Logistic models for 30-day complications for patients undergoing elective cranial neurosurgery by procedure

	Univariable regression			Multivariable regression*		
	Odds ratio	95% confidence interval	*P* value	Odds ratio	95% confidence interval	*P* value
Elective craniotomy for pain						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	1.28	0.40-4.03	0.679	0.43	0.07-2.57	0.355
Hematocrit≥33 to<36	2.36	0.63-8.77	0.201	1.99	0.24-16.53	0.526
Hematocrit≥30 to<33	**1**	-	-	**1**	-	-
Hematocrit<30	11.00	0.94-129.26	0.056	**1**	-	-
Elective craniotomy for extra-axial tumor						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	0.84	0.59-1.20	0.343	0.77	0.47-1.27	0.310
Hematocrit≥33 to<36	**1.62**	1.07-2.46	0.023	0.96	0.49-1.89	0.917
Hematocrit≥30 to<33	**3.29**	1.97-5.48	<0.001	1.25	0.52-3.04	0.615
Hematocrit<30	**2.83**	1.42-5.65	0.003	1.01	0.29-3.57	0.988
Elective craniotomy for intra-axial tumor						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	0.83	0.65-1.07	0.151	0.68	0.45-1.04	0.075
Hematocrit≥33 to<36	1.24	0.93-1.65	0.141	1.03	0.64-1.65	0.912
Hematocrit≥30 to<33	**2.08**	1.45-2.98	<0.001	**2.50**	1.42-4.41	0.002
Hematocrit<30	**1.81**	1.14-2.87	0.011	**2.37**	1.06-5.28	0.035
Elective craniotomy for sellar tumor						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	1.56	0.64-3.80	0.329	1.59	0.36-7.02	0.540
Hematocrit≥33 to<36	1.50	0.54-4.18	0.442	1.36	0.25-7.48	0.725
Hematocrit≥30 to<33	2.49	0.70-8.86	0.158	**14.69**	1.45-148.88	0.023
Hematocrit<30	-	-	-	-	-	-
Elective craniotomy for arteriovenous malformation						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	1.41	0.44-4.56	0.566	1.32	0.27-6.58	0.732
Hematocrit≥33 to<36	1.73	0.49-6.18	0.397	4.69	0.77-28.56	0.094
Hematocrit≥30 to<33	5.39	1.35-21.44	0.017	2.77	0.34-22.94	0.344
Hematocrit<30	6.06	0.49-74.33	0.159	**1**	-	-
Elective craniotomy for aneurysm						
Hematocrit>39	Referent			Referent		
Hematocrit≥36 to<39	0.84	0.48-1.45	0.525	0.83	0.40-1.73	0.624
Hematocrit≥33 to<36	1.41	0.75-2.65	0.290	0.91	0.36-2.29	0.845
Hematocrit≥30 to<33	**3.96**	1.85-8.47	<0.001	2.51	0.89-7.08	0.082
Hematocrit<30	**4.83**	1.68-13.85	0.003	0.53	0.08-3.42	0.504

*Multivariable analysis after adjusting for the following variables: (1) Age, (2) sex, (3) body mass index, (4) smoking status, (5) operation year, (6) work relative value units, (7) wound classification, (8) current wound infection, (9) transfusion<72 h prior to surgery, (10) previous cardiovascular morbidity, (11) previous neurological morbidity, (12) previous respiratory morbidity, (13) previous renal morbidity, (14) diabetic status, (15) steroid use for chronic condition, (16) length of operation, and (17) history of previous operation within 30 days of surgery. Bold type indicates statistical significance

care medicine surrounding acute brain injury.[29] Due to the association of increased postoperative mortality, morbidity, and increased LOS[2] of anemic patients after elective cranial surgery, future prospective studies are needed in order to determine the appropriate management of preoperative anemia.

Multiple basic science experiments and clinical studies have identified a hematocrit of 30-35% as a functional threshold for oxygen carrying capacity. Hint was the first to describe settings in which blood loss, unless severe, should not be replaced because a 30% hematocrit was determined to have the highest oxygen transporting capacity.[21] Wood *et al.* studied the effects of hypervolemic hemodilution with autologous plasma in dogs, concluding that hypervolemic hemodilution decreases cerebral vascular resistance, possibly due to the secondary changes on blood viscosity, with an additional increase in intracranial pressure.[46] The study supports the hypothesis that decreased blood viscosity through

hemodilution can account for the direct relationship observed between cerebral blood flow and cardiac output. Lee *et al*. sought to determine which hematocrit level was optimal post-hemodilution for maximum oxygen delivery to the ischemic neural tissue.[27] The mean infarction volume was determined after isovolemic hemodilution at hematocrit levels of 25%, 30%, 35%, 40%, and in a control group. The infarction size had the lowest average volume at the 30% hematocrit level and was significantly lower than the control group, indicating a hematocrit of 30% is optimal for brain protection. Studies of hemorheology have determined factors contributing to blood viscosity include hematocrit, erythrocyte aggregation and flexibility, platelet accumulation, and plasma constituents.[23,45] While studies suggest that the optimal rheological performance and brain oxygenation is obtained with a hematocrit of approximately 30%, prospective studies are needed to identify the most appropriate trigger levels for transfusion.

Strengths and limitations

Strengths to this study include the use of a large, prospectively collected database, extensive adjustment for confounding variables following univariable analysis, and the diversity of academic and nonacademic international hospital data. Also, NSQIP is collected following yearly quality checks in a standardized fashion with a dedicated surgical nurse at each institution.[15] There are limitations to this study. Causation cannot be established due to the observational nature of prospective data of this study. Also, the NSQIP database only provides having up to 30-day postoperative outcome data, preventing extrapolation of conclusions beyond this window period. Only hematocrit data, not hemoglobin, was available in NSQIP. The WHO defines anemia using both definitions and, as such, we used hematocrit levels. Countermeasures taken to correct anemia before surgery cannot be determined in NSQIP. The only countermeasure available is transfusion <72 h prior to surgery, which was controlled for on multivariable analysis. Other factors, such as volume and fasting status, could affect the hematocrit levels as well. Finally, the reason for preoperative anemia cannot be discerned with the database, but potential causes may be inferred such as alcohol use prior to surgery, steroids to control chronic conditions, and cardiovascular, renal, and pulmonary comorbidities. Future studies to investigate the long-term impact of anemia on neurosurgical outcomes are needed.

CONCLUSION

In this analysis, preoperative anemia in elective cranial neurosurgery was independently associated with an increased risk of 30-day overall postoperative mortality and morbidity when compared to non-anemic patients, after adjusting for preoperative characteristics and comorbidities. Multivariable regression analysis revealed anemic patients have a 30-day mortality that is threefold higher than that of non-anemic patients. Also, anemic patients had significantly higher odds of postoperative morbidity when compared to their non-anemic counterparts. A difference in postoperative morbidity odds was demonstrated in patients above and below the 33% hematocrit level (Hgb 11 g/dl), suggesting this level as a threshold for increased morbidity.

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Commentary

The authors present compelling information gleaned from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database that there is a strong association between preoperative ischemia and preoperative morbidity and mortality. This dataset is a multi-institutional review of 8015 elective craniotomy patients, 1710 of whom were anemic preoperatively by WHO standards. Both 30-day postoperative morbidity and mortality were dramatically statistically significantly increased in anemic patients, controlling for co-diagnoses and co-morbidities by multivariate analysis. A review of statistical methodology is beyond the expertise of this reviewer.

This data analysis and presentation is well ahead of the wave in presenting the potential advantages of the analysis of "big data," and these important results speak for themselves. Particular sources of morbidity are UTI, generalized sepsis, and pulmonary complications including pneumonia. Further confirmation by distinct datasets, and prospective research which modulates both the extent and timing of resolution of pre-operative ischemia will be of great interest. Simple scatter plots for data presentation, particularly in an e-journal, might also be both simple and helpful.

That said, this analysis also points out some of the pitfalls of these techniques, and it is these on which I would like to concentrate in this comment. In the body of the paper, the authors are careful to point out the association between anemia and morbidity, and to distinguish between association and causality, but they fall into that very trap, by implication, in their title, by using the multi-definitional word "increases." The human mind is quintessentially an inference engine, and it is important to take deliberate measures to avoid jumping

to conclusions. Of interest, the peak incidence of adverse effects seemed to lie between hematocrits of 30 and 33, more than with anemic hematocrits either above or below this level of optimum blood flow. This emphasizes the extent to which the important associations of preoperative anemia to outcomes are related in clear, but poorly understood, ways.

(Should the authors wish to change the title to "is associated with" from "increases," I would be happy to modify this point.)

The authors have chosen not to present this study for local IRB approval, from an institution which has a fraught history with research [(see lines 109-113) http://pages.jh.edu/~jhumag/0202web/trials.html]. I believe this is problematic, as considerable recent work has proven that the veil of data anonymization is easily pierced by reverse data analysis (http://www.j-biomed-inform.com/article/S1532-0464(04)00053-X/abstract). Our society has not yet devised a mature and generally accepted response to questions of research privacy. An overcautious approach is, therefore, warranted in this circumstance, though I imply no bad faith on the part of the investigators. The 17 variables of the multiple logistical regression model therefore provide confounding not only of anonymity, but also insofar as they may not be not fully independent, a potential confounding of results. While some see the issue of research consent as overwrought in these circumstances, a failure to respect the obligations of investigators, who have no inherent right to the data mined, is likely ultimately to exacerbate the public distrust of medical science and the practitioners whose first duty must be to the patient, and ultimately further shackle access to scientific evaluation as well.

Finally, it is important to maintain, particularly in "big data" where the quality of input data and data acquisition is less certain, a healthy uncertainty toward the data itself, though this is somewhat mitigated by statistical averaging in larger series. Definitions are not provided of progressive renal insufficiency, acute renal failure, or septic shock; coma >24 h and ventilation >48 h are sometimes deliberate therapeutic strategies and therefore arguably not necessarily morbidities; and the specific definitions of the variables for multivariate analysis are not provided, and have only presumably been standardized and validated inter-institutionally.

Getting "big data" right is very hard, though potentially extraordinarily useful.

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