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Preoperative anemia displays a dose-dependent effect on complications in head and neck oncologic surgery

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Abstract

Introduction: Anemia's effect on head and neck surgical complications is unknown.

Methods: Head and neck cancer operations were acquired from the 2006 to 2013 American College of Surgeons National Surgical Quality Improvement Program databases. Anemia was defined as <39% or <36% hematocrit in men and women, respectively. Multivariable logistic regression analyses were performed.

Results: Major head and neck surgery patients had a 44.2% anemia incidence (n = 527 of 1193). Anemic patients had increased complication rates (27.1%) and mortality (2.1%) vs non-anemic patients at 19.8% ($P = .003$) and 0.5% ($P = .009$), respectively. There was a significant difference in morbidity odds with hematocrit >27% (odds ratio [OR] = 1.09) vs <27% (OR = 4.22). Complication odds were further increased with hematocrit between 24% and 27% (OR = 8.94). There were increased rates of wound dehiscence (6.6% vs 2.7%, $P < .001$), pneumonia (8.5% vs 4.7%, $P = .006$), and myocardial infarction (1.7% vs 0.3%, $P = .01$) in anemic vs non-anemic patients.

Conclusion: Anemia was associated with increased morbidity at hematocrit <27%. An inverse dose-dependent effect of decreasing hematocrit was observed for overall morbidity.

KEYWORDS
anemia, anemic, cancer, complications, head and neck, morbidity, myocardial infarction, NSQIP, oncology, otolaryngology, transfusion

1 | INTRODUCTION

Preoperative anemia has been shown to be an independent risk factor for postoperative morbidity and mortality in a wide range of surgical fields including neurologic, orthopedic, cardiac, general, colorectal, and reconstructive surgery.[1-10] Anemia is of particular concern in head and neck surgery given high rates of preoperative chronic anemia, a highly comorbid population, and the substantial metabolic demand of reconstructions.[4] Within head and neck surgery, anemia has been associated with decreased survival in laryngeal cancer[3] and oropharyngeal cancers.[11] Although hematocrit concentrations are measured over 90% of the time before major head and neck surgery,[12] few studies have examined the implications of preoperative anemia on postoperative outcomes.[1] The impact of preoperative laboratory values on ablative and reconstructive surgery is being actively investigated.[12]

The precise effect of anemia on overall short-term morbidity and mortality remains unclear within the head and neck oncologic population. Therefore, the purpose of this study was to characterize the effect of preoperative anemia on morbidity and mortality in patients undergoing head and neck cancer operations. Additionally, this study aimed at determining an optimal hematocrit level, which could be used to guide future preoperative management of anemia in this patient population.

2 | METHODS

2.1 | Data source and patients

All major head and neck mucosal site resection cases were extracted from the 2006 to 2013 American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) databases. CPT codes were utilized to extract resection cases to include glossectomy (hemiglossectomy [41130], complete [41140/41145], composite with floor of mouth and/or mandibular resection [41150, 41153, 41155]), mandibulectomy (excision of malignant tumor of mandible without [21044] or with [21045] radical resection), laryngectomy (total [31360], hemilaryngectomy [31370, 31375, 21380, 31382, supraglottic [31367]), and pharyngectomy [42892, 42894]. NSQIP is a national prospectively collected database with >450 participating academic and nonacademic hospitals. A dedicated Surgical Clinical Reviewer collects all data prospectively at each institution with a supervisor Surgeon Champion who ensures data reliability. The Massachusetts Eye and Ear Institutional Review Board granted a waiver for NSQIP use and analysis. All data were collected according to the ACS-NSQIP data use agreement as a quality assurance endeavor with only de-identified data received.

2.2 | Anemia

Anemia was defined as a preoperative hematocrit <36% for women and <39% for men for dichotomous analysis and <39% for categorical analysis according to World Health Organization definitions. Anemia was additionally analyzed for each 3% drop to determine if a certain hematocrit threshold increased complications. Hemoglobin values were determined by dividing the hematocrit level by 3. Anemia was analyzed categorically as we hypothesized there was a nonlinear relationship of decreasing hematocrit and increasing complications to determine an inflection point. Patients without hematocrit data were excluded (92 patients [7.7%], 92.3% of all patients included).

2.3 | Complications

Complications were defined as an aggregate of all 30-day postoperative morbidity events including: superficial and deep wound infection, organ space infection, wound dehiscence, pneumonia, unplanned intubation, pulmonary embolism, ventilation requirement >48 hours, progressive renal insufficiency, acute renal failure, urinary tract infection, stroke and/or cerebrovascular accident, myocardial infarction, cardiac arrest requiring cardiopulmonary resuscitation, transfusion of >1 unit of packed red blood cells up to 72 hours postoperatively, graft and/or prosthesis failure, deep vein thrombosis/thrombophlebitis requiring anticoagulation, sepsis, or septic shock. Surgical site infection (SSI) was defined as a grouping of four wound complications: superficial SSI, deep SSI, organ space SSI, and wound dehiscence. Transfusion was defined as receiving more than one unit of packed red blood cells 72 hours after surgery.

2.4 | Analysis

Group comparisons were made using the *t* test and Wilcoxon rank-sum test for continuous variables, dependent on distribution, or the chi-square test for categorical variables, as appropriate with Bonferroni correction (Table 1). Following univariable regression, significant variables ($P < .05$) were included and paired down in a stepwise approach for multivariable logistic regression analysis. Multivariable analysis adjusted for the following variables: (a) age, (b) sex, (c) body mass index (BMI), (d) smoking status, (e) operation year, (f) work relative value units, (g) wound classification, (h) current wound infection, (i) transfusion <72 hours prior to surgery, (j) previous cardiovascular morbidity, (k) previous neurological morbidity, (l) previous respiratory morbidity, (m) previous renal morbidity, (n) diabetic status, (o) steroid use for chronic condition, (p) length of operation, and (q) history of previous operation within 30 days of surgery (Table 2). Results were considered significant if the observed *P*-value was less than .05. Statistical analyses were completed with STATA/MP 14.1.

3 | RESULTS

There were 1193 major head and neck mucosal site resections in the NSQIP database from 2006 to 2013, of which complete blood counts were obtained in 1101 (92.3%) patients. Anemic patients made up 47.9% (527 patients) of the population. The major coded procedure for each resection was glossectomy (n = 551), 394 laryngectomy (n = 394), 191 mandibulectomy (n = 191), 40 pharyngectomy (n = 40), and 17 upper cervical esophagectomy (n = 17). The mean age was 63.4 ± 12.4 years with 67.7% males. The average BMI was 26.0 ± 6.2, 33% were smokers within the past year, 13.5% were chronic alcohol users, and 14.5% were diabetic. Table 1 lists the remaining preoperative characteristics.

Table 3 demonstrates 30-day complications for the population stratified by anemia status. Rates of superficial SSI, deep incisional SSI, and organ space SSI were similar whereas the rate of wound dehiscence was significantly

TABLE 1 Preoperative characteristics of all major head and neck composite resection patients

General variables	All composite resections N = 1101	Non-anemic patients N = 574	Anemic patients N = 527	*P*-value
Age, mean ± SD	63.7 ± 12.5	62.5 ± 11.4	64.9 ± 13.5	**<.001**
BMI, mean ± SD	26.0 ± 6.2	27.0 ± 6.0	25.0 ± 6.4	.14
Sex (male), n (%)	752 (68.3)	422 (73.5)	330 (62.6)	**<.001**
Race, n (%)				**.001**
White	777 (70.6)	424 (73.9)	353 (67.0)	
African American	105 (9.5)	35 (6.1)	70 (13.3)	
Latino	151 (13.7)	82 (14.3)	69 (13.1)	
Asian/American Indian/Native Hawaiian Pacific Islander	33 (3.0)	17 (3.0)	16 (3.0)	
Unknown	35 (3.2)	16 (2.8)	19 (3.6)	
Current smoker, n (%)	364 (33.1)	210 (36.6)	154 (29.2)	**.009**
Diabetes, n (%)				**.007**
None/diet controlled	941 (85.5)	506 (88.2)	435 (82.5)	
Non-insulin dependent	103 (9.4)	49 (8.5)	54 (10.3)	
Insulin dependent	57 (5.2)	19 (3.3)	38 (7.2)	
Operation time, mean minutes ± SD	403.7 ± 238.4	379.4 ± 235.4	430.2 ± 239.1	.71
Alcohol intake in previous 2 weeks[a,b], n (%)	82 (12.8) n = 642	51 (15.5)	31 (9.9)	**.03**
Steroid use for chronic condition, n (%)	47 (4.3)	17 (3.0)	30 (5.7)	**.03**
Operation within previous 30 days[b], n (%)	48 (7.5) n = 639	14 (4.3)	34 (10.9)	**.001**
Charlson comorbidity index score, n (%)				**.005**
0	723 (65.7)	401 (69.9)	322 (61.1)	
1	238 (21.6)	116 (20.2)	122 (23.2)	
2	42 (3.8)	20 (3.5)	22 (4.2)	
≥3	98 (8.9)	37 (6.5)	61 (11.6)	
Hematocrit, mean ± SD	38.8 ± 5.2	42.7 ± 2.8	34.5 ± 3.7	**<.001**
Hematocrit levels				
≥39	574 (52.1)	-	-	-
≥36 to <39	230 (20.9)			
≥33 to <36	152 (13.8)			
≥30 to <33	89 (8.1)			
≥27 to <30	38 (3.5)			
≥24 to <27	13 (1.2)			
≥21 to <24	1 (0.1)			
<21	4 (0.4)			

Note: Data presented as n (% of column total). Bold values indicates statistical significance.
Abbreviations: BMI, body mass index; N, total number of patients.
[a]Less than two drinks per day.
[b]n indicates number of patients with available data.

increased in anemic patients at 6.6% vs 2.7% ($P < .001$). Medical complications including rates of pneumonia (8.5% anemic vs 4.7% non-anemic, $P = .006$) and myocardial infarction (1.7% anemic vs 0.3% non-anemic, $P = .01$) were increased in anemic patients. Other medical complications including unplanned intubation, ventilator requirements

TABLE 2 Logistic regression models for 30-day complications for all patients undergoing major head and neck composite resection

	Univariable regression			Multivariable regression		
	Odds ratio	**95% confidence interval**	***P*-value**	**Odds ratio**	**95% confidence interval**	***P*-value**
Not anemic	Referent			Referent		
Anemic[a]	1.51	1.15-1.97	**.003**	1.15	0.77-1.71	.48
Hematocrit >39						
Hematocrit ≥36 to <39	1.10	0.76-1.58	.63	0.89	0.54-1.48	.66
Hematocrit ≥33 to <36	1.70	1.14-1.53	**.009**	1.34	0.76-2.40	.31
Hematocrit ≥30 to <33	1.76	1.08-2.88	**.02**	1.16	0.56-2.43	.69
Hematocrit ≥27 to <30	2.10	1.05-4.22	**.04**	1.38	0.49-3.95	.54
Hematocrit ≥24 to <27	6.47	2.08-20.11	**.001**	8.93	1.98-40.30	**.004**
Hematocrit ≥21 to <24	-	-	-	-	-	-
Hematocrit ≥39						
Hematocrit ≥27 to <39	1.45	1.10-1.90	**.008**	1.09	0.73-1.62	.68
Hematocrit <27	4.05	1.57-10.39	**.004**	4.22	1.15-15.51	**.03**

[a]Anemia is defined as a hematocrit <39 for men and <36 for women.

>48 hours, acute kidney injury, progressive renal insufficiency, urinary tract infection, CVA/stroke, coma, cardiac arrest requiring CPR, flap failure, DVT/thrombophlebitis, sepsis, and septic shock were equivalent among anemic and non-anemic groups. Unplanned return to the operating room was also similar, with 15.7% in anemic and 13.0% in non-anemic patients ($P = .28$). Overall, the total number of patients with multiple (≥1) complications was significantly higher in anemic vs non-anemic patients (27.1% vs 19.8%, $P = .003$). Mortality rates were also significantly increased to 2.1% in anemic patients compared to non-anemic patients at 0.5% ($P = .009$).

Using anemia as a binary variable defined as a hematocrit <39 for men and <36 for women, there was a significant increase in odds of complication for anemic patients using univariate regression (odds ratio [OR]: 1.51; 95% confidence interval [CI]: 1.15-1.97). Following multivariate logistic regression, anemia as a binary variable did not significantly increase complication odds (OR: 1.15; 95% CI: 0.77-1.71). Hematocrit levels were then subdivided by each 3% drop into >39, ≥36 to <39, ≥33 to <36, ≥30 to <33, ≥27 to <30, ≥24 to <27, and ≥21 to <24 to determine if there was a threshold which increased complications. Univariable regression showed significantly increasing odds for each category except the first 3% drop of ≥36 to <39, at 1.10, 1.70, 1.76, 2.10, and 6.47, respectively. Once multivariable regression was instituted, a threshold of <27 demonstrated increase odds of 30-day complications in anemic patients (OR: 8.93; 95% CI: 1.98-40.30; $P = .004$). Hematocrit less than 24% was a perfect predictor of postoperative complication. To further elucidate this effect, hematocrit was divided into three categories: ≥39, ≥27 to <39, and <27. The ≥27 to <39 compared to ≥39 hematocrit levels did not show a difference in complication odds. However, patients with hematocrit <27 had significantly increased odds of complication compared to patients with normal hematocrit values (OR: 4.22; 95% CI: 1.15-15.51; $P = .03$).

4 | DISCUSSION

Although anemia has been shown to be a risk factor for postoperative complications in a wide range of surgical fields,[1-10] its predictive value has yet to be elucidated in head and neck oncologic surgery. This study demonstrates anemia as an independent risk factor for postoperative complications and increased mortality following head and neck surgery, with a 50% and 200% increase in morbidity and mortality, respectively. Additionally, a hematocrit below 27% was shown to be associated with increased complications. There was an inverse dose-dependent effect of decreasing hematocrit levels on increased postoperative morbidity. Three major categories of complications were associated with anemia: wound dehiscence, pneumonia, and myocardial infarction. Rates of SSI were not correlated with anemic status.

These findings highlight the question of whether anemia should be treated within the perioperative period for head and neck cancer operations, specifically in the preoperative phase as it relates to our findings. Anemia can be treated in the pre- or postoperative state with iron supplementation or transfusion of packed red blood cells, among other options.[13] The benefit of correcting low hemoglobin levels should be weighed against the risk of interventions such as transfusion therapy, which is associated with acute lung injury,[14] acute respiratory distress

TABLE 3 Thirty-day complications of patients undergoing major head and neck composite resection by anemia status

	Non-anemic N = 574	Anemic N = 527	*P*-value
Superficial SSI	40 (6.01)	26 (4.93)	.42
Deep incisional SSI	23 (3.45)	18 (3.42)	.97
Organ space SSI	12 (1.80)	12 (2.28)	.56
Wound dehiscence	18 (2.70)	35 (6.64)	**<.001**
Pneumonia	31 (4.65)	45 (8.54)	**.006**
Unplanned intubation	12 (1.80)	15 (2.85)	.23
Pulmonary embolism	3 (0.45)	2 (0.38)	.85
On ventilator >48 hours	0 (0.00)	0 (0.00)	-
Progressive renal insufficiency	3 (0.45)	1 (0.19)	.44
Acute renal failure	2 (0.30)	2 (0.38)	.81
Urinary tract infection	3 (0.45)	8 (1.52)	.05
CVA/stroke with neurological deficit	1 (0.15)	4 (0.76)	.11
Coma >24 hours	0 (0.00)	1 (0.19)	.26
Cardiac arrest requiring CPR	5 (0.75)	7 (1.33)	.32
Myocardial infarction	2 (0.30)	9 (1.71)	**.01**
Graft/prosthesis failure	11 (1.65)	10 (1.90)	.75
DVT/thrombophlebitis requiring treatment	4 (0.60)	6 (1.14)	.31
Sepsis	14 (2.10)	19 (3.61)	.12
Septic shock	3 (0.45)	5 (0.95)	.29
Unplanned return to operating roomN = 838	60 (13.02)	59 (15.65)	.28
Total morbidity events	301	284	-
Total number of patients with ≥1 morbidity event	132 (19.82)	143 (27.13)	**.003**
Unplanned readmission	31 (4.65)	30 (5.69)	.42
Mortality	3 (0.45)	11 (2.09)	**.009**

Note: Data presented as n (% of column total), unplanned reoperations only recorded post 2011.

Abbreviations: CPR, cardiopulmonary resuscitation; CVA, cerebrovascular accident; DVT, deep vein thrombosis; N, number of patients; SSI, surgical site infection.

syndrome,[15] organ failure,[16] prolonged length of stay,[17] transfusion reactions,[18] and increased infection risk.[19] Intravenous iron administration to patients with anemic cancer has been shown to significantly increase hemoglobin levels independently from the precise anemia mechanism.[20] Preoperative iron therapy may increase quality of life, performance status, and reduce the need for erythropoietin-stimulating agents and/or blood transfusions.[21,22] As little as 1000 mg ferric carboxymaltose as a single injection 14 days prior to surgery has shown hematocrit increases of 3.6%-4.2%.[23] This would be meaningful to move patients ahead of the 27% hematocrit threshold. Preoperative iron injection could have implications for reducing postoperative morbidity, including wound dehiscence, pneumonia, and myocardial infarction as found in our head and neck population.

Postoperative anemic correction is more commonly accomplished with transfusion, as this is typically a combination of a preoperative anemic state and intraoperative blood loss. A more restrictive transfusion strategy is being favored in critical care based on the results of a series of randomized controlled trials (RCTs).[24] In a 2014 meta-analysis of three RCTs including 2364 patients with critical illness or a bleeding event, a restrictive transfusion strategy of hemoglobin <7 g/dL resulted in reduced in-hospital mortality (risk ratio [RR]: 0.74), total mortality (RR: 0.80), rebleeding (RR: 0.64), acute coronary syndrome (RR: 0.44), pulmonary edema (RR: 0.48), and bacterial infections (RR: 0.86), compared with a more liberal strategy. The latest Cochrane Database Systematic Review in 2016 identified 31 trials involving 12 587 patients of critical care and surgical patients demonstrated mortality was not increased nor decreased when comparing restrictive vs liberal transfusion thresholds (RR: 0.97; 95% CI: 0.81-1.16).[25] Cardiac events, myocardial infarction, stroke, pneumonia, thromboembolism, and infection risk were similar. They conclude allogeneic RBC transfusion can be avoided in most patients with hemoglobin thresholds above 7-8 g/dL.

However, these data are an aggregate of a heterogeneous critical care medical and surgical population. Individual medical and surgical disciplines must examine their own patient population. Among cardiac surgery patients, sepsis, wound infection, stroke, myocardial infarction, infarction of the gut, or acute kidney injury were similar among restrictive vs liberal transfusion strategies.[26] Mortality was almost doubled (4.2% vs 2.6%; $P = .04$) in the restrictive group. Restrictive vs liberal transfusion threshold did not show a significant difference of 60-day mortality or ability to walk across a room without human assistance in hip surgery patients.[27] A systematic review of neurosurgical patients found most studies favored a restrictive transfusion threshold of <7 g/dL.[28] Specifically within oncologic neurosurgery and skull base surgery, risk factors for transfusion were age <4 years old, preoperative hemoglobin <12.2 g/dL, and operative time >270 minutes.[29] Tranexamic acid and noninvasive hemoglobin monitoring were found to potentially reduce transfusion rates.[30,31] In the head and neck free flap population, transfusion was found not to compromise flap survival but was associated with wound dehiscence, myocardial infarction, congestive heart failure, respiratory distress, and pneumonia.[32] Otherwise, literature describing transfusion triggers with surgery, including head and neck surgery, is scarce.

The effect of anemia on the survival of patients with head and neck cancer has been studied. A secondary analysis of RTOG 85-27 demonstrated reduced hemoglobin levels were associated with a survival reduction and an increase in locoregional failure in 504 stage III or IV head and neck squamous cell carcinoma patients.[21] The locoregional failure rate at 5 years was significantly less in patients with a normal hematocrit (51.6%) vs anemic patients (67.8%). The survival rate at 5 years for normal hematocrit patients was 35.7% vs 21.7% in anemic patients, a significant increase. These findings remained significant with multivariate regression. Additionally, pretreatment hemoglobin of less than 13 g/dL was correlated with adverse outcomes and decreased response to concurrent chemoradiotherapy in patients with advanced head and neck cancer.[33] Our study adds to this literature demonstrating anemia affects postoperative complications in addition to survival of head and neck oncology patients.

Strengths of this study include the use of a large prospectively collected database of academic and nonacademic hospital data, following yearly quality checks in a standardized fashion with a dedicated surgical nurse at each institution.[34] An additional strength includes the extensive adjustment of confounding variables following univariable analysis, including a wealth of preoperative health markers and comorbidities. Despite adjustment for confounding variables, causation cannot be established due to the observational nature of the prospective data analyzed. An additional limitation stems from the breadth of data available on the NSQIP database. The database provides only up to 30-day postoperative outcome data, preventing extrapolations outside this time period. Additionally, clinical efforts to correct preoperative anemia cannot be determined from the database, with the exception of transfusions received <72 hours prior to surgery, which was accounted for in the multivariable regression. Lastly, neither the etiology of anemia nor factors possibly impacting the hematocrit value, such as volume/fasting status, or prior cancer treatment such as specific chemotherapy or radiotherapy regimens, can be determined from the NSQIP database. Disease-specific expansion, especially in surgical oncology, is a needed expansion within NSQIP. Highlighting stage, grade, adverse pathologic features (LVI, PNI, positive margins, etc), chemotherapy, and radiotherapy treatment would strengthen analyses with this dataset. However, potential causes, such as steroid use and cardiovascular/renal comorbidities, were delineated and adjusted for. Despite these limitations, our data give insight into anemia's effect on head and neck surgery as guidelines for anemia correction in the field of head and neck oncological surgery have yet to be established in the United States. Taken together, this literature reinforces the need for patient population-specific studies to determine appropriate levels for anemic correction.

5 | CONCLUSION

The association between anemia and postoperative complications in head and neck oncologic surgery has yet to be fully elucidated. Decreasing hematocrit levels exhibited an inverse dose-dependent effect on postoperative morbidity. A hematocrit level below 27% was independently associated with increased 30-day complications. Future investigation, in the form of a prospective study or randomized control trial, specific to patients with head and neck cancer can further explore this association, as well as define a preoperative hemoglobin target for transfusion.

DISCLOSURE OF INTERESTS

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