What Should Define Preoperative Anemia in Primary THA?

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Received: 21 February 2017 / Accepted: 1 August 2017 / Published online: 7 August 2017
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Abstract

Background The use of tranexamic acid (TXA) in THA decreases the risk of transfusion after surgery. However, nearly 10% of patients still undergo a transfusion, which has been independently associated with an increased risk of complications. Preoperative anemia has been proven to be a strong predictor of transfusion after THA, but the ideal “cutoff” values in today’s population that maximize sensitivity and specificity to predict transfusion have yet to be established.

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Electronic supplementary material The online version of this article (doi:10.1007/s11999-017-5469-4) contains supplementary material, which is available to authorized users.

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Questions/purposes (1) Which preoperative factors are associated with postoperative transfusion in the setting of TXA use? (2) If preoperative hemoglobin (Hgb) remains associated with transfusion, what are the best-supported preoperative Hgb cutoff values associated with increased transfusion after THA?

Methods A retrospective chart analysis was performed from January 1, 2013, to January 1, 2015, on 558 primary THAs that met prespecified inclusion criteria. A multi-variable logistic regression analysis model was used to identify independent factors associated with transfusion. Area under the receiver-operator curve (AUC) was used to determine the best-supported preoperative Hgb cut point across all participants, as well as adjusted by sex and TXA use. Overall, 60 patients with a blood transfusion were included and compared with 498 control subjects (11% risk of transfusion).

Results After controlling for potential confounding variables such as age, sex, American Society of Anesthesiologist score, intravenous TXA (IV TXA) use, and preoperative Hgb, we found that patients with lower preoperative Hgb (g/dL per 1-unit decrease, odds ratio [OR], 2.6; 95% CI, 2.0–3.5; $p < 0.001$), female sex (vs male, OR, 4.2; 95% CI, 1.7–10.3; $p = 0.002$), and those unable to receive IV TXA (topical TXA/no TXA, OR, 13.5; 95% CI, 6.3–28.6; $p < 0.001$) were more likely to receive a transfusion. Of these, preoperative Hgb was found to be the variable most highly associated with transfusion (AUC, 0.876). A preoperative Hgb cutoff value of 12.6 g/dL maximized the AUC (0.876) for predicting transfusion across all patients unadjusted for baseline characteristics (sensitivity = 83, specificity = 84) with values of 12.5 g/dL (sensitivity = 85, specificity = 77) and 13.5 g/dL (sensitivity = 92, specificity = 77) for women and men, respectively.

Conclusions The 1968 WHO definitions of anemia (preoperative Hgb < 13 g/dL for men and < 12 g/dL for women) used currently may underestimate patients at risk of transfusion after THA today. Further studies are needed to see if blood conservation referral decreases the risk of transfusion with preoperative treatment of anemia.

Level of Evidence Level III, therapeutic study.

Introduction

THA offers predictable pain relief of end-stage hip arthritis but can be associated with substantial blood loss [3, 23]. As an additional concern, 24% to 44% of patients presenting for THA are anemic [39]. Although the routine use of tranexamic acid (TXA) has markedly reduced the risk of transfusion after THA, nationally, 10% of patients undergoing THA are still receiving transfusions [2, 27]. Furthermore, there is a growing body of evidence to suggest that preoperative anemia and blood transfusion are associated with periprosthetic joint infection, longer length of stay (LOS), and increased risk of complications, and, in some analyses, an increased risk of death in this patient population [5–7, 13, 19, 28].

Before the implementation of TXA, multiple studies showed that a lower preoperative hemoglobin (Hgb) is a strong predictor of transfusion after hip and knee arthroplasties [1, 3, 4, 11, 12, 14, 30, 33, 38]. Two studies recently identified preoperative Hgb cutoff values that predicted transfusion risk after TKA [25, 45], but the most-sensitive and most-specific preoperative Hgb value for predicting transfusion after THA in the era of more-widespread TXA use has, to our knowledge, not been investigated. Identifying a robust preoperative Hgb cutoff would allow the treating surgeon to refer patients preoperatively for treatment of their anemia and counsel them regarding their risk of transfusion before the operation. Patients identified as being at high risk for transfusion preoperatively could receive treatment to avoid postoperative transfusions and the associated complications. Because the number of THAs performed annually is expected to increase 174% by 2030 and reimbursement will be tied to outcome measures, preoperative medical management to minimize postoperative complications will be even more essential [8, 21]. Currently, the 1968 WHO definition of anemia (Hgb < 13 g/dL for men and < 12 g/dL for women) is used to guide referral and treatment, but we questioned if this definition adequately applies to today's THA population [44].

Therefore, we asked: (1) Which preoperative factors are associated with postoperative transfusion in the setting of TXA use? (2) If preoperative hemoglobin (Hgb) remains

associated with transfusion, what are the best-supported preoperative Hgb cutoff values associated with increased transfusion after THA?

Patients and Methods

After institutional review board approval, a retrospective chart survey was conducted identifying patients undergoing primary unilateral THA at an academic tertiary care center from January 1, 2013, to January 1, 2015. Patients with revision THA, THA for femoral neck fracture, bilateral simultaneous THAs, and hip resurfacing procedures were excluded. Overall, 608 patients were identified in the preliminary search and 558 patients met preselected criteria for study inclusion. Sixty patients (11%) required a blood transfusion during or after THA during the study period. Of these, one transfusion occurred intraoperatively and the remaining 59 were administered postoperatively. Twenty-two transfusions occurred on postoperative Day 1, 33 on postoperative Day 2, and two on each of postoperative Days 3 and 4. Fellowship-trained adult reconstruction surgeons (SSW, MPB) performed all THAs through a posterior approach. All patients underwent the same preoperative evaluation and surgical clearance through the department of anesthesia. All patients received weight-based intravenous (IV) TXA unless contraindicated. Specific contraindications to IV TXA included cardiac stents or transient ischemic attacks within 6 months, history of deep venous thrombosis (DVT) or pulmonary embolism (PE), history of hypercoagulable state, late onset colorblindness, or a history of seizure. These patients were not excluded from study inclusion but either received topical TXA or no TXA as detailed below. The IV TXA was divided in two doses, one given at incision and a second given at initiation of wound closure because this has been shown to be most efficacious [26, 41]. Those with recent cardiac stents or transient ischemic attack within 6 months were given topical TXA at wound closure (2 g mixed in 100 cc sterile saline). Across all participants, 536 (96%) received TXA. Of these 536 patients, 80% received IV TXA and 20% received topical TXA. In the transfusion group, 17 patients received IV TXA (28%), 41 received topical TXA (68%), and two (9%) received no TXA. Other blood-conservation modalities such as Cell Saver® (Haemonetics, Braintree, MA, USA) and Aquamantys® (Medtronic, Minneapolis, MN, USA) were not used during the study period. The placement of a closed-suction drain (Medline, Mundelein, IL, USA) was determined by the attending surgeon at the conclusion of surgery. If there was persistent, mild bleeding from the wound bed despite electrocautery use, pressure hemostasis, and no singular

source of bleeding identified, a subfascial drain was placed before closure.

Information regarding age, sex, American Anesthesia of Anesthesiologist (ASA) score, preoperative Hgb (g/dL), estimated blood loss, intraoperative packed red blood cell (pRBC) transfusions, TXA use, and drain use were assessed. Postoperative factors including postoperative Hgb obtained on the morning of postoperative Day 1, type of DVT prophylaxis used, LOS (time from incision to discharge), drain duration, postoperative pRBC transfusion, number of units transfused, and discharge disposition were recorded. A postoperative Hgb less than 7 g/dL is an automatic transfusion for trigger at our institution. Transfusions also were given postoperatively if the patient showed new clinical symptoms consistent with symptomatic anemia even if the postoperative Hgb was 7 g/dL or greater. These symptoms specifically included exertional dizziness or weakness that precluded patients from being able to participate, or limited their participation, in physical therapy. No patients included in the study presented with a Hgb less than 7 g/dL. Patients were discharged home when they met physical therapy goals and were medically stable. Patients were categorized by those not requiring blood transfusions and those requiring blood transfusion (either intraoperatively or postoperatively). All of the demographic, preoperative (Appendix 1. Supplemental material is available with the online version of *CORR*[®]), intraoperative, and postoperative data (Appendix 2. Supplemental material is available with the online version of *CORR*[®]) mentioned above were included in a univariable analysis.

Continuous variables are displayed using the mean $\pm$ SD or median and (25th, 75th percentiles) if not normally distributed. Comparisons between transfusion groups used the t-test or Wilcoxon rank-sum test as appropriate. Categorical variables are presented using counts and percentages with group comparisons being performed using the chi-square test or Fisher's exact test (expected cell counts < 5). Pairwise comparisons in sex were performed to compare categorical preoperative Hgb groups based on the WHO cutoffs using the Bonferroni α correction for multiple tests to avoid spurious type I errors ($p < 0.017$ considered significant).

A multivariable logistic regression model was used to assess preoperative Hgb as an independent predictor of transfusion after adjusting for significant differences found in preoperative variables from the univariable analyses. The model considered age (per 5-year increase), sex (male versus female), ASA score (1-2 versus 3-4), IV TXA use (yes or no), and preoperative Hgb. These variables were chosen because they are known before the operation and one of the goals was to identify best-supported cut points before surgery to facilitate referral and treatment if patients at risk were identified. TXA topical use and no TXA-given

groups were combined owing to the low number of transfusions in the subcategories. Neither ASA score nor age was a significant multivariable predictor after inclusion of sex, IV TXA use, and preoperative Hgb. Given the expected differences in preoperative Hgb between males and females, the multivariable logistic regression was applied across all participants and stratified by sex. Owing to the small percentage of patients who received topical or no TXA, stratification by TXA use was not performed because of the low sample size.

Logistic regression models then were further used to determine the preoperative Hgb cutoff value that best predicted dichotomous transfusion using the unadjusted and adjusted models. The cutoff value was determined by maximizing the area under (AUC) the receiver operating characteristic curve (ROC). The cut point was chosen to simultaneously maximize sensitivity and specificity by applying Youden's index to maximize the vertical distance of the ROC curve from the point (x, y) on a diagonal line (45° chance line). Given the information described previously, we considered that false-positives are less serious than false-negatives given the studies available and the associated costs. Cut points are shown that maximize sensitivity, specificity, and AUC.

Unless otherwise stated, a probability less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS[®] Version 9.4 (SAS Inc, Cary, NC, USA).

Results

After controlling for potential confounding variables such as age, sex, ASA score, intravenous TXA (IV TXA) use, and preoperative Hgb, we found that patients with lower preoperative Hgb (g/dL per 1-unit decrease, odds ratio [OR], 2.6; 95% CI, 2.0–3.5; $p < 0.001$), female sex (vs male, OR, 4.2; 95% CI, 1.7–10.3; $p = 0.002$), and those unable to receive IV TXA (versus topical TXA or no TXA, OR, 13.5; 95% CI, 6.3–28.6; $p < 0.001$) were more likely to receive a transfusion (Table 1). Of these, preoperative Hgb was found to be the variable most highly associated with transfusion (AUC, 0.876) followed by inability to receive IV TXA (AUC, 0.774), and female sex (AUC, 0.661) (Fig. 1). These AUC values were generated to maximize sensitivity and specificity for transfusion risk. As expected, when stratified by sex, the risk of transfusion increased for males and females as preoperative Hgb decreased (Fig. 2).

A preoperative Hgb value of 12.6 g/dL maximized the AUC across all patients (sensitivity = 83, specificity = 84) unadjusted for sex or IV TXA use. When stratified by sex, values of 12.5 g/dL (sensitivity = 85, specificity = 77) and

Table 1. Multivariable logistic regression model to assess for predictors of postoperative transfusion across all participants and in sex category

Variable	Multivariable		
	All OR (95% CI) p value	Male OR (95% CI) p value	Female OR (95% CI) p value
Sex	4.2 (1.7–10.3)	–	–
(female versus male)	0.002		
TXA use	13.5 (6.3–28.6)	4.0 (0.9–17.9)	19.7 (8.2–47.6)
(topical/none versus intravenous)	< 0.001	0.069	< 0.001
Hgb (g/dL)	2.6 (2.0–3.5)	2.4 (1.5–3.6)	3.0 (2.0–4.3)
(per 1-unit decrease)	< 0.001	< 0.001	< 0.001

Results presented as odds ratio (OR) with 95% CI; neither age nor American Society of Anesthesiologists score were significant multivariable predictors after adjusting for other variables; TXA = tranexamic acid administered as topical or intravenous; Hgb = preoperative hemoglobin.

Fig. 1 The receiver operator curve (ROC) for predicting transfusion using preoperative Hgb, sex (male or female), and TXA use (yes or no) across all patients is shown. An area of 0.5 indicates no discriminability, whereas an area of 1 indicates perfect ability to predict transfusion with a given covariate. The blue solid line represents preoperative hemoglobin (AUC = 0.8762), the red dash line represents sex (AUC = 0.6661), and the green dash-dot line represents TXA (AUC = 0.7740).

13.5 g/dL (sensitivity = 92, specificity = 77) maximized AUC for women and men, respectively (Table 2).

Discussion

Preoperative anemia is increasingly recognized as an independent risk factor for postoperative complications after THA. Studies have shown that patients with anemia

have an increased risk of, in some analyses, mortality [5, 6, 18], periprosthetic joint infection [13, 28], allogeneic blood transfusion [7, 16, 46], major postoperative complications [31], increased LOS, and increased 90-day readmission rates [19] in retrospective studies and large national database analyses. Similar to prior studies [1, 3, 4, 11, 12, 14, 30, 33, 38], our study showed that preoperative Hgb is independently associated with transfusion risk despite routine TXA use. We found that the best-supported preoperative Hgb cutoff for THA was 12.5 g/dL for females and 13.5 g/dL for males; patients below these cutoffs may benefit from preoperative strategies to decrease the risk of transfusion after THA, such as preoperative erythropoietin stimulating agents, iron supplementation, or preoperative transfusion [15].

However, this study does have limitations. Patients included in this study all were treated at a large tertiary referral center and may have more preoperative comorbidities compared with patients at community hospitals. As a result, the study may lack generalizability to other populations. In addition, the type of preoperative anemia was not included for analysis. Complications related to transfusion were not recorded, because this was not the purpose of this study. Patients receiving topical TXA and no TXA were combined in this study given the low counts for statistical purposes. This may explain the difference in the risk of transfusion between the IV TXA and topical or no TXA formulations since the multivariable analysis adjusted for comorbidities. In addition, drains were used selectively in this study and the indications for their use were not based on objective criteria. If there was persistent, mild bleeding from the wound bed despite electrocautery use, pressure hemostasis, and no singular source of bleeding was identified, a subfascial drain was placed before closure. Drain use was not different between the two groups in this study; although some studies associate drains with a greater risk of transfusion [34], a recent randomized

Fig. 2 The predictive probability of blood transfusion by preoperative Hgb adjusted for sex is shown.

controlled trial found no differences in blood loss or transfusion rate when a drain was used in the setting of routine TXA use and aspirin for DVT prophylaxis [40]. Finally, the retrospective nature of the study results in the inability to draw definite conclusions and only associations can be revealed that will require further verification.

In our study, preoperative Hgb level was the factor most associated with transfusion after controlling for potentially relevant confounding variables. This has important implications preoperatively since compared with sex and the inability to receive TXA, this is a modifiable variable. The identification and treatment of preoperative anemia before lower extremity arthroplasty with specialist referral, iron supplementation, and erythropoietin-stimulating agents have been shown to reduce transfusions, LOS, 90-day readmissions, and costs [9, 15, 17, 20, 22, 24, 36], yet there are no guidelines or cutoffs to suggest which patients would benefit from these treatment programs or to identify preoperative Hgb targets to ensure one is “ready” for THA. We recommend that in addition for screening with BMI and hemoglobin A1c for obesity and diabetes, respectively, patients have preoperative hemoglobin checked 4 weeks before THA [15]. This allows time for adequate referral and treatment given the high risks associated with

transfusion below the values identified herein [29]. Even with the substantial reductions in transfusion associated with TXA use, a low preoperative hemoglobin still warrants appropriate attention and workup as shown in our study.

When adjusted for sex and TXA use, we found values of 12.5 g/dL (sensitivity = 85, specificity = 77) and 13.5 g/dL (sensitivity = 92, specificity = 77) maximized AUC for women and men, respectively. In 1968, the WHO defined anemia as a Hgb less than 13 g/dL for men and less than 12 g/dL for women using population-based studies [44]. When the WHO definitions were applied to the patients in this study, we found these values have a lower sensitivity to predict transfusion compared with the best-supported values determined using the methods above for females (sensitivity = 60, specificity = 86) and males (sensitivity = 67, specificity = 87 (Table 3)). Use of these cutoffs lack sensitivity in today’s THA population and may underestimate the percentage of patients who could benefit from treatment. In choosing a cutoff, one must weigh the risks of treating patients who are not at high risk (false-positives) versus failing to treat those who are at high risk (false-negatives). We believe that the risks of treating patients at low risk are minimal (0.2% incidence of transfusion

Table 2. Cut point for preoperative hemoglobin as determined by logistic regression analysis of unadjusted (hemoglobin only), stratified by sex (hemoglobin only), or covariate-adjusted models (hemoglobin, sex, and/or TXA use) to maximize AUC, sensitivity, and specificity

			Maximize		
Model	Sex	TXA IV	AUC	Sensitivity	Specificity
All patients					
Unadjusted			12.6	14.8	7.7
(Sn, Sp)			(83, 84)	(100, 23)	(2, 100)
Adjusted (Sn, Sp)			(80, 86)	(100, 29)	(2, 100)
	Female		12.6	15.1	7.7
	Male		12.3	14.7	7.4
Adjusted (Sn, Sp)			(83, 88)	(100, 27)	(2, 100)
		Yes	12.6	15.5	6.6
		No	13.7	16.6	7.7
Adjusted (Sn, Sp)			(90, 84)	(100, 24)	(5, 100)
	Female	Yes	13.6	17.3	8.4
		No	15.0	18.6	9.8
	Male	Yes	12.9	16.5	7.7
		No	14.2	17.8	9.0
Female patients					
Unadjusted	Female		12.5	14.8	7.7
(Sn, Sp)			(85, 77)	(100, 3)	(2, 100)
Adjusted (Sn, Sp)			(88, 87)	(100, 68)	(6, 100)
		Yes	12.7	14.0	8.4
		No	14.2	15.3	9.8
Male patients					
Unadjusted	Male		13.5	14.4	9.9
(Sn, Sp)			(92, 77)	(100, 53)	(33, 100)
Adjusted (Sn, Sp)			(92, 76)	(100, 46)	(33, 100)
		Yes	14.0	15.2	9.1
		No	14.8	16.0	9.9

TXA = tranexamic acid administered intravenously; AUC = area under the receiver operating characteristics curve; IV = intravenous; Sn = sensitivity; Sp = specificity.

Table 3. Breakdown of categorical preoperative hemoglobin by sex using the WHO cutoffs

Variable	No transfusion	Transfusion	Sn	Sp	PPV	p value	p value*
Male (number)	265	12					
Hgb category							
< 11.0	2 (1%)	4 (33%)	33	99	67		< 0.001
11.0–13.0 [†]	32 (12%)	4 (33%)	50	96	35		0.002
> 13.0	231 (87%)	4 (33%)	67	87	48	< 0.001	Reference
Female (number)	233	48					
Hgb category						< 0.001	
< 10.0	2 (1%)	4 (8%)	8	99	67		< 0.001
10.0–12.0 [†]	30 (13%)	25 (52%)	29	97	64		< 0.001
> 12.0	201 (86%)	19 (40%)	60	86	19		Reference

*Pairwise comparisons with reference category; [†]midpoint of range used for Sn/Sp cut point analysis; Sn = sensitivity; Sp = specificity; PPV = positive predictive value; Hgb = preoperative hemoglobin.

reactions [32], gastrointestinal upset with oral iron [42], and costs of referral, workup, and medications [15]) compared with the risks of failing to treat patients at high risk (periprosthetic joint infection [13, 28], increased readmissions [19], and death [5, 6, 18]). Furthermore, a study performed at our institution modeling 100 patients with anemia seen during the course of a year using a THA preoperative Hgb cutoff of 11.5 g/dL and estimated 50% transfusion reduction rates still showed substantial cost savings with anemia treatment [15]. Therefore, we believe false-positives are less serious than false-negatives and prefer increased sensitivity at the expense of specificity of our suggested cutoff values compared with the current WHO standard. We recommend that patients with preoperative hemoglobin values below the best-supported values presented above have their THA delayed and be referred for treatment. In addition, these values can help the consulting anemia specialist provide a “goal” for when treatment has been completed.

Previous studies have used other methods in evaluating cutoffs for preoperative Hgb in THA. Evans et al. [10] retrospectively audited the incidence of blood transfusion in 181 patients undergoing primary and revision hip and knee arthroplasties. By combining data for patients undergoing primary THA and those undergoing TKA, they divided patients in low- and high-risk groups using a Hgb cutoff of 12 g/dL in which the incidence of transfusion below this cutoff was 48% and above 7% [10]. Similarly, Saleh et al. [37] identified patients with preoperative Hgb less than 11 g/dL as an independent risk for perioperative transfusion (OR, 13.9; 95% CI, 7.8–24.9). However, similar to the WHO cutoffs, the lower numbers recommended in these studies may not identify a large proportion of patients who would benefit from referral and treatment.

Finally, despite the blood-conservation effects of TXA, routine use should not preclude or prevent the treatment of preoperative anemia. In this study, 96% of the patients received TXA (IV or topical), but 11% still received a transfusion despite use of strict transfusion triggers. A recent meta-analysis showed IV TXA was effective in reducing allogenic blood transfusion by 50% and limiting blood loss intraoperatively and through drains in patients undergoing primary THA [27]. Whiting et al. [43] recently reported that TXA may be beneficial in patients undergoing total joint arthroplasty regardless of preoperative Hgb, with patients with anemia still seeing transfusion reductions. Similar findings also were reported by Phan et al. [35] who found no difference in the risk of transfusion between patients with anemia (Hgb < 12 g/dL) versus those without anemia undergoing THA and receiving TXA. The blood-conserving effects of TXA are further highlighted by the results of the current study in which the inability to receive

IV TXA was an independent risk factor for blood transfusion compared with receiving topical TXA or no TXA. To our knowledge, this finding has not been previously identified.

Currently, there is a lack of consensus and evidence-based practice when it comes to management of preoperative anemia and transfusion protocols in patients undergoing hip arthroplasty. The WHO definitions of preoperative anemia based on sex may underestimate transfusion risk in today’s more-medically complex patients undergoing THA, and with practice patterns involving more-routine TXA use. We recommend that the Hgb cutoffs described here (12.5 g/dL for females and 13.5 g/dL for males) could be used to refer and counsel patients accordingly before THA and in future research on preoperative anemia. Further investigation will be needed to see if treatment for preoperative Hgb below these cutoffs reduces transfusions and the associated complications after THA.

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