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Prophylactic Plasma Transfusion for Surgical Patients With Abnormal Preoperative Coagulation Tests: A Propensity-Adjusted Cohort Study

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Abstract

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Conflicts of Interest

Qing Jia, Michael J. Brown, Leanne Clifford, Gregory A. Wilson, Mark J. Truty, James R. Stubbs, Darrell R. Schroeder, and Andrew C. Hanson have no conflicts of interest to disclose. Ognjen Gajic holds a patent application on critical care-related software applications licensed to Ambient Clinical Analytics Inc. Daryl J. Kor receives royalties from Up-to-Date for authoring a chapter on the topic transfusion-related acute lung injury.

Author Contributions

Qing Jia contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Michael J. Brown contributed to the study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Leanne Clifford contributed to the acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Gregory A. Wilson contributed to the acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Mark J. Truty contributed to the analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. James R. Stubbs contributed to the analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Darrell R. Schroeder contributed to the statistical analyses, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Andrew C. Hanson contributed to the statistical analyses, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Ognjen Gajic contributed to the study concept and design, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Daryl J. Kor contributed to the study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. He also obtained funding for the work presented in this manuscript and provided supervision for the overall conduct of the study.

Daryl J. Kor had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Darrell R. Schroeder takes responsibility for the integrity of the work as a whole, from inception to published article.

Declaration of Interest Statement

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Background—Perioperative hemorrhage negatively impacts patient outcomes and results in substantial health care resource consumption. Plasma transfusions are frequently administered to address abnormal preoperative coagulation tests, with the hope of mitigating bleeding complications. This study aimed to evaluate the associations between preoperative plasma transfusion and bleeding complications in patients with elevated international normalized ratios undergoing noncardiac surgery.

Methods—An observational comparative effectiveness research study evaluating a consecutive sample of adult patients undergoing noncardiac surgery (N=14,743) with preoperative international normalized ratios ≥ 1.5 between January 1, 2008, and December 31, 2011. Among the patients, 1,234 (8.4%) had an international normalized ratio ≥ 1.5 and were included in this investigation. Exposure of interest was transfusion of preoperative plasma for an elevated international normalized ratio. Primary outcome was World Health Organization grade 3 bleeding in the early perioperative period. Secondary outcomes included blood loss, reoperation for bleeding, and additional patient-important outcomes including death and lengths of stay. Hypotheses were tested with univariate and propensity-matched analyses. Multiple sensitivity analyses were performed to further evaluate the robustness of study findings.

Findings—Of 1,234 study participants, 139 (11.3%) received a preoperative plasma transfusion. Those who received plasma had a higher rate of perioperative (52.5% vs 32.0%; $P < .0001$) and intraoperative (40.3% vs 24.5%; $P < .0001$) red blood cell transfusion, as well as an increased rate of reoperation for bleeding (11.5% vs 4.5%; $P = .0005$). The increased rate of perioperative red blood cell transfusion stayed in the propensity-matched analyses (OR, 1.75 [95% CI, 1.09–2.81]; $P = .0210$). Results from multiple sensitivity analyses were qualitatively similar.

Interpretation—Preoperative plasma transfusion for elevated international normalized ratios was associated with an increased rate of perioperative bleeding complications. Findings were robust in the sensitivity analyses, suggestive that more conservative management of abnormal preoperative international normalized ratios is warranted.

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Keywords

coagulation tests; comparative effectiveness research; hemorrhage; perioperative care; plasma transfusion; prevention

Introduction

Perioperative hemorrhage continues to be an important concern because of its substantial impact on patient-important outcomes (1–4) and health care resource utilization (5,6). Reoperation for bleeding and red blood cell (RBC) administration are consistently associated with postoperative complications (2–4,6). Furthermore, the number of RBC units transfused annually approaches 14 million in the United States alone (7). With an estimated cost of \$761 per RBC unit (5), this equates to \$10.5 billion in health care expenditures. Of note, more than a quarter of these transfusions occur in the perioperative environment.

Therefore, strategies that can mitigate perioperative bleeding complications or safely reduce the need for RBC transfusion are of great interest.

A key first step in mitigating perioperative bleeding complications is assessment of patient risk. However, our ability to predict these adverse events, typically estimated with patient- and procedure-related factors (8,9), is incomplete. For patient-related factors, emphasis is often placed on preoperative screening tests, such as international normalized ratio (INR). Indeed, the INR is a major driver of decisions about perioperative plasma transfusion (10–12).

As perioperative health care providers work to mitigate bleeding complications, plasma transfusion remains a cornerstone therapy for patients with elevated INR. A large proportion of the plasma components are transfused in the perioperative environment (10–13). In that setting, plasma frequently is administered prophylactically, in the absence of significant active bleeding. This practice persists despite a growing body of literature questioning its efficacy (10,12,14–17). Moreover, plasma transfusions are recognized increasingly as important contributors to transfusion-related complications, including allergic reactions, transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO) (18, 19).

We aimed to evaluate the associations between preoperative plasma transfusion (PPT) and perioperative bleeding complications for patients with elevated INR. We hypothesized that PPT would not be associated with reduced rates of World Health Organization (WHO) grade 3 bleeding events. Secondly, we aimed to assess the impact of PPT on additional patient-important outcomes.

Methods

This study is an observational comparative effectiveness research analysis using a cohort design. It was approved by the Mayo Clinic Institutional Review Board (Rochester, Minnesota) before initiation. The guidelines of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were used in study design and conduct, as well as the reporting of our results (20).

Study Population

To be considered for study participation, patients needed to have the following criteria: age 18 years, noncardiac surgery between January 1, 2008, and December 31, 2011, and INR 1.5 in the 30 days preceding surgery. The INR cut point of 1.5 was chosen due to the presence of multiple published guidelines recommending consideration of prophylactic plasma transfusion at this threshold (21,22). In addition, the threshold of 1.5 is frequently endorsed as an indication for plasma transfusion at this investigation's participating institution. Due to unique patient and procedure-related characteristics of patients undergoing cardiac surgery, as well as pre-specified desire to evaluate the role of prophylactic plasma transfusion in the specific setting of non-cardiac surgery, patients undergoing cardiac surgery were not included in the present investigation. Exclusion criteria included lack of research authorization, American Society of Anesthesiologists (ASA)

Physical Status VI classification, and prior inclusion in the study. Study participants were evaluated for the outcomes of interest from the time of surgical onset until the time of hospital discharge or death, whichever came first. No patients were lost to follow-up in this investigation.

Outcome Variables

The primary outcome was WHO grade 3 bleeding, defined as the need for early perioperative RBC transfusion. *Perioperative RBC transfusion* was defined as the administration of allogeneic RBC components during the interval beginning with entry into the operating room and ending 24 hours after exiting the operating room. Secondary outcomes included intraoperative RBC transfusions, estimated blood loss, and return to the operating room because of bleeding within 24 hours of the index procedure. Patients with missing values for estimated blood loss were excluded from related analyses. To qualify as an intraoperative transfusion, the transfusion initiation time had to occur during the operative encounter (i.e., from operating room entry to operating room exit). Additional patient-important outcomes were evaluated, including intensive care unit admission and length-of-stay (LOS), need for ventilatory support, duration of hospital stay, and hospital death.

Predictor Variables

The primary exposure variable was administration of a PPT. Because the objective was to assess PPT efficacy, qualifying plasma transfusions were defined as those administered before onset of the surgical procedure. To minimize risk of cause-effect inversion, plasma transfusions administered in the operating room or postoperatively were not considered when determining the primary exposure variable. *Time of plasma transfusion* was defined as transfusion initiation, documented in the electronic health record, rather than the issue time recorded from the transfusion medicine service. Additional baseline information, as well as procedural and anesthesia-related details, was extracted also.

Institutional Transfusion Protocols

The following institutional guidelines for RBC transfusion were in place during the study interval:

1. Massive blood transfusion (MBT): The MBT protocol is initiated by the provider, nurse, or transfusion services lab when a patient receives four (4) units of blood in less than two (2) hours or earlier if the provider anticipates a massive hemorrhage is occurring. The MBT protocol advocates the administration of 1 unit of plasma for every unit of RBC administered during a massive hemorrhage event. It further endorses a single apheresis platelet component for every 6 units of RBC administered as well as 10 units of cryoprecipitate.
2. Non-operating room environment: Institutional guidelines identified the following as potential indications for RBC administration during the study interval: pre-transfusion hemoglobin level < 7 g/dL; peripheral ischemia (coronary, peripheral vascular, cerebrovascular); symptomatic anemia (confusion, tachycardia, hypotension); and early septic shock.

3. Operating room environment: During the study interval, no specific guidelines were in place regarding intraoperative RBC transfusions and the decision to transfuse RBCs was left to the discretion of the surgical team.

Data Sources

Screening for study participants was performed using Perioperative Datamart. This institutional resource captures data for all patients admitted to an acute care environment (e.g., operating room, intensive care unit, progressive care unit) at the study's participating institution (23,24). In addition to information relating to the surgical encounter, this robust data warehouse contains information on baseline demographic and clinical characteristics and on fluid and transfusion therapies, as well as related information pertinent to perioperative course (e.g., medications, laboratory values, postoperative outcome, LOS). Additional relevant baseline characteristics not available in Perioperative Data Mart were obtained from a second database, Mayo Clinic Life Sciences System. As with Perioperative Data Mart, this data source has undergone extensive validation procedures (25,26).

Statistical Considerations

Assuming a perioperative WHO grade 3 bleeding rate of 30% (historical data from the participating institution) and a PPT rate of 25% in patients with INR ≥ 1.5 , we estimated that the sample size required to identify an odds ratio of 0.5 in patients who received PPT vs those who did not was 600 total study participants (two-sided $\alpha = 0.05$; $\beta = 0.20$). To adequately power this investigation for the planned subgroup and sensitivity analyses (e.g., subgroups defined with INR cut points 1.75 and 2.00, surgical subgroups), we chose a four-year period for the cohort, to obtain a total sample size of approximately 1,200 study participants with INR ≥ 1.5 .

Baseline demographic characteristics, clinical characteristics, and procedure-related information are presented as median (25%, 75%) for continuous data and number (%) for categorical data. Comparisons of continuous variables between patients who received PPTs and those who did not were performed using Wilcoxon rank sum test. Comparisons of categorical variables were performed using a chi-square test.

To address the primary aim of this investigation, we explored the relations between PPT and bleeding complications with univariate and multivariate analyses. As observational studies risk unequal distributions of key confounding variables because of the lack of participant randomization, propensity-matched analyses were planned a priori. Logistic regression was used to calculate propensity scores for PPT with all patient and procedural characteristics listed in Table 1 included as explanatory variables with the exception of AIDS and preoperative NSAID, which had very low prevalence, and body mass index and baseline albumin, which were missing for 200 (16%) and 769 (62%) patients respectively. Each patient who received PPT was matched with 1 or 2 patients with a similar propensity score who underwent the same surgical procedure but did not receive PPT. An optimal matching algorithm was used with exact matching on surgical procedure and propensity score matching using a caliper of 0.25 times the standard deviation (27). Standardized mean differences after propensity score adjustment were obtained for each covariate to assess

effectiveness of the propensity score to control for confounding of the observed variables. Conditional logistic regression, taking into account the matched set study design, was then used to assess whether the likelihood of experiencing WHO grade 3 bleeding was associated with PPT. Similar analyses were performed for secondary outcomes with conditional logistic regression for binary outcomes and mixed linear models for hospital LOS. Intensive care unit LOS and duration of mechanical ventilation were analyzed for patients who required these interventions, with Wilcoxon rank sum test used to compare those who received PPT vs not.

To assess the potential influence of preoperative vitamin K use, this variable was obtained for all patients included in the propensity-matched analysis and a post-hoc analysis was performed for the primary endpoint with preoperative vitamin K use included as a covariate. To further assess the robustness of study findings, multiple sensitivity analyses were planned a priori. These prespecified analyses included restriction to 1) study participants undergoing elective surgery, 2) study participants undergoing general surgery, and 3) patients with INR 1.75 and 2.0, respectively. In all final analyses, statistical significance was considered present when the hypothesis test *P* value was < 0.05. All statistical analyses were performed with SAS statistical software version 9.3 (SAS Institute Inc).

Role of the Funding Source

Funding for the design and conduct of the study; collection, analysis, and interpretation of the data; writing of the report; and decision to submit the paper for publication was provided by the Mayo Clinic Department of Anesthesiology and the Critical Care Medicine Independent Multidisciplinary Program Research Committee. The analysis, interpretation of the data, and writing of the report was also supported by the National Institutes of Health, Grant Number: R01 HL121232-01. No author received payment to write this article by a pharmaceutical company or other agency.

Results

Between January 1, 2008, and December 31, 2011, a total of 155,492 patients aged 18 years underwent noncardiac surgery at the participating institution (Figure 1). Of them, 14,743 had an INR measured within 30 days of the index surgical procedure, with 1,234 having INR 1.5. This latter group comprised the analyzed study population. Median (25%, 75%) time from qualifying INR to procedure onset was 6.9 (2.4, 49.3) hours. A total of 139 patients (11.3%) received a qualifying PPT. In those receiving preoperative plasma, median (25%, 75%) time from initiation of the last qualifying plasma component to the onset of the surgical procedure was 0.8 (0.5, 1.7) hours. The median (25%, 75%) volume of prophylactic plasma administered was 5.10 (2.97, 7.16) ml/kg of actual body weight.

Comparisons of baseline and procedure-related characteristics in patients who received preoperative plasma and those who did not are shown in Table 1. Numerous between-group differences were identified. The preoperative plasma cohort had higher ASA physical status scores, greater prevalence of preoperative clopidogrel and heparin administration, and higher baseline creatinine levels. A greater proportion of the PPT cohort also underwent general and emergency surgery; a greater proportion of the nonplasma cohort had orthopedic

procedures. Of note, none of the trauma patients included in this investigation required initiation of the institutional massive blood transfusion protocol.

In total, 423 study participants (34.3%) had WHO grade 3 bleeding as defined in the study protocol. Of these, 324 (76.6%) received an RBC transfusion in the operating room and 260 (61.5%) received a transfusion in the initial 24 hours after operation. Results of unadjusted analyses evaluating the associations between PPTs, perioperative bleeding complications, and patient-important outcomes are shown in Table 2. Frequency of WHO grade 3 bleeding among patients who received preoperative plasma vs those who did not was 52.5% vs 32.0% (OR, 2.35 [95% CI, 1.65–3.36]; $P < .0001$). In those who met criteria for WHO grade 3 bleeding, the median (25%, 75%) volume of RBC transfused was similar for those received preoperative plasma versus not [990 (660, 2156) ml versus 990 (660, 2201) ml, respectively; rank sum test $P = 0.65$]. PPT was associated with an increased rate of all adverse patient-important outcomes evaluated in this study.

A total of 1,147 study participants were assigned a propensity score; 87 (7%) were not assigned a score because of missing data (creatinine, $n = 20$; hemoglobin, $n = 77$; and platelet count, $n = 76$). Among patients with propensity scores, 125 received preoperative plasma and were propensity-matched to 242 patients who did not. Eight patients receiving preoperative plasma were matched to one patient who did not receive a transfusion (nontransfused) and 117 patients were matched to two nontransfused patients. Fourteen patients who received a PPT were removed from matched analyses: 13 because of no suitable nontransfused, propensity-matched study participant and 1 for whom a propensity score could not be assigned because of missing data. Propensity matching was effective in addressing baseline covariate imbalances (Table 1 and Figure 2).

Among the propensity-matched cohort, 65 (52%) of the plasma transfusion study participants had WHO grade 3 bleeding, compared with 97 (40%) of those who did not receive a PPT. Conditional logistic regression analysis on these propensity-matched patients identified a statistically significant increase in risk of WHO grade 3 bleeding for those who received preoperative plasma (OR, 1.75 [95% CI, 1.09–2.81]; $P = .0210$). In the propensity matched sets, the frequency of vitamin K use was found to be higher in those receiving plasma versus not (36.0% vs 19.4%). From a stratified analysis that included vitamin K as a covariate, plasma administration was found to be associated with an increased risk for WHO grade 3 bleeding (OR=1.74, 95% CI [1.07 to 2.82], $P = .0245$), with no association found for vitamin K (OR=1.04, 95% CI [0.55 to 1.97], $P = .90$). Results of the secondary outcome analyses are shown in Table 3. These findings were qualitatively consistent across the multiple sensitivity analyses performed (supplemental table, available online).

Discussion

This investigation's primary aim was to evaluate the association between PPT in patients with INR ≥ 1.5 and perioperative bleeding complications. To this end, we did not find evidence of benefit with plasma administration in this clinical setting. To the contrary, plasma transfusion was associated with an increased rate of WHO grade 3 bleeding. This association appeared robust, persisting in propensity-matched analyses. The associations

between PPT and the secondary outcomes were qualitatively similar, and no performed analyses provided evidence for improved outcomes in those treated with PPTs.

Plasma transfusion continues to be a common intervention in the United States, with estimates suggestive that approximately 3.8 million units were transfused in 2011 alone (7). A large proportion of these plasma units were administered preoperatively to surgical populations (10–13). Despite the frequent use of plasma transfusion, evidence-based indications are limited, with the primary indication being replacement of coagulation factor content in patients with active bleeding who have acquired coagulation factor deficiencies (13,19). Less frequently, plasma transfusion may be indicated in the setting of plasma exchange for such conditions as thrombotic thrombocytopenic purpura or in patients with congenital coagulation factor deficiencies when no specific coagulation factor concentrate exists. More recently, plasma transfusion has been endorsed as a component of massive transfusion protocols (e.g., 1:1:1 transfusion ratio between RBC, plasma, and platelets).

Though these indications for plasma transfusion have been broadly endorsed (28), the more controversial issue of prophylactic plasma transfusion for nonbleeding patients with abnormal preprocedural coagulation screening tests is a matter of much debate (13,28). Indeed, plasma administration is still common in this clinical setting despite the dearth of data suggesting clinical benefit (12,13,28–30). To further complicate matters, international guidelines are conflicting on this point as well (28,31,32). Thus, providers are left with unclear guidance and frequently err on the side of providing a therapy with unclear benefit and thereby exposing patients to the potential harms of plasma transfusion, as well as the substantial costs.

The persistent practice of preoperative plasma administration is presumed to be driven by three assumptions: INR accurately predicts risk for procedure-related bleeding, plasma administration corrects the abnormal coagulation screening test, and plasma transfusion mitigates bleeding complications. Of note, all three assumptions stand on little evidentiary support. Abdel-Wahab and colleagues (10) have shown that INR elevations ranging up to 1.85 correlate poorly with estimated RBC loss. These findings have been corroborated through multiple additional investigations in various clinical contexts (33,34). Of note, plasma also has been observed to have inconsistent and generally limited influence on normalizing mild to moderate INR elevations (10,15,35). Although greater effect may be seen with more substantial INR increases, it is important to recognize that these changes correlate poorly with actual coagulation factor content and often provide an inaccurate picture of true coagulation status (36). Finally, it is assumed that plasma administration reduces the frequency and severity of bleeding complications. Again, available data offer little to support this assertion (16). The recent systematic review of Yang and colleagues (16) is notable for the apparent lack of a meaningful effect in the clinical trials performed thus far. This review included patient populations with liver disease, those undergoing cardiac surgery, and those receiving oral anticoagulant therapy. However, the majority of the included trials have limited sample size, target specific patient populations rather than heterogeneous cohorts, and frequently have important methodologic limitations.

In addition to concerns related to efficacy, plasma administration is not without risk. Risks range from less severe allergic reactions to life-threatening conditions, such as anaphylaxis, TRALI, and TACO (19). Historically, plasma transfusion has been the highest-risk component for both TRALI and TACO (18). Though recent transitions to male-only donor policies for transfusable plasma has reduced substantially the risk of plasma-associated TRALI (18), similar strategies to reduce the risk of plasma-associated TACO are lacking.

Perhaps most interesting in the present investigation is the relation between preoperative plasma administration and increased rates of perioperative WHO grade 3 bleeding. The association necessarily leads to questions relating to the potential mechanism(s) underlying this finding. Although our observational investigation cannot effectively address this important question, several possible answers exist. The first potential explanation relates to provider behavior. Specifically, health care providers who transfuse plasma with increased frequency may likewise transfuse RBC components in a more liberal manner. A second potential mechanism may relate to the impact of intravascular volume expansion on intravascular pressures and the stability of early hemostatic plugs. Similar rationale has been offered when attempting to better understand the recently identified relation between liberal RBC transfusion practices and increased rates of bleeding complications in patients presenting with gastrointestinal hemorrhage (37). This rationale also underlies ongoing interest in permissive hypotension in the setting of major trauma (38). In a third potential explanation, plasma contains important anticoagulant proteins. The greater prevalence of preoperative heparin therapy in the preoperative plasma cohort generates hypotheses regarding potential interactions of this finding with the heparin-catalyzed anticoagulant factors in the plasma products (eg, antithrombin III). A fourth factor that should be noted is the very modest volume of prophylactic plasma administered [5.10 (2.97, 7.16) ml/kg of actual body weight]. Theoretically, the relationships between preoperative plasma administration and bleeding complications may have been impacted by a suboptimal “dose” of plasma transfusion. Finally, a fifth potential explanation is residual confounding-by-indication.

Strengths of the present investigation are large sample size, heterogeneous surgical population, validated electronic data-capture techniques, and rigorous statistical adjustments. However, numerous limitations deserve mention. The observational study design creates potential for confounding and bias that may influence the results. As an example, patient’s who received plasma may have simply been more acutely ill or at greater risk of bleeding when compared to their matched, non-transfused controls. Although efforts were made to control for these issues during protocol development, data extraction, and statistical analyses, the potential for persistent unmeasured confounding remains. Of note, propensity matching did largely address baseline imbalances in the study’s measured variables. Nonetheless, the potential for persistent unmeasured confounding certainly persists. The observational study design also prevented standardization of decisions relating to blood product administration and other important care processes, again increasing the potential for bias and unmeasured confounding. The observational study design therefore precludes any conclusion regarding causality of the observed associations. These particular concerns are only effectively addressed with a randomized trial design.

An additional concern is the exclusion of intraoperative plasma transfusions. Exclusion of these specific transfusion episodes was intentional because of concerns related to cause-effect inversion. More specifically, such transfusions frequently are administered for treatment of active bleeding rather than its prevention, and accurate determination of which was the case is a significant challenge in the operative environment. Furthermore, the hypothesis that this study specifically aimed to test was the impact of PPT in patients with elevated INR. As a result, we cannot comment on the value of intraoperative plasma transfusion, and we acknowledge this study limitation. We also acknowledge the potential for intraoperative and early postoperative RBC transfusions to have been administered for indications other than active bleeding (e.g. anemia of chronic disease). In such circumstances, the RBC transfusion may not have been a clear marker of WHO grade 3 bleeding. Clinical documentation in the perioperative electronic health record does not provide the required granularity regarding indication for RBC transfusion. The imprecise nature of our understanding underlying the specific indication for all perioperative RBC transfusions may attenuate the associations identified between PPT and WHO grade 3 bleeding and we acknowledge this as an additional limitation to this study. The lack of information on baseline bleeding risks for the study participants, such as congenital or acquired bleeding disorders is also a limitation of the present investigation. If the presence of such disorders were unequally distributed between the prophylactic plasma and non-plasma cohorts, this may have resulted in an additional degree of unmeasured confounding. We further acknowledge the potential for changes in operative care over the study period and the potential for such changes to have impacted our associations of interest. We evaluated the potential impact of such changes over time by including calendar year as a covariate in a logistic regression model along with the indicator variable of PPT. Initial analyses were performed with the two-way interaction effect included in the model to assess whether the association between PPT and WHO grade 3 bleeding changed over calendar time. With these analyses, no evidence for interaction was detected ($P = .36$ and $P = .97$ for the overall and propensity matched analyses, respectively). We also found no evidence to suggest that the frequency of WHO grade 3 bleeding changed over time (main effect of calendar time, $P = .33$ and $P = .45$ from overall and propensity matched analyses, respectively). From models that included the main effect of calendar time as a covariate, the odds ratio (95% CI) for PPT was 2.35 (1.64, 3.35) for the overall analysis and 1.75 (1.08, 2.81) for the propensity-matched analysis. As a final concern, the study population arises from a single academic medical center, causing concern about the external validity of our study results. The findings of this investigation will benefit greatly from validation in a large, multicenter cohort.

Though cause-effect relationships cannot be established with observational study designs, the results of this study clearly generate important hypotheses deserving of additional study. Specifically, the results of this investigation suggest that a more definitive clinical trial on the efficacy and risks of prophylactic preoperative plasma transfusion appears warranted. Additionally, when considered in aggregate with the existing literature, the results of this study are consistent and suggest that more conservative management of prophylactic plasma transfusions appear warranted.

Conclusions

Preoperative plasma administration for INR values ≥ 1.5 was not associated with reduced rates of WHO grade 3 bleeding. To the contrary, plasma administration was associated with increased rates of intraoperative and early postoperative RBC transfusion. More conservative management of abnormal preoperative coagulation screening test results appears warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ASA	American Society of Anesthesiologists
INR	international normalized ratio
RBC	red blood cell
LOS	length of stay
PPT	preoperative plasma transfusion
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TACO	transfusion-associated circulatory overload
TRALI	transfusion-related acute lung injury
WHO	World Health Organization

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Figure 1. Study Population Flow Diagram. ASA PS indicates American Society of Anesthesiologists Physical Status; INR, international normalized ratio.

Figure 2.

Standardized Mean Differences Between Groups for Matched (•) and Unmatched (◊) Samples. Points to right of the vertical reference line represent a standardized mean difference >0.1 between patients who received prophylactic preoperative plasma transfusion and patients who did not. ASA PS indicates American Society of Anesthesiologists Physical Status; ENT, ears, nose, throat; INR, international normalized ratio; O/G, obstetrics and gynecology; Pre-OP, preoperative.

Table 1

Baseline Demographic and Clinical Characteristics of the 1,234 Study Participants

Variable ^a	No Therapy (n=1,095)	Preoperative Plasma (n=139)	P Value ^b	
			Unadjusted	Propensity Matched
Demographic characteristics				
Age, y	67.0 (55.0, 79.0)	66.0 (56.0, 79.0)	.97	.61
Body mass index	28.7 (25.1, 33.8)	29.5 (24.6, 34.1)	.85	.97
Male sex	654 (60)	87 (63)	.52	.76
ASA physical status			<.0001	.54
1	5 (0)	1 (1)		
2	162 (15)	9 (6)		
3	667 (61)	73 (53)		
4	249 (23)	47 (34)		
5	12 (1)	9 (6)		
Comorbidities				
Myocardial infarction	152 (14)	24 (17)	.28	.36
Congestive heart failure	358 (33)	53 (38)	.20	.60
Peripheral vascular disease	46 (4)	6 (4)	.95	.15
Cerebrovascular disease	222 (20)	31 (22)	.58	.75
Dementia	23 (2)	3 (2)	.96	.78
Chronic pulmonary disease	130 (12)	24 (17)	.0699	.88
Connective tissue disease	47 (4)	10 (7)	.12	.56
Ulcer disease	47 (4)	6 (4)	.99	.80
Mild liver disease	185 (17)	19 (14)	.33	.59
Diabetes mellitus	389 (36)	49 (35)	.95	.65
Hemiplegia	7 (1)	1 (1)	.91	.63
Moderate to severe renal disease	213 (19)	34 (24)	.16	.61
Diabetes mellitus with end-organ damage	117 (11)	18 (13)	.42	.82
Tumor	299 (27)	38 (27)	.99	.87
Leukemia	21 (2)	1 (1)	.31	.50
Lymphoma	34 (3)	5 (4)	.75	.42
Moderate to severe liver disease	96 (9)	9 (6)	.36	.56
Metastatic solid tumor	265 (24)	34 (24)	.95	.99
AIDS	1 (0)	0 (0)	.72	—
Perioperative medications				
Aspirin	601 (55)	85 (61)	.16	.69
Clopidogrel	37 (3)	11 (8)	.0092	.77
Warfarin	666 (61)	87 (63)	.69	.94
Heparin	209 (19)	42 (30)	.0021	.68
NSAIDs	3 (0)	0 (0)	.54	.31

Variable ^a	No Therapy (n=1,095)	Preoperative Plasma (n=139)	P Value ^b	
			Unadjusted	Propensity Matched
Vitamin K	168 (15)	51 (37)	<.0001	.0005
Baseline laboratory values				
INR	1.7 (1.5, 2.1)	1.7 (1.6, 2.0)	.89	.84
Hemoglobin	11.3 (9.7, 13.2)	11.2 (9.4, 13.3)	.80	.55
Platelet count	185.0 (119.0, 248.0)	173.0 (117.0, 242.0)	.35	.68
APTT	37.0 (31.0, 47.0)	37.0 (32.0, 44.0)	.85	.45
Creatinine	1.1 (0.8, 1.5)	1.2 (0.9, 1.9)	.0202	.41
Albumin	3.4 (2.9, 3.9)	3.5 (3.0, 4.1)	.49	.66
Procedural characteristics				
Procedure type			<.0001	>.99
ENT/oral	85 (8)	4 (3)		
General	296 (27)	81 (58)		
Neurology	20 (2)	4 (3)		
O/G	35 (3)	2 (1)		
Orthopedic	217 (20)	6 (4)		
Spinal	10 (1)	0 (0)		
Thoracic	49 (4)	10 (7)		
Transplant	142 (13)	15 (11)		
Urology	71 (6)	3 (2)		
Vascular	54 (5)	8 (6)		
Trauma	82 (7)	9 (6)		
Other	116 (11)	6 (4)		
Emergency	259 (24)	71 (51)	<.0001	.49
General anesthesia	1,053 (97)	139 (100)	.0296	.31
Surgical duration, min	168.2 (111.4, 273.2)	173.7 (123.2, 245.3)	.65	.80

Abbreviations: AIDS, acquired immunodeficiency syndrome; APTT, activated partial thromboplastin time; ASA, American Society of Anesthesiologists; ENT, ears, nose, throat; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; O/G, obstetrics and gynecology.

^aContinuous variables are presented as median (25%, 75%); categorical variables are presented as number (%). Data were complete for all characteristics with the exception of hemoglobin (missing for 77 patients), platelet count (missing for 76 patients) and creatinine (missing for 20 patients).

^bAfter propensity matching, there were no significant differences between the 2 patient groups.

Table 2

Univariate Analyses of Primary and Secondary Outcomes by the Presence or Absence of Preoperative Plasma Transfusion

Outcome ^a	No Therapy (n=1,095)	Preoperative Plasma (n=139)	P Value ^b	Estimate (95% CI) ^c
Perioperative WHO grade 3 bleeding	350 (32)	73 (53)	<.0001	2.35 (1.65–3.36)
Intraoperative RBC transfusion	268 (24)	56 (40)	<.0001	2.08 (1.44–3.00)
EBL, mL (n=564)	200 (50, 500)	300 (85, 930)	.0844	NA
Reoperation	49 (4)	16 (12)	.0008	2.78 (1.53–5.03)
Postoperative hemoglobin, mg/dL (n=961) ^d	10.1 (9.1, 11.3)	10.2 (9.1, 11.5)	.44	NA
ICU admission	389 (36)	88 (63)	<.0001	3.13 (2.17–4.52)
ICU LOS, d (n=477) ^e	2.0 (1.1, 5.1)	5.1 (1.8, 8.0)	<.0001	NA
Postoperative MV	251 (23)	66 (47)	<.0001	3.04 (2.12–4.36)
Duration of MV, d (n=317) ^e	1.1 (0.4, 5.9)	2.5 (1.2, 7.0)	.0016	NA
Hospital LOS, d	6.0 (2.2, 13.1)	12.8 (6.7, 20.5)	<.0001	6.6 (2.7–10.9)
Discharge hemoglobin, mg/dL (n = 977)	9.8 (9.0, 10.9)	9.8 (9.0, 11.1)	.97	NA
Death	83 (8)	24 (17)	.0002	2.54 (1.55–4.17)

Abbreviations: EBL, estimated blood loss; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NA, not applicable; RBC, red blood cell; WHO, World Health Organization

^aFor binary outcomes, values are presented as numbers (%); for continuous outcomes, values are presented as median (25%, 75%).

^bP values are from logistic regression for binary outcomes and from Wilcoxon rank sum test for continuous outcomes.

^cFor binary outcomes, the estimate is the odds ratio for preoperative plasma transfusion vs no therapy. For continuous outcomes, the estimate is the difference in mean (preoperative plasma minus no therapy) with 95% CI calculated from 10,000 bootstrap samples (Efron B, The jackknife, the bootstrap and other resampling plans, Regional Conference Series in Applied Mathematics, 38. SIAM, Philadelphia, 1982.).

^dPostoperative hemoglobin was defined as the first hemoglobin obtained after completion of the surgical procedure. To qualify, the hemoglobin must have been obtained within 24 hours of the surgical procedure.

^eICU LOS is summarized only for patients admitted to ICU; duration of MV is summarized only for patients who received MV postoperatively.

Table 3

Conditional Regression Analysis in the Propensity-Matched Cohort

Outcome ^a	No Therapy (n=242)	Preoperative Plasma (n=125)	P Value ^b	Estimate (95% CI) ^b
Perioperative WHO grade 3 bleeding	97 (40)	65 (52)	.0210	1.75 (1.09–2.81)
Intraoperative RBC transfusion	75 (31)	49 (39)	.12	1.46 (0.90–2.36)
EBL, mL (n=192)	250 (100, 500)	250 (53, 700)	.89	NA
Reoperation	17 (7)	14 (11)	.18	1.70 (0.78–3.69)
ICU admission	121 (50)	77 (62)	.0437	1.59 (1.01–2.48)
ICU LOS, d (n=198) ^c	3.8 (1.4, 7.8)	5.1 (1.8, 7.7)	.33	NA
Postoperative MV	85 (35)	56 (45)	.0549	1.63 (0.99–2.67)
Duration of MV, d (n=141) ^c	2.4 (0.6, 7.3)	2.4 (1.0, 6.6)	.49	NA
Hospital LOS, d	8.3 (3.5, 18.3)	11.8 (6.7, 18.9)	.61	1.5 (–4.3–7.3)
Deaths	30 (12)	19 (15)	.62	1.17 (0.62–2.22)

Abbreviations: EBL, estimated blood loss; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; NA, not applicable; RBC, red blood cell; WHO, World Health Organization.

^aValues are numbers (%) for categorical outcomes and median (25%, 75%) for continuous outcomes.

^bEstimates and *P* values are from stratified logistic regression for categorical outcomes and mixed effects model for hospital LOS.

^cICU LOS is summarized only for patients admitted to the ICU; duration of MV is summarized only for patients who received MV postoperatively.