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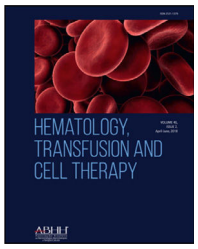

Original article

Blasting the myth of predictive INR changes related to plasma transfusion: an academic institution's experience

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ABSTRACT

Introduction: Plasma transfusion is a common therapeutic strategy used to lower international normalized ratio (INR) values in the non-emergent setting. However, due to lack of evidence of its efficacy, standardized guidelines for this practice have not been well established.

Methods: This retrospective observational cohort study analyzed 276 inpatient encounters that involved plasma transfusions focusing on change in INR values from pre- to post-transfusion, with respect to the following predictor variables: vitamin K co-administration, number of plasma units transfused, order indication and body mass index (BMI).

Results: The overall average change in the INR was 1.35. Patients who received vitamin K showed an average change of 2.51, while patients that did not receive vitamin K demonstrated an average change of 0.70. Increased numbers of plasma units transfused showed benefit up to three-unit orders. Greater decreases in the INR were observed for patients requiring plasma for anticoagulation reversal or active bleeding. There was no significant difference in the change in INR based on the BMI. By multivariate and regression analyses, the stepwise addition of each successive predictor variable demonstrated an increase in the shared variance in the outcome of the post-transfusion INR: the pre-transfusion INR and vitamin K co-administration alone was not significant ($p = 0.45$); the additional number of plasma units transfused was significant ($R^2 = 0.13$, $p < 0.001$), and; the subsequent additional plasma order indications ($R^2 = 0.19$, $p < 0.001$) and BMI ($R^2 = 0.18$, $p < 0.001$) were increasingly significant.

Conclusion: Taking into consideration the combination of multiple predictive factors may aid in a more efficient use of plasma products.

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Introduction

The AABB Recommendation Guidelines for red blood cell and platelet transfusion have been available for several years.[1-3] While general plasma indications have been available for decades from organizations such as the College of American Pathologists, the American Society of Anesthesiologists and the New York State Council on Human and Blood Transfusion Services, the AABB Multidisciplinary Guidelines Panel reviewed plasma product use and could not recommend for or against transfusion of plasma in most clinical situations evaluated.[4-7] The AABB Panel did suggest that plasma be transfused into patients requiring massive transfusion and those with warfarin therapy-related intracranial hemorrhage.[7] More recently, the American Red Cross has published an updated edition of a compendium of transfusion practice guidelines in which general plasma dosing information is primarily based upon recommendations proposed over a decade ago.[6,8-10] Despite these recommendations, studies have shown a wide variation in the use of plasma products without a consensus for indications of their use, dosing or clinical efficacy.[11-13] However, it has been shown that when hospitals have institutional guidelines for plasma transfusion, there is evidence of compliance, suggesting a role for transfusion services to monitor and educate, regarding the use of plasma products.[14]

A commonly utilized method of evaluating plasma transfusion efficacy is to monitor the change in coagulation study laboratory values. However, this method has not proven to be a consistent predictor of plasma transfusion utility. Silbert et al. reported in 1981 that only 47% of patients showed modest changes in abnormal coagulation test results following the transfusion of plasma.[15] In 2006, Abdel-Wahab et al. reported only the post-transfusion normalization of the international normalized ratio (INR) in 0.8% of patients (95% confidence interval (CI)) and the halfway normalization being achieved in only 15% of patients (95% CI).[16] Other studies have reported a greater reduction in the INR in patients with higher pre-transfusion INR values, but minimal reductions in lower pre-transfusion INR ranges.[10,17,18]

Although plasma products are still commonly utilized for the reversal of vitamin K-antagonist therapy (warfarin), some studies have suggested the use of vitamin K alone to treat non-life-threatening bleeding and for the reduction of the INR in pre-surgical patients.[19-21] While some studies have suggested the use of prothrombin complex concentrates (PCCs) as an alternative to plasma transfusion for the emergent warfarin reversal, at least one study reports a higher risk for thromboembolic events in patients receiving 4-factor PCCs, compared to plasma.[22-26] Still other authors suggest there is insufficient data to support the routine use of PCCs rather than plasma for warfarin reversal.[27,28]

At our institution, the computerized provider order entry (CPOE) system requires the ordering provider to include an indication for transfusion on the plasma order request form. Prior studies have not effectively stratified the predicted post-transfusion INR specifically by the order indication or by the presence or absence of vitamin K co-administration. In this study, we aim to evaluate the observed change in the INR secondary to the plasma transfusion, stratified by the concomitant use of vitamin K (phytonadione) or not, the number of plasma units transfused, the plasma order indication given by the ordering provider and the patient's body mass index (BMI), with the goal of defining determining factors, alone or in combination, predictive of a significant INR reduction.

Methods

Approval was obtained from the institutional review board prior to initiating this study. We performed an observational retrospective cohort analysis of the data at the University of Tennessee Medical Center through electronic review of available medical records. The data was collected on hospitalized patients who received plasma transfusions from January through December 2018. The data set excluded all pediatric patients, outpatient transfusions, patients transfused during a surgical procedure and patients transfused under a massive transfusion protocol.

The institution's product inventory includes fresh frozen plasma (FFP), plasma frozen within 24 h after phlebotomy (PF24), plasma held at room temperature for up to 24 h (PF24RT24), and 5-day cold plasma. Regardless of the type of plasma product transfused, each product is considered equally effective for providing plasma proteins in comparable proportions. Our institution is a Level I Trauma Center and plasma units are pre-thawed for immediate availability as a component of emergency preparedness. Pre-thawed units (5-day cold plasma) are issued preferentially to reduce product wastage. The plasma product issued from the blood bank is an ABO-compatible plasma unit with the shortest product outdate. Plasma units vary in total unit volume from 293 to 358 mL (mL). While the institutional recommendation for plasma transfusion is to administer 10 to 15 mL/kg, the individual ordering provider selects the number of units (plasma doses) to be transfused, given the clinical setting.

The data file was initially reviewed for duplicate order information. All duplicate data points were removed. The original data set included information for 516 plasma transfusion orders from 329 inpatient hospital encounters with 316 unique patients. Our CPOE system requires the ordering provider to select an indication for plasma transfusion from a defined choice list, which includes the active bleeding/coagulation factor deficit, invasive procedure with INR > 1.5, multiple transfusions, reversal of anticoagulation, thrombotic thrombocytopenic purpura, thromboelastography, therapeutic apheresis and other. Orders with indications related to thrombotic thrombocytopenic purpura, thromboelastography and therapeutic apheresis were removed from the data set to isolate only patients whose clinical indication for plasma transfusion was based on the pre-transfusion INR value. For the purpose of this study, if during a single hospital encounter multiple plasma transfusion orders were placed, only the initial plasma transfusion order for that hospital encounter was included in the study to prevent a data skew due to a potential cumulative effect from successive transfusions. Thus, all subsequent orders following the initial plasma transfusion order from the same patient encounter were removed from the data set. At our institution, the estimated average time of

order-to-transfusion is approximately 1 hour. In an attempt to ensure that the laboratory test values for the post-transfusion INR were reflective of the plasma transfusion, post-transfusion INR samples obtained less than 2 h or more than 24 h from the time the plasma order was placed, as well as INR values listed as incalculable or greater than 20.0, were removed from the data set. Based on all the exclusion criteria, the final numbers resulted in 276 inpatient encounters from 266 unique patients. The data was then divided into patients who received only the plasma product (Group 1; $n = 177$) and patients who received both the plasma product and vitamin K (Group 2; $n = 99$).

The following data points were collected for analysis for each patient encounter that met all inclusion criteria: the INR value within 24 h before the plasma transfusion order (pre-transfusion INR), first INR value within 24 h after the plasma transfusion order (post-transfusion INR), the time interval between the reported pre- and post-transfusion INR values, order indication, number of plasma units ordered, body mass index, the plasma order and the administration of vitamin K, if applicable.

The collected data were analyzed using the SPSS software to derive descriptive and inferential statistics. Statistical analyses were performed utilizing the *t*-test for equality of means, ANOVA for analysis of variance and regression analysis, as appropriate. A *p*-value of less than 0.05, utilizing a 95% CI, was considered statistically significant.

Results

The patients presented with an average pre-transfusion INR value of 3.02 (median, 2.22; range, 0.96–15.82) and subsequent average post-transfusion INR value of 1.75 (median, 1.52; range, 0.94–7.88), which was performed at an average of 8.58 h (median, 6.76; range, 2.02–23.40 h) after the transfusion order was placed. The average observed change in the INR value from all plasma transfusions in the defined population was 1.27 (median, 0.54; range, −4.91–23.01), with all positive values indicating a decrease in the pre- to post-transfusion INR.

Vitamin K coadministration

Concomitant vitamin K was administered to 35.9% (99/276) of patients who received a plasma transfusion. The average change in INR value in all patients who received vitamin K ($n = 99$) was 2.51 (range, −4.90–14.3), while the patients who did not receive concomitant vitamin K ($n = 177$) demonstrated an average change in INR of 0.58 (range, −2.95–23.01), a significant relationship by univariate analysis ($p < 0.001$). However, in the multivariate analysis, which included the pre-transfusion INR value and use of vitamin K, the model was not significant in predicting the post-transfusion INR value ($p = 0.45$).

Number of plasma units transfused

Dosing of plasma units ranged from one to four units among all patients, regardless of vitamin K administration, with 28% receiving one unit, 62% receiving two units, 3% receiving three units, and 7% receiving four units (Table 1). The number of plasma units transfused in relation to the concomitant vitamin K administration is shown in Table 2. In patients who did not receive vitamin K, the change in the INR did not increase with the number of plasma units administered ($p = 0.97$). Increasing the number of plasma units transfused in patients with concomitant vitamin K administration, however, showed benefit up to three-unit orders. Increasing the dose to a four-unit order showed no additional benefit. Therefore, the

Table 1 – Average change in INR value in relation to the number of plasma units transfused.

Number of units transfused	Number of patients ($n = 276$)	Average change in INR ($p = 0.44$)
1	77	1.05
2	171	1.47
3	8	2.22
4	20	1.11

Table 2 – Average change in INR value in relation to vitamin K administration stratified by the number of plasma units transfused.

Vitamin K administration	Number of units transfused	Number of patients	Average change in INR
No Vitamin K ($n = 177$)	1	53	0.73
	2	105	0.67
	3	5	0.56
	4	14	0.93
Vitamin K ($n = 99$)	1	24	1.77
	2	66	2.75
	3	3	5
	4	6	1.55

Table 3 – Average change in INR value in relation to the transfusion indication provided by the clinician.

Transfusion indication	Number of patients($n = 276$)	Average change in INR
Active bleeding	119	1.69
Invasive procedure with INR > 1.5	83	0.83
Multiple transfusions	28	0.06
Reversal of anticoagulation	22	3.84
Other	24	0.72

multivariate analysis of the patients who received vitamin K showed no significant effect in predicting the change in the INR value, when controlling for the number of units transfused ($p = 0.26$). However, in a regression analysis designed to include the pre-transfusion INR value and the concomitant use or not of vitamin K, in relation to the number of plasma units transfused, there was a significant change in the ability to predict the post-transfusion INR ($R^2 = 0.13$, $p < 0.001$). Additionally, the pre-transfusion INR was a significant predictor ($p < 0.001$), when controlling for vitamin K and the number of plasma units utilized.

Plasma order indication

The indication for plasma transfusion provided by the clinician for all included patients ($n = 276$) was documented as follows: the active bleeding (including coagulation factor deficiency) in 43%, the patient undergoing an invasive procedure with an INR > 1.5 in 30%, the patient who had received multiple transfusions in 10% and the reversal of anticoagulation in 8%, with an additional 9% being documented as 'other'. The observed change in the INR, in relation to the plasma order indication, is documented in Table 3. The greatest decrease in the INR was observed for patients requiring plasma for the anticoagulation reversal (mean, 2.93) and patients with active bleeding (mean, 1.69). The remaining indications showed a drop in the average INR value, which was minimal, when compared to the anticoagulation reversal and active bleeding. In the multivariate regression analysis, using the pre-transfusion INR value, the vitamin K administration, the number of transfused plasma units and the order indication as predictors, there was a significant increase in the ability to predict the post-transfusion INR value ($R^2 = 0.19$, $p < 0.001$). Within this model, the pre-transfusion INR value ($p < 0.001$), the use of vitamin K ($p = 0.02$) and the provided indication of multiple blood transfusions ($p = 0.01$) were considered significant predictors.

Body mass index

The body mass index (BMI) was available for 254 of the patients within the study population. The BMI ranged from 7.59 to 103.51 (average, 29.52; median, 27.62), with 4% underweight, 26% at normal weight, 34% overweight, 26% obese and 10% morbidly obese, based on the Centers for Disease Control and Prevention (CDC) classification.[29] There was no significant difference in the change in the INR value based on the BMI. Table 4 shows the number of plasma units transfused, stratified based on the BMI, which showed no significant relationship with the observed change in the INR ($p = 0.60$). In a repeat regression model, now with the inclusion of the BMI in addition to the predictor variables of the pre-transfusion INR value, concomitant administration of vitamin K, the number of plasma units utilized and the different order

Table 4 – Average change in INR value in relation to BMI classification stratified by the number of plasma units transfused.

BMI category	Number of units transfused	Number of patients	Average change in INR
Underweight ($n = 10$)	1	2	10.04
	2	8	0.94
	3	0	–
	4	0	–
Normal weight ($n = 66$)	1	17	0.85
	2	44	1.26
	3	1	0.15
	4	4	0.80
Overweight ($n = 87$)	1	23	0.90
	2	54	1.30
	3	1	6.26
	4	9	0.73
Obese ($n = 66$)	1	21	0.81
	2	38	2.05
	3	2	0.66
	4	5	2.07
Morbidly obese ($n = 25$)	1	6	0.97
	2	15	1.99
	3	2	4.37
	4	2	1.08

indications, there was a significant increase in the shared variance in the outcome of the post-transfusion INR ($R^2 = 0.18$, p <0.001). This model highlighted the use of vitamin K ($p = 0.006$) and the provided order indication of active bleeding ($p = 0.032$) or multiple blood transfusions ($p = 0.001$) as significant predictors of the decreased post-transfusion INR values. The pre-transfusion INR value ($p < 0.001$) was also found to be a significant predictor in this setting, but of increased post-transfusion INR values.

Discussion

As seen in prior studies, our study shows that there appears to be no direct relationship between the pre-transfusion INR and post-transfusion INR values related to plasma transfusion.[15-18] Prior studies have suggested that vitamin K alone may be effective for warfarin reversal.[19-21] Similarly, our study shows, with univariate analysis, that the concomitant use of plasma transfusion and vitamin K resulted in a more significant change in the INR, compared to those who received plasma alone, although not when controlling for the pre-transfusion INR values.

While Holland and Brooks proposed a formula to predict the post-transfusion INR, based on the number of units transfused,[10] we found no predictable change in the INR, related to the number of plasma units transfused, as a sole predictor in either study group. The change in INR does increase with the number of plasma units transfused up to three units, however, increasing the dose to four plasma units, with or without vitamin K, did not show significant additional benefit. Nevertheless, the pre-transfusion INR seems to be a predictor of the change observed in the post-transfusion INR when more units of plasma are given with concomitant vitamin K administration.

When plasma transfusion indications were compared, the greatest observed change in the INR was observed in patients requiring plasma for the reversal of anticoagulation and in patients with active bleeding. While other indications for plasma transfusion showed a decrease from the pre- to post-INR values, these changes were minimal, when compared to those patients with active bleeding and those requiring the reversal of anticoagulation. While the indication for multiple blood transfusions showed no direct predictable change in the INR with plasma transfusion, multiple blood transfusions as the given indication is a significant predictor of the post-transfusion INR when concomitant vitamin K is administered to a patient with a greater pre-transfusion INR value.

Surprisingly, the BMI did not reveal a predictive value of the post-transfusion INR alone, or when controlling only for the number of plasma units received. However, the inclusion of the BMI as a predictor variable of the post-transfusion INR, in combination with the pre-transfusion INR, the vitamin K administration, the number of plasma units transfused and the order indication, reveals that giving vitamin K in the setting of either multiple blood transfusions or active bleeding and, interestingly, in patients with only mildly elevated pre-transfusion INR values, is a significant predictor of the post-transfusion INR. It is worth noting that the BMI categories were not equally distributed, with both the underweight and morbidly obese categories accounting for only a small percentage of the total patient population.

This study is a retrospective review. Some limitations of our study include no comparison group for patients receiving vitamin K alone. Furthermore, as previously stated, we utilize a variety of plasma products at our institution: FFP, PF24, PF24RT24 and 5-day cold plasma. While each of these plasma products are generally comparable in the percentage of plasma proteins, there is some variation in the volume of each plasma unit (293–358 mL). The volume variation is a normal, standard feature in blood product processing. While the institutional guidelines for plasma recommend 10–15 mL/kg, the number of units transfused (plasma doses) was at the discretion of the ordering provider. Additionally, the order indication for each transfusion is based on that entered by the ordering provider into the CPOE system. The clinical scenario for each patient was not independently verified.

Conclusions

The effect of plasma transfusion on laboratory values for the INR has not shown to have consistent predictive value. Even when stratified by reported indication for the transfusion and BMI, there appears to be no direct correlation with the predictive change in the INR. However, taking into consideration the combination of multiple factors, such as the use of vitamin K, the degree of the elevation in the pre-transfusion INR and the clinical setting, may aid in a more efficient use of plasma products. As programs for patient blood management are continuing to evolve, established recommendations for the monitoring of plasma utilization would be potentially beneficial. Given the unpredictable effects of plasma transfusion and the great variation in clinical use, the consensus for plasma transfusion is likely to be difficult. However, continued research and review of plasma utilization are essential.

Conflict of interest

The authors declare no conflicts of interest.

REFERENCES

1. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012;157(1):49–58.
2. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical practice guidelines from the AABB: red blood cell transfusion thresholds and storage. JAMA. 2016;316(19):2025–35.
3. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med. 2015;162(3):205–13.
4. Practice Guidelines for blood component therapy: a report by the American Society of Anesthesiologists Task Force on blood component therapy. Anesthesiology. 1996;84(3):732–47.

5. Guidelines for the administration of plasma 2004:[1-10 *pp*.]. Available from: https://www.wadsworth.org/sites/default/files/WebDoc/1921494352/plasma%20adminfinal1204.pdf.
6. Cooper ES, Bracey AW, Horvath AE, Shanberge JN, Simon TL, Yawn DH. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. JAMA. 1994;271(10):777–81.
7. Roback JD, Caldwell S, Carson J, Davenport R, Drew MJ, Eder A, et al. Evidence-based practice guidelines for plasma transfusion. Transfusion. 2010;50(6):1227–39.
8. Bachowski G, Borge D, Brunker PA, Eder A, Fialkow L, Fridey JL, et al. A Compendium of Transfusion Practice Guidelines. [51-64 *pp*.]. Available from: http://success.redcross.org/success/file.php/1/TransfusionPractices-Compendium_3rdEdition.pdf.
9. Dzik W, Rao A. Why do physicians request fresh frozen plasma? Transfusion. 2004;44(9):1393–4.
10. Holland LL, Brooks JP. Toward rational fresh frozen plasma transfusion. Am J Clin Pathol. 2006;126(1):133–9.
11. Lauzier F, Cook D, Griffith L, Upton J, Crowther M. Fresh frozen plasma transfusion in critically ill patients. Crit Care Med. 2007;35(7):1655–9.
12. Palo R, Capraro L, Hovilehto S, Koivuranta M, Krusius T, Loponen E, et al. Population-based audit of fresh-frozen plasma transfusion practices. Transfusion. 2006;46(11):1921–5.
13. Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll D, et al. A national study of plasma use in critical care: clinical indications, dose and effect on prothrombin time. Crit Care. 2011;15(2):R108.
14. Alcorn K, Ramsey G, Souers R, Lehman CM. Appropriateness of plasma transfusion: a college of American Pathologists Q-Probes study of guidelines, waste, and serious adverse events. Arch Pathol Lab Med. 2017;141(3):396–401.
15. Silbert JA, Bove JR, Dubin S, Bush WS. Patterns of frozen plasma use. Conn Med. 1981;45(8):507–11.
16. Abdel-Wahab OI, Healy B, Dzik WH. Effect of fresh-frozen plasma transfusion on prothrombin time and bleeding in patients with mild coagulation abnormalities. Transfusion. 2006;46(8):1279–85.
17. Raturi M, Shastry S, Murugesan M, Baliga PB, Chakravarthy K. Effect of plasma component transfusion on conventional coagulation screening tests. Asian J Transfus Sci. 2018;12(1):57–61.
18. Sezik S, Aksay E, Kilic TY. The effect of fresh frozen plasma transfusion on international normalized ratio in emergency department patients. J Emerg Med. 2014;47(5):596–600.
19. Burbury KL, Milner A, Snooks B, Jupe D, Westerman DA. Short-term warfarin reversal for elective surgery–using low-dose intravenous vitamin K: safe, reliable and convenient*. Br J Haematol. 2011;154(5):626–34.
20. Polito NB, Kanouse E, Jones CMC, McCann M, Refaai MA, Acquisto NM. Effect of vitamin K administration on rate of warfarin reversal. Transfusion. 2019;59(4):1202–8.
21. Sahai T, Tavares MF, Sweeney JD. Rapid response to intravenous vitamin K may obviate the need to transfuse prothrombin complex concentrates. Transfusion. 2017;57(8):1885–90.
22. Chai-Adisaksopha C, Hillis C, Siegal DM, Movilla R, Heddle N, Iorio A, et al. Prothrombin complex concentrates versus fresh frozen plasma for warfarin reversal. A systematic review and meta-analysis. Thromb Haemost. 2016;116(5):879–90.
23. Goldstein JN, Refaai MA, Milling Jr. TJ, Lewis B, Goldberg-Alberts R, Hug BA, et al. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet. 2015;385(9982):2077–87.
24. Hill R, Han TS, Lubomirova I, Math N, Bentley P, Sharma P. Prothrombin Complex Concentrates are Superior to Fresh Frozen Plasma for Emergency Reversal of Vitamin K Antagonists: a Meta-Analysis in 2606 Subjects. Drugs. 2019;79(14):1557–65.
25. Holt T, Taylor S, Abraham P, McMillian W, Harris S, Curtis J, et al. Three- versus four-factor prothrombin complex concentrate for the reversal of warfarin-induced bleeding. Int J Crit Illn Inj Sci. 2018;8(1):36–40.
26. Maguire M, Fuh L, Goldstein JN, Marshall AL, Levine M, Howell ML, et al. Thromboembolic risk of 4-factor prothrombin complex concentrate versus fresh frozen plasma for urgent warfarin reversal in the emergency department. West J Emerg Med. 2019;20(4):619–25.
27. Cappabianca G, Mariscalco G, Biancari F, Maselli D, Papesso F, Cottini M, et al. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. Crit Care. 2016;20:5.
28. Johansen M, Wikkelso A, Lunde J, Wetterslev J, Afshari A. Prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding patients. Cochrane Database Syst Rev. 2015(7):CD010555.
29. Defining Adult Overweight and Obesity: Division of Nutrition, Physical Activity, and Obesity, National Center for Chronic Disease Prevention and Health Promotion. [updated April 11, 2017]. Available from: https://www.cdc.gov/obesity/adult/defining.html.