Title: Clinical Outcomes of a Pharmacy-Led Blood Factor Stewardship Program

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Abstract

Objective: To report the results of a pharmacist-directed blood factor stewardship program targeting off-label utilization designed to limit use to established organizational guidelines in high-risk populations.

Methods: Prospective evaluation of recombinant factor VIIa (rFVIIa) and prothrombin complex concentrate (PCC) orders beginning June 2013 through May 2014 and a matched retrospective cohort June 2012-May 2013. Matched cohorts were evaluated for 28-day mortality, change in INR, adverse events, concurrent blood product use and cost savings.

Results: Forty-two orders for blood factor were ordered between June 2013 and May 2014, 70 orders in the year prior (N=112). Twenty-eight-day mortality was not different between the cohorts: 53.9% vs. 50% (p value = 0.77). Blood factor use with underlying liver failure and active bleeding was strongly associated with 28-day mortality: odds ratio, 2.9 (95% CI 1.5-7.14) and 2.91 (95% CI 0.01-2.91) respectively. Blood products dispensed increased over the year with plasma products the most significant (1 vs. 4 p value = 0.004). All other clinical outcomes were non-significant. An annual cost savings of $375,539 was achieved, primarily through a significant reduction in rFVIIa and avoidance in high-risk patients.

Conclusion: Use of off-label blood factors can be controlled through a pharmacist-led stewardship program. Twenty-eight day mortality was not different between the two cohorts; however, identification of risk factors for death associated with blood factor use allows for restriction in high-risk populations, creates a discussion of futile care, and yields cost-savings.

Text

Introduction

Recombinant activated factor VII (rFVIIa, Novoseven®) is a blood factor approved for use in hemophilia with inhibitors; Profilnine SD®, a prothrombin complex concentrate (PCC) contains factors II, IX, X and is approved for hemophilia B. Both agents are used off-label to reverse bleeding from vitamin K antagonism, trauma, or underlying coagulopathy.[1-3] These agents are favored due to their small administration volume, quick onset of action, 15 minutes, and prolonged effect in vivo, between 2.3 hours (rFVIIa) to 24 hours (Profilnine SD®).[4,5]

The efficacy of blood factors in massive transfusion is equivocal. Bowles, et al reviewed all non-hemophiliac patients who received rFVIIa for massive hemorrhage at their institution from 2003-2005.[6] Eighteen patients met these criteria; seven had underlying coagulopathy (leukemia (1), thrombotic thrombocytopenia purpura (1) and end stage liver disease (5)); all seven died during the admission; one of a myocardial infarction, the other six from multi-organ failure. The remaining eleven patients suffered from trauma or surgical procedures; six survived (54%). Eight of 18 patients received more than one dose of rFVIIa, including four of the seven coagulopathic patients; seven of the 8 died during the admission. The authors concluded from this study that patients with underlying uncorrected coagulopathy and those who fail to respond to the initial dose of rFVIIa have a poorer prognosis and that treatment may be considered futile.

A second study by McMillen, et al evaluated all patients with hemorrhagic shock receiving rFVIIa and massive transfusion support (10-12 units of packed red blood cells (pRBC) within 24 hours).[7] Seventy-two patients met these criteria; 45 died (62.5%). Patients were stratified based on survivorship. Patients who died were significantly older (median age 44 vs. 32 years), had longer PT (16.4 vs 12.3) and higher INR (1.6 vs 1.2) at the initiation of the massive transfusion protocol. Age, baseline PT, and

increased FFP administration statistically significantly increased the odds of death. This supports the hypothesis that underlying coagulopathy at presentation renders blood factor use futile.

Blood factors carry significant risks and contraindications; specifically, arterial thrombosis and disseminated intravascular coagulopathy (DIC). A meta-analysis by Levi, et al. evaluated the safety of rFVIIa in 35 clinical trials.[1] The majority of patients received rFVIIa following spontaneous cerebral hemorrhage (31.3%), bleeding from hepatic-induced coagulopathy (27.8%) or trauma (18.7%). This analysis reported a 10% overall incidence of thromboembolic events in the rFVIIa group compared to 8.7% in patients who received placebo. The odds ratio for arterial thrombosis was greater than 1 in patients older than 65 years, those with spontaneous cerebral hemorrhage, and liver failure (2.43, 1.67, 2.19, respectively). There are no reports of thrombosis in three studies evaluating the safety and efficacy of PCC use.[2,3,8] The absence of thrombosis in published literature should not be considered evidence of absence given similar mechanism of action to rFVIIa. Finally, these marginally efficacious agents are expensive: rFVIIa is $2.20/mcg and PCC is $1.32/unit compared to $35/plasma unit.

Off-label blood factor use has marginal benefit, potential serious adverse effects and high monetary cost. This led the development and implementation of a pharmacist led blood factor stewardship program at a tertiary care academic medical hospital. This study reports the mortality and morbidity results of a prospective stewardship program in high-risk patients with an additional goal of cost reduction.

Methods

Beginning June 2013 all orders for off-label rFVIIa and PCC were prospectively reviewed by a single clinical pharmacist. Orders were discussed with the primary team regarding indication, patient specific contraindications, appropriate dosing and timing. Contraindications included: mechanical hardware, DIC or thromboembolism within 6 months. Vascular procedures considered to be high risk warranting blood

factor support included: tunneled line placement with INR $\geq$ 2.5, transjugular liver biopsy with INR $\geq$ 2, right heart catheterization with INR > 1.6, and transjugular intrahepatic portosystemic shunt (TIPS); high risk non-vascular procedures included: renal biopsy, biliary interventions, and nephrostomy tube placement. Blood factor support was used in lower risk procedures when clinically indicated. Blood factors for massive transfusion were evaluated for the presence of contraindications and previous blood product use. If contraindications existed, the procedure was not considered high risk, or the use of blood factor was deemed to be futile the order was voided.

The control group was a matched retrospective cohort from June 2012 through May 2013 of all non-hemophiliac patients who received blood factor at our institution. The primary endpoint of this study was 28-day mortality pre and post stewardship. Secondary endpoints included: change in INR from baseline following first dose of PCC or rFVIIa, adverse events, and units of concurrent blood product dispensed. Twenty-eight-day mortality was evaluated from the last ordered dose in patients with multiple orders; multiple orders for the same patient were evaluated separately for secondary outcomes.

Baseline demographic and clinical characteristics between the two groups were compared using the chi-square or Fisher exact test for categorical variables and the Students t test or Mann-Whitney *U* test as appropriate. Twenty-eight day mortality was analyzed with a logistic regression model which included: active bleeding, whether drug use was for a heart catheterization, history of liver failure, whether or not drug was administered, factor stewardship implementation date (June 10, 2013). All statistical analyses were performed using SPSS 22 (SPSS, Inc., Chicago, IL). Statistical significance was set at 0.05. Indiana University institutional review board approval was granted for this study.

Results

From June 2013-May 2014 42 patients had orders for blood factor; 14 did not receive drug due to contraindications. Mean age was 55.4 years (SD +/- 13.3). There were 72 patients in the control group from June 2012-May 2013; mean age was 53.7 years (SD +/- 14.8). In both cohorts there were multiple orders per patient: in the pre-implementation group there were 103 orders and post-implementation there were 34 orders for 28 patients. Table 1 describes the past medical history. The mean baseline PT was 28 seconds in both groups.

Twenty-eight day mortality was equivalent pre and post stewardship for all evaluated patients: 52.9% (n=70) versus 50% post (n=42), p = 0.77 (Table 2). Fifty percent of patients died within 28-days regardless of receipt of drug in the post-stewardship group. Evaluation of underlying etiology and indication for blood factors by binary logistic regression model demonstrates a significant risk of death within 28 days in patients with underlying liver failure (odds ratio, 2.9; 95% confidence interval [CI] 1.8-7.14) and those with active bleeding (odds ratio, 2.91; 95% CI 1.24-6.88). (Table 3)

Use of plasma product significantly increased with stewardship implementation: median pre-intervention was 1 unit versus 4 units administered within 12 hours pre and post-infusion of factor product. (p = 0.004), other blood products were not significantly changed (Table 4). Venous thromboembolism (VTE) occurred 2.4% following stewardship implementation compared to none in the year prior. Similarly, DIC occurred 9.5% post-implementation and never before. The absence of VTE and DIC pre-implementation may be attributed to a lack of monitoring or documentation. Mean change in INR pre-stewardship was -0.14 compared to +1.15 in the stewardship group; this is likely due to an increase in PCC use which does not affect the INR as strongly as rFVIIa.

Total rFVIIa use declined with the stewardship; pre-implementation 48.6% (147 mg) of blood factor dispensed was rFVIIa, post-implementation this decreased to 16.7% (30 mg) ($p < 0.001$). Total dollars

dispensed for all blood factors pre-implementation was $505,684, this decreased post-implementation to $130,145.30. Total savings over one year was $375,539.

Discussion

The majority of patients in this study had an underlying diagnosis of liver failure. The use of blood factors in patients with liver failure is based on the hypothesis that an elevated PT/INR increases the likelihood of bleeding. However, the PT/INR does not accurately represent the hemostatic status in patients with liver failure because increases in von Willebrand and factor VIII and decreases in antithrombin and protein C, natural anticoagulants, are not accounted for.[9-11] This constellation of changes nullifies the accuracy of the PT/INR as a marker of bleeding and literature evaluating the bleeding risk during invasive procedures in patients with abnormal coagulation supports the hypothesis that cirrhosis patients are at a lower than expected risk of bleeding than the lab values indicate.[12]

While the implementation of the factor stewardship itself did not affect 28-day mortality it is noted that factor administration did not improve mortality in a select subgroup of patients; most notably, those patients with active hemorrhage (OR 2.91, 95% CI 1.23-6.88) and those bleeding with a history of liver disease (OR 2.9, 95% CI 1.8-7.14). Retrospective studies in patients with active hemorrhage due to trauma or hemorrhagic shock have observed decreases in blood product administration with factor use, but survival has not been reported.[13,14] Kwok et al, evaluated rFVIIa in critically ill patients and found that while use as part of a massive transfusion order set inferred a high cost, it did not translate into an overall survival benefit.[15] It is reasonable to conclude that judicious use of factor product in critically ill or trauma patients with active hemorrhage is recommended, but ideal factor candidates have not been a concluded from the literature.

The role of factor use in hepatic disease has generally evaluated surrogate endpoints such as PT goals and blood product administration with limited reports on survival.[16] Bendtsen et al, conducted a

meta-analysis (n=497) of acute variceal bleeding in patients with end stage liver disease receiving rFVIIa or placebo.[17] While factor administration did decrease the recurrence of bleeding within five days of administration it did not affect the five day or 40-day survival of patients. Similarly, our study did not demonstrate a long term benefit of factor administration in patients with liver failure with active hemorrhage leading us to conclude previously evaluated surrogate markers are inappropriate given the risk benefit ratio of factor products.

This study included a small number of patients with a variety of indications. Additionally, multiple patients in both cohorts received more than one dose of blood factor which makes it difficult to assess the underlying coagulopathy at the time of administration and the effect with regards to mortality. Other limitations include: a lack of monitoring for DIC in the pre-stewardship group which contributed to a significant finding of DIC at baseline in the post-implementation group; and the retrospective nature of the study may have contributed to a decreased identification of thromboembolism following blood factor use.

While the role of stewardship has been widely published and recommended for developing and instituting antimicrobials there is limited data and recommendations in other areas of medication use.[18] As inferred by common practice the utilization of order sets may help to curb or limit prescribing habits, but this may not be applicable in real time urgent or critical situations. In this regard the authors would like to convey the importance of a stewardship program that allows real time discussion with clinicians rather than medication reviews as a systematic process. In these acute situations where costly medications with a narrow risk benefit profile have the potential for treating complications it is necessary for real time patient assessment and health care provider dialogue.

Conclusion

Although no difference was observed in 28 day mortality among patients receiving rFVIIa pre or post implementation of a pharmacy stewardship, this study highlights that in routine clinical practice the futility and potential misuse of high-risk, expensive drugs can be controlled. Patient characteristics and rationale for use may vary from institution to institution and the implementation of stewardship should be considered if excess or misuse of rFVIIa is observed. Implementation with a dedicated trained hematology pharmacist is reasonable, similar to the process of having a trained dedicated pharmacist for antimicrobial stewardship.

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Table 1. Baseline Characteristics

Past Medical History

Characteristic, n (%)	June 2012-May 2013 N=70	June 2013-May 2014 N=42	P value
Past Medical History			0.125
Chronic liver failure	48 (68)	30 (71.4)	
Unknown coagulopathy	3 (4.3)	0	
Acute/reversible liver failure	8 (11.4)	1 (2.4)	
Elevated INR/Bleeding from vitamin K antagonism	2 (2.9)	2 (4.8)	
Cancer related liver failure	4 (5.7)	1 (2.4)	
Other	5 (7.1)	8 (19)	
Indication			0.515
Bleeding	35 (50)	19 (45.2)	
Prior to heart catheterization	7 (10)	7 (16.7)	
Prior to other procedure	23 (32.9)	11 (26.2)	
Reversal of vitamin K antagonism	1 (1.4)	2 (4.8)	
Factor VII deficiency	0	1 (2.4)	
Elevated INR without evidence of bleeding	4 (5.7)	2 (4.8)	
Age years, mean	53.8 (+/- 12)	55.4 (+/- 13)	0.362
Vitamin K administered concurrently	48 (46.6)	25 (73.5)	0.006
Baseline PT, mean	28.7 (+/- 19.3)	28.2 (+/- 11.4)	0.13
DIC present at baseline	24 (23.3)	16 (47.1)	0.018

Table 2

28-day mortality

	June 2012 – May 2013 **N = 70**	**June 2013 – May 2014** **N = 42**	**P value**
Intention to prescribe, %	52.9	50	0.086
	Received drug **N = 28**	**Did not receive drug** **N = 14**	
June 2013 – May 2014 Receipt of drug, %	50	50	1

Table 3

Binary logistic regression model

Characteristic	28-day mortality odds ratio (95% confidence interval)
Pre-implementation vs. post-implementation	1.14 (0.42-3.09)
Receipt of drug	1.43 (0.33-6.17)
History of liver failure	2.9 (1.18-7.14)
Heart Catheterization	0.14 (0.02-0.76)
Active bleeding	2.91 (1.24-6.88)

Table 4

Secondary outcomes

	June 2012 – May 2013	June 2013 – May 2014	P value
INR change, mean	-0.14	+1.15	
Packed red blood cells, units mean	2.8	6.4	0.047
Platelets, units mean	1	1.5	0.165
Plasma, units median	1	4	0.004
Cryoprecipitate, units mean	0	1.8	0.046