Journal of Hematology and Therapeutics

Nashett RM et al., J Hematol Ther. 2016, 1(1):1-4
http://dx.doi.org/10.14312/2397-8694.2016-1

NobleResearch
An Open Access Publisher
www.nobleresearch.org

Case Report

Open Access

Lowering INR using four factor prothrombin complex concentrate for procedures in patients with ventricular assist devices: A case series

Rebecca M. Nashett[1,*], Katelyn Sylvester[1] and Jean M. Connors[2]

[1] Department of Pharmacy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA
[2] Hematology Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA

Abstract

This case series describes the use of four factor prothrombin complex concentrate (4FPCC) to reverse warfarin anticoagulation without the need for pre-procedure bridging with a parenteral agent or the use of FFP or vitamin K in patients with ventricular assist devices (VAD) who require invasive procedures. Patients were included if they had a history of recent warfarin use and documentation of temporary warfarin reversal for the procedure. Patients were excluded if their first dose of 4FPCC was for active bleeding. INR was assessed prior to 4FPCC administration, and trended for at least 90 h afterwards. Charts were reviewed for adverse events. In patients who received only 4FPCC for INR correction, the mean INR before 4FPCC was given was 2.7 (SD 0.64), which dropped an average of 35.4% after administration to a mean INR of 1.6 (SD 0.30). In the two patients who also received vitamin K, the average INR before reversal was 2.0 (SD 0.49), and was reduced by 35.9% to 1.3 (SD 0.21). The average number of days until patients re-established a therapeutic INR with 4FPCC alone was 3.2 days post procedure compared to 8.5 days for patients who received concomitant vitamin K. No bleeding or thrombotic events were observed. Using 4FPCC without vitamin K may provide VAD patients and clinicians with safe, effective, and rapid reversal of warfarin with faster recovery to the target INR following the procedure.

Keywords: ventricular assist device; VADs; anticoagulation reversal; prothrombin complex concentrates; INR; warfarin reversal

Introduction

The expanded use of ventricular assist devices (VAD) as either destination therapy or as a bridge-to-transplant (BTT) for patients with end-stage heart failure has increased the number of VAD patients requiring invasive procedures [1]. The majority of these patients are maintained on an anticoagulant, mainly warfarin, and antiplatelet therapy for the duration of their VAD therapy. Providers must weigh the risk of thrombosis when withholding anticoagulation against the risk of bleeding during these invasive procedures. The options for reversal of vitamin-K antagonists have historically included holding warfarin for multiple days prior to the procedure and bridging with a parenteral anticoagulant, administration of vitamin K, fresh frozen plasma, and more recently four factor prothrombin complex concentrate (4FPCC).

For planned or scheduled procedures, warfarin can be held to allow for physiological repletion of vitamin-K dependent clotting factors and slow reversal of the INR to baseline while bridging with a short-acting parenteral anticoagulant, but this can require days to achieve an acceptable INR. Vitamin K is a proven effective means for reversal of warfarin, however the degree to which it decreases INR, and the length of time which it maintains a decreased INR can be prolonged and unpredictable [2]. This can also make establishing a therapeutic INR on re-initiation of warfarin difficult. Fresh frozen plasma (FFP) is often used in conjunction with vitamin K in order to provide immediate reversal of warfarin. Use of FFP in VAD patients may be undesirable due to complications of large volume administration, pro-inflammatory cytokine release, allosensitization that can complicate or even preclude transplantation, and potential transfusion-related acute lung injury (TRALI) [3]. FFP is also limited in the degree to which it can lower INR, and may not lower INR adequately

***Corresponding author:** Rebecca M. Nashett, Department of Pharmacy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA. Tel.: 617-732-7165; Fax: 617-566-2396; Email: rnashett@partners.org

Received 11 November 2015 *Revised* 11 January 2015 *Accepted* 20 January 2015 *Published* 28 January 2016

Citation: Nashett RM Sylvester K, Connors JM. Lowering INR using four factor prothrombin complex concentrate for procedures in patients with ventricular assist devices: A case series. J Heamatol Ther. 2016; 1(1):1-4. DOI:10.14312/2397-8694.2016-1

for some procedures [4]. 4FPCC can decrease the INR more rapidly and decrease the risk of complications associated with plasma [5]. The effect of 4FPCC on the INR is transient due to the half life of the clotting factors and by precluding the need for interruption of warfarin. Because of this more transient effect on the INR, the use of 4FPCC may also prevent the need for a parentaral anticoagulation bridge back to a therapeutic INR post procedure, or at least allow for a shortened bridging course. The purpose of this case series is to describe the use of 4FPCC for decreasing INR in VAD patients undergoing invasive procedures at a tertiary-care academic medical center.

Patients and methods

This study was a retrospective review of 11 consecutive patients who had durable VADs and were administered 4FPCC (Kcentra®) between May 2014 and October 2014. The inclusion criteria for the case series were 1. durable VAD, 2. documented warfarin reversal for a procedure other than heart transplant, 3. history of recent warfarin use and, 4. measurement of INR within 24 hours before and after 4FPCC administration. Patients 1 and 2 also received vitamin K near the time of 4FPCC administration and were analyzed separately. Patients were excluded if their first dose of 4FPCC was for bleeding, if they had not previously been on warfarin, and if there was not enough documentation to confirm 4FPCC administration. Eight separate 4FPCC administrations, each given to a unique patient, are the subject of this report. Patients were followed until INR returned to therapeutic threshold or for at least 90 hours. The medical records for the patients in the case series were examined for eligibility criteria and to describe therapy and its effect.

Manufacturer guidelines recommend 25 units of 4FPCC per kilogram of actual body weight, not to exceed 2500 units, when the INR is less than 4. The guidelines recommend 35 units per kilogram of actual body weight when the INR is between 4 and 6, not to exceed 3500 units. Only whole vials are used. Institutional guidelines allow the pharmacist to adjust the total dose to between 90-120% of the original dose to account for available vial size. The goal INR for the specific procedure, and the urgency of the procedure are also taken into account when deciding what dose to administer. For example, if the procedure requires complete reversal of warfarin (such as INR <1.3) and is urgent enough that there is not time to recheck the INR before the procedure, 50 units/kg may be used regardless of baseline INR. Conversely, if a procedure does not require full reversal of the INR (such as INR <2), 25 units/kg might be given.

The protocol was reviewed and approved by the Partners Healthcare System Institutional Review Board prior to data collection.

Results

Table 1 summarizes the demographic characteristics of the eight patients who met inclusion criteria. Patients 1 and 2 also received vitamin K. The mean patient age was 64.5 years (57-76 years). The majority of patients were male (87.5%). The most common type of VAD was the HeartMate II Left Ventricular Assist Device (LVAD) (50%), followed by Heartware (37.5%) and Thoratec Biventricular Assist Device (BiVAD) (12.5%). All patients were receiving aspirin doses ranging between 81mg (25%) and 325mg (62.5%) daily. Three patients in the 4FPCC-only group had warfarin held for one or more days prior to INR reversal (1-4 days). Liver function tests were normal for the majority of patients. However, 75% of patients had renal insufficiency with a mean serum creatinine of 1.38 mg/dL (range, 0.71-1.9 mg/dL). All eight of the patients had different invasive procedures including a peripherally inserted central catheter (PICC) placement, colonoscopy, VAD change-out, etc (Table 1).

The treatment characteristics of patients who received 4FPCC without vitamin K are described below. Patient 3 was discharged shortly after the procedure and sequential data for his INR is not available. Patients 6 and 7 received additional blood products (one patient received 3 bags of packed red blood cells (PRBC) and the other 2 bags of FFP and 1 bag of PRBC) within 48h of receiving 4FPCC. The specific indication for blood products was not clearly recorded in the patients' charts, however both patients had hematocrit drops prior to blood product administration. Patient 8 received two doses of 37.6 and 27.0 units/kg of 4FPCC, respectively, as the target INR was not achieved. The INRs recorded as before and after reversal apply to the first dose of 4FPCC given. The mean dose of 4FPCC was 29.2 units/kg (range, 24.2-37.6 units/kg). The mean INR before 4FPCC was given was 2.7 (range 1.5-3.7, SD 0.64). The mean percent drop in INR recorded was 35.4% (range, 17-52%), and the mean INR recorded after 4FPCC was 1.6 (range 1-2, SD 0.30). The average time for the INR to begin recovery post-reversal with 4FPCC (defined as the first recorded increase of at least 0.2 in INR) was 34.1 hours. The average number of days until the patient reached a therapeutic INR was 3.2 days post procedure (range 1-6 days, SD 1.8). Warfarin was held for an average of 1.2 days (0-3 days, SD 1.1) after INR reversal. The INR trends can be seen in Figure 1. No procedure-related bleeding was observed. There were no thrombotic events during the period of data collection.

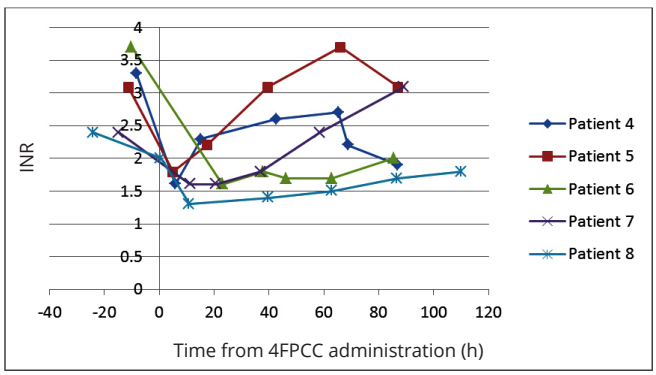

Figure 1 INR trend over time in patients who received 4FPCC without vitamin K.

Treatment characteristics of the two patients who received vitamin K concomitantly were analyzed separately. Both

Table 1 Patient characteristics.

Patient number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*Overall*
MCS device – DT or BTT	HM II LVAD	Thoratec PVAD Bi-VAD TLC II	HM II LVAD	Heartware	HM II	HM II LVAD	Heartware	Heartware LVAD with Tandem RVAD	50% HM II 37.5% HW 12.5% Thoratec
Indication for VAD (DT or BTT)	DT	BTT	BTT	BTT	DT	DT	BTT	DT	50% BTT
Procedure	Replacement of pump	Driveline exploration	Epidural injection	PICC placement	colonoscopy	endoscopy	Arterial line pull	Toe amputations	Not applicable
Baseline INR goal	2 - 3	2.5-3.5	2 - 3	2 - 3	2 - 3	2-2.5	2 - 3	2 - 3	2 - 3
INR before reversal with 4FPCC	1.6	2.3	1.5	3.3	3.1	3.7	2.4	2.4	2.5
Warfarin dose prior to procedure	3mg	8mg	5mg	4mg	5mg	6mg	2mg	2mg	4.4mg
Days warfarin held prior to procedure	2 days	3 days	4 days	0 days	0 days	1 day	1 days	0 days	62.5% held
Male/female	Male	Male	Male	Male	Male	Male	Female	Male	87.5% Male
Age (years)	76	59	65	65	73	57	65	56	64.5
Weight (kg)	75	93.17	93.2	100	121	60	59	97.7	87.4
Height (in)	68	73	70	70	70	71	61	69	69
BMI (kg/m2)	25.1	27	29.4	31.6	38.2	18.9	24.6	31.9	28.3
Anticoagulants	Heparin infusion prior to and after procedure	None	Enoxaparin 1mg/kg within 24h before and after 4FPCC	Bivalirudin 1 day post-4FPCC	None	None	None	None	5/8 none 3/8 yes
Antiplatelets	Aspirin 325mg	Aspirin 325mg	Aspirin 81mg	Aspirin 325mg	Aspirin 81mg	Aspirin at home	Aspirin 325mg	Aspirin 325mg	Aspirin
ALT (U/L)	35	76	23	16	17	8	3	11	WNL
AST (U/L)	37	112	27	14	22	14	55	14	WNL
Alk Phos (U/L)	102	439	56	64	79	52	54	142	WNL
T. Bili (mg/dL)	0.7	4.3	0.8	0.2	1	0.9	0.9	0.3	WNL
D. Bili (mg/dL)	<assay	N/A	0.2	<assay	0.3	0.2	0.5	NA	WNL
SCr (mg/dL)	1.16	1.52	1.9	1.55	1.86	0.83	1.54	0.71	1.38

Abbreviations: MCS=mechanical circulatory support; DT=destination therapy; BTT=bridge to transplant; HM=HeartMate; LVAD=left ventricular assist device; RVAD=right ventricular assist device; INR=international normalized ratio; BMI=body mass index; ALT=alanine transaminase; AST=aspartate aminotransferase; Alk Phos=alkaline phophatase; T. Bili=total bilirubin; D. Bili=direct bilirubin; N/A=not available; SCr=serum creatinine; WNL=within normal limits.

patients received 5mg of vitamin K. The average time for the INR to begin recovery post-reversal with vitamin K and 4FPCC was over 90h (Figure 2) compared to 34.1h in the 4FPCC-only group. The first patient had warfarin withheld for 3 days "prior and 2 days after 4FPCC administration," and reached a therapeutic INR 7 days after anticoagulation reversal. The second patient received FFP and had warfarin withheld for 4 days in addition to vitamin K and 4FPCC administration. A therapeutic INR was not achieved until 11 days after anticoagulation reversal. In the two patients who were given vitamin K, the average time to return to therapeutic INR was 8.5 days "after 4FPCC administration and 5.5 days after resuming warfarin," compared to 3.2 days "after 4FPCC administration and 2 days after resuming warfarin," in the group that received 4FPCC alone.

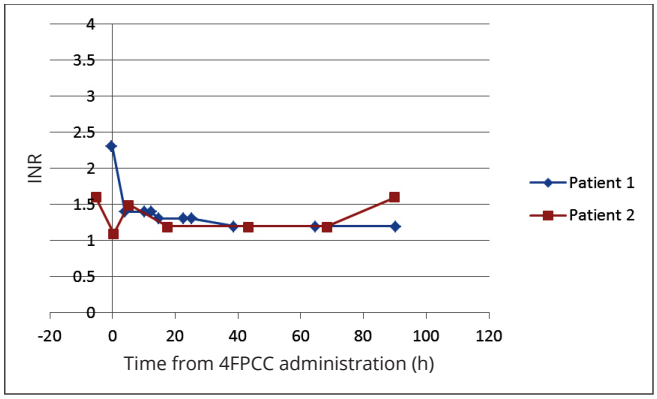

Figure 2 INR trend over time in patients who received 4FPCC and vitamin K.

Discussion

The observations drawn from this case series suggest a faster recovery of therapeutic INR using 4FPCC alone for INR reversal prior to procedure without any observed safety events. There are currently no evidence-based guidelines for the use of 4PCC for warfarin reversal in patients with VADs. Current practice has significant variability regarding

peri-procedure anticoagulation management. Given the results in our institution with 4FPCC for temporary reversal warfarin of anticoagulation and for procedures in VAD patients, we have adopted the following approach for low to moderate risk procedures. Warfarin is not held prior to procedure, 4PCC is administered, and warfarin is restarted post procedure without use of a bridging agent, achieving the target INR rapidly post-procedure. This is further supported by a recent article that has shown superiority in effective hemostasis and rapid INR reduction when comparing 4FPCC to FFP in patients taking a vitamin K antagonist [6].

This change in practice has potential clinical and economic impacts. A clinical advantage to the use of 4FPCC without concomitant vitamin K is the ability to maintain to reverse warfarin anticoagulation without the need for holding warfarin and using a parenteral bridge or using vitamin K, with as little time outside the therapeutic range as possible. Although one dose of 4PCC costs more than FFP or vitamin K, the cost may be justifiable if costs of parenteral bridging agents and length of stay are included.

This is a small retrospective case series. Standard institutional practice did not exist for use of 4PCC to reverse warfarin peri-procedure in VAD patients at the time of this analysis. Duration of follow-up was short. No excess bleeding peri-procedure was observed with the use of this strategy. No cases of thrombotic events were observed during the study period, however we did not assess for events occurring 4 days after 4PCC adminstration.ration.

Conclusion

This case series demonstrates that 4FPCC alone for temporary anticoagulation reversal prior to invasive procedures in patients with VADs is a strategy that has the potential of providing patients and clinicians with a safe, effective, and rapid reversal of warfarin with quicker post-reversal recovery compared with using concomitant vitamin K. Future studies should be directed towards evaluating standardized protocols, cost-effectiveness, hospital length of stay, time period of bridge therapy and subtherapeutic anticoagulation, and relationship to thrombotic.

Conflicts of interest

Authors declare no conflicts of interest.

References

[1] Nicolosi AC, Pagel PS. Perioperative considerations in the patient with a left ventricular assist device. Anesthesiology. 2003; 98(2):565–70.

[2] Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, et al. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med. 2003; 163(20):2469–2473.

[3] Feldman D, Pamboukian SV, Teuteberg JJ, Birks E, Lietz K, et al. The 2013 International Society for Heart and Lung Transplantation Guidelines for mechanical circulatory support: executive summary. J Heart Lung Transplant. 2013; 32(2):157–187.

[4] Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013; 128(11):1234–1243.

[5] Franchini M, Lippi G. Prothrombin complex concentrates: an update. Blood Transfus. 2010; 8(3):149–154.

[6] Goldstein JN, Refaai MA, Milling TJ Jr, Lewis B, Goldberg-Alberts R, 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):2077–2087.