Journal of Critical Care 33 (2016) 252–256

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Is there a difference in efficacy, safety, and cost-effectiveness between 3-factor and 4-factor prothrombin complex concentrates among trauma patients on oral anticoagulants?☆

Alicia Mangram, MD [a,*], Olakunle F. Oguntodu, MD, MS [a,1], James K. Dzandu, PhD, BSc (Hons) [a,2], Alexzandra K. Hollingworth, MD [a,3], Scott Hall, PharmD [b], Christina Cung, PharmD [b], Jason Rodriguez, PharmD [b], Igor Yusupov, MD [c,4], Jeffrey F. Barletta, PharmD [d]

[a] HonorHealth John C. Lincoln Medical Center
[b] Department of Pharmacy Services, HonorHealth John C. Lincoln Medical Center
[c] Neurosurgery Department, HonorHealth John C. Lincoln Medical Center
[d] Midwestern University, College of Pharmacy-Glendale

ARTICLE INFO

Keywords:
Prothrombin complex concentrates
Anticoagulation
Trauma
Warfarin
Reversal
Geriatric

ABSTRACT

Purpose: The aim of this study was to compare the efficacy, safety, and cost-effectiveness of 3-factor prothrombin complex concentrate (3F-PCC) vs 4-factor prothrombin complex concentrate PCC (4F-PCC) in trauma patients requiring reversal of oral anticoagulants.
Materials and methods: All consecutive trauma patients with coagulopathy (international normalized ratio [INR] ≥1.5) secondary to oral anticoagulants who received either 3F-PCC or 4F-PCC from 2010 to 2014 at 2 trauma centers were reviewed. Efficacy was determined by assessing the first INR post–PCC administration, and *successful reversal* was defined as INR less than 1.5. Safety was assessed by reviewing thromboembolic events, and cost-effectiveness was calculated using total treatment costs (drug acquisition plus transfusion costs) per successful reversal.
Results: Forty-six patients received 3F-PCC, and 18 received 4F-PCC. Baseline INR was similar for 3F-PCC and 4F-PCC patients (3.1 ± 2.3 vs 3.4 ± 3.7, $P = .520$). The initial PCC dose was 29 ± 9 U/kg for 3F-PCC and 26 ± 6 U/kg for 4F-PCC ($P = .102$). The follow-up INR was 1.6 ± 0.6 for 3F-PCC and 1.3 ± 0.2 for 4F-PCC ($P = .001$). Successful reversal rates in patients were 83% for 4F-PCC and 50% for 3F-PCC ($P = .022$). Thromboembolic events were observed in 15% of patients with 3F-PCC vs 0% with 4F-PCC ($P = .177$). Cost-effectiveness favored 4F-PCC ($5382 vs $3797).
Conclusions: Three-factor PCC and 4F-PCC were both safe in correcting INR, but 4F-PCC was more effective, leading to better cost-effectiveness. Replacing 3F-PCC with 4F-PCC for urgent coagulopathy reversal may benefit patients and institutions.

1. Introduction

Anticoagulants are widely prescribed for the clinical management and prevention of thromboembolic disease, with greater than 25 million prescriptions filled for the anticoagulant warfarin annually [1]. Patients admitted for acute management of injury, however, often require urgent reversal of their anticoagulation. This is often due to life-threatening hemorrhage or need for an emergent surgery upon admission. Reversal of oral anticoagulants has traditionally been achieved by administration of vitamin K and fresh frozen plasma (FFP). However, the use of recombinant factor VIIa and prothrombin complex concentrates (PCCs) has been increasing. The advantages of these alternatives to vitamin K and FFP include more rapid anticoagulation reversal, decreased volume, and avoidance of blood component transfusion reaction.

In the United States, there are 3 categories of PCC products that have been approved for use by the Food and Drug Administration (FDA): 3-factor PCC (3F-PCC) (Bebulin, Profilnine SD), 4-factor PCC (4F-PCC) (Kcentra), and activated PCC (FEIBA). These products are derived from plasma, purified, and packaged as a lyophilized powder for reconstitution. The primary difference between 3F-PCC and 4F-PCC is the presence of factor VII in 4F-PCC, whereas activated PCC contains activated factor VIIa. 3F-PCC and 4F-PCC are the 2 most common biologics used in warfarin reversal especially among patients requiring emergent surgical or

☆ Statement of disclosure: nothing to disclose.

* Corresponding author. Tel.: +1 602 633 3721; fax: +1 602 995 3795.
E-mail addresses: Alicia.Mangram@HonorHealth.com (A. Mangram), Francis.Oguntodu@HonorHealth.com (O.F. Oguntodu), James.Dzandu@HonorHealth.com (J.K. Dzandu), Alexzandra.Hollingworth@HonorHealth.com (A.K. Hollingworth), scott.hall@HonorHealth.com (S. Hall), Christina.cung@HonorHealth.com (C. Cung), Jason.rodriguez@HonorHealth.com (J. Rodriguez), Igor.Yusupov@HonorHealth.com (I. Yusupov), jbarle@midwestern.edu (J.F. Barletta).
[1] Tel.: +1 602 870 6060x2360.
[2] Tel.: +1 602 870 6060; fax: +1 602 870 6075.
[3] Tel.: +1 602 633 3721.
[4] Tel.: +1 602 266 2272.

http://dx.doi.org/10.1016/j.jcrc.2016.02.018
0883-9441/

invasive procedures. The 3F-PCC is FDA approved for hemorrhagic episodes in hemophilia B patients, whereas 4F-PCC is approved for urgent reversal of coagulation factor deficiency secondary to warfarin [2,3]. Although both have been widely used in several settings including orthopedic surgery, neurosurgery, vascular surgery, general surgery, and trauma surgery, there are limited data comparing 3F-PCC vs 4F-PCC in terms of relative efficacy and safety [4–6]. 4F-PCC may be more effective in lowering international normalized ratio (INR) because of a higher concentration of factor VII, but this may raise concerns for increased thromboembolic events. Furthermore, there are no data describing the cost-effectiveness of these 2 agents. Therefore, the objectives of this study were to compare the efficacy, adverse events, and cost-effectiveness of 3F-PCC vs 4F-PCC in trauma patients with anticoagulation-related coagulopathy.

2. Methods

This retrospective study was conducted at 2 affiliated American College of Surgeons–verified trauma centers: one a level-I trauma center and the second a level-III trauma center. Institutional review board approval was obtained before study initiation. Consecutive adult patients who received either a 3F-PCC or 4F-PCC product from January 2010 to October 2014 and treated by the trauma service were identified using the pharmacy department's medication database and confirmed with trauma registries from the 2 trauma centers. Patients were included if they had a trauma-related admission diagnosis, received oral anticoagulation before admission, and had a baseline INR greater than or equal to 1.5. Patients were excluded if they did not have an INR assessment post–PCC administration or if they received both a 3F-PCC and a 4F-PCC product. Data collected included demographics, indication for anticoagulation, mechanism of injury, severity of illness (injury severity score, Glasgow coma scale, systolic blood pressure), hematology/coagulation-related laboratory values, coagulation-related medications and blood products (packed red blood cells [pRBC], FFP, platelets) received, and adverse events.

Trauma patients with anticoagulation-related coagulopathy meeting inclusion/exclusion criteria were stratified into 2 groups based on the PCC product that was administered: 3F-PCC vs 4F-PCC. Rivaroxaban is one of the new oral anticoagulants that are commonly used. It is considered as an alternative to warfarin, but there is limited experience with this new agent in terms of reversal with PCC. Therefore, the study included patients who were on either warfarin or rivaroxaban. The rationale was to provide information on the effect of PCCs (3F-PCC vs 4F-PCC) on reversal of oral anticoagulants in current use. The specific products used were Bebulin (3F-PCC) and Kcentra (4F-PCC), and the decision to administer PCC was made by the treating physician. There was no formal dosing protocol, but institutional practices consisted of a dose range between 25 and 50 U/kg, with the higher end of the range being considered for INR elevations that were considered extreme (ie, >5). All administered PCC doses (initial and subsequent if necessary) were included in the assessment.

The outcomes assessed were successful INR reversal, adverse effects, and cost-effectiveness. Outcome efficacy was determined by assessing the first INR post–PCC administration. Successful reversal was defined as an INR less than 1.5 upon subsequent INR assessment after the first dose of PCC. Evaluated adverse treatment effects included any thromboembolic complication such as venous thromboembolism, stroke, or myocardial infarction identified via manual medical record review. These events were characterized either as early (within 48 hours of PCC administration) or late (after 48 hours of PCC administration). Cost-effectiveness was determined by comparing the cost per successful reversal. This was calculated using the total reversal-related costs divided by the percentage of successfully reversed patients. The reversal-related costs included were the cost of all administered doses (initial and subsequent if necessary) for each PCC product (using institutional charges) and the cost of all pRBC, FFP, and platelets transfused for 48 hours post–PCC administration.

Data were expressed as mean ± standard deviation or number (n), percentage (%). Continuous data were compared using Student *t* test for normally distributed data or Mann-Whitney *U* test if the data were skewed. To compare dichotomous outcomes data, either Pearson χ^2 test or Fisher exact test was used as appropriate. To control for identified differences in baseline demographics or potential confounding variables, multivariate analysis was performed using logistic regression with a backward, conditional approach. A P value < .05 determined statistical significance. SPSS version 19 (IBM Corp, Armonk, NY) was used for all statistical analyses.

3. Results

3.1. Patient characteristics and baseline INR

There were 64 patients evaluated; 46 received 3F-PCC, and 18 received 4F-PCC. Patients tended to be elderly with the primary mechanism of injury being fall (80%) and atrial fibrillation as the most common indication for anticoagulation (67%). Demographics were similar between groups (Table 1). The average baseline INR was 3.1 ± 2.3 and 3.4 ± 3.7 for the 3F-PCC and 4F-PCC patients, respectively ($P = .520$).

3.2. Initial PCC therapy and dosing

The initial intravenous dose of PCC was 29 ± 9 U/kg for 3F-PCC and 26 ± 6 U/kg for 4F-PCC ($P = .102$). Initial PCC dose was correlated with baseline INR ($r = 0.5$, $P < .001$). A second dose was required in 9 (20%) of 46 3F-PCC patients and 0 (0%) of 18 4F-PCC patients ($P = .052$). Baseline INR values were similar among 3F-PCC patients who received 1 dose vs those who required 2 (3.1 ± 2.5 vs 3.1 ± 1.2, $P = .739$). All patients who received 2 doses were taking warfarin before admission. The total cumulative PCC dose per patient was greater in the 3F-PCC patients (33 ± 15 vs 26 ± 6 IU/kg, $P = .005$). Administration of vitamin K and blood products was similar between groups (Table 2).

3.3. Post–PCC therapy INR

The follow-up INR post–PCC administration was 1.6 ± 0.6 and 1.3 ± 0.2 IU/kg for the 3F-PCC and 4F-PCC patients, respectively ($P = .001$). There was no difference in the time interval between PCC dose and post-PCC INR assessment (3 [0.6–16.5] vs 4.2 [0.6–18.9] hours, $P = .424$). Successful anticoagulation reversal was observed in 23 (50%) of 46 patients who received 3F-PCC and 15 (83%) of 18 patients who received 4F-PCC ($P = .022$) (Fig. 1). This difference remained significant when the 3 patients who received rivaroxaban were excluded from analysis (51% vs 81%, $P = .043$). Upon inclusion of the following factors into a multivariate logistic regression model (age, baseline INR, time INR assessed postdose, vitamin K administration, administration of 4F-PCC), 4F-PCC was retained as an independent predictor for successful anticoagulation reversal (odds ratio [95% confidence interval] = 5 [1.2-19.6], $P = .021$).

3.4. Complications associated with PCC therapy

A total of 7 patients developed and experienced thromboembolic events, all of whom received 3F-PCC (15% vs 0%, $P = .177$). In 6 of these patients, the thromboembolic events occurred within 48 hours of PCC administration and were considered early. All 6 were due to deep vein thrombosis as confirmed by sonography. Late thrombosis (ie, more than 48 hours post–PCC administration) was observed in 1 patient secondary to an ischemic stroke and deep vein thrombosis. Thrombotic events were not related to either the initial PCC dose or number of doses administered. There were 2 patients who died in each group ($P = .313$).