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# EMERGENT WARFARIN REVERSAL (EWR) COMPARING 3 COAGULATION FACTOR PRODUCTS: 3-factor Prothrombin Complex Concentrate, 4-factor Prothrombin Complex Concentrate, and Low Dose Recombinant Factor VIIa

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## Abstract

**Introduction:** 3-factor prothrombin complex concentrate (PCC3), 4-factor prothrombin complex concentrate (PCC4), and low-dose recombinant factor VIIa (LDrFVIIa) have all been used at our Level one Trauma Center for EWR. Data comparing the efficacy and safety of these 3 products are lacking, as are data for specific factor dosing to predict INR response. We compared PCC3, PCC4, and LDrFVIIa for EWR and thromboembolic (TE) events. **Methods:** Medical records of patients (pts) who received PCC3 (20-50 U/kg), PCC4 (20-50 U/kg), or LDrFVIIa (1000 or 1200 mcg) for EWR from August 2007 to June 2014 were reviewed. Demographics, indication for EWR, INR before and after factor dosing, and factor dose were collected. Primary endpoints were achievement of INR ≤ 1.5 and thromboembolic (TE) events. Data were compared using Kruskal-Wallis, Chi-square or Fisher exact tests as appropriate. For p ≤ 0.05, Bonferroni correction was applied. Data are reported as median [IQR]. **Results:** Included were 198 pts, with 100 PCC3 (dose 20.3[19.1-22.3] U/kg), 35 PCC4 (dose 28.1[25-37.3] U/kg), and 63 LDrFVIIa (dose 1000[1000-1000] mcg). Patient demographics, reason for EWR, and vitamin K use were not different between groups. PCC4 and LDrFVIIa equally achieved an INR ≤ 1.5 and were more effective than PCC3 (34% PCC3, vs. 85.7% PCC4, vs. 81% LDrFVIIa, p< 0.001). TE events were equivalent (5 PCC3 vs. vs. 2 PCC4 vs. 3 LDrFVIIa). Change in INR was greater with PCC4 vs. PCC3 (1.9 vs. 1.2, p=0.003) and PCC4 vs. LDrFVIIa (1.9 vs. 1.5, p=0.016). Fewer PCC4 pts received FFP (61.0% PCC3, vs. 22.9 % PCC4 vs. 57.1% LDrFVIIa, p <0.001). Baseline INR was 3.1 PCC vs. 3.7 PCC4 vs. 2.8 LDrFVIIa, p=0.02; p=0.006 for PCC4 vs. LDrFVIIa). INR after treatment was lower with LDrFVIIa (1.2) than with PCC3 (1.7) or PCC4 (1.4), p<0.001. **Conclusions:** PCC4 and LDrFVIIa were more effective at lowering the INR to ≤ 1.5 compared with PCC3. INR after treatment was lower after LDrFVIIa than PCC3 or PCC4. The blunted INR response observed with PCC3 treatment may be related to less factor VII component. TE events were not different between groups.

## Introduction

- Critical bleeding associated with warfarin anticoagulation can lead to major or life-threatening bleeding events, requiring rapid reversal of warfarin effects.[1]
- Administration of PCC3, PCC4, or LDrFVIIa to patients with critical warfarin associated bleeding have been shown to provide rapid correction of warfarin anticoagulation as measured by reduction in the INR.[2,3,4]
- Here we compare the efficacy and safety of PCC3, PCC4, and LDrFVIIa for the emergent reversal of warfarin anticoagulation.

## Hypothesis

PCC3, PCC4, and LDrFVIIa are equally effective and safe for warfarin anticoagulation reversal.

## Inclusion/Exclusion Criteria

**Inclusion:** Patients requiring emergent reversal of warfarin, received either PCC3 or PCC4 (20-50 U/kg rounded to nearest vial) or LDrFVIIa (1000 or 1200 mcg), had one or more INR measurements obtained both pre and post coagulation factor administration.

**Exclusion:** Received both PCC and rFVIIa, no pre or post coagulation factor INR measurement, more than 1 coagulation factor dose administered before post coagulation factor INR measured, PCC dose < 20 or > 50 units/kg or rFVIIa dose > 1200 mcg, and/or not receiving warfarin prior to admission.

## References

1. Holbrook A, et al. *Chest* 2012; 141(2) (Suppl): e152S-e184S.
2. Dager WE, et al. *Pharmacotherapy* 2006; 26: 1091-1098.
3. Leissinger CA, et al. *American Journal of Hematology* 2008; 83: 137-143.
4. Sarode R et. al. *Circulation* 2013;128:1234-1243.

## Methods

### Study Population

- Retrospective chart review of patients who received PCC3, PCC4, or rFVIIa between August 2007 and June 2014.
  - 306 medical records of patients who were prescribed a coagulation factor were reviewed.
  - 8 excluded for receiving both PCC and rFVIIa.
  - 298 further reviewed for inclusion/exclusion criteria.

| Group | PCC3 (n=126) | PCC4 (n=40) | rFVIIa (n=132) |
|---|---|---|---|
| **Total number excluded** | **26** | **5** | **69** |
| • No pre or post coagulation factor INR | 14 | 3 | 3 |
| • Dose outside recommendations | 5 | 1 | 43 |
| • No warfarin PTA | 4 | 1 | 19 |
| • Coagulation factor not administered | 3 | 0 | 4 |

### Data Collection

- Demographic data:
  - Age, gender, weight, indication for warfarin, indication for warfarin reversal.
- Reversal agents administered:
  - Vitamin K (number of patients, dose, route), FFP units, coagulation factor (PCC3, PCC4, or LDrFVIIa) dose.
- Outcome data:
  - Target INR ≤ 1.5 used for determination of successful reversal of warfarin anticoagulation, thromboembolic events, mortality.

### Statistical Analysis

- Kruskal-Wallis test used to compare continuous data and Chi Square or Fisher exact test for categorical data. p≤0.05 considered statistically significant with Bonferroni correction as necessary with statistical significance level of p ≤ 0.017. Data presented as Median (IQR) unless specified otherwise.

### Indication for Warfarin, n (%)

| Group | PCC3 (n=100) | PCC4 (n=35) | LDrFVIIa (n=63) | p value |
|---|---|---|---|---|
| • Atrial Arrhythmias | 58 (58.0%) | 16 (45.7%) | 38 (60.3%) | 0.346 |
| • Valve replacement | 16 (16.0%) | 7 (20.0%) | 11 (17.5%) | 0.862 |
| • DVT/PE prophylaxis or Rx | 23 (23.0%) | 7 (20.0%) | 13 (20.6%) | 0.904 |
| • Ischemia CVA | 5 (5.0%) | 1 (2.9%) | 2 (3.2%) | 0.893 |
| • Other | 2 (2%) | 3 (8.6%) | 5 (7.9%) | 0.087 |

### Indication for Emergent Warfarin Reversal, n (%)

| Group | PCC3 (n=100) | PCC4 (n=35) | LDrFVIIa (n=63) | p value |
|---|---|---|---|---|
| Acute Bleeding*† # | 71 (71.0%) | 35 (100%) | 55 (87.3%) | <0.001 |
| • Neurologic* | 49 (49.0%) | 27 (77.1%) | 42 (66.7%) | 0.005 |
| • Abdominal | 14 (14.0%) | 3 (8.6%) | 6 (9.5%) | 0.632 |
| • Other | 8 (8.0%) | 5 (14.3%) | 7 (11.1%) | 0.540 |
| Acute Surgery (non-bleeding) | 12 (12.0%) | 0 (0.0%) | 5 (7.9%) | 0.073 |
| Other n (%)* | 17 (17.0%) | 0 (0.0%) | 3 (4.8%) | 0.003 |
| *=p≤0.017 for PCC3 vs. PCC4 | †=p ≤0.017 for PCC3 vs. LDrFVIIa | | #=p ≤0.017 PCC4 vs. LDrFVIIa | |

## Results

| Variable | PCC3 (n=100) | PCC4 (n=35) | LDrFVIIa (n=63) | p-Value |
|---|---|---|---|---|
| **Demographics** | | | | |
| **Age (years)** | 74 (62-81) | 71 (60-81) | 68 (60-80) | 0.727 |
| **Gender (M:F), %male** | 60:40, 60% | 18:17, 51% | 40:23, 63% | 0.503 |
| **Weight (kg)** | 83 (72-95) | 84 (66-98) | 87 (71-103) | 0.817 |
| **Reversal Agents Administered** | | | | |
| **Coagulation factor dose (units or mcg)** | 1680 (1500-2200) | 2348 (2078-3135) | 1000 (1000-1000) | N/A |
| **PCC Dose (units/kg)** | 20.3 (19.1-22.3) | 28.1 (25-37.3) | N/A | <0.0001 |
| **Vitamin K, n (%)** | 75 (75%) | 32 (91.4%) | 47 (74.6%) | 0.101 |
| **FFP, n (%)*#** | 61 (61%) | 8 (22.9%) | 36 (57.1%) | <0.001 |
| PCC3 vs. PCC4: p<0.001, PCC3 vs. LDrFVIIa: p=0.456, PCC4 vs. LDrFVIIa: p< 0.001 | | | | |
| **FFP units*#** | 2 (0-4) | 0 (0-0) | 2 (0-4) | <0.001 |
| PCC3 vs. PCC4: p<0.001, PCC3 vs. LDrFVIIa: p=0.767, PCC4 vs. LDrFVIIa: p<0.001 | | | | |
| **Coagulation Parameters** | | | | |
| **INR Pre coagulation factor #** | 3.1 (2.2-4.1) | 3.7 (2.6-4.5) | 2.8 (2.0-3.4) | 0.02 |
| PCC3 vs. PCC4: p=0.18, PCC3 vs. LDrFVIIa: p=0.063, PCC4 vs. LDrFVIIa: p= 0.014 | | | | |
| **INR Post coagulation factor *†#** | 1.7 (1.5-2.0) | 1.4 (1.3-1.5) | 1.2 (1-1.4) | <0.001 |
| PCC3 vs. PCC4: p<0.001, PCC3 vs. LDrFVIIa: p<0.001, PCC4 vs. LDrFVIIa: p= 0.002 | | | | |
| **Time from pre- to post-factor INR** | 4:16 (2:32-7:24) | 5:35 (3:21-8:22) | 4:57 (2:24-4:58) | 0.192 |
| **Change in INR** | 1.2 (0.7-2.2) | 1.9 (1.3-3.3) | 1.5 (0.9-2.1) | 0.008 |
| PCC3 vs. PCC4: p=0.003, PCC3 vs. LDrFVIIa: p=0.318, PCC4 vs. LDrFVIIa: p= 0.016 | | | | |
| **% Change in INR*#** | 39.3 (30.8-56.7) | 59.4 (44.6-69.7) | 53.6 (44.7-62.3) | <0.001 |
| PCC3 vs. PCC4: p<0.001, PCC3 vs. LDrFVIIa: p<0.001, PCC4 vs. LDrFVIIa: p= 0.108 | | | | |
| **n (%) INR ≤ 1.5*†** | 34 (34.0%) | 30 (85.7%) | 51 (81.0%) | <0.001 |
| PCC3 vs. PCC4: p<0.001, PCC3 vs. LDrFVIIa: p<0.001, PCC4 vs. LDrFVIIa: p= 0.551 | | | | |
| **Outcome** | | | | |
| **Thromboembolic events, n (%)** | 5 (5%) | 2 (5.7%) | 3 (4.8%) | 0.979 |
| **Mortality, n (%)** | 24 (24.0%) | 9 (25.7%) | 18 (28.6%) | 0.81 |
| *=p≤0.017 for PCC3 vs. PCC4 | †=p ≤0.017 for PCC3 vs. LDrFVIIa | | #=p ≤0.017 PCC4 vs. LDrFVIIa | |

## Conclusions

- From the coagulation factor doses used in this comparison, PCC4 and LDrFVIIa more effectively corrected INR to ≤ 1.5 than PCC3 as dosed in this comparison.
- The decreased INR response observed with PCC3 may be due to less factor VII in this product compared to the other products.
- The change in INR was greater with PCC4 compared to those who received PCC3 or LDrFVIIa.
- Thromboembolic events and mortality were equivalent between the three products.
- These data support the use of PCC4 for emergent warfarin reversal as proposed by the 2012 ACCP Antithrombotic Therapy Guidelines recommendations.[1]