

Implementation and Evaluation of Fixed Dosing Prothrombin Complex Concentrate for Warfarin Reversal

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BACKGROUND

- 4-Factor Prothrombin Complex Concentrate (4f-PCC) is indicated for reversal of warfarin in patients with acute bleeding or for urgent/emergent surgeries in combination with vitamin K. FDA labeling currently recommends weight-based dosing (units/kg) based on the pre-treatment INR.
- A recent 2020 ACC Expert Consensus Decision Pathway¹ suggests a fixed-dosing strategy may be used:
 - 1,000 units for a major, non-cranial bleed
 - 1,500 units for intracranial hemorrhage (ICH)
- This recommendation was based on evidence suggesting non-inferiority between weight based and fixed dosing for warfarin reversal.
- Following a Drug Utilization Evaluation (DUE) performed at the TUKHS, the Adult Emergent Oral Anticoagulant Reversal Agent order set for warfarin was updated to reflect fixed dosing
 - Intracranial hemorrhage: 1,500 units
 - Consider an additional 500 units (total 2,000 units) if initial INR >10 or if the patient weighs > 100 kg
 - A 500-unit supplemental dose may be administered 30 minutes after last 4f-PCC administration if repeat INR >2 or there are signs/symptoms of bleeding
 - All other indications: 1,000 units
 - A 500-unit supplemental dose may be administered 30 minutes after last 4f-PCC administration if repeat INR >2 or there are signs/symptoms of bleeding

ENDPOINTS

- Primary endpoint:**
 - Achievement of INR reversal (INR ≤2) (%)
- Secondary endpoint:**
 - Number of supplemental doses given
 - Percentage of patients receiving concomitant vitamin K therapy
 - 30-Day Mortality
 - Predicted number of units conserved

METHODS

Study Design: Retrospective, single center chart review after fixed dosing protocol implementation (August 13th, 2020-January 13th, 2021)

Inclusion Criteria:

- Patients ≥ 18 years old during a single inpatient and emergency department encounter
- Received 4f-PCC for warfarin reversal after new protocol implemented

Exclusion Criteria:

- Received 4f-PCC for Direct-Acting Oral Anticoagulant (DOAC) reversal
- Received 4f-PCC for non-warfarin related bleeding (factor deficiency, trauma)
- Received doses outside the recommended dosing protocol
- Pre-treatment INR <2

Data Collected:

- Patient demographics
- Indication for 4f-PCC reversal
- Pre- and post- 4f-PCC INR
- Total dose of 4f-PCC administered, dose of Vitamin K administered
- 30 day mortality

RESULTS

Age (Years)	68 (35-87)
Weight (kg)	83.8 (63.5-284.6)
Sex (Men)-% (n)	83.3% (n=10/12)
Baseline INR	4.8 (2-greater than 10)

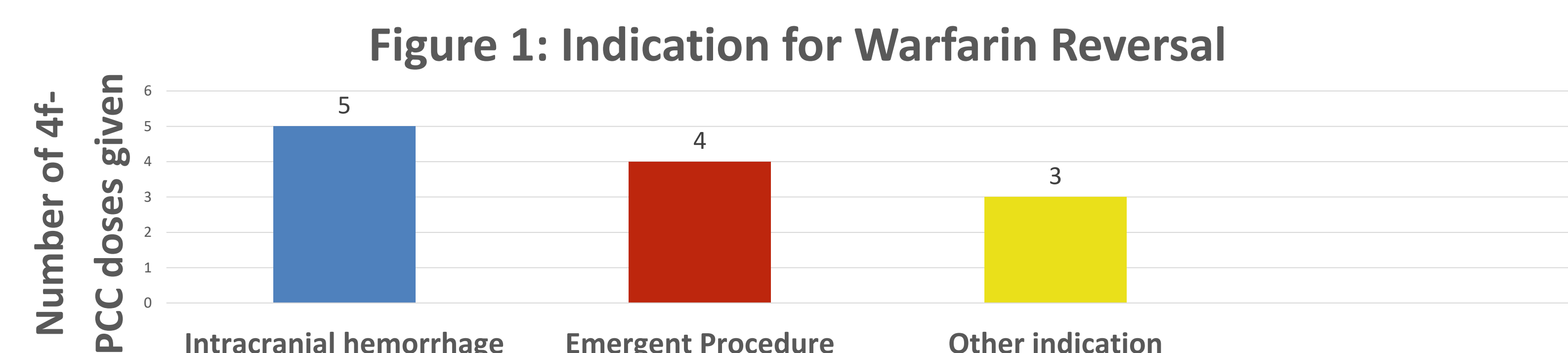
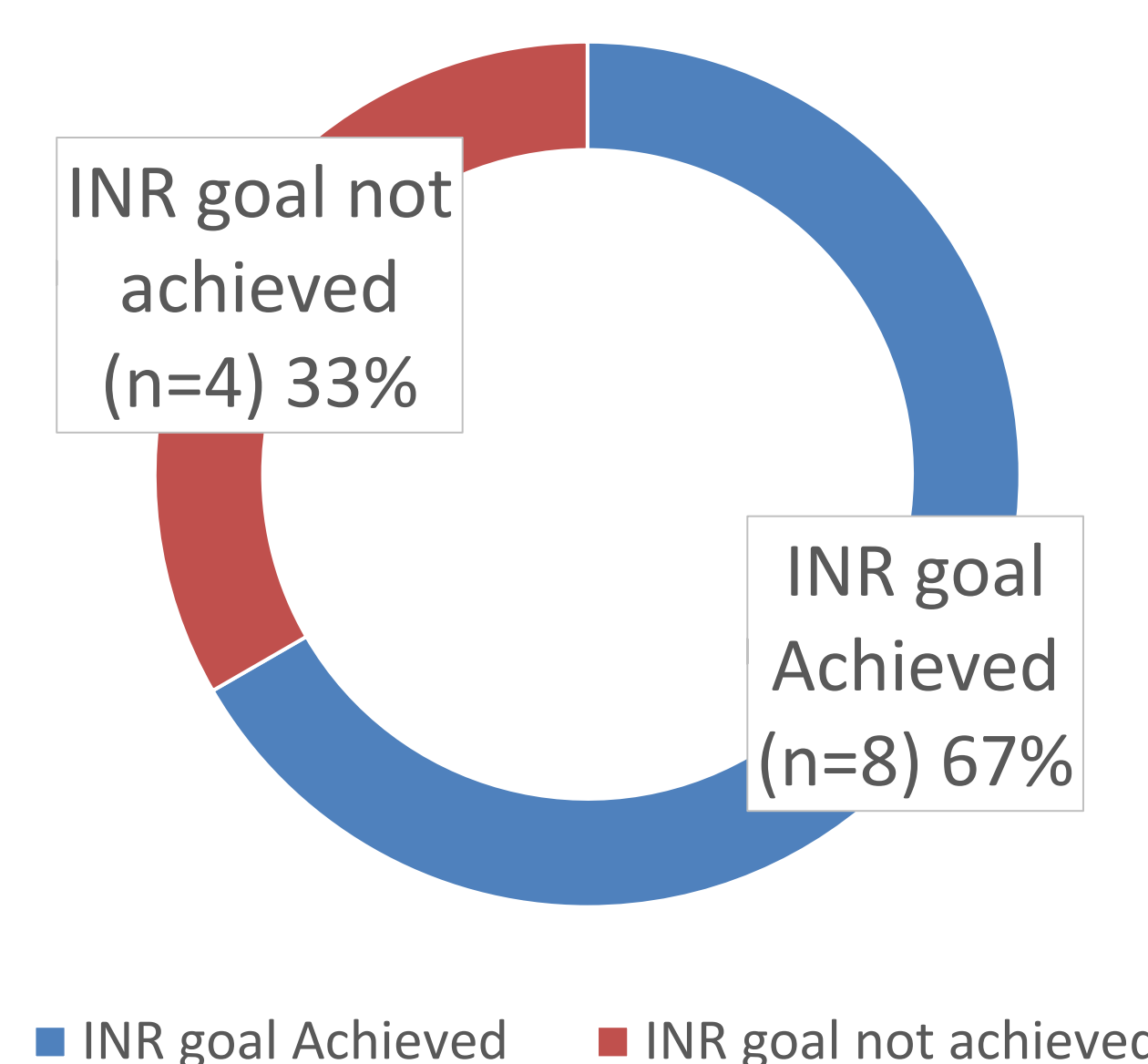


Figure 2: Primary Outcome-Assessment of INR Reversal after 4f-PCC administration



Dose Administered, units-Median (Range)	Intracranial Hemorrhage: 1609 (1533-1653) All other indications: 1035 (960-1090)
Number of Supplemental Doses Given	0
Number of Patients Receiving Vitamin K	100%
30 day mortality-n (%)	1 (8.3%)
Estimated Cost Savings*	\$71,906
*Based on AWP pricing	
Total Units of 4f-PCC Conserved	22,900

DISCUSSION

- Of the 12 patients that received 4f-PCC post implementation, 8 of these patients achieved successful INR reversal
 - Three of the four patients who failed to reverse INR had extremely high pre-treatment INRs (Range 8.5 to >10), received 4f-PCC for GI bleed or reversal for emergent procedure
 - None of the patients with an initial INR >10 received 4f-PCC for intracranial hemorrhage, additional 500 units based on pre-treatment INR not indicated
 - One patient died within 30 days of 4f-PCC, did achieve successful INR reversal
- 12 of 12 patients received concomitant vitamin K therapy
- Despite 4 of the 12 patients not achieving an INR of <2, no supplemental doses given
- Implementation of the fixed dose protocol resulted in measurable product savings
 - Approximately 23,000 units were conserved after implementation

CONCLUSIONS

- All 12 patients received a dose compliant with the fixed dosing recommendations
 - No supplemental doses were given in patients receiving fixed-dosed 4f-PCCs
 - 8 of 12 patients included achieved successful INR reversal
- Additional data, and potential changes to our policy regarding repeat INRs, may be beneficial in analyzing the safety and efficacy of fixed-dose 4f-PCC

FUTURE DIRECTIONS

- Data collection (extended beyond the immediate post-implementation period) is needed to fully assess the efficacy and cost-savings associated with fixed dosed 4f-PCC
- By using a fixed dosing regimen, the process of ordering and administration of 4f-PCC is streamlined. Measuring time from order input to medication administration may illustrate additional clinical benefit.

STUDY LIMITATIONS

- Time to INR reversal is dependent on timing of lab draws, which currently is not standardized. Because of this, there may be delays in repeat INR lab draws, and the INR reported may not be clinically indicative of a patient's real time coagulation status
- This small sample size may not be truly indicative of the safety and efficacy of the fixed dosing regimen; additional data is needed.

SOURCES

Tomaselli GF, Mahaffey KW, Cuker A, et al. 2020 ACC Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 Aug 4;76(5):594-622. doi: 10.1016/j.jacc.2020.04.053. Epub 2020 Jul 14. PMID: 32680646.

CONTACT INFORMATION

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- Authors have no disclosures to report