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Evaluation of a Fixed, Low-Dose Four-Factor Prothrombin Complex Concentrate Dosing Protocol for International Normalized Ratio Reversal at Two Academic Medical Centers

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Background: Emerging data suggest fixed four-factor prothrombin complex concentrate (4F-PCC) dosing may adequately reverse warfarin, minimize time to INR reversal, and reduce medication costs.[1-6] A 4F-PCC fixed, low-dose strategy for INR reversal was implemented January 18, 2019 at The Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center in Baltimore, Maryland, USA. We describe the outcomes associated with implementation of this dosing protocol, and compare outcomes among patients receiving two Kcentra® fixed-dosing strategies.

Methods: According to the 4F-PCC fixed, low-dose protocol, patients with warfarin-induced intracranial hemorrhage (ICH) with actual body weight > 50 kg received Kcentra® (CSL Behring; Kankakee, IL, USA) 1,500 units once, while patients < 50 kg received Kcentra® 1,000 units once. Regardless of the initial dose, all warfarin-induced ICH patients with inadequate INR reversal after initial dosing qualified for repeat dosing with Kcentra® 500-1,000 units if clinically indicated. Patients requiring INR reversal for non-ICH indications received Kcentra® 1,000 units once, with a repeat dose of Kcentra® 1,000 units administered for inadequate INR reversal if clinically indicated. Patients who received fixed, low-dose 4F-PCC (Kcentra® doses ≤ 1,700 units) from January 18, 2019 to June 18, 2019 were included regardless of whether the prescribed fixed-dose adhered to indication-specific dosing recommendations in our protocol. Patients who received Kcentra® doses > 1,700 units due to protocol non-adherence were excluded. Patients were included in the efficacy analysis if they had a baseline INR > 1.4 and a post-Kcentra® administration INR result was available. All patients receiving fixed, low-dose 4F-PCC during this time period were included in the cost savings analysis, regardless of baseline INR. Categorical variables were compared using the Chi-square test except in the case of variables with cell sizes of four or less, in which case the Fisher's Exact test was used.

Results: A total of 51 patients received 52 administrations of fixed, low-dose Kcentra® during the study period. Six patients received the FDA-approved weight- and INR-based Kcentra® dosing, and were excluded. Kcentra® 1,000 units

was administered for non-ICH INR reversal indications in 25 (48%) cases. Kcentra® 1,500 units was administered for INR reversal in the setting of warfarin-induced ICH in 19 (36.5%) cases. Fixed Kcentra® dosing that deviated from our institutional dosing protocol was administered in eight of 52 cases: five administrations (9.6%) of Kcentra® 1,500 units for non-ICH indications for INR reversal, two administrations (3.8%) of Kcentra® 1,000 units for INR reversal in the setting of ICH, and one administration (1.9%) of Kcentra® 500 units for non-ICH. Therefore, protocol adherence during this six-month evaluation period was 75.8%. The most common indications for Kcentra® administration were ICH (36.5%), refractory hemorrhage after cardiac surgery (17%), gastrointestinal bleeding (11.5%), and emergent procedure or surgery (7.7%). For patients in the efficacy analysis (n=39), the median baseline INR was 2.8 (IQR 1.95-4.1), the median time to INR measurement after Kcentra® administration was 83 minutes (IQR 40-173), and the median weight was 70.3 kg (IQR 61.8-92.2). Thirty-two patients (82.1%) in the efficacy analysis received an intravenous dose of vitamin K 10 mg in addition to Kcentra®, and two patients received an intravenous dose of vitamin K 5 mg. The remaining five patients received either oral vitamin K or no vitamin K at all. The change in INR before and after Kcentra® administration is shown in Figure 1. Thirty-seven (94.8%) patients included in the efficacy analysis achieved an INR measurement < 2 following Kcentra® administration. One patient with INR > 2 after Kcentra® administration received an initial dose of Kcentra® 500 units, which was inappropriately low according to dosing recommendations in our institutional protocol. The other patient with INR > 2 following Kcentra® administration received an initial Kcentra® 1,000 unit dose to correct a baseline INR of 8, which lowered the INR to 2.2. Twenty-eight (71.7%) of patients included in the efficacy analysis achieved an INR of < 1.7 following Kcentra® administration. One patient required repeat Kcentra® dosing. This patient's initial INR was 2.1, which corrected to 1.7 after administration of an initial Kcentra® 1,500 unit dose. However, an additional Kcentra® 1,500 unit dose was administered prior to external ventricular drain placement, and the INR dropped to 1.6 thereafter. This repeat dose was higher than recommended in our institutional protocol. When comparing patients who received Kcentra® 1,000 units and 1,500 units, there was no significant difference in achievement of INR values < 2.0 (94.4% vs. 95.2%, p=0.72) or < 1.7 (66.7% vs. 76.2%, p=0.51). Additionally, there was no significant difference in achievement rates of INR values < 1.7 in those with baseline INRs > 4.0 in the Kcentra® 1,000 unit group compared to 1,500 units (66.7% vs. 40%, p=0.392). Utilizing the actual wholesale price of 2.90 USD per unit, the estimated cost savings from use of fixed, low-dose Kcentra® was 148,348 USD.

Conclusions: Administration of Kcentra® 1,000 to 1,500 units effectively reduced the baseline INR to < 2 in 94% of cases. There were no significant differences in achievement of post-treatment INR values of <2.0 or < 1.7 between those who received Kcentra® 1,000 units versus 1,500 units. Achievement rates of INRs < 1.7 after Kcentra® administration in patients with significantly elevated baseline INRs (INR > 4) were also not significantly different between treatment groups. However, these findings must be confirmed in larger studies due to the small sample size in this analysis. Additionally, implementation of a fixed, low-dose Kcentra® protocol is associated with significant cost savings.

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Figure 1: Patient Level Change in INR Pre- and Post-Kcentra® Administration

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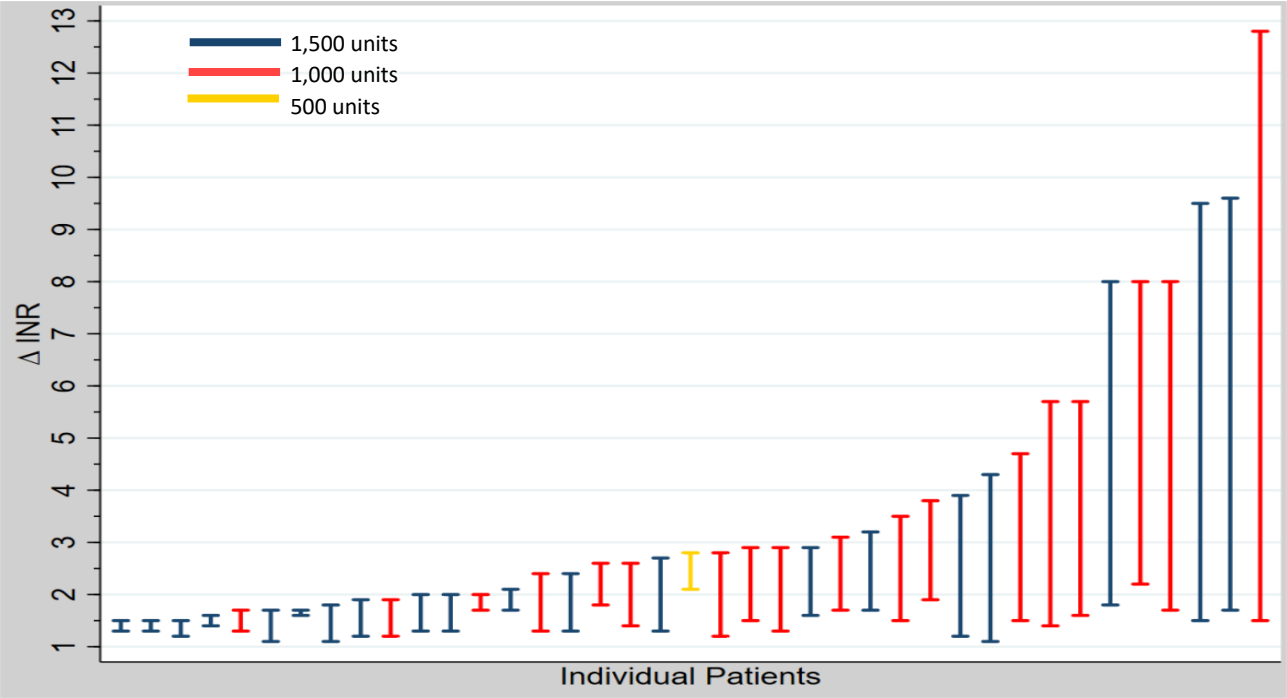

* Includes patients with pre- and post-INR measurement and baseline INR > 1.4

Median time to post-Kcentra® INR: 83 minutes (IQR 40-173)

Predictors of Heparin-Induced Thrombocytopenia in Adult Cardiac Surgery Patients

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Background: The 4Ts, HIT-Expert Probability (HEP), and Post-Cardiopulmonary Bypass (CPB) screening tools for heparin-induced thrombocytopenia (HIT) have not been validated in cardiac surgery patients. Evidence remains unclear regarding which screening tool most accurately predicts HIT in this population.

Methods: HIT-positive and HIT-negative patients who underwent on-pump cardiac surgery within a six-year period were matched 1:2 in a case-control design. Each patient was scored with the 4Ts, HEP, and CPB tools. Sensitivities and specificities of each tool were calculated using standard cut-offs. The Youden method was utilized to determine optimal cut-offs in receiver operating characteristic (ROC) curves of each score, then sensitivities and specificities were recalculated. A multivariable logistic regression was performed to determine the association of scoring tool components and relevant clinical characteristics with HIT.

Results: Using standard cut-offs for the scoring tools, sensitivities for the CPB, HEP, and 4Ts tools were 100%, 93.9%, and 69.4%, respectively. Specificities were 51%, 49%, and 71.4%, respectively. Using the Youden method-derived optimal cut-offs, sensitivity of the CPB score remained 100% with improved specificity to 88.9%. Sensitivity of the 4Ts score declined to 51% and specificity improved to 93.9%. Pattern of platelet decline, absence of clinically significant bleed,

body mass index, coronary artery bypass graft surgery, and postoperative heparin duration were significantly associated with HIT.

Conclusions: The 4Ts score has limited utility in cardiac surgery patients, whereas the CPB and HEP scores with standard cut-offs demonstrated high sensitivity but low specificity. A cut-off of ≥ 3 points on the CPB score could increase specificity while preserving high sensitivity.

Data-Drive Approach to Optimization of a Central Pharmacy Operations: Sterile Compounding (IV Lab)

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Background: At The Johns Hopkins Hospital (JHH), the Central Pharmacy supports the medication distribution process for the academic medical center, which has approximately 1,100 patient beds. The Central Pharmacy IV Lab is staffed for 16 hours daily and prepares compounded sterile products (CSPs) in six different "batches".

Purpose: This project aims to evaluate the existing batching process in the Central Pharmacy IV Lab and determine if changes in workflow are needed to reduce waste, identify duplicative efforts, determine overall cost-mitigation strategies, and improve efficiency.

Methods: Single center study that evaluates all patients admitted to JHH receiving IV CSPs distributed from Central Pharmacy between January 1st, 2019 and December 1st, 2019. Data variables collected and analyzed include but are not limited to: batch and delivery volumes, medication names, dose, frequency, and route, medication order timestamps (i.e., entered, modified, discontinued), CSPs not administered after preparation, and pharmacy technician full time equivalents (FTE) to support operations. Data variables were utilized to create a dashboard to model current operations.

Results: Available waste data shows that 16.5% of doses dispensed from the IV Lab in the previous calendar year were not administered to patients. The highest percentage of not administered drugs correspond to the first three batches of the day dispensed at 05:25, 08:10, and 11:10, with administration times from 10:00 – 20:59. Dispensing volumes indicate an average of 21,119 patient specific CSP doses dispensed per month, with the largest volume corresponding to the batches dispensed at 17:00 and 19:30. The data resulting from further analysis will be utilized to evaluate different workload models, and medication due times will be assessed to understand waste data and batch frequency.

Pancreas Transplant in Patients Older than 50: An Analysis of Outcomes and Immunosuppression

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Purpose: Pancreas transplant (PT) is the ideal therapy for many patients with diabetes and kidney failure. There are limited published data addressing the impact of recipient age on post-transplant outcomes. Kidney transplant literature suggests that immune senescence increases with age, and that immunosuppression should be tailored accordingly. As our recipient profile has aged, we sought to determine if outcomes differed based on age in the context of immunosuppression choice.

Methods: This single-center, retrospective cohort study included adult solitary and combined PT recipients between 1/2000 and 5/2018 stratified by age (18-49 and ≥50). The primary endpoint was graft survival at 1 year. Secondary endpoints included patient survival at 1 year, overall patient and graft survival, and incidence of biopsy-proven acute rejection (BPAR).

Results: This study included 430 patients with 104 that were ≥50 years. Baseline demographics did not differ between groups (Table 1). Median time to last follow-up was 4.81 (18-49 group) and 4.01 (≥50 group) years (p=0.16). There was no difference in tacrolimus or mycophenolate exposure. Graft survival at 1 year was similar between groups (12.6% vs 12.5%, p= 0.98). Despite higher rates of BPAR in the 18-49 group (26.3% vs 11.5%, p<0.05), overall patient and graft survival remained similar between groups (Figures 1 and 2). Patients in the ≥50 group were more likely to receive alemtuzumab induction (38.9% vs 51.9%, p<0.05); however, graft survival was similar between groups irrespective of lymphocyte depleting induction agent (Figure 3).

Conclusion: A lower risk of BPAR was observed among older PT recipients, which may reflect immunosenescence, consistent with kidney literature. Importantly, older recipients did not have worse graft or patient survival. Type of lymphocyte-depleting induction agent in older patients did not impact outcomes. PT in older patients is associated with excellent survival at 1, 5, and 10 years. Alemtuzumab appears to be a safe option for induction in both younger and older recipients.

Table 1. Baseline Demographics

Characteristic	Age <50 (n=326)	Age ≥50 (n=104)
Recipients		
Sex (Male), n (%)	167 (51.2)	61 (58.6)
Race (White), n (%)	245 (75.2)	86 (82.7)
Current transplant type, n (%)		
Pancreas transplant alone	84 (25.8)	22 (21.1)
Pancreas after kidney	52 (15.9)	13 (12.5)
Simultaneous kidney-pancreas	190 (58.3)	69 (66.4)
Prior transplant, n (%)	99 (30.4)	32 (30.8)
Donors		
Age (Years), median (IQR)	22 (18-32)	25 (19-34)
Gender (Male), n (%)	222 (68.1)	69 (67.6)
Donation After Cardiac Death, n (%)	18 (5.8)	7 (6.9)

Figure 1. Overall patient survival

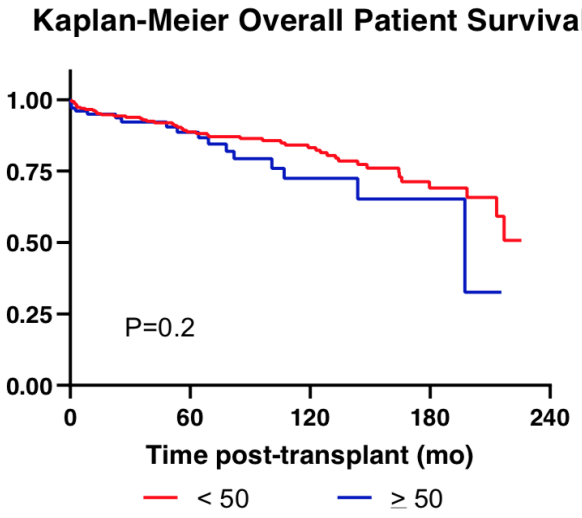

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Figure 2. Overall graft survival

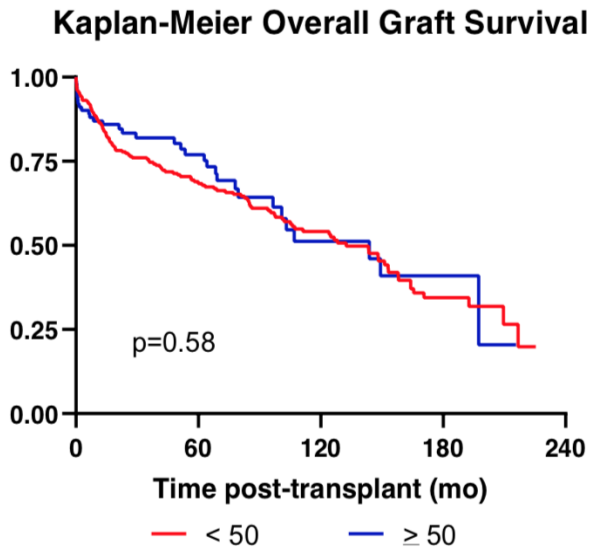

Figure 3. Graft Survival by Induction