Outcomes of Urgent Warfarin Reversal With Frozen Plasma Versus Prothrombin Complex Concentrate in the Emergency Department

Michael Hickey, MD; Mathieu Gatien, MD; Monica Taljaard, PhD; Amiirah Aujnarain, MSc; Antonio Giulivi, MD; Jeffrey J. Perry, MD, MSc

Background—Physicians reverse patients’ warfarin anticoagulation with frozen plasma or prothrombin complex concentrate. Our objective was to determine adverse event frequency after urgent reversal with frozen plasma versus the prothrombin complex concentrate Octaplex.

Methods and Results—This natural before-after retrospective cohort study in 2 tertiary care emergency departments compared anticoagulation reversal with frozen plasma (September 2006–August 2008) and with Octaplex (September 2008–August 2010), without other system changes. We included adult patients on warfarin with an international normalized ratio ≥1.5 who received frozen plasma or Octaplex. Our primary outcome was serious adverse events (death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism, or peripheral arterial thromboembolism) within 7 days. Secondary outcomes included time to international normalized ratio reversal, hospital length of stay, and red blood cells transfused within 48 hours. We included 149 patients receiving frozen plasma and 165 receiving Octaplex. The incidence of serious adverse events for the frozen plasma group was 19.5% compared with 9.7% for the Octaplex group (P=0.014; relative risk, 2.0; 95% confidence interval, 1.1–3.5). This remained significant after adjustment for baseline history and reason for treatment (P=0.038; adjusted relative risk, 1.85; 95% confidence interval, 1.03–3.3) in multivariable regression analysis. Median international normalized ratio reversal was 11.8 hours with frozen plasma and 5.7 hours with Octaplex (P<0.0001). Mean red cell transfusion was 3.2 with frozen plasma and 1.4 with Octaplex (P<0.0001).

Conclusions—Octaplex for urgent reversal of warfarin resulted in faster reversal and lower red cell transfusion requirement with fewer adverse events than frozen plasma. (Circulation. 2013;128:360-364.)

Key Words: anticoagulants ■ critical care ■ emergency service, hospital ■ hemorrhage ■ prothrombin complex concentrates

Warfarin administration has been a standard means of preventing thromboembolism in patients with atrial fibrillation, prothetic heart valves, and venous thromboembolism for >50 years.8 Because of a narrow therapeutic window, as many as 3% to 7% of patients taking warfarin are at risk of major, life-threatening bleeding;2 and it is generally believed that this requires rapid and complete warfarin reversal.3 Current guidelines suggest rapid reversal of anticoagulation with a 4-factor prothrombin complex concentrate in addition to 5 to 10 mg vitamin K intravenously.4 It is believed that the coadministration of vitamin K in this setting prevents rebound increases in the international normalized ratio (INR) and provides sustained reversal of anticoagulation.5

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Frozen plasma and prothrombin complex concentrate are 2 products that are widely used to rapidly achieve replacement of vitamin K–dependent clotting factors.6 Transfusion of frozen plasma for emergency reversal of anticoagulation in the bleeding patient is not ideal. Risks include transmission of infection, allergic reactions, volume overload, incomplete reversal, and increased time to administration because of thawing requirements.5,7 Therefore, reversal of anticoagulation with prothrombin complex concentrate in the patient with major bleeding may be preferable to frozen plasma.8 However, numerous previous studies have reported thromboembolic events in patients treated with prothrombin complex concentrate,1,6,7,9–13 but these studies are limited by their small sample size and lack of a comparison group.

The clinical importance of this subject lies in the fact that administration of prothrombin complex concentrate for emergency reversal of warfarin-induced anticoagulation has become the standard of care at our local tertiary care institutions and at many others, yet we still do not have a complete understanding of the safety profile of these products compared with the previous standard of care, frozen plasma.
The objective of this study is to compare the efficacy and safety of frozen plasma with that of Octaplex, the available 4-factor prothrombin complex concentrate, in our emergency departments (EDs) during the study period. Specifically, we examine adverse effects, time to INR reversal, hospital length of stay, and red cell transfusion requirements.

Methods
Design and Setting
This retrospective cohort study was conducted using health records of patients who were treated with frozen plasma or Octaplex for emergency reversal of warfarin anticoagulation therapy in 2 tertiary EDs at our institution, which see a total of ≈120,000 ED visits per year. We compared patients who received frozen plasma over a 2-year period before the introduction of Octaplex in September 2008 with those who received Octaplex over an equivalent time period after September 2008. The treatments for both groups were given or started in the ED. The dose of Octaplex administered during the study period was governed by the department of Transfusion Medicine. A standard dose of 1500 IU was administered to patients with intracranial hemorrhage, and a dose of 1000 IU was used for all other patients. This study was approved by our institution’s research ethics board.

Study Population
We included patients who were ≥18 years of age, were taking warfarin with an INR of ≥1.5, and had received either frozen plasma or Octaplex in the ED either for active bleeding or before an emergency procedure, whether it was ordered by an emergency physician or consulting service. We excluded patients if they were <18 years of age, if there was no documentation that the patient was taking warfarin, if frozen plasma or Octaplex was administered without an initial INR check, or if they received both frozen plasma and Octaplex within 7 days. There were no predetermined standardized transfusion parameters for either group, and patients who received frozen plasma were assumed to receive usual clinical care with regard to resuscitation and transfusion as determined by the most responsible physician. The standard practice at our institution during the study period was to administer 40 mL Octaplex (=1000 IU prothrombin complex concentrate) and to perform a repeat INR check ≈15 minutes after administration. There were no other changes instituted to patient management over this time period. Because of the retrospective nature of this study, there were no risks imposed on any patients.

Data Collection and Management
Consecutive patients who received frozen plasma over a 2-year period before the introduction of Octaplex were identified by a health records analyst at The Ottawa Hospital using WinRecs software (MED2020 Health Care Software Inc, Ottawa, ON, Canada). Consecutive patients who received Octaplex over a similar period of time were identified by means of an electronic database maintained by the department of Transfusion Medicine that includes all patients who receive Octaplex at the institution. These charts were identified by personnel not directly involved in the study who were unaware of the study design. Once patients were identified, data were collected by means of a review of paper and electronic health records, discharge summaries, diagnostic imaging, and laboratory reports. Data were extracted onto standardized data abstraction sheets by 2 investigators (M.H. and A.A.). The first 15 patients were independently reviewed by a third investigator (M.G.).

Outcome Measures
The primary outcome, incidence of serious adverse events within 7 days of receiving either frozen plasma or Octaplex in the ED, was a composite consisting of the following events: death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism, and peripheral arterial thromboembolism. Secondary outcomes included time to INR reversal (defined by an INR <1.5), hospital length of stay, and number of units of packed red blood cells transfused within 48 hours. Adverse outcomes were defined a priori. Myocardial infarction was defined as per the World Health Organization definition with 2 of the following 3 criteria: documented typical symptoms of infarction, elevation of plasma cardiac biomarkers, and a typical ECG pattern involving the development of Q waves. Ischemic stroke was defined as documented focal neurological deficits consistent with acute ischemic stroke without hemorrhage on neuroimaging. Heart failure was defined as presumed new bilateral pulmonary edema confirmed on a final radiology report of chest radiography combined with documented treatment for volume overload. Pulmonary embolism was defined as confirmed diagnosis on a final radiology report of computed tomography or high-probability ventilation/perfusion scan and treatment with anticoagulation or insertion of an inferior vena cava filter. Deep venous thrombosis was defined as an acute thrombus above the elbow, above the knee, or in abdominal/pelvic veins as confirmed on a final radiology report of a duplex ultrasound. An arterial thromboembolic event was defined as an event confirmed on a final radiology report of conventional or computed tomography angiography or a high suspicion as documented by a vascular surgeon or designate and intervention for the same.

Analysis and Sample Size Calculation
Data were entered into SAS (SAS Institute, Cary, NC) by trained data entry personnel. Baseline characteristics and medical history of study patients were described with mean and standard deviation for continuous variables (median and first and third quartiles for skewed distributions) and frequencies and proportions for categorical variables. Differences between the frozen plasma and Octaplex groups were tested with 2-sample t tests (or Wilcoxon tests) for continuous variables and χ² tests for categorical variables. Differences in the reasons for anticoagulation and reason for treatment between the groups were tested with Fisher exact tests. Variables with either statistically or clinically significant differences between the groups were identified as potential confounders.

The incidence of serious adverse events was compared between the groups with the use of χ² tests (or Fisher exact tests in the case of small expected counts). The relative difference in incidence was described by the use of relative risk and 95% confidence interval. To account for potential confounders, we conducted a multivariable regression analysis with incidence of serious adverse events as the dichotomous dependent variable, group (Octaplex versus frozen plasma) as the primary predictor variable, and all potential confounders entered as covariates. We used modified Poisson regression analysis with robust error variance instead of logistic regression because the effect measure of interest is a relative risk rather than an odds ratio. The modified Poisson regression analysis as described by Zou is easily implemented in standard statistical packages alongside logistic regression by specifying the log-link function, together with the sandwich variance estimator for the regression coefficients. Variables with multiple categories with small counts (eg, indications for reversal) were redefined by combining similar categories before entry in the multivariable model.

Secondary outcomes were compared by the use of 2-sample t tests (or Wilcoxon tests for variables with a skewed distribution).

The sample size was not calculated on the basis of the number of expected outcomes but rather on the basis of the maximum time period for which Octaplex data were available at the time the study was designed.

Results
The Figure depicts the number of patients who were identified and met inclusion criteria for the study. A total of 212 patients were identified in the frozen plasma group and 451 patients in the Octaplex group; 63 and 286 patients, respectively, were excluded, leaving 149 patients who received frozen plasma and 165 patients who received Octaplex in the analysis. The Figure presents details on the excluded patients.
Baseline characteristics for study patients are presented in Table 1. Both groups were similar except more patients in the frozen plasma group had a history of heart failure and ischemic heart disease and more patients in the Octaplex group had venous thromboembolism.

As depicted in Table 2, both groups had similar indications for anticoagulation therapy, with atrial fibrillation being the most common, followed by prophylaxis for an artificial valve and treatment or prophylaxis for previous venous thromboembolism.

Table 3 shows the indications for reversal of anticoagulation in both groups. The majority of patients suffered from gastrointestinal bleeding or intracranial hemorrhage. This pattern is consistent with a recent study that also examined the use of prothrombin complex concentrate in the reversal of warfarin-induced anticoagulation. However, more patients in the plasma group received treatment for intracranial hemorrhage, whereas more patients in the Octaplex group received treatment before a procedure.

Table 4 shows the incidence of each adverse event type observed in the 2 groups. There was a significantly higher incidence of serious adverse events among patients who received frozen plasma (19.5% versus 9.7%; relative risk, 2.01; 95% confidence interval, 1.14–3.54; \( P = 0.0164 \)). Significantly more patients in the frozen plasma group suffered from heart failure after treatment compared with the Octaplex group (2.7% versus 0%; \( P < 0.05 \), Fisher exact test). Full reversal of anticoagulation was significantly more rapid in the Octaplex group, and transfusion requirements for packed red blood cells were significantly lower than in the plasma group (Table 4). Mean hospital length of stay did not differ significantly between groups.

After adjustment for history of heart failure, venous thromboembolism, and ischemic heart disease, as well as indication for reversal (defined as a 4-level categorical variable with the categories of gastrointestinal bleed, intracranial hemorrhage, preprocedure, and other), the incidence of serious adverse events remained significantly higher in the frozen plasma group (relative risk, 1.85; 95% confidence interval, 1.03–3.31; \( P = 0.0384 \); Table 4).

Discussion

We found that the use of Octaplex for emergency reversal of warfarin anticoagulation in the ED achieves reversal faster and is associated with significantly fewer adverse events and lower transfusion requirements. However, hospital lengths of stay were similar between the 2 groups.

**Table 1.** Baseline Characteristics and Past Medical History of Study Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean, SD), yr</td>
<td>76 (11.2)</td>
<td>77 (10.8)</td>
<td>0.664</td>
</tr>
<tr>
<td>Male (%)</td>
<td>81 (54.4)</td>
<td>99 (60)</td>
<td>0.313</td>
</tr>
<tr>
<td>Heart Failure (%)</td>
<td>50 (33.6)</td>
<td>32 (19.4)</td>
<td>0.004</td>
</tr>
<tr>
<td>Venous Thromboembolism (%)</td>
<td>10 (6.7)</td>
<td>22 (13.3)</td>
<td>0.053</td>
</tr>
<tr>
<td>Ischemic Heart Disease (%)</td>
<td>62 (41.6)</td>
<td>52 (31.5)</td>
<td>0.063</td>
</tr>
<tr>
<td>Gastrointestinal Bleed (%)</td>
<td>15 (10.1)</td>
<td>12 (7.3)</td>
<td>0.379</td>
</tr>
<tr>
<td>Hemodialysis (%)</td>
<td>4 (2.7)</td>
<td>6 (3.6)</td>
<td>0.753</td>
</tr>
<tr>
<td>Ischemic Stroke (%)</td>
<td>31 (20.8)</td>
<td>33 (20.0)</td>
<td>0.860</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (%)</td>
<td>13 (8.7)</td>
<td>8 (4.8)</td>
<td>0.170</td>
</tr>
<tr>
<td>Anti-platelet (%)</td>
<td>33 (22.1)</td>
<td>40 (24.2)</td>
<td>0.661</td>
</tr>
<tr>
<td>Initial INR (Median, Q1-Q3)</td>
<td>2.9 (2.2–5.2)</td>
<td>3.0 (2.3–4.5)</td>
<td>0.432</td>
</tr>
<tr>
<td>Reason for Anticoagulation</td>
<td></td>
<td></td>
<td>0.7312</td>
</tr>
<tr>
<td>Atrial Fibrillation (%)</td>
<td>122 (81.9)</td>
<td>126 (76.4)</td>
<td></td>
</tr>
<tr>
<td>Artificial Valve (%)</td>
<td>13 (8.7)</td>
<td>15 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Venous Thromboembolism* (%)</td>
<td>9 (6)</td>
<td>13 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Low Ejection Fraction (%)</td>
<td>2 (1.3)</td>
<td>4 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Previous Stroke (%)</td>
<td>2 (1.3)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
<tr>
<td>Hypercoagulable (%)</td>
<td>1 (0.7)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Unknown (%)</td>
<td>0 (0)</td>
<td>3 (1.8)</td>
<td></td>
</tr>
</tbody>
</table>

*for treatment or secondary prophylaxis of DVT and PE

**Table 2.** Reason for Anticoagulation Reversal Treatment

<table>
<thead>
<tr>
<th>Reason for Reversal Treatment (%)</th>
<th>Frozen Plasma (N=149)</th>
<th>Octaplex (N=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Bleed</td>
<td>63 (42.3)</td>
<td>61 (37.0)</td>
</tr>
<tr>
<td>Intracranial Hemorrhage</td>
<td>44 (29.5)</td>
<td>35 (21.2)</td>
</tr>
<tr>
<td>Pre-procedure</td>
<td>21 (14.1)</td>
<td>37 (22.4)</td>
</tr>
<tr>
<td>Major Trauma</td>
<td>1 (0.7)</td>
<td>4 (2.4)</td>
</tr>
<tr>
<td>Other Bleeding</td>
<td>5 (3.4)</td>
<td>10 (6.1)</td>
</tr>
<tr>
<td>Other</td>
<td>15 (10.1)</td>
<td>18 (10.9)</td>
</tr>
</tbody>
</table>

p-value for difference between groups using Fisher exact test is 0.1398
future research should be done to ascertain the optimal dose of Octaplex to achieve the greatest efficacy while minimizing adverse events.

**Limitations**

There are several limitations to our study. There may have been some unobserved differences between the groups. Although we endeavored to have 2 very similar groups with our design by enrolling consecutive patients in each arm, we may not have been completely successful. Although the groups seem generally well balanced in terms of baseline characteristics, there were more patients in the frozen plasma group with a previous history of heart failure and more patients in the frozen plasma group requiring reversal for an intracranial hemorrhage. We adjusted for these imbalances using multivariable regression analyses and found similar results after adjustment.

Another limitation is that the data were obtained retrospectively. Although retrospective data collection has risks of missing data, the data points collected for our primary outcome and baseline characteristics are reliably available within the medical records. In this retrospective study, we were not able to standardize the timing of the interventions; therefore, there may have been some differences between groups. However, such differences are more likely related to the ease of administration of the frozen plasma or Octaplex because there were no other systematic changes that we are aware of during the study period. Additionally, the timing of INR measurements after administration of frozen plasma and Octaplex was highly variable, despite recommendations in the Octaplex protocol for measurements at 15 minutes, leading to missing time points in our data. We estimate that documentation of effective reversal would have occurred even sooner in the Octaplex group, given its high success rate as measured on first INR.

We limited our follow-up to 7 days because we thought that it would be difficult to attribute a causal link to reversal agents for events occurring outside this time window. In addition, we felt that the majority of patients receiving emergent warfarin reversal would likely still be in hospital or receiving close follow-up during this time period. This would limit the chances of patients having a serious adverse event that was not documented within the health records at our own institution. There is a small risk that some of our patients may have had a serious adverse event that caused their deaths outside the hospital or for which they sought care at another local institution;
however, given that our institution is the only tertiary care center in the region and that most patients were still admitted at 7 days, the likelihood is small. In addition, because of our before-after quasiexperimental design, the likelihood of this is equal in both the frozen plasma and Octaplex groups. Patient outcomes were adjudicated in an unblinded fashion. This may have resulted in some ascertainment bias. We minimized this risk by having a priori definitions of serious adverse events, including clear and strict definitions of each component of this composite outcome. Finally, we excluded patients treated with both frozen plasma and Octaplex. It is possible that more aggressively treated patients may have had different underlying risks for adverse events. The numbers of patients excluded for these reasons were similar, ≈11%, in the 2 groups. Given that this difference is small, we believe that the magnitude of selection bias will be small and unlikely to account for all the differences found.

Conclusions
Our study found that Octaplex administration for emergency reversal of warfarin-induced anticoagulation was faster, led to lower red cell transfusion requirements, and was associated with fewer adverse events than frozen plasma. Our before-after observational study therefore suggests that Octaplex may be superior to frozen plasma when used in this context.

Acknowledgments
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Disclosures
None.

References

**CLINICAL PERSPECTIVE**
This study is the first, to the best of our knowledge, to compare prothrombin complex concentrate with frozen plasma in anticoagulated emergency department patients. Prothrombin complex concentrate is safer and more efficacious for patients with critical bleeding. It is now also used routinely to reverse patients’ warfarin anticoagulation preoperatively, leading to shorter wait times to surgery. Although a cost-benefit analysis was beyond the scope of our study, the baseline cost of a therapeutic dose of prothrombin complex concentrate at our center is lower than that of an appropriate dose of frozen plasma. Centers that currently reverse warfarin anticoagulation routinely with frozen plasma should consider prothrombin complex concentrate as a superior first-line therapy.
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