Results of Octaplex for reversal of warfarin anticoagulation in patients with hip fracture

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Background: Patients with hip fracture who present anticoagulated with warfarin often require reversal of anticoagulation for safe hip fracture surgery. Vitamin K is typically administered for this, but requires 24–48 hours for maximal effect. These patients have an increased delay to surgery and increased mortality. Octaplex is a prothrombin complex concentrate (PCC) that reverses warfarin anticoagulation in less than an hour. This study assesses the effectiveness and safety of Octaplex for reversal of warfarin anticoagulation for hip fracture surgery.

Methods: We reviewed the medical records of all patients with hip fracture in Calgary who received Octaplex between 2009 and 2015. Timing of admission, Octaplex administration and hip fracture surgery were recorded. Mortality and cardiac, thrombotic and orthopedic complications were assessed.

Results: Median time from Octaplex administration to an international normalized ratio of 1.4 or lower was 1.1 hours. The median time from admission to surgery was 22 hours. Thirty-day mortality was 15.2%, with 4 cases of cardiac arrest and 1 respiratory arrest. Patients who received both Octaplex and fresh frozen plasma (FFP) had a lower rate of 30-day survival than those who received only Octaplex (95.7% v. 60.0%, $p = 0.002$).

Conclusion: There were significant rates of cardiac events and 30-day mortality among patients who received Octaplex, but this is unsurprising in this population with multiple medical comorbidities. We caution against administrering both FFP and a PCC in patients for warfarin reversal. Octaplex is effective for rapidly reversing warfarin anticoagulation and reducing delays to hip fracture surgery. Further study comparing Octaplex to reversal using only vitamin K is required.

Contexte : Les patients avec fracture de la hanche qui sont sous anticoagulothérapie par warfarine au moment de consulter ont souvent besoin qu'on inverse leur anticoagulation pour être opérés sans danger. La vitamine K est généralement administrée à cette fin, mais il lui faut de 24 à 48 heures pour exercer son plein effet. Chez ces patients, le délai est plus long avant la chirurgie et la mortalité est plus élevée. Octaplex est un concentré de complexe prothrombique (CCP) qui inverse l'anticoagulation due à la warfarine en moins d'une heure. Cette étude évalue l'efficacité et l'innocuité d'Octaplex pour l'inversion de l'anticoagulation due à la warfarine lors d'une chirurgie pour fracture de la hanche.

Méthodes : Nous avons passé en revue les dossiers médicaux de tous les patients avec fracture de la hanche à Calgary qui ont reçu Octaplex entre 2009 et 2015. Nous avons enregistré le moment de l'admission, de l'administration d'Octaplex et de la chirurgie pour fracture de la hanche. Nous avons évalué la mortalité et les complications cardiaques, thrombotiques et orthopédiques.

Résultats : L'intervalle médian entre l'administration d'Octaplex et l'obtention d'un ratio international normalisé de 1,4 ou moins a été de 1,1 heure. L'intervalle médian entre l'admission et la chirurgie a été de 22 heures. La mortalité à 30 jours a été de 15,2 %, incluant 4 arrêts cardiaques et 1 arrêt respiratoire. Les patients qui ont reçu Octaplex et du plasma frais congelé (PFC) ont eu un taux de survie à 30 jours moins élevé que ceux qui ont reçu Octaplex seulement (95,7 % c. 60,0 %, $p = 0{,}002$).

Conclusion : On a observé des taux significatifs d'événements cardiaques et de mortalité à 30 jours chez les patients traités par Octaplex, mais cela est peu surprenant dans cette population présentant plusieurs comorbidités médicales. Nous formulons une mise en garde contre l'utilisation de PFC et d'un CCP chez les patients soumis à une inversion de l'effet de la warfarine. Octaplex est efficace pour inverser rapidement l'anticoagulation due à la warfarine et accélérer l'accès à la chirurgie pour fracture de la hanche. Il faudra approfondir la recherche et comparer l'inversion par Octaplex plutôt que par la vitamine K seulement.

Hip fractures are a common cause of morbidity and mortality in elderly patients; more than 2400 hip fracture surgeries are performed per year in Alberta.[1] A substantial number of patients with hip fracture present anticoagulated with a vitamin K antagonist (e.g., warfarin) for a number of medical conditions, including atrial fibrillation, venous thromboembolism and mechanical heart valves.[2,3] Reversal of warfarin anticoagulation is necessary for adequate hemostasis during and after hip fracture surgery. An international normalized ratio (INR) of 1.4 or lower permits safe neuroaxial anesthesia and is associated with lower intraoperative and postoperative bleeding risks.[4–6]

Reversal of anticoagulation from warfarin using oral or intravenous vitamin K is superior to simply withholding warfarin in patients with hip fracture.[2,7,8] However, the effect of vitamin K on the normalization of INR is not seen until at least 4 hours after administration, and 24–48 hours are required for maximal effect.[9] However, delays to hip fracture surgery have been shown in multiple studies to increase patient pain, length of stay (LOS), morbidity and mortality.[10] Furthermore, patients with hip fracture who are on warfarin therapy have been shown to have a longer time to surgery, a longer LOS and higher mortality.[11] Fresh frozen plasma (FFP) allows for more rapid reversal of warfarin anticoagulation, but carries significant risks, including fluid overload, transfusion-related acute lung injury and transmission of blood-borne illness.[12]

Octaplex is a prothrombin complex concentrate (PCC) used for emergent reversal of warfarin therapy in patients exhibiting serious or life-threatening bleeding manifestations or patients requiring unplanned/urgent (< 6 h) interventions with risk of bleeding.[13] Octaplex and other PCCs provide rapid reversal of INR (within 15–60 min) with maximal effect for 4–6 hours. With a concentration of clotting factors more than 25 times higher than FFP, Octaplex requires a low volume to be infused (1–2 mL/kg), minimizing the risk of fluid overload and reducing the time required for infusion. As a pasteurized product, Octaplex poses an extremely low risk of disease transmission. Octaplex contains human coagulation factors II, VII, IX and X and proteins C and S, and has been shown to be safe and effective in multiple clinical trials in patients with life-threatening bleeding.[14,15] Other studies have demonstrated the safety of PCCs in other applications including intracranial bleeding[16,17] and before urgent cardiac surgery.[18] Compared with FFP, PCCs more rapidly and completely reverse warfarin anticoagulation while reducing the risk of fluid overload.[19] Although the overall rate of reported thrombotic events has been low, complications of PCC administration, including deep vein thrombosis (DVT), myocardial infarction (MI) and thrombotic stroke, have been reported previously.[19,20] However, most patients who had adverse thrombotic events had comorbidities that may have contributed to their thrombotic risk.

Prothrombin complex concentrate has been recommended for more rapidly reversing warfarin anticoagulation to reduce delays in hip fracture surgery, particularly in patients at risk of volume overload.[21,22] However, patients with hip fracture are a particularly high-risk group, with high mortality and rates of complications including heart failure, DVT, pulmonary embolism (PE), MI and stroke.[23] To our knowledge, there are no studies on the use of Octaplex in patients with hip fracture. Although there is a study showing the effectiveness of PCCs for reversal of acute traumatic coagulopathy in orthopedic trauma patients, it specifically excluded patients taking warfarin before their injury.[24] In the present study, we sought to characterize the effectiveness of Octaplex for the reversal of warfarin anticoagulation in patients with hip fracture.

Methods

We performed a retrospective chart review of all cases of Octaplex use in patients with hip fractures treated in Calgary, Alta., between December 2009 and February 2015. We included patients who had a femoral neck, peritrochanteric, or subtrochanteric hip fracture; presented to hospital with an INR of 1.6 or higher; were taking warfarin for anticoagulation before presentation; were given Octaplex for reversal of INR before hip fracture surgery; and were scheduled to undergo surgery for hip fracture treatment (screw fixation, sliding hip screw, cephalomedullary nail, hemiarthroplasty, or total hip arthroplasty). We excluded patients younger than 18 years and those who had open injuries, neurologic or vascular injury in the affected limb, or pathologic or periprosthetic fractures. We obtained the patient list from a transfusion medicine database of patients who received Octaplex in association with hip or femur fracture surgery or admission. Inpatient paper and electronic medical records as well as initial radiographs were reviewed to remove patients who did not meet the inclusion and exclusion criteria.

The primary outcome measure was the time from Octaplex administration to a measured INR of 1.4 or lower. Other outcome measures assessed are listed in Box 1.

Funding was obtained from the University of Calgary Surgical Research Development Fund. No industry funding was involved in this trial. Approval for the review of medical records was obtained from our institution's Conjoint Health Research Ethics Board.

Statistical analysis

Statistical calculations, including Kaplan–Meier survival analysis, were performed using IBM SPSS version 24. We considered results to be significant at $p < 0.05$.

Results

We identified 33 patients who met our inclusion criteria (Fig. 1). Their demographic and comorbidity data are shown in Table 1. Fracture type and treatment are shown in Table 2. All patients were taking warfarin preoperatively: 26 (82%) for atrial fibrillation and 6 (18%) for previous DVT and/or PE. It is important to note that many of these patients had multiple pre-existing comorbidities, particularly coronary artery disease (55%), congestive heart failure (CHF; 45%) and chronic obstructive pulmonary disease (39%). The mean Charlson Comorbidity Index (CCI) score was 2.82.

Box 1: Outcome measures

Preoperative outcomes
- Time from Octaplex to INR ≤ 1.4
- Change in INR with Octaplex
- Time from Octaplex to surgery
- Time from admission to surgery

Operative outcomes
- Type of anesthesia
- Type of procedure

Postoperative outcomes
- Death within 30 d
- Cardiac complications within 30 d
- Thrombotic complications within 30 d
- Orthopedic complications within 30 d
- Transfusions within 72 h of surgery
- Length of stay

INR = international normalized ratio.

The median time from Octaplex administration to a measured INR of 1.4 or lower was just over 1 hour. This is indicative of the time required for Octaplex infusion and the process of obtaining a repeated coagulation study — theoretically, the onset of action of Octaplex may be as fast as 10 minutes.[15] Table 3 and Table 4 show the results of Octaplex on the INR and time to surgery for our population. A single dose of Octaplex was effective in correcting the INR to 1.4 or lower in 29 patients (88%), with an average dose of 1470 units of Octaplex. Of the 4 remaining patients, 2 required a second dose of Octaplex; 1 underwent surgery with an INR of 1.5 and 1 passed away before surgery. All patients received oral or intravenous vitamin K before surgery, with a mean dose of 19.5 mg (range 5–55 mg) given. Two patients had Octaplex administered after they were brought to the operating room to minimize delays to surgery; therefore, zero hours passed from Octaplex administration to the start of surgery. The median delay from time of admission to surgery was 22 hours.

Spinal anesthesia was used in 20 patients (63%), without any cases of postoperative epidural hematoma. Intraoperative estimated blood loss (EBL) was less than 300 mL in nearly all patients, except for an EBL of 400 mL for a patient undergoing hemiarthroplasty

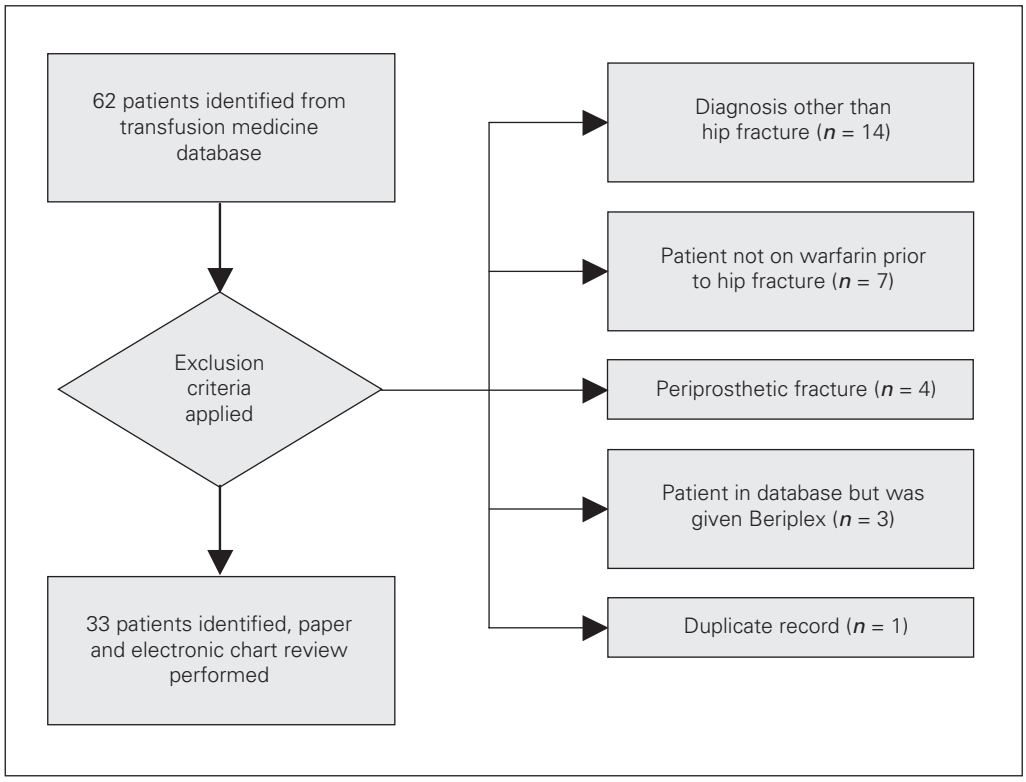

Fig. 1. Selection of patients included in the study.

Table 1. Demographic and clinical characteristics of the study sample

Characteristic	No. (%)*
Sex	
Male	14 (42)
Female	19 (58)
Age, yr; mean ± SD (range)	81 ± 7 (65–95)
Comorbidities	
Coronary artery disease	18 (55)
Congestive heart failure	15 (45)
Chronic pulmonary disease	13 (39)
Cerebrovascular disease	8 (24)
Dementia	7 (21)
Diabetes without complications	6 (18)
Peripheral vascular disease	5 (15)
Diabetes with complications	3 (9)
Severe renal disease	3 (9)
Connective tissue disease	2 (6)
Peptic ulcer disease	2 (6)
Hemiparesis	1 (3)
Moderate or severe liver disease	1 (3)

SD = standard deviation.
*Unless indicated otherwise.

Table 2. Classification and treatment of hip fractures

Fracture	No. (%)
Classification	
Femoral neck fracture	14 (42)
Intertrochanteric fracture	18 (55)
Subtrochanteric fracture	1 (3)
Treatment	
Cephalomedullary nail	15 (45)
Hemiarthroplasty	12 (36)
Sliding hip screw	3 (9)
Cannulated screw	1 (3)
No surgery	2 (6)

Table 3. INR at critical time points during admission

Time point	INR; mean ± SD (range)
Presentation	3.1 ± 1.5 (1.6–9.0)
Before Octaplex administration	2.3 ± 1.6 (1.4–9.0)
After Octaplex administration	1.3 ± 0.2 (1.0–1.9)
Mean change in INR	1.0 ± 1.5 (0.1–7.6)

INR = international normalized ratio; SD = standard deviation.

Table 4. Time course of patients from Octaplex administration to INR reversal and hip fracture surgery

Time course	Mean ± SD (range), h	Median
Octaplex to INR ≤ 1.4	2.2 ± 3.1 (0.5–14.9)	1.1
Octaplex to surgery	8.5 ± 15.8 (0–60.4)	2.6
Admission to surgery	32.5 ± 23.2 (8.4–106.0)	22.0

INR = international normalized ratio; SD = standard deviation.

and an EBL of 800 mL in a patient undergoing cephalomedullary fixation of a subtrochanteric fracture that required open reduction. The overall mean EBL was 244 ± 150.5 mL. Transfusion of packed red blood cells was required intraoperatively or postoperatively in 11 patients (33%), with a range of 0–3 units of blood administered. The median LOS was 11 (range 2–62) days before discharge home or to a rehabilitation facility.

Five out of 33 patients (15.2%) died within 30 days of Octaplex administration or hip fracture surgery, with an overall 30-day survival of 84.8% ± 6.2%. Two patients died before their hip fracture surgery after receiving Octaplex. The first developed electrocardiogram changes consistent with an inferior MI immediately after administration of Octaplex and died shortly thereafter. The second sustained an intraoperative cardiac arrest and died during administration of a spinal anesthetic 6 hours after she received Octaplex. Three patients died within 30 days after hip fracture surgery. Two deaths occurred at 3 and 21 days from a presumed fatal MI or arrhythmia. The final death occurred after the patient experienced a respiratory arrest at their care home 28 days postoperatively. Of these 5 patients who died within 30 days, 4 received both Octaplex and FFP preoperatively.

Ten patients (31%) preoperatively received FFP in addition to Octaplex, and the survival of this subgroup was significantly worse. Seven patients received Octaplex after FFP because of insufficient INR reversal. One

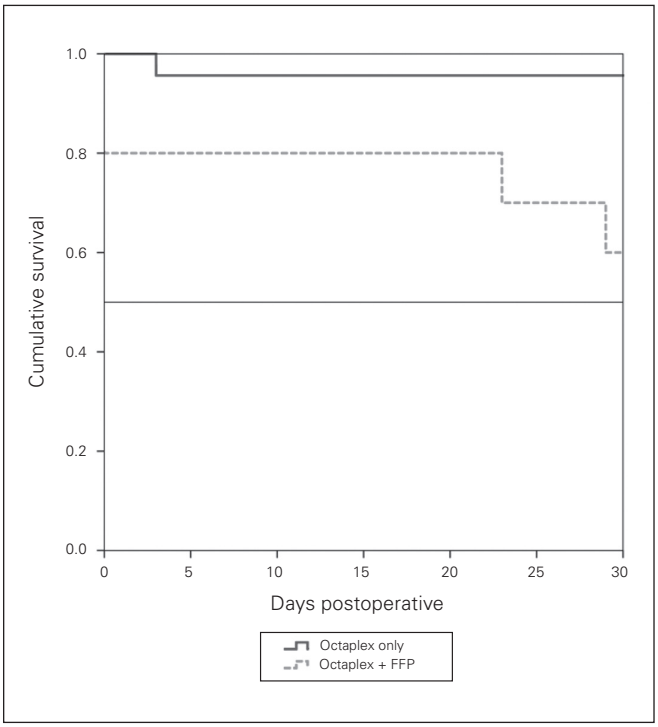

Fig. 2. Kaplan–Meier survival of subgroups who received Octaplex only or Octaplex + fresh frozen plasma (FFP).

patient received Octaplex and FFP simultaneously, and 2 patients received FFP after Octaplex despite a post-Octaplex INR of 1.4 or lower, all for undocumented reasons. In patients who received Octaplex but no FFP, 30-day survival was 95.7% ± 4.3%. However, in patients who received both Octaplex and FFP, 30-day survival was 60.0% ± 15.5%. This difference was statistically significant using a log-rank comparison (p = 0.002). The survival curves are shown in Figure 2. However, these 2 groups are dissimilar in age and comorbidities, as patients who received both Octaplex and FFP were older (mean age 84.1 v. 79.4, p = 0.09) and had more comorbidities (mean CCI score 3.90 v. 2.35, p = 0.049) than those who received only Octaplex.

Aside from the deaths described previously, no other cardiac events were noted postoperatively. No patients experienced CHF between the time of Octaplex administration and their hip fracture surgery. Five patients experienced CHF postoperatively within 30 days of Octaplex administration. Three of these patients were treated with furosemide during their postoperative hospital stay, and 2 required readmission for management of CHF at 20 and 29 days postoperatively. The only venous thromboembolic complication identified was a single case of DVT diagnosed at 7 days postoperatively. No strokes, PEs, or arterial thrombi were identified within 30 days after Octaplex administration.

Three patients experienced orthopedic complications within 30 days of surgery. Two patients had persistent drainage from their surgical wounds after resumption of anticoagulation therapy and were treated with negative pressure wound therapy. This was successful in 1 patient, but the other was readmitted to hospital 22 days postoperatively for a deep infection that required surgical irrigation and débridement followed by home intravenous antibiotic therapy. The organisms identified were *Propionium acnes* and *Staphylococcus aureus* (coagulase negative). The third orthopedic complication involved a patient who had a ground-level fall 29 days after discharge and sustained a periprosthetic fracture around the tip of his long cephalomedullary nail. His fracture was stabilized with a distal femoral locking plate after his anticoagulation was reversed without the use of Octaplex.

Discussion

This case series highlights that patients with hip fracture who receive Octaplex often have a very high perioperative risk profile, with many of our patients having pre-existing coronary artery disease, CHF, or chronic obstructive pulmonary disease. Octaplex provides a rapid and effective method of reversing warfarin anticoagulation, as reflected in previous studies. In this study, Octaplex rapidly corrected the INR to 1.4 or lower in nearly all patients. This allowed for expedited surgery, as shown by a median delay to surgery of less than 24 hours from admission and a median time of 2.6 hours from Octaplex administration to surgery.

Unfortunately a small number of patients in this series had their surgery delayed despite Octaplex administration and INR reversal, usually until the next day to allow for surgeon or operating room availability. Policies to minimize these delays have been enacted in our health region, including better communication between surgical and anesthetic teams to ensure optimal timing for Octaplex administration. As clinician comfort with the use of Octaplex increased during this series, patients were brought to the operating room before or immediately after Octaplex infusion, often without waiting for a repeat INR. This did not result in an increase in intraoperative blood loss or transfusion requirements.

Previous studies have shown the high morbidity and mortality associated with hip fractures.[23,25] The 30-day mortality in the subgroup that received Octaplex but no FFP was 4.3%, which compares favourably to the literature. However, the overall 30-day mortality in this study of 15.2% is higher than previously published in other studies. Nevertheless, our population in this study is particularly high risk, with a very high rate of comorbidities, which may have contributed to the high mortality. We have identified a significantly higher mortality in the subgroup of patients who received both Octaplex and FFP, with a high rate of cardiac events. This may be partially attributed to the older age and increased comorbidities in this subgroup, but we advise caution in administering both a PCC and FFP in patients for warfarin reversal, as this may be associated with higher morbidity and mortality.

Limitations

The primary limitation of this study is the lack of a comparison cohort — a group of patients with hip fracture who did not receive Octaplex for reversal of warfarin anticoagulation. Such a cohort would permit a comparison of time to surgery, morbidity and mortality in patients who did or did not receive Octaplex. In addition, the inpatient and electronic chart review allowed us to identify complications that occurred during the inpatient hospital stay or at another hospital in the local region. However, complications that occurred after the patient was discharged to a remote care facility and that were managed outside of Calgary would not have been identified in this review.

We hope that the results of this study will assist in guiding the conduct of future studies comparing the use of Octaplex to vitamin K with or without FFP for the reversal of warfarin anticoagulation in patients with hip fracture. Using Octaplex will permit much more rapid reversal of warfarin anticoagulation and earlier hip fracture surgery, potentially reducing patient suffering, cost, morbidity and mortality.

Conclusion

Octaplex is quick, safe and effective for the reversal of warfarin anticoagulation in patients with hip fracture. Octaplex reduced delays to hip fracture surgery in these patients, many of whom presented with multiple significant medical comorbidities. Nevertheless these patients remained at high risk, with an overall 30-day mortality of 15.2%. Survival was significantly lower in patients who received both FFP and Octaplex for warfarin reversal, suggesting that coadministration of both FFP and a PCC may be associated with a higher rate of complications. Further study comparing the reversal of warfarin anticoagulation by Octaplex to reversal using only vitamin K will be valuable. Octaplex facilitates earlier surgery in patients with hip fracture with warfarin anticoagulation, potentially reducing morbidity and mortality in this challenging population.

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Competing interests: None declared.

Contibutors: Both authors designed the study. M.-T. Shabani-Rad acquired the data, which both authors analyzed. R. Ng wrote the article, which both authors reviewed and approved for publication.

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