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Clinical Study

Reversal of warfarin associated coagulopathy with 4-factor prothrombin complex concentrate in traumatic brain injury and intracranial hemorrhage

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ABSTRACT

Warfarin-associated intracranial hemorrhage is associated with a high mortality rate. Ongoing coagulopathy increases the likelihood of hematoma expansion and can result in catastrophic hemorrhage if surgery is performed without reversal. The current standard of care for emergency reversal of warfarin is with fresh frozen plasma (FFP). In April 2013, the USA Food and Drug Administration approved a new reversal agent, 4-factor prothrombin complex concentrate (PCC), which has the potential to more rapidly correct coagulopathy. We sought to determine the feasibility and outcomes of using PCC for neurosurgical patients. A prospective, observational study of all patients undergoing coagulopathy reversal for intracranial hemorrhage from April 2013 to December 2013 at a single, tertiary care center was undertaken. Thirty three patients underwent emergent reversal of coagulopathy using either FFP or PCC at the discretion of the treating physician. Intracranial hemorrhage included subdural hematoma, intraparenchymal hematoma, and subarachnoid hemorrhage. FFP was used in 28 patients and PCC was used in five patients. International normalized ratio at presentation was similar between groups (FFP 2.9, PCC 3.1, $p = 0.89$). The time to reversal was significantly shorter in the PCC group (FFP 256 minutes, PCC 65 minutes, $p < 0.05$). When operations were performed, the time delay to perform operations was also significantly shorter in the PCC group (FFP 307 minutes, PCC 159 minutes, $p < 0.05$). In this preliminary experience, PCC appears to provide a rapid reversal of coagulopathy. Normalization of coagulation parameters may prevent further intracranial hematoma expansion and facilitate rapid surgical evacuation, thereby improving neurological outcomes.

1. Introduction

Oral anticoagulation therapy associated intracranial hemorrhage (ICH) carries a nearly 60% 30 day mortality rate, compared to 40% for non-anticoagulated patients [1,2]. Poor outcome in ICH is associated with expansion in hematoma size after admission [3]. While the zone of normal hemostasis can be considered below an international normalized ratio (INR) of 1.7 [4], data in the neurosciences literature suggest that an INR > 1.2 is associated with worse outcomes in ICH [5]. 4-Factor prothrombin complex concentrates (4F-PCC) are shown to reduce INR to < 1.4 within 30 minutes of administration [6]. Specifically, INR was reduced to ⩽ 1.3 in 93% of patients within 30 minutes in the European prospective multinational clinical trial [6] compared to < 10% for fresh frozen plasma (FFP). On average, it takes 8 hours to achieve the same effect with FFP [7]. This is supported by the recent USA-European randomized prospective trial [8]. 4F-PCC, when used with Vitamin K, maintains INR < 1.4 for 48 hours without the administration of other products [6]. Reversal with 4F-PCC has been associated with overall fewer adverse events (death, stroke, myocardial infarction, heart failure, venous thromboembolism, or peripheral arterial thromboembolism) compared to FFP – 9.7% for 4F-PCC *versus* 19.5% for FFP ($p = 0.014$) [9].

4F-PCC contains Factors II, VII, IX and X, and antithrombotic Proteins C and S as a lyophilized concentrate. Kcentra (CSL Behring, King of Prussia, PA, USA) is the only approved 4F-PCC in the USA. It was approved by the Food and Drug Administration on 30 April 2013. Kcentra is produced from human plasma that is purified, heat-treated, nanofiltered and lyophilized into a reconstitutable

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Table 1
Emergency consults requiring the reversal of warfarin

Diagnosis	Total number	Number immediately operative
Traumatic brain injury		
Subarachnoid hemorrhage, GCS 13–15	17	0
Subarachnoid hemorrhage, GCS 9–12	2	0
Subarachnoid hemorrhage, GCS < 9	2	2
Contusion, GCS 13–15	5	2
Contusion, GCS 9–12	3	3
Contusion, GCS < 9	2	2
Acute subdural hematoma < 5 mm thick	4	0
Acute subdural hematoma 5–10 mm thick	2	1
Acute subdural hematoma > 10 mm thick	2	2
Cerebellar hematoma		
<1 cm without hydrocephalus	1	0
>1 cm with hydrocephalus	2	2
Chronic subdural hematoma	8	0
Aneurysmal subarachnoid hemorrhage	2	2
Intraparenchymal hematoma (supratentorial)	9	2
Spinal epidural hematoma	1	1
Other neurosurgical emergencies		
Ventricular shunt failure	2	2
Hydrocephalus requiring external ventricular drain placement	1	1
Total	44	20

GCS = Glasgow Coma Scale.

powder. One mL of reconstituted Kcentra contains approximately the same factor activity as 10 mL of FFP. According the manufacturer, common adverse events with Kcentra include headache, nausea/vomiting, arthralgia, and hypotension. Contraindications to Kcentra use include known anaphylactic or severe systemic reactions to heparin, human albumin, or any of the clotting factors, disseminated intravascular coagulation, and heparin-induced thrombocytopenia.

2. Methods

Following institutional board approval, we assessed 1400 consecutive emergency department neurosurgery consults at our institution, isolated the consults for intracranial and spinal hemorrhage, and categorized them by type (Table 1). Three point one percent of consultations from the emergency department involved reversal of warfarin in the setting of acute neurosurgical pathology. We then assessed the number of each category that required operative intervention. Forty five percent of these patients ultimately required operative or procedural (external ventricular drain, intracranial pressure monitor) intervention within the first 24 hours of hospitalization. On this basis, we have devised general recommendations on intracranial pathology types for which PCC should be used (Table 2).

3. Results

Five patients with acute ICH were treated with 4F-PCC since its approval, comprising one operative acute subdural hematoma, one non-operative posterior fossa hematoma, one non-operative subdural hematoma, and two non-operative intraventricular hemorrhages (Table 3). All patients had an initial INR > 2.0, which was corrected to $\leqslant$ 1.2 in all patients. In the operative cases, the average time from patient arrival in the emergency department to correction of INR (defined as INR < 1.6) was 161 minutes and time to anesthesia induction in the operating room was 159 minutes. The average time from administration of 4F-PCC to corrected INR was 65 minutes. With FFP, the average time to correction of INR to < 1.6 was 256 minutes and time to operating room was 307 minutes. Long-term outcomes remain to be determined in several of these patients.

4. Discussion

There is ample evidence in the literature that warfarin-associated ICH is associated with worse outcomes and the rapidity of intervention may be an important ultimate predictor of outcome. As previously outlined, oral anticoagulation therapy associated ICH carries a nearly 60% 30 day mortality rate, compared to 40% for non-anticoagulated patients [1,2], and indeed poor outcome in ICH is associated with expansion in hematoma size after admission [3].

The literature strongly suggests and our initial findings support the notion that 4F-PCC more rapidly corrects INR and allows neurosurgeons to take patients with acute intracerebral hemorrhage for surgery in a more timely fashion. While PCC appears effective in specifically reversing warfarin-associated coagulopathy, it has no role in the reversal of newer oral anticoagulants, such as dabigatran [10]. While there are no data to show that 4F-PCC improves outcomes in patients with acute ICH in the setting of warfarin-associated coagulopathy, study is underway.

On this preliminary basis, we have devised general recommendations on the use of PCC (Table 2). The general guiding principle in formulating these guidelines was the use of PCC in patients with a high potential to require operative intervention, in an attempt to facilitate rapid and safe surgical intervention. Alternatively, we consider the use of PCC in situations where rapid coagulopathy reversal may avert surgical intervention by arresting the growth of an intracerebral hemorrhage.

To our knowledge, there are two major prospective randomized clinical trials in the literature regarding the use of PCC. In addition,

Table 2
General recommendations for use of 4-factor prothrombin complex concentrate for intracranial hemorrhage with warfarin-associated coagulopathy

1. Any patient suffering from head trauma with an initial or current GCS < 9 (severe TBI) with an abnormal head CT scan (e.g. skull fracture, hydrocephalus, intracranial hemorrhage of any size).
2. Any patient suffering from head trauma with intracranial hemorrhage of any size and initial or current GCS < 13 (moderate or severe TBI).
3. Any patient suffering form intracranial hemorrhage that meets, or is at risk of meeting, criteria for urgent or emergent neurosurgical intervention, regardless of presenting or current GCS. Examples:
   - Acute subdural hematoma $\geqslant$ 3 mm in size
   - Epidural hematoma of any size
   - Cerebellar hematoma of any size
   - Cerebral intraparenchymal hematoma or hemorrhagic contusion > 1 cm in diameter in any plane or > 30 cc in volume
   - Fourth ventricle hemorrhage
   - Aneurysmal subarachnoid hemorrhage
   - Multifocal traumatic subarachnoid hemorrhage
4. Any patient scheduled to undergo an emergency neurosurgical procedure within a 4 hour time period.

cc = cubic centimeter, GCS = Glasgow Coma Scale, TBI = traumatic brain injury.