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Brief Reports

ANTICOAGULATION REVERSAL WITH PROTHROMBIN COMPLEX CONCENTRATE IN ANEURYSMAL SUBARACHNOID HEMORRHAGE

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☐ **Abstract—Background: Intracerebral hemorrhage is a well-recognized complication of anticoagulation therapy. However, there are only a few reports that address the management of aneurysmal subarachnoid hemorrhage (aSAH) in anticoagulated patients. Objective: We report on our experiences with the use of prothrombin complex concentrate (PCC) for rapid anticoagulation reversal in aSAH. Methods: We retrospectively analyzed our institutional database of consecutive patients who received PCC between February 2006 and August 2014 (n > 1000). Data from all anticoagulated patients referred to our hospital for aSAH and those who received PCC were included in this analysis. Patient characteristics as well as treatment modalities were analyzed, with specific focus on results of laboratory examination, PCC administration and bleeding, and thromboembolic complications during the later course. Results: In total, only 9 patients (< 1% of all aSAH patients treated at our institution during the study period) had been anticoagulated at admission. Median international normalized ratio (INR) of patients at admission was 2.31 (interquartile range [IQR] 1.83–2.97) and after median administration of 2500 IU (IQR 2000–3000 IU) PCC, median INR significantly decreased to 1.15 (IQR 1.07–1.19). Surgical and interventional procedures were initiated within a median of 3.9 h (IQR 1.7–9.3 h) after admission. No hemorrhagic or thromboembolic events occurred later in the course. A favorable outcome according to the Glasgow Outcome Scale (scores of 4 and 5) was achieved in 6 patients (67%). Conclusions: Aneurysmal SAH in anticoagulated patients is a rare condition. PCC is an effective option to rapidly reverse anticoagulation in aSAH and might facilitate achieving a favorable outcome in these patients.** © **2015 Elsevier Inc.**

☐ **Keywords—phenprocoumon; warfarin; anticoagulation reversal; hemostasis; cerebral aneurysm**

INTRODUCTION

Subarachnoid hemorrhage (SAH) accounts for approximately 5% of all strokes. As the population ages, anticoagulation therapy with vitamin K antagonists (VKA) is used increasingly in patients for the prevention of thromboembolic events. Although intracerebral hemorrhage (ICH) is a well-recognized complication of anticoagulation therapy, there is little evidence regarding anticoagulated patients with aneurysmal subarachnoid hemorrhage (aSAH). In aSAH, active bleeding during imaging studies has been associated with an unfavorable outcome in patients (1). Coagulation plays a key role in the pathophysiology of aSAH, and impaired hemostasis due to anticoagulation therapy can promote active bleeding (2). It seems reasonable to rapidly reverse anticoagulation effects in order to prevent aneurysm re-rupture in aSAH. In addition, the majority of aSAH patients have to undergo urgent surgical treatment (e.g., insertion of external ventricular drain, microsurgical clipping) and sufficient hemostasis must be established before surgery. Options to reverse

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anticoagulant effects include transfusion of fresh-frozen plasma and administration of activated recombinant factor VII or prothrombin complex concentrates (PCCs). PCCs enable a rapid correction of hemostasis without the need for excessive volume supply, and their use has been implemented in European guidelines for the reversal of anticoagulation in cases of life-threatening bleeding complications (3). Several studies have demonstrated high efficacy and a good safety profile of four-factor PCC for anticoagulation reversal in patients with ICH (4).

In this article, we summarize our experience with the use of four-factor PCC to rapidly restore hemostasis in anticoagulated patients with aSAH. Modalities, timing, and dosage of PCC administration are analyzed, as well as the impact on hemostatic parameters as assessed by laboratory examination. The patients' later courses are studied with specific focus on hemorrhagic/thromboembolic complications and clinical short-term outcomes on the Glasgow Outcome Scale (GOS).

METHODS

This study was approved by the Institutional Review Board at the study institution (S-490/2014). Data from all anticoagulated patients referred to our hospital for aSAH who received PCC from February 2006 to August 2014 were included in this analysis (n = 9). Patients with traumatic and nonaneurysmal SAH were not included. Data were retrospectively obtained from the medical charts of patients. All patients admitted to our department are subjected to examination of blood samples, including full blood count, glucose, electrolytes, urea, creatinine, activated partial thromboplastin time, and prothrombin time. For anticoagulation reversal, three different PCC products were used: Beriplex P/N 500® (CSL Behring GmbH, Marburg, Germany), Octaplex® (Octapharma, Langenfeld, Germany), and PPSB-Human SD/Nano 600® (Octapharma). In order to establish sufficient hemostasis, PCCs were administered as soon as possible to achieve an international normalized ratio (INR) levels of ≤ 1.3 according to manufacturer's instructions. As a standard procedure for anticoagulation reversal, vitamin K was administered intravenously in order to avoid a delayed VKA-associated rebound increase of the INR. All patients underwent digital subtraction angiography (DSA) before surgical or interventional aneurysm treatment. During the patients' later course, diagnostic procedures for thromboembolic or hemorrhagic events were carried out if corresponding clinical symptoms occurred. All patients received low-molecular-weight heparin (Enoxaparin, Clexane®; Sanofi, Frankfurt, Germany) in addition to compression stockings.

For statistical comparison of INR values before and after PCC administration, we used the Mann-Whitney U test (GraphPad Prism 5; GraphPad Software, La Jolla, CA).

RESULTS

Patient Characteristics

Nine patients were included in this analysis. Patient characteristics and modalities of PCC administration are summarized in Table 1. All patients had evidence of SAH on computed tomography imaging and DSA had demonstrated a corresponding cerebral aneurysm. Patients presented with a median World Federation of Neurological Surgeons score of 4 (°I, n = 2; °II, n = 1; °III, n = 1; °IV, n = 3; and °V, n = 2). DSA imaging revealed cerebral aneurysms of the anterior communicating artery (n = 4), middle cerebral artery (n = 3), and posterior communicating artery (n = 2). An external ventricular drainage through burr-hole trepanation was inserted in 8 patients. Aneurysm closure was achieved through microsurgical clipping (n = 6) or interventional coil embolization (n = 2). On admission, patient number 5 had signs of cerebral herniation and, after placement of an external ventricular drainage that demonstrated excessive intracranial hypertension, treatment was transitioned to comfort measures only.

Laboratory Parameters and Modalities of PCC Administration

Median initial INR was 2.31 (IQR 1.83–2.97). PCC were administered with a median dose of 2500 IU (IQR 2000–3000). After PCC administration, median INR significantly decreased to 1.15 (IQR 1.07–1.19; $p < 0.0001$) (Figure 1). Median time from PCC administration to surgical procedures was 3.9 h (IQR 1.7–9.3 h) (Figure 2).

Outcome

Two patients died from cerebral herniation, one of these after development of cerebral vasospasms during in-hospital treatment. No hemorrhagic complications occurred and no signs of thromboembolic events were observed in patients. At hospital discharge, 3 patients (33%) had a favorable outcome (GOS 4 and 5). All patients were transferred to neurologic rehabilitation facilities. Short-term outcome (range 3–18 months) was favorable (GOS 4 and 5) in 6 patients (67%) and unfavorable (GOS 1 and 3) in 3 patients (33%).

DISCUSSION

Literature on the management of anticoagulated patients with aSAH is scarce. A major finding of our analysis is