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Full Length Article

Periprocedural warfarin reversal with prothrombin complex concentrate☆

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ABSTRACT

Introduction: Approximately 10% of chronically anticoagulated patients require an invasive procedure annually. One in 10 procedures is emergent and requires prompt anticoagulation reversal. The study objective is to determine the safety and efficacy of a 3 factor prothrombin complex concentrate (PCC) for periprocedural anticoagulation reversal.

Materials and Methods: Consecutive patients receiving 3 factor PCC for warfarin reversal for either urgent/emergent invasive procedures or major bleeding were analyzed. Primary endpoints included percent achieving INR <1.5, peri-operative major hemorrhage, thromboembolism and death during the 40 day post-infusion period.

Results: Between January 1, 2010–December 31, 2012, 52 patients were treated with PCC for pre-procedural warfarin reversal and 113 patients for major bleeding. Within the peri-procedure group, there were 24 intra-abdominal surgeries, 12 percutaneous interventions, 6 cardiothoracic surgeries, 5 orthopedic and 3 endoscopic procedures. INR values <1.5 were achieved in 51% at 2.5 h post-infusion. Major bleeding (13%), thromboembolism (13%) and mortality rates (15%) were high. Within the major bleeding group, PCC therapy reversed INR values (<1.5) in 75% of patients within 4 h. For this group, thromboembolism (21%) and mortality rates (16%) were likewise high. Post-PCC anticoagulation, reinitiated in 37%, had no impact on bleeding or thrombotic complications. Mortality rates were threefold higher for those patients not restarting warfarin therapy.

Conclusions: Although PCC therapy promptly and effectively reverses INR values for patients requiring urgent/emergent invasive procedure both thromboembolic and fatal complications are soberingly high and call for judicious use of these agents in these high risk populations.

1. Introduction

Between 6 and 8 million Americans currently receive long term anticoagulation for the indications of atrial fibrillation, venous thromboembolism, and mechanical heart valve prostheses [1]. Each year, approximately 10% of patients receiving chronic anticoagulation require an invasive procedure for which anticoagulation must be temporarily discontinued [2,3]. One in ten of these procedures involve an urgent or emergent intervention [2]. A safe, effective, and rapidly acting reversal agent would be clinically useful for the management of these patients.

Prothrombin complex concentrates (PCCs), are highly purified concentrates of coagulation factors which are broadly divided both by number of factors as well as activation state. There are currently two FDA approved "non-activated" PCCs for use in the United States. These PCCs contain either three factors (factor II, IX and X; eg. Bebulin) or four factors (Factor II, VII, IX and X in addition to protein C and protein S; eg. Kcentra). Prothrombin complex concentrates are the guideline endorsed preferred agent for warfarin reversal [4–6]. These recommendations are largely driven by published experience with these agents in the setting of major bleeding, in particular intracranial hemorrhage. Despite these preferences, there are limited data providing outcomes of warfarin reversal with PCCs for urgent or emergent procedures [7].

The aim of this study was to assess the efficacy and safety of warfarin reversal with a three factor PCC (Bebulin) in the setting of urgent or

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emergent invasive procedures. These results were compared to a cohort of patients receiving PCC for the treatment of warfarin associated major hemorrhage. During the time interval of this study, the only FDA approved PCC was Bebulin.

2. Methods

2.1. Patient recruitment

In this retrospective study, all warfarin treated patients receiving the 3 factor PCC, Bebulin (Baxter, Deerfield, IL), from Jan. 1, 2010 through Dec. 31, 2012 were included. To promote the appropriate and unified use of PCCs, a Mayo Clinic guideline was established and distributed across campuses within the Mayo Foundation. Patients were identified using the Data Discovery and Query Builder tool and the Mayo Clinical Notes Search tool. Patients were stratified into one of two groups based on indication for PCC use. The first group consisted of patients requiring "urgent or emergent" invasive procedures. Patients suffering major hemorrhage in the setting of warfarin therapy constituted the second group. Patients were excluded if they had not provided research consent or received other reversal agents (FEIBA, factor IX concentrate, or recombinant factor VII). In addition, patients were excluded if there was inadequate serial laboratory assessment of pre and post PCC infusion or patients who received PCC for indications other than warfarin reversal.

All data were collected from a centralized system that contains complete records of all patients treated and followed at Mayo Medical Center. The Mayo Clinic medical record for each patient contains the details for every inpatient hospitalization, every outpatient visit regardless of the provider, every radiology examination and all laboratory and pathology results (including autopsy reports), death certificates and relevant correspondence. The duration of follow-up extended from the time of the first PCC infusion up to 40 days after the last PCC infusion. Causes of death were determined by a review of medical records, death certificates and autopsy results, when available. The study was approved by the Mayo Clinic Institutional Review Board.

2.2. Study definitions and event adjudication

The International Society on Thrombosis Hemostasis has adopted reporting standards for periprocedural bridging therapy in order to facilitate across-study comparisons and enable meta-analysis. [8] A time frame of 30 days post procedure was recommended. Due to the severity of presentation and concern for missing late events, we have added 10 days to this number. Most events however occurred within 30 days of PCC delivery.

Prothrombin time (PT) and the derived international normalized ratio (INR) were performed as previously published using the RecombiPlasTin 2G (R2G), (Instrumentation Laboratories, Bedford, MA) on the Stago STA Compact or STA-R Evolution coagulation analyzers (Stago, Parsipanny, NJ) [9]. The "pre" INR was defined as the initial INR obtained at the time of clinical presentation either at the referring hospital or at our institution prior to the initiation of PCC or FFP. The "post" INR was defined as the nadir INR obtained following reversal therapy. The "time to INR" was defined as the interval between the initiation of reversal therapy and the nadir INR. Reversal therapy could have included vitamin K (oral or intravenous), fresh frozen plasma in addition to PCC at the discretion of the treating team of health care providers.

Thrombotic events were a priori categorized as either venous or arterial including the vascular territory involved as previously defined [10–14]. Venous thrombotic events included deep venous thrombosis (DVT), pulmonary embolism (PE), or atypical venous thrombosis occurring within venous segments such as cerebral venous sinuses, mesenteric, renal, ovarian or retinal veins. DVT had to be confirmed either by duplex ultrasonography, venography, CT, MRI, or pathology examination of thrombi removed at surgery or autopsy. PE had to be confirmed by pulmonary angiography, contrast enhanced CT, MRI or pathology examination of thrombus removed at surgery or autopsy, or a ventilation–perfusion lung scan interpreted as "high probability". Arterial thrombotic events included unstable angina, myocardial infarction, stroke/transient ischemic attack (TIA) or peripheral embolism [15,16]. Stroke and TIA were defined as a focal neurological deficit of acute onset, persisting for >24 h and ≤24 h respectively, that could not be attributed to another disease process, and with no evidence of intracerebral hemorrhage by computed tomography or magnetic resonance imaging of the head or autopsy, if performed. Amaurosis fugax was defined by the characteristic clinical history and physical examination as recorded in the medical record. Peripheral arterial embolism was defined by appropriate imaging studies.

A major hemorrhage was defined as bleeding resulting in a fall in hemoglobin ≥2 g/dL, hemorrhage requiring transfusion ≥2 units of blood, or intraocular, intracerebral, or retroperitoneal hemorrhage [17]. Clinical stability was defined by hemostatic measures, radiographic imaging, and clinical assessment. Hemostatic stability was defined as normalization of clotting times in addition to the absence of clinical and laboratory measures of continued major blood loss. For the purposes of intracranial hemorrhage, stabilization was defined by reviewing serial brain cross-sectional imaging (brain computed tomography, brain magnetic resonance imaging). Clinical stability for other bleeds was determined by assessing serial hemoglobin values, transfusion requirements, serial cross-sectional imaging showing bleed stabilization, and review of the medical record for opinions of health care providers caring for the patient.

2.3. Statistical analysis

Data was entered into an excel sheet (Microsoft Corporation, Redmond, WA) and descriptive statistics were calculated. All values are presented as mean ± SD. Non-paired Students t-test was used to compare clinical variables between groups. The 40 day cumulative incidence rates for first events of TE, major bleeding, and survival were estimated using the Kaplan–Meier product limit method. The distribution of vitamin K dosing was assessed by the Shapiro–Wilks test. Statistical significance was set at $p < 0.05$.

3. Results

Over the two year time period of this study, 262 patients received Bebulin therapy at our institution. Of these 165 met study inclusion criteria and 94 patients were excluded based on pre-defined exclusion criteria. Stratified by PCC indication, 52 patients required warfarin anticoagulation reversal for an invasive procedure and 113 patients were treated for major bleeding (Table 1). There were no differences in gender, age distribution or indication for chronic anticoagulation between groups. Most patients in both groups had atrial fibrillation as a warfarin indication. Within the periprocedural group, mechanical heart valves were numerically, though not significantly, more common compared to venous thromboembolism as a reason for warfarin therapy. By comparison, VTE was numerically more common compared to mechanical heart valves for those suffering a major bleed.

Within the peri-procedure group, the types of procedures consisted of intra-abdominal surgeries (n = 24), percutaneous interventions (n = 12), cardiothoracic surgeries (n = 6), orthopedic (n = 5), and endoscopic (n = 3) procedures. Of these, 42 were deemed truly urgent based on retrospective review. Notably, there were no neurosurgical cases in this cohort. Within the major bleeding group, the most common bleeding location was intracranial (n = 73) followed by intrathoracic (n = 17), gastrointestinal (n = 14) and retroperitoneal (n = 5) sites. Bleeding into a limb and extracranial sites made up the remainder (n = 4).