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Challenging Management of Warfarinised Patients with Intracranial Hemorrhage Following a Head Injury: A Major Medical Dilemma

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ABSTRACT

Introduction: The use of anticoagulant and antiplatelet medications, especially warfarin and clopidogrel, is on a growing trend. Warfarin usage is commonly accompanied by hemorrhagic complications resulting in a noticeable mortality rate. Patients anticoagulated with warfarin suffers from intracranial hemorrhage after a head injury.

Material and Methods: For the purpose of the study, the relevant articles published from 1966 to January 2017 were searched in several databases, including of Medline, Scopus, Google Scholar, and MEDLINE (through PubMed). The search process was performed using the following medical subject headings: "Warfarin" combined with "Warfarin-associated hemorrhage", "Head injury and warfarin-related intracranial hemorrhage", "Intracerebral hemorrhage", and "Treatment of coagulopathy".

Results: The search process resulted in the inclusion of 242 articles. According to the results of the reviewed studies, the best treatments for the reversal of coagulopathy in warfarinised patients in elective or urgent conditions following a head injury are prothrombin complex concentrate (PCC) and fresh frozen plasma, along with vitamin K, based on the discretion of the treating physician.

Conclusion: According to the studies, the administration of PCC or any other treatments with a similar or close formulation to PCC is significantly more effective and faster in the reversal of coagulopathy and reduction of international normalized ratio in comparison with the use of fresh frozen plasma or other therapies in warfarinised patients admitted with serious intracranial hemorrhage following a head injury. Delivery of an effective treatment to these patients can be accomplished by planning for medical interventions, decreasing time delays for operations, and selecting a suitable or alternative treatment.

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Introduction

The use of anticoagulant and antiplatelet medications, such as warfarin, aspirin, and

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clopedrigrol (Plavix and Osivix), in patients undergoing cardiac surgery, especially mechanical heart valve replacement and other open-heart surgeries (e.g., coronary artery bypass grafting), is steadily increasing and becoming mandatory (1, 2, 3).

Life-threatening warfarin-associated hemorrhage, such as warfarin-related intracerebral hemorrhage, is a common complication, which results in a high mortality rate. The anticoagulated patients are prone to intracranial hemorrhage (ICH) after a head injury (3). In a study, no difference was obtained between the two patient groups using warfarin or dabigatran in terms of mortality and length of stay in the hospital or intensive care unit (3). However, in the mentioned study, the patients on warfarin had a higher rate of ICH (13%), compared to those using dabigatran (8.3%) (3).

The present study was conducted to review the evidence on the reversal of warfarin-associated coagulopathy in hemorrhagic patients with a severe head injury. Most of ICH cases are associated with the use of anticoagulants, such as warfarin (4, 5). In addition, clopedrigrol and other antiplatelet drugs can lead to ICH after a head injury. Head injury has resulted in a high early mortality rate (around 50%) in recent years (6). Treatment of coagulopathy-associated hemorrhage with warfarin in patients with multiple trauma requires a multidisciplinary approach and cooperation among trauma surgeon, cardiologist, and anesthesiologist, especially with regard to the fatality of ongoing hemorrhage (7, 8).

According to the evidence, warfarin enhances the risk of bleeding (9), which usually continues for more than 12-24 h. Neurosurgeons involved in the emergency management of anticoagulant-treated patients presenting with an intracerebral hemorrhage/ICH should perform the urgent correction of coagulopathy to prevent the deterioration of hemorrhage (7-9).

Pregnant women with prosthetic heart valves are the other target group in which the reversal of warfarin-associated coagulopathy is of paramount importance. It is suggested that the consumption of more than 5 mg warfarin can result in abortion. Accordingly, these cases are managed by administering warfarin at a low dosage (5 mg), hospitalization, and heparin therapy (10). A number of therapies have been used alone or in combinations for the treatment of anticoagulant-associated intracerebral hemorrhage to reverse coagulopathy to achieve hemodynamic stability, limit hematoma expansion, and prepare the patient for a potential neurologic surgery (11).

The reversal of coagulopathy with fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC) has been tested mainly in non-trauma settings (7). The idea of "damage control resuscitation" has been adopted in recent decades. This approach includes an early aggressive prescription of blood products, such as FFP, packed red blood cells, and platelets (12-14). This measure decreases the complications of coagulopathy (13-16). However, the administration of FFP and platelets can increase the risk of volume overload, infection, or other potential side effects (17, 18). With this background in mind, the present study was conducted to review the evidence on the management of warfarinised patients with head injury and mechanical heart valves.

Materials and Methods

The relevant articles published from 1966 to January 2017 were searched in several databases, including Medline, Scopus, Google Scholar, and MEDLINE (through PubMed). The search process was performed using the following medical subject headings: "Warfarin" combined with "Warfarin-associated hemorrhage", "Head injury and warfarin-related intracranial hemorrhage", "Intracerebral hemorrhage", and "Treatment of coagulopathy". The search of the databases resulted in the identification of 242 articles related to the subject of interest.

Results

The use of warfarin and other anticoagulants, such as Plavix, by patients with a head injury can be accompanied by developing hematoma expansion in ICH (19). This condition occurs in 40% of patients with head injury in the first few hours following symptom onset (5, 20). There are multiple studies comparing the effects of different blood products on reducing international normalized ratio (INR) level in patients with warfarin-associated ICH to identify the therapy facilitating a better and faster correction of INR.

Comparison of prothrombin complex concentrate and fresh frozen plasma as clotting factor concentrates

The application of PCC (factor IX complex) in medical domain was initiated in 1960 (4). This medication is made of human plasma and contains blood clotting factors II, IX, and VII. It is used to treat and prevent bleeding in hemophilia B and warfarin-associated bleeding. Common side effects of PCC include allergic reactions, headache, vomiting, heart attack, and pulmonary embolism (4, 7). In a study, the patients were subjected to PCC administration with a specific factor VII concentrate or Prothromplex T (Immuno, Vienna), they reported the higher

efficiency of this medication than FFP at reserving factors II, VII, IX, and X (21).

In another retrospective study, it was reported that PCC is significantly faster in INR normalization than FFP (4 h vs. 7 h) (22). Furthermore, in a prospective study performed by Cartmill et al., the PCC group had a significantly faster and more complete reversal, compared to the FFP group (23). In a randomized control study comparing the correction of coagulopathy with FFP alone and FFP along with factor IX complex concentrate (FIXCC=similar to other PCC formulations) in patients with acute ICH, there was a significant difference between the two groups regarding the time and rate of correction (P<0.03). (24).

Factor IX complex is a safe and good agent for the correction of coagulopathy in patients with hemophilia (25). In this regard, in a retrospective study carried out by Safaoui et al. on patients with warfarin-induced coagulopathy, the administration of factor IX complex was reported to significantly reduce INR from 5 to 1.9 without any thrombotic events or allergic reactions after 13.5 min (25). Time of coagulopathy correction is a significant determinant of 24-hour coagulopathy reversal (26).

In a number of studies, the administration of PCC for the management of warfarin-associated ICH (from coagulopathy) was reported to result in thrombosis and early mortality in 7% (out of 57 cases) and 24% of the patients, respectively. Furthermore, seven patients in these series had the subsequent enlargement of ICH and deterioration of this condition (27-29). Many experts suggest minimizing hematoma expansion in the initial 72 h after ICH with careful monitoring to keep the INR level normal (5).

Thromboembolic Events

Majeed et al. identified a reduction in thromboembolic events after treatment with 4-factor PCCs with an incidence rate of 3.8% (30). In a study performed by Leissinger et al. reviewing 14 studies with a total of 460 patients, thrombotic complications occurred in 1.8% of the cases after receiving PCC (31). In another study, Joseph investigated 45 patients with trauma-induced coagulopathy who received PCC (Profilnine SD). In the mentioned study, INR decreased from 2.0 to 1.4, and a significant reduction was observed in packed red blood cells following the administration of PCC. However, no INR variation was observed in the packed red blood cell group (32).

In a prospective and observational study, Yanamadala et al. investigated patients undergoing the reversal of coagulopathy-associated ICH. In the mentioned study, 33 patients underwent an emergency reversal of warfarin-related coagulopathy. The PCC group had a shorter reversal time, and also a shorter time delay to perform operations (33).

Barilari et al. conducted a retrospective study to evaluate the use of PCC in 47 patients divided into two groups, including patients needing homeostatic treatment prior to neurosurgery after head trauma (n=23) and patients with critical hemorrhage due to the overdose of oral anticoagulants (n=24). They obtained similar results to those of Yanamadala et al. (34).

On the other hand, in a retrospective study carried out by Toth, warfarin reversal was audited in 131 consecutive patients. He found significant delays in the transfusion of vitamin k and PCC (3.6-5.2 h). The time durations were 2.7 and 3.0 h in ICH and 17.4 and 15.9 h in emergency procedures. In the mentioned study, the overall mortality rate caused by bleeding was estimated at 7.6%; furthermore, this rate was reported as 22.8% in patients with ICH. Accordingly, Toth concluded that intravenous vitamin K alone may be sufficient in many cases. He also suggested to avoid administering PCC by better planning (34). Based on the evidence, warfarinised patients have a high rate of mortality. As the reviewed studies indicated, PCC stocks should be available in emergency departments to prevent such events. It was also recommended to use PCC transfusion in patients with a strong suspicion of ICH and clear evidence of trauma (35). Administration of prothrombin complex concentrates versus fresh frozen plasma Warfarin inhibits the production of vitamin K-dependent clotting factors; therefore, the patients with warfarin-associated ICH should be subjected to clotting factor depletion. The FFP and PCC are two therapeutic options for the depletion of clotting factors (36). The FFP contains all coagulation factors in a non-concentrated form. This blood product is more universally available at hospitals, especially in the US, compared to PCC (36). However, it is stored frozen and requires at least 15 min to thaw (37).

Large FFP volumes (800-3, 500 ml) are often needed to treat a serious hemorrhage, which may result in acute decompensated heart failure in patients with heart valve diseases and ventricular dysfunction (24). The PCC contains not only coagulation factors, such as II, VII, IX, and X but also proteins C, S, and Z (37). The mean volume of FFP for correction in an average adult patient weighing 70 kg is about 1050 ml (38), and with these volumes of FFP, patients are at the risk of volume overload (39). The optimal PCC dosage is calculated according to patient's age and body weight, severity of INR prolongation, and desired level of INR correction with a typical dosage

range of 25-50 IU/kg (40).

Conclusion

Based on the findings of the reviewed studies, PCC or other therapies with a similar or close formulation (e.g., factor IX concentrate complex+FFP) is significantly more efficient and faster in the reversal of coagulopathy and reduction of INR in comparison with FFP or other treatments in warfarinised patients admitted with serious ICH following a head injury.

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None.

Conflict of Interest

The authors declare that they have no conflicts of interests.

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