REVIEW ARTICLE

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Application of fresh frozen plasma transfusion in the management of excessive warfarin-associated anticoagulation

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Abstract

Warfarin is a commonly used oral anticoagulant. Patients with artificial valve replacement, atrial fibrillation, pulmonary embolism, deep vein thrombosis, and other diseases require long-term anticoagulant oral treatment with warfarin. As warfarin exhibits prompt action with long maintenance time, it has become a key drug for the treatment of patients at risk of developing thrombosis or thromboembolism. Warfarin is a bican coumarin anticoagulant, that exhibits competitive action against vitamin K as its mechanism of action, thereby inhibiting the synthesis of coagulation factors—predominantly the vitamin K-dependent coagulation factors II, VII, IX, and X—in hepatocytes. Long-term warfarin is known to significantly increase the risk of organ bleeding in some patients, while some patients may need to reverse the anticoagulation effect. For instance, patients scheduled for emergency or invasive surgery may require rapid anticoagulation reversal. During such medical circumstances, fresh frozen plasma (FFP) is clinically used for the reversal of excess warfarin-associated anticoagulation, as it contains all the coagulation factors that can alleviate the abnormal blood anticoagulation status in such patients. Accordingly, this article aims to perform an in-depth review of relevant literature on the reversal of warfarin with FFP, and insightful deliberation of the application and efficacy of this clinical intervention.

Keywords: Anticoagulation reversal, Fresh frozen plasma, Warfarin

1. INTRODUCTION

1.1. Physiology of fresh frozen plasma (FFP)

Plasma is the major component of blood, comprising of 90% water. It also contains salt, enzymes, antibodies against pathogens in addition to transport proteins, hormones, and nutrients for different types of cells in the body. It functions to maintain the normal blood pressure and blood volume; and remove the waste products generated via cellular metabolism. According to the "Quality requirements for whole blood and blood components (GB 18469–2012, P. R. China)", FFP is usually prepared within 6 to 8 hours after blood collection, and no more than 18 hours at most. After 1 hour of quick freezing, it is essentially stored at -18°C or lower for future application. It contains all the coagulation factors and plasma proteins and hence, known to participate in the maintenance of immunity and correction of coagulation functions.

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1.2. Principles of warfarin anticoagulation

Warfarin is a double coumarin anticoagulant, used in patients requiring long-term continuous anticoagulant treatment. It is known to suppress anticoagulant synthesis by preventing the carboxylation of vitamin K-dependent coagulation factor II, VII, IX, and X, in order to inhibit blood coagulation, and prevent thrombosis. Patients taking long-term oral warfarin generally exhibit different degrees of deficiency for these factors. Warfarin acts as an indirect anticoagulant that has no anticoagulation effect in vitro and works only in the body. The half-lives of coagulation factors VII, IX, X, and II are about 6, 24, 40, and 60 hours, respectively. Hence, it takes about 2 to 3 days to exert an anticoagulant effect after taking the drug. Furthermore, the deactivation of warfarin restores the normal concentration of coagulation factors after 3 to 5 days, thereby resulting in withdrawal of the anticoagulation effect of the drug (Fig. 1)

1.3. Detection of warfarin concentration

High-performance liquid chromatography (HPLC) is the commonly used method employed for detecting the warfarin concentration. It is an important subdivision of chromatography that uses liquid as the flow phase with a high-pressure infusion system. The liquids used in HPLC consist of a single solvent with different polarities or mixed solvents, buffer liquids, and other mobile phases, which are pumped into the chromatographic column equipped with a fixed phase. After the resolution of the column components, they enter into the detector for the analysis of the test sample.

1.4. Monitoring of warfarin doses

The plasma concentration of warfarin drug combined with anticoagulation monitoring indicators such as international

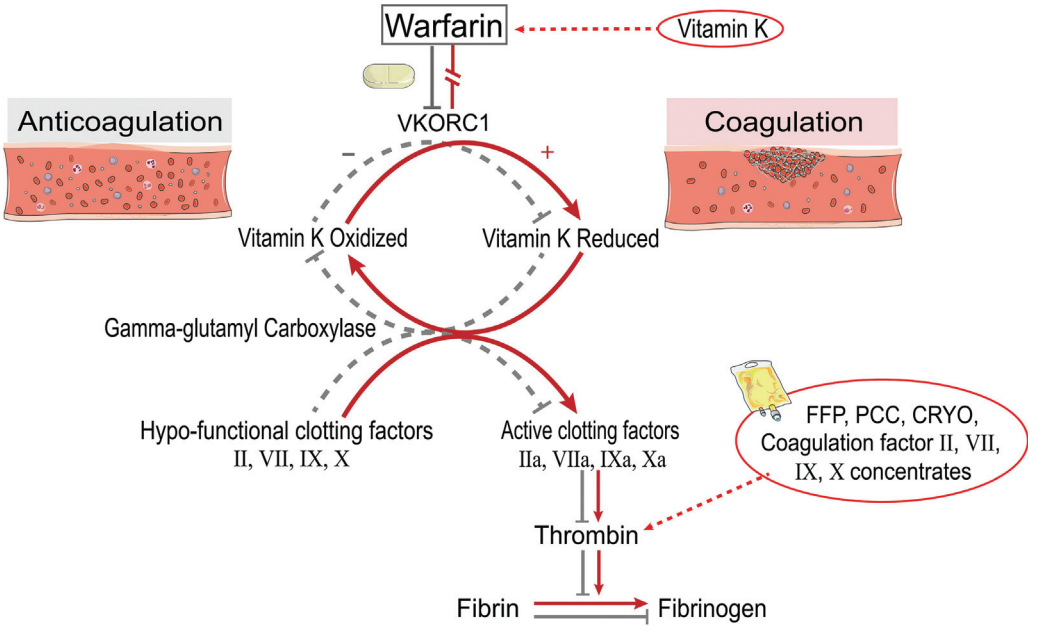

Figure 1. The anticoagulant mechanism of warfarin involves vitamin K antagonism. Warfarin can competitively inhibit vitamin K (VK) epoxide reductase, so that inactive/oxidized VK cannot be reduced to active/reduced VK. This in turn inhibits the carboxylation of coagulation factors II, VII, IX, andX, leading to the production of coagulation factor precursors without coagulation activity, thus playing an anticoagulant role. Vitamin K, infusion of FFP, CRYO, PCC, and coagulation factors II, VII, IX, and X concentrates can reverse the anticoagulation effects of warfarin.

standardized ratios (INR) and activated partial thromboplastin time, serve instructive for deciding the specifics of the anti-coagulation therapy. Especially, INR has important reference value as its detection and monitoring the plasma concentration of warfarin are useful in preventing bleeding, and timely intervention for patients at risk of bleeding. In addition, reversal of the effects of warfarin is crucial for surgical patients and the dosage of the reversal-facilitating drug can be estimated using the INR value.

1.5. Genetic testing as guides for the individualized administration of warfarin

The interpretation of the effectiveness and safety of warfarin anticoagulants has become an emerging field of current research, with the identification of *CYP2C9* and *VKORC1* mutant genotypes being significantly associated with warfarin steady state. Predictive models constructed from genetic and other influencing factors have been shown to effectively predict the steady dose of warfarin in patients with cerebrovascular and non-valvular atrial fibrillation.[1,2] Moreover, it has been shown that despite increased dosage of warfarin, the associated coagulation indicators remain unaffected in patients with long-term usage of warfarin, as a result of the VKORC1 genotype and associated induction of anticoagulant production. These patients were then recommended higher doses of warfarin for the desired therapeutic efficacy. These findings imply that genetic information can serve as a vital indicator for improving the efficacy of warfarin medication, paving the way for personalized medicine in this context.

2. THEORETICAL PROGRESSION OF WARFARIN REVERSAL

2.1. Strategies employed for warfarin reversal (Fig. 1)

2.1.1. Deactivating warfarin. Deactivating warfarin is the simplest anticoagulation reversal method. During the systemic reversal of warfarin, the INR gradually decreases. However, it takes days to reach the ideal level. One study has shown that 12 patients exhibited an INR ranging from 5.0 to 8.0, 24 hours after stopping warfarin treatment, while 12 other patients demonstrated an INR greater than 3.0, of which five patients had an INR greater than 5.0. Furthermore, 48 hours after deactivating the warfarin, ten patients showed an INR greater than 3.0, of which one patient had an INR greater than 5.0. Further, after 3 days of deactivating warfarin, anticoagulant-treated patients with initial levels of INR at 5.0 to 8.0 exhibited the decreased INR levels of 1.5. Besides, when the INR is greater than 8.0, it may take more time for the INR to reach the warfarin reversal treatment levels.[3,4] Therefore, when the clinician's method for over-coagulation of patients with a simple stopper, the absolute risk of bleeding is transient.

2.1.2. Vitamin K.. Vitamin K1 is a lipid-soluble vitamin that is known to activate existing coagulation factors without de novo synthesis and therefore exerts its coagulating effects relatively quickly.[5] Oral administration of 2.5 mg or more of vitamin K1 is effective in recovering patients against over-coagulation. Moreover, while oral administration of vitamin K1 is clinically effective and the effect may be visible within 2 hours, it is generally recommended to wait until 24 to 36 hours to achieve the maximum effect.[5-7] Furthermore, intravenous administration of vitamin K1 has been documented to reverse the effects of warfarin by 6 to 12 hours faster than the oral administration, as the anticoagulant action with oral administration takes 18 to 24 hours.[8] Oral administration of vitamin K1 is the preferred route for patients with mild to moderate treatment for warfarin reversal (INR < 3.0) without major bleeding to delay by 24 to 36 hours.[9] Venous administration of vitamin K1 causes allergic reactions in 3 per 100,000 patients with a recommended maximum rate of slow infusion of 1 mg/min.[10,11] In an emergency, extensive bleeding or immediate surgery usually

requires a rapid reversal of warfarin action. However, under such circumstances it is not advisable to wait for vitamin K1 to play its role. Thus, vitamin K effectively activates coagulation factors to reverse anticoagulation, but rather gradually and that too with significant clinical differences between different patients. Consequently, the development of other rapid warfarin reversal methods is essential.

2.1.3. FFP transfusion.. FFP contains a variety of coagulation factors and is a classic method to reverse anticoagulation, with clinical efficacy. However, the FFP coagulation factor content is limited to emergency reversal and requires long infusion time. In recent years, due to the emergence of prothrombin complex concentration (PCC) and the need to achieve quick reversal of the warfarin effects in case of an emergency surgery, the use of FFP in such scenarios has been reduced. Nevertheless, FFP still plays an important role in normal warfarin reversal in different other conditions.[12]

2.1.4. Cryoprecipitated antihemophilic factor (Cryo) transfusion.. Cryo is a concentrated coagulation factor prepared from FFP, mainly including factor VIII, fibrinogen, von Willebrand factor, and factor XIII. As the process for cryoprecipitate coagulation factor preparation is cumbersome and demands high quality standards, it has become a relatively scarce blood component. Clinically, it is mainly used for the management of hemophilia A, von Willebrand disease, fibrinogen deficiency, and coagulation factor supplementation in patients with major bleeding events. Due to highly enriched levels of coagulation factors in Cryo, it is rational to hypothesize that it can also be used for reversal of warfarin anticoagulation. However, the scarcity of blood components, associated clinical data, and existence of few reports in the literature prevent the potential application of Cryo for warfarin reversal in the clinics.

2.1.5. PCC transfusion.. PCC is a human plasma derivative that is virus-inactivated and consists of highly purified coagulation factors. The concentration of coagulation factors in PCC are about 25 times higher than those in plasma and thus, it can be administered in small volumes to achieve the desired clinical effects. A single 40 mL (1000IU) dose of PCC is functionally equivalent to the adult FFP dose at 10 to 15 mL/kg, which when converted to four units of plasma amount to a total volume of about 1000 mL, all classes of PCC include factors II, IX, and X, while four factor PCC also contain clinically relevant factor VII.[13] In Canada, approved PCC indications include a rapid reversal of warfarin or vitamin K deficiency in patients with severe bleeding or in need of emergency surgery within 6 hours.[14-16] It is not recommended for surgery that may get delayed by 6 to 12 hours, as the reversal of PCC anticoagulant effect is temporary due to the short half-life of factor VII factor that drops after 6 hours. Accordingly, intravenous administration of 10 mg vitamin K1 is recommended with PCC to activate the existing coagulation factors and maintain the reversal effect, as vitamin K1 achieves clinical effect within 6 hours—the duration by which the effects of PCC begin to weaken.

The dose of PCC varies greatly in clinical use and in the published literature.[17] This variability is attributed to the attainment of the target INR value and considerations for balancing bleeding with the risk of thrombosis. In 2008, the Canadian National Blood and Blood Products Advisory Committee recommended administration of a standard dose of 1000 IU (40 mL), regardless of INR or weight.[18] This is a conservative dose to minimize thrombosis and ensure sufficient PCC inventory. With the target INR range of 1.2 to 1.7 being considered appropriate as per the clinical conditions, the latest Canadian Advisory Committee guidelines recommend using patient INR and weight for the determination of dose range with a target INR of 1.5, and a maximum PCC dose of 3000IU (120 mL).[14]

2.1.6. Infusion of coagulation factor II, VII, IX, and X concentrates.. The coagulation factor concentrates are human blood products. After screening and viral inactivation, these concentrated coagulation factors can quickly reverse excess warfarin, making them more suitable for emergency purposes. However, complex preparation procedures, limited inventory, expensive price, strict indications for screening, and clinical inaccessibility prevents its large-scale application.

2.2. Effect of FFP infusion on the reversal of excessive warfarin-associated anticoagulation effects

2.2.1. Prevention of bleeding reversal.. FFP contains a variety of coagulation factors. It is an important blood component that improves clinical coagulation function that plays a key role in excess warfarin reversal, generally used in clinical INR adjustment, prevention of bleeding, and preoperative warfarin reversal. Despite the continuous emergence of new warfarin reversal drugs, FFP still plays an irreplaceable role in clinical practice, because of its cost-effectiveness, ease of access, and popular clinical acceptance as the preferred solution for nonemergency reversal of warfarin. In a North American Perioperative Practice survey, investigating the clinical practice associated with oral anticoagulant reversal that received responses from a total of 2315 anesthetists, 75% of the respondents admitted using FFP for reversing the effects of vitamin K antagonists, despite the contrary recommendations. Hence, it is rational to conclude that FFP is still widely recommended for emergency reversal vitamin K antagonists and oral anticoagulants.[19]

2.2.2. Emergency presurgical anticoagulant reversal.. FFP reversal of warfarin overdose is still widely used prior to emergency surgery, but postoperative complications and patient outcomes associated with it remain controversial. Paisley et al have reviewed patients with cerebral hemorrhage aged over 65 years receiving elderly ground fall treatment at Santa Barbara Cottage Hospital from January 2011 to March 2018, undergoing FFP (n = 25) or PCC (n = 27) mediated reversal. The study revealed that the mortality rates, hospital length of stay, and intensive care unit admission were similar for both FFP and PCC interventions. Moreover, there was no significant difference in the radiological progression of hemorrhage within the first 24 hours of admission. Likewise, among the patients who had their INR values measured prior to intervention, 81% (17 out of 21) of the PCC intervention group, whereas only 29% (4 out of 14) of the FFP intervention group reached an INR value below 1.5 within an 8 hours period post administration ($P = .002$). However, the findings revealed that FFP intervention was as effective as the short-term intervention with PCC in older patients with cerebral hemorrhage after ground fall.[20] Maguire et al have compared the incidences of thromboembolism with FFP and 4-factor prothrombin complex concentration (4F-PCC) treatment for warfarin reversal during a 3-year period in the emergency department (ED) at Massachusetts General Hospital. The patients were included in the study if they were at least 18 years of age and were on warfarin as per the electronic health record, and excluded if they had received both FFP and 4F-PCC

during the same visit. Accordingly, thirty-six patients met the inclusion criteria for the study. The study further revealed that the thromboembolic events within 30 days of therapy were recorded in seven patients (2.7%) from the FFP group, and 14 patients (17.7%) from the 4F-PCC group ($P < .001$). Moreover, death of 39 patients (15.2%) who underwent FFP and 18 patients (22.8%) who underwent 4F-PCC ($P = .115$) was recorded. Thus, this study documented a significantly higher risk of thromboembolic events in patients receiving 4F-PCC than in those receiving FFP interventions for urgent warfarin reversal. Remarkably, the difference remained statistically significant even when controlled for central nervous system bleeds and administration of vitamin K.[21] Stratton et al in a retrospective, single-center, cohort study of patients with life-threatening bleeding or emergency invasive surgery, showed that the administration of 4F-PCC results in faster, and higher INR correction rates and demonstrated similar incidences of adverse events as compared with those subjected to FFP intervention.[22] Strikingly, FFP treatment is considered to be relatively safe in the postoperative thrombosis as compared with PCC intervention. In emergency surgery, FFP mediated warfarin reversal is mostly performed in patients with cerebral hemorrhage. Moreover, emergency reversal using FFP is a convenient option in remote areas and small hospitals lacking the prothrombin complex.

2.2.3. Amount of infusion of each blood component after FFP-mediated warfarin reversal.. Reversion of warfarin with PCC versus FFP is essentially followed by the infusion of variable volume of the individual blood components. Retrospective cohort studies by Hickey et al comparing the anticoagulation reversal effects of frozen plasma and Octaplex-PCC have reported that the administration of PCC reverses warfarin at a faster rate and demonstrates lower demand for red blood cell transfusion, and lesser adverse reactions than that noted with FFP treatment.[23] Wu et al had conducted a retrospective study with 60 patients undergoing heart transplantation, which were divided into PCC and FFP groups. Multiple linear regression analysis showed that PCC intervention is significantly associated with a reduction in intraoperative blood transfusion. Thus, despite the higher costs, the intervention of PCC significantly reduced the transfusion needs of heart transplant recipients.[24] A recent study by Wanek et al reporting a single-center, non-interventional, retrospective cohort study has evaluated heart transplant patients before and after institution of a PCC-based preoperative warfarin reversal protocol for heart transplantation. The patients were classified into PCC and historical control groups (using FFP and vitamin K) with the main purpose of assessing the utilization of individual blood components. Accordingly, the study included 106 consecutive heart transplant patients (PCC cohort, n = 57; historical control cohort, n = 49). The results revealed that there was a significant reduction in FFP utilization in the PCC cohort (6 units vs 8 units, P = .002) as compared to that in the historical control cohort. Furthermore, the rates of packed red blood cell and platelet transfusions were similar between the groups. However, a significant increase in the incidence of cryoprecipitate utilization was observed in the PCC cohort as compared to that in the historical control cohort, which is likely to be attributed to a decreased anti-fibrinolytic utilization. Additionally, there were no differences in the secondary endpoints between the two groups, including thromboembolic events. Nonetheless, the PCC-associated warfarin reversal program significantly reduced the utilization of FFP as compared with that noted in the historical controls without affecting other clinically significant surgical outcomes.[25] For the rapid warfarin reversal essential for emergency surgery, higher volume of plasma is required owing to the limited concentration of the coagulation factors contained in the FFP, which further increases the need for plasma use. Moreover, the use of red blood cells in patients preoperatively subjected to PCC or FFP mediated warfarin reversal is controversial,[26,27] and requires continued validation of extensive clinical data, while limited attention has been paid to the use of platelets and cryoprecipitate.

2.2.4. Improper administration of FFP to reverse the effects of warfarin.. Due to the lax grasp of indications associated with the unreasonable clinical application of FFP, such as a mild increase in INR, no signs of bleeding, no surgery within 24 hours, some patients are even given a preventive infusion. Reddy et al had assumed that prophylactic infusion of FFP in fall patients can reverse the role of vitamin K antagonists (VKA) and that the reversal will lead to a decrease in the delayed intracranial hemorrhages. To validate this hypothesis, they performed a retrospective review of patients with trauma that were admitted to a level 2 community trauma center from January 2010 until November 2012. The inclusion criteria were ground level fall with suspected head trauma, with VKA, and INR > 1.5, in addition to negative head computed tomography (CT). Patients were transfused with FFP to achieve the INR values of less than 1.5. A total of 194 patients met the following criteria: preventive infusion of FFP is not valid for VKA reversal, and it is recommended that during the observation period, in patients with suspected head trauma and the first CT examination was negative with VKA, do not prevent the infusion of the FFP.[28] The unreasonable application of FFP not only caused serious blood waste but it also increased the economic burden on patients and the risk of related infectious diseases. Therefore, the administration of FFP should be performed with strict adherence to the recommended clinical indications.

2.2.5. Effect of individual differences on FFP-mediated warfarin reversal.. FFP administration for excessive warfarin reversal is reportedly prone to individual differences based on various factors, such as medication duration, bleeding site, bleeding, surgical emergency, weight, and failure to meet the expected INR, reversal, or other complications. Therefore, the dosage of FFP should consider individualized factors as reversal of excessive warfarin with FFP, and vitamin K in combination, is also affected by obesity. Phydione (vitamin K1) is fat-soluble vitamin that can be isolated from adipose tissue, and thus can potentially affect the drug distribution in obese patients requiring warfarin reversal. Luc et al had analyzed the effects of obesity on warfarin reversal, and showed that obesity is significantly associated with a reduced probability of warfarin reversal within 72 hours of vitamin K administration.[29] Consequently, FFP infusion should focus on individualized differences, formulated for individualized treatment programs, and administered as per a carefully deliberated medication plan according to different conditions.

2.2.6. Costs. FFP price is relatively low, and therefore reduces the economic burden of patients as compared with that of PCC. Wu et al had compared the cost of PCC with FFP in heart transplantation patients. The findings revealed that the patients who received PCC were younger (50 ± 11 vs 57 ± 13 years, $P = .02$); had higher preoperative hemoglobin (11.8 ± 1.8 vs 10.4 ± 1.8 g/dL, $P = .01$); and received less FFP (2 vs 5 units,

$P = .03$), cryoprecipitate (0 vs 2 units, $P = .05$), and total blood products (9 vs 13.5 units, $P = .03$) intraoperatively as compared with those who received FFP. Moreover, the postoperative INR was slightly higher in the PCC group than that in the FFP group (1.4 vs 1.3).

Remarkably, the total blood bank costs incurred by the PCC group was $4949, while the same was $3677 in case of non-PCC group ($P = .01$), as the cost of FPP-mediated warfarin reversal was relatively low as compared with that of PCC mediated reversal.[24] Moreover, the study of reverse trauma coagulation disorder performed by Joseph et al that compared the patients treated with PCC + FFP and FFP-alone, the use of PCC + FFP was associated with a higher cost of therapy ($1470 ciated with a higher cos > 0.01) but lower overall cost of transfusion ($7110 cost of FP-only patients, as = 0.01) as compared with that associated with the FFP therapy alone. PCC treatment has been documented to reduce the overall costs,[30] the overall costs of FFP reversal varies due to the national and regional blood expenses and individual differences. Hence, it is recommended that clinicians evaluate the indications for FFP administration stringently taking into consideration the regional plasma prices and the individual economic situation of the patients.

2.2.7. Duration for warfarin reversal with FFP. The duration of FFP-mediated warfarin reversal and attain recommended levels of INR for emergency surgery, remains controversial. Most experts recommend rapid warfarin reversal to reduce bleeding, but whether the rapid correction of INR could improve clinical outcomes has not been demonstrated. Akhter et al had performed a retrospective analysis of patients with warfarin-related cerebral hemorrhage at a tertiary hospital from 2000 to 2013 in an attempt to determine whether FFP-mediated reversal and reduction time to achieve recommended INR was associated with decreased hematoma expansion and improved prognosis. The study of the relationship between the outcome of INR reversal time, hematoma enlargement, and prognosis with logistic regression analysis, revealed no evidence of association between faster INR reversal and reduction of hematoma enlargement or improved prognosis.[31] Thus, reversal of excessive warfarin with FFP should not only focus on changes in the INR value, it should also consider clinical symptoms such as reduction in bleeding with improved prognosis of the patient prognosis being the key purpose. Sometimes, INR value does not fully reflect the patient's actual bleeding situation, so the reversal time of INR should be carefully considered in combination with clinical symptoms.

2.2.8. Complications associated with FFP-mediated warfarin reversal. For emergency surgery, INR reversal requires administration of a large amount of FFP. Studies have shown that the shorter the time of FFP infusion, the faster is the INR reversal in patients with warfarin-associated cerebral hemorrhage.[32] However, extensive infusion of plasma in a short period may lead to adverse clinical consequences, especially lung complications such as transfusion-related acute lung injury (TRALI) and transfusion-related circulatory overload (TACO). To study the relationship between plasma dose and pulmonary complications, Marshall et al statistically analyzed the clinical outcomes of a 3-year FFP-mediated warfarin reversal treatment in a major hospital. The study revealed that nearly 20% of the patients developed lung complications post FFP-mediated warfarin reversal, with FFP administration greater than 3 units (200–250 mL/U) demonstrating higher risks. A total of 251 patients met the inclusion criteria for the study, and the results showed that the 49 patients (20%) with pulmonary complications included 30 (12%) TACO patients, 2 (1%) TRALI patients, and 17 (7%) patients with pulmonary edema who did not meet the TACO standard. These findings suggest that administration of more than 3 units of FFP remains a significant risk factor for pulmonary complications (with advantage ratio of 2.49, and a 95% confidence interval of 1.21–5.13).[33] Thus, when an emergency reversal of warfarin mandates a significant infusion of plasma, transfusion departments and clinicians should pay considerable attention to the possible risks and be aware as well as be prepared to handle the associated complications (Table 1).

Table 1

Relationship between warfarin associated bleeding rate and INR.

INR	100 patients/year	More than 48 h being dangerous
2–2.9	4.8*	1/4000
3–4.4	9.5*	1/2000
4.5–6.9	40.5*	1/500
>7.0	200.0*	1/100

INR = International standardized ratio.
* Number of bleeding.

2.3. Advantages and disadvantages of FFP reversal of warfarin

As compared with other methods of warfarin reversal, the FFP-mediated reversal of warfarin has its own advantages and disadvantages, which are summarized in Table 2.

2.4. The warfarin reversal and non-reversal outcomes of FFP administration

For different types of surgical emergencies, as well as different clinical opinions of regional hospitals and clinicians against coagulation interventions, some clinicians opt for non-reversal of warfarin in case of certain invasive operations. However, whether the non-reversal of warfarin has any effect on the clinical outcome in such cases requires a comprehensive clinical data analyses; as the different types of surgery, bleeding volume, and individual differences have a great impact on the outcome. Michael et al have analyzed the clinical outcomes associated with non-reversal of warfarin in patients enrolled for hip-fracture surgery at various hospitals in Northern California from 2006 to 2016 by retrieving the clinical data through electronic databases. The surgical outcomes were compared among patients that were

Table 2

Advantages and disadvantages of FFP-mediated reversal of warfarin.

Advantages	Disadvantages
Easily accessible	The concentration of coagulation factors is low
Lower costs	Large amount is required for therapeutic effect
Contains various coagulation factors	Longer reversal time
Lower risk of thromboembolism	Less applicability for emergency surgery
Availability of more clinical data for long-term usage	Prone to pulmonary complications

Abbreviation: FFP = fresh frozen plasma.

treated versus patients that were untreated with anticoagulation reversal preoperatively. Of the 1984 patients who underwent hip fracture surgery, 1943 (97.9%) were on warfarin, and reversal agents were administered to 1635 (82.4%) patients. The findings revealed that there was no difference in the 30-day mortality of warfarin reversed and unreversed patients (7.8% and 6.0%, respectively; hazard ratio [HR], 1.30 [95% confidence interval (CI), 0.82-2.07]). In patients administered with oral anticoagulant reversal agents, undergoing hip fracture surgery, no significant correlation was found in the 30-day mortality or other clinical indicators with that of those patients not subjected to anticoagulant reversal agents.[34] For patients with similar conditions, the related data were limited to warfarin reversal and unveiled comparisons, and hence further investigation is required.

3. PERSPECTIVES

Warfarin is used in clinical practice since 1941 and has been frequently used as an anticoagulation in atrial fibrillation, venous thromboembolism, mechanical heart valves, and a variety of various other clinical settings. In fact, warfarin is one of the most widely prescribed drugs in the industrialized world,[35] with multiple recent reports also confirming this statement.[36-41] Warfarin causes anticoagulation by inhibiting the vitamin K epoxy reductase—the enzyme which is necessary for posttranslational carboxylation of many coagulation factors including factors II, VII, IX, and X as well as protein C and protein S.[42] Bleeding caused by warfarin is one of the most important complications, which is associated with high morbidity and mortality.[43] It is one of the most reported serious adverse events that were reported in the 1990 s and 2000 s to the US Food and Drug Administration. In fact, it is one of the most common causes of emergency hospitalization in physical-trauma related events.[43,44] Warfarin has been a major means of outpatient anticoagulant for many years, and with the advancement in medical knowledge, new anticoagulants such as subcutaneous heparin injections, and oral direct thrombin inhibitors have gradually emerged in the market. It is known that common heparin suppresses the coagulation cascade by binding to antithrombin III, thus causing conformational changes in the protein and causing its activation. The activated antithrombin III in turn, binds and inhibits thrombin, thereby initiating the inhibitory cascade reaction through the coagulation system. Low-molecular-weight heparin and heparin are similar to ordinary heparin but exhibit weaker binding and are more inhibitory towards the factor X. Moreover, oral thrombin inhibitors directly bind to the active sites of thrombin molecules, which leads to direct competition and reversible inhibition of thrombin action.[2] Due to the inconvenience associated with the subcutaneous injection of heparin, new oral anticoagulants are being more favored by patients like Apixaban, Liavasaban, and Dabbigiga. Recent studies have evaluated their clinical effectiveness. However, as the new anticoagulants have entered the clinical scenarios quite recently, less data for the anticoagulation reversal is available, making the treatment and clinical prediction of bleeding in anticoagulant patients more challenging. New anticoagulant prices are higher than those of warfarin and are more distributed in developed countries. Warfarin has been a major VKA accounting for comprehensive clinical application globally.[45-48] According to the data of 58 EDs in the United States, in 2013 and 2014, warfarin alone was responsible for more drug-related emergency visits in elderly patients than any other drug.[49] These findings suggest that the use of warfarin is still relatively high worldwide and hence, considerable attention needs to be imparted to the complications involving warfarin bleeding.

As warfarin has been used in clinical practice since quite a long time, the practice of warfarin deactivation or administration of vitamin K in patients for the purpose of anticoagulation reversal has been practiced simultaneously to prevent excessive bleeding in patients suffering from invasive physical trauma or undergoing emergency surgery. Recently, FFP alone or in combination with vitamin K has been used for the reversal of warfarin. However, FFP poses risks of spreading infectious diseases, and need more infusion and longer time for warfarin reversal. In 1976, the coagulation factor concentrate began to be used for reversal of anticoagulation. PCC is a virus-inactivated derivative of human plasma that is known to eliminate infection due to pathogens. The coagulation factor complex has been reported to quickly reverse the INR value in patients with emergency surgical bleeding. However, due to short half-life of factor VII, the reversal of anticoagulant effects by PCC is temporary, and therefore, its combination with vitamin K is necessary. As PCC contains high concentrations of thrombin factors, it indirectly increases the risk of thrombosis. Moreover, PCC contains a small amount of heparin and is therefore, off-limits in patients with heparin-induced thrombocytopenia. At present, the adverse reactions and outcomes of PCC-mediated warfarin reversed patients are still controversial.[21,50,51] In addition, PCC is expensive and difficult to obtain in less developed areas. Thus, the warfarin reversal by FFP is still widely used in clinical practice.

Although warfarin has an associated risk of bleeding, it is still the most commonly used anticoagulant.[52] Reasonable use of warfarin reversal agents can reduce the risk of bleeding, through further clinical studies. Moreover, for patients with elevated INR (4.5-10.0), and no bleeding, there is lower risk of bleeding. Accordingly, deactivating warfarin and careful follow-up monitoring seem to be safe in clinical practice. Vitamin K1 can reverse the anticoagulation action of warfarin as its intravenous administration accelerates the warfarin reversal time. Hence, it is the preferred route for warfarin patients with mild to moderate treatment (INR < 3.0) without major bleeding, and for a possible surgical delay of 24 to 36 hours. FFP-mediated warfarin reversal is applicable for only 4 to 12 hours. However, to achieve immediate warfarin reversal, the PCC takes a shorter time than the FFP. Nevertheless, when PCC is not available, FFP can also be used.

In recent years, various novel coagulation factor complexes have been employed in clinical practice.[53] However, FFP has been widely used and there is considerable debate in the literature about the superiority of PCC over FFP, as most studies have not shown any significant morbidity or mortality benefits. Extensive deliberations have been performed to acknowledge the challenges associated with the use of PCC over FFP in order to achieve emergency reversal of warfarin coagulation. Most reports comparing PCC and FFP are corrected using the INR values rather than the clinical outcomes; when compared to FFP, PCC results in faster INR correction, but usually no clear clinical benefits have been reported. Importantly, the magnitude of the INR reversal is not related to how much or how long the bleeding has occurred; the PCC can reverse the INR at any time, but only in the real time treatment of life-threatening bleeding, will the clinical benefits of PCC truly emerge. Consequently, the treatment for less severe bleeding conditions such as chronic

subdural brain hemorrhage may never show superior clinical benefits of PCC over FFP.[54] In developing countries, remote areas, poor economic conditions, and places without thrombin, FFP may be the only viable choice. However, the application of virus-inactivated plasma components (PCC) eliminates the risk of infectious diseases. Thus, the clinicians should reasonably use FFP to reverse the anticoagulation effects of warfarin, grasp the threshold of INR and plasma use, and avoid excessive plasma waste. Overall, FFP has its own advantages and disadvantages but its clinical status remains difficult to be completely replaced.

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