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Prothrombin complex concentrates or recombinant factor VIIa are more effective than fresh-frozen plasma at lowering INR in patients with liver disease

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ABSTRACT A critical appraisal and clinical application of Kwon JO, MacLaren R. Comparison of fresh-frozen plasma, four-factor prothrombin complex concentrates, and recombinant factor VIIa to facilitate procedures in critically ill patients with coagulopathy from liver disease: a retrospective cohort study. *Pharmacotherapy*. 2016;36(10):1047-1054. doi: [10.1002/phar.1827](https://doi.org/10.1002/phar.1827)

Keywords: *INR reversal, prothrombin complex concentrates, recombinant factor VIIa, fresh-frozen plasma, surgical intervention, liver disease*

Clinical Context

A 38-year old man with primary sclerosing cholangitis (PSC) and Crohn's disease was transferred to a tertiary care hospital for further management of decompensated hepatic cirrhosis. Additionally, the patient recently suffered a first-time tonic-clonic seizure and MRI of the brain showed multiple ring-enhancing lesions. These lesions were presumed to be infectious in nature, possibly due to transient bacteremia from a prior scrotal abscess. The patient was started on intravenous meropenem, but repeat MRI showed interval growth and surrounding edema with several new lesions. This warranted further investigation, as there was growing suspicion for an underlying metastatic etiology. However, CT of the chest, abdomen, and pelvis did not reveal a primary tumor and infectious workup continued to come back negative. The working differential diagnosis of an infectious vs. neoplastic process was discussed with the patient, as well as the importance of performing a possible brain biopsy to reach a definitive diagnosis and focused treatment plan. He understood the risks associated with the procedure and was agreeable with this option. However, when neurosurgery was consulted they declined to perform a brain biopsy due to the risk of bleeding from an elevated INR at 1.69. This was communicated with the patient and after educating him about the significance of an elevated INR, he understood the need to address this before undergoing a brain biopsy. Thus, the dilemma was as follows—this patient urgently needed a brain biopsy in order to reach a final diagnosis and subsequent treatment plan, but this required a substantial reduction in his INR to prevent possible life-threatening bleeding during the procedure.

Clinical Question

Should fresh-frozen plasma, prothrombin complex concentrates, or recombinant factor VIIa be used to lower the INR and thus facilitate invasive procedures in patients with liver disease?

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Research Article

Kwon JO, MacLaren R. Comparison of fresh-frozen plasma, four-factor prothrombin complex concentrates, and recombinant factor VIIa to facilitate procedures in critically ill patients with coagulopathy from liver disease: a retrospective cohort study. *Pharmacotherapy.* 2016;36(10):1047-1054. doi: [10.1002/phar.1827](https://doi.org/10.1002/phar.1827)

Related Literature

PubMed was the primary search engine used to identify relevant articles, and publications were limited to the last fifteen years as there has been relatively less research done on INR reversal in patients with liver disease compared to INR reversal in patients being treated with warfarin. Various combinations of the following keywords were used: “INR reversal,” “prothrombin complex concentrates,” “recombinant factor vii,” “fresh frozen plasma,” “surgical intervention,” “coagulopathy,” and “liver disease.” Most combinations included “liver disease” as articles that related to INR reversal in patients with liver disease were preferred over literature describing patients with warfarin-induced coagulopathy. Combinations included 3-4 of the aforementioned keywords, which usually returned 20-50 results depending on the combination used. Even with this strategy, most research on the topic pertained to the role of fresh-frozen plasma (FFP), prothrombin complex concentrates (PCCs) and recombinant factor VIIa (rFVIIa) specifically in the reversal of warfarin therapy. Very few articles directly address their use in lowering the INR of patients with non-medication-induced coagulopathy (e.g., liver disease). Furthermore, articles describing the use of PCCs and rFVIIa in the reversal of supratherapeutic INR were scarce compared to the role of FFP. There is also limited research showing how FFP, PCCs and rFVIIa compare in terms of time to correction of INR and thus expedition of invasive procedures. Therefore, with these limitations in mind, articles were deemed relevant for use in this clinical context if they included INR reversal in patients with liver disease, and/or the use of PCCs and rFVIIa in patients with elevated INR regardless of etiology since these treatment modalities were already rarely described in the literature.

In a retrospective study done by Roitberg et al., neurosurgical patients who were administered rFVIIa had, on average, a greater reduction in INR (2.57 to 1.67) compared to patients administered FFP (2.17 to 1.85).¹ This study also demonstrated that normalization of INR was quicker in patients who received rFVIIa versus FFP, with a mean difference of 40.66 hours. Furthermore, the number of patients with good functional outcome, described as having a Glasgow Outcome Scale score of 5, was greater among patients who received rFVIIa. These results suggest that the use of rFVIIa increases patient safety overall, in addition to a greater and quicker reduction in INR compared to FFP. This article describes coagulopathic patients who needed urgent INR reversal for neurosurgical intervention, closely resembling the patient described in the above clinical context. However, anticoagulation with warfarin was the cause of supratherapeutic INR in almost half of the patients who received rFVIIa, making it less comparable to the patient described in the clinical context. Furthermore, patients in the rFVIIa group were those who had failed initial coagulopathy reversal with FFP, and thus the effects of rFVIIa were not totally attributable to rFVIIa alone.

A systematic review by Chai-Adisaksopha et al. compared the role of PCCs versus FFP in the reduction of INR levels in patients requiring reversal of warfarin therapy. Their results show that the use of PCCs led to more rapid INR correction, a greater reduction in all-cause mortality, and less post-transfusion complications such as volume overload.² Though this article describes the role of PCCs in the reversal of supratherapeutic INR—a topic that is deficient in literature—it unfortunately includes patients with warfarin-induced coagulopathy rather than liver disease. Their review also does not focus on INR reversal specifically for the purpose of urgent surgical intervention.

Ultimately, Kwon and MacLaren’s article was selected for critical appraisal as it applies most to the scenario described in the clinical context above—a patient with coagulopathy secondary to liver disease who needed INR reversal for an invasive procedure.

Critical Appraisal

Kwon and MacLaren conducted a retrospective cohort study that included a total of forty-five patients aged 18-89 with liver impairment and a baseline INR of 1.5 or higher who were admitted to the intensive care unit (ICU) at the University of Colorado Hospital (UCH). Of these 45 patients, 15 patients each received FFP, PCCs, or rFVIIa prior to the procedure. This study design constitutes Level 2c evidence in accordance with the Oxford Centre for Evidence-based Medicine.



Overall, this study demonstrated that PCCs and rFVIIa lowered INR more quickly and to a greater extent than FFP, thus expediting invasive procedures.³ Specifically, only 27% of the patients in the FFP group were able to achieve an INR of less than 1.5 in time for a procedure, compared to 80% in the PCCs group and 87% in the rFVIIa group. Furthermore, the average time to achieve an INR of 1.5 or less was 2.5, 2.1 and 1.8 hours for the FFP, PCCs and rFVIIa groups respectively. Various possible adverse events (e.g., minor or major bleeding, transfusion reactions, thromboembolic events) were also monitored, all of which were similar across all three groups with the exception of one complication—fluid overload. Hypervolemia was seen in 93% of patients in the FFP group versus 40% and 33% in the PCCs and rFVIIa groups respectively.

After thoroughly reviewing the article, there were a few noteworthy positive aspects with regards to the study design. Firstly, Kwon and MacLaren were very careful about which patients to include in the study. Patients were excluded if they were admitted for hemorrhage, if they were anticoagulated at therapeutic doses within 72 hours before the procedure, or if they possessed other etiologies of impaired or enhanced coagulation (e.g., disseminated intravascular coagulation, lupus). Patients were also excluded if their INR within the first 24 hours of admission were considered an outlier, i.e., excessively high or low. Both of these precautions established mean baseline INR values that were comparative across groups. In addition, baseline patient characteristics such as age, sex, ethnicity, and procedures to be performed were similar across all three groups, thus further mitigating the potential for confounding bias. It is also worth noting that an independent third-party data analyst generated the lists of screened patients, thereby addressing the possibility of selection bias.

There were also several limitations to consider in this study, beginning with the reporting of certain adverse events. Minor bleeding was defined by “a notation of bleeding associated with the procedure in the medical record” and major bleeding was defined as “minor bleeding and the need for a transfusion of packed red blood cells during or after the procedure.”³ As this is a retrospective study, the authors had to rely on documented decisions rather than something they could measure themselves. These decisions may not have been made identically for every patient, thus adding some variability and subjectivity to whether bleeding events were classified as minor or major—a form of measurement bias. Furthermore, the vast majority of procedures used in this study included common interventions such as central lines, tracheal intubation, arterial lines, paracentesis, endoscopy, chest tube insertion, and bronchoscopy, with relatively few patients undergoing biopsy in either of the three groups. It is possible that other procedures with higher risks of hemorrhage could have a different bleeding risk profile. Therefore, the scope of this study is, for the most part, limited to the common types of procedures mentioned above. Whether PCCs and rFVIIa reduce the overall bleeding risk for more invasive procedures such as brain biopsy still requires in-depth evaluation.

An additional limitation involves the arbitrary INR value of 1.5 as the threshold for bleeding prevention. This study showed that the application of this INR value to liver patients lacks validity since invasive procedures were still successfully and safely performed in the FFP group despite 73% of these patients not being able to achieve an INR less than 1.5.³ The study’s retrospective design and limited number of subjects also make it less possible to apply Kwon and MacLaren’s findings in the clinical world. Despite these limitations, the study does still have value and surely warrants further investigation, possibly with a larger number of subjects and a prospective study design. Finally, it is possible to calculate the number needed to treat (NNT) with regards to one adverse event—hypervolemia. The NNT values for PCCs and rFVIIa (when comparing to FFP) were 1.89 and 1.67 respectively.

Clinical Application

The patient described in the clinical context closely resembles the patients used in Kwon and MacLaren’s study. This was a patient with coagulopathy due to underlying liver disease who required urgent surgical intervention for diagnostic purposes. His baseline INR within 24 hours of admission was 1.76, a value that would not be considered an outlier by the appraised article’s standards. However, additional concerns not covered by this study led to a final decision to use FFP—a total of 8 units—effectively lowering his INR from 1.69 to 1.40. A brain biopsy was finally performed and confirmed that the lesions were foci of metastases, likely secondary to a primary tumor of gastrointestinal origin that did not reveal itself on CT imaging.

Though Kwon and MacLaren’s paper was discussed and their findings acknowledged by the team, a number of factors guided the clinical decision-making process with regards to using FFP over PCCs or rFVIIa for this patient. Firstly, a brain biopsy is perceived as having a higher risk of hemorrhage and more dangerous in a patient with coagulopathy than other common procedures. Since this specific type of procedure wasn’t thoroughly investigated



in Kwon and MacLaren's study, the team was more wary about applying their findings to the patient and perhaps the reason why a target INR value of 1.40 was chosen as opposed to 1.50. Little research has been done on the use of FFP versus PCCs or rFVIIa for these types of procedures with higher bleeding risk, and as mentioned previously, the small number of subjects used in their study makes it difficult to draw final conclusions about which modality to use in a clinical context. Kwon and MacLaren also mention that though PCCs and rFVIIa effectively lowered INR to a greater extent than FFP, the effects were short lived.³ Again, this poses greater risks of bleeding for neurosurgical procedures and directly impacted the decision to use FFP. Finally, it is also important to note that the team was highly suspicious of malignancy being the etiology of his brain lesions, which would technically place him in a more enhanced state of coagulation compared to a similar liver patient without metastatic disease. This would violate Kwon and MacLaren's criteria for inclusion within the study and thus their findings would not have directly applied to him. Finally, the authors' findings of a greater incidence of hypervolemia in patients receiving FFP was noted by the team, however, this did not take precedence over the aforementioned points arguing against the use of PCCs or rFVIIa.

Learning points:

1. PCCs and rFVIIa lowered INR more quickly and to a greater extent than FFP in patients with coagulopathy due to underlying liver disease, thus expediting time to invasive procedures.
2. The risk of adverse events was similar across all three groups with the exception of hypervolemia, which was lower in patients receiving PCCs or rFVIIa.
3. Each patient with coagulopathy secondary to liver disease has additional clinical factors that contribute to risk of hemorrhage with procedures, and must be considered individually when choosing a therapy. The critically appraised study is necessarily restricted mostly by its retrospective design and cannot address every patient's particular comorbidities that may contribute to variation in bleeding risk profile.

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