Prothrombin Complex Concentrates Use in Intracerebral Hemorrhage

Sven Poli, MD; Florian Härtig, MD; Magdy H. Selim, MD, PhD; Carlos A. Molina, MD, PhD; Dar Dowlatshahi, MD

The Case
A 65-year-old man on warfarin for atrial fibrillation was found down, with Glasgow coma scale score = 6. Head computed tomographic scan reveals a 45 cc right thalamic hemorrhage with intraventricular extension. International normalized ratio (INR) = 1.9.

The Question
Should he be treated with prothrombin complex concentrates (PCCs)?

The Controversy
Should PCCs be routinely used to reverse warfarin-related coagulopathy in patients presenting with intracerebral hemorrhage (ICH)?

Yes: PCCs Should Be Used
Sven Poli and Florian Härtig

We would treat with 4-factor PCCs because otherwise—with an INR of 1.9—there is a high risk of further expansion of an already large ICH. Without reversal of the anticoagulant effects of warfarin, the patient’s life is at stake. At age 65 years, he has a reasonable chance to recover from a right-sided ICH if treated early and aggressively. In our eyes, early withdrawal of care is not an option!

Compared with spontaneous ICH, warfarin-associate ICH (WICH) is associated with an increased risk of hematoma expansion and subsequently higher morbidity and mortality. Achieving rapid hematoma stabilization must, therefore, be the therapeutic goal in this case. It is promoted most effectively by administering PCCs, while the risk of prothrombotic effects is low. Because of ventricular involvement of the bleed, the patient is at a high risk of developing obstructive hydrocephalus. This may warrant placement of an external ventricular drain, which should only be undertaken when the INR is within normal range. INR must be monitored closely; ideally shortly after application of 30 U of PCCs per kilogram of body weight and then at least daily until it is definitely stabilized at normal levels. Within the first 3 hours, we would readminister PCCs if the INR remains elevated—the same dose if the INR is ≥ 2 or 10 U/kg if the INR is > 1.2. For sustained reversal effect, we would also administer 10 mg of vitamin K intravenously during or shortly after the acute admission phase. In addition to coagulation management, blood pressure should be controlled and early complications of ICH associated with severely impaired neurological status (eg, aspiration pneumonia) should be treated appropriately.

In general, the evidence for treatment with PCCs in WICH is limited because of the absence of prospective clinical end point–driven randomized placebo-controlled trials, which must be considered unethical in the light of today’s knowledge: An association of hematoma expansion with ICH-related mortality is plausible and has been repeatedly established in several studies. Early reversal of coagulopathy, on the other hand, leads to a significant decrease in hematoma expansion. Consequently, international stroke guidelines recommend rapid reversal of anticoagulation in WICH with PCCs. The threshold for treatment, however, is still subject to discussion. Alternative means of achieving a normal coagulation status would be infusion of fresh frozen plasma or rFVIIa (recombinant activated factor VII). Fresh frozen plasma, however, has been proven to be of inferior efficacy regarding INR normalization and hematoma stabilization in several studies, including the randomized INCH trial (International Normalised Ratio Normalisation in Patients With Coumarin-Related Intracranial Hemorrhages). Moreover, the required large fresh frozen plasma infusion volumes may lead to fluid overload and transfusion-related acute lung injury. There is currently no data supportive of rFVIIa use in warfarin-related ICH; it is even suggested that rFVIIa does not have a clinically meaningful effect on hemostasis in warfarin-treated patients.

Superiority of 4-factor PCCs over 3-factor PCCs is not established. Presumably, 4-factor PCC should offer a higher efficacy regarding normalization of coagulation status because...
all 4 coagulation factors lacking during treatment with vitamin K antagonists are substituted.

**No: PCCs Should Not Be Routinely Used**

Dar Dowlatshahi

Warfarin-associated ICH is recognized as one of the most severe forms of stroke; hematoma expansion is common and mortality estimates exceed 50%. Early enthusiasm over PCCs as a potential therapy has since been tempered by reports showing poor clinical outcome despite coagulopathy correction; ICH mortality remains at 40%, and the median discharge functional status for survivors is still poor. These realities must be taken into account when considering whether PCCs should be routinely used in WICH. Although there may indeed be a select group of patients who benefit from early coagulopathy correction, there is insufficient evidence of clinical efficacy to make therapy, with PCCs a standard treatment for all patients with WICH.

There is extensive literature cautioning against early prognostication for withdrawal of care in ICH. Some may interpret this to mean that all patients with ICH should initially receive aggressive care, irrespective of baseline prognostic factors. But a distinction should be made between avoiding early prognostication for the purposes of limiting care versus withholding a potentially futile therapy. When the patient is elderly and frail with significant baseline morbidity, or arrives from a nursing home and is dependent for all activities of daily living, or has prior expressed wishes for palliation in the case of a severely disabling condition, I would argue that offering PCCs would be futile or inappropriate.

Conversely, there are clearly situations where urgent PCC therapy must be considered, such as in patients who present early, are rapidly deteriorating, and have relatively small WICH volumes. There is data to support better outcomes in patients who are reversed early, and it stands to reason that clinicians should use PCCs to mitigate hematoma expansion in patients presenting with other known positive prognostic factors, such as smaller volumes, milder deficits, or good functional baseline.

The challenge lies in deciding how to manage patients who fall between the 2 extremes. Currently, there is no accepted strategy to identify those patients with WICH who are likely to respond to PCCs. For example, what should be done with a relatively young patient of age 65 years in the presence of poor prognostic factors: a large hematoma volume with intraventricular extension and low Glasgow coma scale? In scenarios like this, the probability of disability despite INR correction is high but not certain. While my own bias is toward treating such patients, I think it is vital to make this decision in collaboration with the patient or their substitute decision maker. This is analogous to offering hemiancerecomy for malignant middle cerebral artery infarction in an elderly patient or proposing intraventricular thrombolysis for a patient with severe intraventricular hemorrhage. Although these therapies can reduce mortality, there is a high chance of severe residual disability. As a result, these therapies are not routinely performed on all eligible patients.

Of course, it is important to acknowledge that unlike hemicraniectomy or intraventricular thrombolysis, there are no trials to prove the clinical efficacy of WICH reversal. In this respect, PCC therapy for WICH is better compared with surgery for ICH; although it is possible that some patients will benefit, one cannot argue that hematoma evacuation should be routinely offered to all patients with supratentorial ICH. Similarly, without additional evidence of benefit, we must exercise clinical judgment when deciding which patients should receive PCC therapy for WICH.

So can PCC therapy improve clinical outcome in certain patients with WICH? Probably. Should it be offered to carefully selected patients with WICH? Definitely. But should we offer it routinely to all patients presenting with WICH, irrespective of premorbid function, severity of presentation, and prior expressed wishes? Certainly not.

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**Rebuttal by Drs Poli and Härtig**

Even if highly effective therapies are available for certain disorders, there are always patients who will not receive them because of obvious futility, despite a clear indication and lack of alternatives. Take, for example, cardiopulmonary resuscitation in patients with do-not-resuscitate orders. A decision to treat is—and has always been—a matter of discretion of a physician carefully balancing the assumed risks and benefits of his actions and taking a patient’s preference into account. WICH is no exception.

Most WICH cases, like our 65-year-old patient, will fall between the 2 extremes of excellent premorbid status, small baseline hematoma volume, and high INR, which will be treated with PCCs, on the one hand, and large space occupying bleeds in patients from a nursing home where PCCs will be justifiably withheld, on the other hand. A WICH patient, however, will most likely not be able to guide the stroke physician to the right decision by comprehending the full gravity of the situation and expressing his or her own informed preference as he or she is severely incapacitated. Therefore, when in doubt, we strongly advise to treat without unnecessary delay to avoid early but potentially unwanted and irreversible withdrawal of care. The potential futility of a therapy or hypotheses about a patient’s will should not lead to the lack of a general treatment recommendation. In conclusion, we still argue in favor of considering PCC use in all patients with WICH.

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**Rebuttal by Dr Dowlatshahi**

Just because you can reverse the INR does not mean you should. Nor does it mean your patient would want you to. My colleagues argue that because the patient in the illustrative case is 65 years old, he has a reasonable chance to recover from a right-sided ICH if treated early and aggressively. While I wish this were true, I believe this is an overly optimistic prediction. There is a reasonable possibility that aggressive therapy will lead to survival, but I doubt a patient presenting with Glasgow coma scale =6 and a large hematoma with ventricular extension will survive without disability. For this reason, the patient and family’s wishes must be taken into account, and the decision to treat with PCCs must be individualized.
Comments by Drs Selim and Molina

The superiority of PCCs over fresh frozen plasma in rapidly normalizing INR within minutes in patients with WICH is unquestionable. Furthermore, recent evidence from the INCH trial supports the notion that PCCs’ use could reduce hematoma expansion after 24 hours of WICH, an important point-of-concept to justify the use of PCCs to reverse warfarin-associated coagulopathy. However, treatment with PCCs is costly, and questions remain as to whether it translates into an overall reduction in mortality or better functional outcomes of WICH survivors to justify the cost. Several retrospective cohort studies have yielded inconsistent answers, and supporting evidence from large-scale, randomized, controlled trials is lacking.

Our experts voice extremely divergent opinions on the matter. While Drs Poli and Härtig support indiscriminate use of PCCs in all patients with WICH, Dr Dowlatshahi calls for a more selective and individualized approach. Despite the valid reasons outlined by Drs Poli and Härtig in defense of their recommendations, we have to concur with Dr Dowlatshahi; in case of PCCs in WICH like everything else in medicine one-size-does-not-fit-all.

Our experts skillfully navigated the trap of indication-based-on-prognostication in our illustrative case, and we agree that a distinction should be made between avoiding early prognostication for the purposes of limiting care versus withholding a potentially futile costly intervention. Clearly, there are situations where PCCs must be used in WICH. For example, PCCs should be used in our patient if urgent placement of an external ventricular drain is deemed necessary. Intuition suggests that it is probably more efficacious to use PCCs in WICH patients who present within the first few hours after ICH, particularly those with mild deficits who are at risk for further deterioration. On the other hand, the utility and cost-effectiveness of PCCs in WICH patients who are severely disabled at baseline or present with devastating severely disabling large hemorrages are less clear. Clearly, more study is needed to better define the subset of WICH patients who may or may not benefit from PCCs.

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Disclosures

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