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Review article

Reversal of antithrombotic treatment in intracranial hemorrhage – A review of current strategies and guidelines

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ABSTRACT

In the last few years, there has been a rapid increase in patients being treated with various anticoagulation and antiplatelet agents. In clinical neurology, these drugs are administered for primary and secondary stroke prevention or to avoid the consequences of immobilization of severe stroke patients. Additionally, thrombolytic intravenous therapy and, recently, intra-arterial therapy for stroke have been increasingly employed all over the world. These therapies are associated with an increased risk of hemorrhage, including the most dangerous, intracranial hemorrhage. The knowledge of the standards for the treatment of hemorrhagic complications in the central nervous system is crucial for doctors in neurology and stroke units as well as in emergency rooms. Therefore, we conducted a review of various guidelines and recommendations, including manufacturers' opinions contained in the summaries of product characteristics (Polish and British or European versions), in Guidelines of the Polish Neurological Society and in international and American guidelines i.e., European Stroke Organization (ESO) and American Heart Association/American Stroke Association (AHA/ASA). In addition, we compared these guidelines with expert opinions published in recent manuscripts and manuals on intensive care in neurology.

The current usage of anticoagulant and antiplatelet therapies has rapidly increased, especially in secondary and primary prophylactics for ischemic stroke as well as for avoiding the consequences of immobilization in severe stroke patients.

In addition, in the last few years, there has been a significant increase in the number of stroke patients treated intravenously and, more recently, intra-arterially with recombinant tissue plasminogen activator (rtPA).

The increase in the number of patients treated with these drugs is related to the growth in the risk of antiplatelet-, anticoagulation- and thrombolytic-associated intracranial hemorrhages.

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Therefore, knowledge about reversal methods in patients treated with these drugs is crucial for every-day clinical practice.

Unfortunately, the guidelines, recommendations and strategies for the reversal of drug-induced coagulopathy in cerebral hemorrhage are not consistent. Some of these guidelines, recommendations and strategies do not consider cerebral hemorrhage but merely refer to the general treatment of any hemorrhage.

Therefore, we developed a summary of the recommendations from various up-to-date sources and attempted to compare them.

The aim of this paper was to present the methods of reversing the coagulopathy in intracranial hemorrhages caused by the following:

- Anticoagulation agents: heparins, vitamin K antagonists, and non-vitamin K antagonist oral anticoagulants (formerly novel oral anticoagulants (NOACs)) (apixaban, rivaroxaban and dabigatran),
- Antiplatelet agents, including acetylsalicylic acid (aspirin), thienopyridines (as clopidogrel and prasugrel), and ticagrelol.
- Thrombolytic agents (rtPA).

Because the methods of treatment of those coagulopathies differ depending on the hemorrhage etiology, clinical center experience and evidence from clinical trials, we developed a summary of treatment recommendations from the following sources: the summary of product characteristics (SPCs) published by the manufacturer (Polish and British or European versions), current guidelines by Polish (Polish Society of Neurology – PTN) [1], European (ESO) [2], and American (AHA/ASA) [3] scientific organizations and current manuals by leading experts in the field published within the last 3 years [4–6].

The review involves primary intracranial hemorrhage (ICrH) and secondary ICrH after ischemic stroke. A generally accepted rule is that the hemorrhagic transformation of ischemic stroke with deterioration of the neurologic condition requires management that is similar to that in spontaneous ICrH. Clinically insignificant secondary hemorrhages (diagnosed with neuroimaging methods) do not require any additional measures [1].

We reviewed only pharmacological therapies, and the indications for surgical treatment of ICrH will be addressed in another review.

1. Vitamin K antagonists (VKA)

See Table 1.

1.1. *Summary of product characteristics*

1.1.1. *Acenocoumarol*

Summary of product characteristics, Polish version (2013) [7], outlines therapeutic options in hemorrhage after acenocoumarol administration. In clinically insignificant hemorrhages – temporary reduction of the dose. In moderate hemorrhages – vitamin K 2–5 mg p.o. In severe hemorrhages – vitamin K 5–10 mg i.v. (not faster than 1 mg/min). This dose can be repeated every 4 h up to a daily dose of 40 mg. In the case of sudden severe hemorrhage – fresh whole blood or fresh frozen plasma (FFP) or recombinant Factor VIIa (rFVIIa) and vitamin K should be administered.

Additionally, in British version of SPC [8], manufacturer recommends management of severe hemorrhage with administering fresh whole blood or prothrombin complex concentrate (PCC) with vitamin K.

1.1.2. *Warfarin*

Therapeutic options for warfarin (tabl. a 3 and 5 mg) described in summary of product characteristics, Polish version (2013) [9] are as below:

Warfarin's half-life is 20–55 h; therefore, overdoses require longer observation and longer vitamin K administration. In some cases, gastric lavage and activated charcoal p.o. may be useful. If severe bleeding occurs, FFP, PCC or tranexamic acid can be administered.

Manufacturers outline the management of INR increases; this management may be considered ICrH prevention. An INR increase does not automatically lead to a hemorrhage, but it is a definite ICrH risk factor; therefore, below, we present the management of such a condition.

INR > 4 without bleeding – stop warfarin, wait 1 day, adjust the dose. INR > 6 without bleeding – stop warfarin, wait 1–2 days, adjust the dose, check the INR immediately. INR > 8 without bleeding – stop warfarin, consider administering 1–2 mg of vitamin K i.v. or p.o., wait – 2 days, check the INR the following day, adjust the dose.

Small bleeding * – stop warfarin, wait 1–2 days before using warfarin and consider administering 1–2 mg of vitamin K i.v. or p.o.

Severe bleeding* – stop warfarin, rapidly reduce the INR to 1.5–1.6; 10 ml/kg FFP can reduce INR from 7 to 4 or from 4 to 2.2.

Table 1 – The management of VKA-associated ICrH.

SPC [7–10]	PNA [1]	ESO [2]	AHA/ASA [3]	Manual Wijdics [4]	NCC Wijdics [5]	Manual Frontera [6]
Withold oral anticuagulant administration						
Vitamin K p.o. or i.v. PCC or FFP and vitamin K (acenocumarol SPC only: whole blood or rFVIIa + vitamin K)	When INR is >1.4: Vitamin K PCC	Vitamin K i.v. Add PCC or FFP	Vitamin K i.v. PCC, FFP	Vitamin K i.v. PCC, FFP or rFVIIa	Vitamin K i.v. PCC, FFP or rFVIIa	Vitamin K i.v. PCC or FFP

FFP – fresh frozen plasma, PCC – prothrombin complex concentrate, rFVIIa – recombinant factor VIIa.