

Medical Treatment for Spontaneous Anticoagulation-Related Intracerebral Hemorrhage in the Netherlands

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Background: Spontaneous anticoagulation-related intracerebral hemorrhage accounts for up to a quarter of spontaneous intracerebral hemorrhage cases and is associated with higher hematoma volume and a worse outcome. Guidelines recommend rapid anticoagulant reversal but mode and timing are not specified and optimal strategy is uncertain. Variability in everyday practice is unknown. *Methods:* An invitation to a web-based survey was sent to 85 Dutch stroke neurologists in different hospitals, with questions about importance, timing, and medical management of spontaneous anticoagulation-related intracerebral hemorrhage. *Results:* In total, 61 (72%) neurologists completed the survey. Nearly all (97%) deemed rapid anticoagulant reversal important. A local guideline for management of anticoagulant reversal was used in 80% of the hospitals. Most neurologists (56%) estimated anticoagulant reversal in anticoagulation-related intracerebral hemorrhage to start later than intravenous thrombolysis in ischemic stroke. Few (5%) thought it was quicker. A minority (28%) of the hospitals started anticoagulation reversal without waiting for laboratory test results or consulting a specialist in hemostasis. Prothrombin complex concentrate was used by all neurologists for vitamin K antagonist reversal and by most (74%) for reversal of thrombin inhibitors and factor Xa inhibitors (72%). Anticoagulation reversal was initiated at the emergency department according to 89% of the respondents. *Conclusion:* Variability in logistics in acute management of spontaneous anticoagulation-related intracerebral hemorrhage was demonstrated. Anticoagulant reversal is deemed important, but is estimated to have a longer door-to-needle time than alteplase in thrombolysis for ischemic stroke by most neurologists. Several delaying factors were found. These factors might have an impact on outcome. **Key Words:** Anticoagulation-related intracerebral hemorrhage—anticoagulation reversal—intracerebral hemorrhage—coagulopathy—oral anticoagulants—door to reversal. © 2017 National Stroke Association. Published by Elsevier Inc. All rights reserved.

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Received September 7, 2016; revision received March 14, 2017; accepted March 21, 2017.

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1052-3057/\$ - see front matter

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<http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2017.03.019>

Introduction

Intracerebral hemorrhage (ICH) has an estimated incidence of 25/10,000 persons/year and leads to death in 40% within the first month.¹ The survivors have high rates of disability and dependence.¹ Approximately 15%-25% of patients use anticoagulation at the time of ICH.^{2,3}

Spontaneous oral anticoagulation-related intracerebral hemorrhage (OAC-SICH) is associated with larger hematoma volumes and increased rates of hematoma enlargement, leading to higher mortality rates.⁴⁻⁷ Fast reversal of anticoagulation with pharmacological interventions reduces hematoma enlargement in OAC-SICH.⁸⁻¹⁰

Reversal of international normalized ratio (INR) levels below 1.3 within 4 hours after admission is associated with reduced rates of hematoma enlargement.¹⁰ However, whether this improves clinical outcome remains uncertain.⁸⁻¹¹ International guidelines recommend reversal of anticoagulants, but mode and timing are not specified.¹¹⁻¹³

Direct oral anticoagulants (DOACs), direct thrombin inhibitors, and factor Xa inhibitors are increasingly used instead of vitamin K antagonists (VKAs). They have a lower risk of intracranial bleeding and are more user friendly compared to traditionally used VKAs.¹⁴ Optimal pharmacological treatment in OAC-SICH with DOAC is not described in recent international guidelines¹¹⁻¹³ and was uncertain, at least until specific antidotes for thrombin inhibitor dabigatran and factor Xa inhibitors apixaban and rivaroxaban were published in 2015.^{15,16}

We hypothesized considerable variation might exist in logistics and pharmacological treatment of OAC-SICH. We used an online survey to investigate current practice in the Netherlands. The results of this survey can be used to identify points of improvement for future treatment of OAC-SICH.

Materials and Methods

We analyzed ICH guidelines to identify topics where practice variation in pharmacological treatment of OAC-SICH might occur. Furthermore, we hypothesized about possible delays in the operating procedures, in analogy to intravenous thrombolysis in acute stroke. A web-based survey was made using an online survey creator (<http://www.surveymonkey.nl>). The questionnaire consisted of 18 multiple-choice questions, with a free-text field for comments. The questions covered the importance of pharmacological treatment, the mode of anticoagulant reversal in several anticoagulants, and the logistics after arrival in the emergency department. The strategy for reversal was evaluated separately for each oral anticoagulant: VKAs, thrombin inhibitors, and factor Xa inhibitors. Each possible answer option for reversal of anticoagulation in VKA-related SICH included vitamin K. Each possible option answer for anticoagulation reversal in DOAC-

related SICH included active charcoal in case of recent intake of the anticoagulant. Questions are shown in an online supplement. In all Dutch hospitals with emergency care services for stroke, 1 stroke neurologist was asked to participate in an anonymous web-based survey between June and December 2014. All neurologists were working in different hospitals covering the Netherlands, 1 survey per hospital was sent. Most neurologists had participated in an earlier online survey on variation in clinical practice of intravenous thrombolysis in stroke.¹⁷ Two reminders were sent to increase the response rate. Only completed questionnaires were included. Answers were analyzed using SPSS 21.0 (IBM SPSS Statistics for Mac, Version 21.0, IBM Corp, Armonk, NY).

Results

The questionnaire was sent to 85 neurologists. The final response rate was 76.5% (65/85). Sixty-one questionnaires were complete (71.8%).

All neurologists reported that SICH patients were presented at their emergency department. Fifty-nine neurologists (96.7%) deemed rapid anticoagulant reversal in OAC-SICH important. In 49 hospitals (80.3%), a local guideline for management of SICH was present.

Mode of Anticoagulant Reversal

The preferred medical strategy of neurologists for reversal is presented in Table 1. Prothrombin complex concentrate (PCC) was the most selected first choice treatment for reversal of all anticoagulants (Table 1). However, for reversal of thrombin inhibitors and factor Xa inhibitors, some neurologists considered a different treatment strategy. Some neurologists who chose the option "other" would give additional therapies to PCC. They would add thrombocytes if the platelet count was below 100×10^9 per liter, or activated eptacog alfa or activated PCC. Two neurologists considered plasmapheresis for reversal of thrombin inhibitors, none of the neurologists considered this for reversal of factor Xa inhibitors. One neurologist would add tranexamic acid to PCC for factor Xa inhibitor reversal. Several neurologists marked that they had

Table 1. Agent for anticoagulation reversal

	VKAs	Thrombin inhibitors	Xa inhibitors
PCC	60 (98.4%)	41 (67.2%)	42 (68.9%)
Fresh frozen plasma	—	5 (8.2%)	6 (9.8%)
Eptacog alfa, activated	—	2 (3.3%)	1 (1.6%)
PCC, activated	1 (1.6%)	4 (6.6%)	2 (3.3%)
Plasmapheresis*	—	—	—
Other	—	9 (14.8%)	10 (16.4%)

Abbreviations: PCC, prothrombin complex concentrate; VKA, vitamin K antagonist.

*Plasmapheresis was not an answer option for VKA reversal; all other answer options could be chosen for each anticoagulant.

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