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Potential impact of point-of-care INR testing on intravenous thrombolysis

Potencial de impacto do teste capilar rápido para avaliação de INR sobre a trombólise endovenosa

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In this issue of *Arquivos de Neuro-psiquiatria*, Bruch et al. compared international normalized ratio (INR) measurements performed with point-of-care (POC) coagulometers and standard coagulation analysis (SCA) in 80 outpatients in use of oral anticoagulants (warfarin or fenprocoumon). Most of the patients had cardioembolic strokes, metallic prosthetic valves, or cerebral venous thrombosis[1].

The authors evaluated the accuracy of POC measurements to detect INR measurements lower or equal than 1.7. This INR threshold is recommended for decision-making by the American Heart Association/American Stroke Association (AHA/ASO) as well as by Brazilian guidelines, in patients otherwise eligible for intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA)[2,3]. According to these guidelines, an INR >1.7 or a prothrombin time >15 seconds are exclusion criteria for intravenous thrombolysis within 3 hours from symptom onset. Also, according to AHA/ASO guidelines, taking an anticoagulant regardless of INR is a relative exclusion criterion within the time window of 3-4.5 hours from symptom onset[1]. The European rtPA license does not allow intravenous rtPA treatment for patients in use of oral anticoagulants[3].

Guidelines regarding INR results intend to avoid hemorrhages and, in particular, intracranial hemorrhage, the most feared complication of intravenous thrombolysis in patients taking oral anticoagulants. There is evidence that the INR cut-off defined by the AHA/ASO guidelines is appropriate to avoid this devastating condition. In the AHA Get With The Guidelines-Stroke (GWTG-Stroke) Registry, adjusted rates of symptomatic intracranial hemorrhage after thrombolysis were not significantly different in 1802 warfarin-treated patients with INRs ≤1.7, and in 21,635 not-warfarin-treated-patients[4]. Similar results were obtained in 768 warfarin-treated patients with INRs ≤1.7 and 43,651 not-warfarin-treated patients in the Safe Implementation of Thrombolysis in Stroke (SITS) International Stroke Thrombolysis Register[5]. Results of the A Virtual International Stroke Trials Archive (VISTA) indicated that rtPA has a beneficial effect on functional outcomes in patients with INRs ≤1.7[6]. Two meta-analyses suggested an increased risk of intracranial hemorrhage after thrombolysis in patients treated with warfarin, but were criticized by the lack of adjustment for confounding variables[7,8].

Because it is known that "time is brain" in acute stroke, the AHA/ASO guidelines recommend that, in patients *known not to be taking* oral anticoagulants, intravenous thrombolysis can be initiated before results of coagulation tests or platelet counts are available, unless a bleeding abnormality or thrombocytopenia is suspected, the patient has received heparin or other anticoagulants. If thrombolysis is started and then results of these tests shown an INR >1.7 or a PT >15 seconds by *local laboratory standard*, the procedure should be discontinued[1]. The question posed by the authors is: can POC coagulometers substitute PSA and speed decision-making in the acute setting, for patients taking anticoagulants? In order to address the question, INR results were obtained by POC and PSA not in patients in the acute phase after stroke, but in outpatients in use of vitamin K antagonists.

The study provides indirect evidence that POC coagulometers can be useful, because sensitivity to detect an INR≤1.7 was 96.6% (95%CI: 88.4-99.1%), specificity was 60.0% (95%CI: 38.6-78.1%), the positive predictive value was 85.7% (95%CI: 75.9-92.1%) and the negative predictive value, 81.2% (95%CI: 53.7-95.1%), with an accuracy of 81.3% (95%CI: 75.2-87.3%).

These results suggest that thrombolysis might be safely initiated in patients using vitamin K antagonists presenting with acute ischemic stroke and eligible for thrombolysis, if the POC INR is ≤1.7. For those presenting with larger POC INR results, an INR obtained by SCA should be awaited before deciding whether or not rtPA should be administered. In many hospitals in Brazil, INR results may not be available in an emergency setting before many precious hours have elapsed within the rtPA therapeutic window. The availability of a POC INR result may hence have a substantial impact on the ability to administer intravenous thrombolysis to warfarin-treated patients who would otherwise be considered ineligible for treatment.

The authors acknowledged that a limitation of the study was not measuring INRs in patients in an emergency setting. Still, in a study that employed this approach, measurements obtained with POC and PSA were highly correlated in patients using oral anticoagulants (r=0.98). Specifically, the correlation was also high (r=0.97) in those patients submitted to thrombolysis[9]. Almost half an hour was gained, on average, by relying on POC INR to start treatment instead of waiting for PSA results. Importantly, none of the treated patients evolved with intracranial hemorrhages after thrombolysis.

It has been estimated that each minute of onset-to-treatment can grant on average 1.8 days of extra healthy life in patients with stroke submitted to thrombolysis[10]. Saving time by using POC INRs may bring better functional outcomes closer to patients' fingertips.

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