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CE - RESEARCH LETTER TO THE EDITOR

Lumbar puncture after direct oral anticoagulant (DOAC) reversal: a proposed algorithm for the emergency department

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Dear Editor,

The case reported by Spagnolello et al. [1] confirms the safety of emergency lumbar puncture after dabigatran reversal with idarucizumab, as suggested by other authors [2, 3], including ourselves [4] (Table 1). Spagnolello et al. [1] re-present the issue of anticoagulant treatment periprocedural management in patients on direct oral anticoagulants (DOACs) requiring lumbar puncture (LP) to rule out infectious diseases of the central nervous system, or subarachnoid hemorrhage.

Dodd et al. [5] have recently provided evidence-based recommendations for the periprocedural antithrombotic management of lumbar puncture, on the behalf of the Association of British Neurologists. However, they left how to manage patients on DOACs, a relatively novel pharmacological class, under debate. These authors [5] suggest involving a hematologist to discuss the risk/benefit ratio of DOAC withdrawal and that the patient be monitored for new neurological signs/symptoms, if an urgent LP is warranted outside the time frames recommended for a non-urgent LP. Although Dodd et al. mention the interesting possibility of measuring the drug-specific levels to estimate the anticoagulant effect of a DOAC, they do believe that routine testing of DOAC levels before the LP is unnecessary [5]. As expressed in our e-letter [6] to the authors, we are convinced that this is a crucial point. Indeed, specific coagulation assays, developed for the quantification of DOAC plasma levels, are more reliable than routine coagulation tests for the assessment of DOAC anticoagulant effects [7]. Therefore, when available, DOAC drug-specific levels are useful to guide rational clinical management in an emergency setting. Indeed, as long as the drug levels are below the cut-off value chosen to rule out any anticoagulant effect, LP may be performed immediately. Unfortunately, there is still no international consensus and the various advisory bodies, e.g. Societé Francaise de Neurologie Vasculaire (SFNV) and the Groupe Francais d'etudes sur l'Hemostase et la Thrombose (GFHT) [8] and the Swiss operating procedures [9], set different lower threshold limits for the anticoagulant effect of DOACs. They range from 20 to 50 ng/mL for other urgent procedures, such as intravenous thrombolysis. Therefore, international consensus is welcome on DOAC drug level cut-offs for patients requiring urgent or emergent procedures, such as LP or surgery, to rule out adverse anticoagulant effects. In the meantime, based on expert consensus for the management of acute ischaemic stroke by the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation [7], which takes into consideration intravenous thrombolysis in patients on factor Xa inhibitors (rivaroxaban, apixaban and edoxaban), if the DOAC plasma levels are below 30 ng/mL, we suggest adopting for urgent/emergent LP at the same reference cut-off value of 30 ng/mL.

Although DOAC levels within the therapeutical range are challenging for the clinician, a remarkably different and more straightforward management may be prospected if an LP is indicated in patients on dabigatran. Indeed, although literature evidence remains scanty, in our experience an LP after dabigatran emergency reversal by idarucizumab is a safe procedure, even if a haematologist is not consulted, as a time saving measure, and is in agreement with the recent Guidance Statement by the Anticoagulation Forum, a North American organization of anticoagulation providers [10]. However, clinical and

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Table 1 Dabigatran reversal with idarucizumab before lumbar puncture*:* summary of the cases reported

Patient presentation	Idarucizumab administration	Standard coagulation tests		Clinical outcome
		Before idarucizumab administration	After idarucizumab administration	
32-year-old female [1] *Cause of hospital admission* Altered mental status and high fever (39 °C/102.2 F) *Dabigatran treatment* Unprovoked PE 150 mg b.i.d Last intake 11 h before CRP: 9.99 mg/dL	*Reason for administration* Lumbar puncture indicated due to suspicion of infective encephalitis *Time of administration* Not reported *Mode of administration* Intravenous infusion (5 g)	aPTT: 1 s (normal range 0.8–1.2 s)		Lumbar puncture Performed with no bleeding complication; no other information are reported
85-year-old male [2] *Cause of hospital admission* Fever (38.6 °C/101.5° F) and new onset of aphasia *Dabigatran treatment* NVAF 110 mg b.i.d Last intake unknown CRP: 18.5 mg/dL	*Reason for administration* Lumbar puncture indicated due to suspicion of neuroinfection *Time of administration* Immediately before the procedure *Mode of administration* intravenous infusion (5 g)	aPTT: 45.3 s TT: 55.8 s	aPTT: 32.7 s TT: 10.6 s	Lumbar puncture performed with no bleeding complication; neuroinfection disproved and severe carotid artery stenosis and laryngitis diagnosed
81-year-old female [3] *Cause of hospital admission* Somnolence and meningeal symptoms *Dabigatran treatment* NVAF 110 mg b.i.d Last intake on the day of admission CRP: 4.4 mg/dL	*Reason for administration* Lumbar puncture indicated due to suspicion of neuroinfection *Time of administration* Immediately before the procedure *Mode of administration* 10-min intravenous infusion (5 g)	aPTT: 32.8 s	No coagulation tests performed	Lumbar puncture performed with no bleeding complication; neuroinfection disproved and drug (opiate) intoxication diagnosed
82-year-old male [4]	*Reason for administration* *Lumbar puncture indicated due to suspicion of neuroinfection*	aPTT: 49.8 s	aPTT: 28 s	Lumbar puncture performed with no bleeding complication; neuroinfection disproved and septic shock diagnosed

Table 1 (continued)

Patient presentation	Idarucizumab administration	Standard coagulation tests		Clinical outcome
		Before idarucizumab administration	After idarucizumab administration	
Cause of hospital admission *Fever (39 °C/102 °F) and progressive impairment of consciousness up to coma* *Dabigatran treatment* *NVAF* *110 mg b.i.d* *Last intake 7 h before* *CRP: 27.2 mg/dL*	*Time of administration* 15 min before the procedure *Mode of administration* *Bolus intravenous infusion (5 g)*			

aPTT activated partial thromboplastin time, *b.i.d.* twice daily, *PE* pulmonary embolism, *CRP* C-reactive protein, *NVAF* non-valvular atrial fibrillation, *TT* thrombin time

laboratory monitoring is advisable in patients with renal insufficiency, as there may be a rebound of low dabigatran levels 12–24 h after idarucizumab [7].

Clinical management is more challenging in patients on factor Xa inhibitors (rivaroxaban, apixaban and edoxaban). As Dodd et al. [5] report, a reversal agent for these DOACs, i.e. andexanet alfa, was recently approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) (for rivaroxaban and apixaban). Although andexanet alfa may become the first choice therapy in life-threatening bleeding in patients on FXa-inhibitor therapy, the lengthy process required to reverse the DOAC and putative pro-thrombotic effect of andexanet alfa make it an unlikely candidate for an emergency reversal of direct factor Xa inhibitors before LP. Furthermore, the andexanet alfa dosing depends on the DOAC and timing since last intake and, remarkably, the anticoagulant activity may reappear once infusion is stopped [7]. Although the Anticoagulation Forum [10] suggests administering andexanet alfa at the dose used for major bleeding in Xa inhibitor-treated patients requiring an urgent invasive procedure, warranting a reversal agent, we believe that the safety of a LP after a factor Xa inhibitor reversal by andexanet alfa requires further assessment. Should andexanet alfa be unavailable, the Anticoagulation Forum suggests the use of the four-factor Prothrombin Complex Concentrate (4F-PCC) 2000 units [10]. However, there is no evidence, in the emergency context, of the potential benefit of PCC and activated PCC (aPCC), which is debated even in life-threatening bleeding [7].

Moreover, in DOAC treated-patients requiring an invasive procedure such as LP, reversal agents should be used only if the procedure cannot be delayed and there is a demonstration (by specific tests) or reasonable expectation that the patient has clinically relevant plasma DOAC levels [7]. Consequently, we believe decisions should be taken on an individual basis, balancing diagnostic efficacy of the emergent LP against the periprocedural risk, when deciding whether this procedure should be carried out in emergency or postponed to 12–24 h from the last DOAC intake. In an emergency situation where LP is under consideration, we suggest evaluating the individual thrombotic/hemorrhagic risk, based on the main items reported in Table 2. Figure 1 provides a flowchart summarizing our proposed clinical management (Fig. 1).

There is yet another clinical challenge when it comes to DOAC reintroduction after LP, i.e. the timing of the first DOAC dose. As long as renal function is normal, Dodd et al. [5] recommend administering the first DOAC dose 6 h after an atraumatic LP, whatever the urgent or elective context. Whilst, the 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation consider diagnostic LP a high bleeding risk procedure and

Table 2 Main items useful to assess the individual thrombotic/hemorrhagic risk for the peri-procedural management of urgent LP

Thrombotic risk
CHA_2DS_2-VASc[a] score
Previous stroke/transient ischemic attack
Venous thromboembolism-related risk[b] (low/medium/high)
Pro-thrombotic pharmacological interactions
Haemorrhagic risk
Abnormal renal function
HAS-BLED[c] score
IMPROVE[d] score (for patients on DOACs for venous thromboembolism)
Traumatic procedure (for post-procedural risk)
Pro-hemorrhagic pharmacological interactions

[a][11]

[b]Depending on the age of onset of venous thromboembolism, recurrent venous thromboembolism, trombophilic conditions, antiphospholipid syndrome

[c][12]

[d][13]

recommend resuming full dose anticoagulation from the first 48–72 h [7].

So as to balance the risk of periprocedural spinal hematoma and the increased thrombotic risk while the DOAC is suspended, we suggest the first step be that of evaluating the traumatic/atraumatic nature of the LP, followed by a re-assessment of the items listed in Table 2. Although it is no easy feat to provide general advice, we propose the following algorithm for the first DOAC dose after LP, both urgent and elective (Fig. 1). Most of the thrombotic and hemorrhagic risk factors in Table 2 are "weighted" by cut-off scores to guide the clinician's decision on an individual-based strategy. The hemorrhagic risk seems to be the most critical one to balance in the post-procedural phase, whilst in the pre-procedural phase the increased thrombotic risk, related to the DOAC withdrawal, appears to be the most relevant.

Despite the emerging novel clinical scenario for the management of patients on DOACs requiring urgent/emergent LP, with outstanding opportunities provided by specific DOAC level dosages and reversal agents, mainly idarucizumab in dabigatran-treated patients, further studies are required to confirm the safety of DOAC reversal, especially of factor Xa inhibitors. Moreover, international consensus on set clear cut-offs for the anticoagulant effect of DOACs

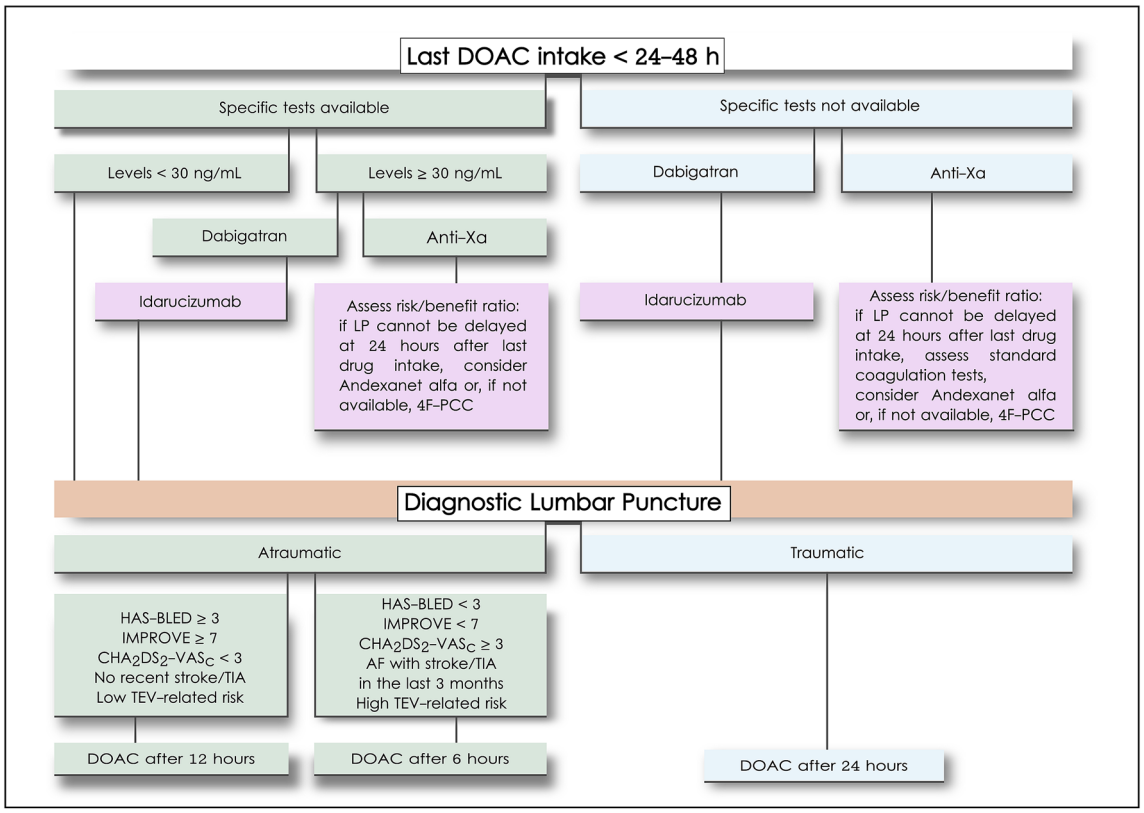

Fig. 1 Flowchart for diagnostic lumbar puncture after DOAC reversal in the emergency. *TEV* Venous thromboembolism, *AF* atrial fibrillation

would be welcome, as would decision pathways to bridge the gaps where many unresolved questions on clinical guidance still remain for a topic where evidence is still limited.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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