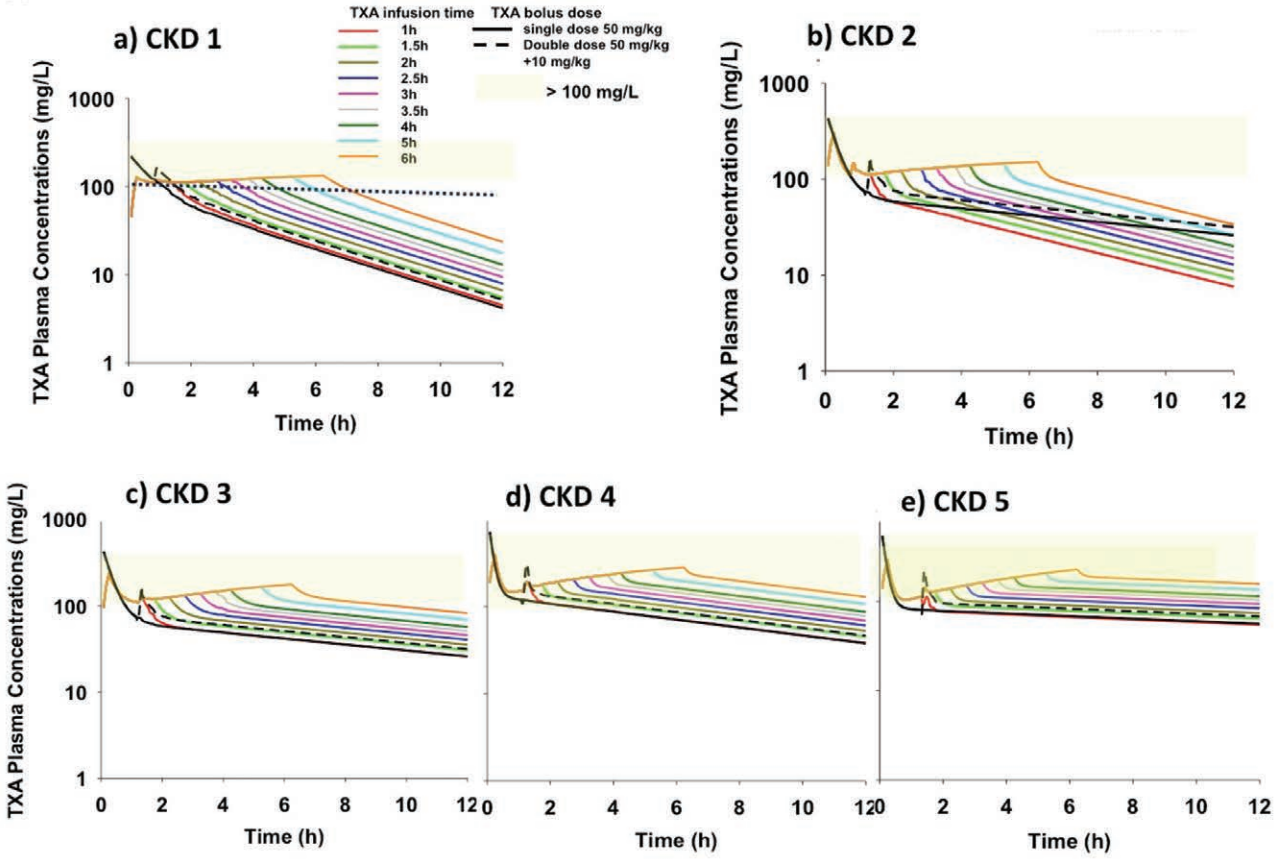
A



CKD Chronic kidney dysfunction; GFR Glomerular filtration rate (ml/min/1.73m2); h hour; TXA Tranexamic acid. CKD 1 GFR ≥90, CKD 2 GFR 60-89, CKD 3 GFR 30-59, CKD 4 GFR 15-29, CKD 5 GFR ≤15 (or dialysis).

B

Glomerular Filtration Rate (ml/min/1.73m²)	LOW BLEEDING RISK [a]	HIGH BLEEDING RISK [a]	
	Post-induction bolus dose	Post-induction bolus dose	Infusion or 2nd bolus dose
≥ 60	50 mg/kg	25 mg/kg	Infusion 12 mg/kg/h for 4 hours
< 60 (or on dialysis)	50 mg/kg	50 mg/kg	Bolus 10 mg/kg after 2 hours

[a] Clinical surgical groups and bleeding risk have been previously defined(1); Low bleeding risk includes isolated aorto-coronary bypass grafting, single valve repair or replacement, and high bleeding risk includes multiple valve repair/replacement, combined aorto-coronary bypass grafting, valve or aortic surgery.

Figure. A, Simulation profiles after altering the duration of TXA infusion between 1 to 6 h or using single or divided TXA bolus dose for CKD stages 1–5. B, Revised dosing regimens based on simulation and previous pharmacokinetic modeling data.[1] CKD indicates chronic kidney dysfunction; TXA, tranexamic acid.

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Questions Regarding the Use of Neostigmine–Atropine to Treat Postdural Puncture Headache

To the Editor

We read with great interest the article titled "Addition of Neostigmine and Atropine to Conventional Management of Postdural Puncture Headache: A Randomized Controlled Trial" by Abdelaal et al.[1] The peak effect of neostigmine for reversing

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neuromuscular blockade occurs at approximately 7–10 minutes, and the duration of action is approximately 55–75 minutes.[2] Although the authors described possible vasoconstriction mediated by neostigmine, it seems unlikely to last for >2 hours. The authors have suggested that increased cerebrospinal fluid secretion may also be a mechanism for symptom resolution. But they do not make clear how it is going to help the loss of cerebrospinal fluid from the puncture site(s).

The present study involved parturients who developed postdural puncture headache after a spinal anesthetic. Patients who experience postdural puncture headache from an inadvertent dural puncture with a larger epidural needle may not respond as well. We wonder whether the authors have any data for this population. Also, an inadvertent dural puncture during epidural placement for analgesia followed by general anesthesia for a major abdominal or thoracic surgery involves use of neuromuscular blockade and subsequent reversal using neostigmine and an anticholinergic agent, now more frequently glycopyrrolate than atropine. Based on authors' findings, such cases might have lesser incidence or lesser severity of postdural puncture headache because they have already received the acetyl cholinesterase inhibitor and anticholinergic combination in a dose more than that described by the authors. Further studies are required to understand this and also to extrapolate the pharmacological regimen suggested by authors in all categories of patients with postdural puncture headache.

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In Response

We appreciate referring to us the letter by Dr Nair[1] concerning our article "Addition of Neostigmine and Atropine to Conventional Management of Postdural Puncture Headache: A Randomized Controlled Trial."[2]

Dr Nair raised the following questions in his letter:

the first question is that the number of attempts required for a successful dural puncture is not mentioned in our study. We agree that this is important information. However, the following facts should be considered: (1) we aimed primarily to assess the effect of neostigmine/atropine as an additive in treating postdural puncture headache, and whatever the mechanism of the dural puncture, it is the severity of the resultant headache and the response of the headache to adding neostigmine/atropine that counts; and (2) our patients received spinal anesthesia, which means, from clinical point of view, in most cases, achieving a dural puncture would have been followed by intrathecal injection of local anesthetic and performing >1 dural puncture for a spinal anesthesia may not be a usual case in clinical practice.

The second question is that the peak effect and duration of action of neostigmine as a reversal for the neuromuscular block may not correlate with its effect in the postdural puncture headache and how much cerebrospinal fluid (CSF) is produced by a single dose of neostigmine. Adhering to evidence-based medicine, the following facts should be considered: (1) there is a difference between the effect of the medications on a neuromuscular junction and their effect on cervical sympathetic ganglia, blood–CSF barrier, and choroid plexus or the sphenoid ganglion. Those mentioned above structures vary among neuromuscular junction, sympathetic ganglion, parasympathetic ganglion, and a secretory structure. (2) With the possible cross of the neostigmine/atropine to the CSF through the blood–CSF barrier, this carries a different pharmacokinetic and pharmacodynamic profile for the medication in the CSF.[3] (3) The neostigmine acts as a cholinesterase inhibitor in the neuromuscular junction while the available explanatory mechanisms of neostigmine/atropine on the other structures are different. In addition, the added atropine has different pharmacokinetic and pharmacodynamic profile that cannot be ignored. The examples mentioned give an idea that we cannot use the pharmacokinetic and pharmacodynamic profile of neostigmine in the neuromuscular junction and apply it elsewhere in the body. To the best of our knowledge, no previous studies determined the amount of CSF produced by a single IV dose of neostigmine/atropine. However, we think future studies may adopt this question to figure out more details on the possible explanatory mechanisms for the clinical findings in our study.

The third question is that what will be the possible effect of neostigmine/atropine in cases with an inadvertent dural puncture with Tuohy needle or in cases that may develop dural puncture during combined general/regional anesthesia with neostigmine is used to reverse the neuromuscular block. We agree that these are good ideas for future research projects that can help us to find out more about the benefits of using neostigmine/atropine in postdural puncture headache in different patients and situations.

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