Tranexamic acid-associated fatal status epilepticus in a paediatric patient

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Dear Editor,

I have read with interest a case report and literature review published in the British journal of pharmacology on tranexamic acid (TXA) associated SE in a 4-year child who underwent tonsillectomy. I would like to congratulate the authors for reporting the case despite the fatal outcome. Considering that the use of TXA is expanding to minimise blood loss in a wide range of surgeries, an evidence-based therapeutic approach for its associated seizures is of paramount importance.

The authors described in their report (also mentioned in Table 2) and concluded that general anaesthetics, propofol and halogenated inhaled anaesthetics are considered the first line of management of TXA-associated seizures due to their direct activity at glycine receptors. In support of their statement, they have quoted three references (references 35,45,46 in their report). However, in their articles, the authors did not recommend the use of general anaesthetics (propofol and halogenated inhalational anaesthetics) as the first line of treatment for TXA-related seizures. It is valuable to point out to the readers that their conclusion is not valid and needs clarification and correction.

TXA-associated hyperexcitability of neural networks is because it is a competitive antagonist of glycine and GABAA receptors. Following IV TXA administration, not all seizures progress to status epilepticus. Although TXA-related seizures commonly manifest as generalised tonic-clonic activity, focal seizures have been
reported; which are not an indication for the use of general anaesthetics. Refractory status epileptics (RSE) and super RSE are uncommon following IV TXA although this is a common feature following intrathecal TXA.\(^3\)

Propofol’s anticonvulsant, hypnotic, sedative and anaesthetic effects are mediated via multiple complex molecular mechanisms, including modulation of GABAA and glycine receptors. GABAA receptor modulation by propofol has distinct dose-dependent effects likely involving multiple sites of action; clinical concentrations of propofol potentiate GABA-activated currents, increase open channel frequency, and reduce the rate of desensitization, while intermediate concentrations directly activate GABAA channels, and even higher concentrations inhibit receptor function.\(^4\)

Propofol can cause neuroexcitatory effects, including tonic-clonic seizures, particularly during the start or weaning from propofol infusion.\(^5\) Among the various mechanisms that have been proposed for these neuroexcitatory symptoms are antagonism of glycine and dopamine receptors, hyposensitization of GABAergic pathways and dysregulated inhibition of NMDA glutamate receptors.\(^6\) Its use is associated with side effects, including hypotension (and the associated use of vasopressors) and respiratory depression. With prolonged infusion, propofol infusion syndrome (PIS) may occur, which may contribute to morbidity and mortality of RSE. Children are more susceptible to developing this complication. Propofol infusion therapy is not recommended as the first line of treatment for TXA-associated seizures, and its use is reserved for severe cases in children.

Inhalational anaesthetics are beneficial for the control of seizure activity via inhibition of NMDA excitotoxicity and potentiation of inhibitory functions of GABAA and glycine receptors. However, it is essential to highlight that there are several limitations to the use of inhalational anaesthetic agents. First, the only clinical evidence of their use is from the minimal number of case reports. Second, TXA-related seizures often manifest in the postoperative period in the recovery room or in ICU, where delivery and scavenging of inhalational agents via ventilator may not be feasible. Third effective end-tidal concentration and optimal therapeutic duration are not known. Finally, in higher concentrations, they cause cardiac depression and cerebral vasodilation. Therefore, their use is limited as salvage therapy for the management of TXA-associated RSE and super RSE.

In summary, the authors’ conclusion is incorrect, and clinicians should follow currently available evidence-based professional guidelines to manage TXA-associated status epilepticus.\(^8,9\)

References:

7. Godec S, Gradisek MJ, Mirkovic T etal. Ventriculolumbar perfusion and inhalational anesthesia with
