Update in
Anaesthesia

Case Report

Intrathecal tranexamic acid during spinal anaesthesia for caesarean deliver

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D G Bishop*, A C Lundgren, N F Moran, I Popov and J Moodley
*Correspondence email: bishop@ukzn.ac.za

Summary

The National Committee on Confidential Enquiries into Maternal Deaths recently received notification of a death in South Africa caused by inadvertent intrathecal administration of tranexamic acid (TXA). TXA is increasingly used during caesarean delivery following updated recommendations from the World Health Organization in 2017. However, its greater availability has led to an international rise in drug errors during obstetric spinal anaesthesia. This case highlights a growing clinical risk, of which all operating theatre staff should be aware. Review of existing operating theatre drug handling practices is required in order to decrease this risk. Recommendations are made that aim to minimise drug errors associated with the use of this potentially life-saving intervention.

INTRODUCTION

The National Committee on Confidential Enquiries into Maternal Deaths recently received notification of a death in South Africa (SA) caused by inadvertent intrathecal administration of tranexamic acid (TXA). This case highlights a growing clinical risk, of which all operating theatre staff should be aware. Review of existing operating theatre drug handling practices is required in order to minimise this risk.

TXA is included in the World Health Organization (WHO) essential medicines list (EML)[1] as well as the SA National Department of Health EML.[2] It is a synthetic lysine analogue that acts to reduce fibrinolysis through competitive inhibition of plasminogen binding sites. TXA is increasingly being used in the perioperative setting as a result of recently updated WHO guidelines recommending early use of intravenous TXA during caesarean delivery (CD) when excessive bleeding occurs.[3] The key messages from this guideline are summarised in Table 1. This change in practice is largely due to the results of the WOMAN trial, a landmark multicentre study including 20,000 patients that showed reduced maternal mortality due to bleeding with the early administration of TXA in the setting of postpartum haemorrhage.[4] The WOMAN trial showed that if TXA was given intravenously within 3 hours of bleeding following normal vaginal delivery or CD, maternal mortality was reduced by 31%, although the absolute reduction was small (1.7 - 1.2%, risk ratio 0.69, 95% confidence interval 0.52 - 0.91; p=0.008). These benefits were most pronounced in low- and middle-income settings such as SA.[4] The WHO states that 'regardless of the level of health system resources, TXA should be recognized as a lifesaving intervention and be made readily available for the management of postpartum haemorrhage in settings where emergency obstetric care is provided'.[3]

SA TXA RECOMMENDATIONS

It has been suggested that the high number of deaths due to obstetric haemorrhage (OH) at or after CD in SA is a national emergency,[5] and despite a recent downward trend, OH remains the third most common cause of maternal mortality at ~17%.[6] Accordingly, the nationally endorsed training programme for obstetric emergencies (Essential Steps in the Management of Obstetric Emergencies: ESMOE)[7] has been revised to recommend early intravenous administration of 1g TXA for bleeding during or after CD. Excessive bleeding is now defined as >500mL in the suction bottle, or a decrease in blood pressure accompanied by a rise in heart rate associated with bleeding, as detected by the anaesthetist. This is earlier than the traditional description of at least 1,000mL blood loss during CD, and TXA is therefore being used with greater frequency. While there may be a role for the administration of TXA before CD,[8,9] there is not yet enough evidence from high-quality research to recommend such prophylaxis at a national level.[10] In particular, there is no evidence that prophylactic TXA before CD reduces maternal death.

D G Bishop **MB CHB, DA, FCA, PHD**
Department of Anaesthesia
School of Clinical Medicine
College of Health Sciences
University of Kwazulu-natal
Pietermaritzburg
SOUTH AFRICA

A C Lundgren, **MB, CHB, DA, FFA, PHD MSC MED (HEALTH HAW AND BIOETHICS)**
Steve Biko Centre for Bioethics
Faculty of Health Sciences
University of the Witwatersrand
Johannesburg
SOUTH AFRICA

N F Moran, BM BCH, MA, FCOG
KwaZulu-Natal Department of Health and Department of Obstetrics and Gynaecology
School of Clinical Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban
SOUTH AFRICA

I Popov, **MC, FCOG (SA)**
Department of Gynaecology and Obstetrics
Port Shepstone Regional Hospital
KwaZulu-Natal
SOUTH AFRICA

J Moodley, MB CHB, FRCOG, MD
Women's Health and HIV Research Group
Department of Obstetrics and Gynaecology
School of Clinical Medicine
College of Health Sciences
University of KwaZulu-Natal
Durban
SOUTH AFRICA

Table 1: Key messages adapted from the updated World Health Organization recommendations on TXA for the treatment of postpartum haemorrhage[3]

Bleeding during CD is defined as a clinical estimate of blood loss >1 000 mL, or blood loss sufficient to cause haemodynamic instability
Early use of TXA (within 3 hours of birth), in addition to standard care, is recommended. The use of TXA >3 hours after birth is not supported
Administer TXA 1g IV over 10 minutes, with a repeat dose if bleeding continues after 30 minutes, or if bleeding restarts within 24 hours of the first dose. Only IV use is currently supported
TXA should be given in all cases of postpartum haemorrhage, regardless of cause
TXA should not be given when a clear contraindication exists, such as thromboembolic disease during pregnancy.

TXA = tranexamic acid; CD = caesarean delivery; IV = intravenous

With increased availability and use of TXA during and immediately following CD, the risk of drug error increases. Our case of maternal death was assessed by independent experts to be due to intrathecal TXA, and occurred in the context of a disturbing international trend. A recent review in Anaesthesia[11] highlighted 21 such cases between 1988 and 2018, 10 of which were fatal. Twenty were due to 'ampoule error'. An accompanying editorial[12] entitled 'Spinal tranexamic acid – a new killer in town' highlighted the dramatic increase in the number of cases since 2009. Seven cases involved CD, 6 of which resulted in death: it appears that mortality is higher following CD than following other surgery. The authors mention anecdotal reports of further cases that have not been formally reported, making the true incidence hard to estimate. Clinicians are understandably reluctant to submit case reports relating to serious medical error. Additionally, cases such as ours that come to light through a confidential enquiry process cannot be published in detail owing to requirements to maintain anonymity. The incidence is therefore probably far higher than currently reported.

CONSEQUENCES OF INTRATHECAL TXA ADMINISTRATION

Intrathecal TXA is a potent neurotoxin and neurological sequelae dominate the clinical presentation, usually with refractory seizures. Massive sympathetic stimulation frequently occurs, often leading to lethal cardiac arrhythmias such as ventricular fibrillation. Treatment is mainly supportive and should occur in an intensive care setting, including antiepileptics such as diazepam, thiopentone and magnesium sulphate[13] and appropriate antiarrhythmic medication. Early cerebrospinal fluid (CSF) lavage is also recommended, following success in the management of similar cases.[11,14,15] CSF lavage consists of removing 10mL of CSF and replacing this with 10 mL of saline, repeated up to four times.[14,15] The increased mortality rate in the obstetric population following intrathecal TXA is possibly due to decreased CSF volume in pregnancy, leading to increased drug concentrations.[11]

Given the consequences of inadvertent intrathecal TXA administration, is the increased risk justifiable? TXA has become an integral part of the management of OH: the WOMAN trial[4] suggested that a maternal life could be saved with every 267 usages following OH. The potential 'number needed to harm' is difficult to estimate: Palanisamy and Kinsella[12] estimate the risk due to drug error to be <1 in 10,000 spinal anaesthetics, although this is necessarily based on a large degree of conjecture. In Africa, the incidence of severe bleeding during or after CD is almost 6%, while 70% of all complications and 25% of all deaths are secondary to bleeding complications.[16] With a lower recommended threshold for the use of TXA, it is likely that the drug will be given in >6% of cases. The benefits clearly outweigh the risks: the focus therefore needs to be on minimising or eliminating drug error.

MINIMISING THE RISK OF INTRATHECAL DRUG ERROR

The incidence of perioperative drug errors ranges from one in 133 anaesthetics in retrospective studies[17] to one in two operations in prospective studies (one in 20 drug administrations).[18] Obstetric neuraxial drug administration errors in particular may result in devastating consequences.[19] There is a lack of randomised controlled trials that examine specific techniques and their ability to reduce drug error; recommendations are therefore based on expert opinion and best available evidence.[20,21]

All health facilities should ensure that they have clearly written policies that minimise medication errors, and then audit and appraise errors that do occur.[22] This approach should nurture a culture of drug safety, including multidisciplinary involvement, ongoing education and specific evidence-based interventions.[22] However, despite vociferous calls for changes in practice, merely exhorting doctors to be more careful is often inadequate.[23] Ideally, system changes should make it impossible for error to occur. A similar problem has been encountered with epidural anaesthesia, where the use of Luer universal connectors has allowed for cross-connectivity, resulting in drug errors. This problem is easily preventable with the use of non-Luer connectors, although uptake has been slow.[23] Non-Luer connectors will not prevent a single-shot spinal anaesthesia drug error, however, as occurs with TXA.

The risk of accidental use of the wrong drug increases when ampoules look similar, or are physically available in close proximity.[24] There are now a large number of generic versions of TXA, and changes in supplier and the appearance of ampoules are increasingly common. Human error is to some degree unavoidable, and rather than attempting to eliminate all mistakes, strategies should aim to reduce predictable errors. Solutions that minimise the possibility of human error should be given highest priority.[24] Technology-assisted drug identification, using barcode readers, is one such intervention, although it is unlikely to be immediately available in SA facilities. Pre-filled syringes may be another, although this may be problematic for manufacturers, as each drug must be tested for stability in a pre-filled syringe. Other solutions include the careful reading and labelling of syringes, and a second person or device checking the drug.[19] More costly methods, such as commercially prepared spinal anaesthesia

Table 2: Recommendations for preventing TXA drug errors during and immediately after caesarean delivery

Raise awareness in health facilities (private and public), both written and verbal. Display a clinical alert warning in operating theatres.
Ensure that warnings reach all cadres of staff involved in CDs, whether in an anaesthetic, surgical, nursing or pharmaceutical roles
Conduct regular in-service training of all health professionals on how to avoid drug errors. In the SA context, this should be included in the ESMOE/EOST anaesthesia module.
Avoid buying drug ampoules that are similar in appearance, and standardise individual drug appearance.
Colour-code syringes/drugs where possible.
Use bar coding and scanner identification or pre-filled syringes if capacity exists.
Physically separate TXA from a dedicated spinal anaesthesia trolley (consider a drug cupboard outside the operating theatre).
Ensure appropriate drug checking practices: careful reading of labels with a second person checking, and minimise distractions during medication preparation.
Report and review all adverse drug events through an incident reporting system.
Minimise staff fatigue.

TXA = tranexamic acid; CDs = caesarean deliveries; SA = South African; ESMOE = Essential Steps in the Management of Obstetric Emergencies; EOST = Emergency Obstetric Simulation Training.

Figure 1. Tranexamic acid, hyperbaric bupivacaine and isobaric bupivacaine.

Figure 2. Tranexamic acid and spinal bupivacaine stored in the same container in a private hospital.

trays including bupivacaine, are unlikely to represent solutions for low- and middle-income countries such as SA. Most importantly, the physical location of TXA must minimise the potential for drug error. There are numerous drugs in theatre that should never be injected intrathecally; we need to ensure that TXA is one of these. Avoiding a drug substitution error mandates meticulous attention to drug checking systems, and above all ensuring that TXA is not kept on or near the spinal anaesthesia trolley. Consideration should be given to storing TXA out of theatre, provided that the drug will be available immediately when requested.

We have made recommendations in Table 2 summarising key interventions aimed at reducing drug error from the relevant literature.

Importantly, this clinical alert applies equally to both the private and public sectors in SA, where different versions and appearances of the drug ampoules are available. Figure 1 illustrates the current appearances of TXA and bupivacaine in the state sector in KwaZulu-Natal Province. Figure 2 illustrates the TXA used by one of the private hospitals in KwaZulu-Natal. This image was taken after discovering these ampoules in the same container, illustrating the potential for drug error.

CONCLUSIONS

The indications for TXA during and after CD continue to expand. The increased use and availability of the drug have led to a concerning increase in inadvertent intrathecal administration worldwide – an error that always results in harm. We need to urgently raise awareness of this potentially lethal mistake and take steps to ensure that we have no further such cases in SA. The first step is to store TXA in a separate location from spinal bupivacaine, and ensure that the drug is never present on the spinal anaesthesia trolley.

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