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Exploratory randomised trial of tranexamic acid to decrease postoperative delirium in adults undergoing lumbar fusion—a trial stopped early

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Abstract

Background: Postoperative delirium may be mediated by systemic inflammation and neuroinflammation. By inhibiting the proinflammatory actions of plasmin, tranexamic acid (TXA) may decrease postoperative delirium. To explore this hypothesis, we modified an ongoing randomised trial of TXA on blood loss, adding measures of delirium, cognition, systemic inflammation, and astrocyte activation.

Methods: Adults undergoing elective posterior lumbar fusion randomly received intraoperative i.v. TXA (n=43: 10 mg kg^{-1} loading dose, 2 mg kg^{-1} h^{-1} infusion) or placebo (n=40). Blood was collected before surgery and 24 h after surgery

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(*n*=32) for biomarkers (cytokines and S100B). Participants had twice daily delirium assessments (*n*=65). Participants underwent four measures of cognitive function before surgery and during post-discharge follow-up.
Results: Postoperative blood loss was ~38% less in the TXA group compared with the placebo group with medians of 128 and 207 ml level^{-1}, respectively, *P*=0.013. Total blood loss in the TXA and placebo groups did not differ with medians of 305 and 333 ml level^{-1}, respectively, *P*=0.472. Delirium incidence in the TXA group (7/32=22%) was not significantly less than in the placebo group (11/33=33%); *P*=0.408, effect size =−0.258 (95% confidence interval −0.744 to 0.229).
Conclusions: A potential 33% relative decrease in postoperative delirium incidence justifies an adequately powered clinical trial to determine if intraoperative TXA decreases delirium in adults undergoing lumbar fusion.
Clinical trial registration: NCT04272606.

Keywords: clinical trial; cytokines; delirium; S100B; spinal fusion; tranexamic acid

Postoperative delirium occurs in 15–40% of patients, varying with patient characteristics and type of procedure.[1,2] Postoperative delirium is associated with a greater incidence of pre-discharge adverse events,[1,3] greater length of hospital stay,[1,3] greater incidence of non-home discharge,[1,3] greater readmissions,[1,3] greater short- and long-term costs,[4] greater mortality,[1] and long-term cognitive decline.[5,6]

Postoperative delirium has been intensively studied in numerous preclinical models and clinical studies. These studies indicate that many factors contribute to postoperative delirium.[1,7,8] Among these factors is the brain's response to systemic injury. Tissue injury, occurring with surgical procedures, trauma, or burns, results in inflammation at the site of injury and in increased circulating concentrations of proinflammatory mediators.[9] These circulating mediators trigger inflammatory responses within the brain (neuroinflammation),[10,11] resulting in changes in behaviour and cognition. In principle, decreasing the magnitude of systemic inflammatory response, decreasing the subsequent neuroinflammatory response, or both, should decrease the incidence, severity, or both, of postoperative delirium. This has been demonstrated in animal models.[12,13]

Tranexamic acid (TXA) is a lysine analogue that competitively blocks plasminogen binding to fibrin, decreasing or preventing fibrinolysis.[14,15] In common clinical use for decades, TXA is often administered off-label to decrease perioperative blood loss.[16–18] It is now known that many cell types have plasmin(ogen) receptors,[19] and that plasmin(ogen) has many physiological roles in addition to fibrinolysis,[20,21] including modulating neuroinflammation.[22] By inhibiting lysine-dependent plasmin(ogen) binding to its receptor, TXA has the potential to decrease plasmin(ogen)-mediated inflammatory responses.[21,23] For example, in some clinical studies, TXA decreases postoperative proinflammatory cytokine concentrations.[24] Plasmin also plays a role in modulating the endothelial blood–brain barrier,[25] and animal studies suggest plasmin inhibition may prevent blood–brain barrier injury.[26] Because of its established capacity to decrease blood loss and transfusion[27] and its potential to decrease plasmin-mediated inflammation and blood–brain barrier injury,[28] some authors have hypothesised that TXA might decrease postoperative delirium.

To explore this hypothesis, we modified an ongoing randomised trial of TXA in adults undergoing lumbar fusion to include additional outcome measures, specifically postoperative delirium, biomarkers of systemic inflammation and neuroinflammation, and post-discharge cognitive function.

Methods

Participant eligibility, original protocol, and outcomes

This study was registered with ClinicalTrials.gov before patient enrolment (NCT04272606; 17 February 2020) and was approved by the University of Iowa Institutional Review Board (IRB) for Human Subjects (#201912099; 23 April 2020). All participants provided written informed consent. Enrolment was delayed because of the onset of the COVID pandemic; the first participant enrolled on 5 November 2020. The original primary outcome measures were postoperative blood loss and transfusion. The original projected enrolment of 150 participants was powered to detect a 50% decrease in mean intraoperative blood loss in participants who received TXA based on a historical mean control value of 600 (standard deviation [SD] 400) ml, alpha 0.05, and 90% power.

Participants were adults (age 18–90 yr) undergoing elective open posterior lumbar, thoracolumbar, or lumbosacral fusion to treat symptoms of degenerative spine disease at the University of Iowa. The participant's sex was as designated in their medical record. There were 29 exclusion criteria that were intended to decrease risks of potential TXA side-effects including (1) prior seizures; (2) preoperative creatinine >133 μmol L^{-1}; (3) any prior intracranial or ophthalmological vascular event; (4) any prior deep venous thrombosis or other condition related to hypercoagulability; (5) preoperative hormonal therapy (e.g. oral contraceptives or testosterone); (6) abnormal colour vision; and (7) any intravascular stents. Other exclusion criteria were intended to decrease the risk of large surgical blood loss, transfusion, or both, including: (1) preoperative haemoglobin <80 g L^{-1} or platelet count <1.5 × 10^5 μl^{-1}; or (2) prothrombin time >15 s or activated partial thromboplastin time >38 s. Potential participants who had severe cardiac, respiratory, or hepatic disorders were also excluded. Exclusion in the interval between consent and the procedure occurred when a new or previously unrecognised exclusion criterion was discovered.

Participants were randomly allocated by the Investigational Pharmacy to one of two study medication groups, either TXA or placebo, using a block size of 10. Study medications were prepared by an investigational pharmacist and provided in bags labelled as study medication. All participants, clinical care providers, and research personnel were blinded to the treatment assignments until all outcome determinations for all participants for the entire study were completed. TXA was given i.v. as a loading dose (10 mg kg^{-1}) started approximately 20 min before incision, followed by continuous intraoperative

infusion (2 mg kg^{-1} h^{-1}) which was discontinued when wound closure was complete.[29] Participants allocated to the placebo group received equivalent volumes of saline.

Participants received routine (non-standardised) postoperative care determined by their surgical teams. Participants were evaluated daily by study personnel for the first 5 days after surgery or until discharge, whichever came first. In addition to postoperative delirium assessments (see Delirium assessments), predefined safety outcome measures included: (1) postoperative day 1 creatinine increase >20% from the preoperative value; (2) any thromboembolic event (e.g. deep venous thrombosis or pulmonary embolism); (3) any surgical wound abnormality (e.g. wound healing problem or infection); (4) any visual symptoms; and (5) seizures. Participants had routine post-discharge follow-up surgical clinic visits at approximately 6 weeks and 3 months after the procedure and were evaluated by study personnel during these visits.

Protocol and outcome modifications

With prior IRB approval, a series of study modifications were made. On 26 July 2021, postoperative delirium was added as a secondary outcome measure and preoperative and post-discharge cognitive testing was added. Delirium was added as an outcome measure based on the report by Taylor and colleagues[28] in which the anti-inflammatory properties of TXA were proposed to potentially decrease delirium incidence. On 24 August 2021, a prior eligibility requirement for fusion to include two or more intervertebral spaces was removed and projected enrolment was increased from 150 to 300 participants. The increase in enrolment was made because it was anticipated that inclusion of participants undergoing less extensive procedures would decrease blood loss in both groups and, consequently increase the number of participants needed to detect TXA's potential effect on blood loss and transfusion. On 2 November 2021 preoperative and postoperative blood collection was added in order to measure biomarkers of systemic inflammation (plasma cytokines, T-lymphocyte immunophenotypes) and astrocyte activation (S100B protein). On 25 March 2022, delirium was changed from a secondary to a primary outcome measure, and biomarkers and cognitive performance were added as secondary outcome measures. Even after these changes, blood loss and transfusion continued to be primary outcomes in the study.

Blood loss and red blood cell transfusion

Intraoperative estimated blood loss was obtained from the anaesthesia record. In four participants for whom blood loss was not recorded, the corresponding surgeon's procedure note was reviewed and, in all cases, the note reported intraoperative blood loss was 'none/minimal'. In these four participants (two from each group), a default intraoperative blood loss of 0 ml was used for analysis.

Postoperative blood loss was based on wound drain output. With the exception of four participants (TXA, $n=1$; placebo, $n=3$), subfascial wound drains (Hemovac®; Zimmer Biomet, Warsaw, Indiana, USA) were inserted during wound closure. Drain collection chambers were emptied and volumes were recorded by nursing staff every 8 h. Drain output from the end of the procedure to 06:59 the next day (postoperative day 1) was designated as wound output (blood loss) for postoperative day 0. Drain output for postoperative day 1 began at 07:00 and consisted of the sum of all volumes for the next 24 h. Drains were removed when their output was <50 ml per 8-h period. The duration of postoperative wound drain placement was defined as the last postoperative day during which the drain was present, even if the drain was not present for the entire 24-h period. Postoperative blood loss equalled the total wound drain output obtained during postoperative days 0–3.

To adjust for the extent of intraoperative tissue injury, intraoperative and postoperative blood loss values were divided by the number of instrumented vertebral levels and is reported as mL per instrumented level. Intraoperative packed red blood cell transfusion was defined as occurring if one or more units were started in the operating room as documented on the anaesthesia record. Red blood cell transfusions that were started after participants left the operating room were designated as postoperative transfusions.

Delirium assessments

Starting on postoperative day 1, participants were evaluated twice daily (at approximately 8:00–10:00 and 15:00–17:00) by study personnel using the 20-item 3-min diagnostic interview for Confusion Assessment Method (3D-CAM)[30,31] as described in 3D-CAM Training Manuals 4.1 and 5.3.[32] Delirium assessments were continued until the afternoon of postoperative day 5 or the morning of the day of discharge, whichever came first. A diagnosis of delirium required the simultaneous presence of 3D-CAM feature 1 (acute onset or fluctuating course; at least one of six items) and feature 2 (inattention; at least one of six items) and either feature 3 (disorganised thinking; at least one of six items) or feature 4 (altered level of consciousness; at least one of two items). For each 3D-CAM assessment, a delirium severity score was calculated *post hoc* as the sum of positive items (range 0–20 points).[33]

When participants were in an ICU and their trachea was intubated or they were receiving sedation, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) delirium assessment instrument was used.[34] The CAM-ICU provides a delirium diagnosis but not a severity score. In instances of missing 3D-CAM or CAM-ICU evaluations, medical records were retrospectively reviewed for the presence of Delirium Observation Screening Scale (DOSS) scores[35,36] which were recorded every 12 h as part of routine nursing practice in patients aged ≥65 yr. Using a DOSS score ≥3 points (out of a maximum of 13) as the diagnostic threshold,[37] one participant in the placebo group had a delirium diagnosis based on DOSS scores.

Participants were considered to have postoperative delirium if diagnostic criteria were satisfied on at least one evaluation before discharge. Delirium day of onset was the first postoperative day in which any delirium examination met the diagnostic criteria. The delirium onset severity score was the severity score for the first delirium diagnosis. The number of days with delirium was the sum of all days during which participants had at least one positive delirium examination; days of delirium were not required to be consecutive. The maximum delirium severity score was the maximum 3D-CAM severity score on any day, irrespective of whether the result met the diagnostic criteria for delirium. The average delirium severity was the average of all delirium severity scores from all assessments on all days, regardless of delirium diagnosis.

Cognitive testing

Four cognitive tests were administered before surgery and during post-discharge follow-up reviews at approximately 6 weeks and 3 months after the procedure (see Results). The Telephone Interview of Cognitive Status—modified (TICSm) assesses global cognition, with an emphasis on learning and memory with scores ranging from 0 to 50 (best possible). TICSm is associated with both short- and long-term memory function[38] and can distinguish among individuals who have normal cognition, mild cognitive impairment, or dementia.[39]

Trail Making Test (TMT), parts A and B, assess the speed of cognitive processing and executive functioning. TMT-A primarily tests visual search and motor speed, whereas TMT-B, which is more difficult, tests higher level (executive) abilities such as mental flexibility.[40,41] Less time to complete a TMT indicates better performance. Raw performance scores were converted to z-scores using age- and education-matched population means and SD.[42] A negative z-score indicates that the participant took less time to complete the test relative to their matched reference population (i.e. better performance).

Controlled Oral Word Association (COWA) test is a verbal fluency test measuring spontaneous production of words belonging to the same category (e.g. animals) or beginning with some designated letter; in this study, the letters C, F, and L. COWA tests language, executive function,[43] or both, and is impaired in the setting of mild (preclinical) cognitive impairment.[43,44] Participants had 1 min to name as many words as possible beginning with the first letter. The procedure was then repeated for the remaining two letters. Raw performance scores were converted to z-scores using age- and education-matched population means and SD.[42] In contrast to TMT, a positive z-score indicates a greater number of words relative to the matched reference population (i.e. better performance).

Biomarkers of systemic inflammation and neuroinflammation

Whole blood for plasma and peripheral blood mononuclear cells (PBMCs) was collected on the day of the procedure before incision (preoperative) and approximately 24 h after the end of the procedure (postoperative). Blood was collected in Vacutainer®, Becton Dickinson, Franklin Lakes, New Jersey, USA Cell Preparation Tubes with Sodium Heparin (CPT™). CPT tubes were centrifuged at room temperature in a horizontal rotor for a minimum of 15 min at 1500×*g*. The top layer (plasma) was pipetted into cryovials and stored at −80°C until analysis. The second layer (PBMCs) was pipetted into 15-ml conical tubes and washed twice with 1× phosphate-buffered saline. Additional methods and results regarding perioperative T-lymphocyte immunophenotypes and their relationships to TXA administration and delirium will be reported separately in a future publication.

All biomarker analyses were performed in the Human Immunology Core of the University of Iowa Holden Comprehensive Cancer Center. As a measure of systemic inflammation, plasma cytokine concentrations for interleukins (IL)-6, -8, and -10, and tumour necrosis factor-alpha (TNFα) were determined using a custom Milliplex Human Cytokine/Chemokine/Growth factor Assay (EMD Millipore, Burlington, MA, USA) following the manufacturer's instructions. As a measure of neuroinflammation (astrocyte activation), plasma was analysed for S100B protein using the Human S100B DuoSet enzyme linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA) following the manufacturer's instructions (the lower limits of detection of each assay are reported in Supplementary Table S1). For the Milliplex, cytokine data were acquired using a BioRad Bio-Plex 200 and analysed using BioRad Bio-Plex Manager Software (BioRad, Hercules, CA, USA). For the S100B immunoassay, data were collected using a SpectraMax iD5 Multi-Mode Microplate Reader (Molecular Devices, San Jose, CA, USA) and analysed using GraphPad Prism software (GraphPad, Boston, MA, USA).

Nesting of delirium exploratory study within a trial that stopped early

Enrolment was stopped early (27 February 2023; 123 enrolled) as the consequence of an *ad hoc* interim analysis of postoperative delirium incidence conducted on 16 February 2023. The interim analysis was performed because of the findings from a retrospective observational study from our group that indicated TXA might decrease postoperative delirium from 21% (controls) to 14% (treatment).[45] A clinical trial to demonstrate a delirium incidence of 21% (controls) and 14% (TXA) (alpha 0.05, power 80%) would require 462 participants per group, 924 in total. Thus, these observational data indicated that our ongoing TXA trial was futile because it was underpowered with a planned enrolment of 300 participants instead of the required 924. Consequently, we stopped the trial early. Reinforcing this decision was publication in January 2023 of a meta-analysis reporting the effectiveness of TXA to decrease blood loss in this specific patient population (posterior lumbar interbody fusion).[18]

Statistical analysis

All analyses were conducted using R statistical software, Vienna, Austria (version 4.3.1). Continuous variables were summarised using medians and 25th and 75th percentiles, and comparisons between groups were made using Wilcoxon rank sum or Kruskal—Wallis tests. Pairwise analyses within a group were made using the Wilcoxon signed rank test. When comparing postoperative blood loss per instrumented level between treatment groups, Cohen's d effect size along with its corresponding interval was also provided. Categorical variables are summarised using counts and percentages, and comparisons between groups are performed using Pearson χ^2 test or Fisher's exact test. Effect sizes and their corresponding confidence intervals were also calculated when comparing delirium incidence between the treatment groups. Variables were also compared between groups by calculating standardised mean differences. Kendall's tau (τ) was used as a non-parametric test of association between two variables. *P*-values are two-sided and the threshold for significance was <0.05 without adjustment for multiple comparisons. *P*-values are reported to three decimal places unless <0.001. *P*-values less than 0.0000001 are reported as <0.0000001.

Results

Participant characteristics

Among 123 consenting participants, 37 (30%) were excluded before their procedure before being allocated to a group (Fig. 1). The most common reason for exclusion was detection of an exclusion criterion in the interval between consent and the day of their procedure (n=14), followed by procedure cancellation (n=8), participant withdrawal from the study (n=5), and the

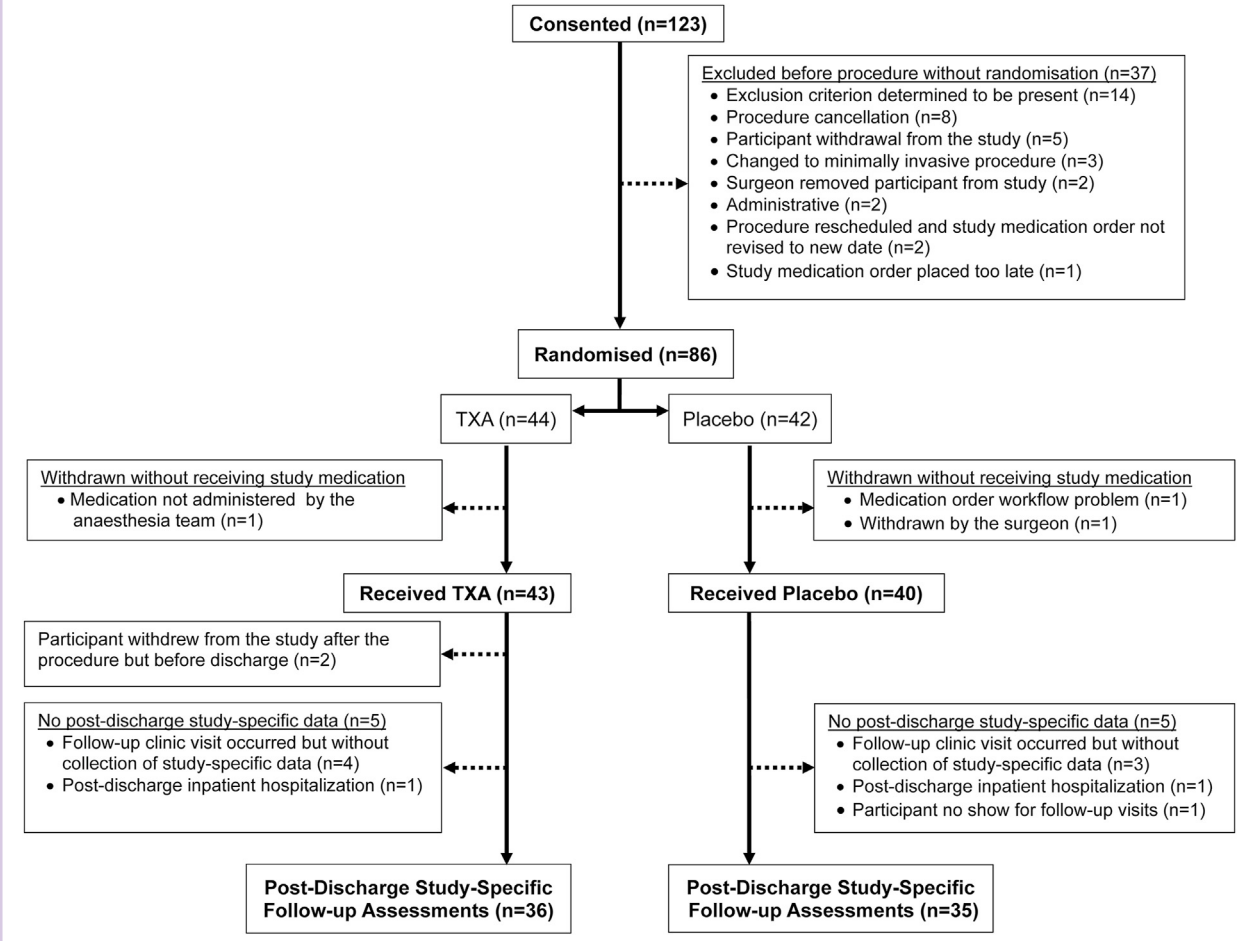

Figure 1. Flow diagram of participant enrolment, exclusion, randomisation, dropout, and assessment. TXA, tranexamic acid.

procedure changed to a minimally invasive procedure (n=3). Among 86 participants allocated to receive study medication, three did not receive it and were withdrawn from the study (no intraoperative or postoperative data were obtained): two patients were withdrawn because of study medication workflow errors and one was withdrawn by the surgeon.

Among 83 participants who received study medication (TXA, n=43; placebo, n=40), all had consented to measurements of blood loss and transfusion. Because of modifications to study outcomes (see Protocol and outcomes modifications in the Methods section) among these 83, 68 had also consented to postoperative delirium assessments and to preoperative and post-discharge cognitive testing, and 43 had also consented to preoperative and postoperative blood collection. Two participants, both of whom received TXA, withdrew from the study before discharge; one on postoperative day 1 and the other on postoperative day 3. Five participants in each group who were eligible for post-discharge follow-up assessments did not receive study-specific assessments.

Based on standardised mean differences >0.20, the TXA and placebo groups appeared to differ in several characteristics (Table 1). For example, although the median number of vertebral levels instrumented did not differ between groups (median=3 levels), the percentage of participants who underwent procedures with instrumentation of ≥5 levels was numerically greater in TXA group (9/43=21%) than in placebo group (3/40=7.5%).

Blood loss and red blood cell transfusion

All blood loss results are reported with adjustment for the number of instrumented levels (Table 2). Intraoperative estimated blood loss in the TXA and placebo groups did not differ; median (25th–75th percentiles) 167 (87–250) *vs* 110 (67–176) ml level^{-1}, respectively, P=0.311. Postoperative day 0 wound drain output was ~37% less in the TXA group compared with the placebo group; 61 (48–85) *vs* 97 (68–140) ml level^{-1}, respectively, P=0.001. The duration of postoperative wound drain placement did not differ between the TXA and placebo groups; 1 (1–2) *vs* 1 (1–2) days, respectively, P=0.258. Postoperative blood loss was ~38% less in the TXA group compared with the placebo group; 128 (97–186) *vs* 207 (132–258) ml level^{-1}, respectively, P=0.013, with no difference in TXA effect size between females (−0.61 [95% CI −1.20 to 0.04]) and males (−0.68 [95% CI −1.30 to −0.03]) (Supplementary Table S2). The total blood loss in the TXA and placebo groups did not differ; 305 (186–412) *vs* 333 (241–428) ml level^{-1}, respectively, P=0.472.

Table 1 Participant, intraoperative, and postoperative characteristics. Data are expressed as range, *n* (%), or median (25th–75th percentiles). *Incision to wound closure.

Variables	Tranexamic acid (*n*=43)	Placebo (*n*=40)	*P*-value	Standardised mean difference
Participant				
Age (yr)	32–79	32–84		0.153
Female sex, *n* (%)	20 (47)	22 (55)		0.168
Weight (kg)	98 (78–111)	94 (80–107)		0.109
Body mass index (kg m^{-2})	32 (28–37)	32 (28–37)		0.021
Smoking, *n* (%)				0.021
Never	16 (37)	17 (43)		
Former	19 (44)	19 (48)		
Current	8 (19)	4 (10)		
Hypertension, *n* (%)	33 (77)	24 (60)		0.362
Diabetes mellitus, *n* (%)	9 (21)	11 (28)		0.152
Preoperative creatinine, μmol L^{-1}	88 (71–97)	80 (63–88)		0.446
Preoperative haemoglobin, g L^{-1}	140 (132–148)	133 (124–145)		0.434
American Society of Anesthesiologists class, *n* (%)				0.298
1	1 (2)	1 (3)		
2	31 (72)	22 (55)		
3	10 (23)	16 (40)		
4	1 (2)	1 (3)		
Intraoperative, *n* (%)				
Surgeon			0.722	0.450
A	5 (12)	5 (13)		
B	3 (7)	6 (15)		
C	4 (9)	4 (10)		
D	1 (2)	0 (0)		
E	10 (23)	5 (13)		
F	12 (28)	10 (25)		
G	8 (19)	10 (25)		
Procedure time* (min)	258 (226–361)	243 (195–307)	0.174	0.362
Vertebral levels instrumented (*n*)	3 (2–4)	3 (2–3)	0.104	0.287
Surgery time per vertebral level instrumented (min)	86 (74–109)	90 (76–102)	0.809	0.039
Postoperative				
Intensive care unit admission, *n* (%)	5 (12)	3 (8)	0.714	0.141
Length of hospital stay (days)	3 (2–6)	3 (2–5)	0.968	0.201
Post-discharge disposition, *n* (%)			0.136	0.457
Home	31 (72)	30 (75)		
Inpatient rehabilitation	12 (28)	7 (18)		
Skilled care	0 (0)	3 (8)		

The percentage of participants who received ≥1 unit of RBCs did not differ between groups intraoperatively (15–16%), after surgery (20–21%), or in total (23–25%); all *P*-values ≥0.853 (Table 2). Additional transfusion results are provided in the Supplementary material.

Delirium

Among the 68 participants who had consented to postoperative delirium assessments (TXA, *n*=34; placebo, *n*=34), three did not have any delirium assessments. Two participants (one in each group) were discharged on the morning of postoperative day 1 before 3D-CAM exams were administered. A third participant (TXA group) withdrew their consent on postoperative day 1 before their delirium assessment. One participant (TXA group) withdrew their consent late on postoperative day 3; delirium data collected before their withdrawal were used in the analysis. Thus, delirium assessments were made in 65 participants (TXA, *n*=32; placebo, *n*=33).

The overall incidence of delirium was 18/65=28% (Table 3). The incidence of delirium was numerically but not significantly less in participants who underwent instrumentation at ≤4 levels (13/55=24%) *vs* those who had instrumentation at ≥5 levels (5/10=50%), *P*=0.124.

The incidence of delirium was numerically but not significantly less in the TXA group (7/32=22%) *vs* placebo group (11/33=33%), *P*=0.408. The incidence of delirium was significantly greater in older (12/27=44%) than in younger participants (6/38=16%), *P*=0.023. Among older participants, the incidence of delirium was numerically but not significantly less in the TXA group (3/10=30%) *vs* placebo group (9/17=53%), *P*=0.424. Among younger participants, the incidence of delirium was not significantly greater in the TXA group (4/22=18%) *vs* placebo group (2/16=13%). The incidence of delirium did not differ between males (8/31=26%) and females (10/34=29%), *P*=0.788. Among males, the incidence of delirium was numerically but not significantly less in the TXA group (3/17=18%) *vs* placebo group (5/14=36%), *P*=0.413. Among females, the incidence of delirium was not significantly less in the TXA group (4/15=27%) *vs* placebo group (6/19=32%), *P*=1 (see Delirium clinical trial implications in the Discussion section). Additional delirium results are provided in Supplementary Table S3.

Table 2 Blood loss and transfusion. Data are expressed as median (25th–75th percentiles) or *n* (%). *Four participants (tranexamic acid, *n*=1; placebo, *n*=3) did not have postoperative wound drains, and therefore did not have postoperative blood loss measurements and did not have total (intraoperative plus postoperative) blood loss measurements. Bold character highlights *P*-value <0.050.

Variables	Tranexamic acid (*n*=43)	Placebo (*n*=40)	*P*-value
Blood loss per instrumented vertebral level (ml level^{-1})			
Intraoperative	167 (87–250)	110 (67–176)	0.311
Postoperative*	128 (97–186)	207 (132–258)	**0.013**
Total*	305 (186–412)	333 (241–428)	0.472
Patients receiving red blood cell transfusion			
Intraoperative	7 (16)	6 (15)	0.873
Postoperative	9 (21)	8 (20)	0.916
Total	10 (23)	10 (25)	0.853

Biomarkers of systemic inflammation and neuroinflammation

Among the 43 participants who consented to perioperative blood sampling, blood for plasma biomarker analysis was collected before surgery in 32 and after surgery in 33. During statistical analysis of cytokine data, it was determined that one participant (TXA group) was an extreme upper outlier for all preoperative cytokine concentrations (data available but not shown). For this reason, this participant was excluded from all preoperative *vs* postoperative biomarker analyses. Thus, there was a total of 32 participants with postoperative plasma samples (TXA, *n*=16; placebo, *n*=16) and 31 participants who had paired preoperative and postoperative plasma samples (TXA, *n*=16; placebo, *n*=15). Among 31 preoperative plasma samples, IL-6 was undetectable in two. For these two participants (one in each group), a default preoperative IL-6 concentration of 0 pg ml^{-1} was used for analysis.

Preoperative concentrations of each of the five biomarkers did not differ between the two groups (all *P*-values ≥0.418; individual *P*-values available but not shown; Table 4). In both groups, postoperative concentrations of three of the five biomarkers were significantly greater than corresponding preoperative concentrations (IL-10, IL-6, and S100B; all *P*-values ≤0.010). In the TXA group, TNFα decreased after surgery (*P*=0.006). Postoperative concentrations of each of the five biomarkers did not differ between the two groups (all *P*-values ≥0.711; individual *P*-values available but not shown).

Postoperative TNFα concentrations were numerically but not significantly greater in participants who had postoperative delirium (*n*=7: 15.71 [10.60–30.66] pg ml^{-1}) *vs* those who did not (*n*=25: 10.03 [5.30–12.36] pg ml^{-1}); *P*=0.055. Postoperative IL-6 concentrations were significantly greater in participants who had postoperative delirium (*n*=7: 90.03 [23.35–401.01] pg ml^{-1}) *vs* those who did not (*n*=25: 17.67 [7.31–35.47] pg ml^{-1}); *P*=0.026.

Cognitive testing

Among the 68 participants who had consented to preoperative and post-discharge cognitive testing, two from the TXA group withdrew from the study on postoperative days 1 and 3 (noted above), such that post-discharge cognitive testing was not done. Among the remaining 66 participants, the following cognitive tests were done both before surgery and during post-discharge follow-up: TICSm (*n*=55), TMT-A (*n*=54), TMT-B (*n*=51), and COWA (*n*=37). With small variations among the four tests, participants underwent post-discharge testing either once (~60% participants) or twice (~40% participants). When tested twice, the second post-discharge test was compared with the preoperative test. With small variations among the four tests, post-discharge cognitive testing was performed 12 (7–18) weeks after the day of the procedure.

Preoperative scores of each of the four cognitive tests did not differ between groups (all *P*-values ≥0.598; individual *P*-values available but not shown; Table 5). For both the TICSm and TMT-A tests, post-discharge test scores did not significantly differ from preoperative scores in either group or overall (all *P*-values ≥0.065). In contrast, there was an overall post-discharge improvement in TMT-B test scores (*P*=0.013); the more negative post-discharge z-scores indicating participants required less time to complete the test. Improvements in post-discharge TMT-B scores were significant in the TXA

Table 3 Delirium incidence. Data are expressed as *n* (%). CI, confidence interval.

Delirium incidence	Tranexamic acid (*n*=32)	Placebo (*n*=33)	*P*-value	Odds ratio (95% CI)	Effect size (h) (95% CI)
Overall, *n* (%)	7/32 (22)	11/33 (33)	0.408	0.56 (0.19 to 1.69)	−0.258 (−0.744 to 0.229)
Delirium incidence—by number of vertebral levels instrumented, *n* (%)					
≤4 levels	4/25 (16)	9/30 (30)	0.341	0.45 (0.09 to 1.94)	−0.336 (−0.867 to 0.195)
≥5 levels	3/7 (43)	2/3 (67)	1	0.41 (0.01 to 11.8)	−0.483 (−1.836 to 0.869)
Delirium incidence—by age, *n* (%)					
Older (≥65 yr)	3/10 (30)	9/17 (53)	0.424	0.38 (0.07 to 1.99)	−0.470 (−1.251 to 0.311)
Younger (<65 yr)	4/22 (18)	2/16 (13)	1	1.56 (0.25 to 9.75)	0.158 (−0.486 to 0.802)
Delirium incidence—by sex, *n* (%)					
Males	3/17 (18)	5/14 (36)	0.413	0.39 (0.07 to 2.03)	−0.414 (−1.121 to 0.293)
Females	4/15 (27)	6/19 (32)	1	0.79 (0.18 to 3.53)	−0.104 (−0.785 to 0.569)

Table 4 Plasma biomarker concentrations. Data are expressed as median (25th–75th percentiles). Only values from samples with paired preoperative and postoperative values (n=31) that were used to calculate the P-values are shown. Bold characters highlight P-values <0.050.

Biomarkers	Tranexamic acid (n=16)	Placebo (n=15)	Overall (n=31)
Interleukin-8, (pg ml^{-1})			
Preoperative	1.40 (0.95–1.80)	1.38 (0.96–1.95)	1.38 (0.93–1.93)
Postoperative	1.79 (0.80–2.55)	1.30 (0.95–3.11)	1.73 (0.87–2.77)
P-value	0.105	0.590	0.134
Interleukin-10, (pg ml^{-1})			
Preoperative	2.25 (1.30–3.42)	2.93 (1.58–3.99)	2.31 (1.46–3.84)
Postoperative	5.59 (3.43–9.91)	5.86 (4.50–10.16)	5.65 (3.56–9.92)
P-value	**0.003**	**0.010**	**0.00004**
Tumour necrosis factor-alpha (pg ml^{-1})			
Preoperative	14.91 (8.59–20.10)	13.13 (9.77–15.84)	14.17 (9.29–16.61)
Postoperative	9.70 (4.72–18.61)	12.10 (8.21–12.62)	10.29 (5.97–14.49)
P-value	**0.006**	0.083	**0.002**
Interleukin-6 (pg ml^{-1})			
Preoperative	1.32 (0.79–3.58)	1.34 (0.56–2.00)	1.34 (0.72–2.80)
Postoperative	28.22 (11.70–36.81)	10.96 (7.78–70.01)	20.70 (8.32–51.47)
P-value	**0.0002**	**0.0001**	**<0.0000001**
S100B (pg ml^{-1})			
Preoperative	118.8 (69.6–174.8)	116.6 (73.3–150.5)	117.4 (68.3–163.5)
Postoperative	229.9 (151.0–271.9)	180.5 (123.1–501.6)	224.7 (126.1–381.5)
P-value	**0.005**	**0.0002**	**0.000003**

Table 5 Cognitive test scores. Data are expressed as median (25th–75th percentiles). Bold characters highlight P-values <0.050.

Cognitive tests	Tranexamic acid	Placebo	Overall
Telephone Interview of Cognitive Status—modified, score			
n	26	29	55
Preoperative	35 (32 to 38)	35 (32 to 38)	35 (32 to 38)
Post-discharge	36 (33 to 40)	35 (33 to 40)	36 (33 to 40)
P-value	0.288	0.360	0.166
Trail Making Test—part A, z-score			
n	26	28	54
Preoperative	−1.08 (−1.31 to −0.52)	−0.88 (−1.25 to −0.37)	−0.99 (−1.31 to −0.45)
Post-discharge	−1.00 (−1.38 to −0.61)	−1.17 (−1.50 to −0.52)	−1.06 (−1.48 to −0.58)
P-value	0.303	0.109	0.065
Trail Making Test—part B, z-score			
n	25	26	51
Preoperative	0.01 (−1.08 to 0.92)	−0.10 (−0.77 to 0.80)	−0.07 (−0.95 to 0.90)
Post-discharge	−0.54 (−1.39 to 0.28)	−0.69 (−1.06 to 0.16)	−0.62 (−1.26 to 0.22)
P-value	**0.007**	0.303	**0.013**
Controlled Oral Word Association, z-score			
n	19	18	37
Preoperative	−0.48 (−0.84 to 0.21)	−0.42 (−1.47 to 0.74)	−0.48 (−1.03 to 0.53)
Post-discharge	−0.11 (−0.52 to 0.48)	−0.44 (−1.07 to 0.97)	−0.27 (−0.83 to 0.74)
P-value	**0.009**	**0.033**	**0.0007**

group (P=0.007) but were not significant in the placebo group (P=0.303). Likewise, there was an overall post-discharge improvement in the COWA z-score (P=0.0007); less negative postoperative COWA z-scores indicating participants provided a greater number of words. COWA scores significantly improved in the TXA group (P=0.009), whereas COWA scores significantly worsened in the placebo group (P=0.033).

Adverse events

The two groups did not differ in the incidence of adverse events (Table 6). Although eight participants had vision-related complaints within 3 months after discharge (TXA, n=7; placebo, n=1), three were caused by pre-existing conditions, two were caused by orthostatic hypotension, and one was caused by a corneal abrasion. The two remaining participants, both of whom had received TXA, had vision complaints on postoperative days 7 and 82 that were unexplained and were temporary.

Discussion

This study has a small sample size. Consequently, it is possible that clinically or mechanistically important effects of TXA were not detected. In addition, because of multiple comparisons it is likely that some of the reported effects of TXA are

Table 6 Adverse events through final post-discharge follow-up. Data are expressed as *n* (%). *Pulmonary embolism 22 days after procedure (*n*=1); embolic stroke 69 days after procedure (*n*=1). †Unilateral vision change on postoperative day 7 (*n*=1); worsening vision occurred briefly on postoperative day 82 (*n*=1) with no subsequent reports regarding vision with either participant.

Adverse event	Tranexamic acid (*n*=43)	Placebo (*n*=40)	*P*-value
Thromboembolic event	0 (0)	2 (5)*	0.229
Vision abnormality	2 (5)†	0 (0)	0.495
Renal dysfunction on postoperative day 1	2 (5)	4 (10)	0.422
Wound complication	2 (5)	2 (5)	1
Seizure	0 (0)	0 (0)	1
Death	0 (0)	0 (0)	1

false positives. Accordingly, we consider this study's findings to be valuable primarily for hypothesis generation. We propose that the potential effect of TXA to decrease delirium incidence by 33% is clinically important and is sufficient to justify an adequately powered clinical trial.

Blood loss and tranexamic acid concentrations

In this study, although TXA did not decrease intraoperative blood loss, TXA significantly decreased postoperative blood loss by ~38%. These findings are compatible with those of a recent observational report of patients who underwent 1–3 level transforaminal lumbar interbody fusion and who received TXA (10 mg kg^{-1}) before incision.[46] TXA did not decrease intraoperative blood loss but decreased postoperative wound drain output by 20–30%.[46]

In our study, the apparent lack of effect of TXA on intraoperative blood loss may be explained by multiple potential sources of error in intraoperative blood loss estimates.[47,48] In contrast, all postoperative blood loss was collected in a single container (wound drains), was not diluted with any fluid, and volumes were objectively measured rather than estimated. Thus, postoperative blood loss volumes are more likely to be accurate. It is also plausible the effect of TXA to decrease blood loss may be proportionately less during surgery than after surgery. TXA decreases blood loss by inhibition of fibrinolysis, promoting clot stability. Intraoperatively, spinal surgeons do not rely solely on clot stability to control intraoperative bleeding. Instead, surgeons directly observe bleeding sites and apply one or more active interventions (e.g. electrocautery). The more effective surgeons' interventions are, the less effect TXA should have on intraoperative blood loss. In contrast, after surgery, there are no active interventions to decrease bleeding and blood loss will be determined only by the balance of clot formation and clot lysis. Accordingly, TXA may have greater potential to decrease postoperative bleeding—both absolutely and relatively—than intraoperative bleeding.

The 38% decrease in postoperative blood loss in this study is consistent with the effect of TXA reported in multiple randomised controlled trials of patients undergoing posterior lumbar interbody fusions, with an average of a 33% reduction (range 20–47%).[18] It is also consistent with a meta-analysis of TXA studies in adults undergoing cardiac procedures in which the maximum effect of TXA on blood loss reduction was 40% (95% credible interval 34–47%).[16]

In vitro studies indicate TXA concentrations of 10–15 mg L^{-1} result in 80% inhibition of plasmin-mediated fibrinolysis.[49] In a meta-analysis of adult cardiac procedures, the systemic TXA concentration necessary to achieve 80% of the maximum decrease in perioperative blood loss was estimated to be 22.4 mg L^{-1} (95% credible interval ~10–40 mg L^{-1}).[16] In a pharmacokinetic study of older patients undergoing elective hip arthroplasty, Lanoiselée and colleagues[50] used a TXA dosing regimen (~13 mg kg^{-1} loading dose; ~1.8 mg kg^{-1} h^{-1} infusion) that was nearly identical to that used in this study (10 mg kg^{-1} loading dose; 2 mg kg^{-1} h^{-1} infusion). The Lanoiselée dosing regimen resulted in a steady-state TXA plasma concentration of ~30 mg L^{-1}, which is substantially greater than the TXA concentration needed for near-maximum inhibition of plasmin-mediated fibrinolysis. Using pharmacokinetic modelling, Lanoiselée and colleagues[50] estimated TXA concentrations would exceed 10 mg L^{-1} for approximately 3 h after cessation of the infusion in patients who had normal renal function. Therefore, the intraoperative TXA dosing regimen used in our study would have resulted in clinically effective TXA concentrations (~30 mg L^{-1}) both intraoperatively and for several hours thereafter. The fact that, in our study, TXA decreased blood loss measured after discontinuation of the infusion provides strong indirect evidence that our TXA dose was sufficient to inhibit plasmin. As will be discussed, brain plasmin inhibition could be a mechanism by which TXA may decrease delirium.

Delirium

The incidence of delirium in the TXA group (7/32=22%) was numerically but not significantly less than that in the placebo group (11/33=33%); *P*=0.408, absolute difference 11%, relative difference 33%, effect size −0.258 (95% CI −0.744 to 0.229). This potential effect of TXA to decrease the incidence of delirium is consistent with a 33% relative decrease in the incidence of delirium reported in our prior retrospective observational study using a propensity score-based analysis; TXA (14%) *vs* controls (21%); *P*=0.004.[45] In addition, in this study, participants who received TXA had significantly improved post-discharge performance in two of the four cognitive tests compared with their preoperative baselines, whereas those who received placebo did not improve in three of the four tests and worsened in one. This suggests that, in addition to potentially decreasing the incidence of postoperative delirium, TXA may have the potential to favourably affect longer-term cognitive outcomes.

Mechanistic hypotheses regarding delirium and tranexamic acid

Cytokines

Although neuroinflammation is considered a primary mechanism of delirium, in this study TXA administration did not significantly affect cytokine concentrations 24 h after surgery. This is likely because TXA has an elimination half-life of 2–3 h in patients who have normal renal function,[51] hence TXA administered only intraoperatively should be entirely eliminated by 24 h after surgery and any earlier anti-inflammatory effect may therefore have been missed.

S100B

S100B is a homo-dimeric protein (molecular weight 21 kDa) that is secreted primarily by astrocytes in response to a wide variety of proinflammatory stimuli.[52] S100B can enter the systemic circulation via the altered blood–brain barrier, via the glymphatic system, or both.[52,53] Because in the systemic circulation S100B elimination half-life is ~1 h,[54] systemic S100B concentrations 24 h after surgery likely reflect ongoing astrocytic secretion and subsequent entry into the systemic circulation.

Several prior observational studies[28,55–57] have reported associations between S100B and either delirium incidence or severity, which suggests that astrocyte activation (or blood–brain barrier dysfunction) is involved in (or is coincident with) the pathophysiology of delirium. In our study, intraoperative TXA administration did not significantly affect S100B concentrations 24 h after surgery. This suggests that TXA's potential effect to decrease delirium may occur downstream of astrocyte activation and S100B secretion.

The potential role of brain plasmin or plasminogen activators in delirium

A biologically plausible mediator of postoperative delirium—which is inhibited by TXA—is brain plasmin(ogen). In animal and *in vitro* models, plasmin mediates neuroinflammation via multiple mechanisms,[22,58] contributing to increased blood–brain barrier permeability, degradation of extracellular matrix proteins, leucocyte diapedesis, and activation of brain immune cells (astrocytes and microglia) to secrete inflammatory cytokines.[59]

In murine models of traumatic brain injury, a single post-insult dose of i.v. TXA normalised blood–brain barrier permeability,[26,60] brain cytokine concentrations,[61] and improved functional[26,60] and histological[61] outcomes. Notably, although TXA increased some systemic cytokine concentrations, it decreased brain cytokine concentrations.[61] Thus, the beneficial effect of TXA did not require a decrease in systemic cytokine concentrations. In another of these three studies, that of Daglas and colleagues,[26] although the beneficial effects of TXA on blood–brain barrier permeability and functional outcome were shown to be plasmin-dependent, these benefits occurred only in male mice. This finding suggests that the potential benefit of TXA on postoperative delirium could be sex-dependent, with a greater benefit in males.

Antagonism of γ-aminobutyric acid receptors

Finally, another potential mechanism by which TXA may decrease delirium is by its stimulant properties, which may counteract the electrophysiological inhibition that is hypothesised to occur in delirium.[62] A recent study reported increased inhibitory interneuron activity in modelling of auditory evoked responses in patients with delirium.[63] Acting through antagonism of γ-aminobutyric acid receptors,[64,65] TXA may directly counter these inhibitory effects, decreasing the severity of delirium. However, given the rapid clearance of TXA from the circulation and CSF,[64] this seems unlikely to be a mechanism by which TXA could decrease delirium beyond the first few hours after the procedure.

Delirium clinical trial implications

Sex

Consistent with the aforementioned preclinical study of Daglas and colleagues,[26] in this study TXA appeared to decrease the incidence of delirium to a greater extent in males (effect size −0.414) than in females (effect size −0.104). We suggest that in a future clinical trial to test the effect of TXA on postoperative delirium, randomisation should be stratified by sex.

Age

Increasing patient age is well established as a risk factor for postoperative delirium.[7] The relatively high incidence of postoperative delirium in older participants observed in this study (44.4%) is consistent with other studies in older patients undergoing spinal fusion; 40.5%[66] and 43.2%.[67] Neuroimmune responses change with age.[68] For example, in a murine model of traumatic brain injury, older animals had a more robust neuroinflammatory response than younger animals.[69] This finding suggests that the potential benefit of TXA on postoperative delirium could be age-dependent, with a greater benefit in older patients. We suggest that in a future clinical trial to test the effect of TXA on postoperative delirium, enrolment should be limited to older patients or randomisation be stratified by age.

Limitations

This trial has numerous operational limitations, the first among them being that, among 123 consenting participants, 37 (30%) were excluded before their procedures without being allocated. This high rate of pre-randomisation exclusion is similar to that reported in another recent study of postoperative delirium in adult spinal procedures (25/124=20%).[70] In our study, the interval between enrolment and the procedure was usually 2–4 weeks, during which additional data from outside healthcare providers was received, new preoperative studies were conducted, and continued procedural planning occurred. The new information, plan, or both often changed participants' eligibility.

Another operational limitation was related to our centre's electronic medical record and the required workflow for physicians to enter orders for study medication. The system did not readily adjust for changes in the scheduled day of the procedure. As a consequence, some participants did not have study medications prepared when they otherwise should have—decreasing the number of consenting participants who entered the study.

Finally, although the basic intervention of this trial remained unchanged, there were numerous changes in outcome measures and their related procedures throughout the course of this trial. Additional challenges and opportunities for errors in study implementation were introduced because of a repeated loss of experienced study personnel. Lack of continuity and familiarity with protocol details contributed to incomplete data collection for many outcome measures. Missing data points decrease the information provided by the participants' service and, by decreasing statistical power, decrease both the ability to detect adverse events and the reliability of findings. Although we stopped the trial early because our planned enrolment size was underpowered to detect the potential benefit of TXA on delirium, all of these other factors influenced our decision to stop enrolment.

Conclusions

Although not statistically significant, delirium incidence in the TXA group (7/32=22%) was numerically less than that in the placebo group (11/33=33%); absolute difference 11%, relative difference 33%, effect size −0.258 (95% CI −0.744 to 0.229). This potential effect of TXA to decrease delirium is consistent with a 33% relative decrease in delirium incidence reported in a prior retrospective observational study in a similar population.[45] The safety of intraoperative TXA at the dose used in this study has been established in numerous prior studies. Because of the consistency and size of the potential treatment effect of TXA to decrease postoperative delirium, a definitive randomised clinical trial is justified.

Authors' contributions

Conceptualisation: MZ, RDS, MAH
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Supervision: BJH, CRO, RWW, MZ, DJO, RDS, MAH
Validation: BJH
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Writing—review and editing: all authors

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Declaration of interests

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bjao.2025.100403.

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