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ORIGINAL CONTRIBUTION

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A double-blind pilot randomized controlled trial of topical tranexamic acid after sinus surgery*

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Abstract

Background: There has been limited study of topical tranexamic acid (TXA) in endoscopic sinus surgery (ESS). We report a pilot study, examining the effects of topical TXA with regards to recovery after ESS.

Methods: A pilot double-blind randomized controlled trial was conducted in 30 patients undergoing comprehensive ESS. Patients received either topical TXA or normal saline (NS) for 60 minutes via cotton pledgets at the conclusion of ESS. Patients were followed-up for a duration of 3-months.

Results: The mean (95% CI) reduction in 22-item Sino-Nasal Outcome Test (SNOT-22) score at 3 months was 39.5/110 (26.9, 52.0) for TXA and 33.4/110 (24.0, 42.9) for NS (p=0.42). The mean (SD) Modified Lund-Mackay Post-operative Endoscopic (MLMES) score at 3 months was 7.79/100 ±7.70 for TXA and 10.9/100 ±9.35 for NS (p=0.12). TXA had a mean (SD) bleeding score of 4.0 ± 2.33 on day 1 compared to 3.64 ± 2.76 in NS group when measured on a Likert scale (p = 0.89). The mean self-reported time to return to work was 4.67 ± 2.22 days for TXA and 6.87 ± 4.42 for NS (p=0.10). Zero cases of confirmed thromboembolism were seen.

Conclusions: Although statistically non-significant differences were observed, data from this pilot study imply that there is merit in a larger study to further assess the effects of topical TXA following ESS. There may be a role for increasing the exposure to topical TXA via a different formulation.

Key words: tranexamic acid, sinusitis, pilot projects, double-blind method, randomized controlled trial

Introduction

The ideal nasal dressing following endoscopic sinus surgery (ESS) is one that is haemostatic but also improves mucosal healing [(1)]. Tranexamic acid (TXA) is a readily available and inexpensive medication that features on the World Health Organization list of essential medications [(2)]. Randomised controlled trials have shown that topical TXA exhibits superior haemostatic effects and higher surgeon satisfaction when used intra-operatively during ESS [(3-6)]. However, the use of topical TXA post-operatively following ESS has not been studied with adequate follow-up time. In vitro studies of respiratory epithelium have shown wound healing and anti-inflammatory effects of TXA [(7-11)] that could theoretically accelerate recovery and improve patient outcomes [(12)]. In this sense, TXA has the potential to contribute to an ideal wound dressing following ESS.

Currently, the practice of the senior author (AJW) is to request the administration of intravenous (IV) TXA at anesthetic induction [(13-16)] prior to ESS and insert cotton pledgets containing TXA topically in the nose and sinuses at the conclusion of the surgery. Surgeons may be cautious to administer two forms of TXA due to concerns of increased risk of thromboembolism, even though, this practice is shown to be safe in multiple systematic reviews and meta-analysis of knee and total hip arthroplasties [(17-20)] and recently in ESS [(15)]. A retrospective study of 177 patients who had undergone comprehensive ESS from our own practice found no cases of thromboembolism attributable to TXA where

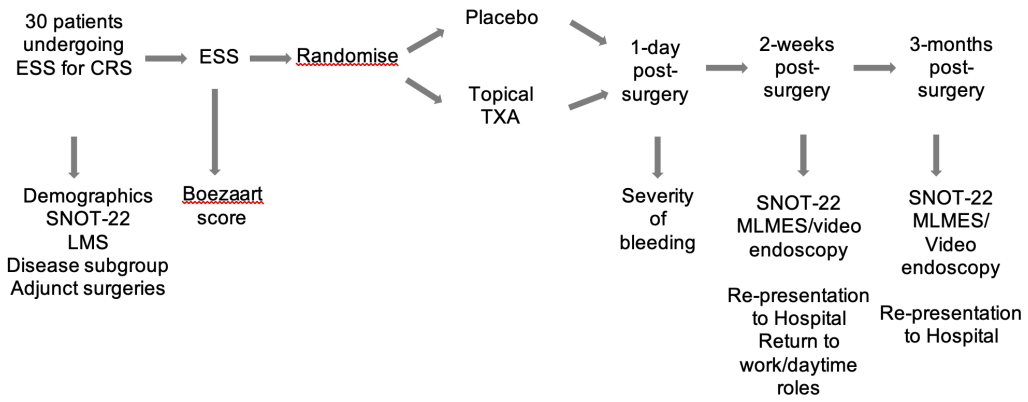

Figure 1. Summary of the study protocol. ESS = Endoscopic sinus surgery: CRS: Chronic RhinoSinusitis: SNOT-22 = 22-item Sinonasal outcome tool; LMS = Lund-Mackay score; MLMES = Modified Lund-Mackay Post-operative endoscopic score.

both forms of TXA were used [12].

Given the evidence from other surgical specialties and our own retrospective study, we conducted a pilot randomised controlled trial assessing the impact of topical TXA on long-term patient outcomes using both subjective and objective outcomes measures to assess healing, recovery, and haemostasis. The primary objective of this pilot study was to facilitate a subsequent, larger study with appropriate power calculations. Ultimately, this has the potential to improve long-term post-operative outcomes for patients undergoing ESS.

Study hypotheses: The primary hypothesis was that the post-operative use of topical TXA after ESS for the treatment of CRS would result in improved long-term outcomes with regards to patient-reported symptoms.

We also hypothesised that the post-operative use of topical TXA would result in objective improvements in CRS treatment and faster recovery of normal function with improved healthcare utility.

Materials and methods

Eligibility criteria

All patients undergoing an Otolaryngological surgical procedure at Waikato Hospital and Braemar Hospital under the care of the senior author between February 2020 – February 2021 were screened against the eligibility criteria. Those undergoing bilateral comprehensive ESS (i.e. complete sphenoethmoidectomy with frontal recess dissection) for the treatment of CRS were invited to participate in the trial. Given the lack of relevant prior studies power analyses were not possible. In accordance with central limit theorem, a sample size of 30 patients was selected.

Exclusion criteria:

- Under the age of 16 years
- Underlying condition predisposing to CRS (e.g., vasculitis, cystic fibrosis)
- Unilateral sinusitis or Lund-Mackay Score (LMS)(21,22) <10 (i.e., radiological evidence of mild sinusitis)
- Known bleeding disorder or contraindication to the use of TXA owing to prior thromboembolic disease
- Prior allergy to study drugs
- Current confirmed or possible pregnancy
- Currently enrolled in another clinical study
- Major medical co-morbidities

Patients were enrolled in the study following informed consent. The following patient demographics were collected: age, ethnicity, LMS, any adjunctive surgical procedure (e.g., Septoplasty, inferior turbinoplasties) and pre-operative 22-item Sino-Nasal Outcome Test (SNOT-22) score [23,24].

Randomisation

Once anaesthetised, enrolled patients were randomised according to an envelope system. Kraft envelopes were prepared prior to the beginning of the trial using a randomly generated sequence in eight blocks of four and one block of two. The randomisation schedule is available at http://www.randomization.com (seed: 12141).

Research subjects were randomised to receive either topical TXA (5ml of 100mg/ml) or 5ml topical 0.9% sodium chloride (normal saline/NS) as placebo. Cotton pledgets soaked in the study medication were placed in the sinus cavities for 60 minutes at the conclusion of ESS. During surgery, routine measures were utilised for bleeding control including hypotensive anaesthesia, intravenous TXA, head-up positioning, injected 0.5% Marcaine with adrenaline for sphenopalatine blockade and topical Moffett's solution [25]. The severity of intra-operative bleeding was graded using a system established by Boezaart et al. [26].

Surgical treatment and post-operative care

With the exception of the randomisation to a treatment arm, all patients underwent the same, routine clinical care both during and after surgery. This included analgesia, antibiotic prophylaxis, topical and systemic steroids and saline lavage. During all post-

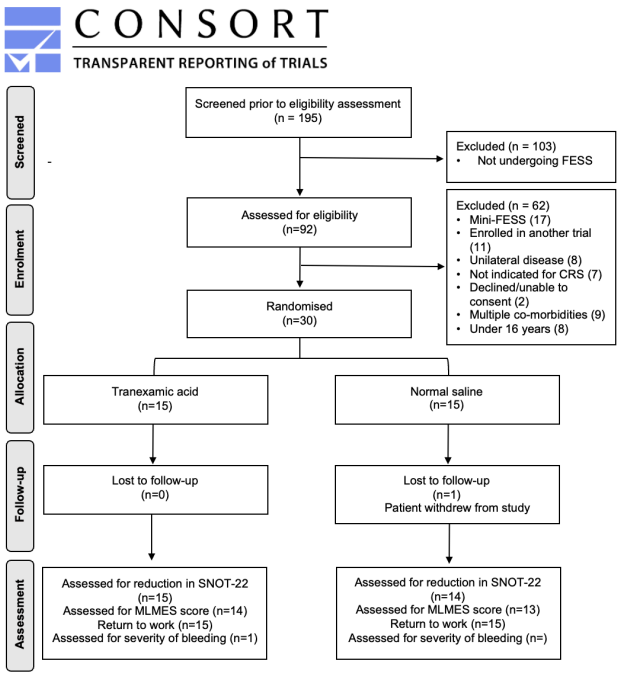

Figure 2. CONSORT 2010 extension to randomised pilot and feasibility trials. FESS = Functional endoscopic sinus surgery: CRS = Chronic Rhînosinusitis; SNOT-22 = 22-item Sinonasal outcome tool; MLMES = Modified Lund-Mackay Post-operative endoscopic score.

operative visits, nasal endoscopy was performed with debridement of the sinuses as required.

Study follow-up/outcome measures

The patients were followed up 1-day, 2-weeks and at 3-months following surgery.

The primary outcome measure was to compare the absolute reduction in the SNOT-22 score (calculated from the pre-operative and 3-month scores) in the TXA and placebo groups. Secondary outcome measures included the Modified Lund-Mackay Endoscopic Score (MLMES) at 2 weeks and 3 months follow-up, which measure the cumulative inflammatory burden post-ESS to give a total score out of 100 [27].

Patient recovery time reported as days before returning to work/daytime roles. The severity of patients' post-operative bleeding was measured using a Likert scale scored from 0-10 and Clinical graduation of post-operative bleeding as established by Kastl et al. [28]. This was then used as a measure of short-term patient-reported outcomes.

The following adverse events were measured: re-presentations to the Hospital during follow-up period as a measure of healthcare utility, undesirable effects such as ophthalmic, cardiac, neurological symptoms or nausea during study follow-up, post-operative imaging performed due to suspicion of thromboembolisms and confirmed cases of thromboembolisms such as myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary embolism (PE), stroke or transient ischaemic attacks (TIA's). Please refer to Figure 1 for a summary of the study protocol.

Statistical analysis

Descriptive statistics were used to report mean, standard deviation (SD) in normally distributed and median (range) in non-normally distributed data. For completion, differences in baseline characteristics were tested. For continuous variables that were normally distributed, Independent Samples T-test was used. Otherwise, Mann-Whitney U-test was utilised. For categorical variables, Chi-square test for Independence or Fisher's exact testing was used.

To compare the effectiveness of the interventions assessed using SNOT-22, MLMES and severity of bleeding over the study follow-up, Mixed Between – Within Subjects Analysis of Variance (ANOVA) was performed. To compare the absolute reduction in SNOT-22 scores (pre-operative vs 3-months) between interventions, One-way ANOVA with contrasts was used. Recovery time was assessed using Independent Samples T-test. Adverse events were reported using descriptive statistics and compared using Fisher's exact test.

Differences between the means were reported as mean and 95% confidence interval (95% CI). Unless otherwise stated, $p<0.05$ was considered statistically significant. Where appropriate, Bonferroni correction was applied. In all cases, two-tailed p-value was reported. All statistical analyses were carried out using IBM SPSS (v. 27).

Ethics approval

Health and Disability Ethics Committee approval (HDEC): 19/STH/205

Trial registration

Australia and New Zealand Clinical Trials Registry Number: ACTRN12619001512112p.

Universal Trial Number: U1111-1242-0177.

Waikato District Health Board/ Te Puna Oranga Māori Health Research Review Committee Approval: RD019123.

Results

92 patients were assessed for eligibility. 62 patients were excluded and 30 were recruited and randomised to the experimental arms. One patient did not complete full 3-months follow-up and two patients did not have MLMES scores due to COVID-19 pandemic restrictions meaning that assessment occurred remotely. Please refer to Figure 2 for CONSORT [29] patient flow chart.

Patient characteristics for both experimental groups were similar at baseline with no statistically significant differences. The mean age (SD) for TXA group was 50 ± 13.8 years and for NS group, 51 ±16.5 years (p=0.88). In both groups, most patients were male and of European ethnicity. Table 1 outlines a full comparison.

Table 1. Baseline patient characteristics.

Characteristic	Tranexamic acid (n=15)	Normal saline (n=15)	Total (n=30)	p-value
Age (years)	50.0 ± 13.8	50.9 ± 16.5	50.4 ± 15.0	0.88
Gender				1.00
Male	11 (73.3%)	11 (73.3%)	22 (73.3%)	
Female	4 (26.7%)	4 (26.7%)	8 (26.7%)	
Ethnicity				1.00
European	12 (80.0%)	11 (73.3%)	23 (76.7%)	
Māori	2 (13.3%)	2 (13.3%)	4 (13.3%)	
Pacific people	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	
MEELA	1 (6.7%)	2 (13.3%)	3 (10.0%)	
Adjunctive surgical procedure				0.43
Yes	12 (80.0%)	9 (60.0%)	21 (70.0%)	
No	3 (20.0%)	6 (40.0%)	9 (30.0%)	
Pre-operative SNOT-22 score	54.4 ± 17.8	52.2 ± 18.2	53.3 (17.7)	0.74
Lund-McKay score	13.9 (2.5)	14.5 ± 3.7	14.2 (3.11)	0.61
Intra-operative Boezaart score [22]	2.36 ± 0.84	2.33 ± 0.82	2.34 ± 0.81	0.94

MELAA = Middle Eastern/Latin American/ African; SNOT-22 = 22-item Sino-nasal Outcome Tool. Data expressed as mean ± standard deviation (SD) or as number (%). p-values are based on Independent Sample T-test continuous variables and Chi-square or Fisher's Exact test for categorical variables.

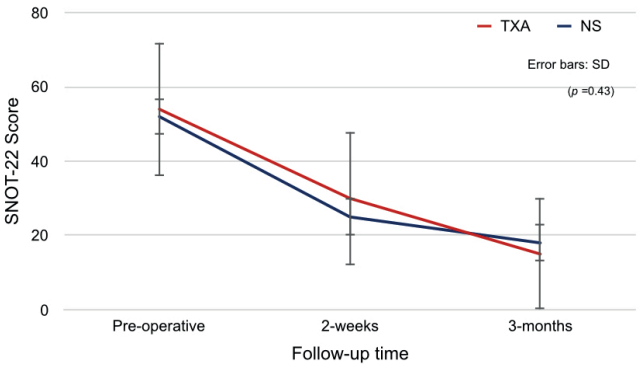

Figure 3. Subjective symptom score. (SNOT-22) Over time
SNOT-22 = 22-item Sino-Nasal Outcome Tool; TXA = Topical Tranexamic acid; NS= topical normal saline: Error bars indicate standard deviafion (SD); p values are based on Mixed Between-Within Subjects Analysis of Variance.

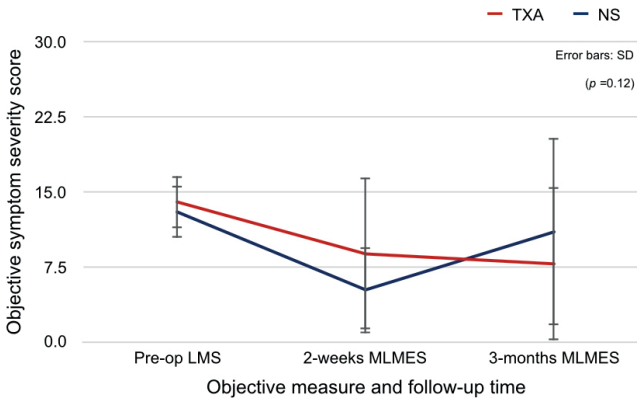

Figure 4. Objective CRS. Severity measures (LMS and MLMES) over time.
LMS = Lund-Mackay Score; MLMES = Modified Lund-Mackay Post-operative Endoscopie Score: TXA = Topical Tranexamic acid; NS= topicaJ normal saline; Error bars indicate standard deviation (SD): p-values are based on Mixed Between-Within Subjects Analysis of Variance.

SNOT-22 score

SNOT-22 score was used to quantify the long-term improvement in patient reported symptoms. As one patient in the TXA group did not complete full 3-month follow-up, only 29 patients were included in the final analysis.

For the TXA group, the mean ± SD of pre-operative score was 54.4 ± 17.8 points, compared to 3-months score of 14.9 ± 15.4. The absolute reduction (95% CI) was 39.5 points (26.9, 52.0).

For the NS group, the mean pre-operative score was 51.8 ± 18.8 compared to 3-month score of 18.4 ± 14.9. (Please refer to Figure 3 for a comparison). The absolute reduction between the two time points was therefore lower at 33.4 points (24.0, 42.9). However, one-way ANOVA found the mean difference (95% CI) of 6.04 (-9.12, 21.2) points between the experimental arms non-significant (p=0.42). Furthermore, Mixed Between-Within Subjects ANOVA showed that the SNOT-22 scores for TXA did not differ significantly to NS across any of the follow-up time points (p=0.43).

Table 2. Patient outcomes.

Outcome	Tranexamic acid	Normal Saline	p-value
SNOT-22 score, mean (SD)			0.43
Pre-operative	54.4 ±17.8	51.8 ± 18.8	
2-weeks	29.7 ± 17.9	24.8 ± 14.9	
3-months	14.9 ± 15.4	18.4 ± 14.9	
Absolute reduction in score	-39.5 ± 22.7	-33.4 ± 16.3	0.42
MLMES score, mean (SD)			0.12
2-weeks	8.79 ± 7.60	5.23 ± 4.30	
3-months	7.79 ± 7.70	10.9 ± 9.35	
Recovery time (days), mean (SD)	4.67 ± 2.22	6.87 ± 4.42	
Mean difference (95% CI)	2.2 (-0.46, 4.86)	0.10	
Severity of bleeding – Likert scale, mean (SD)			0.89
Day 1	4.00 ± 2.33	3.64 ± 2.76	
2-weeks	2.27 ± 2.40	2.21 ± 1.72	
3-months	0.20 ± 0.41	0.29 ± 0.61	
Severity of bleeding – Clinical graduation scale (24), mean (SD)			0.92
Day 1	1.67 ± 0.72	1.50 ± 0.76	
2-weeks	1.13 ± 0.64	1.00 ± 0.39	
3-months	0.20 ± 0.41	0.14 ± 0.36	
Re-presentation to hospital, n (%)			0.33
Post-op bleeding	2 (13%)	2 (13%)	
Chest pain	2 (13%)	0 (0%)	
Imaging within follow-up, n (%)	2 (13%)	0 (%)	0.48
Adverse symptoms, n (%)			0.36
Neurological	4 (27%)	1 (6.7%)	
Ophthalmic	0 (0%)	3 (20%)	
Respiratory	1 (6.7%)	0 (0%)	
Nausea	1 (6.7%)	1 (3.3%)	
Other	1 (6.7%)	0 (0%)	
Total	7 (47%)	5 (33%)	
Confirmed VTE, n (%)	0 (0%)	0 (0%)	-

SNOT-22 = 22-item Sino-Nasal Outcome Tool; MLMES = Modified Lund-Mackay Post-operative Endoscopic Score; VTE = venous thromboembolism; SD = Standard Deviation.

MLMES score

MLMES score was used to measure the objective improvement in CRS disease severity. The 2-week MLMES score was unavailable for three patients due to COVID-19 pandemic restrictions. Therefore, only 27 patients were included in the final analysis. The mean MLMES score for TXA at 2-weeks was 8.79 ± 7.60 and 7.79 ± 7.70 points at 3-months. The NS group had a 2-week score of 5.23 ± 4.30 and 10.9 ± 9.35 points at 3-months. (Please refer to Figure 4 for a comparison). Mixed Between-Within Subjects ANOVA found that the MLMES scores did not differ significantly between TXA and NS over follow-up time (p=0.12).

Patient recovery

Number of days before patients returned to their normal daytime roles/work was used as patient recovery time. The TXA group required a mean of 4.67 ± 2.22 days, compared to NS of 6.87 ± 4.42 days. Independent samples t-test found the mean difference (95% CI) of 2.2 days (-0.46, 4.86) was not statistically significant (p = 0.10).

Severity of post-operative bleeding

The severity of bleeding was measured on two scales, a Likert scale (0-10) and a clinical graduation scale (0-4). One patient did not complete the 3-month follow-up visit. Therefore, only 29

patients were included in this analysis.
On the Likert scale, TXA had a mean score of 4.0 ± 2.33 on day 1 and 2.27 ± 2.40 at 2-weeks compared to NS which had a score of 3.64 ± 2.76 on post-operative day 1 and 2.21 ± 1.72 at 2-weeks. On the clinical graduation scale, TXA had a mean score of 1.67 ± 0.72 on day 1 and 1.13 ± 0.64 at 2-weeks compared to NS, which has 1.50 ± 0.76 on day 1 and 1.00 ± 0.39 at 2-weeks. Mixed-within subjects' ANOVA found that the severity of post-operative bleeding over follow-up time did not differ significantly between TXA and NS when measured on the Likert scale ($p = 0.89$) or on the clinical graduation scale ($p = 0.92$).

Adverse events

During the study follow-up of 3-months, no confirmed cases of thromboembolic disease were reported in either experimental group. Overall, 12 patients reported adverse symptoms during study follow-up, seven (47%) patients of the TXA group and five (33%) of the NS group. Most noted symptom was neurological concerns such as headaches which was seen in four (27%) of the patients in the TXA group and one (6.7%) in the NS group. All three cases of ophthalmic concerns such as dry eyes and changes in vision was reported in the normal saline group. Two patients complained of nausea, one in each experimental group. Overall, both groups had a low healthcare utility in the post-operative period. A total of six patients attended ED within follow-up period, four in the TXA and two in the NS group. Two patients from the TXA group presented with chest symptoms and underwent imaging. In both cases, the chest symptoms were attributed to a cause other than the use of TXA.
Only four patients in the study population had an adverse post-operative bleeding event, two in each experimental group. No patient required surgical management for post-operative bleeding. Fisher's exact testing found no significant differences between the two groups in incidence of re-presentation to hospital ($p=0.33$), imaging within follow-up period ($p=0.48$), or adverse symptoms ($p=0.36$).

Discussion

In this study, we hypothesised that the post-operative use of topical TXA in ESS would result in improved long-term outcomes with regards to patient-reported and objective measures. Intended as a pilot study, this study has, unsurprisingly yielded non-significant comparisons with regards to the major outcomes measured. Based on these data, a change in practice is not recommended. It is noted however that the SNOT-22 scores and endoscopic scores at 3 months as well as the data around return to work all show a trend towards favouring TXA, implying that our hypothesis has potential merit and further study is warranted.
There are some theories as to why topical TXA could generate superior outcomes. In a previous scoping review conducted by the authors [12] TXA demonstrated a faster and higher magnitude of wound healing compared to normal saline or no treatment in an in-vitro setting in both respiratory and other types of epithelia [7-11,30,31]. In addition, TXA demonstrated anti-fibrinolytic and anti-inflammatory effects which in combination with wound healing could afford a greater improvement in SNOT-22 score, improved objective endoscopic score and faster return to normal functioning.
It is worth noting that, although statistically non-significant, patients who received TXA returned to daytime functioning on average 2.2 days earlier than those who received NS. CRS is associated with an estimated 18.7 missed workdays a year [32]. Although there is no recognised minimally clinically important difference (MCID) for return to work, we would suggest that any earlier return to work, especially if confirmed in future studies would be expected to be clinically important. It is noted that the MCID threshold for improvement after sinus surgery in SNOT-22 score has been reported to be 9.0 (33). In that context, an absolute improvement of 6.04 points between TXA and NS groups in this study could be seen to be relatively modest. However, the promising results from this study encourages us to also consider studying increased use of topical TXA from the described 60 minutes of exposure, perhaps in the form of a longer-term dressing or by regularly adding TXA to post-operative lavage solutions.
We hypothesised improved healthcare utility with the use of topical TXA. In total, only four (23%) patients re-presented to Hospital during the study period. Two of these patients re-presented due to chest symptoms and both had received topical TXA. One of these patients developed cardiac symptoms due to new onset atrial fibrillation. For the other, the chest symptoms were associated with recurrent chest infections. Therefore, the cause of the re-presentation cannot be fully attributed to the use of TXA. Regardless, observation for complications and side-effects associated with TXA would need to be a part of any future study. What is reassuring in this study is the zero cases of major complications in the form of thromboembolic disease.
Surprisingly, we found no significant differences between TXA and NS in patient-reported severity of post-operative bleeding. This contrasts with most current literature in both cardiac, and to a lesser extent, ENT surgery that found superior haemostatic properties and reduced post-operative bleeding with the use of topical TXA [34-38]. There are a few reasons why our results may vary from published literature. The biggest limitation in our analysis was the small sample size which leads to a large probability of missing an actual effect. Although multiple factors are relevant including delivery method and renal function, the plasma half-life of TXA is generally measured around 2-3 hours [39,40]. It is possible therefore that topical application of TXA for 60 minutes only aids in the stabilization of the fibrin clot and reduction in bleeding in the initial hours, which our methodology may not have captured.

The biggest limitation in this pilot study is the small sample size. With only 30 patients, there is a high probability of committing a Type II error and thus concluding no difference when one such exists in the population [41]. Post-hoc power calculation showed that 30 patients only accounted for 13.1% of the study power when detecting a difference of six points in the SNOT-22 score between interventions. Thus, we are at a risk of committing a type II error 87.5% of the time when the minimum acceptable probability is 20% [41]. Therefore, to make generally applicable treatment recommendations, it would be prudent to conduct a trial that is adequately powered to find a difference. Our power calculations show that to detect a statistically significant difference of 6-points in SNOT-22 scores between interventions, with a population standard deviation of 22.7 points, as it was observed in our study, we would need approximately 222 patients in each intervention group. This would achieve alpha-level of 0.05 and 80% power [42,43]. If however we were to pursue patient recovery as the primary outcome, to detect a statistically significant difference of 2.2 days with a population standard deviation of 2.22 days, we would only require a sample size of 32 patients.

Conclusions

We performed a pilot randomised controlled trial comparing the use of topical TXA to NS in improving long-term patient outcomes after ESS. Although not statistically significant, our results encourage us to pursue hypotheses around improved subjective and objective outcomes associated with topical TXA. If proven in a larger study, being inexpensive, safe, and readily available, topical TXA has the potential to make an excellent addition to medical management after ESS.

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Authorship contribution

Study design, data collection, statistical analysis, manuscript writing (ARK), Study design, data collection, manuscript review (AW).

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Conflict of interest

Nil.

References

1. Valentine R, Wormald PJ. Nasal dressings after endoscopic sinus surgery: what and why? Curr Opin Otolaryngol Head Neck Surg. 2010;18(1):44-48.
2. World Health Organization. World Health Organization model list of essential medicines: 21st list 2019. World Health Organization;2019.
3. Athanasiadis T, Beule AG, Wormald PJ. Effects of topical antifibrinolytics in endoscopic sinus surgery: a pilot randomized controlled trial. Am J Rhinol. 2007;21(6):737-742.
4. Baradaranfar MH, Dadgarnia MH, Mahmoudi H, et al. The Effect of Topical Tranexamic Acid on Bleeding Reduction during Functional Endoscopic Sinus Surgery. Iran J Otorhinolaryngol. 2017;29(91):69-74.
5. Jahanshahi J, Hashemian F, Pazira S, et al. Effect of topical tranexamic acid on bleeding and quality of surgical field during functional endoscopic sinus surgery in patients with chronic rhinosinusitis: a triple blind randomized clinical trial. PloS One. 2014;9(8):e104477-e104477.
6. Shehata A, Ibrahim M, Abd-El-Fattah M. Topical tranexamic acid versus hot saline for field quality during endoscopic sinus surgery. EJO. 2014;30(4):327-331.
7. Dos Reis LG, Ghadiri M, Young P, Traini D. Nasal Powder Formulation of Tranexamic Acid and Hyaluronic Acid for the Treatment of Epistaxis. Pharm Res. 2020;37(10):1-14.
8. Gholizadeh H, Messerotti E, Pozzoli M, et al. Application of a Thermosensitive In Situ Gel of Chitosan-Based Nasal Spray Loaded with Tranexamic Acid for Localised Treatment of Nasal Wounds. AAPS PharmSciTech. 2019;20(7):299.
9. Haghi M, van den Oetelaar W, Moir LM, et al. Inhalable tranexamic acid for haemoptysis treatment. Eur J Pharm Biopharm. 2015;93:311-319.
10. Wyrwa R, Otto K, Voigt S, et al. Electrospun mucosal wound dressings containing styptics for bleeding control. Mater Sci Eng C Mater Biol Appl. 2018;93:419-428.
11. R Baylis J, Finkelstein-Kulka A, Macias-Valle L, et al. Rapid hemostasis in a sheep model using particles that propel thrombin and tranexamic acid. Laryngoscope. 2017;127(4):787-793.
12. Ratnayake Kumar A, Wood AJ. The safety of topical and intravenous tranexamic acid in endoscopic sinus surgery. Presented at: The NZ Society of Otolaryngology and Head and Neck Surgery - 73rd Annual General and Scientific Meeting; October 2020; Auckland, New Zealand.
13. Kim DH, Kim S, Kang H, Jin HJ, Hwang SH. Efficacy of tranexamic acid on operative bleeding in endoscopic sinus surgery: A meta-analysis and systematic review. Laryngoscope. 2019;129(4):800-807.
14. Ping WD, Zhao QM, Sun HF, Lu HS, Li F. Role of tranexamic acid in nasal surgery A systemic review and meta-analysis of randomized control trial. Medicine (Baltimore). 2019;98(16):9.
15. El-Ozairy HSE, Mady OM, Tawfik GM, et al. Outcomes of combined use of topical and intravenous tranexamic acid on surgical field quality during functional endoscopic

sinus surgery: Randomized controlled trial. Head Neck. 2021;43(5):1389-1397.
16. Nuhi S, Goljanian Tabrizi A, Zarkhah L, Rashedi Ashrafi B. Impact of Intravenous Tranexamic Acid on Hemorrhage During Endoscopic Sinus Surgery. Iran J Otorhinolaryngol. 2015;27(82):349-354.
17. Wang Z, Shen X. The efficacy of combined intra-articular and intravenous tranexamic acid for blood loss in primary total knee arthroplasty: A meta-analysis. Medicine (Baltimore). 2017;96(42):e8123.
18. Peng Zhang MM, Jifeng Li MM, Xiao Wang MM. Combined versus single application of tranexamic acid in total knee and hip arthroplasty: A meta-analysis of randomized controlled trials. Int J Surg. 2017;43:171-180.
19. Sun Y, Jiang C, Li Q. A systematic review and meta-analysis comparing combined intravenous and topical tranexamic acid with intravenous administration alone in THA. PLoS One. 2017;12(10):e0186174.
20. Xiong H, Liu Y, Zeng Y, Wu Y, Shen B. The efficacy and safety of combined administration of intravenous and topical tranexamic acid in primary total knee arthroplasty: a meta-analysis of randomized controlled trials. BMC Musculoskelet Disord. 2018;19(1):321.
21. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? Otolaryngol Head Neck Surg. 2007;137(4):555-561.
22. Lund VJ, Mackay IS. Staging in rhinosinusitis. Rhinology. 1993;31:183-183.
23. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. Clin Otolaryngol. 2009;34(5):447-454.
24. Gillett S, Hopkins C, Slack R, Browne JP. A pilot study of the SNOT 22 score in adults with no sinonasal disease. Clin Otolaryngol. 2009;34(5):467-469.
25. Moffett AJ. Postural Instillation: A Method of Inducing Local Anæsthesia in the Nose. J Laryngol Otol. 1941;56(12):429-436.
26. Boezaart AP, van der Merwe J, Coetzee A. Comparison of sodium nitroprusside- and esmolol-induced controlled hypotension for functional endoscopic sinus surgery. Can J Anaesth. 1995;42(5 Pt 1):373-376.
27. Snidvongs K, Dalgorf D, Kalish L, Sacks R, Pratt E, Harvey RJ. Modified Lund Mackay Postoperative Endoscopy Score for defining inflammatory burden in chronic rhinosinusitis. Rhinology. 2014;52(1):53-59.
28. Kastl KG, Betz CS, Siedek V, Leunig A. Control of bleeding following functional endoscopic sinus surgery using carboxymethylated cellulose packing. Eur Arch Otorhinolaryngol. 2009;266(8):1239-1243.
29. Eldridge SM, Chan CL, Campbell MJ, et al. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. In: Pilot Feasibility Stud. Vol 2.2016:64.
30. Yuan C, Wang XM, Yang LJ, Wu PL. Tranexamic acid accelerates skin barrier recovery and upregulates occludin in damaged skin. Int J Dermatol. 2014;53(8):959-965.
31. Çevik HB, Eceviz E, Çilingir Kaya Ö T, Ercan F, Çeçen GS. The effect of topical and systemic tranexamic acid on fracture healing in rats. Acta Orthop Traumatol Turc. 2020;54(2):207-212.
32. Wahid NW, Smith R, Clark A, Salam M, Philpott C. The socioeconomic cost of chronic rhinosinusitis study. Rhinology. 2020;58(2):112-125.
33. Chowdhury NI, Mace JC, Bodner TE, et al. Investigating the minimal clinically important difference for SNOT-22 symptom domains in surgically managed chronic rhinosinusitis. Int Forum Allergy Rhinol. 2017;7(12):1149-1155.
34. Chaudhary FA, Pervaz Z, Ilyas S, Niaz MN. Topical use of tranexamic acid in open heart surgery. J Pak Med Assoc. 2018;68(4):538-542.
35. Hosseini H, Rahimianfar AA, Abdollahi MH, et al. Evaluations of topical application of tranexamic acid on post-operative blood loss in off-pump coronary artery bypass surgery. Saudi J Anaesth. 2014;8(2):224-228.
36. Dell'Amore A, Caroli G, Nizar A, et al. Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation. Heart Lung Circ. 2012;21(11):706-710.
37. Sabry MM, Sallam AA, Elgebaly AS, Abdelwahab AA. Evaluation of local intrapleural application of tranexamic acid on postoperative blood loss in lung decortication surgery, a prospective, randomized, double-blind, placebo-controlled study. Ann Card Anaesth. 2018;21(4):409-412.
38. Albirmawy OA, Saafan ME, Shehata EM, Basuni AS, Eldaba AA. Topical application of tranexamic acid after adenoidectomy: a double-blind, prospective, randomized, controlled study. Int J Pediatr Otorhinolaryngol. 2013;77(7):1139-1142.
39. Nilsson IM. Clinical pharmacology of aminocaproic and tranexamic acids. J Clin Pathol Suppl (R Coll Pathol). 1980;14:41-47.
40. Ausen K, Pleym H, Liu J, et al. Serum Concentrations and Pharmacokinetics of Tranexamic Acid after Two Means of Topical Administration in Massive Weight Loss Skin-Reducing Surgery. Plast Reconstr Surg. 2019;143(6):1169e-1178e.
41. Field A. Discovering Statistics Using IBM SPSS Statistics 5th ed. United Kingdom: SAGE Publications Ltd; 2017.
42. Jones SR, Carley S, Harrison M. An introduction to power and sample size estimation. Emerg Med J. 2003;20(5):453-8.
43. Noordzij M, Dekker FW, Zoccali C, Jager KJ. Sample size calculations. Nephron Clin Pract. 2011;118(4):c319-23.

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