EGYPTIAN JOURNAL OF ANAESTHESIA
2024, VOL. 40, NO. 1, 105–111
https://doi.org/10.1080/11101849.2024.2313414

"The efficacy of oral versus intravenous tranexamic acid in functional endoscopic sinus surgery". A prospective, randomized, controlled trial

Tamer Abdelaziz, Hatem Elsayed, Marwa Salem and Noura Youssri Mahmoud

Faculty of Medicine, Ain Shams University, Cairo, Egypt

ABSTRACT

Background: Functional endoscopic sinus surgery (FESS) is a common procedure for the treatment of chronic sinusitis and minimal bleeding inside the narrow surgical field affects the surgical visualization, prolongs operative time, and increases ocular and intracranial injuries. Our study aims to evaluate and compare the effectiveness of oral versus intravenous Tranexamic acid on surgical field bleeding in endoscopic sinus surgery.

Methods: A prospective, randomized, controlled trial enrolled 159 participants (ASA I-II, both sex and age 18–40 years) undergoing FESS who were equally randomized into 3 groups. Group O received 2 gm of TXA orally 2 hours before surgery, Group I received 15 mg/kg of IV TXA slowly after induction of anesthesia, and Group C didn't receive any. Intraoperative surgical field bleeding was assessed by the Wormald grading scale and Surgeon satisfaction on a 5-point Likert scale. At 24 hours post-operatively, the incidence of nasal bleeding, PONV, and D-dimer level were recorded.

Results: Showed significantly higher surgical field score, duration of surgery, recovery time, and postoperative (24 hours) D-dimer in group-C (p-value <0.001) with no difference between groups-I and O, while surgeon satisfaction was significantly lower in group-C (p-value <0.001) with no difference between groups-I and O. No differences regarding hemodynamic parameters, postoperative bleeding, pain, and PONV were found.

Conclusions: Oral TXA was safe, cheap, and as effective as IV TXA regarding surgical field visualization, surgeon satisfaction, and operative time during FESS; with limited adverse effects and no evidence of thromboembolic complications.

ARTICLE HISTORY
Received 27 December 2023
Revised 24 January 2024
Accepted 29 January 2024

KEYWORDS
Antifibrinolytics; endoscopic sinus surgery; intravenous; oral; tranexamic acid

1. Introduction

Functional endoscopic sinus surgery (FESS) is a common procedure for the treatment of chronic sinusitis and minimal bleeding inside the narrow surgical field affects the surgical visualization [1,2], prolongs operative time, and increases ocular and intracranial injuries [3].

Different techniques are available to decrease field bleeding such as head-up position, local infiltration of vasoconstrictors, IV steroid, and permissive hypotension; However, profound hypotension could delay recovery, increase the incidence of myocardial infarction and brain damage [4,5].

Tranexamic acid, as an antifibrinolytic drug, can occupy the fibrin binding site of the plasminogen molecule and prevent its conversion to active plasmin, the proteolytic enzyme responsible for fibrin breakdown, formation of FDP and D-dimer; So, TXA can decrease tissue oozing, intra- and postoperative bleeding after different surgeries as nasal, orthopedic, cardiac, obstetric surgeries [6–10], either in elective or emergencies [11,12].

TXA lowers the D-dimer blood level through its antifibrinolytic activity without affecting the other coagulation tests [13] nor increasing the thromboembolic complications after surgery [14].

TXA is available in oral and intravenous forms; Oral TXA is safer, simpler, and cheaper [15] than intravenous TXA that might increase the incidence of dizziness, headache, hypotension, nausea, and vomiting after rapid injection [16].

Our study aims to evaluate and compare the effectiveness of oral versus intravenous Tranexamic acid in endoscopic sinus surgery regarding surgical field quality and surgeon satisfaction.

The primary outcome was the assessment of intraoperative surgical field quality using a Wormald grading scale (where 0= no bleeding and 10= severe bleeding with sphenoid fill <10 seconds) [17] and **secondary outcomes** were the surgeon satisfaction (5-point Likert scale [17]), the incidence of

CONTACT Tamer Abdelaziz drtasamir@hotmail.com Faculty of Medicine, Ain Shams University, Cairo, Egypt
On behalf of all the contributors, I will act as guarantor and will correspond with the journal from this point onward.
Supplemental data for this article can be accessed online at https://doi.org/10.1080/11101849.2024.2313414

postoperative nasal bleeding and PONV at 24 hours. As well as the effect of TXA on D-dimer level at 24 hours.

2. Materials and methods

A prospective, randomized, controlled, and parallel study was conducted in the university hospital between **3rd December 2022 and 30th April 2023** after the Ethics committee approval, obtaining written informed consent from all participants, and registration at Clinicaltrials.gov; The study follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants scheduled for FESS and fulfilled the inclusion criteria (ASA I – II, both sexes and 18–40 years old) were randomly allocated into one of the study groups using **program-generated numbers in black sealed envelopes with a one-to-one ratio** by a resident not directly involved in the research.

- Group C (Control group) ($n = 53$): The participants didn't receive any intervention.
- Group O (oral group) ($n = 53$): The participants received 4 tablets of TXA 500 mg (equal 2 gm) 2 hours before surgery in the ward by a nurse [19].
- Group I (intravenous group) ($n = 53$): The participants received 15 mg/kg TXA in a 20 ml syringe slowly during induction by an anesthesia physician [20].

The pharmacist prepared the TXA tablets in a unit bag and IV TXA in 20 ml syringe labelled with patient number and time of administration, so the nurse and anesthesia physician were blinded.

Intra- and postoperative follow-ups were done by residents unaware of the group allocation. So, the participants, operative team, allocating residents, and follow-up residents were blinded.

Any case that has a history of cerebrovascular stroke, arterial or venous thrombosis, pulmonary embolism, or cardiovascular diseases such as atrial fibrillation, ischemia, or uncontrolled hypertension was excluded from the study, as well as the patient refused to participate or had an allergy to TXA, bleeding tendency, end-stage renal disease, or liver cell failure.

Preoperative clinical evaluation, full laboratory tests, and ECG in addition to baseline D-dimer were done for all participants.

In the operating room, participants connected to the standard monitoring and basal hemodynamic parameters were recorded then every 5 minutes; An intravenous cannula was inserted.

Anesthesia was started with 2 mg/kg propofol, 2 µg/kg fentanyl, and 0.5 mg/kg atracurium, then an oral endotracheal tube was inserted after preoxygenation with 100% O2 for 2 minutes. Respiratory rate and tidal volume were adjusted to maintain normocarbia (end-tidal CO2) and anesthesia was maintained with isoflurane (1%-2%) and 1–2 µg/kg fentanyl (Maximum of 4 µg/kg) to obtain an adequate depth of anesthesia (HR 60–70 bpm and MAP 70–80 mmHg); 2% lidocaine HCL + 1:100,000 epinephrine solution was infiltrated locally after frequent aspiration by the surgeon to control pain and bleeding; Slow IV injection of labetalol 10 mg every 10 minutes was incrementally given with total dose 300 mg during the procedure if blood obscured the surgical field after isoflurane 2% and total fentanyl 4 µg/kg; While IV ephedrine 2.5 mg was given incrementally when the MAP was less than 60 mmHg [21].

In head-up 30° position, one surgical team operated all surgeries with the same technique and scored the surgical field bleeding by Wormald grading scale (where 0= no bleeding and 10= severe bleeding with sphenoid fill <10 seconds) at the end of surgery (17); The team was blind to the study group.

After regaining spontaneous respiration and adequate recovery, the endotracheal tube was removed smoothly at the end of surgery; In the recovery room, the hemodynamic parameters and pain severity by VAS score (0–10) were recorded in addition to the incidence of PONV; the 5-point Likert scale scored the surgeon satisfaction [18].

IV paracetamol 1 gm every 8 hours and pethidine (25–50 mg) if their VAS score ≥ 4 were given; Moreover, iv ondansetron (4 mg) was given for PONV. Participants were followed up for 1 hour in the PACU and transferred to wards with a modified Aldrete recovery score > 9.

Follow-up D-dimer at 24 hours and bilateral lower limb duplex at one week were done.

By using Power Analysis and Sample Size Software (PASS 11) (Version 11.0.08) for sample size calculation, to achieve power 80%, at an alpha error of 5%, and after reviewing previous study results (El-Ozairy et al., 2020) [12], and after assuming that among patients undergoing functional endoscopic sinus surgery, a medium effect size difference (h = 0.5) in the median of surgical field quality score between those took tranexamic acid 15 mg/kg intravenous slowly and those took oral tranexamic acid and the control group; a sample size of at least 159 patients undergoing functional endoscopic sinus surgery divided into 3 groups (53 patients in each group) would have been sufficient to achieve study objective.

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS statistics (Statistical Package for Social Sciences) software version 28.0, IBM Corp., Chicago, USA, 2021. Quantitative data was tested for normality using the Shapiro-Wilk test, then described as mean±SD (standard deviation), and then compared using the ANOVA test. Qualitative data is described as numbers and

percentages and compared using the Chi-square test as well as Fisher's Exact test for variables with small-expected numbers. The post hoc Bonferroni test was used for pairwise comparison. The level of significance was taken at p-value <0.05.

3. Results

After screening two hundred twenty-one patients, sixty-two patients were excluded (54 did not fulfill the criteria and 8 refused participation) and the remaining 159 participants were randomized into study groups equally and their data were analyzed (Figure 1).

Table 1 showed that there were no significant differences between the studied groups regarding demographic characteristics, age, sex, BMI, and ASA.

Table 2 showed that no significant differences between the studied groups regarding vital blood pressure, heart rate, SPO2, and baseline D-dimer; While, the mean postoperative (24 hours) D-dimer were significantly higher in group C (1.12 ± 0.11 ng/ml) and p-value <0.001 with no significant difference between groups-I and O.

Table 3 showed that: The mean surgical field score, duration of surgery, and recovery time were significantly higher in group C (5.5 ± 0.9, 110.8 ± 8 minutes, and 12.5 ± 1.1 minutes) respectively, and p-value <0.001 with no significant difference between groups I and O. The mean surgeon satisfaction was significantly lower in group C (2.7 ± 0.6) and p-value <0.001 with no significant difference between groups I and O (Figure 2). Postoperative bleeding and the need for rescue analgesia were non-significantly higher in group-C [$n = 5$ (9.4%) and $n = 9$ (17.0%) with p-value = 0.278 and 0.116] respectively. No significant differences between the studied groups regarding postoperative pain score and PONV.

4. Discussion

In the current study, TXA significantly improved the surgical field quality compared to the control group as reflected by significantly higher surgeon satisfaction and shorter duration of surgery; Oral TXA was as effective as IV. We used the Wormald grading scale as it was found reliable, sensitive, and overcoming some of the Boezaart scale limitations [17].

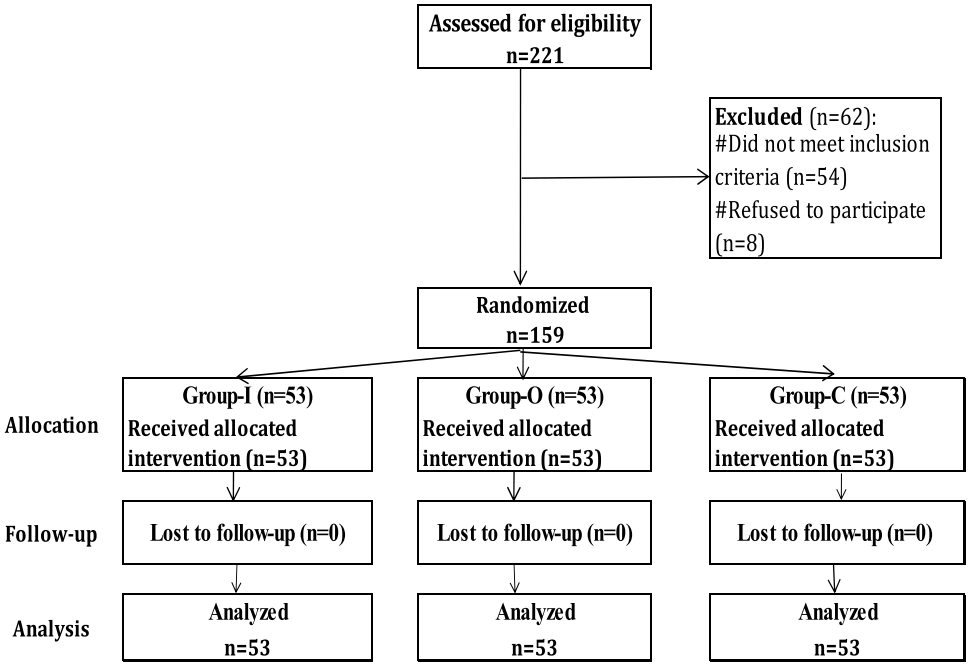

Figure 1. CONSORT flow diagram.

Table 1. Comparison regarding demographic characteristics.

Variables		Group-I (Total = 53)	Group-O (Total = 53)	Group-C (Total = 53)	p-value
Age (years)		30.7 ± 6.2	31.2 ± 6.0	30.6 ± 5.8	^0.855
Sex	Male	31 (58.5%)	35 (66.0%)	33 (62.3%)	#0.725
	Female	22 (41.5%)	18 (34.0%)	20 (37.7%)	
BMI (kg/m^2)		24.7 ± 2.7	24.9 ± 2.7	24.6 ± 2.6	^0.868
ASA	I	40 (75.5%)	39 (73.6%)	38 (71.7%)	#0.907
	II	13 (24.5%)	14 (26.4%)	15 (28.3%)	

BMI: Body Mass Index. ASA: American Society of Anesthesiologists. Data presented as Mean±SD or n (%). ^ANOVA test. #Chi square test.

Table 2. Comparison regarding vital blood pressure, heart rate, SPO_2 and D-dimer.

Variables	Time	Group-I (Total = 53)	Group-O (Total = 53)	Group-C (Total = 53)	p-value
Systolic blood pressure (mmHg)	Baseline	134.0 ± 8.1	133.3 ± 7.8	133.0 ± 8.2	^0.820
	Operation min.	109.3 ± 5.9	109.0 ± 5.7	109.3 ± 6.5	^0.951
	Operation max.	117.9 ± 6.0	117.1 ± 5.5	117.5 ± 6.3	^0.815
Diastolic blood pressure (mmHg)	Baseline	75.8 ± 7.3	76.1 ± 7.0	76.1 ± 7.2	^0.979
	Operation min.	62.4 ± 5.5	62.8 ± 5.1	62.8 ± 5.4	^0.904
	Operation max.	67.7 ± 5.5	68.8 ± 4.9	68.0 ± 5.3	^0.548
Mean blood pressure (mmHg)	Baseline	95.3 ± 7.3	95.2 ± 7.0	95.1 ± 7.1	^0.992
	Operation min.	78.1 ± 5.5	78.2 ± 5.1	78.3 ± 5.4	^0.977
	Operation max.	84.4 ± 5.4	84.9 ± 4.8	84.5 ± 5.2	^0.891
Heart rate (beat/min.)	Baseline	76.5 ± 9.1	75.9 ± 8.5	76.6 ± 8.6	^0.897
	Operation min.	60.5 ± 6.3	61.0 ± 5.7	61.3 ± 5.7	^0.784
	Operation max.	67.4 ± 6.9	67.6 ± 5.9	68.2 ± 6.1	^0.762
SPO_2 (%)	Baseline	97.7 ± 0.7	97.6 ± 0.7	97.6 ± 0.7	^0.961
	Operation min.	97.6 ± 0.5	97.7 ± 0.5	97.6 ± 0.5	^0.604
	Operation max.	99.8 ± 0.4	99.8 ± 0.4	99.8 ± 0.4	^0.871
	Postoperative	97.5 ± 0.7	97.5 ± 0.8	97.5 ± 0.7	^0.904
D-dimer (ng/mL)	Baseline	1.12 ± 0.11	1.12 ± 0.11	1.11 ± 0.11	^0.759
	Postoperative (24 hour)	1.03 ± 0.10a	1.00 ± 0.11a	1.12 ± 0.11b	<0.001*

Data presented as Mean±SD. ^ANOVA test. *Significant. Homogenous groups had the same symbol based on post hoc Bonferroni test "a,b".

Table 3. Comparison regarding operative and postoperative outcomes.

Variables	Group-I (Total = 53)	Group-O (Total = 53)	Group-C (Total = 53)	p-value
Surgical field score	2.1 ± 0.9a	2.2 ± 0.8a	5.5 ± 0.9b	<0.001*
Duration of surgery (min.)	92.5 ± 6.9a	94.2 ± 7.8a	110.8 ± 8.0b	<0.001*
Surgeon satisfaction	3.8 ± 0.6a	3.7 ± 0.6a	2.7 ± 0.6b	<0.001*
Recovery time (min.)	10.6 ± 1.2a	11.1 ± 1.1a	12.5 ± 1.1b	<0.001*
Postoperative bleeding	2 (3.8%)	1 (1.9%)	5 (9.4%)	§0.278
Postoperative pain score	2.4 ± 0.8	2.5 ± 0.9	2.8 ± 1.1	^0.058
Postoperative need to analgesia	3 (5.7%)	4 (7.5%)	9 (17.0%)	#0.116
Postoperative nausea and vomiting	2 (3.8%)	3 (5.7%)	2 (3.8%)	§0.999

Data presented as Mean±SD or n (%). ^ANOVA test. #Chi square test. §Fisher's Exact test. *Significant. Homogenous groups had the same symbol based on post hoc Bonferroni test "a,b".

FESS is a common procedure with a narrow surgical field inside the nasal cavity, where minimal bleeding affects the surgical field visualization [1,2].

Tranexamic acid, as an antifibrinolytic drug, can occupy the fibrin binding site of the plasminogen molecule and prevent its conversion to active plasmin, the proteolytic enzyme responsible for fibrin breakdown, formation of FDP and D-dimer; So, TXA can decrease tissue oozing, intra- and postoperative bleeding after different surgeries as orthopedic, cardiac, obstetric surgeries [6–10], either in elective or emergencies [11,12].

TXA is available in oral and intravenous forms; Oral TXA is safer, simpler, and cheaper [15] than intravenous TXA might increase the risk of thromboembolic events [22–24] and slow infusion reduces

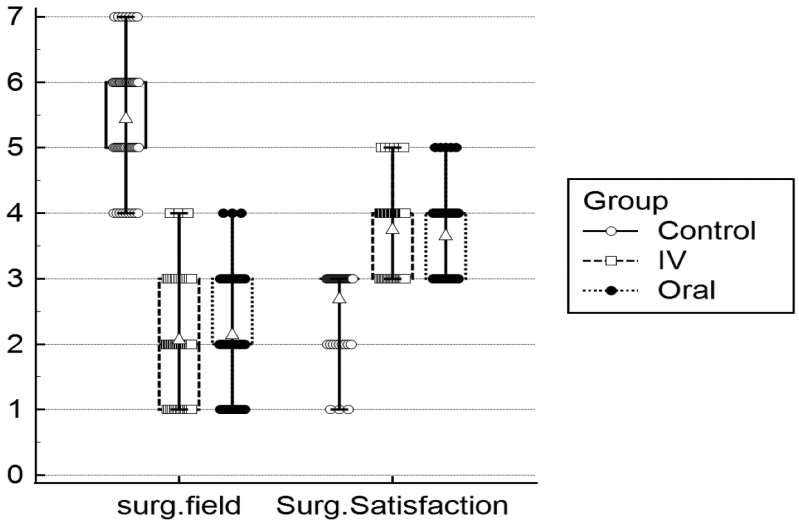

Figure 2. Box plot for surgical fields score and surgeon satisfaction. Box represents the interquartile range. Arrowhead inside the box represents the mean. Whiskers represent minimum and maximum values. ●, □, ○ represent cases.

the incidence of nausea, vomiting, and hypotension [25].

To the best of our knowledge no previous study compared oral and intravenous TXA in FESS; And after a review of the previous literature, we chose intravenous TXA 15 mg/kg and oral TXA 2 g; Those doses showed no significant adverse events after administration [26–29]

Our results coincide with Nuhi et al., Dongare, and Saundattikar who compared a single intravenous dose of 15 mg/kg TXA to a placebo, and Langille MA et al. who used a TXA bolus dose of 15 mg/kg (IV) followed by infusion dose of 1 mg/kg/hour and all reported a significant reduction in intraoperative bleeding, better surgical field, and shorter procedure time [26,30,31].

Abbasi et al. and Pannerselvam et al. compared 2 doses of IV TXA (5 mg/kg and 15 mg/kg) and reported that 15 mg/kg IV TXA significantly enhanced the operative field using the Boezaart scale [32] and Wormald grading scale [27], with shorter operative time and better surgical satisfaction.

Also, EL Ozairy et al. evaluated different routes of TXA administration on the surgical field during FESS, they compared topical TXA 2 gm, intravenous TXA(15 mg/kg), and both combined (topical and IV) versus placebo where they found better surgical field quality by Boezaart scale in the combined group followed by the intravenous group compared with placebo group [12]; Moreover, Yang et al. found that IV TXA 15 mg/kg preoperatively improved field visualization during FESS for participants with chronic Rhinosinusitis and Lund-Mackay score ≥ 12 [33]. On the other hand, Mottaghi et al. found no differences between placebo and IV TXA 500 mg regarding bleeding [34], this might be due to the low dose of TXA taken [35].

Oral TXA 1 gm was given 2 hours before rhinoplasty and significantly decreased intraoperative bleeding and operative time with higher surgeon satisfaction [15]. Also, Yanif et al. gave 1 gm oral TXA 2 hours before nasal surgeries and every 8 hours after that for 5 days and reported a significant reduction in intraoperative and postoperative bleeding with minimal adverse events [24].

Although the research compared intravenous versus oral TXA related mainly to orthopedic procedures [35]; A meta-analysis evaluated TXA in rhinoplasty, found a higher reduction in intra-operative bleeding with oral TXA 1 gm 2 hours before surgery than IV TXA 10 mg/kg and attributed the difference to plasma concentration of TXA that remained within the therapeutic level for 6 hours with oral than IV TXA that showed mono-exponential decay [36].

Oral TXA 2 gm taken 2 hours before knee arthroplasty compared with IV TXA 1 gm injected 15 min before surgery, showed equal efficacy of both interventions regarding blood loss with no significant reduction of hemoglobin [28].

Regarding post-operative nasal bleeding, in the current study, it was non-significantly higher in the control group than in both IV or oral TXA groups, which differs from the results reported by Yaniv et al. [24] and Zaman et al. [37]. This may be due to their use of TXA after surgery.

PONV is a common side effect of tranexamic acid, however in our study, only 7 participants reported PONV with no significant differences between the study groups, this could be attributed to anesthetics used. These results are like the previous studies [24,31].

The elevation of D-dimer level after surgery indicates inflammatory and fibrinolytic processes activation with the peak level 6–18 hours post-operatively; So, TXA as an antifibrinolytic agent could decrease perioperative bleeding and lower D-dimer level when compared with placebo as reported by the previous studies [38–40] and these findings coincide with ours. Although thromboembolic complications are theoretically possible, neither our study nor the previous literature reported it [12,15,24–33].

4.1. Limitations

We didn't consider the degree of chronic sinusitis that affects vascularity and intraoperative bleeding; Frequent intraoperative time points evaluation for surgical field score were needed; Further studies are needed using more accurate tools for measurement of perioperative bleeding to confirm TXA effects.

5. Conclusion

Oral TXA was safe, cheap, and as effective as IV TXA regarding surgical field visualization, surgeon satisfaction, and operative time during FESS; with limited adverse effects and no evidence of thromboembolic complications.

List of abbreviations

ASA-PS	American Society of Anesthesiologists- Physical status.
FESS	Functional endoscopic sinus surgery
HR	Heart rate.
IV	Intravenous
MAP	Mean arterial blood pressure.
OR	Operating room.
PACU	Post anesthesia care unit.
PONV	Postoperative nausea and vomiting.
TXA	Tranexamic acid.
VAS	Visual Analogue score.

Disclosure statement

The authors declare that no potential conflict of interest relevant to this article was reported.

ORCID

Tamer Abdelaziz http://orcid.org/0000-0002-6964-1418
Hatem Elsayed http://orcid.org/0009-0009-1124-3132
Marwa Salem http://orcid.org/0000-0002-1223-5670
Noura Youssri Mahmoud http://orcid.org/0009-0003-9884-1050

Authors' contributions

TA: study conception, design, data collection, data analysis, results interpretation, writing discussion, preparing manuscript, and journal submission.

HE: study conception, design, data collection, results interpretation, and writing discussion.

MS: study conception, design, data collection, and writing discussion.

NM: data collection, data analysis, results interpretation, writing discussion.

The manuscript and results were reviewed and approved by all authors.

The manuscript has not been published, simultaneously submitted, or accepted for publication elsewhere.

The paper is prepared according to the *"Instructions for Authors"*.

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Consent for participation and publication

Written informed consent was obtained from all participants.

Availability of data and material

All data are available upon reasonable request.

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