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Prevention of postoperative bleeding in hip fractures treated with prosthetic replacement: efficacy and safety of fibrin sealant and tranexamic acid. A randomised controlled clinical trial (TRANEXFER study)

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Abstract

Introduction We assessed the efficacy of fibrin sealant (FS) and tranexamic acid (TXA) administered topically in patients with a hip fracture treated with prosthetic replacement.

Materials and methods Parallel, multicentre, open label, randomised, clinical trial. We compared three interventions to reduce blood loss: (1) 10 ml of FS, (2) 1 g of topical TXA, both administered at the end of the surgery, and (3) usual haemostasis (control group). The main outcome was blood loss collected in drains. Other secondary variables were total blood loss, hidden blood loss, transfusion rate, average hospital stay, complications, adverse events, and mortality.

Results A total of 158 patients were included, 56 in the FS group, 52 in the TXA group, and 50 in the control group. The total amount of blood collected in drains was lower in the TXA group (148.6 ml, SD 122.7 in TXA; 168.2 ml, SD 137.4 in FS; and 201.5 ml, SD 166.5 in control group) without achieving statistical significance ($p=0.178$). The transfusion rate was lower in the TXA group (32.7%), compared with FS group (42.9%) and control group (44.0%), without statistical significance ($p=0.341$). There were no complications or adverse effects related to the evaluated interventions.

Conclusions The use of TXA and FS administered topically prior to surgical closure in patients with a sub-capital femoral fracture undergoing arthroplasty did not significantly reduce either postoperative blood loss or transfusion rate, compared with a group that only received usual haemostasis.

Keywords Hip fracture · Tranexamic acid · Fibrin sealant · Randomised clinical trial

Introduction

Proximal femoral fractures are usually caused by high-energy trauma in young adults, but by a low-energy trauma in the elderly [1]. This condition occurs more often in the elderly, presenting one of the highest incidences of morbidity and mortality. Specifically, mortality incidence ranges from 18 to 33% per year [2]. Age, sex, dementia, and frailty are associated with increased mortality [2].

Despite the advances in surgical techniques and materials in the treatment of femoral fractures, the blood loss causes anaemia and increases perioperative morbidity and mortality [3–5]. Pharmacological and non-pharmacological strategies should be applied to reduce bleeding and to avoid transfusions. One strategy is the intraoperative administration of topical or intravenous haemostatic agents. Tranexamic acid (TXA) inhibits fibrinolysis by blocking the lysine-binding sites on plasminogen, and facilitates the coagulation process [6]. Fibrin Sealant (FS) is a biological adhesive which initiates the final stages of coagulation. It is derived from the transformation of fibrinogen in fibrin by thrombin [7]. Several clinical trials and meta-analyses have studied the

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efficacy of FS and topical TXA in patients undergoing elective prosthetic hip and knee surgery [8–13], but the research in hip fractures is scarce. At the time we designed our study, in patients with proximal femoral fracture, only two clinical trials of the use of intravenous TXA had been reported and no studies about topical administration [14, 15]. One of them found a diminution of blood loss and transfusion in the TXA group, but found an increased risk of cardiovascular adverse events [15]. For these reasons, we conducted a randomised controlled trial with the hypothesis that FS and TXA administered topically (with a lower systemic absorption) would reduce postoperative blood loss, and minimize the adverse events in patients undergoing prosthetic replacement for proximal femoral fracture.

Materials and methods

This study is a multicentre, open label, three-arm, randomised, parallel-group clinical trial. It is registered at ClinicalTrials.gov (number NCT02150720).

The protocol was approved by the local Research Ethics Committees of seven participating university hospitals and the Spanish National Agency of Medicines and Health Products. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained before surgery from all included participants.

Patient population

We recruited consecutive patients from February 2013 to March 2015. Inclusion criteria were adult patients, aged 18 or older, with unilateral sub-capital femoral fracture, requiring (total or partial) hip replacement, who agreed to participate and signed the consent form or the legal representative. Older patients and patients with dementia were included.

Exclusion criteria were known allergy to FS or TXA, multiple fractures, use of intraoperative blood salvage, history of coagulopathy or thromboembolic events like history of thromboembolic events like cerebral vascular accident, myocardial infarction or angina, deep vein thrombosis, pulmonary embolism, peripheral arterial vasculopathy, patients with thrombogenic arrhythmias, patients with cardiovascular stents, prothrombotic alteration in coagulation; patients treated with anticoagulant (anticumarin, direct anticoagulants), antiplatelets (including AAS 100 mg) or contraceptive or estrogens and, patients who refused to participate.

Randomisation

Patients were randomised to receive topical FS (Evicel®, Omrix Biopharmaceuticals N.V, Diegem, Belgium), topical TXA (Amchafibrin®, Rottafarm SL, Valencia, Spain), or routine haemostasis only.

A table of random numbers was computer-generated and stratified by centre. Random allocation was made before surgery, via phone call to the coordinating centre. The treatment allocation sequence was concealed to clinical investigators.

Group 1. Evicel® 5.0 ml was administered following the manufacturer's instructions; 5 ml of fibrinogen solution (50–90 mg/ml) was combined with 5 ml of human thrombin (800–1200 UI/ml), and the 10 ml product was applied using a special syringe that was supplied with the product.

Group 2. The TXA group received a single 1 g dose of TXA in a 10 ml solution topically by syringe-spray. We chose this dose based on our experience in a previous study with topical TXA in knee arthroplasty that showed a significant reduction in blood loss compared with routine haemostasis [9].

In both groups, routine haemostasis was applied and after the prosthesis was inserted, the entire surgical site was thoroughly rinsed and meticulously dried. FS and TXA were applied on the surrounding soft tissues and the exposed surfaces of the femur.

Group 3. The control group only received routine haemostasis consisting only in the electro-coagulation of all bleeding points and vessels.

Operative and postoperative procedures

Surgery was performed by senior orthopaedic surgeons who decided the type of prosthesis, cemented or non-cemented. The used anaesthetic technique was intra-spinal with controlled hypotension. An intravenous prophylactic antibiotic was administered during anaesthetic induction, lasting for 24 h after surgery. Electro-coagulation of blood vessels was performed during surgery in all patients (routine haemostasis). One number eight vacuum drain was inserted before closing the wound, and was removed 24–48 h after surgery. We clamped the drain during 1 h preventing the loss of topical medications through the drain and favouring its effect. In the control group the drain was also clamped during 1 h after surgery.

All patients received low-molecular-weight heparin for 30 days to prevent thromboembolic complications. All participating hospitals followed the same blood-transfusion protocol. The transfusion was indicated when haemoglobin (Hb) was ≤ 7 g/dl and patients were ≤ 65 years old without history of cardiovascular disease; Hb was ≤ 8 g/dl and patients > 65 years or with history of cardiovascular or respiratory disease or an increase in O_2 consumption; Hb ≤ 9–10 g/dl and patients with history of angina or myocardial infarction or left ventricular insufficiency. The decision of transfusing allogeneic blood was made by the anaesthesiologist during surgery or by the ward physician during the postoperative

period. Patients remained seated from hour 24 to 48 after surgery. Progressively, with the support of physical therapists, they started walking with load and ongoing support with crutches and/or walkers.

Outcomes

The primary outcome was the blood collected postoperatively in the vacuum drains. Secondary outcomes were total blood loss and hidden blood loss (blood lost during surgery or retained in the wound or in adjacent tissues), the rate of perioperative blood transfusion, the preoperative and postoperative haemoglobin levels, the units of transfused blood, the rate of surgical infections, the length of hospital stay, the rate of venous thrombosis, treatment-related adverse events, and mortality.

The data of blood loss collected in drains were extracted from the daily nursing records. Total blood loss and hidden blood loss were calculated based on haemoglobin balance according to equations described by Nadler et al. [16].

The intensity of adverse events was classified as mild (not interfering with the patients' normal activities), moderate (interfering with normal activities), and severe (preventing normal activities).

Patients were followed up during the postoperative days until hospital discharge and at day 30 (± 15 days after hospital discharge). One year after surgery we examined the patients' medical records or contacted by telephone with them to assess the mortality rate.

Statistical analysis

Based on a previous clinical trial [13], we assumed 230 ml less blood in drains in the experimental groups than in the control group, a 15% drop-out rate, an alpha risk of 0.05, and a beta risk of 0.2. The number of patients required for each group was 55, that is, 165 in total.

The main analysis was by Intention to Treat (ITT), and, secondarily, Per Protocol (PP). For categorical data we calculated frequency count. For quantitative data, when appropriate, we calculated mean and standard deviation (SD), or mean difference and 95% confidence interval (CI). Pearson's Chi square tests were used for categorical data. Blood loss was analysed using one-way ANOVA. Statistical significance was set at $p \leq 0.05$.

Results

Four hundred and eighteen patients were screened, 257 (61%) of which were excluded, mainly because they did not meet the inclusion criteria. A total of 161 patients were thus randomised and homogeneously allocated to one of the three treatment groups: 56 to FS (group 1), 53 to TXA (group 2), and 52 to control (group 3). Three patients retired the consent to participate in the study and 14 patients did not receive the intervention. Additionally, a patient was excluded because he underwent an open reduction and an internal fixation surgery. Therefore, the number of assessable patients by ITT was 56 in the FS group, 52 in the TXA group, and 50 in the control group; the number of patients included PP was 143, 45 in the FS group, 48 in the TXA group, and 50 in the control group (see flow diagram in Fig. 1). During the 12 month follow-up, 21 (13%) patients died (five in TXA, seven in FS and nine in control group).

Patients' mean age was 83.8 (SD 8.5) years; 122 (77.2%) patients were women and 36 (22.8%), men. The mean BMI was 24.6 (SD 3.9). Treatment groups showed no differences in their baseline characteristics or co-morbidities (Table 1). The co-morbidities with higher rates were hypertension and previous surgery. Seventeen patients presented dementia. The most frequent previous surgeries were general (25 patients), orthopaedic (21 patients) and cataract (14 patients) surgeries. Most patients had an American Society of Anesthesiologists (ASA) score of II–III. Ninety-two percent of prosthesis were hemi-arthroplasties. There were no significant differences between the treatment groups regarding preoperative anaemia, time from admission to surgery, duration of surgery, type of prosthesis, and prosthesis cementation (Table 1).

The blood loss collected by the drains was lower in the TXA group than in the other groups, but had no statistically significant difference: 148.6 (SD 122.7) ml in the TXA group, 168.2 (SD 137.4) ml in the FS group and 201.5 (SD 166.5) ml ($p = 0.178$) (Table 2). The PP analysis showed similar results.

Total blood loss was 1192.9 (SD 785.7) ml in the TXA group, 1620.4 (SD 1042.7) ml in the FS group and, 1557.2 (SD 847.1) ml in the control group ($p = 0.063$). Total blood loss in PP analysis was significantly lower in the TXA group: 1177.9 (SD 733.6) ml in the TXA group, 1557.2 (SD 847.1) ml in the control group and 1653.8 (SD 1085.0) ml in the FS group ($p = 0.048$). The hidden blood loss was lower in the TXA group than in the other groups, in both ITT (Table 2) and PP analyses, but had no statistically significant difference.

The mean overall Hb levels of patients prior to surgery were 12.3 g/dl (SD 1. 7) with no differences between groups. The overall pre-transfusional Hb was 8.4 g/dl (SD 1.1). Sixty-three patients (39.9%) needed postoperative transfusion. The TXA group received fewer transfusions, but with no statistically significant differences between groups ($p = 0.431$). The total number of units of transfused red blood cells was 122. Likewise, the group with TXA received the lowest number of blood units, but with no statistically significant differences ($p = 0.722$) (Table 3). The overall

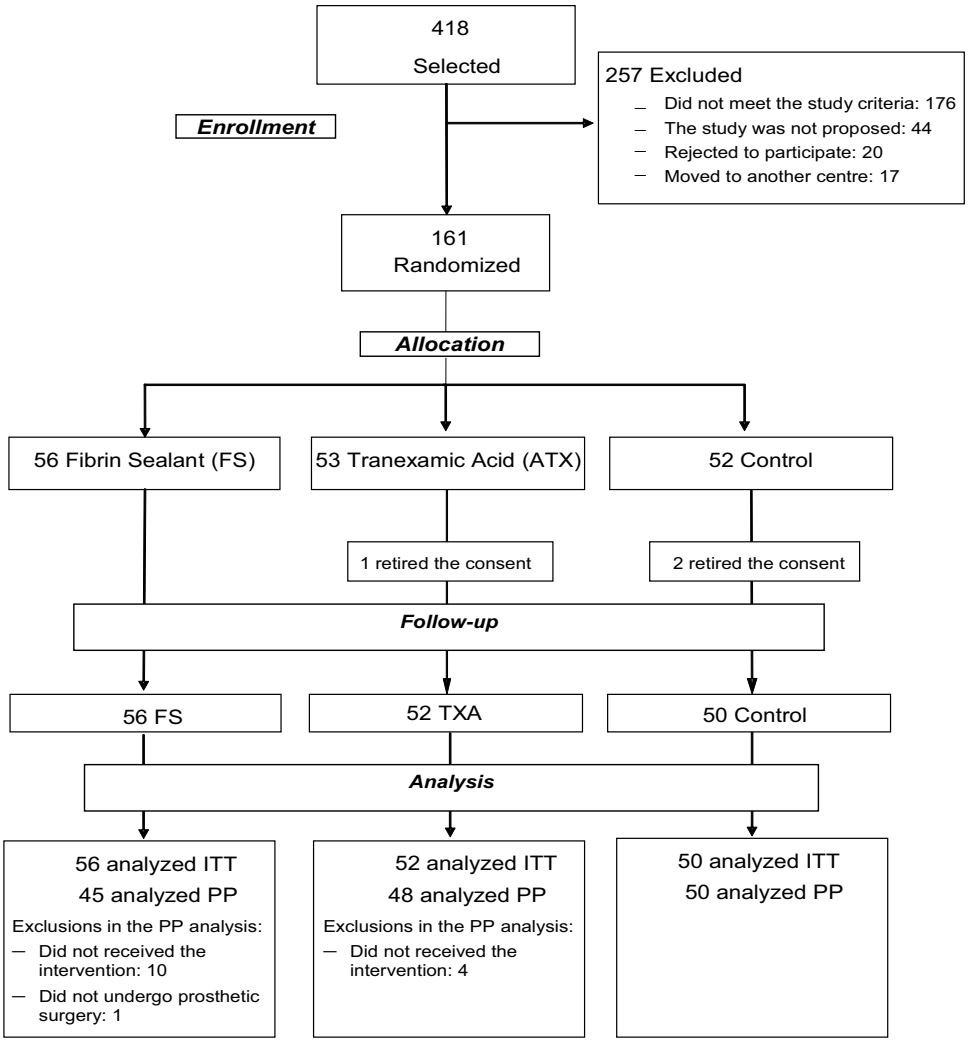

Fig. 1 Flow chart of participants

mean hospital stay of study patients was 11.5 (SD 11.1) days, with no statistically significant difference between groups ($p = 0.969$).

There were no adverse events with a certain causal relationship associated to the study interventions. However, there was one event with a possible causal relationship.

One patient in the TXA group suffered a stroke secondary to an arrhythmia in the immediate postoperative period associated with massive pulmonary thromboembolism and exitus. Another six patients died during the first 30 postoperative days (two intra-operatively, two of cardiorespiratory arrest, one due to a hospital pneumonia, and one of fever of unknown origin after discharge). Additionally, 14 patients died from 30 postoperative days to the end of 12 month follow-up. Therefore, the overall mortality rate one year after surgery was 13% (21 patients; five in TXA, seven in FS and nine in control group).

Thirty-three patients presented medical complications with no differences between treatment groups. The most frequent medical complication was urinary tract infection in nine patients. There were two cases of early prosthetic infection unrelated to the treatments. Fifteen patients presented surgery-related complications; 12 of these were severe. Seven patients (4.5%) required a re-intervention, six patients due to prosthesis dislocation and one patient because a prosthesis infection. Four patients were of TXA group and three to control group.

Discussion

Based on the main results of our study, FS or topical TXA does not reduce postoperative bleeding and transfusion requirements in patients undergoing hip replacement for subcapital femoral fracture. Only topical TXA showed a significant reduction in the secondary outcome, total blood loss. Cardiovascular complications, thromboembolism, infection rates or mortality were similar in all compared groups.

Published studies have assessed FS [13, 16–18] and topical TXA [19–23] efficacy in primary elective hip

Table 1 Participants' baseline characteristics

	FS $N = 56$ n (%)	TXA $N = 52$ n (%)	Control $N = 50$ n (%)	p
Age (mean, SD)	83.00 (8.2)	84.08 (6.9)	84.56 (10.4)	0.626
Sex (women)	42 (75.0)	43 (82.7)	37 (74.0)	0.513
BMI (mean, SD)	25.53 (4.7)	24.49 (3.1)	23.78 (3.8)	0.127
Medical background				
Hypertension	31 (55.3)	30 (57.7)	30 (60.0)	0.992
Surgery	33 (58.9)	30 (57.7)	29 (58.0)	0.478
Diabetes	12 (21.4)	5 (9.6)	12 (24.0)	0.394
Chronic obstructive pulmonary disease	8 (14.3)	7 (13.5)	2 (4.0)	–
Chronic renal disease	5 (8.9)	5 (9.6)	6 (12.0)	–
Digestive ulcer	3 (5.3)	0	1 (2.0)	–
Haematological disease	3 (5.3)	1 (1.9)	0	–
Chronic liver disease	0	0	2 (4.0)	–
Pre-operative anaemia[a]	19 (33.9)	25 (48.1)	22 (44.0)	0.428
ASA				
I	1 (1.8)	0	1 (2.0)	–
II	19 (33.9)	23 (44.2)	20 (40.0)	
III	14 (25.0)	19 (36.5)	20 (40.0)	
IV	2 (3.58)	0	1 (2.0)	
Unknown	20 (35.7)	10 (19.2)	8 (16.0)	
Time from admission to surgery (days, mean and SD)	3.29 (4.0)	2.81 (2.8)	2.41 (2.0)	0.353
Surgery duration (minutes, mean and SD)	76.04 (24.2)	79.36 (19.5)	77.08 (24.6)	0.755
	$N = 55$	$N = 50$	$N = 50$	
Type of prosthesis				
Monopolar	31 (56.4)	26 (50.0)	27 (54.0)	–
Bipolar	19 (34.5)	21 (40.)	20 (40.0)	
Total	5 (9.1)	5 (9.6)	3 (6.0)	
Prosthesis model				
Austin Moore®	30 (54.6)	25 (48.1)	27 (54.0)	–
Karey®	15 (27.3)	20 (38.5)	15 (30.0)	
Furlong®	3 (5.4)	3 (5.7)	2 (4.0)	
Others	7 (12.7)	4 (7.7)	6 (12. 0)	
Cementation	28 (50.9)	26 (50.0)	21 (42.0)	0.645

SD Standard deviation, *BMI* body mass index, *ASA* Scale of surgical risk assessment of the American Society of Anaesthesiologists

[a]Defined as haemoglobin < 120 g/dl in women and < 130 g/dl in men

arthroplasty, but we only found Emara et al. [24] and Kang et al. [25] studies evaluating topical TXA, and no studies assessing FS in hip fractures.

Emara et al. [24] study differed in regard to our clinical trial because patients were younger (50–60 years old) and the inclusion criteria were more restrictive (patients with preoperative anaemia or associated medical pathology were excluded). Furthermore, the dose of topical TXA used was higher than in our study, 1.5 g diluted in 150 ml of saline solution.

Kang et al. [25] included 160 patients divided in two groups of 80 patients each, undergoing total hip arthroplasty for osteoarthritis or hemi-arthroplasty for femoral fracture. Each of these groups was subdivided in two groups of 40 patients: one group with topical TXA and the other was a control group. The dose used of TXA was also higher than in our trial (3 g diluted in 100 ml of saline solution) and administered in a different way (through surgical drainage after wound closure, leaving drain aspiration closed for 30 min). In Kang et al. study, there was a statistically significant decrease in bleeding and transfusions in patients treated with topical TXA with hip osteoarthritis but not in those with femoral fracture.

We could partially explain our results because of the characteristics of the included population, i.e., advanced age, frailty and associated co-morbidities, a precarious

Table 2 Perioperative blood loss (ml)

	ITT analysis (available cases)				PP analysis			
	FS Mean (SD)	TXA Mean (SD)	Control Mean (SD)	*p*	FS Mean (SD)	TXA Mean (SD)	Control Mean (SD)	*p*
	N = 52	*N* = 51	*N* = 49		*N* = 45	*N* = 47	*N* = 49	
Total postoperative blood loss by drains	168.2 (137.4)	148.6 (122.7)	201.5 (166.5)	0.178	169.5 (138. 8)	139.3 (116.8)	201.5 (166.5)	0.104
	N = 40	*N* = 44	*N* = 40		*N* = 34	*N* = 41	*N* = 40	
Total blood loss	1620.4 (1042.7)	1192.9 (785.7)	1557.2 (847.1)	0.063	1653.8 (1085.0)	1177.9 (733.6)	1557.2 (847.1)	0.048
	N = 38	*N* = 39	*N* = 39		*N* = 34	*N* = 37	*N* = 39	
Hidden blood loss	1463.1 (1035.4)	1172.5 (695.3)	1370.2 (822.7)	0.321	1486.4 (1059.4)	1123.3 (679.3)	1370.2 (822.7)	0.194

SD standard deviation

Table 3 Perioperative haemoglobin levels and transfusions

	FS *N* = 56 Mean (SD)	ATX *N* = 52 Mean (SD)	Control *N* = 50 Mean (SD)	*p*
Haemoglobin (g/dl)				
Preoperative	12.5 (1.4)	12.0 (2.7)	12.7 (1.5)	0.270
2 h Postoperative	11.6 (1.7)	11.7 (1.5)	11.5 (2.0)	0.934
12–24 h Postoperative	10.2 (1.9)	10.1 (1.9)	9.9 (1.8)	0.664
5 Days postoperative	9.7 (1.6)	10.1 (1.1)	9.6 (1.7)	0.236
Haemoglobin (g/dl) pretransfusion				
Surgery	9.2 (2.3)	8.8 (2.8)	–	–
Day 1 postoperative	7.8 (0.9)	8.2 (0.3)	8.2 (0.3)	–
Day 2 postoperative	8.2 (0.9)	7.9 (0.8)	7.9 (0.8)	0.661
Day 3 postoperative	8.6 (0.4)	–	8.4 (0.3)	–
Transfused patients				
	n (%)	*n* (%)	*n* (%)	
Surgery	2	2	0	–
Day 1 postoperative	7	4	1	–
Day 2 postoperative	18	13	20	0.661
Day 3 postoperative	4	0	4	–
Total transfused patients postoperative	24 (42.9)	17 (32.7)	22 (44.0)	0.431
Units of transfused blood	50	31	41	0.722

SD standard deviation

haemostasis, and the hyperfibrinolysis state due to fracture and increased by surgery. Another reason could be related to the drug dose and the dilution of the product in saline solution. Except in one trial [19]—which used 1 g of TXA—, previous studies in hip arthroplasty had most frequently used a 3 g dose; the amount of saline solution in which the TXA was diluted ranged from 50 to 150 ml [20–25]. However, we only used 1 g of TXA in a 10 ml solution, possibly insufficient to produce a clinical effect in reducing blood loss.

Furthermore, the FS administered dose in our study was similar to other, but its administration by drip probably did not cover the entire surgical site, as we could expect using an air pressure pump.

Among the strengths of our study there is the fact that it was a prospective, controlled, randomised, multicentre study with an adequate sample size to detect differences between groups. The surgical procedure and transfusion criteria were standardised. Furthermore, we compared the effect of haemostatic treatments to reduce bleeding in a little-studied population group.

Nevertheless, our study presented some limitations. It was not blinded due to difficulties in concealing interventions. Yet, the nursing staff who recorded blood losses was unaware of the study hypothesis. There were difficulties in recruiting patients, which forced us to extend the study period and the number of centres. Despite being a multicentre study, 76% of the included patients belonged to one single centre. Due to the potential prothrombotic effect of TXA, we applied strict exclusion criteria to avoid complications; as a result, 42% of potential patients were excluded, mainly for history or risk of thromboembolic events.

In conclusion, the use of 10 ml FS and 1 g topical TXA in patients undergoing surgery due to a hip fracture did not significantly reduce postoperative blood loss and transfusion requirements compared with usual haemostasis. Further randomised controlled clinical trials are needed to evaluate the efficacy and safety, especially of topical TXA administered at higher doses.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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