Italian Journal of
Gynæcology & Obstetrics
March 2022 - Vol. 34 - N. 1 - Quarterly - ISSN 2385 - 0868

# The effect of intravenous (IV) tranexamic acid plus buccal misoprostol on blood loss during and after cesarean delivery: a randomized double-blind study

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**ARTICLE INFO**

**History**
**Received:** 23 December 2020
**Received in revised form:** 29 July 2021
**Accepted:** 27 August 2021
**Available online:** 14 March 2022

**DOI:** 10.36129/jog.34.01.06

**Key words**
*Tranexamic acid; misoprostol; oxytocin; postpartum hemorrhage.*

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**ABSTRACT**

**Objective.** To investigate the efficacy and safety of tranexamic acid (TA) plus buccal misoprostol *versus* intravenous oxytocin in reducing bleeding during and after cesarean delivery in women with risk factors for postpartum hemorrhage.
**Patients and methods.** A randomized clinical trial (NCT03505333) conducted on 400 pregnant women at term (37-40 weeks) gestation, scheduled for elective cesarean delivery, who were assigned to either 1 gm intravenous (IV) tranexamic acid plus buccal misoprostol 400 mcg or intravenous infusion of 20 units of oxytocin after delivery of the neonate. The main outcome measures were blood loss at cesarean section and 6 hours after cesarean delivery, the need for any additional oxytocic drugs, and drug-related side effects.
**Results.** The overall mean blood loss was significantly lower in the misoprostol group compared to the oxytocin group (863.48 ± 194.95 mL *vs* 1047.10 ± 290.96 mL; p = 0.0001). There was a need for additional oxytocic therapy in 27% and 57% after the use of misoprostol and oxytocin, respectively (p = 0.0001). The incidence of side effects such as shivering and the metallic taste was significantly higher in the misoprostol group compared to the oxytocin group (p = 0.0001).
**Conclusions.** IV TA plus buccal misoprostol is more effective than an intravenous infusion of oxytocin in reducing total blood loss during and after cesarean delivery.

## INTRODUCTION

Postpartum hemorrhage (PPH) is the main etiology of maternal death in both developed and developing countries [1]. Because it is a leading etiology of mortality and morbidity to the parturient women, and most maternal mortality is due to substandard care, prioritize the prevention and treatment of PPH in low-resource countries should be a priority in the development of national care guidelines [2].
The risk of PPH is much higher for women undergoing cesarean delivery, so the methods used to decrease blood loss during cesarean delivery have a great benefit to decrease postoperative morbidity and decrease the risks associated with blood transfusions [3].
Although many hospitals use oxytocin as the first line to prevent uterine inertia during cesarean delivery, it may not be the ideal agent for the prevention of PPH, especially in compromised patients with preeclampsia, cardiac disease, or prolonged labor [5]. Oxytocin only has a half-life of 4-10 min [4]; therefore, at cesarean section oxytocin must be administered as a continuous intravenous infusion to attain sustained uterotonic activity throughout the surgical procedure and the immediate postpartum period.
Misoprostol is a thermostable compound that is effective when given orally, buccal, sublingually,

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vaginally, or rectally, raised the exciting possibility that it might be used especially in developing countries as it is cheap, where women are at most risk from the rapidly fatal effects of severe PPH [6]. Buccal misoprostol requires less skill to administer and is cheaper than oxytocin infusion. It is also probably more suitable for the lady as it relieves the restriction imposed by an infusion line. This is in addition to the superior heat stability and longer shelf life of misoprostol compared with oxytocin [6].

TA is an inexpensive, widely available medicine that has been shown to reduce bleeding in surgery and reduce the risk of death in bleeding trauma patients [7]. It is therefore unsurprising that there is interest in its role in the prevention of postpartum hemorrhage.

TA given at the time of delivery could prevent severe postpartum bleeding. Plasma t-PA (the main fibrinolytic activator) doubles within an hour of delivery, probably due to the trauma of childbirth [8]. In our previous study, prophylactic utilization of 1000 mg oral TA in addition to 600 μg buccal misoprostol during vaginal delivery effectively reduces the postpartum blood loss, blood transfusion needs as well as lower the incidence of PPH than misoprostol alone [9].

The current study compares the efficacy of TA plus buccal misoprostol to intravenous oxytocin in the prevention of blood loss following cesarean delivery in women with risk factors for postpartum hemorrhage.

## MATERIALS AND METHODS

It was a clinically registered randomized, double-blind, clinical trial (ClinicalTrials.gov: NCT03710304) conducted in a tertiary university hospital. The ethical review board approved the study by a grant number of (Aswu/273/7/18). The study participants were women who attended the outpatient obstetric clinic, seeking antenatal care and they were scheduled for elective cesarean delivery (CD) and had risk factors for postpartum hemorrhage from 1st of January 2019 to 30th of June 2020. Women who met the selection criteria of the study were invited to participate after signing informed consent. This trial was conducted and reported according to the CONSORT updated guidelines for reporting parallel group randomized trials [10], and according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting randomized clinical trials.

### *Eligible participants*

Study inclusion criteria were women who were scheduled for elective CD and had risk factors for postpartum hemorrhage. Exclusion criteria were:

1. patients with any medical or metabolic disorders or take medications that can interact with the drugs in the study, for example cardiac, preeclampsia, renal, hepatic, severe anemia, thromboembolic disease or diabetes miletus;
2. patients with placenta previa;
3. patients had an allergy to tranexamic acid, oxytocin, or misoprostol;
4. patients with any pelvic pathology need extra surgical interference, for example severe endometriosis, uterine leiomyoma, severe pelvic adhesion, *etc*.;
5. patients having any contraindications for spinal anesthesia.

450 patients were asked to participate, 50 patients were excluded, 35 patients did not meet inclusion criteria and 15 patients refused to participate. Therefore the remaining 400 patients were included in the study. All participants underwent detailed history, general, and obstetric examinations, body weight, and Hight were calculated and preoperative hemoglobin was done for all participants after that an abdominal ultrasound examination was undertaken. The participants who fulfilled the eligibility criteria were explained about the study with the beneficial and possible adverse effects of misoprostol and tranexamic acid. Informed consent was obtained from them after that participants were randomized to 2 groups (the oxytocin group (group 1) and the TA plus buccal misoprostol group (group 2)) (**Figure 1**).

### *Randomization*

Patients were randomized to two groups, each composed of 200 patients according to a two-blocked randomization list which was coded (I or II) at a 1:1 ratio. The two parallel groups were prepared using a computer-generated randomization system. The allocated groups were concealed in serially numbered sealed opaque envelopes that were only opened after recruitment. Patient allocation was performed before the induction of spinal anesthesia by an independent person, who was not otherwise involved in this study. The trial was appropriately blinded; the participants, outcome assessors, and the surgeon performing the procedure were blinded to the used medication type.

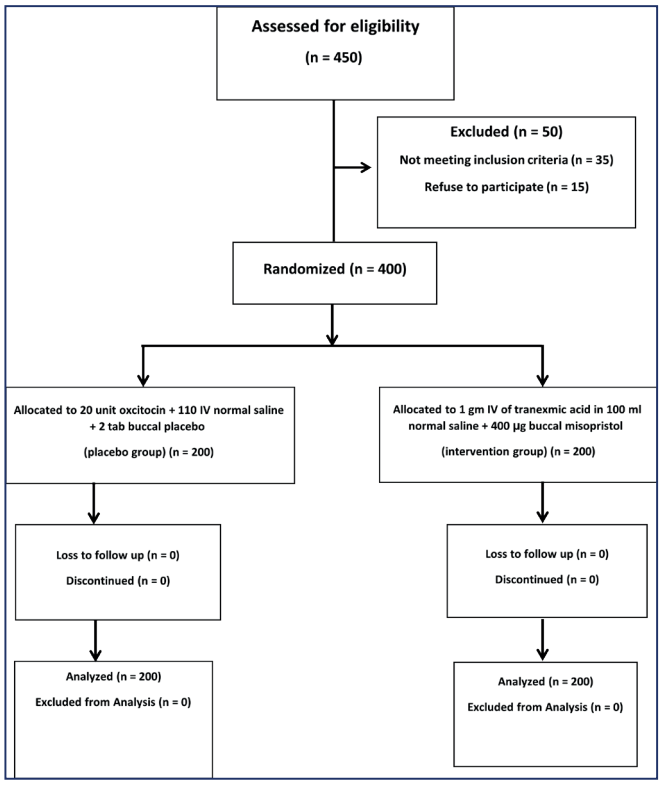


**Figure 1.** *Flow chart of the study.*

### *Intervention*

Eligible participants were allocated to one of the two groups after induction of spinal anesthesia and immediately after delivery of the neonate.

The oxytocin group (group 1) received 20 IU oxytocin dissolved in 500 mL of lactated Ringer's and infused at the rate of 75 mL/h, immediately after delivery of the neonate, plus placebo to buccal misoprostol in form of 2 tablets buccal (ranitidine) plus placebo to TA (110 normal salines) by slow intravenous injection at an approximate rate of 1 mL per min.

The TA plus buccal misoprostol group (group 2) received 1 gm TA plus 400 µg of sublingual misoprostol. It received 400 µg buccal misoprostol (2 tablets of 200 µg) plus 1-gram tranexamic acid (10 mL) in 100 mL saline infusion by slow intravenous injection at an approximate rate of 1 mL per min plus placebo to oxytocin infusion (500 mL of lactated Ringer's and infused at the rate of 75 mL/h). The uterine tone was assessed according to a 5-point Likert scale (0 floppy, 4 rock hard) by the operating obstetrician immediately after delivery of the placenta and then every 5 min until abdominal closure began.

Additional oxytocic therapy was given if the uterine tone was inadequate or the cesarean section become hemorrhagic. The available options were ergonovine and 15-methyl prostaglandin $F_{2\alpha}$.

### *Blood loss estimation*

Intraoperative blood loss was measured by adding the volume of the contents of the suction bottle after delivery of the baby and placenta and the difference in weight (in grams) between the dry and the soaked operation sheets and towels (1 gram = 1 mL). Post-operative blood loss was measured through vaginal blood loss during the first 24 hours post-operative by calculating the difference in weight (in grams) between the dry and the soaked vaginal pads (1 gram = 1 mL). Then the estimated total blood loss was calculated by the addition of intraoperative and postoperative blood loss.

### *Study outcome*

The primary outcome was the estimation of blood loss during and after cesarean delivery following administration of TA plus buccal misoprostol or intravenous oxytocin.

The secondary outcome measures included the need for any additional oxytocic drugs, postoperative Hemoglobin concentration, the incidence of postpartum hemorrhage, operative time, and incidence of side effects (unpleasant taste, fever, shivering, nausea, vomiting, and diarrhea).

### *Sample size*

The sample size was calculated based on the primary outcome (blood loss in women after cesarean delivery), taking mean blood loss with the use of oxytocin as 974 mL with a standard deviation of 285 mL [11]. Assuming that TA plus buccal misoprostol is more effective than oxytocin in reducing blood loss by 125 mL, 200 participants in each group will have > 85% power at 5% significance to detect such a difference (Epi-info: Centers for Disease Control and Prevention, Atlanta, GA, USA).

### *Statistical analysis*

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. A Chi-square test was used for comparison between groups. Quantitative data were described as means (SD) or medians, as appropriate. They were tested for normality by the Kolmogorov-Smirnov test. In the normally distributed variables, independent

samples t-test was used for comparison between groups. In the non-normally distributed variables, the Mann-Whitney test was used for comparison between groups. Odds ratios and their 95% confidence interval were calculated. P-value ≤ 0.05 was considered to be statistically significant.

## RESULTS

Our study started with 450 patients who were asked to participate, 50 patients were excluded, 35 patients did not meet inclusion criteria and 15 patients refused to participate. Therefore, the remaining 400 patients were randomized into 2 groups each group comprised 200 patients.

Group I: received 110 gm IV normal saline + 2 tablets placebo buccal (ranitidine) just before skin incision + 20 unit oxytocin in 500 mL of IV saline infusion over 15 min after delivery of the baby.

Group II: received 400 μg buccal misoprostol (2 tablets of 200 μg) + 1 gm tranexamic acid in 100 mL normal saline over 30-60 seconds before skin incision + 500 mL normal saline IV over 15 min after delivery of the baby).

There was no significant difference between the two groups concerning their age, weight, height, body mass index (BMI), parity, gestational age, initial hemoglobin, and an indication of CS (**Table 1**).

Group II showed a significant reduction in intraoperative blood loss compared with Group I, (p = 0.0001), but no significant difference between the two groups in postoperative blood loss (p = 0.624), however the overall estimated blood loss in group II showed a highly significant reduction compared with group I (p = 0.0001) (**Table 2**).

**Table 1.** *Preoperative characteristics of pregnant women in the study groups.*

| Parameters | Group I (n = 200) | Group II (n = 200) | Significance |
|---|---|---|---|
| **Age (year)** | 29.02 ± 4.32 | 29.05 ± 4.04 | 0.943 |
| **Weight (kg)** | 69.32 ± 6.87 | 69.29 ± 6.21 | 0.970 |
| **Height (cm)** | 162.94 ± 4.18 | 163.44 ± 4.28 | 0.248 |
| **BMI** | 26.07 ± 2.06 | 25.94 ± 2.11 | 0.536 |
| **Parity (median) (minimum-maximum)** | 2 (0-6) | 2 (0-5) | 0.525 |
| **Gestational age (weeks)** | 38.27 ± 0.84 | 38.33 ± 0.87 | 0.521 |
| **Initial hemoglobin** | 10.624 ± 0.74 | 10.616 ± 0.79 | 0.917 |
| **indication of CS (%)** | | | |
| **repeated cs** | 108 (54) | 110 (55) | 0.978 |
| **breech** | 37 (18.5) | 34 (17) | |
| **macrosomia** | 25 (12.5) | 24 (12) | |
| **twin** | 24 (12) | 24 (12) | |
| **patient request** | 6 (3) | 8 (4) | |

BMI: body mass index; CS: cesarean Section; variables are presented as mean and standard deviation, median (minimum-maximum) and number (percentage).

**Table 2.** *Primary outcome in the study groups.*

| Blood loss | Group I (n = 200) | Group II (n = 200) | Significance |
|---|---|---|---|
| **Intraoperative** | 879.25 ± 280.57 | 694.70 ± 186.15 | 0.0001* |
| **Postoperative** | 167.85 ± 39.03 | 169.78 ± 39.48 | 0.624 |
| **Total blood loss** | 1047.10 ± 290.96 | 863.48 ± 194.95 | 0.0001* |
| **Additional uterotonics (%)** | 114 (57) | 54 (27) | 0.0001* |

*Statistically significant difference; variables are presented as mean and standard deviation and number (percentage).

The incidence of the need for additional uterotonics was a significant decrease in group II, 54 (27%) patients compared to group I, 114 (57%) patients (p = 0.0001). Also, the incidence of postpartum hemorrhage was a significant decrease in group II, 23 (11.5%) patients compared to group I, 68 (34%) patients (p = 0.0001). Patients who needed extra surgical intervention also had a significant decrease in group II, 21 (10.5%) compared to 66 (33%) patients in group I (p = 0.0001). Also, the incidence of blood transfusion was decreased in group II, 19 (9.5%) patients compared with 51 (25.5%) patients in group I, (p = 0.0001). However, no significant difference between the two groups concerning post-operative hemoglobin (p = 0.089).

There was a significant decrease in operative time in group II compared with group I (p = 0.0001). But no significant difference between the two groups concerning the duration of in-hospital stay (p = 0.474).

Finally, we found that the drugs complications in form of unpleasant taste, fever, and shivering were significant increase in group II [18 (9%), 22 (11%), and 26 (13%)] patients compared to [2 (1%), 8 (4%), and 5 (2.5%)] patients in group I (p = 0.0001, 0.008, and 0.0001), respectively. However, no significant difference concerning nausea, vomiting and diarrhea between the two groups (p = 0.111, 0.065, and 0.066 respectively) (**Table 3**).

## DISCUSSION

This study is the first double-blind randomized placebo-controlled trial comparing the effectiveness of intravenous TA plus buccal misoprostol *versus* intravenous oxytocin for diminishing blood loss for pregnant ladies who are experiencing CD. The outcomes demonstrated that the intravenous

**Table 3.** *Secondary outcome in the study groups.*

| Variables | Group I (n = 200) | Group II (n = 200) | Significance |
|---|---|---|---|
| **Post hemoglobin** | 9.74 ± 0.61 | 9.85 ± 0.68 | 0.089 |
| **Operative time** | 72.96 ± 16.32 | 67.17 ± 12.35 | 0.0001* |
| **Hospital stay** | 4.22 ± 0.58 | 4.18 ± 0.54 | 0.474 |
| **Post-partum hemorrhage (%)** | 68 (34) | 23 (11.5) | 0.0001* |
| **Need Blood Transfusion (%)** | 51 (25.5) | 19 (9.5) | 0.0001* |
| **Extra surgical intervention (%)** | 66 (33) | 21 (10.5) | 0.0001* |
| | 2 (1) | 18 (9) | 0.0001* |
| **Unpleasant taste shivering** | 5 (2.5) | 26 (13) | 0.0001* |
| **Fever (%)** | 8 (4) | 22 (11) | 0.008* |
| **Nausea (%)** | 13 (6.5) | 22 (11) | 0.111 |
| **Vomiting (%)** | 4 (2) | 11 (5.5) | 0.065 |
| **Diarrhea (%)** | 6 (3) | 14 (7) | 0.066 |

*Statistically significant difference; variables are presented as mean and standard deviation and number (percentage).

TA plus buccal misoprostol could essentially decrease the intraoperative and total blood loss, blood transfusion after CD, the incidence of postpartum hemorrhage, and the need for extra additional uterotonics. Also, no cases with deep venous thrombosis as well as respiratory embolism were recognized.

To the best of our knowledge for the utilization of TA plus buccal misoprostol in reducing blood loss during CD, no studies were recognized. Past principal research had detailed that the degrees of plasminogen activators expanded 30 minutes after the initiation of surgery [8]. Thus, the hypothetical basis could clarify an expected efficiency of TA for decreasing loss for surgical procedures with special concern with CD and can use as adjunctive to misoprostol in reducing blood loss during CD especially in situations oxytocin is not available. TA offers an alternative way to support hemostasis by inhibiting the enzymatic action of plasmin on fibrin. Given that tranexamic acid reduces surgical bleeding, it had the potential to improve outcomes for women with postpartum hemorrhage.

Our study showed that there was a significant increase in estimated blood loss in the oxytocin group compared with TA plus misoprostol group ($p = 0.0001$). These results were also following findings from Osman *et al*. [12], Vlassoff *et al*. [13], Nielsen *et al*. [14], Owonikoko *et al*. [15] have reported that the hemoglobin concentration tends to be less in the misoprostol group than other groups.

Our study was also following findings from Ugwu *et al*. [10], Okonofua *et al*. [16], Blum *et al*. [17], and Eftekhari *et al*. [18] who found that oral/sublingual misoprostol 400 μg appears to be as effective in minimizing blood loss in the third stage of labor as oxytocin.

Mousa *et al*. conducted a meta-analysis to evaluate the role of misoprostol in postpartum hemorrhage and they concluded that oxytocin infusion is more effective and causes fewer side effects when used as first-line therapy for the treatment of primary postpartum hemorrhage. The review suggests that among women who received oxytocin for the treatment of primary postpartum hemorrhage, the adjunctive use of misoprostol confers no added benefit [19].

A systematic review and meta-analysis was finished by Conde-Agudelo to assess the utilization of misoprostol during CD and found no factually significant differences among misoprostol and oxytocin in diminishing intraoperative and postoperative blood loss at CD [20]. There were no huge contrasts in the intraoperative and postoperative drain when misoprostol was contrasted with oxytocin. However, these findings were based on a few trials with methodological constraints. Seventeen studies (3174 ladies) were incorporated of which 7 assessed misoprostol *vs* oxytocin and 8 assessed misoprostol plus oxytocin *vs* oxytocin alone. Overall, there were no significant differences in intraoperative and postoperative blood loss between sublingual or oral misoprostol and oxytocin.

Our study supports the hypothesis that intravenous TA plus buccal misoprostol is more effective than oxytocin in reducing postpartum blood loss and that more patients in the oxytocin group required additional oxytocic drugs with statistical significance. The long life outside the refrigerator and oral administration of misoprostol make it attractive for use in the prevention and management of postpartum hemorrhage especially in low-resource areas due to ease of storage and distribution. It also has no effect on blood pressure or causes Bronchoconstriction, and so can be safely used in women with asthma [3].

During delivery, when the placenta separates from the uterine wall, sequential physiologic and hemostatic changes occur and reduce bleeding, including strong myometrial contractions, increased platelet activity, and a massive release of coagulant factors; however, at the same time, fibrinolytic activity increases [21]. While misoprostol administration enhances the first mechanism, TA administration might be able to counter the latter and thus

facilitate the hemostatic process. Finally, the close relation observed between reduced fibrinogen levels and outcome in cases of PPH further suggests that TA might be effective in PPH [22].
The incidence of side effects such as shivering and an unpleasant taste in women receiving misoprostol was significantly higher than that in the oxytocin group. These findings are similar to the results of other studies [11, 12, 16, 17].
Chunbo Li *et al*. conduct a systematic review and meta-analysis to assess the efficacy and safety of tranexamic acid (TA) in reducing blood loss and lowering transfusion needs for patients undergoing cesarean section (CS) or vaginal delivery (VD). They conclude that intravenous TA for patients undergoing CS was effective and safe. Although prophylactic TA administration is associated with reduced PPH [23].
Faraoni *et al*. [24] conducted a meta-analysis with ten studies that demonstrate the efficacy of TA administration in reducing blood loss for women undergoing CS or VD. They concluded that TA administration significantly reduced blood loss and lowered the occurrence rate of PPH regardless of the mode of delivery.
Simonazzi *et al*. conducted a meta-analysis on the prophylactic administration of TXA at the time of the cesarean section [25]. Results show significant decreases in surgical blood loss, rates of postpartum hemorrhage, postoperative drops in hemoglobin, and risk of requiring a blood transfusion. In these studies, there were no reported adverse events of statistical significance such as deep-vein thrombosis (DVT), pulmonary embolism, stroke, or seizure.
A recent Cochrane review showed that timely administration of TA in patients with postpartum hemorrhage following delivery by any route resulted in not only reduced total blood loss but also decreased maternal mortality due to hemorrhage (relative risk RR 0.81; 95% CI: 0.65-1.00) [8]. These results were also following findings of the world maternal antifibrinolytic trial [26, 27].
The study had its limitations. First, was a single-center study and we have not used the alkaline hematin method which is a validated method for accurate measurement of blood loss but uses instate a gravimetric method to measure the amount of blood loss. However, Marcel *et al*. 2004 in veterinary surgery compare gravimetric and colorimetric methods of quantifying surgical blood loss and conclude that Estimation of blood loss using a gravimetric method is an accurate and objective tool to evaluate intraoperative blood loss [26].
Additionally, blood loss can also be related to proper surgical complications that are not considered in our study. Moreover, between 37 and 40 weeks there is a difference in the susceptibility of the uterine receptors to oxytocin, however, there is no statistically significant difference between the study groups regarding gestation age at CD.
One of the strengths of our investigation was that a double-blind randomized examination was adequately powered to compare the effect of intravenous TA plus buccal misoprostol versus intravenous oxytocin on the amount of perioperative blood loss. Another quality of the investigation lies in its simplicity of use of buccal misoprostol and intravenous TA can bring about a clinically significant decrease in intraoperative blood loss.

## CONCLUSIONS

IV TA plus buccal misoprostol is more effective than an intravenous infusion of oxytocin in reducing blood loss during and after CD. Adding tranexamic acid may increase the efficacy of buccal misoprostol to decrease blood loss during and after CD. In settings in which oxytocin is not available or its provision is not feasible, alternative buccal misoprostol plus tranexamic may be considered for use.

## COMPLIANCE WITH ETHICAL STANDARDS

### *Authors contribution*

N.S.: design, literature review, manuscript preparation. H.S.: conception and design, literature review, manuscript preparation. H.S.: manuscript preparation.

### *Funding*

None.

### *Study registration*

ClinicalTrials.gov. Identifier: NCT03505333.

### *Disclosure of interests*

The authors declare that they have no conflict of interests.

### *Ethical approval*

The study protocol was approved by the Ethics Committee of Aswan University Faculty of Medicine (ASWU/273/7/18). The study was in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### *Informed consent*

Informed consent was obtained from all individual participants included in the study.

### *Data sharing*

The data are available under reasonable request to the corresponding author.

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