Original Article

Could the topical application of tranexamic acid preserve the balance between surgical field hemostasis and a systemic anticoagulation state in sleeve gastrectomy patients? A prospective randomized study

Tarek A. Osman, Mohamed E. Elserafy and Ahmed S.M. Omar

Department of General Surgery, Ain Shams University, Cairo, Egypt.

ABSTRACT

Background: Tranexamic acid (TXA) is an effective, cheap antifibrinolytic medication. The parenteral route could be associated with acute neurological and visual side effects, with some concern about the possible long-held belief of thromboembolic events. The topical TXA is used in many surgical specialties to produce the same effect but not to induce the aforementioned adverse effects. The topical TXA has not been tried previously in bariatric surgery, and there is scarce conflicting data regarding the parenteral TXA.

Objectives: In this study, we aimed to compare the effects of intravenous and topical TXA on reducing staple line bleeding (SLB) and postlaparoscopic sleeve gastrectomy (LSG) bleeding and unveil the possible adverse effects linked to both routes.

Patients and Methods: This prospective randomized controlled study has been conducted at Ain Shams University hospitals, Cairo, Egypt, on 81 patients who underwent LSG from October 2022 to March 2023. Patients of either sex aged 18–65 years and are candidates for LSG, were enrolled. Exclusion criteria included allergy to TXA, heavy sweet-eaters, bleeding disorders, and those unfit for general anesthesia. The patients were randomized into two groups: group A (given 1 g intravenous TXA at the start of dissection) and group B had topical TXA (after stapling).

Results: Eighty-one patients underwent LSG with a mean age of 34.2±11.3 years. Forty-two patients were included in group A, and 39 were enrolled in group B. Both groups were comparable in terms of baseline characteristics. The topical route significantly decreased SLB (*P=0.013*) and postoperative bleeding (*P=0.024*) compared to the parenteral route. Two patients in group A developed acute gastrointestinal tract and visual adverse effects. There were no cases of leakage or thromboembolic in either group.

Conclusion: The topical route significantly decreased both SLB and postoperative bleeding, with a high safety profile compared to the parenteral route.

Key Words: Bariatric surgery complications, postsleeve bleeding, sleeve gastrectomy, staple line bleeding, tranexamic acid.

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Corresponding Author: Tarek A. Osman, MD, Department of General Surgery, College of Medicine, Ain Shams University, Cairo, Egypt. **Tel.:** +201003114199, **E-mail:** tarekabouzeid@med.asu.edu.eg

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INTRODUCTION

Despite being low, complications after laparoscopic sleeve gastrectomy (LSG) could be fatal[1]. Being the second most important complication after LSG, postoperative hemorrhage is reported in 0.7-9% of cases[2–7]. Unfortunately, up to 3% of them require reoperation[8].

Six decades ago, the molecule of tranexamic acid (TXA) was introduced to the world by Japanese researchers at Shosuke Okamoto's Center to treat menorrhagia[9]. Over time, its efficiency has been confirmed and its indications have expanded to include several aspects of medical and surgical bleeding, including trauma[10]. Nowadays, TXA has become the most common antifibrinolytic medication after the BART trial[11] unveiled the serious renal side effects and increased mortality risk associated with aprotinin use[12].

It is a safe, effective cheap medication, therefore, it was added to the WHO's list of essential medications[13]. Systemic use could be associated with acute gastrointestinal and visual disturbances[12,14,15]. The most feared complication linked to TXA is the risk of thromboembolic (TE), which was reported by few studies in this context. The topical TXA is proposed to produce the same hemostatic effect but not induce the aforementioned stormy adverse reactions. TXA is tried in many surgical fields, including but not limited to orthopedic[15–18], gynecology[14], plastic[19], pelvic[18], and oral surgery, with perfect hemostatic effects.

The topical TXA has not been tried previously in bariatric surgery, and in this setting of scarce conflicting data regarding the safety and efficacy of the parenteral route, we aimed to compare the effects of intravenous (i.v.) and topical TXA on reducing staple line bleeding (SLB)

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and post-LSG bleeding and unveil the possible adverse effects linked to both routes.

PATIENTS AND METHODS:

Upon approval of the Institutional Review Committee, a prospective randomized study was conducted at Ain Shams University hospitals, Cairo, Egypt, on 81 patients who underwent LSG as a primary procedure from October 2022 to March 2023. Patients of either sex, aged 18-65 years, had a BMI of more than 40 kg/m^2 or greater than 35 kg/m^2 associated with relevant comorbidities and were candidates for LSG were enrolled in this study after consulting the bariatric multidisciplinary team and signing an informed consent.

Exclusion criteria included allergy to TXA, heavy sweet-eaters, patients with large hiatal hernia, bleeding disorders, psychiatric disorders, history of seizures, history of TE complications, history of malignancy, and those unfit for general anesthesia.

The primary outcome was the number of titanium clips used to control bleeding points from the SLB. A bleeding point is an active oozing or spurting point from the staple line that needs immediate intervention such as clips or sutures[20]. Secondary outcomes are overall morbidity, mortality, estimated postoperative bleeding, and the rate of TE within 3 months postoperatively. Postoperative bleeding is diagnosed clinically by the presence of tachycardia and/or hypotension and is confirmed by significant hematocrit reduction (at least 10 U drop) from the preoperative value[20].

The sample size was calculated with a power of the study of 80%, beta error accepted up to 20%, and alpha error was set to 5%. It was estimated to be a minimum of 72 patients. The patients were randomized via the research randomizer program (Social Psychology Network, Ver 4, USA) and were allocated into one of the two groups: group A was given i.v. TXA, or group B, had topical TXA installed at the end of the operation.

Preoperative preparation

Routine preoperative investigations were done along with arterial blood pressure (ABP) measurement. Hypertensive patients were instructed to strictly take their medications, especially on the day of operation. A history of previous severe surgical bleeding or during a dental procedure, history of blood transfusion, family history of bleeding disorders, and the use of antiplatelet or anticoagulant medications mandates a hematologist consultation as stated by the recent guidelines from the European Society of Anaesthesiology[21].

Surgical technique

All operations were done under general anesthesia, with the patients placed in the French position. We started with the gastric dissection from the greater omentum by Ligasure Vessel Sealing System (Valleylab, Longbow, Loveland, Colorado, USA) till the left crus. The stapling was started 3–5 cm from the pylorus with the Endo GIA Tri-Staple black and purple cartridges (Medtronic, Minneapolis, Minnesota, USA) over a calibration 362Fr bougie tube. At this stage, we ask the anesthesiologist to raise the systolic ABP to 140 mmHg and reduce the pneumoperitoneal pressure to 10 mmHg.

TXA characteristically has a small volume of distribution with no diffusion into the fatty tissues[22]; therefore, we chose to give a weight-independent dose of 1 g (for group A). Given its short half-life (<3 h), we preferred to give it at the start of dissection to check its maximal efficacy in the reduction of both SLB and postoperative bleeding. Regarding group B, topical TXA was installed by a special 5 mm laparoscopic catheter (GEM SRL, Viareggio, Italy) (Figs 1,2) introduced from the left hypochondrial port (Fig. 3) on the staple line (Fig. 4a–c), dissected omentum (Fig. 5), and trocar sites. The topical TXA was prepared as a single ampoule of Kapron 500 mg/5 ml that was diluted on 15 ml of normal saline. The staple line was monitored for 3 min for any spurting points. These points were counted and were clipped via medium–large titanium clips. Suction of the residual injected fluid from the abdominal cavity after 3 min (to prevent inadvertent systemic absorption and local toxicity).

Follow-up

The number of transfused units was recorded. The patients were assessed for any TE complications (such as myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism) on follow-up at 2 weeks, 1 , and 3 months. The demographic, metabolic, and operative data were collected along with the postoperative complications and coded into a Microsoft Excel sheet (Microsoft Company, Redmond, Washington, USA).

Statistical analysis

The categorical data were expressed as absolute numbers with percentages, whereas the continuous variables (variables with normal distribution) were expressed as mean±SD. The unpaired (independent) t test was applied to compare the means of the two independent groups. The χ^2 test and Fisher's exact test were used to test the significance between two categorical variables. The statistical difference between the number of hemostatic clips used in both groups was analyzed using the Mann–Whitney test. Statistical analyses were performed using the Statistical Package for the Social Sciences software

package for Windows, version 29.0.1 (SPSS Inc., Chicago, Illinois, USA). *P value* is considered significant if it is less than 0.05, and highly significant if it is less than 0.01.

Fig. 1: The 5 mm laparoscopic catheter (GEM SRL, Viareggio, Italy).

Fig. 2: The laparoscopic catheter components (blue arrow: outer sheath part, orange arrow: inner tubal and port components).

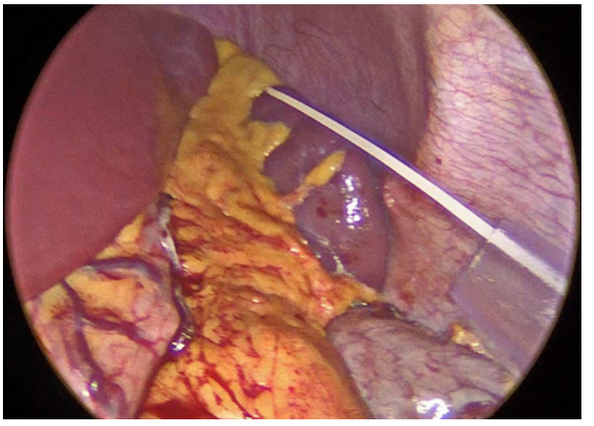

Fig. 3: Introduction of the laparoscopic catheter from the left hypochondrial port.

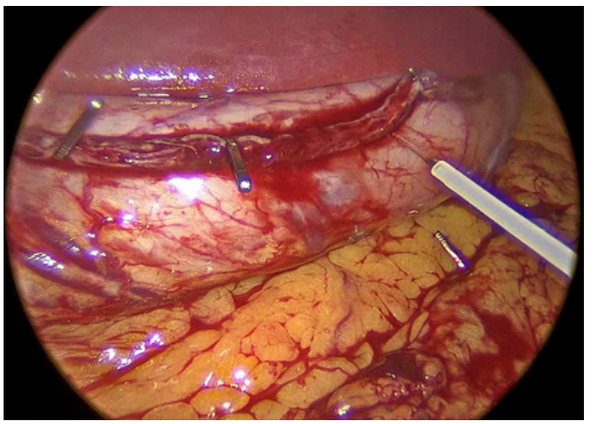

Fig 4a.

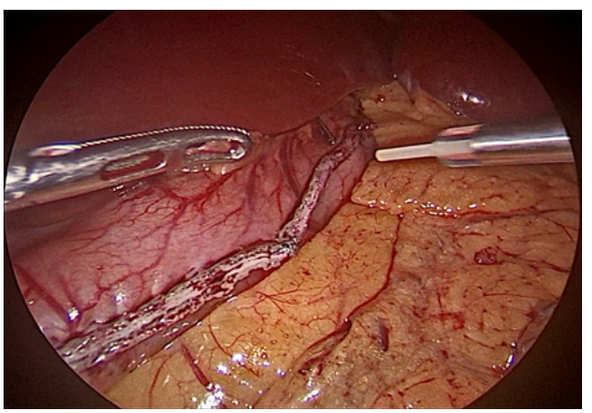

Fig 4b.

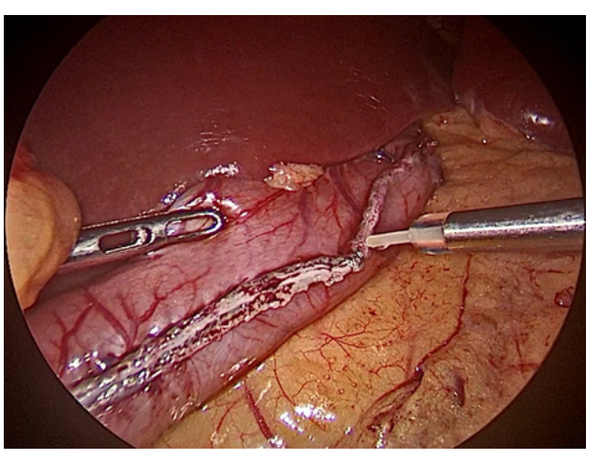

Fig 4c.

Fig. 4: (a, b, c) TXA installation on the staple line by the laparoscopic catheter. TXA, tranexamic acid.

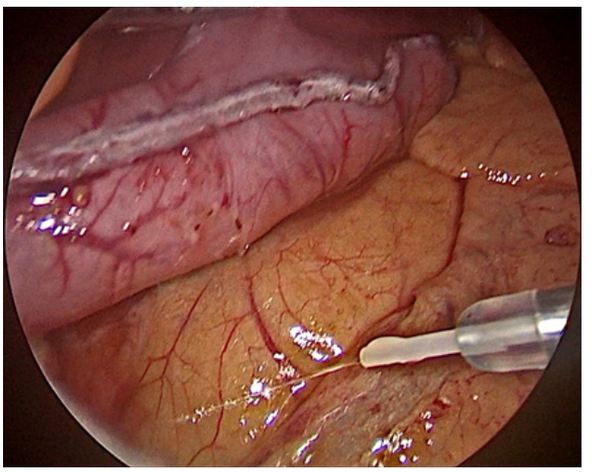

Fig. 5: TXA installation over the dissected omentum. TXA, tranexamic acid.

RESULTS:

During the defined period of the study, 86 patients underwent LSG, and six patients dropped out and did not complete the routine follow-up. Therefore, 81 patients were enrolled in the study with a mean age of 34.2 ±11.3 years. Sixty (74%) patients were females. Forty-two patients were included in group A, and 39 were enrolled in group B. Both groups were comparable regarding the baseline demographic and metabolic data (Table 1).

There was no statistically significant difference in the duration of operation between both groups. The topical route appeared to significantly decrease SLB represented by the number of used titanium hemostatic clips (5 vs. 17, *P=0.013*) as illustrated in (Table 2). The local administration of TXA significantly reduced postoperative bleeding compared to the parenteral route (*P=0.024*). More strikingly, the topical route was associated with a lower drop in the postoperative hematocrit compared to the i.v. route. Only one patient needed a transfusion of two packed red blood cells (in group A). Regarding complications, two patients in group A developed gastrointestinal tract and visual adverse effects, which were less safety linked to the parenteral route. There were no cases of leakage or TE in either group. There was no mortality in this study.

Table 1: The baseline characteristics of the patients

Variables	Group A (*N*=42)	Group B (*N*=39)	*P* value
Age (mean±SD)	34.3±11.3 years	33.9±12.9 years	0.81*
Female sex	31	29	0.63€
BMI (kg/m^2)	44.9 (36.8–56.8)	45.3 (35.7–57.1)	0.36¥
Comorbidity			
DM	8	10	0.16∞
Hypertension	13	11	0.43€
Dyslipidemia	17	19	0.11∞

DM, diabetes mellitus.
*Student's t test.
€χ^2 test.
¥Mann–Whitney's test.
∞Fisher exact test.

Table 2: The operative and postoperative variables

Variables	Group A	Group B	*P* value
Number of used metallic clips	17 (9–25)	5 (3–16)	0.013¥
Duration of the operation (min)	34 (28–51)	32 (27–49)	0.18¥
Postoperative bleeding (ml)	36 (18–248)	21 (16–207)	0.024*
Preoperative Ht (mean±SD)	33.9±2.5	34.2±2.3	0.64*
Postoperative Ht (mean±SD)	31.2±2.9	33.6±3.1	0.043*

¥Mann–Whitney's test.
*Student's t test.

DISCUSSION

The long staple line in the richly vascularized stomach in an obese patient who may have some comorbidities (such as hypertension, diabetes mellitus, and fatty liver) markedly escalates the risk of perioperative bleeding associated with LSG[23].

The coagulation cascade system and the fibrinolytic pathway are physiologically balanced. High doses of hemostatic medication could alter this balance and lead to TE complications. Similarly, prophylactic postoperative anticoagulant leads to an increase in the risk of surgical bleeding. In bariatric surgery, maintaining this physiological balance and preventing both bleeding and TE represents a great challenge. Therefore, identifying a medication that can ameliorate this high risk of bleeding without inducing TE complications is of utmost importance.

By targeting the five lysine binding sites on the plasminogen molecule, TXA prevents its proteolysis into plasmin (inhibits fibrinolysis) and stabilizes clot formation[6]. Its hemostatic properties could also be attributed to its direct inhibition of the already formed plasmin[20,24,25], preventing its procoagulant effect[13].

Its anti-inflammatory properties are mainly due to its inhibition of plasmin-mediated activation of the complement cascade, polymorphonuclear cells, and monocytes[19]. Indeed, TXA can decrease the plasmin levels of interleukin 6 and C-reactive protein[25]. Understanding these effects could explain its obvious effect in esthetic surgery, where it decreases seroma and edema and drains effluent. TXA is used efficiently for the reversal of some drug-induced bleeding (such as fondaparinux, dabigatran, and rivaroxaban)[24]. More importantly, high-dose TXA can prevent fibroblast adherence and detach fibroblast in vitro. This antiadhesive effect may help prevent postoperative adhesions[26].

The pharmacokinetics studies reported that a serum TXA concentration of 10 µg/ml is the minimal concentration that can effectively inhibit the fibrinolytic pathway, and this inhibition is dose-dependent[27]. The parenteral TXA could be given as a single dose of 10-20 mg/kg with a maximal daily dose of 1.5 g[28,29] or via a multiple-dose regimen of 10 mg/kg before and after the procedure[30].

It is worth mentioning that if TXA was given within 1 h of injury, this could save 128 000 lives worldwide[24]. Further scientific research[14,31,32] continued to reveal the effectiveness of TXA in elective abdominal and pelvic surgery. Hence, in the UK, it is recommended that TXA be given routinely for any major operation that could be associated with more than 500 ml of blood loss[25].

Despite the fact that TXA molecule has been available since the 1960s[9], its use in bariatric surgery was first published in 2016 by Chakravartty *et al*.[20]. They tried to unveil the effect of i.v. TXA on post-LSG bleeding. In their prospective study, which was done in King's College on 50 patients, they found that 1 g i.v. TXA during the induction of anesthesia significantly decreased intraoperative bleeding and duration of surgery. They used the number of bleeding points on the stable line to indicate intraoperative bleeding. Four years later, the PATAS study protocol (preoperative administration of TXA in sleeve gastrectomy)[29] was published by Leeman and colleagues comparing the effect of 1.5 g i.v. TXA during the induction of anesthesia and placebo, but the results are still awaited.

Given that ~70% of bleeding after gastrointestinal surgical procedures occur within the first 4 h[33], and the short half-life (t½) of TXA (3 h), Hossain *et al*.[34] in the largest retrospective cohort study (of 418 patients) studied giving TXA at the extubation to have the maximal guard against postoperative bleeding. They found that TXA significantly reduced postoperative hemorrhage without causing TE risk. Others[35] stated that 60-s stapler compression before firing with 1 g i.v. TXA at the induction (that was repeated every 8 h postoperatively) significantly decreased the rate of transfusion in 750 patients from 1% to near 0. Sermet and Ozsoy[22], in their randomized control trial (RCT) by injecting 1 g intraoperatively and 1 g in the first 8 h postoperatively found that TXA is effective in decreasing postoperative bleeding, but they did not find any statistically significant difference between giving TXA during the induction or extubation on postoperative bleeding. However, they reported that giving TXA at the induction of anesthesia significantly decreases the intraoperative bleeding points.

On the other hand, a recent double-blinded Dutch RCT[2] of 101 patients compared i.v. 1.5 g TXA (dissolved in normal saline) and a control group speculated that TXA-injected patients showed minor peroperative changes in their vital data (pulse, ABP) and hemoglobin measurements and less length of hospital stay compared to the control group. They reported that TXA use is associated with a statistically nonsignificant decrease in the hemostatic clips used. From our point of view, this could be due to three important reasons: first, due to their use of the more hemostatic gold cartridge (ECHELON FLEX GST) (rarely green cartridge), and second, their approach to operate in hypotensive anesthesia and to normalize the systolic ABP at the end of the procedure (they did not increase it to 140 mmHg as usual). Both reasons could decrease the identified SLB points and make the difference between both groups nonsignificant.

Klaassen *et al*.[28] reported in a retrospective trial on 1388 bariatric patients that parenteral TXA use in case of suspicion of bleeding (44 patients) is associated with a very low rate of reoperation (0.4%, only four patients) for the whole included patients when compared to the standard rate (0.8–2.5%) with no TE complications. A recent meta-analysis[31] done in Nottingham University Hospitals on 2205 patients stated that TXA reduces intraoperative bleeding and the need for blood transfusion in abdominal, pelvic, gynecological, or urological surgical procedures. These results are further augmented by a retrospective study[8] of 314 patients describing a significant decrease in intraoperative bleeding from 22.3 to 10.8% and a decreased reoperation rate from 1.9 to 0%. They followed up on cases for 6 months and found no increase in the TE manifestations.

Nevertheless, as widely pointed out by several published studies, the risk of TE associated with parenteral TXA is a highly controversial issue. The CRASH-II trial (Clinical Randomisation of an Antifibrinolytic in Significant Hemorrhage)[36] concluded that TXA decreased mortality risk caused by bleeding without TE complications. Along the same lines, several large, well-designed RCTs and meta-analyses[2,28,31,34,36–38] found no statistical relation between TE and TXA use. However, there are some limitations in these studies[29], such as the exclusion of patients who are at risk of TE (those who have a history of deep venous thrombosis, myocardial infarction, and hypercoagulable state). Nonetheless, other studies found that it could be given safely to geriatric patients[39,40] and trauma patients[8,36] without any increase in TE risk.

On the contrary, Wu *et al*.[13] confirmed that the multiple-dose regimen of TXA can induce a hypercoagulable state; therefore they did not consider it safe except if combined with an anticoagulant. One year later, disappointing results were concluded by the HALT- IT trial[41] about the efficacy of TXA in abdominal surgery. It speculated that TXA does not decrease blood loss or transfusion rate after upper gastrointestinal hemorrhage, along with a significant increase in TE manifestations. This could be explained by analyzing the characters of the population enrolled in this study because most of them are cirrhotic. Therefore, the parenteral TXA may lead to some dangerous sequelae[42]. The evidence of that is still not weak[13,20,24].

Regarding the safety of TXA, in this study, there were no cases of TE after 3 months of follow-up, which is the same as concluded by others[2,23,34]. Only two patients in group A developed gastrointestinal tract and visual adverse effects, which means less safety linked to the parenteral route.

The topical route has emerged as a perfect solution that induces hemostasis in the surgical field without inducing systemic side effects or TE[15]. The pharmaceutical studies[43,44] detected a high concentration of TXA at the bleeding sites after topical application with a very low serum level (90% less) compared to the parenteral route. Therefore, TXA can be used without concern in renal patients[45].

Topical TXA was first tried in orthopedic operations with exceptional results[13,16,17]. They used TXA by adding it to the irrigation fluid or moistening the surface with a wet gauze. In 2011, a large systematic review and meta-analysis of 129 RCTs (including 10 488 cases) was published by Ker *et al*.[32]. They found that topical TXA is associated with a 30% reduction in the blood transfusion risk without increasing the risk of vaso-occlusive events. Montroy *et al*.[10] using a meta-regression analysis model, have proved that local TXA use can decrease the transfusion risk. These data confirm that a low concentration of 5 mg/dl or lower of TXA is still effective[20,27,29,45].

The literature review revealed that there is no data regarding the technique of application, minimal effective dose, or toxic dose of topical TXA. We studied the orthopedic experience in this context and found that we could not reproduce the results of their trials for two important reasons. The first one is the different physiological characteristics between the two anatomical fields (synovial membrane differs from the peritoneum regarding the absorptive capacity; the peritoneum can absorb small locally applied doses into the systemic circulation, leading to a higher plasma concentration and hence different outcomes and inadvertent systemic side effects), and the second reason is the various techniques and doses of topical application.

From our point of view, the application technique must be very precise, delivering the optimal concentration of TXA to the stable linewhile avoiding toxicity. Therefore, irrigation fluid is not a good option because it will disperse widely and reach the stable line in a minimal concentration with a high possibility of peritoneal absorption and systemic adverse effects. We used a special laparoscopic 5 mm catheter to instal a TXA-diluted fluid precisely on the staple line. Our results confirmed that the topical route significantly decreased SLB and postoperative bleeding. This is in accordance with the results of a well-designed large meta-analysis of 71 trials on 7539 patients (5450 orthopedic patients and 1909 nonorthopedic patients), Teoh *et al*.[46] documented that topical TXA reduced the incidence of intraoperative bleeding and blood transfusion without any increase in the TE events.

As expected, most of the research on toxicity was in-vitro studies[15,47,48] done on chondrocytes, fibroblasts, tenocytes, synoviocytes, and keratinocytes. The serum level, effect, and toxicity of topical TXA application are the outcomes of the pharmaceutical form, volume, concentration, time, surface area, microstructural vascularization, and nature of the contact area[27]. Eikebrokk *et al*.[15] from St Olav Hospital, Norway, reported that topical TXA use for 10 min was safe and well tolerated. For intermediate exposure (100 min), Furst *et al*.[47] found that a concentration of 100 mg/ml resulted in 50% microscopic viability of the fibroblasts that increased to 65% viability with the use of half concentration (50 mg/ml). Regarding chronic exposure (>24 h), a concentration of 5-10 mg/ml appeared to be safe for synoviocytes, tenocytes, and chondrocytes[48], while a concentration of 25 mg/ml prevented re-epithelialization and induced cytotoxicity. There is no published data on the toxicity of gastric cells upon exposure to TXA.

To the best of our knowledge, this study is the first one to discuss the topical route of application of TXA and to compare it to the parenteral route in the field of bariatric surgery, and its results were promising in decreasing both SLB and postoperative bleeding. The trials in cardiac surgery aiming to compare the parenteral and topical TXA administration yielded conflicting results. One of them[49] identified no difference in the blood transfusion rate while the other[50] reported that topical application is associated with a higher risk of transfusion. Another double-blind RCT[14] concluded that topical and i.v. TXA has the same efficacy and side effects after abdominal hysterectomy.

A similar result was illustrated in a recent meta-analysis conducted by Montroy *et al*.[10], who tried to explore the efficacy and safety of the topical route by comparing it with the systemic route and placebo. It included 67 studies done on 6034 participants in the orthopedic, urology, plastic, otolaryngology, spinal, and dental surgery. They found that both the topical and the systemic routes are effective, with no statistically significant difference between them with no increase in the TE complications.

We herein report that there was no statistically significant difference between i.v. TXA and topical TXA in decreasing operative duration in our study. The limitations of this study were its relatively small number of cases. Further large-scale studies are needed to confirm the outcomes of this study.

CONCLUSION

TXA through both routes (parenteral and topical) appeared safe with no recorded TE complications. However, the topical route was more efficient in significantly decreasing SLB and postoperative bleeding.

CONFLICT OF INTEREST

There are no conflicts of interest.

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