ORIGINAL CONTRIBUTION

Tranexamic Acid for Lower GI Hemorrhage: A Randomized Placebo-Controlled Clinical Trial

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BACKGROUND: Lower GI hemorrhage is a common source of morbidity and mortality. Tranexamic acid is an antifibrinolytic that has been shown to reduce blood loss in a variety of clinical conditions. Information regarding the use of tranexamic acid in treating lower GI hemorrhage is lacking.

OBJECTIVE: The aim of this trial was to determine the clinical efficacy of tranexamic acid when used for lower GI hemorrhage.

DESIGN: This was a prospective, double-blind, placebo-controlled, randomized clinical trial.

SETTINGS: The study was conducted at a tertiary referral university hospital in Australia.

PATIENTS: Consecutive patients aged >18 years with lower GI hemorrhage requiring hospital admission from November 2011 to January 2014 were screened for trial eligibility (N = 265).

INTERVENTIONS: A total of 100 patients were recruited after exclusions and were randomly assigned 1:1 to either tranexamic acid or placebo.

MAIN OUTCOME MEASURES: The primary outcome was blood loss as determined by reduction in hemoglobin levels. The secondary outcomes were transfusion rates, transfusion volume, intervention rates for bleeding, length of hospital stay, readmission, and complication rates.

RESULTS: There was no difference between groups with respect to hemoglobin drop (11 g/L of tranexamic acid vs 13 g/L of placebo; $p = 0.9445$). There was no difference with respect to transfusion rates (14/49 tranexamic acid vs 16/47 placebo; $p = 0.661$), mean transfusion volume (1.27 vs 1.93 units; $p = 0.355$), intervention rates (7/49 vs 13/47; $p = 0.134$), length of hospital stay (4.67 vs 4.74 d; $p = 0.934$), readmission, or complication rates. No complications occurred as a direct result of tranexamic acid use.

LIMITATIONS: A larger multicenter trial may be required to determine whether there are more subtle advantages with tranexamic acid use in some of the secondary outcomes.

CONCLUSIONS: Tranexamic acid does not appear to decrease blood loss or improve clinical outcomes in patients presenting with lower GI hemorrhage in the context of this trial. see **Video Abstract** at http://links.lww.com/DCR/A453.

KEY WORDS: Clinical; Gastrointestinal; Hemorrhage; Lower; Randomized; Tranexamic acid.

Lower GI hemorrhage (LGIH) most commonly presents as rectal bleeding and represents a significant cause of morbidity and mortality among patients requiring surgical admission.[1] The stepwise management of LGIH is typically conservative initially. Patients are monitored for ongoing bleeding, whereas blood replacement and correction of the coagulation profile are performed if required.[1,2] Conservative management is highly effective for most patients, and investigative colonoscopy can be performed in this group. When conservative treatment fails, management nor-

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mally requires identification of the source of bleeding. This is usually achieved using ≥1 of the following modalities: red cell scanning, CT angiography, mesenteric angiography, and colonoscopy.[1,2] After source identification, treatment commonly requires the interventional forms of colonoscopy or mesenteric angiography, with resectional surgery being reserved as a last resort if all other interventions fail.[1,2]

Tranexamic acid (TXA) is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin and noncompetitively inhibits the action of plasmin.[3] By doing this, it prevents plasmin from degrading fibrin, a protein that forms the framework of blood clots, and thus potentially decreases blood loss in a variety of circumstances.[4]

As a result of this action, TXA has been shown to be efficacious in a number of surgical conditions, resulting in less postoperative blood loss.[4] In the case of patients presenting after major trauma, its administration also results in lower mortality.[5]

We hypothesized that TXA, when given to patients presenting with LGIH, resulted in reduced blood loss as well as a reduction in the complications of blood loss and its associated interventions. In a prospective, randomized, placebo-controlled clinical trial, we investigated the effect of TXA on LGIH.

PATIENTS AND METHODS

Trial Design

This was a single-center, placebo-controlled, patient- and observer-blinded, randomized clinical trial, with 2 parallel study groups. Ethical approval was given by the institutional ethical review board, Hunter New England Human Research Ethics Committee, New South Wales Health (New South Wales, Australia; HNEHREC 11/07/20/3.06). The study was registered prospectively with the Australia New Zealand Clinical Trials Register (ACTRN:12611000865910), and there were no changes to methods outlined in the study protocol after trial commencement. The use of TXA for this indication was off license, so approval was obtained through the Australian Therapeutic Goods Act for use in a clinical trial.

Participants

From November 2011 to January 2014, all patients aged ≥18 years requiring admission with LGIH to the John Hunter Hospital (Newcastle, New South Wales, Australia) were screened for trial eligibility. Exclusion criteria were age <18 years, inability to give informed consent, history or strong family history of thromboembolic disease, known GI malignancy, warfarin or other anticoagulant treatment, drug-eluting stent inserted within 12 months or bare metal stent inserted within 12 weeks, pregnancy or breastfeeding, and known allergy to TXA or its excipients. Patients with known upper GI hemorrhage (UGIH) were excluded, and where doubt existed, either nasogastric tube insertion or gastroscopy was performed to exclude those with an UGIH.

TABLE 1. Tranexamic acid dose guidelines for renal impairment

Renal function (eGFR, mL · min · 1.73 m²)	*Weight, kg*	*Dose, mg*
>90	Any	1000 mg 4 times daily
60–89	>65	1000 mg twice daily
	<65	500 mg twice daily
30–59	>65	1000 mg daily
	<65	500 mg daily
<29	>65	1000 mg second daily
	<65	500 mg second daily

eGFR = estimated glomerular filtration rate.

Interventions

Patients were screened for eligibility, with all of the eligible patients invited to participate. After written informed consent, participants were randomly assigned to either intervention (TXA) or placebo. Dosing was based on the product information guidelines for use of TXA in the prevention of bleeding after elective surgery: 1000 mg every 6 hours given orally. Intervention was continued for 4 days while participants were in hospital and ceased at the time of discharge if this occurred before the fourth day. Dose adjustment for renal impairment was made as per product information guidelines (Table 1). Patients in both groups were treated otherwise in a similar fashion. Treatment involved blood replacement as per Australian Red Cross transfusion guidelines (no transfusion for hemoglobin >100 g/L, transfusion for hemoglobin <70 g/L, and only transfusion for hemoglobin 70–100 g/L if cardiorespiratory symptoms), gut rest for the first 24 hours of admission, and ongoing dietary restrictions as per the treating surgical team. Thromboembolic prophylaxis and peptic ulcer prophylaxis were as per the treating team. The initial investigation included CT angiography (CTA) with subsequent intervention if there was clinical evidence of ongoing bleeding, including interventional angiography or segmental colectomy for a positive blush and observation for no blush. Those who had ongoing clinical bleeding with no blush on initial CTA underwent either repeat CTA or colonoscopy. All of the patients underwent diagnostic colonoscopy, either on or after discharge, if considered medically fit enough to do so.

Primary Outcome

The primary outcome was blood loss as determined by the mean reduction in the level of hemoglobin (in grams per liter). Individual blood loss was calculated as the differ-

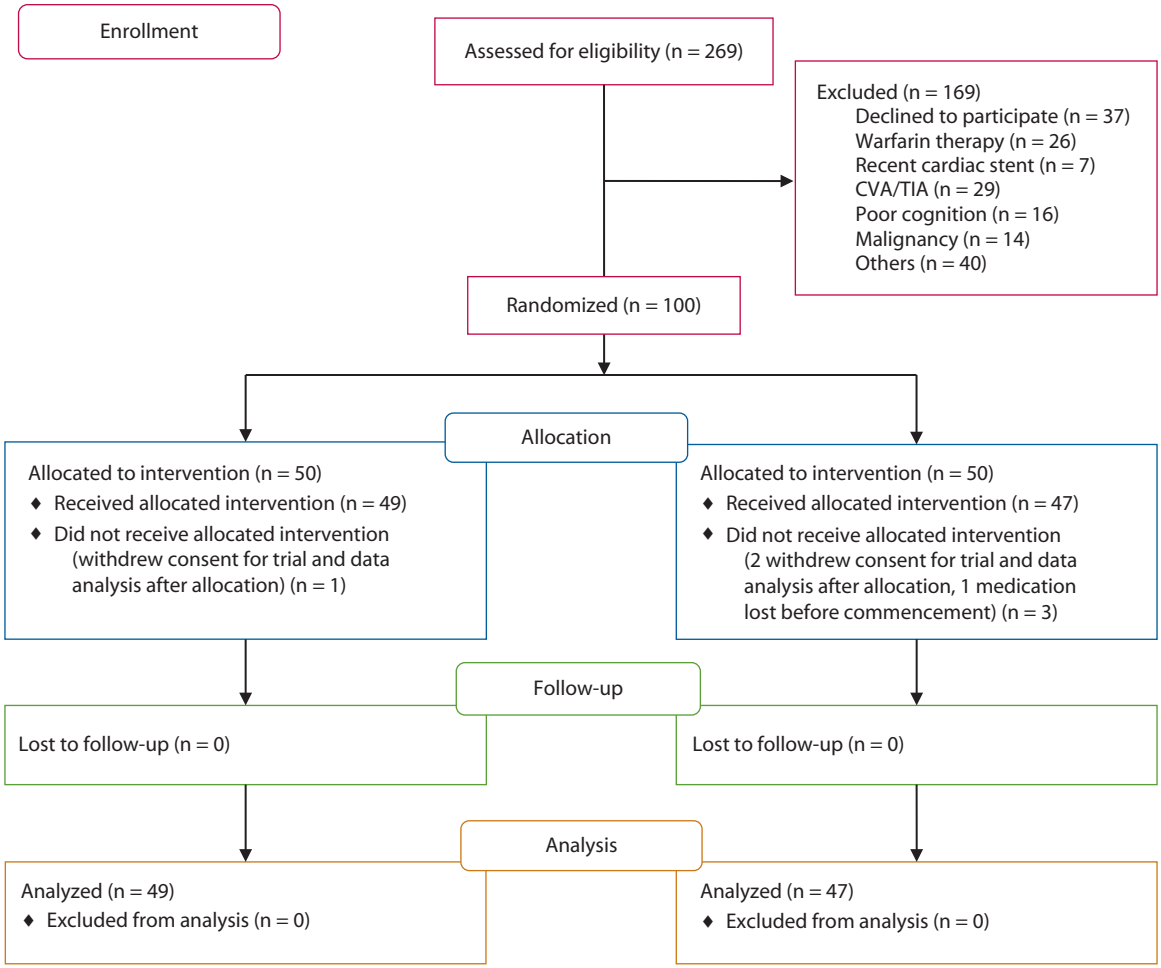

FIGURE 1. Consolidated Standards of Reporting Trials flow diagram. CVA = cerebrovascular accident; TIA = transient ischemic attack.

ence between the highest and lowest recorded hemoglobin levels during admission, and hemoglobin levels were taken on a daily basis with a view to do so more frequently if clinically indicated.

Secondary Outcomes

Secondary outcomes were transfusion rates, intervention rates for bleeding, length of hospital stay, 28-day mortality and readmission, and predefined complication rates (venous thromboembolic events, cerebrovascular accidents, transient ischemic attacks, or acute coronary syndrome). No changes to trial outcome measures occurred.

Sample Size

Sample size was based on the primary end point of hemoglobin drop during admission. A pilot study was performed on 50 consecutive patients presenting to John Hunter Hospital with LGIH, indicating a mean hemoglobin drop of 18.86 g/L (SD = 14.6 g/L). On the basis that an improvement of 10g/L with intervention would represent a clinically relevant outcome (≈1 transfusion of packed red cells), a group sample size of 46 was required to detect this difference with 90% power and a level of significance of 5%. Allowing for ≈10% dropout rate, a total of 100 patients (50 in each arm) was chosen as a recruitment target. No interim analysis was planned, and an independent safety committee was established to review serious adverse events and determine whether any were directly related to TXA.

Randomization

All of the patients admitted to John Hunter Hospital under the Acute General Surgical Unit were screened for trial eligibility. A screening log was kept of every admission with LGIH, and these patients were approached on initial review by the treating surgical team for trial participation. If considered to be eligible after a detailed history, written informed consent was obtained, and randomization and allocation was performed. Patients were randomly assigned in a 1:1 ratio to either intervention (TXA) or placebo. Randomization was performed using a centralized 24-hour access Web site (CReDITSS, HMRI: Clinical Research Design IT and Statistical Support, Hunter Medical Research Institute)

TABLE 2. Characteristics of patients

Variable	*Placebo (n = 47)*	*Intervention (n = 49)*	*Total (N = 96)*	*p*
Age, y				
Median (minimum, maximum)	70 (25, 89)	72 (26, 96)	71 (25, 96)	0.9185
Mean (SD)	68 (16)	68 (16)	68 (16)	0.9922
Hemoglobin on admission, g/L				
Mean (SD)	117 (24)	118 (20)	118 (22)	0.9521
Median (minimum, maximum)	122 (70, 162)	122 (71, 154)	122 (70, 162)	0.9767
Sex, %				
Women	16 (34)	17 (35)	33 (34)	
Men	31 (66)	32 (65)	63 (66)	1.0000
Final etiology, %				
Diverticula	22	18	40 (42)	
Angiodysplasia	9	8	17 (18)	
Postpolypectomy	4	7	11 (11)	
Colitis	5	5	10 (10)	
Upper GIH	2	1	3 (3)	
Other	5	10	15 (16)	0.6635

GIH = GI hemorrhage.

in blocks of 10 without stratification. The number generated matched 1 labeled medical dispensing packet of a batch of 10, stored in the dispensing area of the surgical ward, that was dispensed to the patient after labeling with both patient and study identification numbers. The allocation number was written on the patients medical chart, and administration of the drug was performed by the treating nurse on the surgical ward, ensuring that the numbers matched.

Blinding

Intervention and placebo medications and packs were identical in every detail with the exception of the allocation number. Access to allocation numbers was available only to a central pharmacist, who was not involved in either patient care or running the trial. The need for urgent unblinding was determined by the principal investigator or a coinvestigator, in the case of principal investigator absence, based on clinical need.

The entire episode of patient treatment was performed by clinicians blinded to patient allocation. All of the data collection and outcome assessment were also performed by assessors blinded to allocation details.

Statistical Methods

Patients were analyzed according to intention-to-treat principles. The data collector was blinded as to which group was control or intervention (groups were designated *A* or *B* by a third party for analysis).

All of the primary (hemoglobin drop) and secondary (transfusion requirements, length of stay, intervention rate, complications, and 28-day mortality) outcomes were examined for their distributions using summary statistics (frequencies, mean, and median) and plots according to the treatment or placebo group. The median hemoglobin drop and length of stay were compared according to intervention group using the Kruskal–Wallis test, because both outcomes were right skewed. Mortality (28 day), intervention rate (colonoscopy, angiogram, embolization, colectomy, or other interventions), and complications (pulmonary embolism, deep vein thrombosis, cerebrovascular accident/transient ischemic attack, or acute myocardial infarction) were compared using the Fisher exact test. Total transfusion count was compared by intervention group using a generalized linear model with a negative binomial distribution.

The effect of baseline hemoglobin on outcomes was investigated by analysis, using quantile regression for the median drop and median lowest hemoglobin. Intervention group, baseline hemoglobin (divided into tertiles), and their interaction were added as predictors. Statistical analysis was performed by CReDITSS, HMRI, using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Between November 2011 and January 2014, 269 consecutive patients presenting to the Acute General Surgical Unit of John Hunter Hospital, with LGIH, were assessed for trial inclusion. A total of 169 patients were excluded, with the most common reasons being refusal of consent, previous CVAs or TIAs, warfarin therapy, poor cognition, an underlying malignancy, or recent cardiac stenting. After exclusions, 100 patients were randomly assigned to placebo (n = 50) or TXA (n = 50). Final analysis was performed in 96 patients, with 3 patients withdrawing consent for data analysis (2 in the placebo arm and 1 in the intervention arm) and 1 medication pack being lost between the emergency department and the surgical ward, before trial commencement. See Figure 1 for full flow chart. Patient characteristics were similar for both groups, with no statistically significant difference in baseline hemoglobin on admission (Table 2).

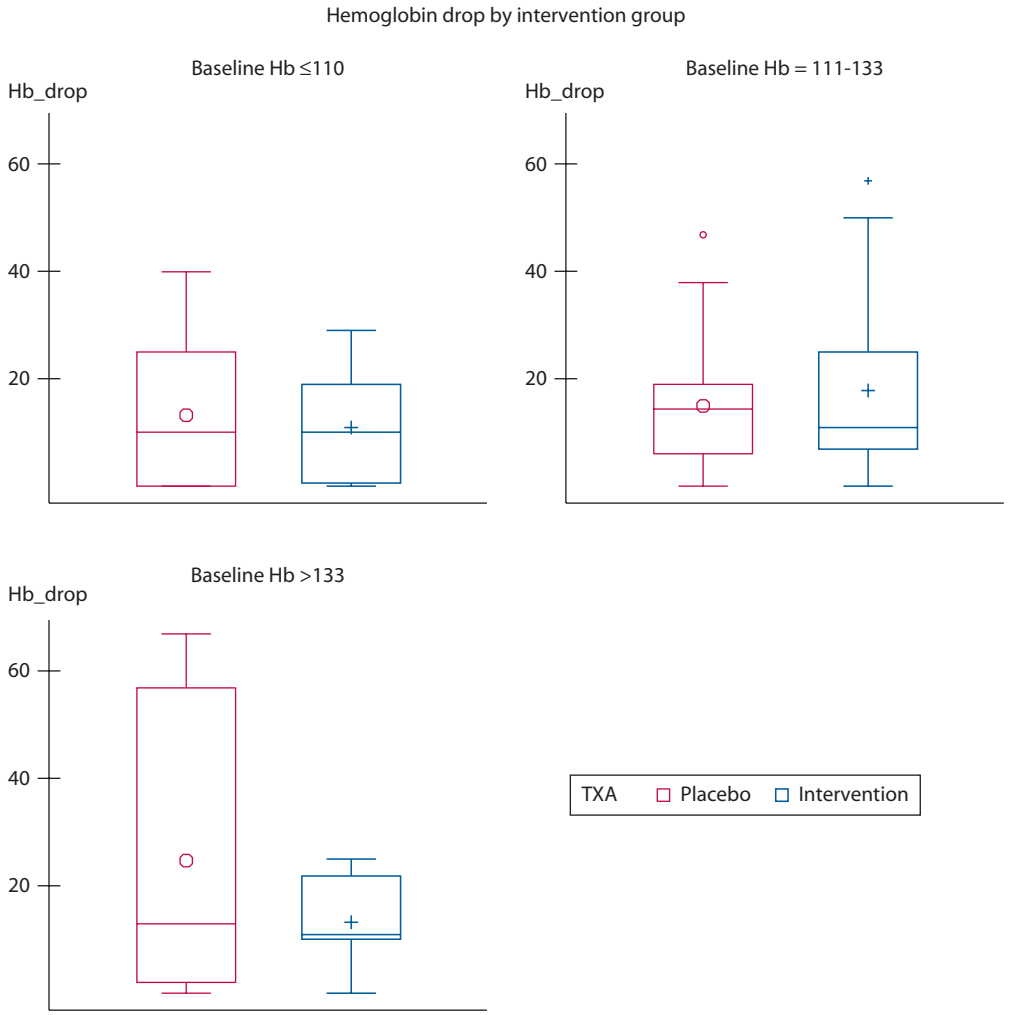

FIGURE 2. Boxplots of hemoglobin drop by intervention group and baseline hemoglobin. Hb = hemoglobin; TXA = tranexamic acid; whiskers = range; box = median and quartiles; o = mean for placebo; + = mean for intervention.

Primary Outcome

Primary outcome data were available for all 96 patients. There was no statistically significant difference between intervention and control with respect to median reduction (11 g/L TXA vs 13 g/L control; $p = 0.9445$) in hemoglobin levels. Likewise, there was no statistically significant difference between intervention and control groups with respect to the median (104 g/L TXA vs 102 g/L control; $p = 0.524$) of the lowest recorded hemoglobin level.

Figure 2 charts the effect of baseline hemoglobin on hemoglobin drop, showing no evidence of an intervention effect on hemoglobin drop, after adjusting for baseline. Figure 3 charts the effect of baseline hemoglobin on lowest recorded hemoglobin. There is no evidence of an intervention effect on lowest hemoglobin after adjusting for baseline.

Secondary Outcomes

There was no statistically significant difference between intervention and control groups with respect to the outcomes of transfusion rates, intervention rates for bleeding, length of hospital stay, 28 day mortality, and readmission and complication rates (Table 3 highlights primary and secondary outcome results).

Adverse Events

There were 3 deaths in the study, including 2 in the intervention group (1 major UGIH secondary to gastric cancer and 1 from combined sepsis and renal failure) and 1 in the control group (major UGIH secondary to multiple stress ulcers). One patient in the control arm had a thromboembolic event within 30 days of admission (acute coronary syndrome), however there were no adverse events or complications related directly to TXA. No unplanned analyses were performed.

DISCUSSION

This randomized clinical trial indicates that TXA, when used for LGIH, does not appear to result in an improvement in blood loss, as determined by hemoglobin levels.

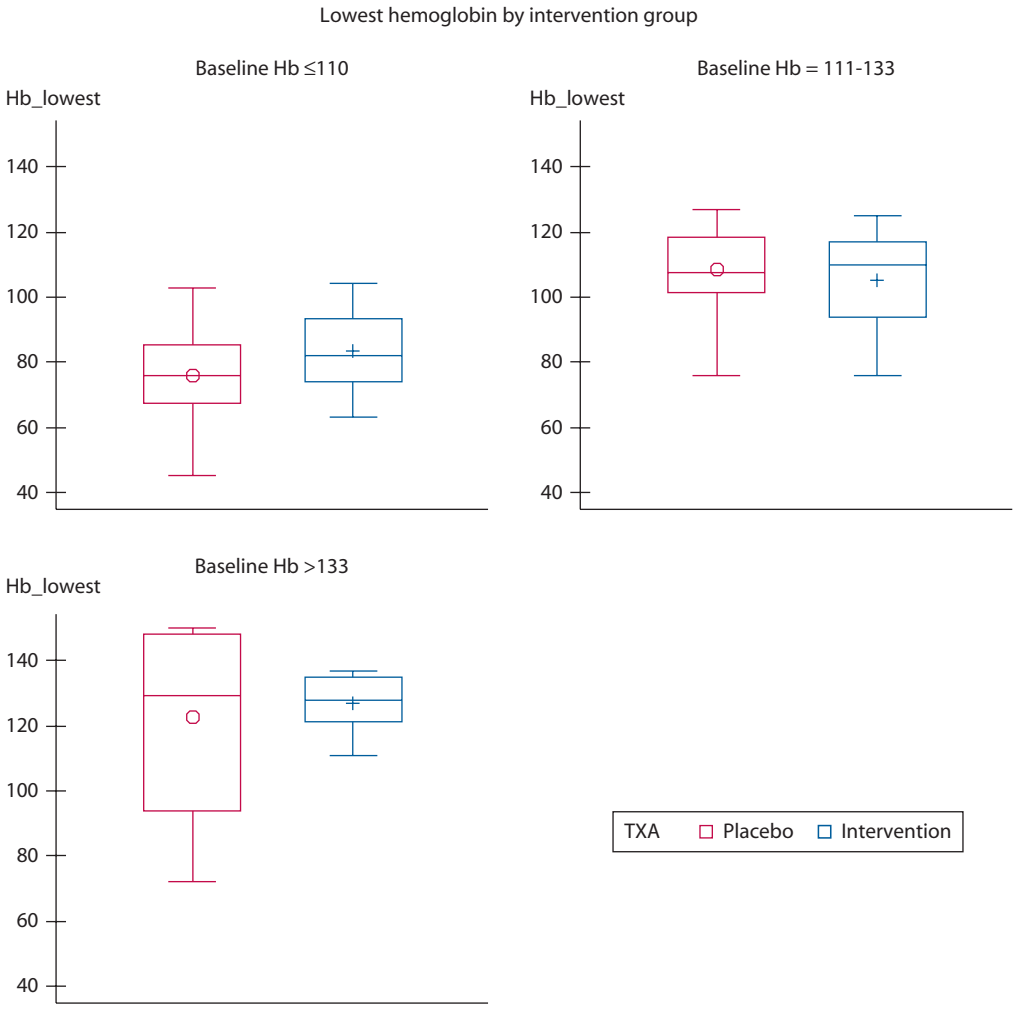

FIGURE 3. Boxplots of lowest recorded hemoglobin by intervention group and baseline hemoglobin. Hb = hemoglobin; TXA = tranexamic acid; whiskers = range; box = median and quartiles; o = mean for placebo; + = mean for intervention.

In addition, there was no difference between groups with regard to the secondary outcomes of transfusion rates, intervention rates for bleeding, length of hospital stay, and readmission and complication rates.

Acute LGIH is a significant cause of morbidity and mortality that typically presents acutely with hematochezia and is more common in the elderly and the male sex.[6] The most common underlying causes of acute LGIH in Western society are diverticular disease and vascular ectasias, although less frequent causes include postpolypectomy hemorrhage; inflammatory, infectious, and ischemic colitis; neoplasms; hemorrhoids; and solitary rectal ulcer.[6] Comorbid disease, particularly in the elderly, increases morbidity and mortality, whereas polypharmacy (nonsteroidal anti-inflammatory drugs and anticoagulants) is a contributing factor to LGIH and increases the complexity of management.[7] Imaging (angiography or radionuclide scanning) and colonoscopy form the mainstay of diagnosis and treatment in acute LGIH,[8–12] although a high proportion of these hemorrhages resolve spontaneously.[8,9]

Colonoscopic intervention is often difficult because of problems with visualization in the setting of large bleeds,[13] whereas angiographic intervention requires expertise and can be associated with ischaemic complications.[14] There is no known medical intervention, with the exception of replacing blood products and reversing anticoagulation, that is used routinely for acute LGIH.[15] In light of the difficulty with interventional therapy, there is a need to determine whether some form of medical intervention can be identified to improve outcomes associated with LGIH. TXA has been used in a number of other bleeding conditions with success,[4] and considering these factors was put to the test in this trial.

This is the first randomized clinical trial to our knowledge that assessed the role of TXA in LGIH. The findings contrast with other research that highlights the efficacy of TXA in decreasing blood loss and mortality after major trauma[5] and minimizing blood loss subsequent to cardiac,[16] orthopedic,[17] gynecologic,[18] and prostate[19] surgery. There are potential clinical explanations for the differing

TABLE 3. Comparison of primary and secondary outcomes according to intervention group

Variable	*Placebo (n = 47)*	*Intervention (n = 49)*	*Total (N = 96)*	*p*
Hemoglobin drop, g/L				
Median (minimum, maximum)	13 (0, 67)	11 (0, 57)	13 (0, 67)	0.9445
Mean (SD)	16.7 (17)	14.6 (13)	16 (15)	
Lowest hemoglobin, g/L				
Median (minimum, maximum)	102 (45, 150)	104 (63, 137)	103 (45, 150)	0.6374
Mean (SD)	101 (26)	103 (21)	102 (23)	
Total transfusions				
Median (minimum, maximum)	0 (0, 23)	0 (0, 12)	0 (0, 23)	0.4386
Mean (SD)	2 (4)	1 (3)	2 (3)	
Interventions for bleeding, n (%)				
No	35 (74)	40 (82)	75 (78)	0.4635
Yes	12 (26)	9 (18)	21 (22)	
Length of stay				
Median (minimum, maximum)	3 (2, 23)	4 (2, 25)	4 (2, 25)	0.8928
Mean (SD)	5 (4)	5 (4)	5 (4)	
Readmissions, n (%)				
No	46 (98)	48 (98)	94 (98)	1.0000
Yes	1 (2)	1 (2)	2 (2)	
Complications, n (%)				
No	46 (98)	48 (98)	94 (98)	1.0000
Yes	1 (2)	1 (2)	2 (2)	
28-d Mortality, n (%)				
No	46 (98)	47 (96)	93 (97)	1.0000
Yes	1 (2)	2 (4)	3 (3)	
Thrombotic complications, n (%)				
No	46 (98)	49 (100)	95 (99)	
Yes	1 (2)	0 (0)	1 (1)	

findings. In the traumatic and postoperative setting, there is what can best be described as raw surface bleeding, where clot stabilization is paramount. Most lower GI bleeding occurs directly from a vessel (arteriovenous malformations or diverticula vessels),[20] without physical trauma, where vasospasm is the key component required to arrest bleeding, because there is no raw surface for clots to form and minimize ongoing blood loss. In addition, trauma and surgery result in a proinflammatory state with subsequent coagulopathy that responds to reversal of the thrombolytic state.[21] It would seem to make logical sense that noninflammatory related bleeding, such as what occurs in LGIH, would not respond as readily to inhibition of fibrin degradation. Another potential clinical explanation may be the microbiology of the environment in which lower GI bleeding occurs, making clot stabilization difficult.[22]

Being a double-blinded, placebo-controlled trial eliminates many potential sources of bias and confounding, but by being the first trial of its nature to examine the effect of TXA on LGIH, 1 of the potential weaknesses of this study is that the chosen primary outcome may not have been the ideal outcome with which to power the study. The choice of primary outcome was a difficult one, particularly given the paucity of RCTs on lower GI hemorrhage. Assessment of blood loss is extremely difficult in patients with GI bleeding. Mortality difference as a primary end point is impossible to assess in a single-center study of this nature, whereas transfusion requirements and intervention rates are also too low to make comparison. Our pilot study revealed a reasonably significant drop in hemoglobin during admission (mean = 18.9 g/L, SD = 14.6 g/L), implying that an intervention that was successful in arresting hemorrhage could be potentially identified using this as the outcome measure.

As a result of the choice of primary outcome, this trial, therefore, may have been underpowered to determine subtle differences in some of the important and clinically relevant secondary outcomes. Another potential weakness of this trial, in terms of its applicability or generalizability, was the proportion of patients with LGIH who could not participate in the trial as result of contraindications to TXA. Although follow-up rates were high in enrolled patients, 169 of 269 patients were excluded from participation because of a combination of medical reasons. Obviously the patient population with LGIH is different from the trauma, orthopedic, and gynecologic populations, but it is quite possible that those who stood the most to gain from minimizing blood loss in LGIH were those who had contraindications to the intervention.

The mortality rate in this trial (3/100; 3%) was acceptably low given the patient cohort and when compared with the literature. One of the potential reasons for this may have been the low intervention rate. Given that most

LGIH resolves spontaneously, the desire to rapidly identify and intervene may actually be counterintuitive. The low intervention rate seen in this study probably represents an institutional approach toward watching and waiting, rather than an approach of rapid intervention. Perhaps avoiding treating the blush and only treating the blush that fails to spontaneously stop is an approach worth considering on the basis of outcomes in this trial.

In the context of this randomized placebo-controlled clinical trial there does not appear to be any advantage associated with the use of TXA for patients presenting with LGIH. A larger multicenter trial could be considered to further investigate some of the secondary outcomes described in this study, particularly in patients who have persistent bleeding or for specific indications such as postpolypectomy hemorrhage. In the absence of such research, the routine use of TXA for this indication cannot currently be recommended.

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