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The effects of tranexamic acid on blood loss and transfusion rate in colorectal surgery

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ABSTRACT

Background: The present study aimed to evaluate safety of tranexamic acid (TA) administration and to assess bleeding risk in colorectal surgery (CRS).
Methods: Retrospective cohort study including consecutive patients undergoing elective CRS by a single surgeon between August 2014 and May 2015. All patients received 1 g of TA intravenously at induction and at closure. Demographics, operative and postoperative details were prospectively assessed and compared to a historical control cohort.
Results: 213 patients were evaluated. TA did not increase complications, readmissions, or reoperation rates. Significant postoperative hemoglobin (Hgb) drop (≥3 g/dL) (TA: n = 6, 7.4%, Control: n = 22, 16.6%; p = 0.193) and transfusion rates (intraoperative: TA: n = 2, 2.5%, Control: n = 2, 1.5%; p = 0.586, postoperative: TA: n = 1, 1.2%, Control: 9, 6.8%; p = 0.065) were not statistically different.
Conclusions: Postoperative hemoglobin drop and transfusion rates were not decreased statistically. Further study is warranted given the large clinical differences in favor of TA.

Introduction

Perioperative blood transfusions are associated with several risks including immunological complications, higher rates of postoperative infections, prolonged hospitalization, and a potential to increase cancer recurrence.[1–4] A shortage of blood products throughout the nation creates negative logistical and health system pressures.[5,6] One could significantly impact the cost and quality of care if blood transfusions can be safely avoided.[7]

Fibrinolysis regulates the balance of clot formation and degradation by promoting the generation of plasmin, via plasminogen, which leads to the breakdown of fibrin, fibrinogen, and eventually clot.[8] This pathway is commonly targeted in an attempt to decrease bleeding and resultant blood transfusions. Historically, aprotinin, an antifibrinolytic drug, was effective at decreasing blood loss in surgical patients, but secondary to cardiac complications and mortality it was pulled from the market in 2008.[9,10] Alternative approaches are needed in order to positively impact patients, hospitals, and health care quality and economics related to blood loss and transfusions.

Tranexamic acid (TA) is a lysine analog that inhibits the degradation of fibrin and fibrinogen by reversibly blocking lysine binding sites on plasmin and plasminogen.[11,12] Recent systematic reviews and meta-analyses have shown that TA decreases blood loss and transfusion requirements in cardiac, orthopedic, and gynecologic procedures.[13–16] In more than 20,000 trauma patients, TA significantly reduced the risk of death from bleeding.[17] A recent randomized trial however failed to demonstrate blood loss reduction or improved clinical outcomes in patients admitted to the hospital with lower GI hemorrhage.[18] Transfusion rates for colon and rectal surgeries range from 5 to 10%, though the ability of TA to affect perioperative blood transfusions and blood loss has not been studied.[19]

The purpose of this pilot study was to determine if TA can be safely administered while reducing blood loss and transfusion risk in patients undergoing colorectal surgery.

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Material and methods

Using a prospectively maintained database, a retrospective review of all elective colon and rectal surgeries performed by one colorectal surgeon (D.W.L) using TA between August 2014 and May 2015 was performed and compared to a control cohort treated without TA (November 2013 to August 2014). One gram of TA was administered intravenously at the beginning (induction of anesthesia) and end (skin closure) of surgery. All patients older than or equal to 18 years of age were candidates for study eligibility. Exclusion criteria included age younger than 18 years, preoperative use of anticoagulants by the time of inclusion, emergency operations, and multidisciplinary procedures with additional organ resection. The Mayo Clinic Institutional Review Board approved this study and all patients provided informed consent before enrollment. Only institutional funds were used to conduct this study.

Institutional standardized guidelines dictated intraoperative transfusions for hemodynamic compromise and/or significant intraoperative blood loss with a hemoglobin (Hgb) level less than 7 g/dL. Postoperatively, a significant decrease in Hgb was defined as a ≥3 g/dL drop within 24 h of surgery compared to the preoperative (baseline) level (= perioperative Hgb change). Postoperative transfusions were administered for Hgb <7 g/dL, or Hgb less than 8 g/dL with signs of systemic compromise (heart rate >120 bpm, systolic blood pressure <100 mmHg, orthostatic hypotension, or dizziness and/or a fall). Estimated blood loss (EBL) in the operating room was documented by the surgical team at the end of the procedure and stratified into three tiered groups (0–250 ml, 250–500 ml, >500 ml). Of note, according to institutional guidelines, all patients received DVT prophylaxis (5000 units of heparin SC at induction and while hospitalized (≥50 kg: 3x/day, < 50 kg: 2x/day)).

Data were prospectively collected by the surgical care team and registered in a dedicated institutional database and included baseline demographics, body mass index (BMI), American Society of Anesthesiologists (ASA) score, smoking status, presence of diabetes, history of pulmonary embolism (PE)/deep venous thrombosis (DVT), both of which were confirmed by board-certified radiologists. Indication for surgery including active medications, type of procedure (partial (left, right or transverse) colectomy, total colectomy, rectal resection (including abdominoperineal resection and low anterior resection) and other (including pouch surgery and ostomy procedures) 30 day postoperative complications according to National Surgical Quality Improvement Program (NSQIP) guidelines and definitions,[20] and transfusion requirements (units of administered packed red blood cells) were recorded.

In a second step, identical items as specified above were abstracted by the same surgical care team from the institutional database to constitute the control group, which consisted of consecutive patients operated by the same surgeon (D.W.L.) between November 2013 and August 2014, with previously defined inclusion and exclusion criteria.

Statistical methods

Continuous variables were examined with histograms and summarized with mean and standard deviation or median and interquartile range for symmetric or skewed distributions, respectively. Categorical variables were described with frequencies and percentages. The comparisons of continuous variables between the control and TA groups were performed with nonparametric tests (Mann-Whitney) or two sample t-tests as appropriate. For categorical variables Fisher's exact test was used. Comparisons for small samples with sparse structures (transfusions) were performed using Firth's penalized likelihood procedure that corrects for bias.[21] All analyses used R v. 3.1.2 and JMP. A two-sided p-value less than 0.05 was considered statistically significant.

Results

A total of 213 patients were identified, of which 81 (38%) were enrolled to be treated with TA and compared to 132 patients (62%) treated without TA (control group). Baseline factors, pharmacotherapy, past medical history, and surgical indications of the two groups are displayed in Tables 1 and 2. Compared to the control group, patients treated with TA were older and had higher ASA scores. Other than a larger number of chronic ulcerative colitis (CUC) patients in the control group (23.5 versus 9.9%, p = 0.017),

Table 1
Baseline factors.

	Control (N = 132)	Tranexamic Acid (N = 81)	Total (N = 213)	p-value
Gender				0.198
Female	60 (45.5%)	29 (35.8%)	89 (41.8%)	
Male	72 (54.5%)	52 (64.2%)	124 (58.2%)	
Age				0.004
Mean (SD)	50.64 (17.09)	57.27 (15.37)	50.64 (15.74)	
Median (IQR)	51.50 (37.00, 63.00)	58.00 (50.00, 68.00)	54.00 (41.00, 65.00)	
Smoker				0.202
Current	8 (6.1%)	9 (11.1%)	17 (8.0%)	
Not Current[a]	124 (93.9%)	72 (88.9%)	196 (92.0%)	
Diabetic				0.820
Yes	15 (11.4%)	9 (11.1%)	24 (11.3%)	
No	117 (88.6%)	72 (88.9%)	189 (88.7%)	
BMI				0.547
Mean (SD)	27.18 (6.46)	27.31 (5.38)	27.23 (6.06)	
ASA				0.015
1	9 (6.8%)	2 (2.5%)	11 (5.2%)	
2	99 (75.0%)	51 (63.0%)	150 (70.4%)	
3	24 (18.2%)	28 (34.6%)	52 (24.4%)	
Race				0.418
Caucasian	123 (93.2%)	77 (95.1%)	200 (93.9%)	
Not Caucasian	9 (6.8%)	4 (4.9%)	13 (6.1%)	

[a] Not Current includes never and past smokers, BMI Body mass index, ASA Physical status classification system, SD Standard deviation, IQR Intra quartile range.

Table 2
Preoperative medical history and surgical details.

	Control (N = 132)	Tranexamic Acid (N = 81)	Total (N = 213)	p-value
Medical History				
On Steroids	16 (12.1%)	14 (17.3%)	30 (14.1%)	0.315
On Biologics	10 (7.6%)	8 (9.9%)	18 (8.5%)	0.616
Recent CRT	35 (26.5%)	22 (27.2%)	57 (26.8%)	1.000
Indication				
Colon Cancer	13 (9.8%)	12 (14.8%)	25 (11.7%)	0.282
Rectal Cancer	36 (27.3%)	23 (28.4%)	59 (27.7%)	0.876
Metastatic CRC	5 (3.8%)	4 (4.9%)	9 (4.2%)	0.733
Crohn's Disease	23 (17.4%)	12 (14.8%)	35 (16.4%)	0.705
CUC	31 (23.5%)	8 (9.9%)	39 (18.3%)	0.0169
Diverticulitis	21 (15.9%)	16 (19.6%)	37 (17.4%)	0.577
Polyps	7 (5.3%)	5 (6.2%)	12 (5.6%)	0.769
Other	10 (7.6%)	10 (12.3%)	2 (9.4%)	0.334
Surgical procedure				
Partial colectomy	59 (44.7%)	33 (40.7%)	92 (43.2%)	0.571
Total colectomy	7 (5.3%)	7 (8.7%)	14 (6.6%)	0.339
Rectal resection	50 (37.9%)	32 (39.5%)	82 (38.5%)	0.813
Other	16 (12.1%)	9 (11.1%)	25 (11.7%)	0.824

Totals may add to greater than 100% due to multiple indications for surgery. CRC-colorectal cancer, CRT-Chemoradiotherapy, CUC-Chronic ulcerative colitis.

there were no differences noted between the two groups regarding medical history, use of medications, smoking status, or indication for surgery and type of surgery. Postoperative complications, reoperations, and readmissions were similar in both groups (Table 3).

Pre- and postoperative Hgb values did not differ between the two groups (TA vs. control): preoperative: 13.04 ± 1.64 g/dL vs. 12.98 ± 1.88 g/dL (p = 0.788), postoperative: 11.41 ± 1.46 g/dL vs. 11.08 ± 1.86 g/dL (p = 0.146). The proportion of patients with a significant postoperative Hgb decrease was not statistically different between the two groups (Table 4).

Overall there were no statistically significant differences in EBL (p = 0.227), although there was a higher proportion of patients with minimal blood loss (0–250 mL) in the TA (92.5%) compared to the control group (87.8%), as well as fewer larger volume losses (>250 mL) in the TA group (5.0% vs. 12.2%) (Fig. 1). A total of 14 patients (6.6%) received transfusions (4 intra- and 10 post-operatively). Nine patients required transfusion in the control group compared to a single patient in the TA group in the post-operative period. The odds ratio of receiving a postoperative transfusion following treatment with TA was 0.24 (95% CI: 0.025–1.08, p = 0.065, Table 4).

Discussion

TA is known to reduce bleeding and transfusion requirements in patients undergoing a wide range of surgical procedures.[13–15] However, the available literature focuses on surgical procedures with higher rates of blood loss and transfusion requirements and to date, colorectal surgery has not been evaluated. This pilot series failed to demonstrate a statistically significant difference in the rate of Hgb drop or transfusion rate in an unselected consecutive cohort of patients undergoing colorectal resections. Furthermore, TA did not negatively impact postoperative complications.

The clinically relevant findings of a decrease of more than 50% in large drops in Hgb and a 4-fold decreased postoperative transfusion rate suggest that further study is warranted. However, these

Table 3
Surgical outcomes of control and TA treated patients.

	Control (N = 132)	Tranexamic Acid (N = 81)	Total (N = 213)	p-value
Outcomes				
Any Complication	63 (47.7%)	39 (48.1%)	102 (47.9%)	1.000
Anastomotic Leak	4 (5.3%)	0 (0.0%)	7 (3.3%)	0.300
Abscess	17 (12.9%)	5 (6.2%)	22 (10.3%)	0.172
SSI	2 (1.5%)	3 (3.7%)	5 (2.3%)	0.376
DVT	1 (0.8%)	1 (1.2%)	2 (0.9%)	1.000
PE	0 (0.0%	0 (0.0%)	0 (0.0%)	NA
UTI	5 (3.8%)	5 (6.2%)	10 (4.7%)	0.514
Neurological	2 (1.5%)	1 (1.2%)	3 (1.4%)	1.000
Ileus/SBO	38 (28.8%)	12 (14.8%)	50 (23.5%)	0.071
Stomal Prolapse	1 (0.8%)	0 (0.0%)	1 (0.5%)	1.000
Number of complications				0.181
0	69 (52.2%)	42 (51.9%)	111 (52.1%)	0.471
1	43 (32.6%)	24 (29.6%)	67 (31.5%)	
2	15 (11.4%)	15 (18.5%)	30 (14.1%)	
3+	5 (3.8%)	0	5 (2.3%)	
Readmission	27 (20.5%)	12 (14.8%)	39 (18.3%)	
Re-operation	13 (9.8%)	6 (7.4%)	19 (8.9%)	0.631

SSI – surgical site infection, DVT – deep venous thrombosis, PE – pulmonary embolism.
UTI – urinary tract infection, SBO – small bowel obstruction.

Table 4
Transfusion outcomes of control and TA treated patients.

	Control (N = 132)	Tranexamic Acid (N = 81)	Total (N = 213)	OR (95% CI)	p-value
Hgb change > 3 g/dL	22 (16.6%)	6 (7.4%)	28 (13.1%)	0.52 (0.19–1.27)	0.193
Transfusion					
- Intraoperative	2 (1.5%)	2 (2.5%)	4 (1.9%)	1.64 (0.25–10.82)	0.586
- Postoperative	9 (6.8%)	1 (1.2%)	10 (4.7%)	0.24 (0.025–1.08)	0.065

Hgb – hemoglobin, OR –Firth's penalized odds ratio.

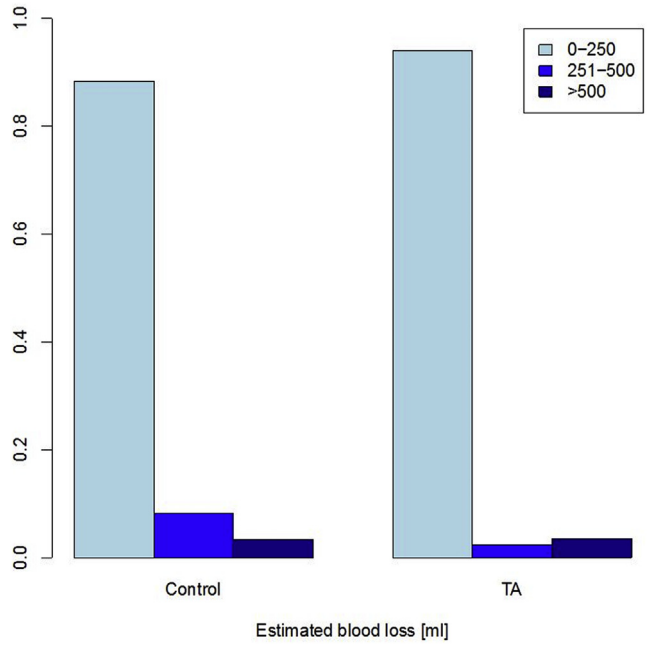

Fig. 1. Proportion of estimated blood loss (EBL) in control and tranexamic acid (TA) treated groups. EBL was measured in milliliters and separated into three categories. There was a higher proportion of patients with lower blood loss in the TA group, and a larger proportion of patients with higher blood loss in the control group ($p = 0.227$).

clinically significant findings need yet to be replicated by larger series, ideally in the setting of a prospective, randomized and adequately powered study. Confirmation of our preliminary findings may represent a significant opportunity for TA to improve quality of care. Furthermore, a significant reduction of postoperative transfusion rates in the field of colorectal surgery could potentially translate in important cost savings for patients and healthcare providers, as previously demonstrated in orthopedic surgery.[7] Reducing transfusion rates benefit the patient and institution in many ways. Decreasing exposure to transfusions has the potential to reduce inherent risk of nosocomial infection by 50% in critically ill patients, reduces the risk of lung injury, which remains a rare but potentially serious complication, and avoids immunological issues.[22–24]

There is no standard dosing of TA and multiple regimens have been described.[25–27] The dosing regimen selected for our population (1 g intravenously at the initiation and end of surgery) was based on institutional experience with orthopedic practice.[5] This simple dosing regimen was feasible to implement, avoids the cumbersome nature of bolus then infusion regimens and decreases the potential for weight based errors. The meta-analysis by Ker and colleagues (13) showed no additional benefit with doses greater than 1 g. This regimen is well below the various dosing regimens used historically in cardiac surgery which safely avoids the risk of neurologic events leading to seizures seen in with doses exceeding 60 mg/kg and up to 250 mg/kg.[26] Even in our extreme low weight patients (30 kg), 1 g (33 mg/kg) is well below the risk threshold for seizures.

Intraoperative transfusions are typically secondary to technical issues in comparison to the postoperative setting where coagulopathies that promote continued blood loss are more common. We found clinically lower rates of postoperative transfusions in the TA (1.2%) compared to the control group (6.8%). Future series within colorectal surgery may thus particularly focus on the role of TA in the postoperative setting.

Ultimately the question colorectal and general surgeons must answer for clinical decision making revolves around the risk versus benefit for particular therapy. This present study was not sufficiently powered or designed to answer all the questions but provides insight into potential benefits of perioperative TA administration in colorectal surgery. No therapy is risk free. If the goal is to reduce transfusions it also means a decreased exposure of patients to known risks, including but not limited to bacterial contamination of platelets (1:2000–3000 transfusions), transfusion errors from patient misidentification (1:16,000–19,000) and transfusion related acute lung injury (1:1000–5000).[23,27] The clinical relevance of our series may in fact outweigh the risk of transfusion side effects given no additional risk was identified in patients exposed to TA. In particular, there were no increases in adverse venous thromboembolic events in the TA group, which mirrors other major work in this area, which however requires larger series to assure equivalence.[28]

Limitations to our study include, although are not limited to, its nonrandomized retrospective nature and comparison to a historical control group. Data on unselected, consecutive eligible patients was however prospectively collected over the entire study period, and a uniform approach by a single surgeon (D.W.L.) and single-institution were followed to limit selection bias. The small cohort size leaves us with yet inconclusive results due to potential type II error and points toward future prospective studies with adequate sample size calculation (approximately 400 patients) to support these preliminary findings.

Conclusions

In conclusion tranexamic acid appears to be a safe drug in the setting of colorectal resections. Larger series need to be pursued in a randomized fashion to determine if the clinically significant benefits in our series can be replicated.

Conflicts of interest

No conflict of interest to declare for all authors.

Author contributions

Conception and design: FG, SB, JA, DWL.

Acquisition, analysis, interpretation of data: all authors.

Drafting the work or revising it critically for important intellectual content: all authors.

Final approval of the version to be published: all authors.

Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: all authors.

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