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Research Article

A Randomized Double-Blind Study Evaluating Fibrinogen-Tranexamic Acid Preventive Therapy Versus a Combined Low-Dose Regimen on Surgical Bleeding Management and Critical Care Outcomes in Patients Undergoing Radical Cystectomy

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ABSTRACT

Background: Radical cystectomy (RC) remains the standard of care for high-risk bladder cancer despite being associated with elevated perioperative morbidity. The procedure commonly results in substantial intraoperative blood loss, frequently requiring perioperative blood transfusions (PBT), which are associated with adverse events including transfusion-related complications and heightened healthcare expenditures. Pharmacological interventions such as tranexamic acid (TXA) and fibrinogen may decrease transfusion requirements, though TXA's potential thrombogenic effects raise safety concerns. This randomized controlled trial (RCT) aims to investigate the efficacy of combined fibrinogen and TXA delivery protocol in minimizing surgical blood loss and enhancing postoperative recovery in RC patients.

Methods: This randomized controlled trial (RCT) enrolled 140 participants scheduled for elective radical cystectomy (RC) procedures. Eligible individuals were randomly allocated to four study arms: one administered fibrinogen concentrate, a second receiving tranexamic acid (TXA), a third assigned to a lower-dose combination of both agents, and a control group receiving placebo. Primary outcomes evaluated perioperative blood loss (intraoperative and postoperative), while secondary outcomes encompased vital physiological markers and the incidence of postoperative adverse events.

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Results: Patients administered fibrinogen, TXA, or a combination of both demonstrated a marked decrease in postoperative hemorrhage (1,437–1,463 mL vs. 2,727 mL in controls). Furthermore, surgical timeframes showed significant contraction in the intervention groups (4.76–4.79 hours) compared to controls (5.58 hours). These treatments were also associated with shorter hospital stays and reduced transfusion volumes of packed red blood cells and fresh frozen plasma (FFP). No statistically significant variations in acidosis or hemoglobin concentrations were observed across groups. Conversely, fibrinogen and TXA delivery protocol substantially elevated fibrinogen levels, though no clinically relevant differences emerged between the intervention patient groups.

Conclusion: The trial demonstrates that adjusting fibrinogen and TXA dosage protocols effectively reduces surgical bleeding during radical cystectomy. While combination therapy showed comparable efficacy to individual agents, these pharmacological strategies decreased transfusion dependency and hospitalization duration without increasing thromboembolic risks.

Introduction

Bladder cancer represents the ninth most prevalent malignancy worldwide, with approximately 614,000 new diagnoses and 220,000 deaths recorded worldwide in 2022 [1].

Blood transfusions administered during or after radical cystectomy correlate with significantly higher likelihood of cancer reappearance and patient mortality, underscoring the critical need to reduce transfusion dependency in this population to optimize clinical outcomes [2].

Radical cystectomy (RC) combined with bilateral pelvic lymphadenectomy remains the gold-standard therapeutic approach for patients diagnosed with muscle-invasive or high-risk non-muscle-invasive forms of bladder cancer [3]. Nevertheless, the procedure is linked to a markedly elevated incidence of perioperative adverse events [4-5]. The intricate nature of the surgical intervention and distinct pathological characteristics of the tumor are key factors driving the heightened risk of intraoperative bleeding. Substantial hemorrhage during radical cystectomy (RC) represents a major clinical concern, frequently requiring perioperative blood transfusion (PBT) in 30–65% of patients undergoing the procedure [6].

Perioperative blood transfusion is commonly advised as a supportive measure integrated into established clinical guidelines for individuals undergoing radical cystectomy (RC) [7]. Nevertheless, perioperative blood transfusion (PBT) is linked to inherent risks such as transfusion-related adverse events, infectious disease transmission, and substantial financial strain on healthcare systems [8].

Emerging evidence suggests that requiring blood transfusions in the early postoperative phase following radical cystectomy (RC) may serve as a significant predictor of adverse cancer-specific survival outcomes [9-11]. Current clinical guidelines emphasize limiting transfusion dependency in patients undergoing radical cystectomy (RC) to mitigate associated risks and enhance survival prognoses [12].

Systemic pharmacological agents have gained prominence as adjunctive therapies aimed at minimizing perioperative blood transfusion needs. Key agents under investigation include tranexamic acid (TXA) [13] and fibrinogen concentrate [14], which are increasingly recognized for their potential to mitigate transfusion dependency in surgical settings These agents serve a critical function in enhancing clot stability. As a synthetic lysine analog, tranexamic acid (TXA) prevents fibrin degradation through its antifibrinolytic activity, positioning it as an effective therapeutic agent for managing hemorrhage in postoperative or trauma-related scenarios [15-16]. A major barrier to the widespread adoption of tranexamic acid (TXA) in surgical settings is its thrombogenic potential, which elevates the risk of perioperative thromboembolic complications [17-18]. Myers et al. notably reported an association between TXA delivery protocol in trauma patients and an elevated incidence of venous thromboembolism (VTE) [19]. However, clinical evidence from surgical studies has predominantly shown no significant association between TXA delivery protocol and thromboembolic complications [20-21]. In contrast, fibrinogen acts as the primary plasma protein essential for hemostatic balance and is the first clotting factor to reach critical levels in cases of significant intraoperative blood loss [22]. Conversely, some studies have reported no significant association between baseline fibrinogen concentrations and intraoperative hemorrhage volume [23-24].

Another investigation demonstrated that higher preoperative fibrinogen levels correlate with increased transfusion demands during surgical procedures [25].
Given the inconsistent findings across studies regarding the therapeutic efficacy of fibrinogen and tranexamic acid (TXA), this randomized controlled trial (RCT) seeks to evaluate the efficacy of a low-dose combination regimen in mitigating perioperative hemorrhage during radical cystectomy and optimizing intensive care unit (ICU)-related outcomes.

Methods

Design and population

This research was carried out within the Surgical Department of Modarres Hospital, a tertiary academic medical center under the auspices of Shahid Beheshti University of Medical Sciences in Tehran, Iran. The investigation enrolled 140 male patients aged 40–80 years undergoing elective radical cystectomy at the institution.

Eligibility

All enrolled individuals were assessed against predefined inclusion criteria, requiring candidacy for elective radical cystectomy performed under general anesthesia with neuromuscular blockade and mechanical ventilation. Exclusion criteria comprised:

Current anticoagulant therapy or documented hematologic disorders (e.g., coagulopathies);

Chronic hepatic impairment, chronic renal impairment (serum creatinine exceeding 2 mg/dL), or preoperatively measured plasma fibrinogen concentrations outside the 150–400 mg/dL range;

History of myocardial infarction (MI), deep vein thrombosis (DVT), pulmonary thromboembolism (PTE), or cerebrovascular accident (stroke).

Ethical Approval

Ethical clearance for this investigation was granted by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (Approval Code: IR.SBMU.RETECH.REC.1402.415). Prior to participant enrollment, the trial protocol was formally registered with the Iranian Clinical Trial Registry (IRCT identifier: IRCT20191013045091N1). Written informed consent was secured from all enrolled subjects in accordance with institutional guidelines.

Protocols and intervention

The sample size for this trial was determined using methodological frameworks described by Karlsson et al. [26] during the study's design phase. Following the acquisition of written informed consent, eligible participants were assigned to one of four treatment patient groups through stratified randomization:

Group 1 (Fibrinogen): Participants received 2 g of fibrinogen concentrate (Haemocomplettan® P, CSL Behring, Germany), reconstituted in 100 mL sterile water, administered intravenously 15–30 minutes preoperatively.

Group 2 (TXA): Tranexamic acid (15 mg/kg) was infused slowly in 100 mL normal saline.

Group 3 (Combination): A reduced-dose regimen of 1 g fibrinogen and 5 mg/kg TXA, prepared in 100 mL normal saline, was administered 15–30 minutes before incision by an independent anesthesiology technician.

Placebo Group: Identical-appearing 100 mL normal saline was administered as a control.

All solutions were indistinguishable in appearance and prepared/administered by a technician uninvolved in postoperative data collection.

The attending anesthesiologist, blinded to group assignments, quantified intraoperative blood loss via standardized measurement of irrigation fluid and surgical suction canisters.

An 18-gauge intravenous catheter was inserted preoperatively for fluid/drug delivery. General anesthesia was induced with preoxygenation (FiO₂ 1.0 for 3 minutes), followed by midazolam (0.02 mg/kg), fentanyl (4 µg/kg), propofol (2 mg/kg), and cisatracurium (0.15 mg/kg). Anesthesia maintenance included isoflurane (1 MAC) in 50% oxygen/air.

Surgeons and patients remained blinded to treatment allocations throughout the trial.

Operation technique and measurements

Intraoperative Monitoring and Surgical Protocol:

Continuous intraoperative monitoring encompassed electrocardiography (ECG), invasive arterial pressure (IAP), pulse oximetry (SpO_2), end-tidal carbon dioxide ($EtCO_2$), core temperature, and bispectral index (BIS). All radical cystectomy procedures were performed under general anesthesia by a single surgical team.

Patients underwent systematic postoperative evaluation for:

Hemorrhagic complications and hemoglobin decline (serum levels measured at 6/24 hours postoperatively);

Transfusion requirements, including volume of packed red blood cells administered;

Morbidity indicators:

Pulmonary infection, surgical site infections, thromboembolic events (pulmonary embolism [PE], deep vein thrombosis [DVT]), cerebrovascular accidents;

Healthcare utilization metrics: intensive care unit (ICU) admission duration, total hospitalization length, and operative time.

Postoperative blood loss was quantified via standardized suction canister measurement.

Additional diagnostic evaluations were tailored to individual clinical presentations.

Antimicrobial prophylaxis ceased 72 hours post-surgery.

Nasogastric tubes were removed 3–5 days postoperatively; ureteral stents and urinary catheters were extracted 1–2 weeks post-procedure.

Participants meeting discharge criteria (uncomplicated recovery) were released on postoperative day two, concurrent with urinary catheter removal.

Vigilant surveillance for treatment-related adverse events—including hypersensitivity reactions (e.g., anaphylaxis) and thromboembolic complications (e.g., myocardial infarction, PE)—was maintained throughout

hospitalization and during a scheduled one-week follow-up consultation.

Outcome measures

The study's primary objectives focused on evaluating the efficacy of fibrinogen and tranexamic acid (TXA) in reducing surgical and post-procedural hemorrhage quantification. Secondary metrics assessed included:

Transfusion requirements: Volume of packed red blood cells and fresh frozen plasma administered, Irrigating fluid volume, Hemodynamic stability (heart rate, invasive blood pressure), Acid-base balance (serum pH, bicarbonate levels [HCO_3^-]), Peripheral oxygen saturation (SpO_2), Core temperature (°C).

Temporal outcomes: Operative duration and post-anesthesia care unit (PACU) recovery time (minutes).

Healthcare utilization: Length of hospitalization and intensive care unit (ICU) admission (days).

Statistical analysis

A priori statistical parameters included an alpha level of 0.05 (95% confidence interval) and a two-tailed hypothesis testing framework. Sample size determination per study arm was calculated to achieve 82% power, yielding a target enrollment of 35 participants per group. Comparative analyses between patient groups employed parametric (Student's t-test) and non-parametric (Mann-Whitney U, Kolmogorov-Smirnov) tests, as appropriate to data distribution. Bivariate Pearson correlation analysis evaluated associations between intraoperative hemorrhage volume and excised tissue mass. Missing data from post-randomization withdrawals were addressed using the last observation carried forward (LOCF) imputation method. All analyses were performed in SPSS Statistics (Version 22.0, IBM Corporation, Armonk, NY), with statistical significance defined as $P < 0.05$.

Results

This randomized controlled trial (RCT) enrolled 140 patients undergoing elective radical cystectomy. Demographic and clinical characteristics—including age, weight, body mass index (BMI), and preoperative laboratory values—were documented and are detailed in (Table 1). No statistically significant intergroup differences were observed in baseline parameters ($P> 0.05$). Postoperative clinical outcomes across the four treatment arms are summarized in (Table 2).

Table 1- Comparison of baseline characteristics of patients.

	Control N = 35	Fib N = 35	TXA N = 35	TXA + Fib N = 35	P value
Age (years)	42.39(5.72)	42.17(9.76)	48.30(9.56)	40.67(6.62)	0.6
BMI (kg/m^2)	30.67(3.41)	30.20(2.34)	29.89(2.01)	28.00(2.82)	0.9
Weight (kg)	78.85(10.94)	75.31(10.86)	78.82(9.93)	76.40(6.67_	0.8
Hb (g/dL)	12.4±1.08	12.6±0.95	12±1.5	12.5±0.84	0.7

Table 2- The postoperative outcomes of the four groups.

Characteristic	Control N = 301	Fib N = 351	TXA N = 341	TXA + Fib N = 351	P value
Duration of surgery	5.58(0.42)	4.76(0.39)	4.78(0.37)	4.79(0.37)	<0.001
Blood loss	2,727(592)	1,437(289)	1,418(272)	1,463(262)	<0.001
Acidosis					0.064
0 vial	4 (13%)	14 (40%)	12 (35%)	12 (34%)	
1-2 vial NaHCo3	10 (33%)	14 (40%)	14 (41%)	15 (43%)	
2-4 vial NaHCo3	16 (53%)	7 (20%)	8 (24%)	8 (23%)	
The length of hospitalization	12.9(4.5)	5.3(2.7)	5.4(2.7)	5.3(2.5)	<0.001
In ICU stay	12.9(4.5)	5.3(2.7)	5.4(2.7)	5.3(2.5)	<0.001
Intraoperative hemodynamic					0.082
HOTN + Tachycardia	20 (67%)	15 (43%)	14 (41%)	13 (37%)	
nl	10 (33%)	20 (57%)	20 (59%)	22 (63%)	
PC	6.43(1.52)	3.54(0.92)	3.50(0.90)	3.62(0.85)	<0.001
FFP	3.13(0.94)	1.54(0.85)	1.53(0.86)	1.54(0.85)	<0.001
Hb	10.15(1.40)	10.13(1.20)	10.13(1.16)	10.37(1.19)	0.7
Fibrinogen	166(43)	242(43)	239(43)	244(42)	<0.001

1: Mean (SD); n (%); 2: Kruskal-Wallis rank sum test; Fisher's exact test; Pearson's Chi-squared test; HOTN; Hypotension, PC; Red packed cell, FFP; Fresh frozen plasma, Hb; Hemoglobin

Surgical duration averaged 4.76 ± 0.39 hours in the fibrinogen-administered patient group, 4.78 ± 0.37 hours in the TXA group, and 4.79 ± 0.37 hours in the combination therapy patient group. These intervention groups demonstrated statistically significant reductions

in operative time ($P < 0.001$) compared to the control group (5.58 ± 0.42 hours).

Postoperative hemorrhage volumes were 1,437 ± 289 mL (fibrinogen), 1,418 ± 272 mL (TXA), and 1,463 ± 262 mL (combination therapy). All intervention patient groups exhibited markedly lower bleeding volumes ($P < 0.001$) relative to the placebo group (2,727 ± 592 mL).

No statistically meaningful disparities in acidosis were observed between the intervention patient groups and the control group ($P = 0.064$). However, treatment with fibrinogen, TXA, or their combination demonstrated a marked reduction in hospital stay duration ($P < 0.001$). Similarly, transfusion volumes of packed red blood cells and fresh frozen plasma (FFP) were substantially lower in these groups compared to controls ($P < 0.001$). Hemoglobin (Hb) concentrations showed no intergroup variation ($P = 0.7$). Notably, fibrinogen levels were significantly elevated in subjects receiving fibrinogen, TXA, or combination therapy ($P < 0.001$), though no clinically relevant differences emerged among the intervention arms themselves.

Discussion

This randomized controlled trial (RCT) evaluated the efficacy of preoperative fibrinogen and tranexamic acid (TXA) delivery protocol versus concurrent low-dose combination therapy in minimizing perioperative blood loss and enhancing postoperative recovery metrics following radical cystectomy

Madathil et al. reported in a prospective observational investigation that high-dose tranexamic acid (TXA) delivery protocol was associated with reduced intraoperative hemorrhage in pediatric patient groups undergoing cardiac surgical procedures [27]. In a clinical investigation, Sayadi et al. demonstrated that prophylactic fibrinogen delivery protocol significantly reduced perioperative hemorrhage in parturients undergoing cesarean delivery [28]. In a related investigation, Shakeri et al. observed that prophylactic fibrinogen delivery protocol correlated with diminished intraoperative blood loss in patients undergoing total hip arthroplasty [29]. Comparable clinical outcomes were observed in patients undergoing open radical cystectomy and those receiving corrective surgery for adolescent idiopathic scoliosis (AIS) [30-32]. Our findings correspond with previous clinical observations; however, Soleimani et al. observed that preoperative fibrinogen delivery protocol did not yield a significant reduction in intraoperative hemorrhage during transurethral prostate resection [24].

Sayadi et al. demonstrated that preoperative fibrinogen delivery protocol in patients undergoing cesarean delivery significantly reduced the need for blood transfusions [28]. Shakeri et al. reported congruent findings. In our investigation, transfusion volumes of packed red blood cells and fresh frozen plasma (FFP) were markedly reduced with TXA monotherapy or combined fibrinogen-TXA regimens relative to controls. Conversely, Madathil et al. [27] observed no significant differences in transfusion requirements between low-dose and high-dose TXA protocols.

Preoperative fibrinogen delivery protocol in patients undergoing total hip arthroplasty was associated with decreased hemoglobin (Hb) levels and elevated fibrinogen concentrations compared to baseline measurements [29]. Our findings revealed that preoperative delivery protocol of fibrinogen, tranexamic acid (TXA), or a combined regimen prior to radical cystectomy significantly elevated postoperative fibrinogen levels compared to the control group. In contrast, hemoglobin (Hb) concentrations showed no statistically significant intergroup differences.

Our trial demonstrated that preoperative delivery protocol of fibrinogen, tranexamic acid (TXA), or combination therapy significantly reduced operative duration in radical cystectomy patients compared to controls. In contrast, Soleimani et al. reported no statistically significant variation in surgical time between intervention and placebo groups [24].

This randomized controlled trial (RCT) demonstrated that preoperative delivery protocol of fibrinogen and tranexamic acid (TXA), either as monotherapy or combined therapy, significantly reduces perioperative hemorrhage and enhances postoperative recovery metrics in radical cystectomy (RC) patients. These results align with prior evidence highlighting the efficacy of these agents in controlling intraoperative hemorrhage and transfusion dependency across diverse surgical settings. While conflicting evidence exists regarding their impact on hemoglobin stabilization and operative duration, our findings corroborate the therapeutic utility of fibrinogen and TXA in optimizing surgical outcomes. Notably, the study revealed no clinically meaningful superiority of combination therapy over individual agent delivery protocol.

Notably, TXA delivery protocol significantly lowered intraoperative hemorrhage, transfusion requirements, and hospital stay duration. Nevertheless, existing literature highlights its thromboembolic risk, underscoring the need for cautious clinical application [19, 33]. Contrary to concerns, a systematic review and meta-analysis found no significant association between fibrinogen delivery protocol and elevated thromboembolic risk [33]. Further research is warranted to assess the safety profiles of fibrinogen and TXA, both as monotherapies and in combination therapy.

Conclusion

In conclusion, the findings suggest that optimizing fibrinogen and tranexamic acid (TXA) dosing regimens

may effectively mitigate perioperative hemorrhage during radical cystectomy. Further investigation is warranted to establish standardized protocols for their synergistic application in surgical settings.

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