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Use of tranexamic acid in hepatectomy under controlled low central venous pressure: a randomized controlled study

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Abstract

Objective The objective of this study was to investigate the efficacy and safety of tranexamic acid (TXA) in hepatectomy when administered as per the standardized protocol of controlled low central venous pressure (CLCVP).

Methods This study was a randomized, double-blind, controlled study. Patients who fulfilled the inclusion criteria were randomly assigned to the TXA group (group T) or the placebo group (group N). The central venous pressure (CVP) was maintained at below 5 cmH2O before complete dissection of the liver parenchyma. Patients in group T received an intravenous infusion of 10 mg/kg of TXA 30 min before surgery, and it was continuously pumped intravenously at a rate of 1 mg/(kg.h) until the end of surgery. Patients in group N were infused with 1 mL/kg of normal saline 30 min before surgery, and it was continuously pumped intravenously at a rate of 0.1 mL/(kg.h) until the end of surgery. The primary outcome indicators were intraoperative blood loss, blood transfusion rate, intraperitoneal drainage at 24 h after surgery, and the occurrence of compound bleeding within 30 days.

Results The baseline indicators were similar ($P > 0.05$), and there was no significant difference in intraoperative blood loss between the two groups, but the red blood cell transfusion rate was lower in the T group than in the N group ($P < 0.05$). The infusion volume, surgical field grade, and surgery duration were comparable between the two groups ($P > 0.05$). Patients in group T had a shorter hilar occlusion time, lower D-dimer and fibrinogen degradation products (FDPs) on the day of surgery, and significantly less intraperitoneal drainage at 24 h after surgery (all $P < 0.05$). There were two cases of compound bleeding and three cases of thromboembolism among patients in group N, but there were no such complications in group T.

Conclusion The use of TXA in hepatectomy under CLCVP reduced the intraoperative blood transfusion rate and improved the postoperative bleeding outcome without increasing the risk of adverse events such as hepatic and renal insufficiency and thrombosis.

Keywords Blood loss, Blood transfusion rate, Controlled low central venous pressure, Hepatectomy, Tranexamic acid

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Introduction

The liver has a complex anatomy with abundant blood supply, and the portal vein delivers 75% of the blood flow into the liver. Hepatectomy carries a considerable risk of bleeding during the procedure, and bleeding can inhibit hepatocyte regeneration, leading to liver injury and even liver failure. It has been estimated that 23–26% of patients undergoing hepatectomy require intraoperative red blood cell transfusion [1–3], and this can compromise short-term prognostic outcomes and increase the 30-day mortality [4]. Blood loss and blood transfusion directly influence postoperative complications and prognosis. Therefore, the difficulties and priorities of anesthesia management include reducing intraoperative blood loss, ensuring the perfusion of vital organs, and minimizing the need for blood transfusion.

A growing number of studies have shown that controlled low central venous pressure (CLCVP) is safe and effective in hepatectomy [5–7]. This refers to controlling central venous pressure (CVP) at 0–5 cmH2O, thereby reducing blood flow from the hepatic vein and inferior vena cava, reducing hepatic venous pressure, reducing bleeding, and providing a clear field for the surgeon as well.

Patients undergoing hepatectomy can have impaired liver function, underlying coagulopathy, direct liver injury from surgery, intraoperative hypothermia, acidosis, and a systemic inflammatory response, which can result in hyperfibrinolysis and increased bleeding. Tranexamic acid (TXA) is an antifibrinolytic drug that can reduce hyperfibrinolysis and minimize the need for blood transfusion after hepatectomy [8]. Guidelines for the management of severe perioperative bleeding also recommend the use of TXA for preventing bleeding during major surgery as well as for treating hyperfibrinolysis-induced bleeding [9].

Bleeding during hepatectomy can occur not only during liver parenchymal dissection but also after liver parenchymal dissection due to damage and bleeding of adjacent tissues or organs, or blood oozing. In addition, it has been found that reducing CVP with nitroglycerin and esmolol provides the best surgical field under the same fluid-restriction strategy, because 60 to 80% of the blood supply is from the portal vein, after clamping the hepatic artery, which supplies 20 to 40% of the blood, the effect of arterial pressure on mitigating hepatic surgical field bleeding decreased [6, 10]. The risk of pulmonary embolism is also increased in laparoscopic hepatectomy when the pneumoperitoneal pressure is higher than the CVP if low airway pressure is present [11]. Additionally, there can be varying degrees of hyperfibrinolysis after hepatectomy [12]. CLCVP alone is insufficient to control the bleeding, and antifibrinolytic drugs are required to remedy this situation.

The use of a combination of TXA and CLCVP in hepatectomy can reduce intraoperative blood loss and the need for blood transfusions to a significant extent. However, identifying the duration and optimum dose of TXA combined with CLCVP are still in the exploratory stage. Therefore, in this study, we investigated the effect of TXA in hepatectomy under CLCVP.

Materials and methods

Inclusion and exclusion criteria

All the patients included in the study signed the informed consent form. We enrolled a total of 119 patients who underwent hepatectomy between 2021 and 2023 in the Second Affiliated Hospital of Kunming Medical University. Patients were aged between 18 and 70 years, with an American Society of Anesthesiologists (ASA) physical status grade of I–III, and Child-Pugh class A or B. Exclusion criteria: patients who were obese (BMI > 32 kg/m^2); patients with severe cardiopulmonary dysfunction; patients with a history of myocardial infarction or cerebral infarction; patients with renal insufficiency, coagulation dysfunction, pre-existing thromboembolism, tranexamic acid allergy, or contraindications.

Randomization and blind

In this study, a block randomization method was used (block size of 4). A statistician generated the random number table using the statistical software SPSS 23.0, and the patients were randomly assigned into groups in a 1:1 ratio. The group assignments were sealed in envelopes. Blinding was maintained for the patients, researchers, and clinicians throughout the study. Unblinding occurred after the trial was completed and data analysis was finalized.

Interventions

We assigned the patients to one of two groups, namely the tranexamic acid group (group T) and the placebo group (group N). TXA and normal saline were similar in appearance, and patients, researchers, and clinicians were blinded to the intervention measures. The CVP of the patients in the two groups was maintained at below 5 cmH2O before complete dissection of the liver parenchyma.

Patients in group T received an intravenous infusion of 10 mg/kg of TXA 30 min before surgery, and it was continuously pumped intravenously at a rate of 1 mg/(kg.h) until the end of surgery. Patients in group N were infused with 1 mL/kg of normal saline 30 min before surgery, and it was continuously pumped intravenously at a rate of 0.1 mL/(kg.h) until the end of surgery.

Anesthetization procedure

After the tripartite verification was completed in the operating room, the ECG, blood pressure, and oxygen saturation of the patient were monitored. Radial artery and internal jugular vein puncture and catheterization were performed, and the invasive blood pressure, cardiac output, and CVP were monitored. Anesthesia was induced by an intravenous bolus injection of 0.4 μg/kg of sufentanil, followed by 2 mg/kg of propofol and 0.6 mg/kg of rocuronium bromide. Endotracheal intubation was performed when the patient was unconscious and sufficiently relaxed.

Anesthesia was maintained with continuous inhalation of 2% sevoflurane to keep the minimum alveolar effective concentration at 0.7–0.8, continuous pumping of 0.15 μg/(kg.min) of remifentanil, and administration of one-third of the induction dose of rocuronium bromide every 40–60 min. During the procedure, BIS depth was continuously monitored and maintained at 40–60.

Before the liver parenchymal dissection, the CVP was maintained at below 5 cmH2O during the surgery by restricting fluid infusion. After the patient was brought into the operating room, normal saline and hydroxyethyl starch in a ratio of 1:1 were infused at a rate of 3–5 mL/(kg.h). If the target value could not be reached, nitroglycerin (1–3 mg/h) was intravenously pumped to reduce the CVP.

When the liver parenchyma was completely dissected, fluid resuscitation was carried out so as to increase the CVP to 8 cmH2O. If the mean arterial pressure was < 60 mmHg during the surgery, an intravenous injection of norepinephrine was administered to increase the blood pressure, and a blood transfusion was considered based on the results of the arterial blood gas analysis during the surgery. Blood transfusion was considered if the hemoglobin was < 7 g/dL or < 10 g/dL for patients with preoperative severe cardiovascular diseases or intraoperative active bleeding.

Calculation of sample size

Before starting the trial, we conducted a pilot study with 24 patients, randomly assigning 12 patients to each group. The pilot followed the same procedure and intervention protocol as the formal trial. Based on the results of this pilot study, we collected data on intraoperative blood loss for both groups. From this data, the difference in blood loss between group T and group N was 67 mL, with a standard deviation of 123. Using an α value of 0.05 and a power (1-β) of 0.8, we calculated that each group would require 53 patients. Accounting for a potential 10% dropout rate, we estimated the final sample size to be 59 patients per group.

Observation indicators

Primary outcomes: Intraoperative blood loss (reported as median and interquartile range, as blood loss is not normally distributed), including the minimum-maximum range for each group; Blood transfusion rate (with hemoglobin, hematocrit, and platelet count compared between groups). Transfusion triggers were based on hemoglobin levels < 7 g/dL or < 10 g/dL for patients with severe cardiovascular conditions or active bleeding.

Secondary outcomes: Intraperitoneal drainage volume at 24 h after surgery. Compound bleeding within 30 days, which includes both life-threatening bleeding and bleeding requiring re-surgery.

Primary efficacy indicators: Intraoperative blood loss (median, interquartile range, and min-max range); Blood transfusion rate; Compound bleeding within 30 days; Intraperitoneal drainage volume at 24 h post-surgery;

Secondary efficacy indicators: Coagulation function indexes on the day of surgery, including: prothrombin time (PT), activated partial thromboplastin time (APTT, fibrinogen (FIB), D-dimer quantification (D-D), fibrinogen degradation products (FDPs), and antithrombin III (ATIII).

Primary safety indicators: Postoperative cerebral infarction and thrombotic events (myocardial infarction; ischemic stroke, peripheral arterial embolism, venous thrombosis, pulmonary embolism).

Secondary safety indicators: seizures, myocardial injury, acute kidney injury, ICU stay, postoperative hospital stay, and 30-day mortality.

Additional observation indicators: Hemodynamic data, including perioperative central venous pressure (CVP) and vasopressor use (if available); infusion volume, surgical field grade, hilar occlusion time, duration of surgery, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cre), and high-sensitivity troponin T (hs-TNT) before and on the day of surgery.

Statistical analysis

We used SPSS 26.0 software for statistical analysis of the data in this study. Normally distributed data are expressed as mean ± standard deviation, and non-normally distributed data are expressed as median and interquartile range. For normally distributed data, we used the paired t-test for intra-group comparison and the independent sample t-test for between-group comparison. The Mann–Whitney U test was performed to compare non-normally distributed data. The Chi-square test was used for counting data, which was represented as frequency and percentage. The rank-sum test was used for data that did not conform to a normal distribution. A P value of < 0.05 was considered statistically significant.

Results

Comparison of general data

We included a total of 119 patients in this study, and one patient was excluded from group N due to a change of the surgery method during surgery. The final analysis was done on 118 patients (Figs. 1 and 2).

There were no significant differences between the two groups with regard to baseline indicators, namely, gender, ASA grade, preoperative Child-Pugh grade, age, height, weight, and resection range of hepatectomy ($P>0.05$) (Table 1).

Comparison of intraoperative factors between the two groups

There were no significant differences between the two groups in intraoperative blood loss, infusion volume, surgical field grade, or duration of surgery. Compared with group N, patients in group T had a significantly lower red blood cell transfusion rate and a significantly shorter hilar occlusion time ($P<0.05$) (Table 2).

Comparison of coagulation function and fibrinolysis indexes before and on the day of surgery

There were no significant differences between the two groups in PT, APTT, FIB, ATIII, DD2, and FDPS before surgery, as well as in PT, APTT, FIB, and ATIII on the day of surgery. When compared with group N, DD2 and FDPS were significantly lower in group T on the day of surgery ($P<0.05$) (Table 3).

Comparison of liver and kidney function and hs-TNT before and on the day of surgery

There were no significant differences in ALT, AST, CR, and hs-TNT between the two groups before and on the day of surgery (Table 4).

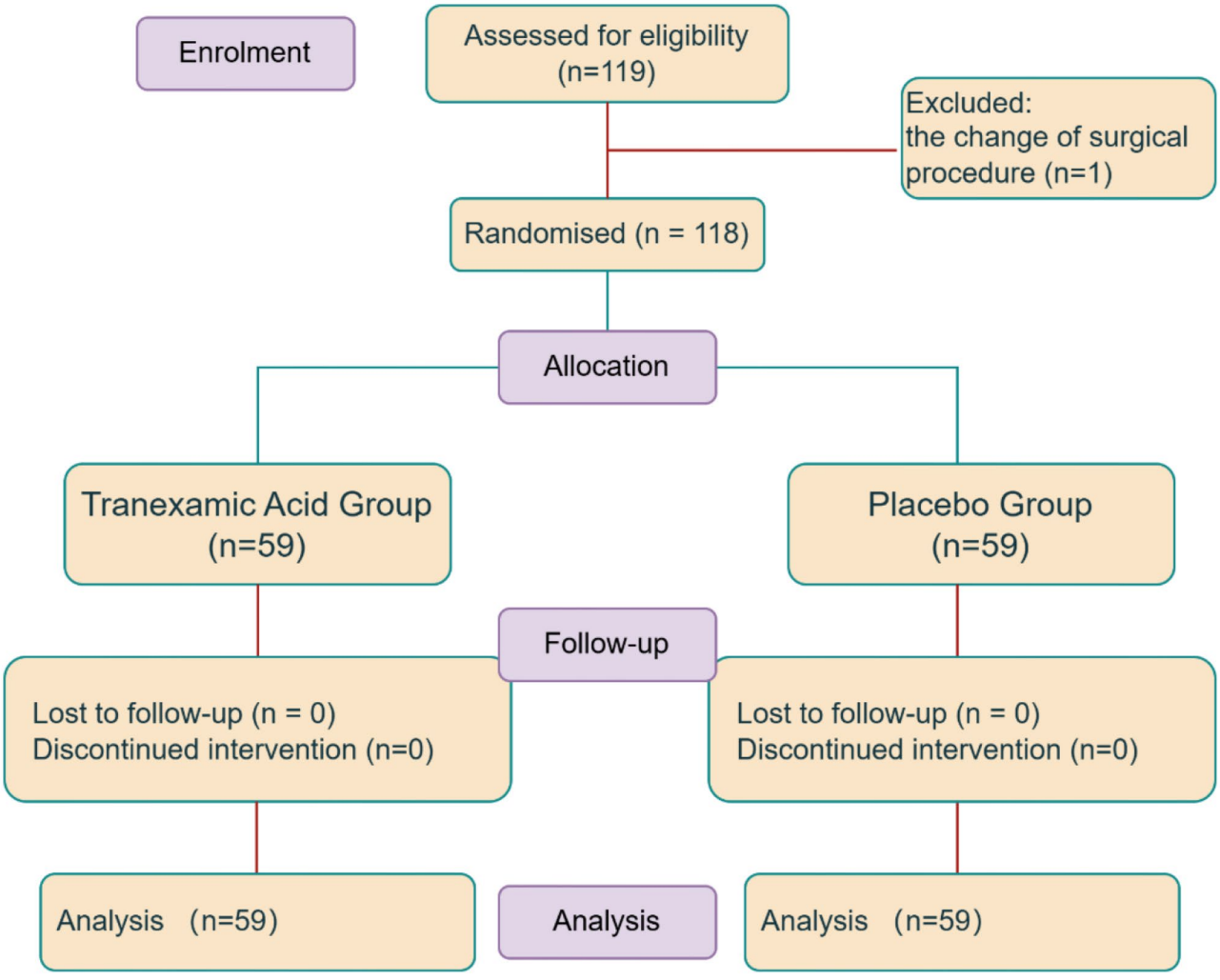

Fig. 1 Flowchart of patient enrollment and analysis

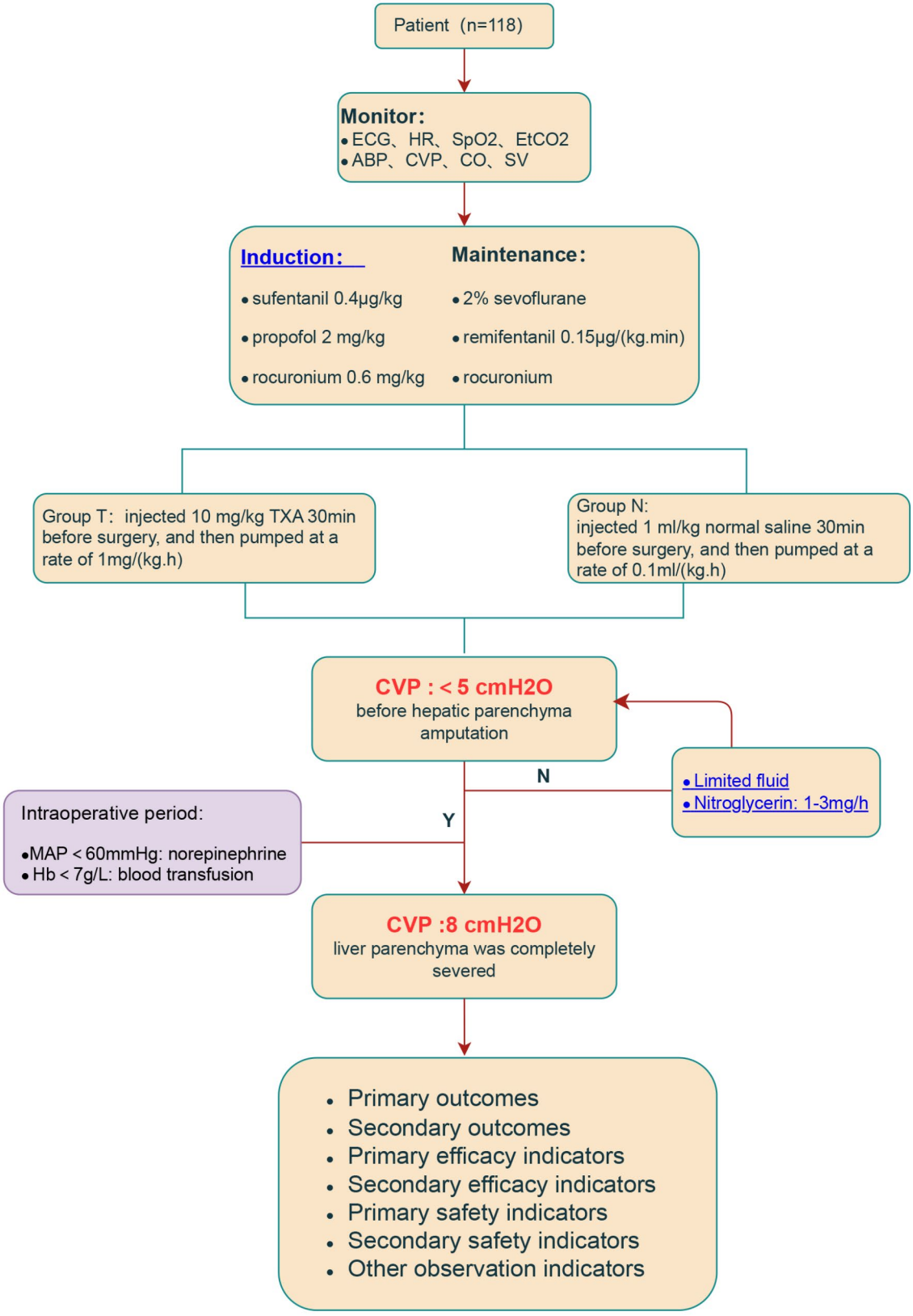

Fig. 2 Flowchart of anesthesia management and intervention protocols

Table 1 Comparison of the general data of the two groups

Indicators	Group T (*n* = 59)	Group N (*n* = 59)	*P* value
Male/Female (n)	25(42.4)/34(57.6)	30(50.8)/29(49.2)	0.356
ASA grade I/II/III (n)	1(1.7)/45(76.3)/13(22)	1(1.7)/35(59.3)/23(39)	0.133
Child-Pugh grade A/B (n)	59(100)/0(0)	58(98.3)/1(1.7)	1.0
Age (years)	51.36 ± 12.22	53.58 ± 10.41	0.29
Height (cm)	162.54 ± 7.30	162.41 ± 7.98	0.92
Body mass index (kg/m^2)	22.52 ± 2.80	23.25 ± 2.78	0.16
Dissection range of hepatectomy			0.16
segmental hepatectomy or lobectomy	33(55.9)	43(72.9)	
right hemihepatectomy	5(8.5)	3(5.1)	
left hemihepatectomy	17(28.8)	8(13.6)	
left lateral lobectomy (n)	4(6.8)	5(8.5)	
Diagnosis type(n)			0.30
Liver Neoplasms(malignant)	21	29	
Liver Neoplasms(benign)	17	15	
hepatolithiasis	21	15	

Table 2 Comparison of the intraoperative factors of the two groups

Indicators	Group T (*n* = 59)	Group N (*n* = 59)	*P* value
Intraoperative blood loss (mL)	250.00(150.00~400.00)	150.00(100.00~300.00)	0.051
Red blood cell transfusion yes/no (n)	1(1.7)/58(98.3)[a]	8(4.5)/51(54.5)	0.037
Infusion volume (mL)	2204.41 ± 646.29	2431.69 ± 878.82	0.112
Surgical field grade I/II/III (n)	35(59.3)/17(28.8)/7(11.9)	36(61.0)/14(23.7)/9(15.3)	0.758
Hilar occlusion time (min)	30.00 ± 23.55[a]	45.47 ± 39.36	0.011
Duration of surgery (h)	3.97 ± 1.98	4.32 ± 2.18	0.362

Note: Compared with group N, [a]$P < 0.05$

Table 3 Comparison of coagulation function and fibrinolysis indexes between the two groups before and on the day of surgery

Indicators	Before surgery			On the day of surgery		
	Group T (*n* = 59)	Group N (*n* = 59)	*P*	Group T (*n* = 59)	Group N (*n* = 59)	*P*
PT (S)	11.52 ± 1.22	11.86 ± 1.90	0.250	13.69 ± 1.84	14.21 ± 1.97	0.140
APTT (S)	27.07 ± 3.49	27.55 ± 4.52	0.523	32.86 ± 6.21	32.78 ± 5.65	0.943
FIB (g/L)	3.46 ± 1.57	3.42 ± 1.44	0.892	2.79 ± 1.30	2.73 ± 1.19	0.805
AT III (%)	92.76 ± 17.11	88.07 ± 16.94	0.170	65.62 ± 18.01	63.51 ± 13.80	0.480
D-D (ug/mL)	1.00 ± 1.33	1.05 ± 1.81	0.894	2.41 ± 2.11[a]	3.48 ± 2.60	0.016
FDPS (ug/mL)	3.72 ± 2.80	4.16 ± 4.71	0.560	7.08 ± 5.50[a]	11.37 ± 9.65	0.004

Note: Compared with group N at the same time point, [a]$P < 0.05$

PT: Prothrombin time; APTT: Activated partial thromboplastin time; FIB: Fibrinogen; AT III: Antithrombin III; D-D: D-Dimer; FDPS: Fibrinogen Degradation Products

Table 4 Comparison of liver and kidney function and high-sensitivity troponin T between the two groups before and on the day after surgery

Indicators	Before surgery			On the day of surgery		
	Group T (*n* = 59)	Group N (*n* = 59)	*P*	Group T (*n* = 59)	Group N (*n* = 59)	*P*
ALT (μ/L)	50.14 ± 64.46	56.12 ± 91.20	0.681	177.78 ± 129.20	220.37 ± 245.38	0.241
AST (μ/L)	53.22 ± 70.28	52.34 ± 88.57	0.952	204.64 ± 165.43	262.02 ± 260.45	0.156
Cre (μmoL/L)	66.64 ± 19.00	71.46 ± 21.13	0.196	61.29 ± 21.07	67.92 ± 19.76	0.081
hs-TNT (ng/mL)	0.005 ± 0.004	0.007 ± 0.008	0.153	0.011 ± 0.018	0.012 ± 0.015	0.726

ALT: Alanine Transaminase; AST: Aspartate Transaminase; Cre: Creatinine; hs-TNT: High sensitivity troponin T

Comparison of postoperative conditions

There was no significant difference in the duration of ICU stay and postoperative hospital stay between the two groups, and there was no pulmonary embolism, cerebral infarction, seizures, or death within 30 days in either group. Compared with group N, patients in group T had significantly less intraperitoneal drainage 24 h after surgery ($P < 0.05$). In group N, there were two cases of

Table 5 Comparison of the postoperative factors of the two groups

Indicators	Group T ($n=59$)	Group N ($n=59$)	*P* value
Compound bleeding [n (%)]	0	2(3.3)	--
Intraperitoneal drainage at 24 h after surgery (mL)	103.30 ± 120.84[a]	189.75 ± 211.55	0.007
Duration of ICU stay ($\bar{x}s$, d)	0.49 ± 0.85	0.54 ± 1.15	0.811
Duration of postoperative hospital stay ($\bar{x}s$, d)	9.22 ± 4.61	9.59 ± 5.12	0.678
Thromboembolism [n (%)]	0(0)	3(5)	--

Note: Compared with group N at the same time point, [a]$P < 0.05$

compound bleeding after surgery. Of those, one patient had intraperitoneal drainage of 600 mL of bright red blood on the 3rd day after surgery that required resurgery for hemostasis, and the other patient had intraperitoneal drainage of 400 mL of bloody fluid on the 7th day after surgery, which was treated with interventional embolization. There were three cases of thromboembolism in group N, including right hepatic vein thrombosis, thrombosis due to internal jugular vein catheterization, and muscular calf vein thrombosis of both lower limbs, while there were none in group T (Table 5).

Discussion

In this study, both groups of patients underwent CLCVP under the same surgical conditions. Contrary to findings from other studies [12–14], TXA did not reduce intraoperative bleeding compared to the control group. However, TXA significantly decreased the requirement for intraoperative blood transfusions and reduced the intraperitoneal drainage volume 24 h post-surgery. Importantly, no cases of life-threatening bleeding were observed postoperatively.

Hepatic hilar occlusion and low CVP are commonly used during hepatectomy to control bleeding, with hepatic sinusoids and venous bleeding being the main sources of intraoperative blood loss. In this study, there were no significant differences between the groups in terms of intraoperative blood loss or surgical field clarity, likely due to use of the same fluid restriction strategy to maintain CVP.

TXA, an antifibrinolytic agent, inhibits plasminogen activation, reducing blood loss during surgery. Studies have demonstrated its efficacy in reducing bleeding and transfusion requirements in surgeries, including hepatectomy and liver transplantation [15–17] In this trial, TXA was administered at 10 mg/kg preoperatively, followed by a continuous infusion during surgery. Compared with the control group, patients receiving TXA had a significantly lower red blood cell transfusion rate and reduced postoperative drainage. Two cases of compound bleeding occurred in the control group, requiring surgical intervention, while none were seen in the TXA group, indicating TXA's benefit in minimizing transfusion needs and improving bleeding outcomes.

The dosing regimen of TXA used in this study reflects one of the standard approaches developed at our institution. Another regimen, which involves a loading dose of 100 mg/kg before skin incision followed by a maintenance infusion, has been effectively used in severe scoliosis surgeries at our hospital, significantly reducing blood loss (PMID: 25457470). However, the current study employed a lower TXA dose, which is in line with our institutional protocol for hepatectomy. While the absence of thromboembolic events in the TXA group is noteworthy, it may be influenced by our standard practice of early anticoagulation after surgery, which could limit the detection of such events. Nonetheless, previous research has also reported a low incidence of thromboembolic complications with TXA use, even at higher doses.

Although TXA's antifibrinolytic effect was evident in reducing D-dimer and fibrinogen degradation products, intraoperative fibrinolysis was not monitored, which represents a limitation of the study. Additionally, although no adverse thrombotic events or seizures were observed in the TXA group, the potential for TXA-related complications such as seizures or thromboembolism has been documented in other studies, especially with higher doses [18–20]. In this study, the use of low-dose TXA did not increase the risk of postoperative thrombotic events, seizures, or liver and kidney dysfunction.

Finally, while no difference in blood loss was observed between groups, the dose of TXA used in this study was relatively low. Higher doses, as shown in other surgical studies, may offer greater reductions in transfusion rates without increasing adverse events, but further research is needed to determine the optimal TXA dosing strategy for hepatectomy under CLCVP [21, 22]. One limitation of this study is that laboratory results and drainage losses were only collected on the day of surgery, with no measurements taken during the immediate postoperative period. Although blood samples were drawn on the day of surgery, results were often available the following day, leading us to classify them as intraoperative results. This approach may limit the ability to assess early postoperative trends in laboratory markers or drainage, which could provide additional insights into the patient's recovery. Additionally, further studies should explore different TXA doses under varying CLCVP targets to better understand its hemostatic potential in hepatectomy.

Conclusion

In this study, we found that the use of TXA in hepatectomy under CLCVP was effective in reducing the intraoperative blood transfusion rate and improving postoperative bleeding outcomes without increasing the

risk of hepatic and renal insufficiency, thrombotic events, seizures, or 30-day mortality.

Abbreviations

CLCVP	Controlled Low Central Venous Pressure
CVP	Central Venous Pressure
TXA	Tranexamic Acid
BMI	Body mass index
BIS	Bispectral index
ASA	American Society of Anesthesiologists
ICU	Intensive care unit
PT	Prothrombin time
APTT	Activated partial thromboplastin time
FIB	Fibrinogen
D-D	D-Dimer
FDPS	Fibrinogen Degradation Products
AT III	Antithrombin III
ALT	Alanine Transaminase
AST	Aspartate Transaminase
Cre	Creatinine
hs-TNT	High sensitivity troponin T

Supplementary Information

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Supplementary Material 1

Author contributions

Conception and design of the research: Jie Ouyang, Yong-Yu SiAcquisition of data: Chen Zhou, Qiu-Xuan Wei, Shu-Xian ShiAnalysis and interpretation of the data: Ying Chen, Jia-Yan Luo, Qiu-Xuan Wei, Chen ZhouStatistical analysis: Chen Zhou, Jia-Yan Luo, Shu-Xian Shi, Ying ChenObtaining financing: Yong-Yu SiWriting of the manuscript: Shu-Xian Shi, Jie OuyangCritical revision of the manuscript for intellectual content: Jie Ouyang, Yong-Yu SiAll authors read and approved the final draft.

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Data availability

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Declarations

Human ethics and consent to participate

This study was conducted with approval from the Ethics Committee of Second Affiliated Hospital of Kunming Medical University (Approval Number: shen-YJ-2023-159). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

Clinical registration

This study was registered in registered in the Chinese Clinical Trial Registration Center (No. ChiCTR2300076300) on September 29, 2023.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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