

# Safe and Effective Blood Preservation Through Acute Normovolemic Hemodilution and Low-Dose Tranexamic Acid in Open Partial Hepatectomy

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**Objective:** In this study, we evaluated the efficacy of tranexamic acid (TXA) and acute normovolemic hemodilution (ANH) with 6% hydroxyethyl starch (130/0.4) in minimizing blood loss during open partial liver resection. Coagulation function was assessed using thromboelastography (TEG) and hemostasis tests, while renal function changes were tracked through serum creatinine values post-surgery.

**Methods:** Thirty patients undergoing open partial liver resection were allocated to two groups: Group T received TXA + ANH, and Group A received ANH alone. Blood was drawn from the radial artery under general anesthesia. Both groups received peripheral vein injections of 6% hydroxyethyl starch 130/0.4. Group T additionally received intravenous TXA. Primary outcomes included blood loss and allogeneic blood transfusions. TEG assessed coagulation status and renal function was monitored.

**Results:** Group T demonstrated superior outcomes compared to Group A. Group T had significantly lower intraoperative blood loss (700 mL vs 1200 mL) and a lower bleeding rate per kilogram of body weight (13.3 mL/kg vs 20.4 mL/kg). Coagulation parameters favored Group T, with higher TEG maximum amplitude (55.91 mm vs 45.88 mm) and lower activated partial thromboplastin time (38.04 seconds vs 41.49 seconds). Neither group experienced acute renal injury or kidney function deficiency during hospitalization.

**Conclusion:** TXA and ANH in a small dose during liver resection stabilize clotting, reduce blood loss by 6% compared to hydroxyethyl starch 130/0.4, and do not affect renal function.

**Keywords:** acute normovolemic hemodilution, coagulation function, liver resection, thromboelastography, tranexamic acid

## Introduction

The liver is a highly vascularized organ with delicate tissue. Its basic anatomical units, hepatic lobules, are centered around the central vein. Operating on the liver presents challenges due to its role in synthesizing most coagulation factors, making it tricky to manage effectively with a single approach. Managing blood loss and the need for transfusions has always been a concern in liver surgery. Simultaneously, using allogeneic blood transfusions during the perioperative period can lead to adverse patient reactions, including transfusion reactions, the potential transmission of viruses, immune suppression, and transfusion-related lung injuries.

Studies have demonstrated that perioperative allogeneic blood transfusions are associated with poorer patient outcomes, especially in those undergoing tumor resection procedures.<sup>1,2</sup> To address these issues, clinicians are focusing on increasing hemoglobin levels in patients, carefully determining when blood transfusions are necessary, and minimizing blood loss during surgery. This involves implementing strategies like maintaining low central venous pressure, using blood clotting techniques, employing various surgical tools, adjusting anesthesia methods, and administering specific medications to reduce blood loss during liver surgeries.<sup>3</sup> Acute normovolemic hemodilution is a blood conservation

technique used prior to surgery after anesthesia. It involves replacing the extracted whole blood with an equal volume of artificial colloidal solution, all without increasing the return of blood to the liver. As a result, there is no increase in the pressure within the right atrium and inferior vena cava, leading to a reduction in blood stagnation within the liver. This, in turn, helps to minimize blood loss during partial liver resection. Additionally, following hepatectomy, transfusing whole blood with the same proportion of coagulation factors may yield some improvement in coagulation. Research studies have verified that acute normovolemic hemodilution can effectively decrease blood loss during surgery and reduce the need for blood transfusions both during and after the procedure. Moreover, postoperative complications and the duration of hospital stays do not exhibit significant changes as a result of this approach.<sup>4-6</sup> When acute normovolemic hemodilution is combined with maintaining a low central venous pressure during hepatectomy, it can further reduce blood loss and the requirement for allogeneic transfusions. However, it does not have a substantial impact on coagulation function.<sup>7</sup> It is important to note that changes in coagulation function can occur during surgery due to intraoperative blood loss and fluid resuscitation. Research has indicated that acute normovolemic hemodilution may prolong the values of PT, APTT, and TT while reducing plasma fibrinogen concentrations.<sup>8</sup> Tranexamic acid is a commonly used antifibrinolytic medication in various medical fields, including trauma, orthopedic surgery, and obstetric surgery.<sup>9</sup> Studies have demonstrated its effectiveness in reducing blood loss and the need for blood transfusions in hepatectomy procedures.<sup>10,11</sup> The primary objective of this study was to investigate whether combining tranexamic acid with acute isovolemic hemodilution could result in greater blood loss reduction compared to acute normovolemic hemodilution. Additionally, we aimed to closely monitor coagulation function to establish a theoretical foundation for implementing blood-saving strategies during hepatectomy. It is worth noting that both acute normovolemic hemodilution and tranexamic acid are associated with potential kidney-related side effects.<sup>12,13</sup> We also tracked the occurrence of acute kidney injury and renal insufficiency from 48 hours post-surgery until the discharge of patient.

## Materials and Methods

### Patients

Thirty patients who were scheduled to have a liver resection using laparotomy (not hemi-hepatectomy) and acute normovolemic hemodilution (ANH), with a scope of liver resection equal to or greater than three segments or a diameter for any single lesion equal to or greater than 5 cm, were included in our study. Patients or their representatives signed the consent form after being informed of the study. The study was approved by the hospital's ethics committee.

### Inclusion Criteria

- ① Patients who were willing to undergo the liver resection with ANH, and who signed the consent form and the ANH consent form themselves or had them signed by their family members.
- ② Patients who fall within the age range of 18 and 75 years, have an ASA (American Society of Anesthesiologists) grading of I or II, and weigh more than or equal to 50 kg.
- ③ Patients with a Child-Pugh grade of A or B,  $\geq 3$  liver segments removed via laparotomy, or any single lesions with diameters  $\geq 5$  cm.
- ④ Hematocrit (HCT, also known as packed cell volume [PCV])  $\geq 33\%$ , platelet count  $\geq 100 \times 10^9/L$ , and hemoglobin  $\geq 110$  g/L prior to operation.
- ⑤ Patients without serious liver or renal failure, apparent defective coagulation functioning, coagulation-related diseases, or a history of anticoagulant usage, and without heart- or lung-related ailments.

### Exclusion Criteria

- ① Patients with cirrhosis and portal hypertension.
- ② Patients who may have an inferior vena cava tumor thrombus or a portal vein tumor thrombus.
- ③ Patients who experienced surgically-induced vascular invasion or unintentional vascular damage.

## Methods

### ANH

Based on the results of preoperative exams and tests (T0) of the 30 participants, they were randomly divided into two groups—Group A and Group T. Under general anesthesia, blood was collected from the radial artery of each group, and a sodium chloride solution with 6% hydroxyethyl starch 130/0.4 was administered equally to each group. Subsequently, Group T received 1% TXA intravenously dripped for 30 minutes at a loading dose of 10 mg/kg, then 1% TXA was continuously pumped at a rate of 1 mg/(kg h) until the skin suture was completed, while Group A received normal saline administered at the same rate after blood was drawn. The blood volume of the patients was calculated based on their body weights:

$$\text{Male blood volume (mL)} = \text{body weight (kg)} \times 70$$

$$\text{Female blood volume (mL)} = \text{body weight (kg)} \times 65$$

Formula for blood sampling:

$$\text{Blood drawn (mL)} = \text{blood volume} \times 2 \times (\text{HCT actual value} - \text{HCT target value}) / (\text{HCT actual value} + \text{HCT target value})$$

Either the hemoglobin level was 100 g/L or the HCT target value was 30%. The maximum blood drawn was  $\leq 30\%$  of the blood volume.

The ACD (A: citric acid, C: trisodium citrate, and D: dextrose) blood storage bag was positioned on a swinging balancer during blood collection. The blood was drawn, labelled with the patient's name, gender, age, blood type, hospital case number, and precise collection time, and kept refrigerated at 4 °C. When connecting and replacing blood storage bags, certain hygienic procedures were followed. During surgery, a 1:1 ratio of crystalloid to colloid was infused. The same chief surgeon carried out each operation. With intermittent closure of the first hepatic portal (the Pringle maneuver), the liver was severed using the forceps clamp technique. Peripheral venous blood was collected and monitored for hemoglobin and platelet count using blood cell analysis before blood was drawn (T1), after blood was drawn (T2), after liver parenchyma dissection and hemostasis but before autotransfusion (T3), after autotransfusion but before skin suture (T4), after skin suture (T5), within 24 hours after surgery (T6), and within 48 hours after surgery (T7). Peripheral venous blood was collected to assess thromboelastography (TEG) after liver parenchyma dissection and hemostasis but before autotransfusion (T3). We noted the duration of the procedure, the amount of blood lost during the procedure, the amount of blood transfused, and the amount of urine produced.

### Intraoperative Transfusion Strategies

- ① Red blood cell transfusion: Red blood cell transfusions were done following liver resection hemostasis or when a patient's hemoglobin level was below 70 g/L. Allogeneic blood was then transfused after the autologous blood.
- ② Fresh frozen plasma: Prothrombin time (PT) or activated partial thromboplastin time (APTT) took 1.5 times longer than expected, or there was substantial intraoperative hemorrhage.
- ③ Cryoprecipitation: Plasma fibrinogen levels below 1.5 g/dL indicated a lack of functional fibrinogen, as determined by TEG monitoring.
- ④ The body temperature was maintained between 35.5 °C and 37 °C and the nasopharyngeal temperature was regularly monitored.
- ⑤ The calcium ion level was maintained at  $\text{Ca}^{2+} \geq 0.9$  mmol/L.
- ⑥ CVP (central venous pressure) was maintained at a level of  $< 5$  mmHg throughout the dissection of the liver parenchyma.
- ⑦ MAP (mean arterial pressure) was maintained at  $\geq 65$  mmHg.

#### Observation Results

### Primary Outcomes

Blood loss and transfusion

① Number of transfusion cases and allogeneic blood transfusion volume during operation; intraoperative blood losses.

### Secondary Outcomes

① Coagulation function: TEG and hemostasis assessments are conducted to assess the performance of coagulation functions. ② Kidney function: Renal insufficiency was evaluated through serum creatinine levels within the first 48 hours following surgery and monitored for any signs of occurrence between the postoperative period and discharge.

#### TEG

A TEG device known as kaolin thromboelastography, using the TEG<sup>®</sup> 5000 system from Haemoscope (Haemonetics), operates with a setup where a pin is suspended from a torsion wire and immersed in a cup containing whole blood. This cup is placed within a heating block and continuously oscillates at an angle of 4°45' every 5 seconds. Any alterations in the viscoelastic strength of the clot directly affect the torsion wire, which is then detected by an electromechanical transducer. This system offers real-time analysis of the viscoelastic characteristics of clot formation and dissolution within whole blood. Clinically, four parameters are typically employed:

R, referring to the reaction time or clotting time, represents the moment of initial significant clot formation.

Angle signifies the kinetics of clot development, indicating the speed at which thrombin generation, fibrin deposition, and cross-linking occur.

MA, denoting Maximum Amplitude, represents the peak strength of the clot.

Ly30, or percent Lysis 30 minutes after MA, quantifies the degree of clot dissolution 30 minutes following its maximum strength.

### Statistical Analysis

The statistical software SPSS 26.0 was used to process and analyze all the data. Normally distributed measurement data are reported as mean  $\pm$  standard deviation and subjected to statistical analysis using independent samples *t*-test and paired *t*-test. Non-normally distributed measurement data were subjected to a nonparametric rank sum test and expressed as the median (the minimum value to the maximum value). Two-factor repeated measures analysis of variance was used to examine blood cell analysis and creatinine value analysis at each time point. Gender and transfusion rate were analyzed using the Fisher's exact test or the chi-squared test. A statistically significant difference was observed by a *p*-value of less than 0.05 ( $p < 0.05$ ).

## Results

### Demographic Data, Tests, and Examinations Before the Surgery (T0)

Groups T and A did not differ statistically from one another in terms of demographic information, hemoglobin, platelet count, hemostasis tests, and TEG (Table 1).

### Comparison of Intraoperative Condition

The median of total blood loss in Group T was 700 mL, which was lower than the 1200 mL in Group A ( $U = 61.500$ ,  $P = 0.033$ ) as shown by the results of the Mann–Whitney *U*-test; the median blood loss in Group T was 13.3 mL/kg, which was lower than the 20.4 mL/kg in Group A ( $U = 54.500$ ,  $P = 0.015$ ). In terms of the volume of blood drawn, the duration of the procedure, the volume of intraoperative blood transfusions, and the volume of intraoperative urine, there was no statistically significant difference between Groups T and A (Table 2).

### TEG at the Completion of Liver Resection

At the completion of liver resection (T3, after the severing of liver parenchyma), the maximum amplitude (MA) value of TEG in Group T was  $55.91 \pm 7.97$  mm, which was higher than the  $45.88 \pm 19.79$  mm in Group A, with a difference of 10.023 (95% confidence interval [CI]:  $-1.531$ – $21.576$ ). The results of independent samples *t*-test showed  $t' = 1.820$ ,  $P = 0.043$  with a statistically significant difference, and MA in Group A was lower than the normal lower limit (50 mm). There was no statistically significant difference with respect to the other TEG data (Table 3).

**Table 1** Demographic Data and Preoperative Tests, Examinations

		Group A (n=15)	Group T (n=15)	Statistical value	P value
Demographic data	Gender (male/female)	9/6	10/5	$\chi^2=0.144$	0.705
	Child-Pugh (A/B)	9/6	7/8	$\chi^2=0.536$	0.464
Haemostasis tests	Age (year)	48.8±11.8	55.8±11.1	t=1.673	0.105
	Height (cm)	163.8±8.9	166.3±8.0	t=0.809	0.425
	Weight (kg)	60.2±8.3	63.9±8.6	t=1.199	0.241
	Hb (g/L)	143.1±20.9	145.8±15.9	t=0.398	0.694
	PLT ( $\times 10^9/L$ )	231.4±68.0	241.9±79.1	t=-0.390	0.700
	PT(s)	12.4±1.2	12.0±1.0	t=-0.992	0.330
	APTT(s)	33.7±3.8	33.7±5.5	t=0.043	0.966
	INR	1.03±0.09	0.96±0.10	t=-1.863	0.073
	FIB(g/L)	3.3±0.9	3.7±1.1	t=1.019	0.317
	D <sub>2</sub> (g/L)	1.24±1.55	1.01±1.10	t=-1.297	0.205
TEG	FDPs( $\mu\text{g/mL}$ )	3.83±4.34	3.42±3.04	t=-0.300	0.767
	TT(s)	17.40±1.12	16.87±1.11	t=1.302	0.203
	R(s)	3.71±1.25	4.49±1.14	t=1.786	0.085
	Angle(°)	63.37±7.69	67.35±8.58	t=1.338	0.192
	MA (mm)	62.84±9.03	61.62±7.87	t=-0.394	0.696
	Ly30(%)	0.32±0.59	0.43±0.82	U=125.000	0.624

## Comparison of Postoperative Coagulation Function

There was no statistically significant difference in preoperative coagulation function between Groups T and A ( $P > 0.05$ ). Both groups had statistically significant differences ( $P < 0.05$ ) in coagulation function, significantly prolonged PT, APTT, INR (international normalized ratio), decreased Fib (fibrillation), increased D-dimer, and decreased FDPs (fibrin degradation products) when their postoperative data were compared to those before surgery, as shown by the results of the intra-group paired *t*-test. By the end of the procedure (T5), the APTT in Group T was  $38.04 \pm 3.59$  s (seconds), which was 3.450 s (95% CI: -6.785 - -0.115) shorter than the  $41.49 \pm 5.18$  s in Group A, were within normal threshold. The results of the independent sample *t*-test revealed a statistically significant difference of -2.119,  $P = 0.043$ . Based on the data displayed in Table 4, there was no statistically significant difference in the other coagulation function characteristics between Groups T and A ( $P > 0.05$ ).

## Evaluation of Blood Cell Count Results

The following comparison was made between the Hb (hemoglobin) readings of the two groups: The Hb values in Groups T and A were at their lowest points at the conclusion of the liver dissection (T3), began to rise at T4, and exhibited no statistically significant difference at T5, T6, or T7 ( $P > 0.05$ ). T3 signaled the start of Group T's Hb value exceeding that of Group A. At T3, the Hb value for Group T was  $93.2 \pm 14.4$  g/L, which was significantly higher than the Hb value for Group A, which was  $78.8 \pm 13.8$  g/L ( $T = 2.816$ ,  $P = 0.009$ ). At T4, the Hb value for Group T was  $100.2 \pm 15.4$  g/L, which was significantly higher than the Hb value for Group A, which was  $87.2 \pm 14.1$  g/L ( $T = 2.411$ ,  $P = 0.023$ ). Comparison of PLT (platelet count) values between Groups T and A: There was no statistically significant difference in the PLT value between the two groups at T1, T2, T3, T4, T5, and T7 ( $P > 0.05$ ), and all PLT values at T1, T2, T3, T4, T5, and T6 were within the normal range ( $125\text{--}350 \times 10^9/L$ ) (Figure 1).

## Variation in Kidney Function Between Groups T and a

The serum creatinine readings in Group T after surgery, within 24 hours following surgery, and within 48 hours following surgery, were all within a normal range, and were greater than those in Group A. There was no statistically significant difference in the blood creatinine value before and after surgery at each time point based on intra-group comparisons within

**Table 2** Volume of Blood Drawn, Blood Loss, Operation Duration, Urine Volume, Allogeneic Blood Transfusion

Group	Volume of Blood Drawn (mL)	Volume of Blood Drawn (mL/kg)	Blood Loss (mL)	Blood Loss (mL/kg)	RBC (Transfusion/no)	FFP (Transfusion/no)	Duration of Operation (h)	Urine Volume (mL)	Urine Volume {mL/(kg h)}
Group A (n=15)	800 (600–900)	12.6 ±3.0	1200 (550–2300)	20.4 (7.9–39.2)	4/11	4/11	5.86±1.95	713.3±423.6	2.04±1.02
Group T (n=15)	800 (600–1200)	12.0 ±2.5	700 (400–2500)	13.3 (6.3–33.8)	2/13	2/13	6.57±1.15	824.7±428.4	2.02±1.14
P value	0.831	0.819	0.033 <sup>#</sup>	0.015 <sup>#</sup>	0.651	0.651	0.243	0.473	0.961

**Note:** <sup>#</sup>Indicates  $p < 0.05$  for comparison between the two groups.

**Table 3** TEG at the Time of Hepatic Parenchyma Was Severed and Hemostasis Was Completed

TEG Threshold Range	R (min) 5~10	Angle (°) 53~72	MA (mm) 50~70	Ly30 (%) 0~0.8
Group A (n=15)	5.39±1.19	57.79±15.34	45.88±19.79 <sup>#</sup>	1.37±1.74
Group T (n=15)	4.94±1.29	58.13±13.26	55.91±7.97 <sup>#</sup>	0.75 ±1.29

Note: <sup>#</sup>Indicates  $p < 0.05$  for comparison between the two groups.

Groups T and A. The Cr (creatinine) values in Group A showed a downward trend, while the Cr values in Group T showed an upward trend. During postoperative hospitalization, neither group experienced renal function impairment (Table 5).

## Discussion

Open partial hepatectomy remains a commonly employed surgical procedure in clinical practice, particularly in cases where laparoscopic surgery is challenging due to limited visibility, restricted space, or unique lesion locations, such as those in the caudate lobe or large tumors, including but not limited to hepatocellular carcinoma, cholangiocarcinoma, hepatic hemangioma, and intrahepatic bile duct calculus.

The liver, given its vital role in clotting factor synthesis and its proximity to major blood vessels like the inferior vena cava and abdominal aorta, poses a risk of significant blood loss and necessitates potential allogeneic transfusions during liver resection. To mitigate these risks, various blood-saving techniques such as maintaining low central venous pressure, blood flow obstruction methods, ANH, and TXA have gained widespread acceptance in partial hepatectomy procedures.

In our research, we employed a low CVP approach (CVP < 5 mm Hg, equivalent to 1.33 cm H<sub>2</sub>O) prior to liver parenchyma dissection. Previous studies have already demonstrated the efficacy of maintaining low CVP in reducing intraoperative blood loss.<sup>14,15</sup> ANH, either alone or in conjunction with a low CVP strategy, significantly decreased the need for allogeneic blood transfusions during hepatectomy.<sup>16,17</sup>

We specifically found that when TXA was combined with ANH, the median blood loss was 700 mL (13.3 mL/kg), a substantial reduction compared to the 1200 mL (20.4 mL/kg) observed in the ANH-only group, with statistical significance ( $P < 0.05$ ). While two out of the 15 patients in the TXA and ANH group required blood transfusions and plasma infusions during the operation, this figure was lower than the 4 patients in the ANH-only group, although this difference did not reach statistical significance ( $P > 0.05$ ), likely due to the small sample size. These findings underscore the effectiveness of combining TXA and ANH as strategies to minimize blood loss in open partial hepatectomy, resulting in fewer patients requiring allogeneic blood transfusions. Receiving allogeneic transfusions during perioperative hepatectomy is associated with an unfavorable prognosis.<sup>18</sup> To mitigate the need for such transfusions during partial hepatectomy, the primary focus is on minimizing blood loss. Surgeons and anesthesiologists are actively exploring strategies to reduce surgical blood loss.

One viable approach is ANH, a blood preservation technique commonly used in cardiac surgery with cardiopulmonary bypass (CPB). ANH entails the extraction of a fraction of the patient's blood immediately following the induction of anesthesia, followed by its substitution with either an artificial colloid solution or a volume of crystalloid solution equivalent to three times the amount of blood withdrawn. The stored blood is then reintroduced to the patient when a specific hematocrit (Hct) level is reached or when clinically necessary. It is crucial to achieve an appropriate level of blood dilution to maximize the benefits of ANH while avoiding circulation overload, which can lead to excessive surgical blood loss due to coagulation factor dilution.

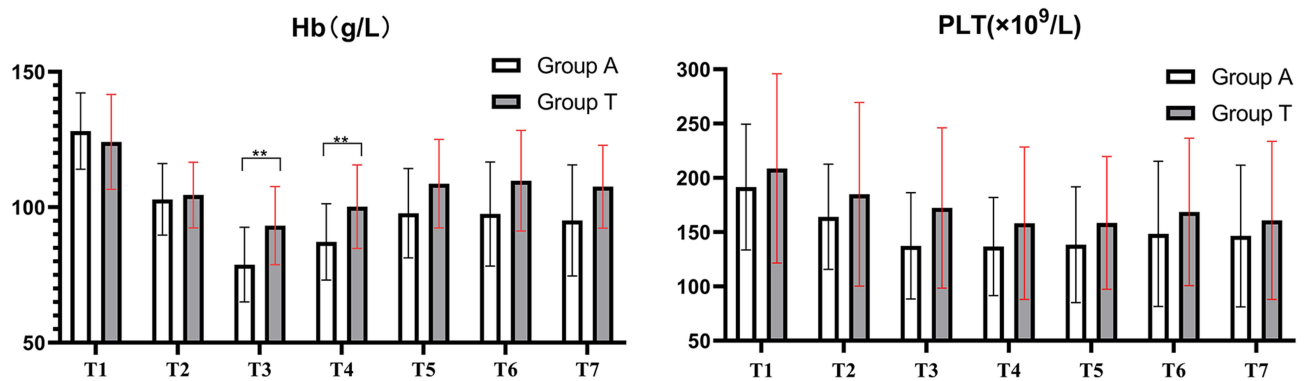
In our study, we aimed for a target hemoglobin level of 100g/L (Hct 33%). Using an equivalent amount of colloid to supplement the circulating blood volume helped prevent high central venous pressure during hepatectomy. A study by Jones et al<sup>19</sup> compared various diluents for ANH (Ringer's solution, 5% albumin, succinyl gelatin, and hydroxyethyl starch) with a target hemoglobin of 90g/L. The results indicated that hydroxyethyl starch and succinyl gelatin caused increased APTT, decreased MA value, and decreased  $\alpha$  angle of TEG.

**Table 4** Coagulation Function at the End of Surgery

Coagulation Function Threshold Range	PT(s) 11.0~15.0		APTT(s) 28.0~43.5		INR 0.80~1.30		Fib (g/L) 2.00~4.00		DD (μg/mL) 0.00~0.50		FDPs (μg/mL) 0.00~5.00		TT(s) 14.0~21.0	
	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>	T <sub>0</sub>	T <sub>5</sub>
Group A (n=15)	12.38±1.17	16.80 <sup>a</sup> ±2.60	33.66±3.81	41.49 <sup>a#</sup> ±5.18	1.03±0.10	1.41 <sup>a</sup> ±0.29	3.32±0.88	1.89 <sup>a</sup> ±0.57	1.24±1.55	2.56 <sup>a</sup> ±1.57	3.83±4.38	1.89 <sup>a</sup> ±0.57	17.40±1.12	15.03 <sup>a</sup> ±1.20
Group T (n=15)	11.99±0.96	15.4 <sup>a</sup> ±1.94	33.74±5.48	38.04 <sup>a#</sup> ±3.59	0.96±0.10	1.25 <sup>a</sup> ±0.20	3.68±1.06	2.00 <sup>a</sup> ±0.63	0.95±1.09	2.45 <sup>a</sup> ±2.07	3.42±3.03	2.00 <sup>a</sup> ±0.63	16.87±1.11	15.63 <sup>a</sup> ±1.21

**Notes:** <sup>a</sup>Means  $p < 0.05$  compared with the same group before surgery (T<sub>0</sub>); <sup>#</sup>Indicates  $p < 0.05$  for comparison between the two groups.





**Figure 1** Blood cells count results between the two groups. T1: the time interval before blood was drawn; T2: the time interval after blood was drawn; T3: the time interval before autotransfusion when the liver's parenchyma was severed and hemostasis was complete; T4: the time interval after autotransfusion; T5: the time interval during which the surgery was completed; T6: within 24 hours after surgery; T7: within 48 hours after surgery. \*\*Means  $p < 0.05$ .

Notably, blood dilution with 6% hydroxyethyl starch (130/0.4) can negatively impact clotting function, possibly due to its effect on platelet activity via von Willebrand factor and FVIII factor.<sup>20</sup> Studies on cardiopulmonary bypass heart surgery have shown reduced platelet aggregation function in ANH-collected blood samples, although thrombin production remains unaffected.<sup>21</sup> While ANH-collected blood stored at room temperature for up to 8 hours has a hemostatic effect,<sup>22</sup> preserving it at 4 °C helps maintain platelet activity.<sup>23</sup>

In our study, we used a 4 °C refrigerator to maximize blood clotting function preservation. Transfusing fresh whole blood can partially enhance coagulation function. Clinical trials in hepatectomy patients have demonstrated that ANH can reduce the need for red blood cell and plasma transfusions post-surgery.<sup>5</sup> The blood collected in our study was transfused back into the patient after liver resection and hemostasis, resulting in increased hemoglobin and platelet values. There were no significant differences in preoperative hemoglobin levels or blood collections between the two groups.

Following hepatic parenchymal separation and hemostasis, the hemoglobin level in the group that received TXA in combination with ANH was significantly higher at  $93.2 \pm 14.4$  g/L compared to the ANH-only group at  $78.8 \pm 13.8$  g/L ( $P < 0.05$ ). After blood transfusion, the Hb value in the TXA combined with ANH group further increased to  $100.2 \pm 15.4$  g/L, significantly surpassing the ANH group with  $87.2 \pm 14.1$  g/L ( $P < 0.05$ ). For patients undergoing ANH, the addition of TXA proves to be an effective blood preservation intervention, resulting in higher hemoglobin levels during the perioperative period. Tranexamic acid, a synthetic derivative of lysine, functions as an antifibrinolytic medication. It is widely employed to both prevent and treat significant blood loss in various medical contexts such as cardiac surgery, orthopedic surgery, and trauma cases. The mechanism of action of tranexamic acid involves its strong affinity for the lysine binding site of plasminogen, thereby obstructing the interaction between fibrin and plasminase. Although plasminase can continue to be produced, it becomes incapable of binding to fibrin or fibrin monomers due to the presence of tranexamic acid. Consequently, tranexamic acid effectively prevents plasminase from breaking down the formed fibrin, ultimately achieving hemostasis.

The hemostatic effect of tranexamic acid varies depending on the dosage. Low doses of tranexamic acid inhibit the activation of plasminogen, while higher doses directly inhibit plasminogen activity, leading to a more pronounced

**Table 5** Comparison of Serum Creatinine Cr (umol/L)

	Pre-Operation Cr (T <sub>0</sub> )	End of Operation Cr (T <sub>5</sub> )	24h After Operation Cr (T <sub>6</sub> )	48h After Operation Cr (T <sub>7</sub> )
Group A (n=15)	62.46±10.98	60.53±13.09	57.40±11.60 <sup>#</sup>	54.67±11.83 <sup>#</sup>
Group T (n=15)	68.87±13.95	67.73±15.12	70.60±16.25 <sup>#</sup>	73.67±24.23 <sup>#</sup>

**Note:** <sup>#</sup>Indicates  $p < 0.05$  for comparison between the two groups.

hemostatic effect. Findings from prior research has demonstrated that tranexamic acid can significantly reduce blood loss during liver resection.<sup>10,24</sup> In a systematic review, it was found that tranexamic acid partially inhibits fibrinolysis at concentrations ranging from 5 to 10mg/L, and it effectively inhibits fibrinolysis at concentrations ranging from 10 to 15mg/L.<sup>25</sup>

In our study, we administered tranexamic acid intravenously in group T at a loading dose of 10 mg/kg immediately following AHN. Subsequently, tranexamic acid was continuously administered at a rate of 1 mg/kg/h until the procedure concluded. This dosing regimen aligns with the recommended prophylactic administration of tranexamic acid. Comparing the coagulation function between the two groups, we observed differences. According to the TEG results obtained after liver resection, the MA value of TEG in Group T was notably higher compared to Group A ( $55.91 \pm 7.97$ mm in Group T vs  $45.88 \pm 19.79$  mm in Group A, with a significance of  $P < 0.05$ ). This discrepancy may be attributed to the use of TXA in Group T, which reduces fibrinolysis within formed blood clots.

Additionally, when measuring whole blood with TEG, Group T experienced reduced blood loss, with fewer losses of clotting factors and higher blood cell and hemoglobin levels, resulting in stronger clot intensity. Towards the end of the operation, both groups exhibited similar trends in their hemostasis tests. In comparison to pre-operation values, both groups displayed simultaneous elongation of R value, a decrease in  $\alpha$  angle, a reduction in MA value, and an increase in Ly30. D-dimer showed a slight increase, FDPs increased slightly, and fibrinogen slightly decreased. These changes remained within the range of normal values without clinical significance.

Notably, APTT in Group T was  $38.04 \pm 3.59$  s, which was shorter than the  $41.49 \pm 5.18$  s in Group A ( $t = -2.119$ ,  $P < 0.05$ ). It is possible that neither ANH nor the blood loss from hepatectomy triggered hyperfibrinolysis, and the dose of TXA administered may not have been sufficient to inhibit fibrinolysis significantly.

However, our study had limitations. Thrombin antithrombin complex (TAT) and plasmin- $\alpha$ 2-antiplasmin complex (PAP) were not determined, and sensitive and specific markers such as thrombomodulin and tissue-type plasminogen activator-inhibitor-1 complex (tPAI. C) were not used to assess the clotting status. Additionally, the concentration and activity of clotting factors were not measured. Monitoring TXA concentration in blood in conjunction with clinical conditions may be necessary for future research. In our research, we utilized a 130/0.4 hydroxyethyl starch solution as the diluent for ANH, and it is worth noting that this solution has the potential to impede platelet function. Findings from prior studies have demonstrated that tranexamic acid can enhance platelet function in patients, regardless of whether they are undergoing antiplatelet therapy.<sup>26,27</sup> Additionally, tranexamic acid not only has the capacity to inhibit fibrinolysis in individuals with chronic renal failure but also to ameliorate platelet function in such patients.<sup>28</sup>

It is important to mention that the MA value of 80% is indicative of platelet function, whereas approximately 20% of MA pertains to fibrin function.<sup>29,30</sup> In cases where there is no clear evidence of substantial hyperfibrinolysis and fibrinolysis inhibition, it is plausible to hypothesize that tranexamic acid might enhance platelet function, thereby contributing to the stability of already formed blood clots. Nonetheless, further investigations are necessary to validate this hypothesis. Existing research suggests that low CVP, ANH, and TXA are all risk factors that may compromise kidney function.<sup>31-33</sup> In order to better protect the patients, we set the maximum limit for high CVP at 5 mmHg, a reduced loading dose of TXA of 10 mg/kg, a lower maintenance dose of TXA of 1 mg/kg per hour, a higher target hemoglobin value of ANH at 100 g/L, and a MAP of greater than 65 mmHg. According to an animal study, the myocardium, brain, and spinal cord are able to maintain oxygen supply during ANH as the heart index rises and peripheral vascular resistance falls, but renal oxygen supply starts to decline at an HCT of 30% and is only 25% of the baseline value at an HCT of 10%.<sup>32,34</sup> Patients who were administered high-dose TXA [at a loading dose of 100 mg/kg and a maintenance dose of 10 mg/kg per hour] and had normal kidney function did not have substantial renal impairment.<sup>35</sup> This aligns with our results indicating that individuals in both cohorts exhibited no indications of clinical or laboratory-related acute or chronic kidney dysfunction within 48 hours following the surgical procedure and throughout their stay in the postoperative care unit.

## Conclusion

In summary, the combined utilization of low-dose TXA and ANH appears to offer potential benefits for patients undergoing open hepatectomy surgery. These potential advantages encompass diminished blood loss, stabilized clotting

and coagulation functions, and the absence of adverse effects on renal function. To validate and further substantiate these findings, additional randomized double-blind studies are warranted to ensure the robustness and precision of these results.

## Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

## Ethics Approval and Consent to Participate

I confirm that I have read the Editorial Policy pages. This study was conducted with approval from the Ethics Committee of Second Affiliated Hospital of Kunming Medical University. This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from all participants.

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## Disclosure

The authors declare that they have no competing interests.

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