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The efficacy of aggressive warming combined with tranexamic acid during total hip arthroplasty: a single-center retrospective study from southern China

F.-L. LI[1], Y. HUANG[2], X. HUANG[1], B.-F. MO[2], W.-H. LIU[1], W.-W. HUANG[1], D. YIN[1]

[1]Department of Joint Surgery and Sports Medicine, [2]Department of Trauma, Microscopy and Hand Surgery, The People's Hospital of Guangxi Zhuang Autonomous Region, Guangxi Province, China

Abstract. – OBJECTIVE: The aim of the study was to evaluate the efficacy of aggressive warming combined with tranexamic acid (TXA) during total hip arthroplasty (THA).

PATIENTS AND METHODS: A total of 832 patients who underwent THA from October 2013 to June 2019 were divided into three groups according to the order of admission. There were 210 patients from October 2013 to March 2015 in group A, 302 patients from April 2015 to April 2017 in group B, and 320 patients from May 2017 to June 2019 in group C. Group A was the control group and was not given any measures. Group B was administered intravenously with 15 mg/kg TXA before skin incision and 3 h later without aggressive warming. Group C was administered intravenously with 15 mg/kg TXA before skin incision and 3 h later with aggressive warming. We evaluated the differences in the intraoperative blood loss, changes in core body temperature of patients at different stages during the operation, postoperative drainage, hidden blood loss, transfusion rate, drop of hemoglobin (Hb) on postoperative day 1 (POD1), prothrombin time (PT) of POD1, average hospitalization day, and complications.

RESULTS: There were statistically significant differences among the three groups during the intraoperative blood loss, intraoperative changes in core body temperature, postoperative drainage, hidden blood loss, blood transfusion rate, drop of Hb on POD1 and average hospital stay ($p<0.05$). There was no statistical difference in PT on POD1 and the incidence of complications ($p>0.05$).

CONCLUSIONS: Aggressive warming combined with TXA can significantly reduce the blood loss and transfusion rate of THA, and accelerate the recovery. We also observed that it does not increase the postoperative complications.

Key Words:
Aggressive warming, Tranexamic acid, Total hip arthroplasty.

Introduction

Total hip arthroplasty (THA) often requires extensive stripping of soft tissues, and large surgical wounds cause much blood loss during the perioperative period. Normally, excessive blood loss affects patients' postoperative recovery increases the length of hospital stay and hospitalization costs and may also increase the risk of serious complications, such as postoperative infections[1]. Therefore, it is important to take effective measures to reduce blood loss and accelerate recovery during the perioperative period of THA. Tranexamic acid (TXA) is a synthetic anti-fibrinolytic drug, and some of reports[2-5] have shown that it has a significant hemostatic effect in THA and total knee arthroplasty (TKA) without increasing the incidence of thrombotic complications. However, there are few studies[4] on the hemostatic effect of TXA combined with aggressive warming. Hypothermia is a common problem that we easily ignore during the perioperative period. The literature[6] reports that the incidence of hypothermia is as high as 60%. The low temperature environment of the operating room and various anesthesia and surgical operations can easily lead to hypothermia[6]. The studies[6,7] pointed out that even mild hypothermia could cause a serious series of problems, such as increasing the risk of postoperative wound infection, prolonging the resuscitation after anesthesia, slowing the speed of postoperative recovery, and increasing the amount of bleeding in patients. However, there are few studies[6] on the hemostatic effect of TXA combined with aggressive warming. The purpose of this study was to evaluate the efficacy of thermal intervention combined with TXA during the perioperative period of THA.

Corresponding Author: Dong Yin, MD; e-mail: yindong@cug.edu.cn

Patients and Methods

There were 846 patients, of whom 8 were not eligible and 4 declined to participate (Figure 1), including 520 male patients and 312 female patients. Patients who received THA from October 2013 to June 2019 were divided into three groups according to the order of admission. There were 210 patients from October 2013 to March 2015 in group A, 302 patients from April 2015 to April 2017 in group B, and 302 patients from May 2017 to June 2019 in group C. Among them, in group A there were 131 males and 79 females, aging from 28 to 76 years, with an average age of (61.71±7.81) years. There were 106 cases of aseptic necrosis of the femoral head (ANF), 50 cases of osteoarthritis (OA), and 33 cases of development dysplasia hip (DDH), 16 cases of femoral neck fracture (FNF) and 5 cases of rheumatoid arthritis (RA). Group B were 190 males and 112 females, aging from 46 to 78 years, with an average of (62.66±7.45) years, and 147 cases of which were ANF, 75 cases were OA, 47 cases were DDH, 27 cases were FNF, and 6 cases were RA. Group C were 203 males and 117 females, aging from 23 to 77 years, with an average age of (62.66±7.68) years. Among them, 172 were ANF, 77 OA, 35 DDH, 28 FNF and 8 RA.

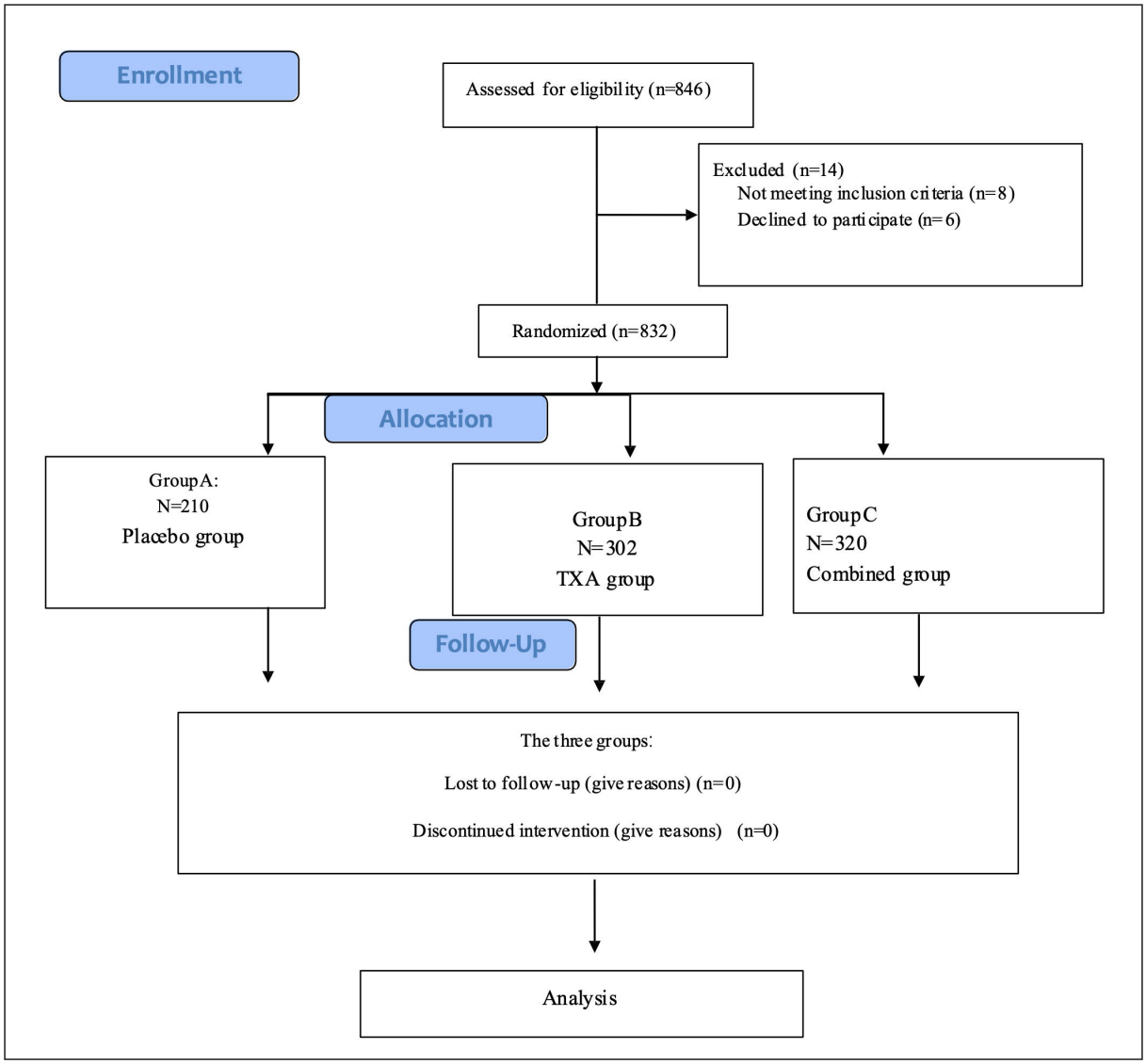

Figure 1. The CONSORT 2010 flow diagram.

Inclusion Criteria

We included in the study the patients who underwent primary unilateral THA.

Exclusion Criteria

The exclusion criteria were: 1) total hip revision or bilateral THA; 2) severe liver and kidney damage and coagulopathy; 3) hematological disease; 4) preoperative Hb below 90 g/L; 5) use of anticoagulants past 1w.

All operations were performed by the same group of senior physicians. As the control group, the group A had no TXA or thermal intervention. Group B was given 15 mg /kg TXA for reoperation, 3 h after operation, without any thermal intervention. Group C was given thermal intervention based on group B. All patients were given anticoagulant therapy (low molecular weight heparin sodium, 3,500 IU, subcutaneous injection) 8 hours after surgery. 10 mg rivaroxaban were given at discharge, until 35 days after surgery.

Aggressive Warming Methods

Axillary temperature measurement was used to observe the patient's body temperature change. Anesthesiologists and circuit nurses assisted to record the temperature changes of the three groups before surgery and at various time periods after anesthesia started. Aggressive warming measures include controllable electric heating blankets, infusion heating, and operating room temperature control (24°C). During the operation, the temperature of the controllable thermal blanket and the infusion were adjusted according to the changes of the patient's body core temperature, and the temperature should be kept above 36°C.

After returning to the ward, routine ankle pump, functional exercises and limb barometric therapy were used to prevent deep vein thrombosis (DVT). The drainage tubes were removed within 48 hours post operation, and abduction-free functional training was performed. Parecoxib and sequential celecoxib were served as perioperative analgesia drugs.

Statistical indicators: Armpit temperature (preoperative 30 mins, 60 mins, 90 mins after anesthesia, end of surgery), intraoperative blood loss, postoperative drainage, hidden blood loss, average hospitalization day, drop of hemoglobin (Hb) and prothrombin time (PT) on postoperative day1 (POD1), the incidence of venous thrombus (VTE) before discharge and the hidden blood loss were calculated according to Nadler et al[8].

Statistical Analysis

Sample size calculations were analyzed by PASS 2011 (NCSS, LLC. Kaysville, UT, USA; available at https://www.ncss.com/software/pass/) software, based on the analysis of variance. All data were analyzed by SPSS 22.0 (IBM Corp., Armonk, NY, USA; available at https://www.ibm.com/analytics/spss-statistics-software) and Pearson's Chi-square test or Fisher exact test were used to analyze qualitative comparative data; $p<0.05$ was considered statistically significant.

Results

Baseline Data (Table I)

There were no significant differences in age, sex, body mass index (BMI), etiology, preoperative Hb, and PT among the three groups ($p>0.05$). The temperature of the three groups is shown in Figure 2.

Table I. Comparison of baseline data.

Baseline data		A (n=210)	B (n=302)	C (n=320)	p
Gender	M	131	190	203	0.97
	F	79	112	117	
Years		61.71±7.81	62.66±7.45	62.66±7.68	0.30
BMI (kg/m^2)		25.37±3.18	25.22±3.20	25.31±3.15	0.86
	ANF	106	147	172	
	OA	50	75	77	
Etiology	DDH	33	47	35	0.81
	FNF	16	27	28	
	RA	5	6	8	
Hb (g/L)		125.16±7.92	125.05±7.61	124.51±7.67	0.56
PT (s)		13.02±0.46	13.06±0.48	13.08±0.51	0.44

BMI: body mass index, Hb: hemoglobin, PT: prothrombin time.

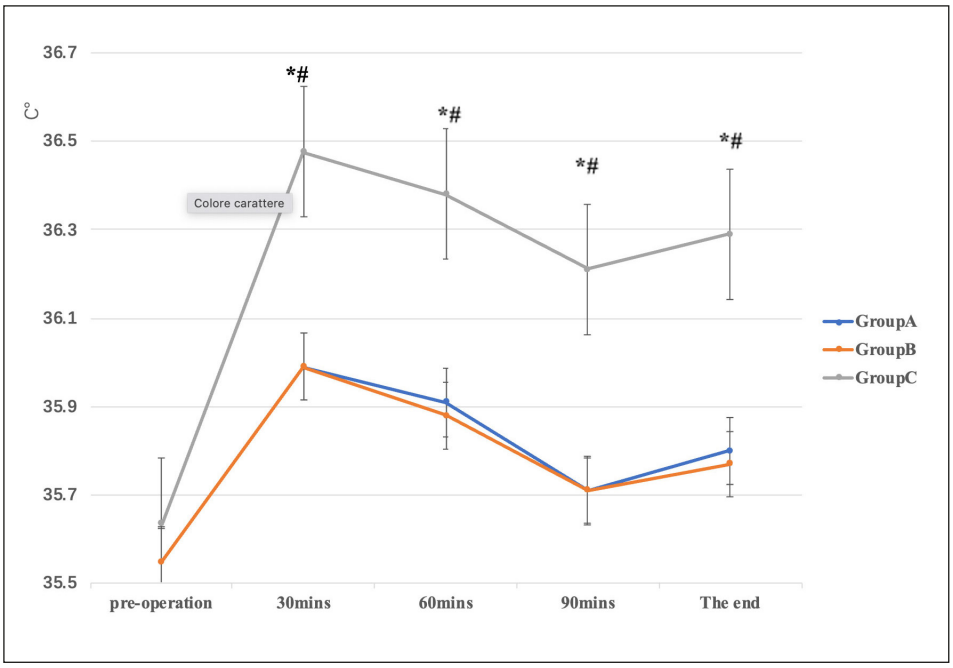

Figure 2. The comparison of various temperatures at different stages among the three groups. The One-way ANOVA was performed to detect the difference among the groups. *: A *vs.* C $p<0.05$; #: B *vs.* C, $p<0.05$.

Temperature at different stages

There was no significant difference in the preoperative temperature among the three groups (F=0.35, $p>0.05$).

The difference in temperatures of the three patients' groups under anesthesia for 30 mins, 60 mins, 90 mins, and at the end of the operation was statistically significant ($p<0.05$). Among them, group C was (36.47±0.25)°C, (36.38±0.22)°C, (36.29±0.21)°C, and (36.21±0.19)°C under anesthesia at 30 mins, 60 mins, 90 mins, and at the end of the operation, which were significantly higher than those in group A and B, and the differences were statistically significant ($p<0.05$). There was no significant difference in temperature between groups A and B at different stages of surgery ($p>0.05$).

Comparison of Various Data of the Three Groups

Intraoperative blood loss (IBL)

The difference in intraoperative blood loss among the three groups was statistically significant (F=105.63, $p=0.00$). Among them, the intraoperative blood loss was the highest in group A, which was (354.70±48.70) mL, and that was significantly higher than group B [(311.89±54.50) ml] and group C [(282.22±61.97) ml]; the comparison was statistically significant ($p<0.05$) (Figure 3).

Postoperative drainage volume (PDV)

The difference in postoperative drainage volume among the three groups was statistically significant (F=8.94, $p=0.00$). Specifically, the postoperative drainage volume of the group A [(464.09±66.78) mL] was the highest, which was significantly higher than the group B [(445.97±57.77) ml] and group C [(441.29±63.50) ml]; the difference was statistically significant ($p<0.05$), but the difference between group B and C was not statistically significant ($p>0.05$) (Figure 3).

Hidden blood loss (HBL)

The differences in hidden blood loss among the three groups were statistically significant (F=55.66, $p=0.00$). Specifically, the hidden blood loss of patients in group A [(360.25±48.84) mL] was the highest, which was significantly higher than group B [(324.12±49.94) ml] and group C [(308.98±63.11) ml]; the difference was statistically significant ($p<0.05$). Besides, the difference between the three groups of patients was also statistically significant ($p<0.05$) (Figure 3).

Drop of Hb

The drop of Hb on POD1 was significantly different among the three groups (F=63.08, $p=0.00$). Among them, the POD1 of Hb drop after operation in group A was the highest [(32.98±8.55) g/L], being significantly higher than group B

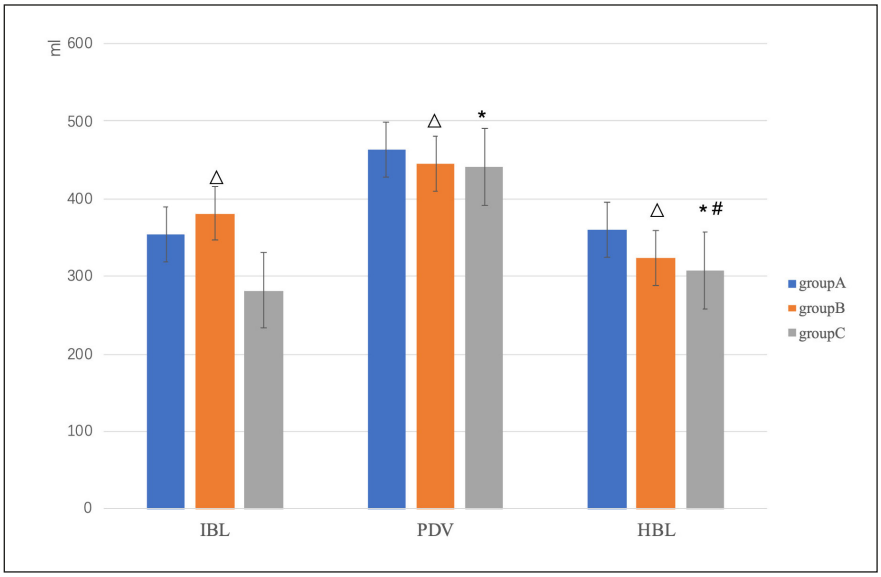

Figure 3. The comparison of various blood loss volumes among the three groups. The One-way ANOVA was performed to detect the difference among the groups. Δ: A *vs.* B, $p<0.05$; *A *vs.* C, $p<0.05$; #: B *vs.* C, $p<0.05$.
IBL: intraoperative blood loss; PDV: Postoperative drainage volume; HBL: Hidden blood loss.

[(30.13±6.08) g/L] and group C [(26.80±4.48) g/L]; the difference was statistically significant ($p<0.05$). Besides, the comparison among the three groups of patients was also statistically significant ($p<0.05$) (Figure 4).

PT on POD1

There was no significant difference in PT among the three groups ($p>0.05$) (Table II).

Blood transfusion rate

The difference of blood transfusion rate of the three groups was statistically significant ($^2=6.91$, $p=0.032$). Among them, the blood transfusion rate of group A was 10.48% (22/210), which was significantly higher than that of group C [4.69% (15/320)]; the difference was statistically significant ($p<0.05$), which was also higher than group B [6.29% (19/302)], but the difference was not statistically significant ($p=0.063$). The transfusion rate of group C was lower than that of group B, but the difference was not statistically significant ($p=0.424$) (Table II).

Average hospitalization days (AHDs)

The differences between the average hospitalization days in the three groups were statistically significant (F=6.78, $p=0.01$). Among them, the

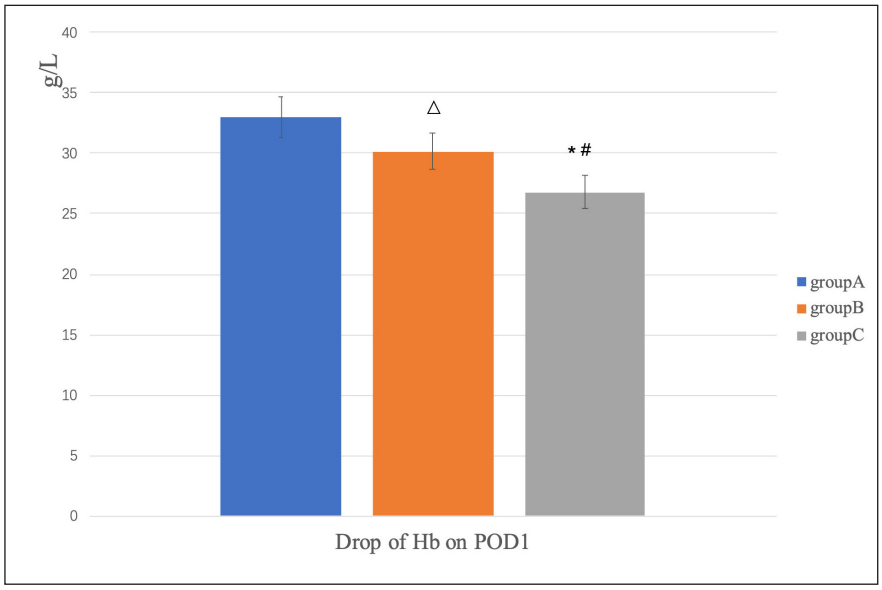

Figure 4. The comparison of the drop of Hb on POD1 among the three groups. The One-way ANOVA was performed to detect the difference among the groups. Δ: A *vs.* B, $p<0.05$; *: A *vs.* C, $p<0.05$; #: B *vs.* C, $p<0.05$.
POD1: Postoperative Day1.

Table II. Comparison of various data.

	Group A (n=210)	Group B (n=302)	Group C (n=320)	*p*	*p*AB	*p*AC	*p*BC
PT on POD1 (s)	13.27±0.67	13.29±0.70	13.20±0.64	0.25	0.67	0.30	0.10
Transfusion	22	19	15				
No transfusion	188	283	305	0.032	0.063	0.009	0.42
Transfusion rate	10.48%	6.29%	4.69%				
AHDs	11.92±4.99	11.14±4.93	10.38±4.44	0.01	0.07	0.00	0.04

AHD: average hospitalization days, PT: prothrombin time, POD1: postoperative Day 1.

average hospitalization day of group C was the shortest [(10.38±4.44) d], which was significantly lower than that of group A [(11.92±4.99) d] and B group [(11.14±4.93) d]; the difference was statistically significant ($p<0.05$), but the difference between the A and B was not statistically significant ($p>0.05$) (Table II).

Comparison of complications (Table III)

There was no significant difference of complications among the three groups ($p>0.05$). The incidence of VTE was little difference among the three groups and there was not any PE. The incision complications of group A were 4.28% (9/210), mildly higher than group B [3.00% (9/302)] and group C [2.5% (8/320)], but the difference was not statistically significant ($p>0.05$).

Discussion

THA is one of the most effective treatments for the end of the hip, which can effectively improve the hip function and improve the patients' quality of life. ANF is the most common reason for THA, which is usually related to hormone or alcohol abuse. Blood interruptions in the femoral head, such as intravascular embolization and extravascular compression, are the most commonly recognized mechanisms[9]. In modern times, the pathogenesis theory of abnormal lipid metabolism in vascular coagulation, audiogenic differentiation, apoptosis, autophagy, osteoporosis, and gene polymorphism, have been supported by a wide scientific basis[10]. However, none of the mechanisms has been approved with the consensus of most scholars so far.

It is well known[1] that blood is a natural resource with very poor regenerative capacity. With the development of surgical technology, there are more and more difficult, complex and traumatic surgical operations[11]. Large blood loss and high transfusion rate during THA are the concerns of most joint surgeons, and the risk of infection will increase because of blood transfusions. Therefore, we are working to improve our strategy to further reduce blood loss and the incidence of allogeneic blood transfusions[14]. The studies[15-17] point out that TXA is an effective drug in reducing blood loss and allogeneic blood transfusion during THA perioperative period and does not increase the risk of thrombosis in patients after surgery, which has become an important strategy for blood protection of joint replacement. Our study confirmed the results of previous studies[16] and proved a favorable effect on TXA. Besides, TXA could reduce blood loss and blood transfusion rate.

Table III. Comparison of complications.

		Group A (n=210)	Group B (n=302)	Group C (n=320)	*p*	*p*AB	*p*AC	*p*BC
VTE	ITE	6	7	7	0.88	0.70	0.62	0.92
	DVT	2	1	2	0.67	0.37	0.63	0.64
Complications	Fat liquefaction	2	3	1				
	Thrum reaction	2	1	2	0.54	0.41	0.28	0.77
	Infection	3	2	2				
	Others	2	3	2				

IVT: Intermuscular venous thrombosis, DVT: deep vein thrombosis.

The low temperature environment of the operating room and various anesthesia, infusion, and surgical operations can easily lead to hypothermia[18,19]. Regarding perioperative hypothermia, there is no clear definition. Usually, the core body temperature after anesthesia is between 32°C and 36°C. The incidence of hypothermia is also rarely reported, and varies widely, ranging from 20% to 74%[20-22]. Hypothermia often leads to coagulopathy, which reduces the enzymatic kinetic activity of prothrombin, affects the morphology and function of platelets, damages platelet aggregation, inhibits the coagulation cascade, reduces the activity of coagulation substances, the activation of fibrinolytic system, blood viscosity and blood loss during surgery. Even mild hypothermia (reducing core temperature <1°C) may increase blood loss during surgery and increase the risk of periprosthetic joint infection(PJI)[23,24]. Besides, the research pointed out that hypothermia may lead to aggravation of coagulation disorders, and the degree of hypothermia is closely related to mortality[25,26]. We maintained the normal temperature range by adjusting the room temperature, warming blanket and infusion heating devices during the perioperative period. *In vitro* experiments have found that hypothermia can inhibit the activity of platelets, coagulation factors, and thrombin, affecting the generation of blood thrombin over 40%, which may cause increased blood loss[27-29]. Rajagopalan et al[18] also found that even mild hypothermia (reducing core body temperature <1°C) could increase intraoperative blood loss up to 16%, and the relative risk of intraoperative blood transfusion increased up to 22%. The greatest temperature reduction usually occurs within 40-60 minutes after surgery. Inhalation of gas (such as isoflurane, sevoflurane, or nitrous oxide) or the use of intravenous anesthesia inducers (such as propofol or opioids) can cause peripheral vasodilation and lead to core temperature shifting to the periphery, which causes to dropping of the temperature rapidly compared to induction of anesthesia. In addition, the effect related to induction of anesthesia is usually unavoidable[30,31]. Therefore, it is particularly important to maintain the temperature within the normal range by adjusting the room temperature, using temperature changing blankets or infusion heaters, and reduce the risk of blood loss and transfusion during the operation.

Generally, it is believed that the important indicators for evaluating the effect of thermal intervention combined with TXA are blood loss and transfusion rate. In this study, the differences in blood loss, postoperative drainage, hidden blood loss, drop of Hb on POD1, and transfusion rate among the three groups of patients were calculated. For the application of TXA, many efforts have been made by predecessors. Many scholars[32-34] have confirmed that TXA can effectively reduce blood loss during the perioperative period of joint replacement without increasing complications, such as DVT or PE. Reina et al[35] observed that 941 cases underwent THA in a prospective case study to investigate the effects of mild hypothermia on TXA and record blood transfusions and complications. Studies[35] have shown that the incidence of hypothermia in THA is as high as 84.2%, and mild hypothermia does not affect the effect of TXA, which can effectively reduce perioperative blood loss and blood transfusion rate. Compared with groups A and B in this study, intraoperative blood loss, postoperative drainage volume, hidden blood loss and blood transfusion rate were also reached similar conclusions. However, Reina[35] also showed that mild hypothermia would not increase the blood loss of THA, which was contrary to the conclusion of this study. The author believes that the concept of mild hypothermia has not been clearly clarified in that study, and there are whether significant differences between groups in the temperature of different cases have not been statistically referred, which needs further research to confirm. Schmied et al[36] conducted a prospective controlled trial about 60 patients under unilateral THA, divided into a normal temperature group [core temperature (36.6±0.4)°C] and mild hypothermia group [core temperature (35.0±0.5)°C], and the intraoperative blood loss was (1.7LVS2.2L), postoperative drainage volume was (0.3LVS0.5L), and mild hypothermia increased blood loss up to 500 ml, which was statistically significant difference (p<0.001). Thus, it was confirmed that maintaining normal temperature during surgery could reduce blood loss and transfusion rate in THA and further explain the adverse consequences of hypothermia during THA. Winkler et al[37] studied the changes of core temperature, blood transfusion rate, and length of hospital stay about 143,157 patients during THA. The study found that the core temperature decreased during the first hour and then increased. In the first hour, the average minimum core temperature was (35.7±0.6)°C. 64% of patients had a core temperature threshold below 36°C after induction and 29% reached the core temperature threshold below 35.5°C. Besides, nearly half of the patients had a low core temperature below 36°C and 20%

of patients had a core temperature below 35.5°C for more than 1 hour. 20% of patients had a core temperature below 36°C for more than 2 hours, and 8% of which had a core temperature below 35.5°C for more than 2 hours. Hypothermia is normal during the first hour of anesthesia even with high body temperature, which confirms that hypothermia may increase the transfusion rate, and aggressive warming can reduce the blood loss of THA and reduce complications. Steelman et al[38] reached similar conclusions. Compared to the previous ones, this study not only confirms the efficacy of TXA, but also the efficacy of thermal intervention. In our study, group A was considered as the blank group, and group B was administered intravenously with 15 mg/kg TXA. The intraoperative blood loss, postoperative drainage volume, hidden blood loss, and drop of Hb on POD1 after operation were (360.25±48.84) ml *vs.* (311.89±54.50) ml, (464.09±66.78) ml *vs.* (445.97±57.77) ml, (360.25±48.84) ml *vs.* (324.12±49.94) ml, (32.98±8.55) g/L *vs.* (30.13±6.08) g/L. The differences between them were statistically significant ($p<0.05$), but there was no statistical difference between the two groups in terms of postoperative coagulation function ($p>0.05$). Besides, the effect of thermal intervention could be confirmed by analyzing groups B and C. The intraoperative blood loss, postoperative drainage volume, hidden blood loss, drop of Hb on POD1 and average hospitalization days of group C were (282.22±61.97) ml, (441.29±63.50) ml, (308.98±63.11) ml, (26.80±4.48) g/L and (10.38±4.44) d, which were statistically significant when compared to group B ($p<0.05$). Besides, the transfusion rate of group C was 4.69% (15/320), while it was 10.48% (22/210) in group A. The difference was statistically significant ($p<0.05$), confirming that the effect of thermal intervention combined with TXA could reduce the blood loss of THA, the transfusion rate and the complications caused by transfusion, shorten the average hospital stay, and accelerate recovery after surgery. However, there was no statistical difference in postoperative drainage between groups B and C ($p>0.05$), which raised the following question: Is the TXA sufficient after surgery?

There was no significant difference in the incidence of perioperative DVT or PE among the three groups in this study ($p>0.05$), which is the same result of previous studies[32-34,39], further confirming the safety of TXA. Many previous studies[24,25,38,39] have pointed out that hypothermia in THA increases the risk of PJI. Among the three groups, the incidence of postoperative incisional infection in group C was 0.63% (2/320), which was mildly higher than group B [0.66% (2/302)] and group A [1.43% (3/210)], but there was no statistical significance ($p>0.05$), being consistent with the results of Deren et al[40]. We still believe that hypothermia may increase the risk of postoperative infection. We considered that the difference was mainly caused by the poor cases and the little incidence of PJI in this study.

It should be noted that some studies[41-43] have pointed out that forced air heating systems might interfere with laminar airflow in the operating room and increase the risk of infection. In addition, Moretti et al[44] clearly emphasized that maintaining normal temperature during the perioperative period of THA will increase the number of bacteria per unit volume, but the active heating system does not increase the risk of incision infection, which should be vigilant.

Conclusions

In summary, this study confirms that aggressive warming combined with TXA can significantly reduce blood loss, transfusion rate, accelerate postoperative recovery, and shorten the average hospital stay during THA, which is a reliable and worthy technique.

Clinical Trial Registration

Clinical trial registration number: ChiCTR2000034377; date of registration: 4/7/2020.

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Authors' Contributions

Fulin Li performed the data collection and analysis and participated in manuscript writing. Yu Huang, Xiao Huang, Bingfeng Mo, Wenhui Liu, Wenwen Huang performed the database setup and statistical analysis. Dong Yin performed the operations and participated in the study design and coordination and helped to draft the manuscript. All authors have read and approved the final manuscript.

Conflict of Interests

The authors declare that they have no competing interests.

Ethics Approval

We confirmed that all experimental protocols were approved by the the Medical Ethics Committee of the Guangxi Zhuang Autonomous Region People's Hospital. All methods were carried out in accordance with the relevant guidelines and regulations in the manuscript.

Informed Consent

The informed consent was obtained from our responsible Investigational Ethics Review Board and all patients agreed to be included in the study and signed informed consent.

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