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Original article

The effects of efficacy of tranexamic acid on postoperative erythrocyte, ALT, AST and FDP

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ABSTRACT

Objective: The study aims at discussing the clinical efficacy of tranexamic acid in knee arthroplasty and its effects on erythrocyte, ALT (alanine aminotransferase), AST (aspartate aminotransferase) and FDP (fibrinogen degradation product) after the operation.
Method: Totally, 94 patients who underwent knee arthroplasty in our hospital from June 2015 to June 2017 were randomly divided into the control group and the observation group, with 47 patients, respectively. The patients in the observation group were given tranexamic acid at a dose of 15 mg/kg dissolved in 100 mL normal saline before knee replacement, while those in the control group were given 100 mL normal saline. The dominant blood loss, recessive blood loss, total blood loss, intraoperative blood loss and the drainage, blood transfusion and blood transfusion rate 24 h in postoperative were counted and observed in both groups, and then the differences of HCT (hematocrit), Hb (hemoglobin), ALT, AST and FDP before and 4d after the operation in two groups were compared, to research and analyze the clinical efficacy of tranexamic acid in knee arthroplasty and its effects on erythrocyte, ALT, AST and FDP after the operation.
Results: Firstly, the total blood loss, dominant blood loss, recessive blood loss, intraoperative blood loss, postoperative blood flow, blood transfusion volume and blood transfusion rate in the observation group were lower than those in the control group ($P < 0.01$). Secondly, the Hb and HCT of the observation group were significantly lower than those of the control group ($P < 0.01$). Thirdly, ALT, AST and FDP in the two groups were higher than those before operation ($P < 0.01$). There was no significant difference in ALT, AST and FDP between the observation group and the control group ($P > 0.05$).
Conclusion: The application of tranexamic acid before knee arthroplasty can reduce intraoperative and postoperative blood loss, and do not affect the coagulation function and liver function of patients, and has high drug safety.

1. Introduction

When knee deformity, injury, osteoarthritis and so on are treated, the knee arthroplasty is the most important measurement method at present (Han et al., 2016). The knee joint is the big joint of human body, with good blood supply, and the operation must go through osteotomy, filing, reaming, osteophyte cleaning, with great trauma. Therefore, the perioperative blood loss of knee replacement surgery is greater than that of general surgery. During the operation, separation of soft tissue, increase of operation time, resection of bone tissue and so on may increase blood loss of the patient, push up possibilities of postoperative anemia and bacterial infection, augment the risk of operation success and affect normal recovery of the patient after the operation (Bendtsen et al., 2016). In the studies on knee arthroplasty, one of major directions concerned by the clinicians is how to decrease blood loss of the patient during and after the operation and some studies have counted that operational blood loss is 1500 mL (Pinsornsak et al., 2016).

As a lysine synthesis derivative, carbamic acid can competitively bind to plasminogen, reducing the degradation rate of fibrin, but not the synthesis rate of fibrin. The combination of tranexamic

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acid and the fibrinolytic enzyme can reduce the decomposition of fibrin so that the hemostatic effect of fibrin and thrombin complex can be fully exerted. As an antifibrinolytic agent, the safety and effectiveness of tranexamic acid in knee arthroplasty have been paid more and more attention. After intravenous injection before operation, it can affect the hyperfibrinolysis in the whole body. It can not only reduce the amount of dominant bleeding during the operation, but also reduce the amount of recessive bleeding after the operation. At present, some studies have demonstrated that tranexamic acid can reduce intraoperative blood loss during knee arthroplasty (Tsukada et al., 2019), but there are few studies for the effect of tranexamic acid on blood coagulation and liver functions after the operation. In this dissertation, the patients treated by knee arthroplasty in our hospital from June 2015 to June 2017 were taken as the subjects to carry out research and analysis of tranexamic acid, of which main research contents are as follows.

2. Materials and methods

2.1. Subjects

Totally, 94 patients who underwent knee arthroplasty in our hospital from June 2015 to June 2017 were randomly divided into a control group and an observation group, with 47 patients, respectively: Control Group: totally 47 cases, including 23 males and 24 females, with age range of 39–47 and mean age of 43.22 ± 2.97, height range of 155–178 cm and mean height of 160 ± 4.86 cm, and weight range of 48–71 kg and mean weight of 66.31 ± 7.06 k g; Observation Group: totally 47 cases, including 25 males and 22 females, with age range of 38–48 and mean age of 43.71 ± 3.0 1, height range of 156–179 cm and mean height of 161 ± 4.77 cm, and weight range of 49–73 kg and mean weight of 68.03 ± 6.87 kg. For the patients of both groups, there is no significant difference ($P > 0.05$) in weight, height, age, hemoglobin content, hematocrit, alanine aminotransferase, aspartate aminotransferase, and fibrinogen degradation product.

Inclusion standard: Firstly, the patient underwent unilateral knee replacement for the first time. Secondly, the preoperative diagnosis was in line with the standard of knee arthroplasty (Gan et al., 2016), i.e. it was considered that there was primary knee arthritis. Thirdly, HCT, Hb, platelet, and coagulation were all at a normal level. Fourthly, there was no clear venous thrombus in the patients who had routine examination before operation. Among them, the diagnosis standard of primary knee arthritis referred to the diagnosis standard of knee arthritis specified in the guidelines for diagnosis and treatment of osteoarthritis. Firstly, the patient had recurrent knee pain within one month. Secondly, the erythrocyte sedimentation rate was less than 20 mm/1 h. Thirdly, the line showed that the patient's acetabulum margin was hyperplasia or osteophyte formation. Fourthly, the X-ray showed that the patient's knee joint space became narrow. The diagnosis of knee arthritis did not need to meet the four criteria. When the patient had 1, 2 and met any of the criteria in 3, 4, it could be diagnosed as knee arthritis.

Exclusion standard: the patients are sensitive to tranexamic acid or cannot normally discharge tranexamic acid, and suffer from anemia; poor anticoagulation system; poor hematogenesis; damaged liver functions; thrombus or gangrene disease; immune or contagious diseases (Tille et al., 2019).

Shedding and exclusion criteria: firstly, the patients did not take the medicine according to the prescribed time or were forced to terminate the treatment due to the unexpected circumstances. Secondly, the patients had serious adverse reactions in the clinical trial treatment process, and could not continue to accept the trial. Thirdly, the lack of patient data affected the results of the study.

3. Research method

Operation procedure of knee joint replacement: general anesthesia was used for all patients. The anterior and middle incision of the knee joint was used in the operation. The soft tissue was removed and the osteotomy was performed in the total knee arthroplasty.

No patellar replacement was performed in all patients, but the extra bone around the patella was removed by using bone nipping forceps. The obvious bleeding points around the knee joint wound were hemostasis with an electric knife, and the peripheral patella was treated with electric coagulation and cauterization. Before the operation, blood was collected from the affected limb, and the upper third of the femur was compressed and inflated with an electric airbag tourniquet to stop bleeding. After osteotomy, the wounds were washed with high-pressure pulse gun. The bone cement type total knee joint replacement material was placed properly. Before the bone cement hardened, it was necessary to remove the excess bone cement overflowed by extrusion and treat the obvious bleeding points with the electric knife again. When the degree of hardening of bone cement was satisfied, the wound needed to be rinsed again from the shallow layer to the deep layer, and the diluted iodophor was used to wash the wound. The capsule was carefully sutured and the drainage tube was placed. The incision of outer skin and soft tissue was carefully sutured layer by layer. In order to make the joint cavity have a certain pressure, it was necessary to give dry gauze and bandage and apply appropriate pressure bandage. Finally, it was necessary to cooperate with the anesthesiologist to loosen and remove the tourniquet slowly.

The patients in the two groups were given general nursing such as oxygen inhalation and electrocardiographic monitoring after operation, and were given postoperative nutrition support to maintain the acid-base balance of water and electrolyte. Half an hour before operation and 48 h after operation, the patients were given antibiotics to prevent infection. 12 h after the operation, the patient was given enoxaparin anticoagulation treatment. The drainage was opened 4 h later. The drainage tube should be removed within 24 h. The operation of the control group and the observation group were performed by the same group of doctors. The patients in the observation group were given tranexamic acid (Chinese medicine quasi character H20093031; Xi'an Libang Pharmaceutical Co., Ltd.) in 15 mg/kg and intravenous drip in 100 mL normal saline before knee replacement. In the control group, 100 mL normal saline was infused intravenously. The operation method, postoperative observation, and other treatments were the same in the two groups.

3.1. Test index and evaluation standard

(1) Blood loss: Blood loss was recorded during the perioperative period, which includes dominant blood loss, recessive blood loss, total blood loss and intraoperative blood loss.

Total blood volume = a* height 3 + b* weight + c, male: a = 0.3669; b = 0.03219; c = 0.6041, female: a = 0.3561; b = 0.03308; c = 0.1833 [8]; the height and weight of each patient should be measured and weighed before the operation;

Total blood loss = preoperative total blood volume *(preoperative hematocrit – postoperative hematocrit);

Dominant blood loss = intraoperative blood loss + postoperative drainage;

Recessive blood loss = total blood loss – dominant blood loss – homologous blood transfusion

Intraoperative blood loss = liquid volume in suction apparatus – intra-operative flushing fluid volume – additional net weight of gauze pad weighing

(2) Postoperative drainage and blood transfusion: Record postoperative drainage in postoperative 24 h after drainage tubes are removed from the patients of both groups;

If hematocrit is less than 30% and hemoglobin less than 90 mg/ml in 24 h after the operation, it is required to transfuse blood to the patient [9]. Meanwhile, blood transfusion volumes and the relevant number of patients should be recorded.

(3) Other indices: The peripheral venous blood was taken before and 48 h after operation. The differences of hematocrit (HCT), hemoglobin (Hb), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and fibrinogen degradation product (FDP) before and 4 d after operation between both groups were compared.
(4) Postoperative safety analysis of tranexamic acid: Observe and count healing of operative wounds between both groups, and check whether there is infection, hematoma, gangrene or other conditions and whether there is thrombus.

3.2. Data analysis

Adopt SPSS17.0 to process and analyze experimental data; measurement data are expressed with mean ± standard deviation and analyzed by T-test; enumeration data are expressed by percentage and analyzed by $\chi 2$ test; $P < 0.05$ indicates that the data have a significant difference.

4. Result

4.1. Analysis of blood loss between both groups

It can be seen from Table 1 that preoperative blood volumes of both groups were significantly different, $P > 0.05$. The total blood loss, dominant blood loss, recessive blood loss and intraoperative blood loss of the patients intravenously injected with tranexamic acid before the operation were less than those not injected with tranexamic acid, and the above indices had significant difference ($P < 0.01$) between both groups.

4.2. Analysis of postoperative drainage and blood transfusion between both groups

It can be seen from Table 2 that postoperative drainage, blood transfusion, and blood transfusion rate of the patients intravenously injected with tranexamic acid before the operation were less than those not injected with tranexamic acid, and the above indices had significant difference ($P < 0.01$) between both groups.

4.3. Analysis of other indices before and after operation between both groups

It can be seen from Table 3 that postoperative Hb and HCT of both groups decreased, and there was significant difference ($P < 0.01$) between preoperative Hb and HCT and postoperative ones. In addition, after the operation, Hb and HCT of Observation Group were higher than those of Control Group, and there was a significant difference for Hb and HCT between both groups, $P < 0.01(t = 5.039;\ t = 12.067)$.

It can be seen from Table 4 that postoperative ALT, AST, and FDP of both groups increased, and there was significant difference ($P < 0.01$) for preoperative ALT, AST and FDP, and postoperative ones. After the operation, there was no significant difference for ALT, AST, and FDP between both groups, $P > 0.05(t = 4.693;\ t = 5.098;\ t = 6.013)$.

4.4. Analysis of postoperative safety of tranexamic acid between both groups

Operational incisions of both groups healed up during Stage I and were free of bacterial infection, tissue hematoma or gangrene, or thrombus.

5. Discussion

During the knee arthroplasty before, the tourniquet was mainly used for hemostasis. Although the tourniquet could reduce blood loss of the patient during the operation, yet it stimulated occurrence of fibrinolytic system and accordingly increased postoperative blood loss (Schnettler et al., 2017). The total knee arthroplasty can effectively release knee pain, improve force line of lower limbs, enhance functions of knee joint and greatly advance post-operative living quality of the patient. Some data indicate that (Delanois et al., 2017), a hundred thousand of patients accept total knee arthroplasty every year in the United States of America. In several recent years, clinical total knee arthroplasty has been developed quickly in China and more and more patients have been accepting total knee arthroplasty (Cheng et al., 2009). Although total knee arthroplasty can improve functions of patients' knee joints, intraoperative blood loss is relatively great and deep venous thrombus may be formed easily after the operation (Schmidt-Braekling et al., 2017). Some patients, who have received total knee arthroplasty, should need anemia treatment after the operation. Although blood transfusion can improve anemia, it may increase the onset of blood infectious diseases. Although anticoagulation treatment was adopted during the operation, its clinical effect was limited (Cundy et al., 2017). However, post-operative concealed hemorrhage could not joint in blood circulation of the body. The concealed hemorrhage might account for 50% of total blood loss (Zhaoning et al., 2013). So, if concealed hemorrhage could be reduced effectively, it would be possible to decrease allogeneic blood transfusion, lower stresses and inhibit post-operative Hb decrease of the patients (Sehat et al., 2000). Some studies showed (Maempel et al., 2016) that, after the knee arthroplasty, many patients required blood transfusion. However, blood transfusion might bring other problems. For example, allogeneic blood transfusion might be repulsed by the immune system of the patient (Muñoz et al., 2006a,b, Muñoz et al., 2005). Therefore, in order to improve clinical treatment quality for the patient, it is quite important for find out a drug, which can reduce the risks of intraoperative blood loss and postoperative complications.

Tranexamic acid is a synthetic fibrinolysin inhibitor and a lysine analog (Ng et al., 2015). At present, it has been widely used in various operative treatments. The tranexamic acid mainly inhibits degradation of fibrinogen by lysine bonding points, where plasminogen and plasmin are bonded competitively, so as to decrease fibrinolysin activity, promote blood coagulation and reduce blood loss. In recent years, tranexamic acid was gradually used because the people gradually made much account of recessive blood loss in the process of knee arthroplasty. Some studies have proved that tranexamic acid intravenously injected before the operation can reduce intraoperative and postoperative blood loss, which is identical to the research result of this study. In addition, some relevant studies have demonstrated that clinical risk of tranexamic acid is acceptable (Hunt, 2015; Ramirez et al., 2017), which is also consistent with postoperative safety analysis of tranexamic acid in this paper, namely the patients injected with tranexamic acid have not caught corresponding complications. In a study of bilateral total knee arthroplasty, some scholars discovered that, after tranexamic acid was intravenously injected, the total blood loss decreased and blood transfusion rate decreased (Li and Li, 2017), of which thee changing trend was identical to the research result

Table 1
Analysis of blood loss between both groups.

Indices	Observation Group	Control Group	*t*	*P*
Case	47	47	—	—
Preoperative total blood loss (ml)	19071.071 ± 873.27	18937.97 ± 797.31		>0.05
Total blood loss (ml)	1038.42 ± 89.37	1907.01 ± 90.07	20.071	<0.01
Dominant blood loss (ml)	431.89 ± 47.81	743.37 ± 31.29	8.079	<0.01
Recessive blood loss (ml)	237.41 ± 37.92	439.37 ± 41.07	7.271	<0.01
Intraoperative blood loss (ml)	127.39 ± 13.47	237.21 ± 20.71	5.876	<0.01

Table 2
Analysis of postoperative drainage and blood transfusion between both groups.

Group	Case	postoperative drainage(ml)	blood transfusion (ml)	blood transfusion rate
Observation Group	47	317.47 ± 49.38	377.12 ± 67.98	17.02% (8/47)
Control Group	47	501.43 ± 67.38	678.41 ± 93.38	42.55% (20/47)
$t/\chi 2$	—	7.079	8.099	8.193
P	—	<0.01	<0.01	<0.01

Table 3
Analysis Hb and HCT before and after treatment between both groups.

Group	Case	/	Hb (mg/ml)	HCT (%)
Observation Group	47	Before treatment	137.41 ± 5.37	41.37 ± 2.93
		After treatment	101.93 ± 4.07*	35.71 ± 1.67*
t	—	—	23.197	10.27
P	—	—	<0.01	<0.01
Control Group	47	Before treatment	136.39 ± 5.71	40.93 ± 2.87
		After treatment	94.38 ± 4.77	30.03 ± 1.27
t	—	—	28.319	23.191
P	—	—	<0.01	<0.01

Table 4
Analysis of ALT, AST, and FDP before and after treatment between both groups.

Group	Case	/	ALT(U/L)	AST(U/L)	FDP (μg/ml)
Observation Group	47	Before treatment	17.38 ± 9.87	24.37 ± 5.21	3.67 ± 0.71
		After treatment	22.17 ± 11.78	73.69 ± 23.19	5.63 ± 0.83
t	—	—	5.321	13.287	6.311
P	—	—	<0.01	<0.01	<0.01
Control Group	47	Before treatment	17.61 ± 9.16	22.19 ± 6.01	3.59 ± 0.81
		After treatment	22.31 ± 10.07	69.31 ± 15.38	5.67 ± 1.12
t	—	—	5.098	14.872	6.078
P	—	—	<0.01	<0.01	<0.01

of this paper. The tranexamic acid has a relatively short half-life. Meanwhile, hyperfibrinolysis treatment along with functional training for the patients after total knee arthroplasty can obviously improve the coagulation function and fibrinolytic system of these patients. At present, the pneumatic tourniquet is commonly used during the total knee arthroplasty. It is beneficial to make the operative field clear, reduce intraoperative blood loss and shorten the operative time. However, the pneumatic tourniquet may increase ischemia time of the lower limbs. After sudden release of the tourniquet, the veins in the patients' lower limbs may be filled with and dilated by blood and the fibrinolytic system is activated suddenly so that its activity is increased, which may increase blood loss during the total knee arthroplasty on the contrary. Some scholars questioned the effectiveness of the tranexamic acid and thought that the tranexamic acid used during total knee arthroplasty could not have stypticity. It was related to increase of bleeding amount after the fibrinolytic system was activated suddenly (Ellis et al., 2001). Moreover, some scholars found in studies that the tranexamic acid might increase the incidence of deep venous thrombus.

It is notable that, although tranexamic acid can effectively improve drainage volume and autologous blood transfusion volume, red cell morphology may be affected after filtering of autologous drainage blood and the oxygen-carrying capacity may decrease. At present, there is not united administration scheme for tranexamic acid. The administration time and dose are quite different in various studies. Among the others, it has been widely accepted that tranexamic acid should be immediately dripped when the tourniquet is loosened. Single-dose of tranexamic acid can only maintain a short period of blood drug level and does not have effective hemostasia effect. Repeated administration may gain a desirable effect. Some studies have found that the possibility of venous thrombus is higher in repeated administration than in single administration, but the difference in possibilities of both groups is not statistically significant. After total knee arthroplasty, coagulation of extravasated blood may occur easily, increasing the incidence of edema in the patients' lower limbs, delaying healing of wound and requiring more time in hospital (Muschart and Vincent, 2016). When external capillary hemorrhage seeps into tissues around the affected limb, it may aggravate pain and

stiffness in it. Most of all, recessive blood loss is relatively great, possibly induces postoperative anemia of the patients and is adverse to early function rehabilitation.

Some studies have verified that tranexamic acid can inhibit the occurrence of fibrinogen dissolution and DIC (Pong et al., 2018). In this study, preoperative use of tranexamic acid did not cause DIC and there was no significant difference for FDP when tranexamic acid was used or not used, which indicated that tranexamic acid did not change the immune system of the patient during knee arthroplasty. ALT and AST are indices of liver function. In this study, after the patients were intravenously injected with tranexamic acid, ALT and AST did not change significantly and were within the normal range, which indicated that the tranexamic acid did not have any effect on liver function. This study has some deficiencies: firstly, blind grouping adopted was not much targetable; secondly, small sample size and short follow-up time might not effectively evaluate long-range curative effect. In the process of follow-up, the long-range post-operative life quality of the patients has not been evaluated and the relevancy between tranexamic acid and post-operative life quality has not been evaluated. Although many studies have proved the effectiveness and safety of tranexamic acid in total knee arthroplasty, there are no united dose, time and administration methods at present, and many experimental investigations and clinical observations are still required for further improvement.

In conclusion, the injection of tranexamic acid before the knee arthroplasty can reduce intraoperative and postoperative blood loss of the patients and has no effect on blood coagulation and liver functions. Besides intravenous administration, the route of administration of tranexamic acid also includes injection around the joint. In this study, there was no comparison between the effects of the two methods of administration. In addition, the dosage is also a problem worthy of discussion, which will be further analyzed in future research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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