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Original Article

Safety and efficacy of tranexamic acid in the application of spinal tuberculosis surgery

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Abstract: Objective: To discuss the safety and efficacy of the application of tranexamic acid in spinal tuberculosis surgery. Methods: One hundred cases of patients in our hospital who had accepted spinal tuberculosis surgery were divided into tranexamic acid group (50 cases) and control group (50 cases) according to a random number table method. Before the surgery, all the patients underwent blood routine examination, coagulation routine examination, double extremity venous ultrasound and so on. Besides, the patients of tranexamic acid group had an intravenous drip of tranexamic acid before skin incision in 10 min, while the acid first dose and maintenance dose were 15 mg/kg and 2 mg (kg·h) respectively, the control group had an intravenous drip of isodose of normal saline. Then, compare the blood loss in surgery, the drainage 48 hours after surgery, amount of blood transfusion, transfusion rate, the haemoglobin (HB), hematocrit (HCT) after the surgery, the difference between them before and after the surgery, pulmonary infection, incision infection and the incidence of deep vein thrombosis (DVT) between the two groups. Results: All the drainage in 48 hours after the surgery, the amount of blood transfusion, the blood transfusion rate, the HB and HCT after the surgery, the difference of the HB, HCT before and after the surgery and the incidence of DVT of the patients of tranexamic acid group were lower than those of the control group ($P<0.05$). But the blood loss, the postoperative pulmonary and incision infection between the two groups were no statistical differences ($P>0.05$). Conclusion: Tranexamic acid can significantly reduce the spinal tuberculosis surgery patients' 48 hour-drainage, the amount of blood transfusion, the blood transfusion rate, the difference between the HB and HCT before and after the surgery as well as the incidence of DVT, but it didn't decrease the blood loss during the surgery or increase the postoperative pulmonary and incision infection risk. In a word, this program is a safe and effective method to control body fluid loss during perioperative period in patients with spinal tuberculosis.

Keywords: Tranexamic acid, spinal tuberculosis surgery, blood loss, postoperative complications

Introduction

In recent years, spinal tuberculosis has been one of the common forms of tuberculosis of bone and joint [1]. And it is caused by the damage of mycobacterium tuberculosis in the spine. When the vertebrae collapsed or got damaged and pus accumulated on and within the spinal canal, the formation of granulation tissue and other reasons were dragged in the spinal cord, complicated with spinal cord compression, in which the serious cases would appear as paraplegia. The surgical treatment has been the main method for clinical treatment of spinal tuberculosis at present [2]. However, due to the spinal cord and its surrounding structures have been rich blood flow, the operation has been usually accompanied by a large amount of blood loss [3]. Hence, many patients should be treated with blood transfusion during or after the surgery [4]. But transfusion can not only bring a lot of risk, such as the spread of infectious disease, transfusion related acute lung injury, increased postoperative infection and other adverse outcomes [5], but also increase the patient's hospitalization costs [6]. Although there were a lot of measures to control bleeding in spinal tuberculosis surgery, the usage of hemostatic drugs still remains many problems.

Tranexamic acid (tranexamic, TAX) is a synthetic lysine derivative, it reversibly blocked the high affinity of lysine binding site on plasminogen molecule, thus directly restraining the proteolytic enzymes activity of plasmin. At present, it can resist the pyrolysis of fibrin and play a vital

Table 1. Comparison of the general data before operation between the two groups ($\bar{X}$±S)

	Tranexamic acid group	Control group	*P*-values
Gender (male/female)	26/24	25/25	0.77
Age (years old)	49.1±4.4	48.2±3.5	0.23
BMI (kb/m^2)	23.8±1.5	23.1±1.8	0.38
HB (g/L) before operation	132.9±14.8	131.5±14.9	0.79
HCT (%) before operation	39.0±4.2	38.8±3.9	0.95

BMI: body mass index; HB: hemoglobin; HCT: hematocrit.

role in hemostasis of cardiac surgery and orthopaedics of hip and knee. A small dose of it can restrain the activity of protein and the application in high joint replacement has proved that it can reduce the amount of blood loss [7-9]. However, the research of TAX application was relatively rare in the tuberculosis of the spine surgery. We retrospectively analyzed the clinical data of the patients with spine tuberculosis and evaluated the efficacy and safety of TAX in the surgery.

Materials and methods

General materials

One hundred patients undergoing spine tuberculosis surgery at the department of orthopedics in our hospital from January 2014 to June 2016 were selected in this study. All patients were informed of trial contents, methods, potential risks and complications and signed the informed consents.

Inclusion criteria: 1. Primary spine tuberculosis; 2. The results of examinations such as preoperative blood routine examination, coagulation function, double lower extremity venous ultrasound, etc. were all within the normal limits; 3. The ASA grade was I or II, preoperative haemoglobin >90 g/L, hematocrit >35%.

Exclusion criteria: 1. People suffering from the second surgery of spine tuberculosis; 2. Tranexamic acid allergy; 3. People who previously used warfarin and other anticoagulant drugs; 4. People with severe renal insufficiency, renal pelvis or ureteral solid lesions, diabetes and other diseases that may affect coagulation function; 5. People who had previous history of deep vein thrombosis.

The patients who met the above criteria were divided into the tranexamic acid group and the control group with 50 cases in each according to the random number table.

Methods

Preoperative preparation: After entering the hospital, patients were given routine examinations, including blood routine examination, coagulation function, liver and kidney function, electrocardiogram, chest X-ray, lower extremity venous ultrasound, etc. and selectively examined lung function, ultrasonic cardiogram, dynamic electrocardiogram, etc. according to the patients' general situation.

Operation methods: After entering the operation room, peripheral vein was opened, the left radial artery and the right internal jugular vein were punctured with catheterization. All the patients were operated by endotracheal intubation combined with intravenous anesthesia and induced with 2 mg/kg propofol, 0.1 mg/kg vecuronium, 0.04 mg/kg midazolam, 1.5 ug/kg remifentanil and N_2O. The speed of continuous intravenous infusion was kept at 3~4 mg/(kg·h) for propofol and 0.2 ug/(kg·h) for remifentanil and the speed of intermittent intravenous administration was kept at 0.05 mg/kg for vecuronium. And the vital signs such as ART, CVP, ECG, SpO_2, HR, urine volume, etc. were monitored conventionally during operation. Patients of tranexamic acid group were given an initial dose of 15 mg/kg tranexamic 10 min before surgical incision and the maintenance dose of 2 mg/(kg·h) tranexamic until the end of surgery. Patients in the control group were given intraoperative intravenous infusion of the isodose normal saline. After the beginning of the operation, infusions of concentrated red blood cells and fresh frozen plasma were started when the blood loss reached 30% of blood volume, while infusions of platelets and cryoprecipitation were given when the blood loss reached 100% of blood volume. Maintain intraoperative haemoglobin above 70 g/L and keep the state of intraoperative central venous pressure in 5-10 cm H_2O of blood volume.

Statistical indicators

Preoperative data: All the information of sex, age, body mass index (BMI), preoperative

Table 2. Comparison of patients' data before and after operation between the two groups

	Tranexamic acid group	Control group	*P*-values
Blood loss during operation (ml)	129±36	142±50	>0.05
Postoperative drainage volume in 48 hours (ml)	385±30	540±10	<0.05
Postoperative HB (g/L)	94.5±13.8	102.9±13.1	<0.05
Postoperative HCT (%)	28.1±3.7	30.5±3.5	<0.05
Difference in HB between pre-operation and post operation (g/L)	31.8±7.1	38.1±8.2	<0.05
Difference in HCT between pre-operation and post operation (%)	9.3±2.3	11.2±2.4	<0.05
Proportion of existing transfusion triggers	5/50	12/50	<0.05
Injected volume of allogeneic red blood cells/ml	420±40	860±80	<0.05
Injected volume of fresh frozen plasma/ml	250±25	425±30	<0.05
Postoperative DVT rate	0/50	5/50	<0.05
Postoperative pulmonary infection	1/50	2/50	>0.05
Postoperative incision infection	0/50	0/50	>0.05

hemoglobin (HB), hematocrit (HCT) of two groups of patients was statistically analyzed.

Data during and after operation: Collect patients' index information including the blood loss during operation, the postoperative drainage volume within 48 hours after operation, the postoperative haemoglobin (HB) and hematocrit (HCT). The differences in HB and HCT between pre-operation and post operation as well as the postoperative blood transfusion should also be involved in. Moreover, the lower extremities should be observed every day after operation to verify whether there occurred complications such as swelling, ache, pressing pain, bruising, extravasated blood, superficial vein engorgement, Homans, deep vein thrombosis (DVT), pulmonary infection and incision infection.

Statistical analysis

Data were analyzed by using SPSS13.0 statistical software. The measurement data were analyzed by using the X^2 test; the measurement data which accord with the normal distribution were shown in the form of mean ± standard deviation ($\overline{X}$±S) and analyzed by using t test. *P*<0.05 indicated that the differences were statistically significant.

Results

Data before operation

There was no statistically significant differences in patients' gender, age, body mass index (BMI), preoperative hemoglobin (HB), preoperative hematocrit (HCT), lower extremity deep venous ultrasound test results and other aspects between the two groups (P>0.05), so the two groups of patients were comparable. As shown in **Table 1**.

Data during and after operation

During the operation, the blood loss of patients in the tranexamic acid group and control group were (129±36) ml and (142±50) ml respectively, and the difference was not statistically significant. The postoperative drainage volume within 48 hours in the tranexamic acid group decreased by about 155 ml compared to the control group (385±30 ml *vs.* 540±10 ml; P<0.05). The mean value of the postoperative haemoglobin (HB) in the control group was less by about 3.8 g/L; P<0.05). Likewise, the postoperative hematocrit (HCT) in the control group (28.1±3.7)% was lower than that in the tranexamic acid group (30.5±3.5)%, and the difference was statistically significant (P< 0.05). Moreover, the differences of haemoglobin (HB) and hematocrit (HCT) between preoperation and post operation in the tranexamic acid group were lower than those in the control group, and the differences were statistically significant (31.8±7.1 g/L *vs.* 38.1±8.2 g/L; P<0.05 and 9.3±2.3% *vs.* 11.2±2.4%; P<0.05).

Post-operative blood transfusion

Transfusion triggers were found in 5 patients in the tranexamic acid group while 12 patients in

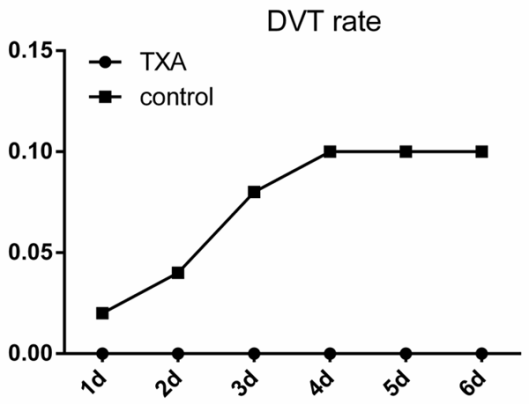

Figure 1. The postoperative DVT rate of the two groups.

the control group, and the difference was statistically significant (P<0.05). The injected volume of allogeneic red blood cells in the tranexamic acid group was about 440 ml less than that in the control group (420±40 ml *vs.* 860±80 ml; P<0.05). The injected volume of fresh frozen plasma (FFP) in the tranexamic acid group was about 175 ml less than that in the control group (250±25 ml *vs.* 425±30 ml; P<0.05). As shown in **Table 2**.

Post-operative complications

Postoperative deep vein thrombosis (DVT) was found in no case of the tranexamic acid group while 5 cases in the control group, and the difference was statistically significant (P<0.05). In addition, the fastigium of DVT rate appeared within six days after operation, as shown in **Figure 1**. Postoperative pulmonary infection was found in one case of the tranexamic acid group while 2 cases in the control group, and the difference was not statistically significant (P>0.05). Incision infection was found in no cases of the two groups and the difference was not statistically significant (P>0.05), as shown in **Table 2**.

Discussion

Tuberculosis of the spine is the most common tuberculosis of bone and joint, accounting for 50% of the bone tuberculosis and 3%~5% of all the tuberculosis [10-12]. In recent years, the morbidity of tuberculosis of the spine has been significantly increasing [13]. Because tuberculosis of the spine is not typical and with different degrees of anemia and hypoproteinemia at the early stage [13], at present, there are medical and surgical treatments for tuberculosis clinically. It is necessary for surgery at the early stage [14]. Different degrees of hemorrhage and postoperative complications were often associated in the process of surgery, so tranexamic acid and other hemostasia drug are widely and clinically used.

In 1976, it was first reported that tranexamic acid was used in spinal tuberculosis surgery and achieved good hemostatic effects [15]. Tranexamic acid can combine with plasminogen and lysine binding site (LBS) of fibrin affinity on plasminogen to inhibit the combination of plasmin, plasminogen and fibrin, inhibit the degradation of plasmin to fibrin, make antifibrinolytic effect and reach the purpose of hemostasis [16]. The stress of surgery can promote the release of systematical TPA (tissue plasminogen activator) and activate the dissolution of fibrin [17]. The natural process of fibrin dissolution will be inhibited in 24 h after surgery. But anti-fibrinolysis agents can activate this process at an earlier stage so that hemorrhage can be decreased. With the clinical application of TXA, surgeons has started to pay attention to its curative effect and done researches to discuss through kinds of experiments. Royston [18] has started to use TXA for thoratic surgical procedures patients since 1995. He has sprayed it in thoracic cavity and got the satisfying result of hemostasis. In this study, we used patients with spinal tuberculosis surgery as the object of research and found that TXA could decrease the amount of blood transfusion in surgery. It was consistent with the findings of Wong [19] and others. A similar set of Elwatidy [20] and others' reports also drew the same conclusion. This study found that tranexamic acid could not reduce the blood loss in spinal surgery. But Elgagy [21] and others have made retrospective analysis and research to the problem that drugs could reduce blood loss in spinal surgery in the past 20 years. Then they have found that tranexamic acid could reduce the blood loss and the input of heterologous blood in spinal surgery. This finding was not consistent with our results. The reason remained to be further studied.

This experiment also focused on the drainage within 48 h after surgery and the comparison of haemoglobin, hematocrit and their difference values before and after operation, which resulted in various factors for the patients' drainage after operation, including patients' age, coagulation function, nutriture and so on. The usage of hemostasis drugs and tranexamic acid is also an important factor. It is often used as one of the evaluation indexes of clinical effect. The results showed that compared with the control group, the application of tranexamic acid could obviously reduce the postoperative drainage in 48 hours, the haemoglobin and hematocrit before and after operation.

The results of study showed that the application of tranexamic acid in spinal tuberculosis surgery could reduce the risk of postoperative deep vein thrombosis. Lower extremity deep vein thrombosis and pulmonary embolism is a kind of common and dangerous complication for orthopaedic patients [22]. Its incidence was low but the consequences could be very serious. So it is the emphasis on preoperative Doppler ultrasound examination to monitor the occurrence and follow-up visit of lower extremities deep vein thrombosis [23]. The results were consistent with the Ergusson DA [23] and Orpen NM [24] which once reported. Through performing magnetic resonance venography and radionuclide pulmonary perfusion/ventilation on the patients who received TXA intravenous injections to acquire the imaging, Ergusson DA got the results that TXA would lower the incidence of lower extremity deep vein thrombosis and pulmonary embolism. And there were a lot of reports confirming that appropriate doses of TXA used for clinical treatments could obviously reduce the risk of complications such as postoperative deep vein thrombosis. It was worth mentioning that although the security of TXA obtained the affirmation, we would not suggest elderly patients with a history of thrombembolia to use it [25].

The experiment made statistical analysis on pulmonary infections and incision infections. The results showed that tranexamic acid could effectively lower the incidence of postoperative infections [26]. It was known to us all that after spinal tuberculosis surgery, it would release a variety of inflammatory mediators and often cause systemic inflammatory response. Tranexamic acid has double effects of anti-inflammatory and hemostasia. Its possible mechanism is that: the tranexamic acid selectively reduced the production of extracorporeal circulation of the blood vessel active ingredients, at the same time, it helped platelets to inhibit the leukocytic activation, adhesion, aggregation and activation of endothelial cells, thereby reducing arachidonic acid metabolites and the release of inflammatory mediators, so as to reduce the occurrence of postoperative inflammatory reactions.

There are many limitations in this study. Since the number of the patient sample was small, it is necessary to expand the sample cases to study whether the tranexamic acid used in spinal tuberculosis surgery can reduce blood loss and the incidence of adverse reactions in the surgery, thus improving the prognostic quality of patients.

Conclusion

The application of tranexamic acid in spinal tuberculosis surgery reduced postoperative drainage, the amount of blood transfusion and haemoglobin, the differences of hematocrit and the incidence rate of postoperative deep vein thrombosis. But it did not reduce the blood loss nor increase the risk of incision infections. Because tranexamic acid can reduce the spinal tuberculosis surgery patients' 48 hour-drainage, the amount of blood transfusion and the blood transfusion rate, so it can be a safe and effective way to prevent body fluid from losing in spinal surgery.

Disclosure of conflict of interest

None.

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