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Local administration of tranexamic acid in off-pump coronary artery bypass

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Abstract

Purpose: We administered tranexamic acid locally to patients undergoing off-pump coronary artery bypass, to investigate the hemostatic effects and safety.

Patients and methods: The subjects were 100 consecutive patients who underwent off-pump coronary artery bypass between July 2009 and January 2011. We assigned 50 patients in the early phase, in which tranexamic acid was not employed, to group N, and 50 in the late phase, in which tranexamic acid was employed, to group T. In group T, 10 mL of a solution containing 1 g of tranexamic acid in was sprayed into the pericardial cavity and mediastinum before the sternum was closed. We compared the volume of postoperative blood loss, blood transfusion volume, and complications between the 2 groups.

Results: The volume of blood loss in 24 h after intensive care unit admission was 492 mL in group N and 303 mL in group T ($p < 0.0001$); the decrease in blood loss in the group receiving tranexamic acid was approximately 40%. There was no significant difference in the blood transfusion volumes. There were no side effects of tranexamic acid.

Conclusion: In patients undergoing off-pump coronary artery bypass, local administration of tranexamic acid may decrease the volume of postoperative blood loss. The local administration method is simple, inexpensive, and safe.

Keywords

Antifibrinolytic agents, blood loss, surgical, blood transfusion, coronary artery bypass, off-pump, tranexamic acid

Introduction

Postoperative hemorrhage related to open heart surgery increases the rates of complications and mortality, representing a serious issue.[1] Systemic administration of antifibrinolytic agents has been commonly employed in the field of cardiac surgery, and many studies have reported their hemostatic effects.[2] However, many cases of serious complications related to systemic administration have been reported. The BART trial in 2008 showed that aprotinin administration increased the mortality rate. Subsequently, the sale of this agent was discontinued.[3] On the other hand, previous studies have reported the local administration of antifibrinolytic agents.[4,5] This therapy has been highlighted since the BART trial, due to its low incidence of side effects.[6,7] In this study, we locally administered an antifibrinolytic agent, tranexamic acid, to patients undergoing off-pump coronary artery bypass (OPCAB) to investigate its hemostatic effects and safety.

Patients and methods

The study enrolled 100 consecutive patients who underwent OPCAB between July 2009 and January 2011. We assigned 50 patients in the early phase, in which tranexamic acid was not employed, to group N, and 50 in the late phase, in which tranexamic acid was employed, to group T. There were no significant differences in any preoperative factors between the 2 groups (Table 1).

Under general anesthesia, a median sternotomy was performed. The internal thoracic artery was harvested and fully skeletonized using a harmonic scalpel. After graft preparation, heparin was administered

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Table 1. Preoperative data in 100 patients undergoing off-pump coronary artery bypass.

Variable	Group N	Group T	*p* value
No. of patients	50	50	
Age (years)	67 ± 9	67 ± 10	0.8323
Sex (male/female)	43/7	41/9	0.5873
Body mass index ($kg \cdot m^{-2}$)	23 ± 3	24 ± 3	0.3741
Chronic kidney disease	15	15	
Emergency surgery	10	10	
Ejection fraction	52% ± 16	57% ± 11	0.789
Hematocrit	36% ± 5%	37% ± 5%	0.3254
Antiplatelet agents	31	31	

Group N: no tranexamic acid; group T: tranexamic acid before sternal closure.

Table 2. Operative data in 100 patients undergoing off-pump coronary artery bypass.

Variable	Group N	Group T	*p* value
Operation time (min)	276 ± 52	278 ± 59	0.8686
No. of coronary anastomoses	3.4 ± 1	3.5 ± 1	0.6903
Internal thoracic artery grafts	1.8 ± 0.1	1.9 ± 0.1	0.7805

Group N: no tranexamic acid; group T: tranexamic acid before sternal closure.

Table 3. Postoperative data in 100 patients undergoing off-pump coronary artery bypass.

Variable	Group N	Group T	*p* value
24-h blood loss (mL)	492 ± 180	303 ± 112	<0.0001
Blood transfusion (units)			
Red cells	10	5	0.2337
Fresh-frozen plasma	5	1	0.4592
Platelets	0	0	0.2337
Intubation time (h)	14.2 ± 8.4	12.8 ± 7.1	0.4181
Reexploration	0	0	
Atrial fibrillation	13	11	0.6413
Sternal infection	4	0	0.0423
Renal failure	1	0	0.3173
Seizure	0	0	
Stroke	0	2	0.1552
Myocardial infarction	0	1	0.3173
Graft patency	97.3%	94.2%	0.9278
Intensive care unit stay (days)	1.0 ± 0.3	1.0 ± 0.1	0.4130
Hospital death	0	0	

Group N: no tranexamic acid; group T: tranexamic acid before sternal closure.

systemically so that the activated clotting time was 400 sec or more, and graft anastomosis was conducted. After completion of the anastomoses, protamine was administered to ensure hemostasis. The pericardial cavity was loosely closed by drawing up the peripheral fat or pericardium. Silicon drains (28F) were inserted into the pericardial cavity and mediastinum. The sternum was wired, washed with 2000 mL of warm physiological saline, and closed. In group T, 1 g of tranexamic acid in 10 mL was sprayed into the pericardial cavity and mediastinum immediately before the sternum was closed. The drain was clamped for approximately 10 min until wound closure, so that the tranexamic acid penetrated sufficiently. On completion of surgery, the drain was opened. We compared the volume of postoperative blood loss, blood transfusion volume, and complications between the 2 groups. Patients with a serum creatinine level of $1.3\,mg \cdot dL^{-1}$ or more before surgery were regarded as having chronic renal failure. Concerning postoperative blood transfusion, concentrated erythrocytes were employed in patients with a hematocrit value of 25% or less. Fresh frozen plasma and concentrated platelets were selected based on the attending physician's evaluation. Patients with a serum creatinine level of $1.5\,mg \cdot dL^{-1}$ or more on discharge or an increase of $0.5\,mg \cdot dL^{-1}$ or more compared to the pretreatment value were regarded as having kidney dysfunction.

Statistical analysis was conducted using the chi-squared and Student's *t* tests. A *p* value <0.05 was regarded as significant.

Results

There were no significant differences in intraoperative factors between the 2 groups, with respect to operation time, number of coronary anastomoses, or number of internal thoracic artery grafts (Table 2). Postoperative factors are presented in Table 3. The volume of blood loss in the first 24 h after intensive care unit admission was 492 ± 180 mL in group N and 303 ± 112 mL in group T ($p < 0.0001$); the latter showed a significant decrease of approximately 40% (Figure 1). There was no significant difference in the blood transfusion volume. There were also no significant differences in the incidences of kidney dysfunction, convulsion, cerebral infarction, postoperative myocardial infarction, graft patency rate, or intensive care unit stay between the 2 groups. There was no death during admission in either group.

Discussion

Since the introduction of OPCAB, the incidence of postoperative hemorrhage has decreased, with

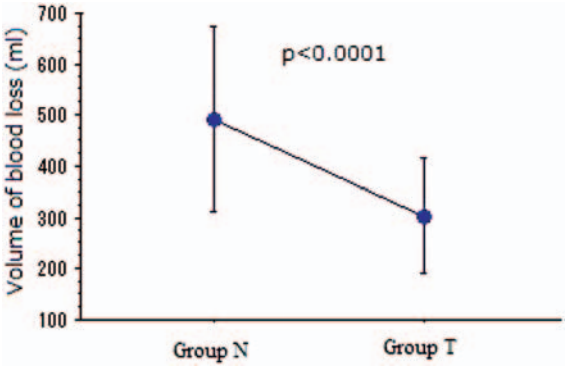

Figure 1. Volume of blood loss in 50 patients who received local tranexamic acid (group T) and 50 controls (group N).

reductions in the dose of heparin administered during surgery and pericardial operations, minimizing the necessity for blood transfusion and additional thoracotomy.[8] However, surgery is becoming indicated for an increasing number of patients due to the low degree of invasiveness of OPCAB; the number of elderly and high-risk patients with a high incidence of complications, in whom surgery was not selected previously, has increased. In addition, the number of patients with the risk of hemorrhage may also be increasing. A study reported that risk factors for postoperative hemorrhage, blood transfusion, and reexploration included age 75 years or older, renal failure, anemia, emergency surgery, body mass index $<25\,kg{\cdot}m^{-2}$, and oral administration of antiplatelet agents.[9] In this study, patients aged 75 years or older accounted for 25%. Renal failure was noted in 30% of patients, and anemia in 33%. Emergency surgery was performed in 20%, and the body mass index was less than $25\,kg{\cdot}m^{-2}$ in 75%; 96% had 1 or more risk factors. Furthermore, 62% of our patients had received antiplatelet agents until the day before surgery.

A previous study indicated the involvement of the fibrinolytic system in 25% to 45% of patients with postoperative hemorrhage.[10] In the 1980s, local administration of antifibrinolytic agents was introduced as an effective method of administration with a low incidence of side effects in the fields of oral surgery, neurosurgery, otorhinolaryngology, urology, obstetrics and gynecology. Several studies have reported the hemostatic effects and safety of antifibrinolytic agents.[11] In the field of cardiac surgery, Tatar and colleagues[4] locally administered aprotinin into the pericardial cavity for the first time in 1993. Since the withdrawal of aprotinin, many studies have reported the local administration of tranexamic acid and epsilon aminocaproic acid.[5–7] However, these studies involved patients who had surgery under cardiopulmonary bypass. No study has reported local administration of antifibrinolytic agents to OPCAB patients.

In this study, we locally administered tranexamic acid to OPCAB patients, which is inexpensive and exhibits the most marked hemostatic effects among antifibrinolytic agents;[11] there was an approximately 40% decrease in blood loss in the first 24 h after surgery. Tranexamic acid inhibits fibrin adsorption by binding to plasminogen, producing antifibrinolytic actions.[12] This agent is known to show antiinflammatory and antiallergic actions in addition to hemostatic effects. It has been added to dental paste to achieve gingival hemostasis and reduce inflammation, and is commonly employed for local administration.[13] The mechanism of action of locally administered tranexamic acid remains to be clarified, but several studies have indicated that it reduces postoperative hemorrhage.[5–7] Tissue plasminogen activator is secreted by mesothelial cells to physiologically prevent adhesion in vivo. In the pericardial cavity, a similar function also acts to prevent adhesion and maintain flow ability.[14] In addition, during open heart surgery, trauma may further enhance the activity of the fibrinolytic system.[15] Philipe and colleagues[16] reported that many fibrinolytic factors including plasminogen were present in the pericardial cavity after open heart surgery, and that the activity of the fibrinolytic system was enhanced. In the pericardial cavity after open heart surgery, surgical invasion activates the fibrinolytic system in addition to tissue plasminogen activator secretion mediated by a physiological adhesion-preventing mechanism; therefore, coagulation and fibrinolysis are repeated in response to oozing at the capillary level. This may be related to changes in postoperative hemorrhage. The local administration of antifibrinolytic agents may inhibit the repeated coagulation-fibrinolysis cycle, reducing hemorrhage. Fibrinolytic factors in the pericardial cavity may also diffuse into the mediastinum due to heart beat, exhibiting the fibrinolytic effects demonstrated in the pericardial cavity. The local administration of tranexamic acid may decrease the volume of postoperative blood loss by reducing the activity of the fibrinolytic system in both the pericardial cavity and mediastinum, and inhibiting fibrin decomposition.

In this study, there was no drain occlusion or delayed cardiac tamponade early after surgery. Local administration may prevent additional hemorrhage by inhibiting thrombolysis at the affected capillary site, rather than strong thrombus formation from blood in the pericardial cavity and mediastinum, thus decreasing the volume of blood loss. According to Isgro and colleagues[17] who compared the blood loss volumes between systematic and local administration of aprotinin in coronary artery bypass patients on heart-lung machines, there was no significant difference in blood loss at 24 h after the operation. In addition, they recognized that local administration of aprotinin had an

advantage, considering the side effects caused by systematic administration, such as vein bypass occlusion, myocardial infarction, renal failure, and membrane stabilization effects on platelets. We could not compare our study because there is no research regarding the systematical administration of tranexamic acid in OPCAB patients. Aprotinin is a similar antifibrinolytic agent to tranexamic acid, thus it would be expected that tranexamic acid has similar effects. The systematic administration of tranexamic acid has similar side effects to those of aprotinin.[18] We recommend local administration in OPCAB patients for safety reasons if both tranexamic acid administration methods have the same hemostatic effects.

We found no marked difference in the postoperative blood transfusion volume between the 2 groups. In contrast, a study by Abul-Azm and Abdullah[5] reported that local administration of tranexamic acid decreased the postoperative blood transfusion volume. Their study involved coronary artery bypass in patients on cardiopulmonary bypass, and the volume of postoperative blood loss in the control and tranexamic acid-treated groups was 1208 and 733 mL, respectively. These values are more than twice as high as those in our study (492 ± 180 vs. 303 ± 112 mL). There was no difference in the postoperative blood transfusion volumes between the 2 groups, possibly because only a small number of patients met the criterion for blood transfusion in our hospital (hematocrit of 25% or less). Furthermore, no significant differences have been found in the incidences of complications such as atrial fibrillation, renal failure, embolism, or spasm after intravenous administration of tranexamic acid.[18] Kolettis and colleagues[19] conducted an animal experiment that indicated that intrapericardial drug absorption was restricted. Considering that the half-life of tranexamic acid ranges from 1 to 1.5 h, the side effects observed after intravenous administration may not occur. However, a study suggested involvement of the fibrinolysis system in adhesion and peritonitis after laparotomy.[20] The local administration of tranexamic acid might cause enhancement of intrapericardial adhesion or pericarditis in the late phase, hence close follow-up is needed.

As we did not employ a double-blind method in this study, there may have been a bias in hemostatic procedures among surgeons responsible for sternal closure. However, there was no significant difference in the operation time between the 2 groups. Therefore, there may have been no marked difference in hemostasis. We concluded that local administration of tranexamic acid is simple, inexpensive, and safe. In the future, this procedure may be applied in other fields of cardiovascular surgery, and another action of tranexamic acid, an antiinflammatory effect in local areas, should be investigated.

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Conflicts of interest statement

None declared.

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