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Comparing Vancomycin-Tranexamic Acid Paste to Vancomycin-Normal Saline Paste in Reducing Post Coronary Artery Bypass Graft Surgery Bleeding

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ABSTRACT

Background: Postoperative bleeding is a common problem, specially in cardiac surgery. The bone edges at the sternotomy site are one of the major sites of bleeding. Previously, some materials, such as vancomycin paste, have been applied to the sternum prior to the closure of sternum in order to reduce postoperative hemorrhage. In addition, fibrinolytic drugs, such as tranexamic acid, have been used locally to reduce postoperative bleeding.
Objectives: This study aimed to assess the effect of vancomycin paste made with tranexamic acid on reducing postoperative mediastinal bleeding.
Methods: In this double-blind clinical trial, all patients undergoing on-pump coronary artery bypass graft surgery were included and divided into two groups by simple randomization method. In the control group, two grams of vancomycin paste were made with two mls of normal saline solution. In the intervention group, two grams of vancomycin paste were made with two mls (containing 200 mgs) of tranexamic acid. The paste in each group was applied to the sternal bone edges just prior to sternal closure. Both groups were compared in terms of demographic data, operation data, packed red blood cell transfusion, hemoglobin change, and amount of postoperative bleeding 12, 24, and 48 hours post-surgery. Postoperative sternal wound infection and dehiscence were also evaluated two months after the surgery. Comparisons were done using independent t-test, Fisher's exact test, and Mann-Whitney test using the SPSS software, version 22.
Results: Fifty patients completed the trial. Both groups were similar regarding the demographic data and operation data, such as pump time and operation duration. The amount of postoperative bleeding was respectively 268, 624, and 844 mls in the control group and 174, 362, and 485 mls in the invention group 12, 24, and 48 hours after the operation ($P < 0.001$). The results revealed no significant difference between the two groups concerning postoperative transfusion and hemoglobin changes. Postoperative sternal wound complications, including infection and dehiscence, were not seen in any of the study groups.
Conclusions: In comparison to vancomycin paste alone, vancomycin-tranexamic acid paste had a significantly superior effect on the reduction of post-coronary artery bypass graft surgery bleeding.

1. Background

Despite advances in cardiac surgery, postoperative bleeding still remains one of the most common complications after these operations (1). As a result of postoperative bleeding, blood transfusions may be needed and, consequently, their administration is common after cardiac surgery (2). Nonetheless, blood transfusions may cause additional morbidity and mortality (3-5). One of the major sites of bleeding is the edges of the sternal bone. The sternum is composed of a highly vascular marrow or spongiosa covered with two inner and outer compact bone layers. When median sternotomy is done, the marrow may cause significant bleeding, which cannot be controlled by usual hemostasic tools, such as cautery. One of the methods

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for controlling sternotomy site bleeding is the application of some filling and hemostatic agents into the marrow prior to sternal closure. One such material is bone wax, which is made of a sterilized, white, bleached, honeybees wax blended with a softening agent such as paraffin, which works as a physical barrier and inhibits osteoblasts from reaching the bone defect, but hinders osteogenesis (6, 7). Some studies have shown that bone wax usage at the sternal edges might increase the infection rates (8), while others have failed to show this association clearly (9, 10). Moreover, some centers have used antifibrinolytic drugs in intravenous or topical forms for the prevention of postoperative bleeding. Clinical trials on the intravenous application of tranexamic acid have shown different outcomes of postoperative bleeding control (11, 12). On the other hand, there have been some concerns about graft thrombosis of diseased targets after the systemic use of tranexamic acid (13). Topical usage of tranexamic acid when poured in the pericardial cavity just prior to sternal closure has not clearly shown positive outcomes in terms of bleeding control (14, 15). Furthermore, vancomycin is an antibiotic that, if used in the form of a powder, can make a sticky material when mixed with normal saline. Application of vancomycin paste on sternal bone edges just prior to sternal closure has been promising in bleeding control among post sternotomy patients (16, 17). Vancomycin paste was first applied to sternal edges to decrease sternal site infection (13, 16, 18). In addition, it has been found to have hemostatic effects and to reduce postoperative bleeding (16, 17).

2. Objectives

In the present study, vancomycin powder was mixed with tranexamic acid to make a new paste, aiming at comparison of its hemostatic effects to the well-known former vancomycin paste.

3. Patients and Methods

This double-blind clinical trial was conducted in Chamran Hospital, Isfahan, Iran (clinical trial registration code: IRCT20190714044205N1). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's Human Research Committee. The inclusion criteria of the study were being admitted for elective on-pump Coronary Artery Bypass Graft (CABG) surgery, aging between 35 and 80 years, having discontinued antiplatelets (aspirin and clopidogrel) at least five days prior to the operation, warfarin or rivaroxaban at least three days before the operation, and low molecular weight heaparin at least 12 hours prior to the surgery, having a platelet count more than 100000/mL, having no history of bleeding disorders, and not suffering from renal or hepatic failure. The exclusion criteria were pump time more than 100 minutes, reoperation due to a surgical cause of bleeding, intravenous administration of antifibrinolytics, intraoperative or postoperative platelet or Fresh Frozen Plasma (FFP) administration, bone wax usage, and mortality before data collection (19). Written informed consent forms were obtained from all patients.

This study was conducted on 55 patients. The participants were selected via simple randomization method using the random allocation software. In doing so, every patient was given a code by the statistician of which the surgeon and the appraiser were not aware; only the assistant who was responsible for paste making was aware of the code.

To make a sticky paste in the control group, two grams of vancomycin powder (Exir Pharmaceutical Company, Tehran) were mixed with two mls of normal saline. In the intervention group, two grams of vancomycin powder were mixed with two mls (containing 200 mgs) of tranexamic acid (Caspian Tamin Pharmaceutical Company, Rasht). The paste was applied to sternal bone edges just prior to sternal closure. Activated Clotting Time (ACT) was checked after protamine administration and if it was more than 120 seconds, more protamine was given.

Demographic data, including age, gender, and weight, were recorded. Lab data, including serum creatinine level, Prothrombine Time (PT), Partial Thromboplastine Time (PTT) before the operation, and hemoglobin levels before and 12, 24, and 48 hours after the operation, were also collected. Operation data, such as clamp time, pump time, body surface area, ACT after protamine use, and administration of blood products such as FFP, platelets, and packed cells, were recorded in both groups, as well. In addition, the amount of postoperative bleeding was precisely collected 12, 24, and 48 hours after the operation. The patients were followed for two months after the operation and any sternal wound infection or dehiscence was recorded.

Comparisons were done using independent t-test, Fisher's exact test, and Mann-Whitney test via the SPSS software, version 22. The results were reported as percentages or means ± Standard Deviations (SD). $P < 0.05$ was considered statistically significant.t.

4. Results

This study was conducted on 26 patients in the control group and 29 patients in the intervention group (Figure 1). One patient was excluded from the control group because of surgical bleeding requiring reoperation. In addition, four patients were excluded from the intervention group; one because of surgical bleeding requiring reoperation, two for application of bone wax at the time of internal mammary artery harvesting, and one for intravenous administration of tranexamic acid. Finally, 50 patients completed the study; 25 patients in the control group and 25 ones in the intervention group. Both groups were matched (Table 1) in terms of age, weight, gender, preoperative serum creatinine level ($P = 0.11$), preoperative PT value ($P = 0.78$), and preoperative PTT value ($P = 1.00$).

The intraoperative results of both groups have been summarized in Table 2. The results revealed no significant difference between the control and intervention groups regarding ACT after protamine use, pump time, and ischemic time. The amounts of intraoperative and postoperative blood transfusion were also the same in the two groups. Moreover, no significant difference was observed between the two groups regarding the hemoglobin levels preoperatively and 12, 24, and 48 hours after the operation ($P = 0.65$, $P = 0.72$, $P = 0.76$, and $P = 0.91$, respectively).

The amount of postoperative bleeding was respectively

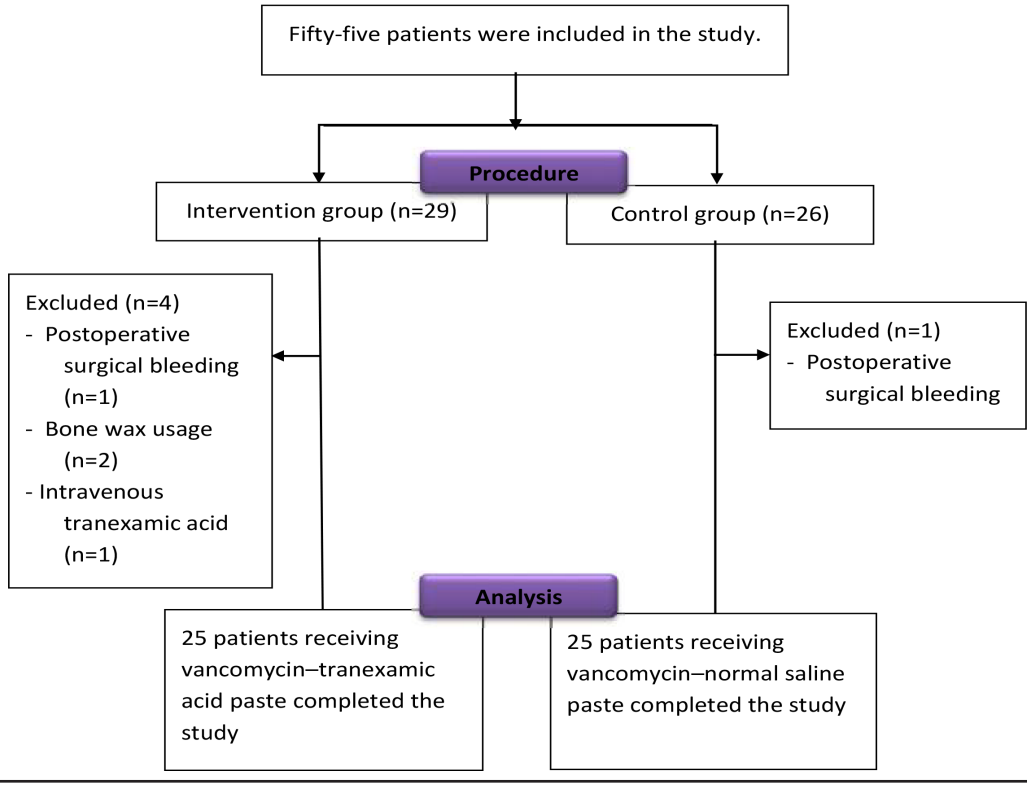

Figure 1. Flowchart of the Included and Excluded Patients

Table 1. Demographic Data of the two Study Groups (Fisher's Exact Test, Independent T-Test)

Study Group		Control	Intervention	P-value
Gender (Percent) (Number)	Female	4 (16%)	4 (16%)	1.00
	Male	21 (84%)	21 (84%)	
Age (years) (Mean ± SD)		52.52 ± 9.84	58.02 ± 10.51	0.64
Weight (kg) (Mean ± SD)		74.28 ± 13.82	76.88 ± 14.01	0.24
Preoperative hemoglobin (Mean ± SD)		14.32 ± 1.51	14.50 ± 1.34	0.65

Table 2. Intraoperative Data of the Two Study Groups (Independent T-Test, Mann-Whitney Test)

Study Group		Control, Mean ± SD	Intervention, Mean ± SD	P-value
Aortic clamp (min)		42.12 ± 11.32	42.40 ± 17.14	0.92
Cardiopulmonary bypass time (min)		62.24 ± 14.15	65.44 ± 17.14	0.47
Body surface area		1.78 ± 0.23	1.87 ± 0.21	0.20
Activated clotting time (seconds)		96.00 ± 9.68	97.20 ± 10.41	0.27
Urine output		748 ± 432.88	625 ± 397.77	0.60
Blood product (units)	Fresh frozen plasma	0.0 ± 0.0	0.0 ± 0.0	
	Packed red blood cell	1.40 ± 0.51	1.37 ± 0.74	0.76
	Platelet	0.0 ± 0.0	0.0 ± 0.0	

268, 624, and 844 mls in the control group and 174, 362, and 485 mls in the intervention group 12, 24, and 48 hours after the operation, and the difference between the two groups was statistically significant ($P < 0.001$) (Table 3, Figure 2).

5. Discussion

Vancomycin paste was first used on sternal edges to reduce post cardiac surgery sternal wound infection (13, 16, 18). Topical application of vancomycin paste on sternal edges of pigs after surgery indicated that vancomycin serum level returned to the baseline value by the sixth postoperative day with no increased risk of postoperative resistance to bacterial infections and renal or otic toxicity for at least 90 days after surgery (20). A recent meta-analysis done by Kowalewski et al. also showed that vancomycin paste was associated with a 76% reduction in Deep Sternal Wound Infections (DSWIs) (19). Furthermore, antifibrinolytics have been used systematically and locally after cardiac operations to reduce the risk of postoperative bleeding (11, 12). However, there have been some concerns about graft thrombosis after the systemic usage of tranexamic acid in CABG surgery patients (11). Therefore, it has been proposed to be applied locally to reduce the subsequent risk of graft thrombosis (14). However, some recent larger randomized clinical trials have shown no statistically significant reduction in post CABG surgery bleeding when

Table 3. Postoperative Bleeding in the Two Groups (Independent T-Test)

Postoperative Bleeding	Control, Mean ± SD	Intervention, Mean ± SD	P-value
12 hours after surgery (mL)	268 ± 184.21	174 ± 81.82	< 0.001
24 hours after surgery (mL)	624 ± 213.65	362 ± 112.98	< 0.001
Second 24 hours after surgery (mL)	220 ± 134.62	96 ± 93.45	< 0.001
Overall 48 hours after surgery (mL)	844 ± 192.74	485 ± 140.44	< 0.001

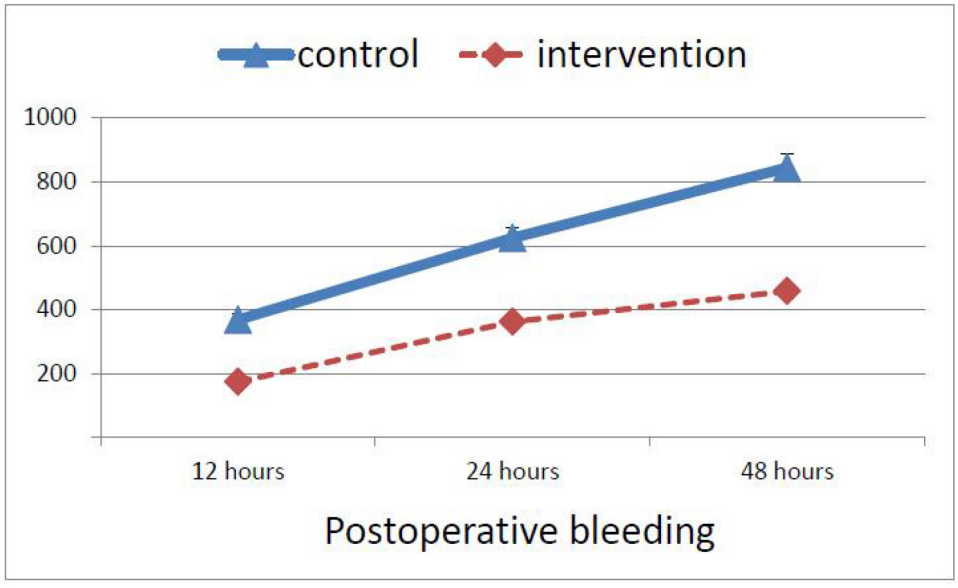

Figure 2. Postoperative Bleeding in the Intervention Group (Vancomycin-Tranexamic Acid) and the Control Group (Vancomycin-Normal Saline)

tranexamic acid was poured locally on the pericardium prior to sternal closure (15).

Normally, vancomycin powder changes into a sticky paste when mixed with a carrier, such as normal saline, at the 1:1 ratio (17). In the previous cases, two grams of vancomycin were mixed with two mls of normal saline and the paste was applied to sternal edges just prior to sternal closure. When two mls equivalent to 200 mgs of tranexamic acid were mixed with two grams of vancomycin powder, it made a sticky paste. In the present study, these two methods were compared among on-pump CABG surgery patients. For this purpose, the two groups were matched completely regarding age, gender, weight, serum creatinine level, preoperative hemoglobin level, and preoperative PT and PTT values. In all cases, the ACT target was below 120 seconds after protamine administration. It should also be noted that all operations were carried out by a single surgeon, and pump time and ischemic time were similar in the two groups. The results showed that the group in which vancomycin paste was made with tranexamic acid had significantly lower amounts of bleeding 12, 24, and 48 hours postoperatively ($P < 0.001$). This reduction in postoperative bleeding was not accompanied with decreased amounts of packed cell infusion in both groups. All cases were followed for two months and no sternal dehiscence or infection was seen. As there were no prior studies on vancomycin-tranexamic acid paste, the results could not be compared. This superior action of the paste on bleeding with no increased risk of wound problems may present this method as a novel clinical method for preventing excessive mediastinal bleeding from sternal edges.

In this study, in order to match the groups and decrease bias, the patients receiving anticoagulants and antiplatelets had to be excluded. Therefore, further studies are recommended to evaluate the effect of this paste in patients with abnormal coagulation.

5.1. Conclusion

Compared to vancomycin paste made with normal saline, vancomycin paste made with tranexamic acid reduced post on-pump CABG surgery bleeding more effectively. Yet, both pastes had equal safety considering sternal infection and dehiscence.

5.2. Clinical Trial Registration Code

IRCT20190714044205N1

5.3. Ethical Approval

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Authors' Contribution

Study concept: A.M.; study design: A.M. and H.A.; analysis and interpretation of data: A.M. and H.A.; drafting the manuscript: A.M. and H.A.; critical revision of the manuscript for important intellectual content: A.M.; statistical analysis: H.A.

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The authors have no financial interests related to the material in the manuscript.

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