RoleofEpsilonAminocaproicacid&Tranexamic Acid, vs Placebo in Reduction of mediastinal Bleeding following Open Heart Surgery

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Abstract

Background: Post-operative bleeding is one of the Challenging issues in cardiacsurgery. The Excessive bleeding and need for transfusion of blood products may increases the patients' mortality and morbidity. Although use of antifibrinolytics has long been the issue of interest but recently according to some reports of sudden death after use of aprotinin has encountered great limitations. So we decided to find an alternative drug for aprotinin.

Methods and Materials: This study was performed as a Double blind Randomized clinical traial. Three hundred patients underwent open heart surgery using CPB to Shahid Rajaee Heart Center. The patients were divided into 3 groups; each containing 100 patients. Group A Amicar (Caproamin) , group B (Tranexamic acid) and group C (Control). The mean age was 56.5 yr. (Ranged 16-79). 65.3% were male and 85.7% underwent CABG. Need for blood and blood products transfusion in operating room, ICU & ward, as well ad post-op drainage volume during 6, 12, 24 hours were evaluated. The probable post-op complications including post-op myocardial infarction or CNS, renal complications were also recorded.

Results:
The average volume of hemorrhage in group A was 427 cc, 558 cc in group B & 659 cc, in group C, but these differences were not significant statistically (P=0.55). In group A 46% of patients need 1-8 unit of blood, in group B this rate was 60% and in group C was 69% (P=0.093). Prevalence of post op MI was zero in group A 2% in group B and 3% in group C (P=0.377). Incidence of Re-explorationwas 4% in group A, 5% in group B & 6% in group C (P=0.810). The length of hospital stay was the least in group A and was the most in group B, but this difference was also not as significant (P=0.964)

Comment:
Antifibrinolytics, particularly Caproamin can play a role in decreasing post operative mediastinal bleeding, especially non surgical bleeding.
Both Transamin and Caproamin are safe and do not increase thromboembolic events and other complications. These drugs do not cause significant reduction in volume of postoperative bleeding and transfusion requirements in OR and ICU, but when just CABG cases are considered, Caproamin causes significant reduction in post op hemorrhage and as a result reduction in transfusion requirements of blood products.

Keywords: CABG, Mediastinal bleeding, Antifibrinolytic, Open Heart Surgery

Introduction:

Excessive bleeding following open heart surgery is one of the most important issues that may complicate operations. Approximately 60-75% of patients undergoing open heart surgery, receive blood. Incidence of re-exploration due to bleeding is 2-6% and mortality rate may reaches 10-22% (1) . In addition to its effect on complications and mortality, bleeding and re-exploration increases the time of operation, use of blood products, and lengthens time of ICU and hospital stay.
Incomplete hemostasis is the primary cause of mediastinal bleeding. So it's essential to pay attention to meticulous hemostasis in the surgical field and also to prevent fibrinolysis and coagulation disorders judiciously and to treat them in the event of occurrence.
Advent of antifibrinolytics has prompted great enthusiasm among cardiac surgeons. They include tranexamic acid, aminocaproic acid, aprotinin prophylactic use of antifibrinolytics is one method

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to reduce post-op bleeding. Aprotinin is expensive and has thrombotic and allergic complications (5). There is few evidence that other antifibrinolytics increase the risk of thrombotic complications(7). Recently according to reports of sudden death and renal complications, the use of aprotinin has greatly bean limited and it's not approved by FDA anymore. So we decided to select and alternative drug for aprotinin with respect to cost and complications. Therefore € Aminokaproic acic (Caproamin) was evaluated in our study to analyze its effect on lowering the rate of post-op bleeding compared to tranexamic acid and Placebo.

Methods and Materials:

This Double bind randomized study was performed on patients referring to Tehran Shahid Rajaie Heart Center who underwent open heart surgery using CPB. This was an interventional clinical trial from 23 Sep. 2008 to 5 May 2009 on 300 consecutive patients underwent open heart surgery in this center.

Samples were divided randomly into 3 groups:

(1) Group A: Caproamin, 100 cases.
(2) Group B: Tranexamic acid, 100 cases.
(3) Placebo (Normal saline) group, 100 cases.

Preliminary data and all required variables were gathered and incorporated into a special questionnaire. Samples were categorized via balanced block randomization method randomly into 3 groups. Surgeon, perfusionist, anesthesiologist and ICU nurses were not aware of the type of used drug Normal saline were used for control group. For tranexamic acid group, the primary dose of 10 mg/kg through infusion coincident with surgical incision and the maintenance dose of 0.5-2 mg/kg/h in proportion to creatinine and additional 500 mg via pump prim solution were given. For Caproamin group 150 mg/kg was given as loading dose at the beginning of surgical procedure and 1 gr/h during the whole surgery. Doses of antifibrinolytics were adjust based on serum creatinin (Table 1). The data were analyzed by SPSS software version 15. To compare qualitative amounts between intervention and control group, Chi-square and Fischer exact; and to compare quantitative amounts, T-test were implemented

Results:

Regarding the preoperative patient characteristic including age, sex, diabetes, hypertension, history of MI, renal failure, use of plavix or ASA, history of bleeding disorders, distribution of blood groups and the type and times of operation there were not statistically significant difference between the 3 study groups (Table II).

Two hundred fifty seven patients (87.7%) underwent CABG & 43 patients (14.3%) underwent valve replacement. Considering the use of blood products, 274 (91.3%) did not receive platelet and the remaining 17 patients received 0-6 unit of platelet (mean = 1.4 unit). One hundred twenty seven patients (42.3%) did not receive pack cell in the ICU and the remaining, received packed cell between 1-8 units. 244 (74.7%) were not given FFP during ICU stay & 76 (25.3%) received 1-9 units of only 4 patients (7%) need for platelet transfusion from 2 to 11 units.

Sixteen seven (22.3%) weaned from CPB off by support of inotropic agents. Six cases (2%) transferred to OR drainage to of tamponade with a subxyphiod approach. Fifteen (5%) patients re-explored due to mediastinal bleeding. Of these, 11 patients (3.7%) had surgical cause & 4 (1.3%) had no any surgical bleeding source and they experienced coagullopathy. Thirteen patients (4.3%) developed EKG changes in ICU (as Q wave & ST-T changes) & 5 (1.7%) had the clinical presentation of MI.

Seven patients (2.3%) complicated by superficial wound infection & 4 (1.3%) by deep wound infection. Nine cases (3%) developed pleural effusion and chest tube was inserted for 5 (1.7%). The volume of post-op mediastinal hemorrhage during first 6 h of operation was 0-1350cc (mean 252/8 cc). 0-1900cc (mean 402/3cc) for 12 hr and was 50-2450cc (mean 548/12cc) for the first day of ICU stay. Figure I shows the comparison of bleeding volume between the study groups in three periods of time.

The need for blood products in ICU, was 0-8 units of packed cell (mean 1.18 units), 0-9 units of FFP (mean 0.85 unit) and 0-11 units of platelet (mean 0.35 unit).

Length of ICU stay was 2-32 days (mean 3.6 days) and hospitalization was 7.77 day (mean 9.9 days). Hemotocrit at the time of discharge from hospital was 20.3-45% (mean 31%).

Considering transfusion of FFP & platelet during operation, there was not statistically significant difference between the 3 groups. Although the need for inotrope to wean from CPB was by far lower for Caproamin group, but it could not be perceived as reasonable relation.

In spite of the need for transfusion of FFP in ICU (P=0.128) there were no significant difference statistically between the 3 groups. Table II shows the need for platelet transfusion in the groups.

Also, incidence of tamponad, need for re-exploration, occurrence of wound infection & pleural effusion were not different statistically significant. The incidence of pericardial effusion was 33% in Transamine group, 16% for Caproamin group & 23% for control group which were statistically significant. Consequently the use of Caproamin can lower the rate of pericardial effusion via reduction in post-op bleeding (P value: 0.018).

Post-op complications including cerebrovascular & cardiac complications were very low for 3 groups without significant difference (P value: 0.384).

The need for transfusion of pack cell in Transamine group was 3%, 1% in Caproamin group & 9% in control group. So it's clear that the need for transfusion of blood in control group was

remarkably higher than the other 2 groups and in the Caproamin group, the least requirement for blood transfusion was noted during hospitalization, after discharge from ICU (Fig III).

Discussion:

Mediastinal hemorrhage secondary to open hart surgery is one of the most known and fairly common complications of heart surgery. Although technical errors in hemostasis account for the majority of cases, but fibrinolysis and coagulopathy originating from heart lung machine are the most common nonsurgical causes, leading to augment the need for blood product transfusions.

Post-op bleeding is among the most important issues, increasing morbidity, hospital charges and the length of hospital stay. Several antifibrinolytics have been introduced to decrease bleeding due to heart lung machine. Aprotinin was one of the most effective drug of this class which its use was discouraged by the FDA., following some reports of sudden death Caproamin & tranexamic acid are the other 2 drugs of this class multiple studies suggested their usefulness in the reduction of post-open heart surgical bleeding. In our study demographic characteristics of patients in either 3 groups were similar and were not different significantly from statistical point of view.

Average amount of hemorrhage following surgery in Caproamin & tranexamic groups were lower than control group but this difference was not significant statistically. In the Caproamin group no hemorrhage due to non-surgically causes were detected versus one in Transamine and 3 in control group. In the two latter groups severe coagulopathy accounted for mediastinal bleeding. This difference was however not significant statistically (P=0.363) (Figure IV).

The concern that might be occurred with the use of antifibrinolytics, would be acute graft thrombosis following CABG due to reduction in fibrinolysis resulting in a hypercoagulable state. We compared the incidence of post-op MI in 3 study groups. By definition, post-op MI was present only when 2 of the following 3 criteria were met, EKG changes, increase in specific myocardial enzymes (CPK-MB, Troponin I) and changes in myocardial segmental motion observed in echocardiography. According to this definition, there were not statistically significant increase in the incidence of post-op MI in Transamine & Caproamin group compared to control group (P=0.377). So it seems the fear of increasing the risk of graft thrombosis with the use of antifibrinolytics is not the case, as it presumed previously. To evaluate post-op hemorrhagic complications, we implemented pericardial & pleural effusion as indirect indices. It was clarified that the prevalence of mild to moderate pericardial effusion without the need for surgical intervention was 33% in Transamine group, 16% in Caproamin to 23% in control group which was significant from statistical view. So it reveals that the prevalence of pericardial effusion in the Caproamin group was by for lower than the other 2 groups.

The prevalence of pleural effusion requiring intervention as pleural tap or chest tube insertion were not different significantly (P=0.5).

Given the fact that cerebral thromboembolic complications were not significantly different among the 3 groups (P=0.3), so antifibrinolytics could not increase the risk of cerebral thromboembolism in present study. As mentioned previously the need for transfusion of blood in the Caproamin group was slightly lower than the other groups, but this difference was not statistically significant. However after discharge of ICU and during hospitalization in surgical ward, the need for blood transfusion was 9% for control group, 3% in Transamine groups 1% in Caproamin group (P=0.02). As a result antifibrinolytics especially Caproamin decrease considerably the need for packed cell transfusion during hospitalization.

The need for pack cell transfusion in operation room and during ICU stay was not significantly different statistically between the 3 groups.

Although the need for FFP & platelet transfusion was slightly lower in Caproamin group than other groups but this was not determined as significant, statistically (P=0.128).

Considering the volume of drainage during 6, 12, 24 hours after surgery, though it was lower in Caproamin group in relation to other groups from numerical view, but the difference was not significant as well.

Incidence of post-op complications including cardiac, pulmonary, renal, cerebral and infective complications was the same in 3 groups. Taking into consideration the length of hospital stay, it was the longest for control group (9.3±11 days) and the shortest for Caproamin group (3.9±8.2 days), but this difference was also not significant (P=0.17).

When data was analyzed just for the CABG cases showed more prominent role of Caproamin in reducing the non surgical postoperative mediastinal hemorrhage and also need for surgical re intervention and need for blood products. Therefore we are continuing the study exclusively for CABG patients.

In summary according to this study, it could be stated that antifibrinolytics, particularly Caproamin can play a considerable role in decreasing post operative mediastinal bleeding, especially non surgical bleeding and also overall pack cell requirements during hospitalization.

Antifibrinolytics do not increase the risk of cerebral thromboembolism or thrombosis of vascular grafts in patients underwent CABG. As well as, these drugs do not increase renal complications. Which remains to be established is concerning the role of these during in high risk patients for bleeding & coagulopathy, through further studies to determine the benefits of antifibrinolytics more accurately.

Acknowledgement: We would like to thank to all our colleagues in operating room, intensive care units and surgical ward for their helps.

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	Tranexamic acid		Caproamine
Loading dose	10 mg/Kg		150 mg/Kg
Maintenance dose	Cr<1.3 mg% 1.3<Cr<1.6 1.6<Cr<3 Cr>3	2mg/Kg 1.5 mg/Kg 1mg/Kg 0.5mg/Kg	1 g/hour

TableI: Protocol for anti-fibrinolytic drugs administration.

	Group A	Group B	Group C	P value
Age (mean)	59+/-10	56+/-11	54+/-13	0.483
Sex (male/female)	71/29	67/33	58/42	0.141
Diabetes mellitus	40%	35%	41%	0.647
HTN	39%	33%	34%	0.636
Previous MI	27%	26%	28%	0.950
Use of Plavix	47%	42%	37%	0.358
Use of Aspirin	98%	88%	92%	0.023
Hemorrhagic diathesis	1%	1%	2%	0.471
Operative procedure				0.0471
CABG	95%	88%	74%	
Valve surgery	5%	12%	26%	
Graft no. (mean)	3.3+/-0.8	3.2+/-0.7	3.3+/-0.7	0.811
Frequency of surgery				0.114
First operation	98%	93%	92%	
Second operation	2%	5%	8%	
Third operation	0	2%	0	

Table II: Preoperative and operative patients' characteristics in the 3 study group.

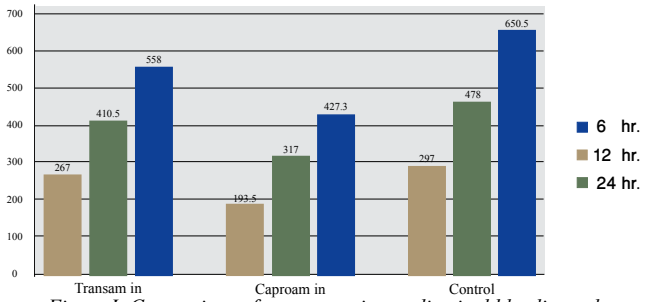

Figure I: Comparison of post operative mediastinal bleeding value (6hr. , 12hr. , 24hr.) between three groups

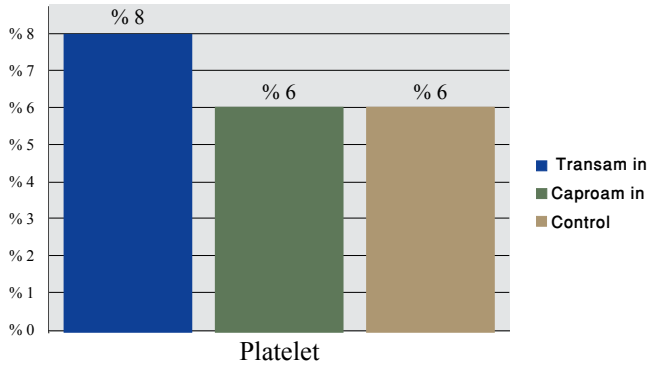

Figure II: Prevalence post operative platelet requirement between 3 groups

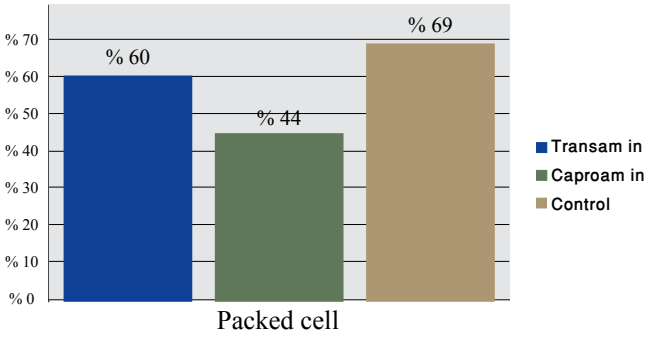

Figure III: Post operative blood transfusion between 3 groups

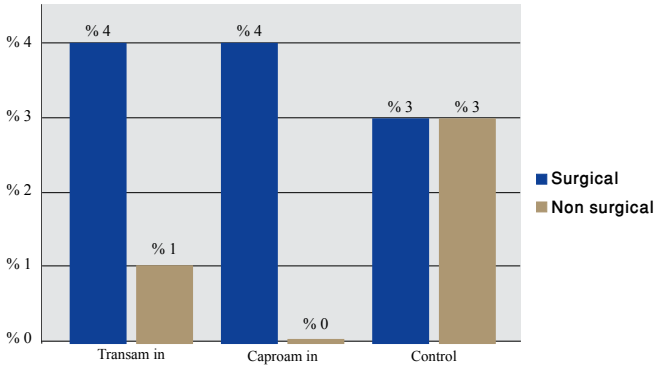

Figure IV: Post operative mediastinal bleeding sources between 3 groups