COMPARISON OF TOPICAL USE OF PROTAMINE AND TRANEXAMIC ACID IN SURGICAL PATIENTS REQUIRING CARDIO-PULMONARY BYPASS

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ABSTRACT

Objective: To determine the effectiveness of local protamine in reducing post-operative blood loss compared to local tranexamic acid.

Study Design: Randomized controlled trial.

Place and Duration of Study: Armed Forces Institute of Cardiology / National Institute of Heart Diseases Rawalpindi from January 2011 to September 2011.

Patients and Methods: One hundred and twenty cardiac surgical patients were randomly divided into two equal groups, one receiving local protamine while the other group receiving local tranexamic acid before chest closure. The efficiency was measured as post-operative blood loss and requirement of blood and blood products in the post-surgical ICU.

Results: Average blood loss in protamine group was significantly less (252.97 ml) compared to tranexamic acid group (680.67 ml). Number of patients requiring no post-operative blood transfusion was significantly higher in protamine group (76.7%) compared to tranexamic acid group (53.3%).

Conclusion: Local protamine is more effective in reducing post-operative blood loss than local tranexamic acid.

Keywords: Cardiac surgery, Protamine, Tranexamic acid, Post-operative blood loss.

INTRODUCTION

There has been a tremendous change in practice of transfusion of blood and related products over the previous decade or so due to improved awareness of transfusion related hazards. The efforts have been successful in reducing blood transfusions to a great extent but coagulopathy remains a serious problem in patients after coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB). The combination of factors like thrombocytopenia, acquired platelet dysfunction, clotting factors loss, free heparin, and increased fibrinolysis results in coagulopathy[1-3]. A number of patients (2-7%) require re-exploration for bleeding following cardiac surgery with CPB. Of these, 50–80% was found to be medical rather than surgical bleeding[4]. Lemmer et al[5] found that extracorporeal circulation results in significant fibrinolysis, as reflected by increased concentrations of plasmin and fibrin degradation products (FDP), both of which have deleterious effects on platelet function. Fibrinolysis was found to be responsible for 25–45% of significant post bypass bleeding[6]. Antifibrinolytic agents like aminocaproic acid[4], aprotinin[7], and tranexamic acid (TA)[8] have been used to diminish post-bypass bleeding. Tranexamic acid has been found to bind to lysine binding sites of plasmin and plasminogen. Plasminogen is displaced from these sites as they are saturated by tranexamic acid thus inhibiting fibrinolysis[9]. TA has been used both systemically and topically. Topical TA has been used successfully in controlling bleeding in gynaecological, bladder, oral, and otolaryngeal surgeries[10-12]. Intravenous TA administration increased the risk of early graft closure in coronary artery bypass grafting[13]. When used topically, TA was found effective in controlling bleeding in patients who were being treated with anticoagulants pre-operatively.

Heparin is used as an anticoagnlant during cardiac surgeries. By inactivating thrombin, heparin not only prevents fibrin formation but

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also inhibits thrombin-induced activation of platelets and of factors V and VIII[14].

Protamine sulfate is a cationic polypeptide derived from salmon sperm that can bind negatively charged unfractionated heparin (UFH)[15]. The exact mechanisms of the molecular interaction between protamine and heparin are not well defined but this binding serves to neutralize the antithrombin-mediated anticoagulant properties of heparin. The resultant protamine-heparin complex is rapidly cleared by the reticuloendothelial system[16]. Consequently, for more than three decades, protamine has been widely used to reverse the anticoagulant effects of UFH. Protamine is the treatment of choice for patients who develop significant bleeding while on UFH[17,18]. Furthermore, protamine is routinely administered postoperatively to reverse the high concentrations of UFH required for patients undergoing cardiac surgery and cardiopulmonary bypass (CPB)[19].

Many studies have been done to look for an appropriate dose of protamine to completely reverse the effects of heparin[20,21] without much success. The consensus guidelines recommend the use of 1 mg protamine for 100 IU heparin[17,18] (protamine paper) mainly to avoid overdose of protamine which in itself can have anticoagulant effects[22-24]. We could not find topical use of protamine in immediate post surgical phase in medical literature. Topical application of protamine in the immediate post surgical phase will rapidly reverse heparin function at the site of surgery which will allow the clot formation process to start quickly and effectively while systemic protamine will take care of heparin in the peripheral circulation.

The purpose of this study was to determine the effectiveness of local protamine in reducing post-operative blood loss and adopt a protocol for preventing post–op blood loss in our clinical setting.

MATERIALS AND METHODS

This randomized double-blind controlled trial was carried out at the Armed Forces Institute of Cardiology – National Institute of Heart Diseases (AFIC-NIHD) from Jan 2011 to Sep 2011. After approval from the Institutional Review Board, 120 consecutive patients undergoing elective cardiac surgery were included in the study. Patients undergoing combined CABG and valve surgery, redo surgery and those having pre-existing liver disease and/or bleeding disorders, patients on antiplatelet drugs and heparin pre-operatively, were excluded. The patients were randomly divided into two groups, 'A' and 'B' of 60 patients each, using random numbers table.

Surgery was performed by the same team of surgeons in all cases. At the termination of bypass, heparin was reversed with protamine using empiric dosage of 3 mg/Kg slow intravenously, further titrated to achieve the activated clotting time (ACT) within 10% of the baseline. Before the insertion of sternal wires, the mediastinal cavity was irrigated with the "irrigation solution" while keeping clamps on the drain tubes. The irrigation solution was constituted of 30 ml of warm normal saline with 100 mg of protamine in group 'A' and 2000 mg of tranexamic acid in group 'B' keeping the surgeon blind. After skin closure, the drain clamp was removed and the retaining time of the irrigation fluid was noted in addition to the total cardiopulmonary bypass (CPB) time and cross-clamp times.

In the post-surgical ICU, the patients were monitored for blood loss half hourly in the first four hours and then hourly for next 20 hours. Transfusion requirements for blood and blood products (packed RBCs, fresh frozen plasma and platelets were also noted for 24 hours in the post-operative period keeping haemoglobin (Hb) above 8.5 g/dL.

Data was analyzed using SPSS version 17. Descriptive statistics were used to describe the results i.e. mean, standard deviation (SD) and standard error (SE) for quantitative variables while frequency and percentages for qualitative variables. For the comparison of quantitative

variables independent sample t-test was applied while chi-square test was applied for qualitative variables between the two groups.

Table-1: Comparison of demographic data in both groups.

	Group A	Group B
Mean Age (in years)	50.43 years (SE = 1.94)	49.77 years (SE = 1.79)
Male Female ratio	1:2.5	1:3.6
Mean CPB Time	65 (SE = 2.2)	68 (SE = 1.65)
Mean Cross Clamp Time	34 (SE = 1.5)	33 (SE = 1.9)

Table-2: Comparison of Blood loss between both the groups.

Blood Loss (ml)	Group A (n = 60)	Group B (n = 60)
Mean ± SD	252.97 ± 17.07	680.67 ± 31.91
Median	210	625
Inter-quartile range	150 - 300	457.5 - 890
p-value	< 0.001	

Table 3: Comparison of fresh frozen plasma and platelets between both the groups.

	Group A (n = 60)	Group B (n = 60)	*p*-value
Fresh Frozen Plasma			
0 units	58 (96.7%)	30 (50%)	< 0.001
2 units	0 (0%)	7 (11.7%)	
3 units	2 (3.3%)	19 (31.7%)	
6 units	0 (0%)	4 (6.7%)	
Platelets			
0 bags	58 (96.7%)	34 (56.7%)	< 0.001
2 bags	0 (0%)	4 (6.7%)	
3 bags	2 (3.3%)	17 (28.3%)	
4 bags	0 (0%)	1 (1.7%)	
6	0 (0%)	4 (6.7%)	

RESULTS

Data was available for all 120 patients (90 males and 30 females). Mean age in group 'A' was 50.43 years (SE = 1.94) and in group B'' it was 49.77 years (SE = 1.79). There was no significant difference in the mean CPB and cross-clamp times in both the groups (Table-1). There were 43 (71.7%) males in group A while in group B there were 47 (48.3%) males.

In the post-operative period, patients in group B had significantly higher blood loss as compared to group A (Table-2). In group A majority i.e. 76.7% of the patients didn't need any blood transfusion followed by 1 pack in the rest 23.3% patients while in group B majority i.e. 53.3% patients had 1 pack of blood transfusion followed by 2 packs in 28.3% patients. Group B had significantly more blood transfusions as compared to group A (Figure-1). Group B needed significantly higher units of fresh frozen plasma as compared to group A ($p < 0.001$). Similarly group B needed significantly higher number of

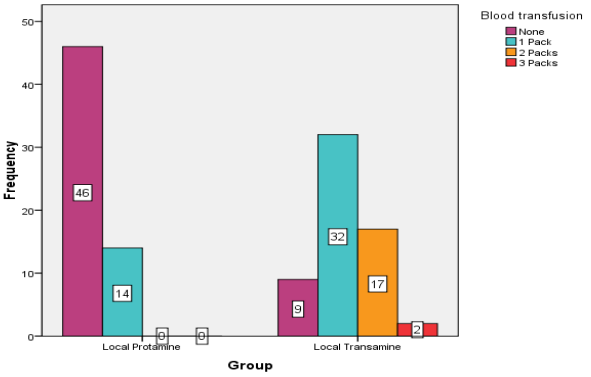

Figure-1: Description of Blood transfusion between both the groups.

bags for platelets as compared to group A (Table 3).

DISCUSSION

This study shows significant difference between the two groups in terms of requirements of transfusion of blood products. Topical use of protamine proved very effective in our study to reduce post operative blood transfusions. One would expect protamine to achieve this by improving the haemostasis after surgery which we believe was due to better reversal of effect of heparin at surgical site. The initial few hours after the surgery are crucial in terms of haemostasis and better wound healing.

Modern understanding is that in vivo haemostasis begins with tissue factor (TF) and circulating factor VII[25]. A network of reactions is triggered with platelets playing a central role, rather than a unidirectional enzyme cascade. TF is a transmembrane glycoprotein expressed on cells outside the bloodstream. Coagulation is initiated when TF becomes exposed at the site of vessel injury, binds and activates circulating factor VII.

Coagulation overlaps with inflammatory pathways; for example, activated platelets release inflammatory cytokines and thrombin activates monocytes. Coagulation can activate the inflammatory system and vice versa. This becomes relevant with extreme activation of either system, such as in systemic inflammation.

During CPB for open heart surgery, heparin is required to prevent blood clotting within the CPB circuit[3,27]. By facilitating the action of antithrombin III, heparin inhibits thrombin. It clearly shows that thrombin plays a pivotal role in the coagulation cascade and protamine reverses the effect of heparin which blocks the activity of thrombin.

Clotting time in normal plasma is 5-7 minutes which means that in the absence of inhibitors the clotting factors will work within minutes at the site of surgery. Topical protamine effectively provides clotting factors in such environment. Since heparin can only stop the formation of the clot but can not break an existing clot, the initial 30 minutes of protamine exposure (heparin free environment) start the process of clot formation. Intravenous protamine will continue to neutralize heparin but even if heparin effect bounces back in 30 minutes after the protamine is removed from site of surgery the initial steps in the clot formation can not be reversed by heparin which then lead to better haemostasis.

Our study does not give the exact details of the mechanism behind the better haemostasis with local use of protamine but clearly shows the need for further studies with local use of protamine to improve the haemostasis.

CONCLUSION

We concluded from our study that local protamine was more effective in reducing post operative bleeding than tranexamic acid.

Conflict of Interest

This study has no conflict of interest to declare by any author.

REFERENCES

1. Kucuk O, Kwaan HC, Frederickson J, Wade L, Green D. Increased fibrinolytic activity in patients undergoing cardiopulmonary bypass operation. Am J Hematol 1986; 23: 223-9.
2. Harker LA, Malpass TW, Branson HE, Hessel EA II, Slichter SJ. Mechanism of abnormal bleeding in patients undergoing cardiopulmonary bypass: acquired transient platelet dysfunction associated with selective alpha-granule release. Blood 1980; 56: 824-34.
3. Depotis GJ, Santoro SA, Spitznagel E, Kater KM, Cox JL, Barnes P et al. Prospective evaluation and clinical utility of on-site monitoring of coagulation in patients undergoing cardiac operation. J Thorac Cardiovasc Surg. 1994; 107(1): 271-9.
4. Daily PO, Lamphere JA, Dembitsky WP, Adamson RM, Dans NF. Effect of prophylactic epsilon-aminocaproic acid on blood loss and transfusion requitments in patients undergoing first-time coronary artery bypass grafting: a randomized, prospective, double-blind study. J Thorac Cardiovasc Surg 1994; 108: 99-105.
5. Lemmer JH Jr, Stanford W, Bonney SL, Breen JF, Chomka EV, Elderge WJ et al. Aprotonin for coronary bypass operations: efficacy, safety, and influence on early saphenous graft patency-a multicenter, randomized, double blind, placebo-controlled study. J Thorac Cardiovasc Surg 1994; 107: 543-3.
6. Kevy SV, Glickman RM, Bernhard WF, Diamond LK, Grass RE. The pathogenesis and control of the hemorrhagic defect in open heart surgery. Surg Gynecol Obstet 1966; 123: 313-8.
7. Cosgrove DM, Heric B, Lytle BW, Taylor PC, Novoa R, Golding LA et al. Aprotonin therapy for reoperative myocardial revascularization: a placebo-controlled study. Ann Thorac Surg 1992; 54: 1031-8.
8. Horrow JC, Van Riper DF, Strong MD, Brodsky I, Parmet JL. Haemostatic effects of Tranexamic acid and Desmopressin during cardiac surgery. Circulation 1991; 84: 2063-70.
9. Longstaff C. Studies on the mechanisms of action of Aprotonin and Tranexamic acid as plasmin inhibitors and antifibrinolytic agents. Blood Coagul Fibrinolysis 1994; 5: 537-42.

10. Versraette M. Clinical application of inhibitors of fibrionolysis. Drugs 1985; 29: 236-61.
11. Valsecchi A. Further notes on the topical use of Tranexamic acid in the treatment of gynaecological haemorrhage. Minerva Ginecol 1980; 32: 825-30.
12. Sindet-Pedersen S, Ramtro G, Bernvil S, Blomback M. Haemostatic effect of tranexamic acid mouthwash in anticoagulant-treated patients undergoing oral surgery. N Engl J Med 1989; 320: 840-3.
13. Ovrum E, Holen EA, Abdelnoor M, Oystese R, Ringdal ML. Tranexamic acid (Cyklokapron) in not necessary to reduce blood loss after coronary artery operations. J Thorac Cardivasc Surg 1993; 105: 78-83.
14. Hirsh J, Anand SS, Halperin JL, Fuster V. Mechanism of Action and Pharmacology of Unfractionated Heparin. Arterioscler Thromb Vasc Biol. 2001; 21: 1094-6.
15. Horrow JC. Protamine: a review of its toxicity. Anesth Analg 1985; 64: 348-61.
16. Carr JA, Silverman N. The heparin-protamine interaction: a review. J Cardiovasc Surg 1999; 40: 659-66.
17. Baglin T, Barrowcliffe TW, Cohen A, Greaves M. Guidelines on the use and monitoring of heparin. Br J Haematol 2006; 133: 19-34.
18. Hirsh J, Bauer KA, Donati MB, Gould M, Samama MM, Weitz JI. Parenteral anticoagulants: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133 suppl 6: 141S-159S.
19. Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U et al. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008; 34: 73-92.
20. Miyashita T, Nakajima T, Hayashi Y, Kuro M. Hemostatic effects of low-dose protamine following cardiopulmonary bypass. Am J Hematol. 2000; 64(2): 112-5.
21. Charnaia MA, Morozov IUA, Gladysheva VG. [A method for calculating the additional quantity of protamine sulfate during cardiosurgical operations]. Klin Lab Diagn. 2007; (5): 28-9.
22. Brecher AS, Roland AR. Protamine inhibits formation of the covalent factor IXa-anti-thrombin complex. Blood Coagul Fibrinolysis 2008; 19: 591-6.
23. Chu AJ, Wang ZG, Raicu M, Beydoun S, Ramos N. Protamine inhibits tissue factor - initiated extrinsic coagulation. Br J Haematol 2001; 115: 392-9.
24. Mochizuki T, Olson PJ, Szlam F, Ramsay JG, Levy JH. Protamine - reversal of heparin affects platelet aggregation and activated clotting time after cardiopulmonary bypass. Anesth Analg 1998; 87: 781-5.
25. Hoffman M, Monroe D. Rethinking the coagulation cascade. Current Haematology Reports 2005; 4: 391-6.