ABNORMAL POST-OPERATIVE BLEEDING IN PATIENTS WITH CONGENITAL HEART DISEASES UNDERGOING OPEN HEART SURGERY

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ABSTRACT

Objective: *To report the incidence of postoperative bleeding and to evaluate perioperative parameters and its relationship with the volume of blood loss & blood transfusion requirement.*

Methodology: *This was a retrospective study of 49 patients with congenital heart diseases undergoing open heart surgery developing abnormal post operative bleeding in Ibn Al-Bitar hospital for cardiac surgery from January 1st, 2004 to December 31st, 2008, There were 29 males (59%), and 20 females (41%). Age ranged from 3-38 years with an average of 20 years. The study involved data obtained when the patients arrived at the intensive care unit (ICU) and for the following 24 hours.*

Results: *Young children, female gender, lower body weight & surface area, cyanotic heart diseases, types of procedures, longer time of CPB & aortic clamping time, low temperature, type of oxygenator used in CPB (affinity), higher total intra- operative doses of heparin & protamine, all were shown to significantly increase postoperative blood loss & transfusion requirement. The incidence of postoperative bleeding was 9.35%. Twelve percent needed reoperation to control hemorrhage. The morbidity was 24.3% and the mortality was 4.1%.*

Conclusion: *Factors that may contribute to increased blood loss and transfusion requirement include age below 10 years, female gender, low body weight and surface area, prolonged duration of CPB, hypothermia, preoperative anemia, and high doses of heparin & protamine.*

Key Words: *Post-operative bleeding, Congenital Heart Disease, Open Heart Surgery*

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INTRODUCTION

Cardiopulmonary bypass (CPB) for open-heart surgery (OHS) is commonly performed in hospitals throughout the world, in which the blood is under obligatory exposure to a large foreign surface leading to a wide range of changes in blood that are still being investigated. With improvements in surgical techniques and extracorporeal oxygenation, Patients undergoing cardiac surgery with CPB are at increased risk for excessive perioperative blood loss requiring transfusion of blood products. Such bleeding is related to both the surgical damage to the blood vessels (mechanical) and acquired defect in hemostasis (coagulopathy) involving platelets, coagulation and fibrinolytic systems. CPB activates platelets with resultant structural and biochemical changes. These changes are: 1- Changes in Platelet Surface Molecules[1], 2- Formation of Platelet Conjugates[2], 3- Effect on Platelet Count[3], 4- Altered Platelet Force Generation[4]. There is excessive activation of the hemostatic system, which is related to interaction of blood with the extensive, nonendothelial CPB surfaces[5], activation of the extrinsic clotting pathway[6] secondary to surgical trauma and retransfusion of pericardial blood[7]. Activation of fibrinolysis occurs simultaneously by means of several mechanisms. Tissue plasminogen activator (t-PA) release contributes to fibrinolysis and is promoted by CPB-mediated contact activation of factor XII, thrombin, hypothermia, traumatized endothelial cells, and returned blood from the pericardiotomy suction[8].

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Thrombin has recently been shown to activate the inflammatory system, specifically complement[9]. Thrombin, in combination with thrombomodulin on the endothelial cell surface, activates protein C, which acts to clear the previously generated activated factors V and VIII. Thrombin also down-regulates hemostasis by releasing tissue factor pathway inhibitor, which inhibits the tissue factor pathway and stimulates release of t-PA, which cleaves plasminogen to plasmin. Plasmin cleaves fibrinogen and fibrin monomer into fibrin split products and cross-linked fibrin polymer into D-dimers, respectively, inactivates coagulation factors V and VIII, and has direct effects on platelet membrane receptors. Specifically, plasmin leads to either internalization or destruction of the adhesive glycoprotein Ib receptor on the platelet surface[3], and may detrimentally affect IIb/IIIa receptors. An exaggerated inflammatory response may also affect the hemostatic system as mediated by means of elastase released from leukocytes or complement activation. Mechanisms related to heparin and protamine are additional factors. Patients with cyanotic congenital heart disease show abnormalities in hemostasis mechanism and normally involved factors synthesized in the liver, which is the vitamin K dependent factors (prothrombin, factors VII and IX, and factor V). No evidence was found of activation of the coagulation or fibrinolytic systems[10]. The defects can be explained by deficient synthesis resulting from systemic hypoxia as well as from sluggishness of the local microcirculation caused by high blood viscosity[11]. Thrombocytopenia in cyanotic diseases is dangerous and it related to immune thrombocytopenia, polycythemia, hyperviscosity, pseudothrombocytopenia, and drugs[12]. In addition to that platelet dysfunction[13] and an abnormality of the von Willebrand's factor[14] have been described. Children with acyanotic CHD may also have a bleeding disorder, which is usually mild and characterized by a prolonged bleeding time and normal platelet count[15]. The aim of our study is to report the incidence of postoperative bleeding and to evaluate perioperative parameters and its relationship with the volume of blood loss & blood transfusion requirement.

METHODOLOGY

A retrospective study was performed for 49 patients with congenital heart diseases developing abnormal post operative bleeding acceptable blood loss 2ml/kg/hr for the 1st 3 hours, 1ml/kg/hr for the next 3 hours,and less than o.5ml/kg/hr for 12 hours post-closure[16] who underwent open heart surgery at Ibn Al-Bitar hospital for cardiac surgery starting January 1st, 2004 to December 31st ,2008. The study involved data obtained when the patients arrived to the intensive care unit (ICU) and for the following 24 hours. Different parameters concerning the cardiac pathology, anesthesia, operation, and post-operative course were recorded from the patient records. Body surface area of the patients was obtained by nomogram using height and weight of the patient.

Pre-operatively obtained laboratory hematological assays included complete blood cell count with platelet count and prothrombine time (PT). Partial thromboplastin time and bleeding time not done. All patients had PT less than 15 seconds and platelets count between 150000/cc to 250000/cc.

ACT (activated clotting time) had been done after induction of anesthesia, 10 minutes after giving heparin, on CPB, and after administration of protamine. Standardized surgical and CPB technique was used with cooling to mild to moderate hypothermia (25-32 C). Cold crystalloid potassium cardioplegia for myocardial preservation was used to maintain myocardial temperature below 15 C. Anesthesia was induced and maintained with fentanyle and sometimes with droperidol and valium. Muscle relaxation was achieved with pancuronium and patients were ventilated with 100% oxygen. Non hemic crystalloid solution (Ringer lactate, sodium bicarbonate and mannitol) was used for priming of CPB circuit. For cyanotic congenital heart diseases, the crystalloid prime solution was used with the addition of human albumin. The oxygenator used where of membrane type, but of three different origins, {Dideco, Mirandola, Mo, Italy. Affinity, NT, Medtronic, Netherlands. Safe II, vitalcor, inc. US,}.

The protocol for heparin and protamine dosage used in patients differed according to anaesthetist trend. The systemic anticoagulation was accomplished with heparin with an initial dose of 3 mg/kg. Adequate anticoagulation for CPB was assessed with ACT test and further doses of heparin were administered prior to and during CPB to maintain the ACT above 480 seconds. After re-warming the patient to 37 C, CPB was discontinued and heparin was neutralized with protamine in different dose:ratio protocols were used according to anaesthetist trend as 1:1, 1.5:1, 2:1, or >2.1:1protamine:heparin ratio. Additional protamine was administered during the intra-operative period based on the lack of return of the ACT to the patient's pre-CPB baseline value. Chest drainage during the first postoperative 24 hours was divided on body weight to indicate parameter for postoperative blood loss. Statistical analysis was performed using one way analysis of

variance, t-test for unequal variances to calculate P value. $P < 0.05$ was considered significant.

RESULTS

The total number of the patients was 49 , There were 29 male (59%), and 20 female (41%). Age ranged from 3-38 years with an average of 20 years , Only 1 patient had scoliosis, no patient had history of subacute bacterial endocarditis (SBE), no patient had received any drug that may affect hemostasis (e.g aspirin, heparin) pre-operatively. Operations done by 8 different surgeons. 25 patients received Tranexamic acid perioperatively. All the patients who reached ICU received blood (stored & fresh) during the first 24 postoperative hours of ICU stay. The mean blood loss in all patients was 25ml/kg, and the mean blood transfusion was 26ml/kg. 40 patients (82%) received FFP. And no patient receives platelets. The annual incidence of abnormal bleeding in congenital heart diseases is shown in Table 1, and the total incidence is (9.3%). Bleeding and transfusion requirements were examined with different parameters. There was increase in amount of blood loss with a correlated increase in transfusion requirement in young children (below 10 years) in comparison to teen age and middle age group (P=0.01). Female gender (in different age groups) had more blood loss and transfusion requirement than male (P=0.02).

A progressive decrease in blood loss and transfusion requirement was noted with increase in body weight and body surface area (figure 1) (P=0.01), (figure 2) (P=0.02) consequently. Significant increases in blood loss and transfusion requirement with cyanotic heart diseases were found in comparison to acyanotic heart diseases (P=0.02). There was a significant direct correlation between duration of CPB and aortic clamping time and postoperative blood loss and transfusion requirement (figure 3) (P=0.03),. Temperature during CPB also had a relation with blood loss and transfusion requirement (figure 4) (P=0.04). Increase in both intraoperative heparin and protamine doses have shown a significant increase in blood loss and transfusion requirement (P=0.02), (P=0.015) consequently. In addition a significant relation was found with protamine: heparin ratio (P=0.02). Preoperative hematocrit value was shown to be important (in its extreme values) in postoperative blood loss and transfusion

Table 1: Annual Numbers of Patients with Congenital Heart Diseases and Incidence of Abnormal Postoperative Bleeding

Year	No. of Patient with Bleeding	Total no. of Patient with CHD	Incidence %
2004	15	121	12.3%
2005	10	130	7.7%
2006	7	100	7.0%
2007	9	83	10.8%
2008	8	90	8.8%
Total	49	524	9.3%

Figure 1: Blood loss and transfusion requirement by body weight (P=0.01)

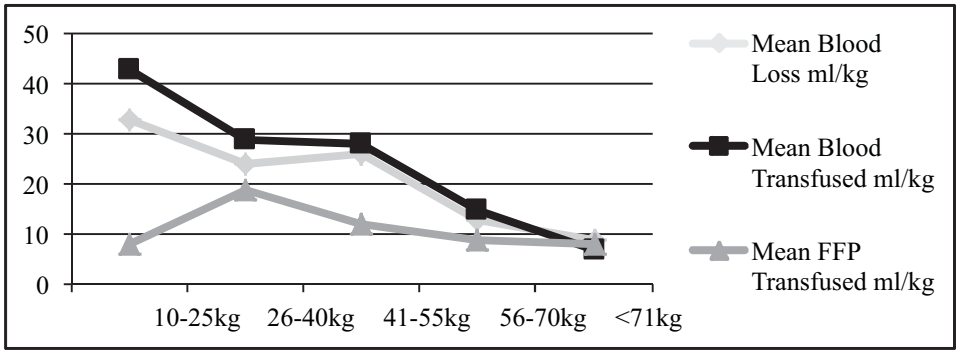


Figure 2: Blood loss and transfusion requirement by body surface area (m^2) (P=0.02)

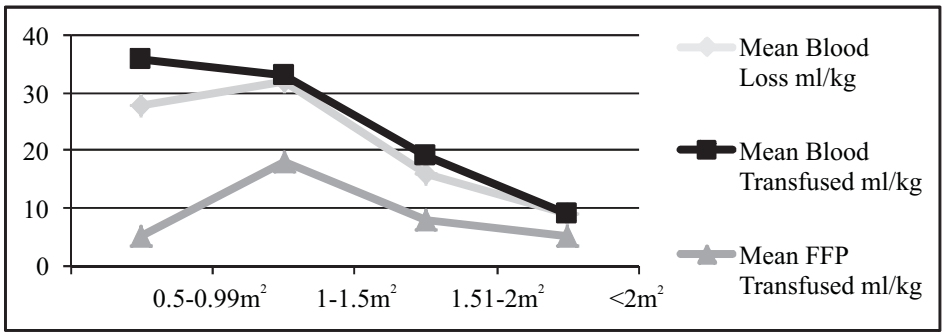


Figure 3: Blood loss and transfusion requirement by CPB time (P=0.03)

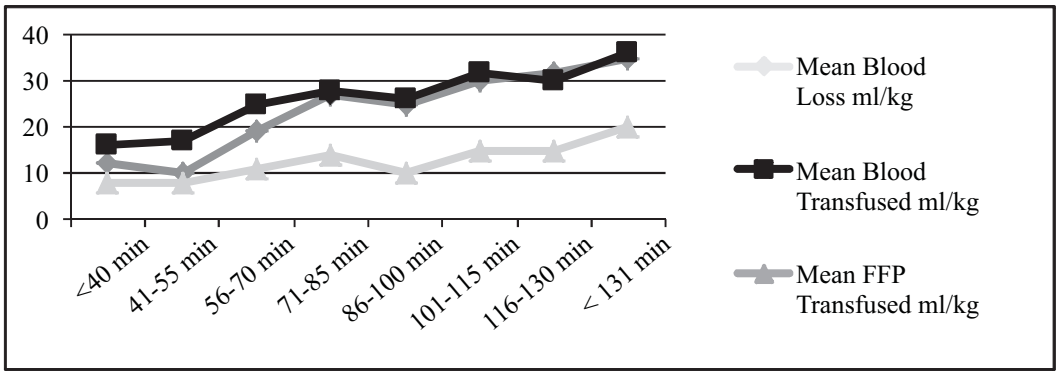
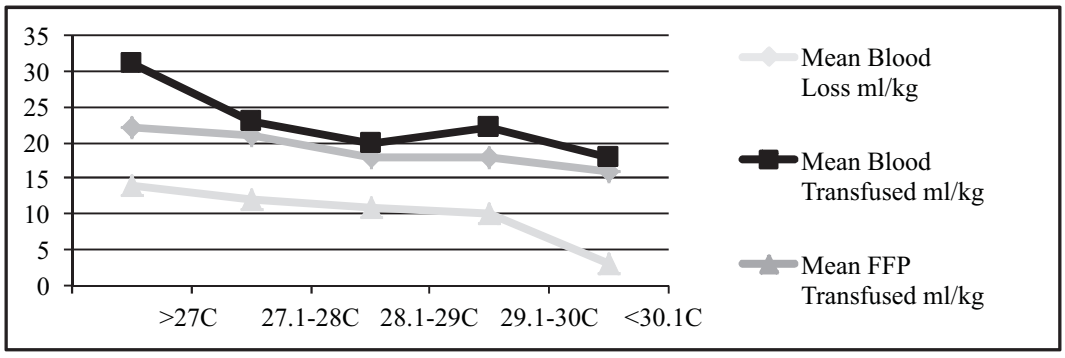


Figure 4: Blood loss and transfusion requirement by temperature during CPB (0.04)



requirement (P=0.03). Administration of Tranexamic acid has a significant role in decreasing postoperative blood loss and transfusion requirement (P=0.01).

Bleeding in 6 patients (12.2%) necessitated reopening to stop bleeding , of those 5 patients (84%) had cyanotic congenital heart diseases. Two patient (16%) were clinically and operatively found to be with acute cardiac tamponade. 3 patients had ACT test that was done in the ICU and was identical to the standard pre-bypass value. Two patients had an added protamine doses before decision of reoperation. Table 2 illustrate the complications associated with post operative bleeding.

Table 2: Complications of Post-Operative Bleeding

Complication	Number of Patients	Percentage
Reopening for Control of Bleeding	6	12.2%
Renal failure	1	2%
Empyema	1	2%
Cerebrovascular stroke	1	2%
Cardiac arrhythmias	1	2%
Death	2	4.1%
Total	12	24.3%

DISCUSSION

Cardiac operation using cardiopulmonary bypass results in various hemodynamic, microcirculatory, and metabolic alterations. Changes in coagulation are the most often seen sequelae of CPB. Approximately 10% to 20% of patients undergoing cardiac operations exhibit inadequate hemostasis varying in its duration and severity [17]. Identification of patients at high risk of postoperative bleeding (by determination of the factors associated with excessive bleeding) is important, because those patients may benefit from blood conservation strategies.

In the present study, we found that age continues to be an important predictor of bleeding. Blood loss and transfusion requirement were inversely related to age, this result was confirmed by other studies by William et al [18]. Several factors that may contribute to increased blood loss were found to be age associated; these included preoperative clinical status and drug therapy, results of coagulation tests before and during CPB, CPB duration and technique, and complexity of operation. In addition to increased heparin sensitivity in children less than 10 years [19], and the need for RBCs to replace the blood lost in blood samples makes RBCs transfusions almost unavoidable in those children[20].

Female gender is an important operative risk factor. It is well established that women require more red cell transfusions during cardiac surgery. This is partly related to the impact of CPB-related hemodilution[21]. One possible explanation is that gender-related differences in hypercoagulability may predispose female patients to an accelerated consumption of coagulation during extracorporeal circulation, which may be aggravated by inadequate heparin anticoagulation.

An obligatory volume of blood is lost in most patients during cardiac surgical procedures, both in the oxygenator and from chest incisions. These amounts represent a relatively greater loss in patients with small blood volume and hence body weight and body surface area. The same amount of blood loss in a patient with a large body mass represents a relatively small percentage of the total blood volume[22].

Patients with cyanotic congenital heart diseases show more blood loss and transfusion requirement than those patients with acyanotic heart diseases, this difference due to multiple factors including, impairment of platelet aggregation (48% in cyanotic, and 14% in acyanotic)[23]. The severity of thrombocytopenia, shortened platelet survival, and platelet dysfunction seems to be related to the degree of arterial hypoxemia and hemoconcentration[24]. With more profound hypoxemia the hepatic synthesis of clotting factors may be depressed, while the compensatory hemoconcentration lead to a relative plasma deficiency and impaired clot formation.

As the CPB duration increased a progressive impairment in platelet function occurred[25], excessive bleeding after long CPB intervals may be related, in part, to a thrombin-mediated consumptive state (systemic thrombin generation has been shown to occur in stepwise, time dependent fashion), since fibrin monomer, thrombin/antithrombin complexes, and prothrombin fragment 1.2 levels increase progressively with time on CPB when ACT-based anticoagulation protocols are used. In addition to that prolonged CPB time mean prolongation of time of contact of blood to extracorporeal circuit, more exposure to hypothermia and more heparin doses are used, and usually associated with more complex procedures.

Hypothermia leads to significant reduction of platelet aggregation. Other investigators have confirmed that hypothermia appears to be an important factor concerning platelet function[26]. Thrombin/antithrombin III complex, which represents a sensitive marker for coagulation activation during CPB, was higher in hypothermic

than in normothermic patients indicating that the coagulation system was more activated in the hypothermic patients. Altered microcirculation and a more activated coagulation system at the microcirculatory level may be one possible explanation for the higher thrombin/antithrombin III complex levels in the hypothermic than in the normothermic patients.

The optimal amount of heparin for adequate anticoagulation during CPB is still controversial. Heparin can be administered based on either fixed dosage schedules using weight and CPB time or based on monitoring protocols. Major limitations of fixed dosage schedules include the lack of confirmation that adequate anticoagulation has been achieved and maintained (i.e., variable response to heparin secondary to heparin preparation and patient response) and the pharmacokinetic variability in heparin concentration during CPB which has been attributed to the variable degree of hemodilution[27].

Excessive bleeding may be related to a coagulopathy resulting from greater heparin doses during CPB as guided by dosing protocols based on body weight and ACT values[28], or with maintenance of a defined heparin concentration. Although other study[29], showed lower total heparin dose was associated with increased blood loss post-operatively as larger heparin doses may preserve coagulation and inhibit thrombin. The association between greater protamine dose and the transfusion of hemostatic blood products in our present study may have been, at least in part, related to the empiric administration of protamine in patients with excessive intraoperative bleeding. Another study demonstrated that higher heparin levels during extracorporeal circulation are associated with transient decreases in platelet function due to heparin-mediated suppression of platelet activation when stimulated with exogenous collagen[30]. In addition to that other studies showed that heparin and protamine adversely affect platelet number and function[31], and these drugs in combination inhibit ADP-induced platelet aggregation and attenuate human platelet responsiveness to thrombin.

Tranexamic acid, have been shown to reduce blood loss after cardiac operations . TA may improve hemostasis after operation by two mechanisms. First, TA inhibits post-CPB plasmin-induced fibrinolysis by binding to the lysine binding site on plasmin and plasminogen. Second, TA inhibits plasmin-induced platelet activation, consequently preserving platelet function[32]. Concentrations of the TA administered before the CPB period may fall to less than half of the original level after CPB, because the elimination half-life of TA is about 80 minutes. To counteract a post-CPB fibrinolytic status, maintenance of the concentration of TA may be important. Therefore an additional bolus dose of TA given soon after CPB might prevent reactivation of fibrinolysis and reinforce hemostasis. Blood loss in the TA group was significantly reduced. Furthermore, our study failed to show any increased incidence of perioperative thrombotic complications. We conclude that with additional administration of TA after CPB, blood loss after cardiac operations involving CPB will be safely reduced.

Preoperative anemia in cardiac surgery as defined by low HCT (<35%) is an important health issue. Preoperative anemia is important because it is the single most important determinant of perioperative RBCs transfusions[33], which have many risks and side effects[34].

It was a new finding that high hematocrit value, irrespective of whether it was caused by cyanosis or a neonatal age, was associated with platelet use. The mechanism may be that those patients with high preoperative hematocrit value had greater relative reduction in hematocrit value during CPB. This resulted in greater dilution of all plasma proteins including clotting factors during and immediately after the operation [35]. These results indicate that it should be prospectively studied as to whether those patients with a high hematocrit value could have a higher target hematocrit value during and after CPB, bearing in mind the potential negative rheological effects.

CONCLUSIONS & RECOMMENDATIONS

Several factors that may contribute to increased blood loss and transfusion requirement including: age below 10 years, female gender, low body weight and surface area, prolonged duration of CPB, hypothermia, preoperative anemia, and high doses of heparin & protamine. Strategies to reduce the requirements for homologous blood transfusion following CPB are widely used now including the Pharmacological agents. Although some strategies regarded as safe have yet to show their benefits. Strategies to optimize administration of heparin and protamine and assessment of their effects on coagulation are undergoing reevaluation as they are associated with adverse effect on blood loss & transfusion requirements. And the use of heparin concentration assays to maintain a defined heparin level during CPB is recommended. TA have been shown to be an effective drug to reduce blood loss & transfusion requirements after cardiac surgery and the regimen is differ in different centers.

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CONTRIBUTORS

SAK conceived the idea and supervised the study. FAAA collected the data and planned & analyzed the study. Both the authors contributed significantly to the research that resulted in the submitted manuscript.