Effect of Retransfusion of Heparin Remaining in the Salvaged Blood on Postoperative Blood Loss in Coronary Artery Bypass Grafting: Comparison with Homologous Blood Transfusion (Running title: Postoperative Blood Loss in CABG)

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Abstract

Background: One of the typical problems of cell savers is the retransfusion of the heparin added to the system. The aim of this study was to determine whether or not heparin, remaining in the prepared sample of retransfusion blood, might be responsible for disturbance in coagulation and increase in blood loss.

Methods: Fifty patients undergoing coronary artery bypass grafting surgery (CABG) were randomly divided into two groups: group C (n=25) received cell-saver blood and group H (n=25) received homologous blood. Volumes of the intraoperative autologous and homologous transfusion, activated clotting time (ACT) of the transfused bloods, and ACT and amount of blood loss in the patients were measured intra and postoperatively.

Results: There was no statistical difference between the groups in terms of demographics, preoperative characteristics, or operative details. Cell saver was used in 25 cases, and the average volume of blood autotransfused was 504± 158 mL. A significant statistical difference was observed in the mean volumes (460±200 vs. 80±160 mL; P = 0.0001) of perioperative allogeneic blood transfusions between groups H and C. Despite significant further cell-saver blood transfusion (504± 158 cc vs. 338±123 cc; P=0.001) and a significantly longer ACT of cell-saver blood than homologous blood (959±85 sec vs. 478±58 sec; P =0.0001) intraoperatively, there was no significant difference between the two groups in terms of postoperative blood loss (510 ± 270 cc in group H vs. 454 ± 150 cc in group C; P =0.362).

Conclusion: Utilization of a cell saver was safe, with no increased risk of bleeding despite heparin added to the system. ***(Iranian Heart Journal 2012; 13(2):24-34).***

Keywords: Cell saver■ Coronary artery bypass grafting■ Autologous blood transfusion

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Introduction

Bleeding is the primary complication of cardiac surgery requiring cardiopulmonary bypass (CPB). In fact, 15% to 20% of the blood product use in the United States is associated with cardiac surgery.[1-3] There are many investigations and articles that show the association between transfusion and increased rates of hospital mortality,[4,5] perioperative infection and sepsis,[6,7] pulmonary dysfunction, prolonged mechanical ventilation,[8] and renal dysfunction,[5,9,10,11] as well as persistent reduction in quality of life and death after surgery.[12-16] For these reasons and as a result of the growing concern over the increasing use of blood and its components during surgical procedures requiring CPB, The National Institutes of Health in 1973 recommended increased use of autologous blood transfusions.[17]

A method suggested for handling blood and fluid in the surgical field is the cell salvage and washing system, which is thought to improve patient outcomes by removing debris from shed blood and thus decreasing the risk of stroke or neurocognitive dysfunction. In coronary artery bypass grafting surgery (CABG), intraoperative cell salvage is the optimal mechanical method for reducing the perioperative transfusion of allogeneic red blood cells.[18,19] This procedure is considered safe.[20] But it is unknown whether the re-infusion of the salvaged blood affects the postoperative blood loss in patients. Although all cell savers adequately remove heparin from retransfused blood, previous studies have demonstrated that small amounts of heparin might remain in the prepared retransfused blood during intraoperative autotransfusion.[21,22] Our hypothesis was that heparin remaining in the prepared sample of retransfusion blood might be responsible for postoperative bleeding in comparison with transfusion of homologous blood. We studied to what extent heparin is washed out during the preparation of retransfusion blood, when it is used as an anticoagulant for the autotransfusion cell-saver (Dideco) through the measurement of activated clotting time (ACT). There are no adequately powered studies in the literature comparing postoperative blood loss when autologous or homologous blood is used.

Methods

The study was designed as a randomized clinical trial and was performed at Shaheed Rajaei Cardiovascular, Medical and Research Center, Tehran University of Medical Sciences, Tehran, Iran. After the Research Ethics Committee's approval, 50 patients underwent primary, elective, isolated on-pump CABG surgery and met the criteria for inclusion in this study.

Two groups were identified based on the use of packed red blood cell (homologous blood) as group H (n=25) or cell-saver blood (autologous blood) as group C (n=25). Intraoperative cell salvage of shed blood was used in all the patients of group C, from skin incision to the closure of the sternum at the completion of surgery. The inclusion criteria were as follows: primary, elective, on-pump CABG surgery; age between 30 and 70 years; left ventricular ejection fraction ≥45%, pump time <2 hours; and aortic clumping time <45 minutes. The exclusion criteria were: patients with known coagulation disorders; redo or emergency surgery; patients on Warfarin, heparin, or other systemic anticoagulant drugs and antiplatelet drugs such as Aspirin (the patients either did not take Aspirin or took a maximum dose of 80 mg/day) preoperatively; and co-existing diseases (renal and hepatic disease diabetes mellitus, hypertension, and endocrine and hematology disorders).

All the patients received standard crystalloid maintenance volumes as well as standard anesthesia and perioperative care and were operated on by the same surgeon. The induction of anesthesia with standard doses of Etomidate, Sufentanil, and Cisatracurium and the maintenance of anesthesia with continuous infusion of Midazolam, Sufentanil, and Atracurium were done. Prior to skin incision, the cell-saver device was started in the automatic mode using 1000 ml saline as a washing solution. ACT of the patient was obtained and recorded preoperatively as baseline or pre-heparin ACT (ACT before heparin administration). Before cannulation, bovine lung heparin 300 IU/kg was administered to achieve an ACT ≥ 480 sec. If this ACT was not achieved, the patient was excluded from the study. Since the heparin dose has a significant influence on the heparin concentration in the retransfusion blood, the CPB-circuit, priming fluid (500 ml Hydroxyethyl starch 10% and 1000 ml lactated Ringer' solution), the myocardial protection method (cold blood cardioplegia), and surgical techniques (by one surgeon) were uniform in all the patients. Cardiopulmonary bypass flow was 2.4 liter/ min/ m^2.

While the patient was on CPB, the trigger for the transfusion of allogeneic red blood cells was a hemoglobin concentration of <7 g/dL (hematocrit (HCT) <21%), the patients were cooled to 32°C, and the mean arterial pressure was maintained between 50 and 80 mm Hg with the use of Phenylephrine or nitroglycerin. After re-warming and completion of the aspects of surgery requiring CPB, blood samples were collected from the oxygenator and from autologous blood following concentration and washing with saline solution in the cell saver in group C or from the homologous blood in group H to measure ACT. Then the patients were weaned from the CPB machine. After the termination of CPB, heparin was neutralized using Protamine in a 1:1 ratio. In group C, the blood aspirated from the wound area and the operative field as well as the blood within the CPB circuit and the residual blood from the heart-lung machine was collected in the cell-saver reservoir, which was primed with 150 ml of normal saline with 30,000 IU heparin/L added, washed, and concentrated with a continuous-flow cell saver before retransfusion. The ACT of the blood collected in the cell-saver bag and bank blood before transfusion was checked. The trigger for the transfusion of packed red blood cells in group H after CPB was a hemoglobin concentration <8.0 g /dL (HCT <24%). The following time point for ACT measurement was employed 10 minutes after Protamine reversal and the transfusion of packed red blood cells in group H or the retransfusion of cell-saver blood in group C. Reinfusion of cell-saver blood regardless of post-CPB HCT was done. Postoperative blood loss was immediately measured after weaning of the patients from CPB and in the Intensive Care Unit (ICU) at the first, second, and third 8 hours and all the 24 hours after surgery.

Postoperatively, the only identifying marks of the two groups were the patient's name and study identification. All the study investigators, patients, surgeon, anesthetist, and persons involved in the patient's intraoperative care were blinded to the amount of bleeding and treatment allocation in the ICUs. The persons involved in the patient's postoperative care were blinded to the use of homologous or autologous blood for the patients. Because of the importance of hemodynamic stability, and specifically the effectiveness of blood pressure and blood volume on blood loss, the mean arterial pressure (MAP) and central venous pressure (CVP) were measured and recorded before,

during, and after surgery and at the first, second, and third 8 postoperative hours. The study population's demographics (age, sex, and weight), cardiac variables (ejection fraction), intraoperative hemodynamic variables (MAP and CVP), and CPB status (aortic cross-clamping time and CPB time) were recorded.

The data are described as mean ±standard deviation for the interval and count (%) for the categorical variables. A one-sample Kolmogorov-Smirnov test was used to examine the fitness of interval variables to normal distribution. The associations between the type of transfusion and the other variables, including the patients` background, study outcomes, and other possible determinants, were investigated using the Student *t*-test for the interval data, the Pearson chi square for the nominal data, and the Mann-Whitney U test for the ordinal variables. The follow-up data were analyzed via the repeated measure analysis of variance (ANOVA) models. A p value <0.05 was considered statistically significant. The statistical analyses were performed with SPSS® 15 for Windows® (SPSS Inc., Chicago, Illinois).

Results

Fifty patients undergoing on-pump CABG surgery were divided into two groups as was described earlier. Comparison of the values between the two groups was performed. The values were considered significant with a p value <0.05. There were no significant differences between the groups in the listed variables, including the demographic, cardiac variables, and CPB status (Table 1).

Comparison of the perioperative hemodynamic parameters, including MAP and CVP, between the two groups demonstrated statistically significant differences only in the baseline MAP of the patients and not in the other stages (Figures 1 and 2).

Comparison of the group receiving only homologous blood (group H) with the group receiving only autologous blood (group C) during the perioperative periods revealed that the use of the cell saver resulted in less requirement to packed red blood cells transfusion (460±200 mL in group H vs. 80±160 mL in group C; P = 0.0001) and thus fewer subsequent donor exposures. Based on our hypothesis about the effects of residual heparin in the cell-saver system on postoperative bleeding and its verification by ACT measurement at different times, we found no significant differences between the ACT of the samples drawn from the patients. Nevertheless, there were statistically significant differences between the ACT of the samples drawn from packed red blood cell bags and cell-saver blood bags (478±58 vs. 910±72; P =0.0001). Despite the high ACT of the prepared cell-saver blood (910±72), there was no statistically significant difference between the ACT of the two groups measured and recorded at 10 minutes after Protamine reversal and transfusion of blood post CPB (119±18 vs. 129±19; P =0.058) (Figure 3 and Table 2).

In our study, the mean volume of autologous blood transfusion intraoperatively was 504±158 mL, which could not induce bleeding more than the intraoperative transfusion of homologous blood with a mean volume of 338 ± 123 mL in the ICU at the first, second, and third 8 postoperative hours and all the 24 postoperative hours (Table 3).

Intraoperatively, the mean volume of blood transfused in the two groups was 338 ± 123 mL, parallel with 4.8 ± 2 cc/kg in

group H vs. 504 ±158 mL, parallel with 7 ± 2 cc/kg in group C; P =0.0001, while the mean volume of blood loss in the first 24 hours following surgery in the groups was 510± 270 ml in group H vs. 454± 150 ml in group C; P =0.362. These data demonstrated that despite significant differences between the groups in terms of the amount of intraoperative blood received, there were no statistically significant differences with respect to postoperative blood loss. Autotransfusion did not produce any significant blood loss when compared with homologous blood transfusion (P =0.512, ANOVA).

Fifteen patients in the two groups received transfusion of allogeneic red blood cells postoperatively, but the total of the packed cell units transfused in group H was higher than that in group C (16 units vs. 11 units). Seven patients from group C and 8 patients from group H required packed red blood cells postoperatively (8/25, group H vs. 7/25, group C). There was reduced requirement for homologous blood products during the first 24 hours following surgery when a cell-saver apparatus was employed intraoperatively (16 units totally or an average of 0.7± 1 units in group H vs. 11 units totally or an average of 0.4± 0.8 units in group C); however, there was no statistically significant difference between the two groups (P =0. 429). No patient was explored for excessive bleeding, and all the patients survived to discharge.

Table1: Demographic and cardiac variables and cardiopulmonary bypass status

CPB= cardiopulmonary bypass
LVEF= left ventricular ejection fraction

	Group H	Group C	p value
Sex (M/F)	16/9	17/8	0.107
Age (yr)	58±5.4	55±14	0.239
Weight (kg)	72±7	74±6	0.820
CPB time (min)	73±19	69±17	0.491
Clamp time (min)	38±15	32±10	0.128
LVEF (%)	48±4.8	48±4.5	0.881

Table 2 : Intraoperative Activated Clotting Time measurement

ACT (sec)	Group H	Ggroup C	p value
Baseline (pre heparin)	152±33	151±30	0.979
2 minutes post heparin	633±150	582±127	0.200
5 minutes pre-CPB weaning	573±114	556±101	0.595
ACT of bloods (C&H)	478±370	959±85	0.000
10minutes post transfusion	119±18	129±19	0.058

Note: ACT= Activated Clotting Time CPB=Cardiopulmonary Bypass
5 minutes pre-CPB weaning means: ACT measurement 5 min before weaning of CPB.
ACT of bloods means: ACT of salvaged blood and homologous blood before transfusion.
10 minutes post- transfusion means: ACT measurement 10 min after Protamine reversal and transfusion of autologous and homologous blood.

Table 3 : Postoperative blood loss

Blood Loss (mL/kg) Blood Loss (mL)	group H	group C	p value
First 8 hours post-op	3.3 ± 2.5 242 ± 184	3.0 ± 1.6 210 ± 103	0.635 0.463
Second 8 hours post-op	2.2 ± 2 156 ± 127	1.6 ± 1.0 112 ± 76	0.127 0.144
Third 8 hours post-op	1.4 ± 1.5 105 ± 105	1.8 ± 1.0 131 ± 79	0.288 0.333
Total 24 hours post-op	7.0 ± 3.7 510 ± 270	6.4 ± 2.2 454 ± 150	0.512 0.362

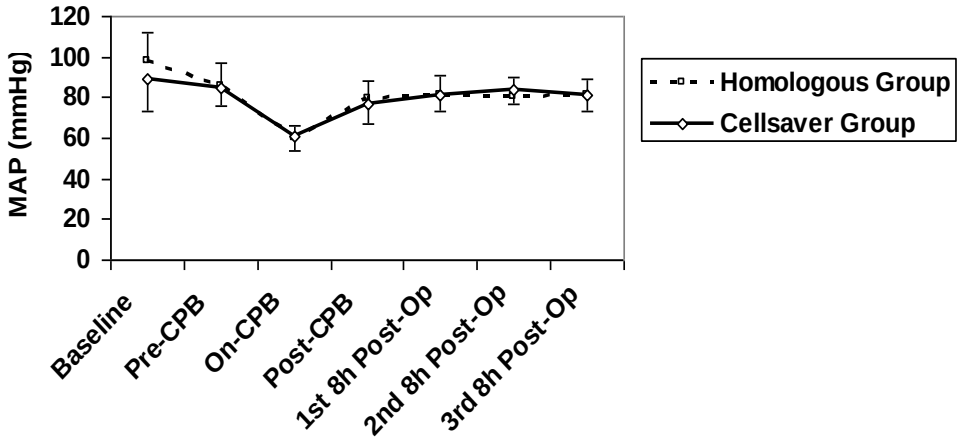

Figure 1: Perioperative Mean Arterial Pressure

MAP= Mean Arterial Pressure

CPB=Cardiopulmonary Bypass Op=Operation

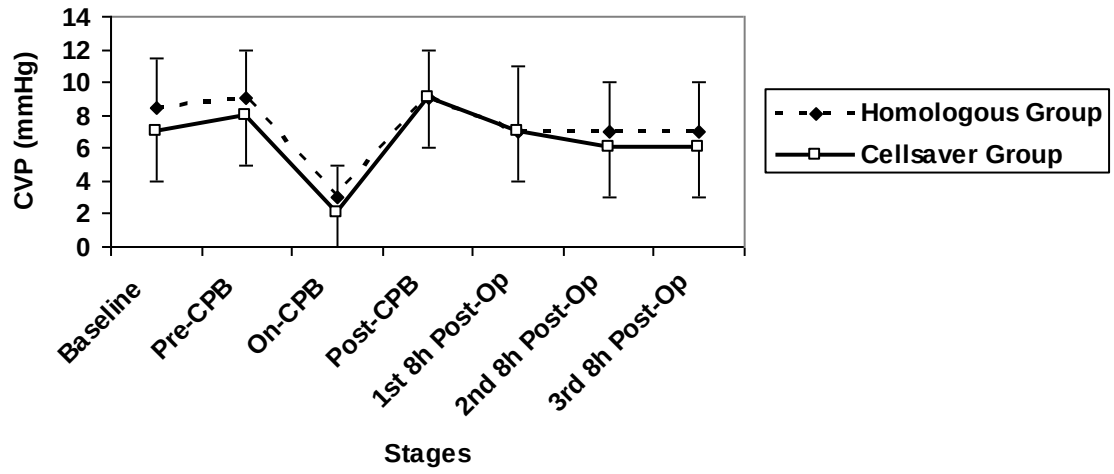

Figure 2: Perioperative Central Venous Pressure

CVP= central venous pressure CPB=Cardiopulmonary Bypass Op=Operation

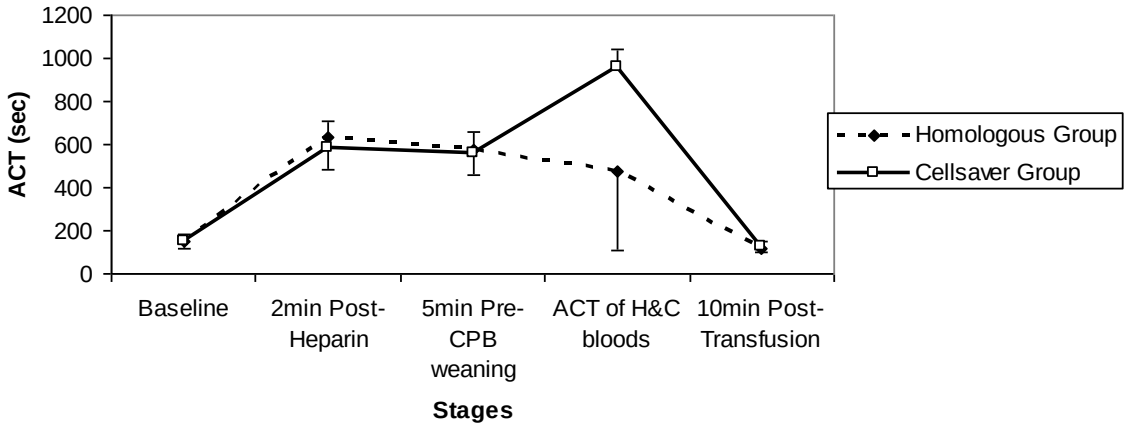

Figure 3: Intraoperative Activated Clotting Time measurement

Discussion

The causes of bleeding in cardiac surgery are surgical damage to blood vessels and the development of coagulopathy resulting from a combination of an acquired defect in platelet function, inappropriate fibrinolysis, and a reduction in circulating coagulation factors.[22 -24] Some of these causes relate to the aspects of perioperative care. Various methods to reduce blood consumption are used in cardiac surgery, including mechanical and pharmacological techniques. [25] These methods may maintain a patient's HCT, reduce the need for homologous blood transfusion, reduce the development of coagulopathy, and perhaps reduce intraoperative and

postoperative blood loss, but based on the results of a meta-analysis in 2009, the use of a cell saver has no effect on hospital mortality, postoperative stroke or transient ischemia attack, atrial fibrillation, renal dysfunction, infection, patients requiring fresh frozen plasma, and patients requiring platelet transfusions.[26] The optimal methods in CABG is the intraoperative use of a cell saver. Disorders in blood coagulation and RBC function during the use of mechanical cell salvage and autotransfusion have been reported in previous and recent studies. [27-29] On the other hand, there are studies that confirm the safety and efficiency of perioperative cell salvage and autotransfusion after CABG. [21] The present study was performed to verify whether or not heparin, remaining in the prepared sample of retransfusion blood, might be responsible for postoperative blood loss.

This prospective randomized control trial compared the amount of postoperative

bleeding after the retransfusion of cell-saver blood with homologous blood in patients undergoing on-pump CABG. The results demonstrated that in comparison with the transfusion of packed red blood cells, the reinfusion of cell-saver blood was not responsible for postoperative blood loss and autotransfusion was a safe and effective method for reducing the use of homologous bank blood after first-time CABG. These results are consistent with the findings of **Gavin J. Murphy and his colleagues** in 2004.[21]

All cell savers adequately remove heparin from retransfused blood. Be that as it may, there is concern that cell-saver suction may cause increased fragmentation of erythrocytes and removal of platelets [26-29] and so it may cause postoperative blood loss. Reents et al. found increased levels of free hemoglobin and fewer platelets with cell-saver suction compared with cardiotomy suction. [30] On the other hand, the mechanical cell salvage procedure affects the RBC function in patients undergoing cardiac surgery with CPB. Disorders in blood coagulation during the use of autotransfusion have been reported in previous studies. [28,29] Investigation of heparin management during cardiac surgery by Boldt et al. through comparison of six various blood-conservation techniques demonstrated that fibrinogen concentration and antithrombin-III levels were lower in the cell-saver group but they were not decreased critically during the entire investigation period. [31] In another study, **Andrew A. Klein** et al. found that patients in the cell-salvage group had a lower platelet count and fibrinogen level one hour postoperatively, but there was no difference in postoperative bleeding between the two groups. [32] That is consistent with our finding. According to our results, the patients showed no irregular heparin load and abnormal ACT following the transfusion of autologous blood with high ACT levels. As a result, the use of the cell saver is not associated with an increased risk of bleeding. We found no difference between the two groups regarding postoperative blood loss requirement for re-exploration for bleeding, but there was need for packed red blood cell transfusions in some of the patients in the two groups.

Our results demonstrated that the use of cell salvage in patients undergoing elective first-time cardiac surgery could reduce the number of patients exposed to allogeneic blood transfusion. When considering only patients not requiring reoperation for postoperative bleeding, we did find a reduction in the number of the units of allogeneic blood transfused in the cell-salvage group compared with the homologous group.

Conclusion

This prospective study demonstrated that intraoperative salvaging of blood during cardiac surgery utilizing the Dideco cell-saver device did not increase the risk of postoperative bleeding and did not impose any additional requirement for homologous blood products.

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