No benefit of intraoperative whole blood sequestration and autotransfusion during coronary artery bypass grafting: Results of a randomized clinical trial

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Objectives: In a randomized clinical trial of patients undergoing elective coronary artery bypass grafting, we evaluated the effect of intraoperative whole blood sequestration and autotransfusion on postoperative blood loss and the use of allogeneic blood products.

Methods: Male patients were included if it was possible to obtain at least 500 mL of autologous blood. For patients in group H (heparin autotransfusion, 50 patients; mean age 59 ± 8 years), an average of 670 ± 160 mL heparinized blood was drawn before bypass and reinfused after the period of the extracorporeal circulation. For patients in group C (citrate autotransfusion, 48 patients; mean age 60 ± 10 years), 450 ± 109 mL of citrate blood, drawn before administration of heparin, was used. Controls (N-group) consisted of 46 patients aged 62 ± 8 years. Strict transfusion criteria were used, and blood loss and use of allogeneic blood products during the hospital stays of all patients were recorded. Mean differences with their 95% confidence intervals adjusted for potential confounders were obtained by multiple linear regression.

Results: The mean difference (95% confidence interval) of blood loss of group H minus N was -93 mL (-307 to 139) and for C minus N was -66 mL (-186 to 179). The mean number of allogeneic blood transfusions for group H was 0.85 ± 1.74 . Group C and group N used 0.94 ± 1.56 and 0.84 ± 1.24 .

Conclusion: In coronary artery bypass grafting there is no effect of heparin or citrate intraoperative whole blood sequestration with regard to blood loss or use of allogeneic blood.

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In recent years, the interest in blood-saving strategies has increased greatly because of the recognition of deleterious effects on health (acquired immunodeficiency syndrome and immunosuppression), as well as the cost aspects of blood transfusion. Coronary artery bypass grafting (CABG) has always claimed a considerable percentage of blood donations. Fresh blood autotransfusion and hemodilution have been investigated for their effect in CABG to reduce the number of blood donations. Several studies show remarkable reductions in allogeneic blood use.¹⁻⁴ However these studies are sometimes outdated, not randomized or controlled, or are inconclusive. Some authors suggest inconclusive results regarding the effect of autotransfusion from the use of heparin as an anticoagulation method.^{5,6} The aim of our trial was to evaluate the effectiveness of intraoperative whole blood sequestration, comparing heparin and citrate as anticoagulants, for decreasing blood loss and use of allogeneic blood products.

Material and Methods

Study Design

A randomized, partly blinded clinical trial was performed in a peripheral hospital, with all consecutive patients scheduled for CABG during a 6-month period. After written informed consent was obtained, patients were randomized over three groups. This was achieved by block-randomization with concealed envelopes. All data were registered by an independent investigator, and the intensive care unit (ICU) staff on the ward was blinded for the randomization. The hospital medical ethical committee approved our study design. This was a trial where patients entered the study when they discontinued receiving aspirin at least 7 days before surgery. No antifibrinolytic drugs were used during the trial.

Patients

All patients scheduled for CABG were included when the following criteria were met: male sex, age between 18 and 75 years, normal left ventricular function test result (tested by echocardiography), and an adequate hematocrit level and weight to allow withdrawal of at least 500 mL of whole blood. Calculations were based on the preoperative hematocrit level, estimated circulating blood volume (70 mL/kg body weight is A , see formula), the priming of the cardiopulmonary bypass (CPB) (2000 mL), and an estimation of the volume of cardioplegic solution needed (1000 mL). We used the formula $A \times \text{preoperative hematocrit level} - B \times 0.25$ to determine the blood volume that could be safely donated by each patient. B is the value 3000 mL, cardioplegia and pump-priming values combined, and 0.25 is the aimed lowest hematocrit value during bypass. Exclusion criteria were coronary artery main stem disease, liver disease, and known or suspected bleeding disorders.

Interventions

There were three treatment arms: a heparin autotransfusion group (H group), a citrate autotransfusion group (C group), and a control group (no autotransfusion, N group). In the C group, blood was withdrawn before the initiation of the CPB and administration of heparin. This blood was collected in routine citrate suspension to prevent clotting. In the H group, blood withdrawal was conducted after administration of heparin through the CPB before starting the CPB. It is clear that the heparin was used as the anticoagulant for the harvested fresh blood in this group. For both autotransfusion groups, normal aseptic guidelines were followed during harvesting. The blood was kept at room temperature to keep the platelet function as optimal as possible. The targeted hematocrit level for hemodilution for all patients was 25%. The need for fluid infusion was closely monitored by the attending anesthesiologist; if necessary extra saline solution was infused. The fresh autologous blood was returned to the patient after protamine was given to the patient at the end of the operation.

Transfusion Guidelines

Extensive postoperative bleeding in our department is defined as more than 500 mL lost in the first postoperative hour, more than 400 mL lost in the second hour, or more than 300 mL lost in the third hour. Packed cells were given if the patient had a hematocrit level lower than 0.25 in the postoperative period combined with extensive bleeding. Fresh frozen plasma (FFP) was given with an

international normalized ratio (INR) greater than 1.6 and extensive bleeding. The indication for platelet transfusion was a platelet number less than 80 combined with extensive bleeding.

Other Standard Procedures

Anesthesia was standardized to a benzodiazepine-medium opioid and pancuronium scheme. Blood pressure was regulated with sodium nitroprusside, and nitroglycerin 1 mg/hour was infused routinely. Before cannulation of the aorta, heparin 300 IE/kg body weight was given to achieve an actual clotting time (ACT) of more than 450 seconds. The ACT was measured with a Hemo-Chron 401 (Technidyne Corp, Edison, NJ). CPB was standardized with pump flows of $2.4 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$. Body surface area (BSA) at 32°C nasopharyngeal temperature and a membrane oxygenator were used. Pump prime and cardioplegic solution were standardized and contained no blood. Only moderate hypothermia down to 28°C nasopharyngeal temperature was used.

Data Collection, Statistical Analysis, and Sample Size Calculation

Operation variables, number of bypasses, use of the internal thoracic artery, total clamping time, and total CPB time were recorded. At the ICU department, patients were monitored for blood loss, use of allogeneic blood or blood products, hemodynamic parameters, use of intra-aortic balloon pump (IABP), urine production, need of ventilation, extubation time, need of rethoracotomy, and number of days in the ICU and the postoperative clinical ward. Hematologic and coagulation parameters were collected 1, 3, and 12 hours after surgery and at 1, 2, and 7 days after surgery. Possible blood donations in the postoperative ward and side effects of autotransfusion were registered. Statistical evaluation took place with the SPSS statistical battery (SPSS, Inc, Chicago, Ill), in which mean and standard deviations, mean difference, and the 95% confidence intervals were calculated. We used multiple linear regression to evaluate confounding factors. To detect a clinically significant 300-mL difference in blood loss, with an Alfa of .05, a power 80%, and a standard deviation of 450 mL, we calculated that we needed at least 40 patients in each group.

Results

During the period of our study, 397 men were scheduled for CABGs, and only 144 (36.3%) patients met the inclusion criteria. The reasons for exclusion, before the start of the study, were a hematocrit level too low for allowing intraoperative blood donation ($n = 110$), a decreased left ventricular function ($n = 51$), renal or hepatic disorder ($n = 34$), use of heparin before the operation because of unstable angina pectoris ($n = 27$), lack of informed consent ($n = 9$), and miscellaneous ($n = 22$). After randomization, no patients were excluded from the study or analysis of data. Forty-six, 50, and 48 patients were randomized to the N (normal control subjects), H, and C groups, respectively, and all groups were comparable for the baseline characteristics as shown in Table 1. There was a difference in the amount of blood collection for patients in the C and H groups. The reason for this was that it was easier to collect

TABLE 1. Preoperative and intraoperative baseline-characteristics of patients in the 3 groups: mean (SD)

	N (n = 46)	H (n = 50)	C (n = 48)
Age (y)	61.9 (8.1)	58.3 (8.1)	59.5 (9.6)
Weight (kg)	84 (7)	86 (8)	83 (10)
Plasma sodium (mmol/L)	139 (2)	140 (2)	139 (2)
Plasma creatinine (mmol/L)	100 (16)	97 (14)	96 (14)
ASAT (U/L)	17 (7)	18 (14)	17 (9)
Operating time (min)	256 (62)	270 (86)	250 (57)
CPB time (min)	103 (34)	105 (41)	96 (35)
Aorta clamp time (min)	70 (28)	75 (34)	67 (27)
No. of anastomoses	6 (1)	5 (1)	5 (1)
Use internal thoracic artery (No. of patients)	41	44	45
Decreased left ventricular function (No. of patients)	2	0	1
Volume of blood donation (mL)	0	670 (160)	450 (109)

blood from the H group during CPB. For C-group patients, collection was done before bypass through a wide-bore intravenous catheter residing in the internal jugular vein.

Blood loss in the control group (N) and the autotransfusion groups (H and C) were comparable (Table 2). The mean blood loss in the control group was 931 mL. In the H and C groups, the average blood loss was 1024 mL and 997 mL, respectively. The mean difference (95% confidence interval) of blood loss of between the N and H groups was -93 mL (-307 to 139 mL) and for N and C -66 mL (-187 to 179 mL). There were no outliers with regard to blood loss and use of allogeneic blood products in the three groups. Table 2 also shows that there was no reduction in postoperative allogeneic transfusions.

The number of packed cells transfused during the postoperative period were 39, 43, and 45 units for the N, H, and C groups, respectively. The percentages of patients that did not receive homologous blood transfusions in groups H, C, and N were 70%, 63%, and 62%, respectively. The mean number of transfusions was 0.85 ± 1.74 in the H group, 0.94 ± 1.56 in the C group, and 0.84 ± 1.24 in the N group. The mean difference was -0.02 (-0.06 to 0.6) for N minus H and -0.09 (-0.7 to 0.5) for N minus C.

The units of FFP used in the autotransfusion groups were comparable in the three groups (Table 2). Platelet donations were more frequently used in the control group when compared with citrate autotransfusion, but statistical significance was not reached (Table 2).

Figure 1 shows the hemoglobin level for the three groups of patients during the intraoperative and postoperative period. The hemoglobin level for all three groups showed an expected drop at the end of the CPB. There were no significant differences between the groups. Figure 2 shows the mean values of the platelet number during and after operation. There are no significant differences among the H, C,

and N groups. Figure 3 shows the intraoperative and postoperative ACT. We observed an initial increase in ACT at the end of CPB when the heparin had not yet been antagonized. There were no significant differences among the groups.

The IABP was not used in any of the patients. There was no change in the incidence of repeat thoracotomy for bleeding. The incidence of repeat thoracotomy in the control group was 4.3% and was comparable with the 2.0% and the 6.3% of the autotransfusion groups. The mean duration of artificial ventilation for all patients was 11 ± 6 hours, the mean ICU stay was 2.4 ± 1.2 days, and the total hospital stay was 6.2 ± 2.5 days, with no significant differences among the groups. No side effects were recorded in the autotransfusion groups, and none of the patients died after surgery.

Discussion

This study demonstrated that the use of fresh autologous blood, administered during the operation with heparin or citrate anticoagulation, is not effective in reducing either the need for allogeneic blood or the postoperative blood loss. Postoperative bleeding is believed to be partly due to the deleterious effects of CPB on platelet function because of activation of the clotting system.⁷⁻⁹ Finding no effect of autotransfusion may be due to bias in our study protocol.

We tried to minimize information bias by using one person to obtain the data, strict transfusion criteria, and blinding the staff responsible for homologous blood transfusions. We restricted confounding bias by use of multiple regression to adjust for potential confounding factors. It is possible that our inclusion criteria, donation of at least 500 mL blood, may have led to a "healthier" group or a group of patients with a low risk of postoperative bleeding and use of allogeneic blood use. Some randomized trials^{10,11} focused retrospectively during their analysis on the question of whether intraoperative blood sequestration was beneficial, in a subgroup of patients undergoing CABG with a high risk for postoperative bleeding or use of allogeneic blood, and found a positive effect. However, we know the value of retrospective studies.

Another reason for finding no effect could be that we performed less optimal hemodilution. Petry and associates¹² found an effect after randomization; they autotransfused patients with their own blood after hemodilution until a hematocrit level of 20% was reached. One quarter of our patients had the lowest hematocrit level during bypass (between 18% and 20%). Our department aimed at a hematocrit level of 25% to avoid hazardous and negative outcomes for the patients. According to our data on hemostasis and the coagulation profile during the postoperative period, we do not expect that a lower hematocrit level would lead to a beneficial effect because we could not observe any small

Figure 1. Mean hemoglobin level during and after surgery.

TABLE 2. Blood loss and use of blood products: mean differences (S.D.) between intervention groups and control subjects

	H	C	N	Mean difference	95% CI	P value
Blood loss, mL	1024 ± 576	997 ± 475	931 ± 483	−93*	−307-139	.5
				−66†	−186-179	1
Packed red cells, units	43	45	39	−0.01*	−0.06-0.6	1
Units/patient	0.85	0.94	0.85	−0.09†	0.7-0.5	.8
FFP, units	12	13	11	−0.01*	−0.29-0.29	1
Units/patient	0.24	0.27	0.24	−0.03†	−0.3-0.3	.8
Platelets (5 units)	4	2	5	0.03*	−0.12-0.2	.7
Units/patient	0.08	0.04	0.11	0.07†	−0.06-0.2	.3

FFP, Fresh frozen plasma.

*N vs H group.

†N vs. C-group.

positive hemostatic effects. In addition, lowering the hematocrit level during bypass to a value of, for example, 18% will decrease oxygen-carrying capacity to a dangerous level for the patient.

Others^{5,6} emphasized that the use of heparin as anticoagulant is the reason that a possible effect of fresh blood autotransfusion could not be measured. We tried to overcome the problem and used citrate autotransfusion. With the claim of reaching good hemostatic effects with citrate and heparin autotransfusion of fresh blood,¹⁻⁴ we expected that patients receiving autotransfusion would benefit. However, we could not confirm this. There is still a 5% chance that our results are not true and that there is a beneficial effect of intraoperative whole blood sequestration and autotransfusion in patients undergoing CABG.

Randomized clinical trials evaluating the effect of fresh autologous blood transfusions are scarce and inconclusive.^{1,3,11,13} In 237 patients undergoing CABG, Wasser and

colleagues¹¹ found differences in hemoglobin levels and platelet count, but these were small and without clinical significance in patients undergoing autotransfusion. Szezi and associates¹⁴ in 1989 and Kochamba and associates¹³ in 1996 reported a positive effect of fresh blood autotransfusion. Reductions for allogeneic blood with 40% and 45%, respectively, were reached. Postoperative blood loss was reduced in these trials, with 24% and 28% compared with control subjects. However, it should be noted that Szezi and associates¹⁴ did not use strict transfusion criteria or blinding to control for information bias, whereas Kochamba and associates¹³ did. Others^{15,16} used strict transfusion criteria but included a small amount of patients during their trial—35 and 30 patients, respectively. So we must be careful with interpretations.

In a study by Ovrurn and colleagues,⁴ less than 3% of patients needed allogeneic donations during their postoperative hospital stay. Important differences from our study

Figure 2. Mean platelet level during and after surgery.

Figure 3. Activated clotting time during and after surgery.

include their use of fresh heparinized autologous blood combined with shed mediastinal blood; furthermore, their study was not randomized controlled. Others¹⁷ could not find an additional effect of autotransfusion of shed mediastinal blood, and clinical problems such as fever, immunologic reactions, disturbances in laboratory measurements (creatinine kinase [CK] and alanine aminotransferase [ALAT] values), wound infections,¹⁸⁻²⁰ and even excessive bleeding may occur.²¹ The rationale of using fresh blood without shed mediastinal blood is that activation of platelets and coagulation factors is prevented and improves postoperative hemostasis.²² However, we and others¹¹ did not observe any

positive changes regarding the hemostasis profile or platelet count with patients receiving autotransfusion.

The value of reducing blood loss and use of allogeneic blood was recently reappraised by Michalopoulos and colleagues.²³ They found that the use of allogeneic blood has a deleterious effect on survival after CABG. The mortality rate increased if blood donations were needed in conjunction with inotropic agents in the immediate postoperative period. The preoperative level of hemoglobin is known to be the best predictor of the blood loss and need of allogeneic blood.²⁴ Other predicting factors that are influencing the use of allogeneic blood remain to be discovered. With this trial

we have one answer already. Intraoperative whole blood sequestration, anticoagulated with heparin or citrate, does not have a positive effect in patients undergoing CABG when a mean volume of 670 mL or 450 mL is used in patients at low risk. Whether there is an effect with the same or larger volume of blood donated in patients at high risk is yet to be examined in prospective randomized trials. A main limitation of intraoperative whole blood sequestration and autotransfusion seems to be the applicability towards the patients. In our study, only 36.2% of the patients were eligible for blood donation.

In conclusion we can say that there is no positive effect of intraoperative whole blood sequestration and autotransfusion in male patients undergoing CABG with regard to blood loss, use of allogeneic blood, and hemostasis. The clinical implication is that this technique is not indicated in the patients at low risk. In the future, patient trials regarding aggressive blood salvage techniques should focus on patients with a high risk for blood loss and use of allogeneic blood.

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