INTRAOPERATIVE MINIMAL ACUTE NORMOVOLEMIC HEMODILUTION IN PATIENTS UNDERGOING CORONARY ARTERY BYPASS SURGERY

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Abstract

Background & Objective: Efficacy of minimal acute normovolemic hemodilution (ANH) in avoiding homologous blood transfusion during cardiovascular surgery remains controversial. Postoperative bleeding and transfusion remain a source of morbidity and cost after open heart operations. Our objective was to evaluate the impact of minimal ANH on blood transfusion requirements during open cardiovascular surgery using cardiopulmonary bypass (CPB).

Methods: This study was a randomized controlled trial. One hundred one patients scheduled for elective coronary artery bypass graft (CABG) under cardiopulmonary bypass in October 2007 through March 2008 in Imam Khomeini hospital were randomly assigned to a control group (standard care, no = 47) or an ANH or study group (no = 54). We used minimal ANH (representing 10% of patients' blood volume). Mean 490±50 mL of fresh autologous blood was removed after induction of anesthesia and reinfused at the end of CPB. The blood transfusion guidelines were uniformly applied to all patients.

Results: Significant decrease in the number of red blood cell units transfused per patient per group (1.39 ± 1.0 and 2.551.9± units; $p < 0.0001$) in the ANH group versus the control group was observed. Conversely, chest tube output, postoperative hematocrits, and platelet count did not differ between two groups. Percentage of patients in whom allogeneic red blood cells were transfused was 44% in study group versus 76% in control group; ($p < 0.01$). No patient was transfused with platelet concentrates or fresh frozen plasma.

Conclusions: Minimal ANH is safe and cost effective and its routine use in eligible patients is therefore justified. Intraoperative autologous blood donation in CABG surgery decreased perioperative allogeneic blood requirement. However, the removal and reinfusion of about one unit autologous blood had no effect on postoperative bleeding or platelet count.

Key words: Transfusion, Autologous, Hemodilution, Coronary Artery Bypass Graft.

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Introduction

Autologous blood transfusion was employed as early as 1818, and preoperative blood donation was used in the 1930[1]. In recent years, the potential benefits of avoiding homologous blood transfusion and optimizing oxygen delivery in vital organs have led to a renewed interest for autologous blood transfusion and acute normovolemic hemodilution (ANH) in major surgery[26-].

Primary reasons for autologous blood transfusion employment are, avoidance of complications related to allogeneic blood transfusion, and conservation of blood resources. The introduction of complex operative procedures such as: cardiac surgery and organ transplantation, has led to search and attention for alternatives to allogeneic transfusion.

Coronary artery bypass graft surgery (CABG) is one of the most frequently performed major operations and is highly effective in improving life expectancy and quality of life in patients with coronary artery disease[7]. Although the number of surgical procedures will continue to decline along with the advances in interventional cardiology, the proportion of higher-risk patients requiring complex surgical procedures will likely continue to increase in the near future[8].

In these types of surgeries, as with other autologous transfusion techniques, ANH can be used to reduce the need for allogeneic blood transfusion. There are additional benefits of ANH that are not common to other autologous transfusion modalities. When the blood is kept in the same operating room, the chances of clerical error are eliminated. On the other hand, because blood collected by ANH is stored at room temperature and is usually returned to the patient within eight hours of collection, there is little deterioration of platelets or coagulation factors[1].

Recently, various studies have demonstrated cardio-protective effects of acute normovolemic hemodilution in cardiac surgeries under cardiopulmonary bypass (CPB), and in addition to conventional myocardial preservation techniques, preoperative ANH achieved further cardiac protection in patients undergoing on-pump myocardial revascularization and severe aortic stenosis[9-10].

In some studies that ANH was employed during CABG, net blood loss, amount of reinfused shed blood, postoperative blood requirements, the percentage of patients who received allogeneic blood and the number of blood units transfused per patients, were less in the ANH group[1113-]. Despite the fact that some believe that preoperative or intraoperative collection of platelet-rich plasma during cardiopulmonary bypass surgery may improve hemostasis and decrease allogeneic exposures, others however have found no benefit, and various studies have questioned the efficacy of intraoperative acute normovolemic hemodilution (ANH) in reducing bleeding and the need for allogeneic transfusions in cardiac surgery and its capacity to reduce perioperative allogeneic transfusion remains controversial[1415-].

The effect of "minimal" ANH on postoperative blood requirements have not been studied, the aim of the present study was to evaluate the effects of a "minimal" ANH in elective, coronary artery bypass graft.

Methods and Materials

After approval by the local Ethics Committee, written informed consent was obtained from all patients scheduled for elective CABG and thought to meet the eligibility criteria.

Exclusion criteria were left main coronary artery stenosis; left ventricular ejection fraction less than 40%; anemia (hematocrit <34% and hemoglobin <11.5 g/dL); pump time >2.5h; need for reoperation; history of hematological disorders; advanced chronic renal failure (serum creatinine >2 mg/dL); active chronic hepatitis; or cirrhosis.

One hundred one patients to undergoe CABG surgery in October 2007 through March 2008 in our hospital were included in this prospective, randomized controlled trial to evaluate the merits and practicability of autologous blood transfusion.

By using a computer-generated random-number sequence, the 101 patients were prospectively randomized to one of the two groups: the ANH group (no = 54) and the standard care group (no = 47).

All patients had same protocol for anesthesia

and surgery. On the morning of operation, the patients were premedicated with morphine, 5µg/kg. Standard monitorings such as pulse oximetry, leads II and V5 of the ECG for heart rate and automated ST-segment trend analysis, continuous measurements of central venous pressures and mean arterial, end-tidal capnography, bispectral index analysis of the EEG (BIS A-2000 XP; Aspect Medical Systems;) and nasopharyngeal temperature were performed perioperatively.

Balanced anesthesia with propofol, fentanyl, midazolam, isoflurane, and pipecuronium was performed in all patients. Inhaled isoflurane (0.5 to 1% in the pre-bypass period), was administered to enhance cardiac protection before aortic clamping (anesthetic preconditioning). In the two groups, a similar depth of anesthesia was obtained by targeting bispectral EEG values between 40 and 60 arbitrary units.

In the ANH group, we used minimal ANH (representing 10% of patients' blood volume)[1]. After the induction of anesthesia and before systemic heparinization, blood was withdrawn from a central vein by gravity into citrate-phosphate-dextrose collection bags. Simultaneous gelatin solution (1 mL for each 1 mL of blood withdrawn) was infused through a 16-gauge peripheral catheter on the opposite arm. The autologous blood was labeled and stored at the room temperature and reinfused intraoperatively when the transfusion criteria were met.

Cardiopulmonary bypass (CPB) and myocardial preservation strategies were uniform among the two participating surgeons. After heparinization (300 IU/kg), CPB including a membrane oxygenator and a circuit primed with a 2-L normal saline solution was performed using non-pulsatile flow (2.2 to 2.5 L/min/m2) and hypothermia (28 to 30°C). An α stat control for acid-base management was applied, and mean arterial pressure was targeted between 50 and 80 mm Hg with pharmacologic and pump flow manipulation as necessary.

All patients were operated on in our Institution with standardized techniques. The left internal mammary artery (LIMA) was isolated through an extra-pleural approach in all patients for left anterior descending artery (LAD) graft. The saphenous vein also was used for other grafts. The radial and the gastroepiploic artery were not used in any patient.

After achieving a nasopharyngeal temperature 37°C, weaning from CPB was performed by standard hemodynamic measurements. The pump flow was gradually reduced while the heart was progressively filled in order to optimize the preload-recruitable stroke volume and to reach a mean arterial pressure more than 70 mm Hg. The heart was electrically paced if it failed to maintain a heart rate more than 60 beats/min. Inotropes were not routinely administered during weaning from CPB.

At the end of CPB, protamine was administered to neutralize circulating heparin, and then in the ANH group, the whole autologous blood volume was reinfused. Allogeneic Packed red blood cells (PRBC) were transfused with hemoglobin <10 g/dL and hematocrit <30%.

Before closure of the chest, mediastinal and pleural drains were positioned, and low-grade suction was instituted.

Hemoglobin, and platelet count, were measured in blood samples obtained before the induction of anesthesia; at arrival in the intensive care unit (ICU) after completion of the reinfusion of autologous blood; 24 and 48 h after surgery; and before discharge from the cardiac intensive care unit. During surgery, hematocrit, hemoglobin and electrolytes and blood gasses were monitored in serial samples drawn for blood gas determinations (nova biomedical, phox plus).

All data were analyzed using statistical software (version 16 for Windows; SPPS; Chicago, IL). Values were expressed as mean (±SD). Dichotomous variables were compared by the x^2 statistic or Fisher exact test, as appropriate, and quantitative variables were compared with unpaired Student t test. Differences were considered statistically significant with p values less than 0.05.

Results

Demographic, preoperative characteristics and operative data are shown in Table 1. No significant differences were observed between groups with regard to age, sex, body surface area, and preoperative left ventricular ejection fraction.

Table 1
*Demographic data, Preoperative and operative characteristics of patients**

Variable	ANH group no = 54	Control group no = 47	P Value
Age (y)	55±12	58±9	0.149
Sex: male/female (%)	46/8 (17.3)	40/7 (17.5)	0.991
Weight (kg)	67.45	71.90	0.224
BSA (m^2)	1.8±0.14	1.7±0.19	0.148
LVEF (%)	46±6	47±6	0.725
Hemoglobin (g/dl)	13.7±1	13.2±1	0.069
Hematocrit (%)	40±4	39±4	0.089
Platelet count (mm3)	230981±62	257361±10	0.123
Preoperative treatment			
ß blockers (%)	60	62	0.654
ACE inhibitors (%)	31	31	0.996
Diuretics (%)	16	18	0.256
Aspirin (%)	78	79	0.086
Grafted coronary arteries (n)	3±0.8	3±0.7	0.137
Duration of CPB (min)	75±21	75±25	0.898
Aortic clamp (min)	116±29	121±31	0.46
Removed autologous blood	490±50	-	-

* Data are presented as mean (95% confidence interval) unless otherwise indicated.
ANH = acute normovolemic hemodilution, BSA = body surface area;
LVEF = left ventricular ejection fraction.

Also, the number of grafted coronary arteries, as well as the duration of aortic cross-clamping and CPB, preoperative hemoglobin, hematocrit and platelet count, were comparable (Table 2). Mean removal of blood in the ANH group was 490±50 mL. No patient in the ANH group experienced complications related to normovolemic blood withdrawal.

Hemoglobin concentration preoperatively and postoperatively did not differ among groups. Significant decrease in the number of red blood cell units transfused per patient (1.39 ± 1.0 and 2.55±1.9 units; $p < 0.0001$) in the ANH group versus the control group was observed (Fig. 1). Conversely, chest tube output, postoperative hemoglobin and platelet count did not differ between two groups, but a significantly larger number of patients in the control group required allogeneic transfusions.

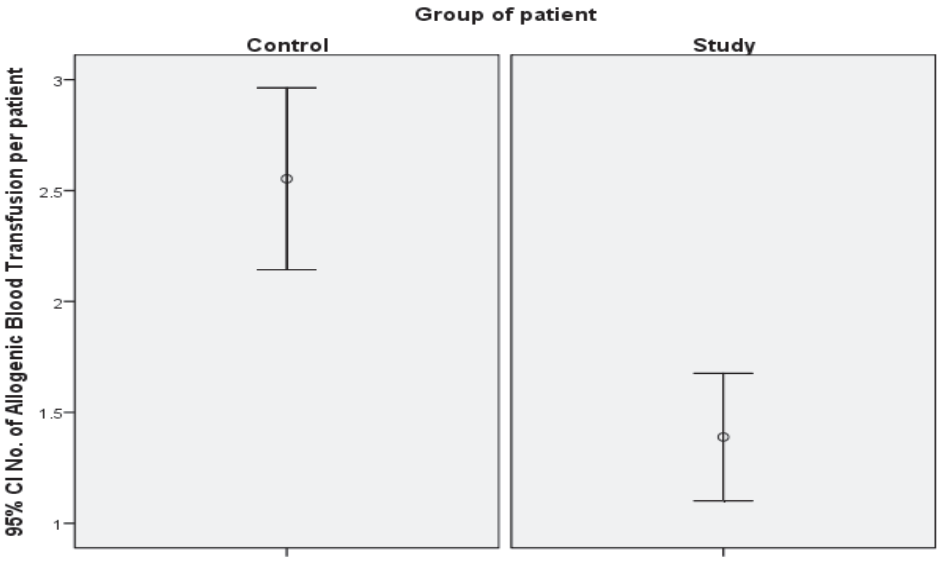
The total number of PRBC units transfused was significantly more in the control group (120 vs. 75; P = 0.001). Percentage of patients in whom allogeneic red blood cells were transfused was 44% in study group

Table 2
Postoperative data and perioperative allogeneic blood transfusions*

Variable	ANH group no = 54	Control group no = 47	P Value
Chest tube drainage, mL/48h	871±48	975±59	NS
Hemoglobin (g/dl)	10±1	11±1	NS
Platelet count (mm3)	170804±69	178428±70	NS
Patients transfused with PRBC (n, %)	23, 44#	35, 76	0.0001
No. of PRBC transfused per patient (n)	1.39 ± 1.0#	2.55±1.9	0.0001
Total FFP (U)	0	0	NS
Total Platelet concentrate (U)	0	0	NS
Total number of PRBC transfused (n)	75#	120	0.001

* Data are expressed as mean±SD unless otherwise indicated.
# $p < 0.05$ between two groups.
PRBC = packed red blood cells; FFP= fresh frozen plasma.

Fig. 1
Packed red blood cell units transfused per patient

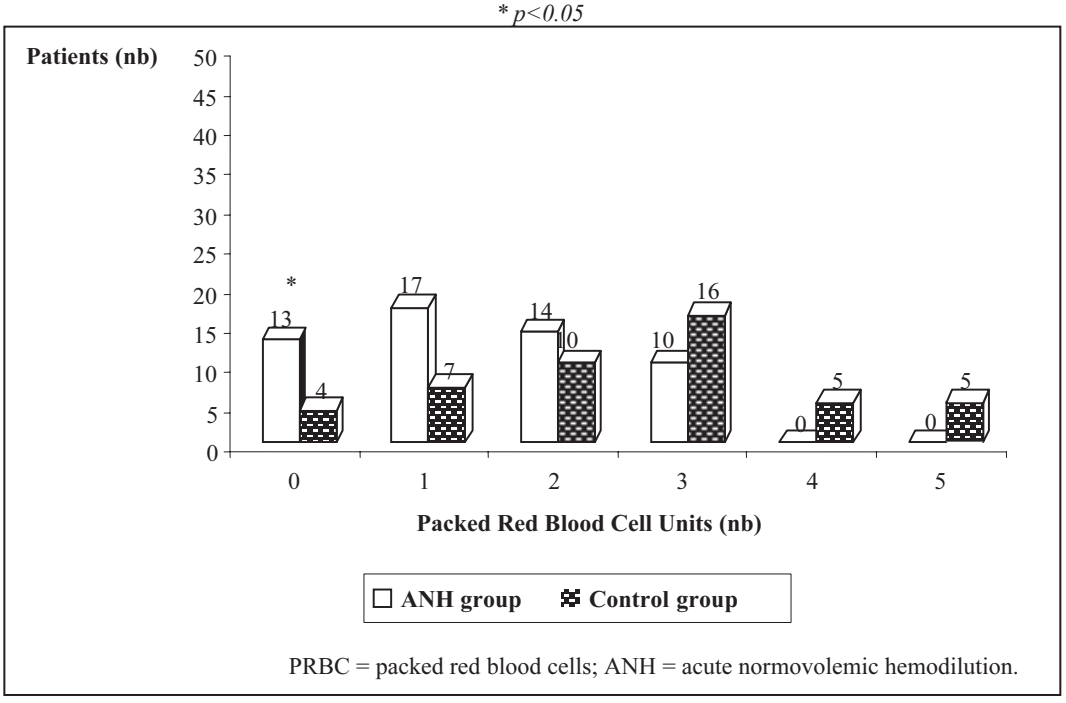


* 1.39 ± 1.0 in the ANH group versus 2.55±1.9 units in the control group (p<0.05).
ANH = acute normovolemic hemodilution.

versus 76% in control group; (p < 0.01). Fig. 2 shown the total allogeneic blood exposure or number of patients who received between 0-5 units PRBC in two study groups. Thirteen patients in the ANH group, versus 4 patients in the control group, did not require any PRBC transfusions. In the control group ten patients received more than three units whereas in the ANH group no patient received more than three unit of PRBC.

All patients in each group who required re-exploration for excessive bleeding were excluded from study. No patient was transfused with platelet concentrates or fresh frozen plasma (FFP).

Fig. 2
Total allogeneic blood exposure in the two groups (0-5 units PRBC)
** p<0.05*



PRBC = packed red blood cells; ANH = acute normovolemic hemodilution.

In the ANH group, the autologous blood was reinfused after CPB in all the patients as the transfusion threshold was reached.

Discussion

The application of minimal ANH decreased allogeneic blood exposure in patients undergoing CABG. This effect was essentially related to a reduction in perioperative allogeneic blood product use. This result was obtained without any increase in early postoperative morbidity or mortality. The results of this investigation demonstrate that minimal ANH prior to on-pump CABG reduced the number of red blood cell units transfused per patient and the total number of transfused PRBC. This is the first study to evaluate the effects of minimal ANH on allogeneic blood requirement in patients submitted to CABG surgery under CPB. Mean withdrawal blood was 490±50 mL. Although intraoperative masking was not possible, the ICU staffs were blinded to allocation to group, perioperative medical care was standardized, and similar clinical and physiologic end points were achieved in the two groups. Preoperative cardiac condition and intraoperative surgical treatment were also comparable.

Use of minimal ANH in present study resulted reduction in the number of patients transfused with donor blood. Accordingly, we observed a reduction in the number of PRBC units transfused. Because blood collected by ANH is stored at room temperature and is usually returned to the patient within eight hours of collection, there is little deterioration of platelets or coagulation factors.

Our results are very similar to those of Jalali et al[16]. They used ANH and concluded that the use of ANH can reduce the need for PRBC and FFP by 58% and 74%, respectively. In present study the percentage of patients in whom allogeneic red blood cells were transfused was 44% in study group versus 76% in control group and any of patients did not need to FFP or platelet concentrates transfusion.

In our study the total blood loss was similar in the two groups of patient and the 24 h chest tube output, postoperative hemoglobin, and platelet count did not differ between the two groups. Most of the blood loss occurred during surgery or in the first postoperative hours, and the blood-sparing properties of ANH are mainly related to increased dilution of the intraoperative blood loss, leading to a smaller net loss of red blood cells[17]. A clinical analysis of patients who had undergone minimal ANH (representing 15% or less of patients' blood volume) estimated that only 100 mL of RBCs (the equivalent of 1/2 unit of blood) was saved under these conditions[1].

Whole blood withdrawal and administration of crystalloid or colloid solution decreases arterial oxygen content, but compensatory hemodynamic mechanisms and the existence of surplus oxygen delivery capacity make ANH safe. Sudden decrease of RBC concentration lowers blood viscosity, thereby decreasing peripheral resistance and increasing cardiac output. Some studies demonstrated that acute preoperative hemodilution attenuates the deleterious effects of aortic cross-clamping and improves myocardial recovery in patients undergoing CABG[10]. In our study because of the relatively small degree of hemodilution and the attention paid to maintain normovolemia, no patient in this series experienced intraoperative myocardial ischemia, and the outcomes and postoperative complications did not differ between the two treatment groups. As suggested by some authors, more profound hemodilution might lead to serious complications, such as metabolic acidosis, peripheral edema, pulmonary and neurological sequel, and, especially in coronary patients, myocardial ischemia[18,19].

In present study, to assess the pure effect of minimal ANH on allogeneic blood requirement, we select the low risk patients and excluded the high risk patients who needed reoperation due to inadequate surgical hemostasis. Also the patients were monitored and assessed for postoperative acute myocardial infarction, on the basis of ECG abnormalities and a significant increase in myocardial enzymes, but no patients in two groups had evidence of postoperative myocardial ischemia.

In conclusion, minimal ANH can lead to a significant reduction in the number of patients who require allogeneic blood transfusions. The optimal value of hematocrit levels before CPB remains unknown. Further studies are warranted to confirm these results, to test the efficacy of this simple procedure in higher-risk patients with poor ventricular function and those requiring complex cardiac surgery.

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