



Effect of Retrograde Autologous Priming on Clinical Outcome of Cardiopulmonary Bypassing on Patients Undergoing Coronary Artery bypass Grafting

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Abstract

Introduction: Cardiopulmonary bypass is a standard and low mortality-associated method used across the world. This method allows cardiac surgery to be performed in a bloodless environment. The study aimed to compare Conventional priming and Retrograde autologous prime (RAP) on patients undergoing coronary artery bypass grafting (CABG).

Methods: The study population was patients undergoing CABG using cardiopulmonary bypass in Rajaei Hospital, of whom 80 patients were selected by simple random sampling convenience sampling and then were randomly assigned to two groups: Conventional priming and RAP. Demographic information, blood components transfused in the operating room and the intensive care unit, ejection fraction (EF) of left ventricle and changes in blood gases were collect.

Results: The mean requirement for red blood cell transfusion bags to the patient during surgery was lower in the RAP group than the conventional priming group ($P = 0.002$). But the difference after surgery in both groups was not significant statistically ($P = 0.2$). The difference amount of platelet transfusion during operation the difference was not statistically significant ($P = 0.4$). The difference postoperative platelet transfusion was not statistically significant ($P = 0.7$). The fresh frozen plasma transfusion during surgery in the RAP group lower than the usual prime group, but the difference was not statistically significant ($P = 0.406$). The Fresh frozen plasma (FFP) transfusion after surgery in the two groups was not statistically significant ($P = 0.217$).

Conclusion: RAP is compared with conventional priming a safe and low-cost technique in reducing the priming volume of the CPB system, causes less hemodilution, and reduces the need for intra- and postoperative blood transfusion. Therefore, it is recommended to consider RAP as an effective and low-cost technique of priming Cardiopulmonary bypass circuits.

INTRODUCTION

Cardiopulmonary bypass (CPB) is a standard and low mortality-associated method used across the world. This method allows cardiac surgery to be performed in

a bloodless environment but preparing the CPB circuits before operation requires to prime it by about 1500 ml of crystalloid solution which is a cause of significant

hemodilution. This hemodilution leads to disrupted homeostasis and increased need for blood transfusions during and after surgery in patients [1]. Decreased blood viscosity, improved microcirculation and enhanced venous return with the following increase in cardiac output are known benefits of moderate hemodilution. However, severe hemodilution with subsequent anemia may result in ischemic organ injury.

Decreased hematocrit results in decreased blood oxygen content and oxygen delivery to the tissues. Hypoxia leads to increased tissue damage and mortality [2]. Particularly, anemia in heart surgery, when hematocrit reaches less than 20%, is an important risk factor for stroke, renal failure, and increased mortality [3]. Besides, bleeding and anemia after the operation cause some specific issues that reduce the body's ability to provide adequate perfusion to the body's major organs, such as the brain, heart, and kidneys, leading to failure of these organs exacerbated by hemodilution. However, resolving this problem using blood components transfusion also causes issues such as blood type incompatibility (1:10,000), blood-borne infections (1:350,000), lung damage (1:50,000), cerebral edema and kidney dysfunction [4]. Reducing the volume of prime is the technique that decreases hemodilution and blood transfusion during cardiopulmonary bypass. Retrograde autologous priming (RAP), developed in 1998 by Rosenberg, is a non-pharmacological method for keeping blood. In this method, before the initiation of the bypass, blood from the arterial and venous cannulas is directed toward the bypass circuit and the blood inside the crystalloid circuit is directed toward a bag [5].

By increasing blood osmotic pressure and reducing pulmonary edema, RAP improves patient outcomes and reduces the postoperative mechanical ventilation time [6,7]. Hwang et al's study on regional brain oxygenation showed that RAP increased oxygenation of the brain by reducing hemodilution [8]. Severdija et al. reported that hemofiltration and bleeding during and 24 hours after the surgery were lower in the RAP group than the control, and intraoperative hematocrit was higher in the RAP group than the control and the total number of patients and the units of blood given were lower in the RAP group than the control [9]. A study in Sao Paulo, Brazil showed that RAP increases hematocrit during surgery, especially in people with anemia, followed by decreased hemolytic reactions due to decreased blood transfusion. However, some results reported the RAP as a useful method while some others not [10]. Kearsy et al. study showed that there were no differences in blood transfusion, platelet, frozen plasma, 30-day mortality, re-operation, and the amount of hemoglobin between the RAP and the control group [11]. Another study showed that this technique did not affect the clinical outcome of patients [12]. In a prospective study conducted by Nanjapa et al., RAP did not affect hemoglobin,

hematocrit level and blood product transfusion [13]. A retrospective cohort study demonstrated that RAP was ineffective in bleeding control in the operating room while performing this technique caused hemodynamic instability [14].

According to the results of studies, there were no pieces of evidence over the usefulness of RAP before cardiopulmonary bypass regarding the clinical outcomes, therefore, further studies are needed to determine the effects of RAP on the clinical outcomes. We aimed to investigate the effect of RAP on the clinical outcomes of cardiopulmonary bypass in patients undergoing coronary artery bypass graft (CABG).

METHODS

This study is a randomized clinical trial and received the ethical approval from the ethics committee of Iran University of Medical Sciences and Rajaei Hospital (IR.IUMS.REC1395.9311584002). Written consensus has been obtained from all the patients.

Study Population

The research population in this study includes all patients undergoing CABG using cardiopulmonary bypass in Rajaei Hospital. Adult patients undergoing CABG without previous heart surgery, aged 18 to 70 years, weight over 45 and less than 100 kg, hemoglobin levels over 8.5 and less than 14 mg/dL, and left ventricular ejection fraction over 35% were enrolled in the study. Patients undergoing emergency surgery, having preoperative coagulation problems, undergoing mechanical ventilation prior to surgery, patients with carotid plaque leading to stenosis more than 60%, COPD patients, patients with serum creatinine levels over 1.2 mg/dL, using hemo-filter, cell saver and patients with bleeding after surgery were excluded from the study. If mean arterial pressure decreases to less than 60 mmHg during the operating of RAP, the technique is stopped and the data were excluded from the study. Eligible patients were randomly assigned to either the retrograde autologous priming or conventional priming. The randomization was performed according to a random number sequence generated by the computer.

Intraoperative Detail and CPB Management

Anesthesia was performed in all patients using a single technique. To achieve this purpose, 10 $\mu\text{g.kg}^{-1}$ fentanyl and 0.1 mg.kg^{-1} of midazolam, and then, to maintain anesthesia, 0.5 $\text{mg.kg}^{-1}.\text{hr}^{-1}$ fentanyl and 1 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$ Midazolam was administered. In patients with low EF, attempts have been made to prevent hemodynamic changes and prevent the reduction in heart rate and blood pressure and avoidance of arrhythmias. CPB was performed in all patients with a roller pump and non-pulsatile flow (2.4 $\text{L.m}^2.\text{min}$). Mean arterial pressure was maintained above 60 mm Hg. CPB circuits were primed with 1000 ml of ringer lactate and 500 ml of hydroxyethyl starch.

A median sternotomy was performed in all patients, and arterial and venous cannulation was conducted after systemic heparinization and before the onset of CPB. 300 u.kg⁻¹ Heparin was given to maintain activated clotting time (ACT) over 480 seconds during CPB. Patients were cooled to 32 °C during aortic clamp and heated to 37 °C after opening the aortic clamp. At the completion of the surgery, protamine was used to neutralize the effect of heparin.

Study Design and Study Variable

When the arterial cannula that had been placed in the patient's aorta was connected to the arterial line of CPB, the patient was placed in the Trendelenburg position and clamp was removed from the arterial line so that the blood could retrogradely enter in the arterial line, oxygenator, and arterial filter and replace the fluid in them that exited from the circuit and entered the collecting bag. By coordination between perfusion and anesthetic teams, preventing the reduction of mean arterial pressure to less than 60 mmHg and, if needed vasopressor was used to prevent hypotension.

For the implementation of RAP, a 1.4-inch line that connected the arterial route to the oxygenator (the line that returned blood to the venous reservoir) was used. This line was connected to a 1-liter tank to collect the liquid. RAP was implemented after the ACT reached over 400 seconds through three steps. In the first step recirculation line was open. This allowed blood to move reversibly from the arterial line to the arterial filter and the liquid contained in this line was transferred into the collecting bag. In the second step, the liquid in venous reservoir and oxygenator was depleted; in this step, the line between the oxygenator and arterial line was closed and the recirculation line was opened, arterial pump slowly progressed and fluid in the venous reservoir passed into the collecting bag until the volume of fluid in the venous reservoir reached approximately 200 ml. Then, the exit of the arterial filter was open and the arterial pump continued until the fluid that exited the oxygenator became sanguineous; then, the arterial pump stopped and the recirculation line was clamped.

In the third step, which coincided with the start of CPB, the fluid in the venous line entered the collecting bag until the effluent fluid became sanguineous. Afterward, the recirculation line was clamped and the fluid that was collected in the bag was maintained to be added to the system if the crystalloid fluid was needed. The tools used to collect information were two checklists one of which was used to collect demographic information including name, age, sex, body surface, height, weight, the group to which the participant was assigned, and the number of grafts. The other checklist completed during and after the CPB was used to collect data on total bypass duration, aortic cross-clamp and surgery duration, the duration of being connected to the mechanical ventilation device, the blood components transfused in

the operating room and the intensive care unit, ejection fraction (EF) of left ventricle and changes in blood gases were recorded. Both medical and nursing staff in the ICU and the postoperative wards were blinded from the priming techniques used for this study. The data were collected during the CPB, surgery, and hospitalization in both the intensive care unit and otherwise for both groups and recorded in the checklists.

The present study was registered in the Iranian Registry of Clinical Trials (IRCT registration number: IRCT2016073029123N1).

Statistical Analysis

All statistical analyses were performed in SPSS (Version 23.0, SPSS Inc., Chicago, IL, USA) using descriptive statistics (mean ± SD). The sample size was determined with a 95% confidence interval and 80% power, and assuming that RAP could prevent the reduction in hemoglobin by $d = 1$ for its effect to be considered statistically significant. It is noteworthy that in a similar study, the standard deviation of hemoglobin was estimated at 1.5 (SD = 1.5) and sample size in each group was estimated 40 considering 10% dropout. Chi-square test was used to compare qualitative data (sex) and an independent t-test was used to compare quantitative data (age, height, weight, hemoglobin, haematocrit, blood components transfusion, Duration of mechanical ventilation, blood gases, Ejection Fraction). P-value < 0.05 was considered statistically significant.

RESULTS

General Characteristics

In this study, 80 patients, assigned to two groups of 40 each: RAP and conventional priming, were studied. According to statistical analysis, there was no significant difference in age, sex, height, weight, graft number, duration of the total bypass, and duration of aortic cross-clamping between the two groups ($P > 0.05$) (Table 1). The difference in haemoglobin (mg/dl) (11.45 ± 1.17 vs. 11.61 ± 1.23) and hematocrit (%) (36.17 ± 5.78 vs. 36.39 ± 7.03) before the pump was not significant between the RAP group and the conventional priming group. But, there was a significant difference in haemoglobin (mg/dl) (8.99 ± 0.95 vs. 8.65 ± 0.97) and hematocrit (%) (28.95 ± 3.23 vs. 27.65 ± 3.62) after the pump. Besides, during the first 30 min of CPB, hemoglobin (mg/dl) (8.5 ± 0.89 vs. 7.29 ± 0.64) and HCT (%) (27.7 ± 3.12 vs. 25.49 ± 2.24) were significantly higher in the RAP group compared to the conventional priming group. This finding confirmed that hemodilution is reduced by using RAP.

Comparison of the Need for Blood Components Transfusion during and After Surgery

Transfusion of PRBC and other blood products were not significantly different during and after the operation (Table 2).

Duration of Mechanical Ventilation

The mean duration of mechanical ventilation (h) was significantly shorter in the RAP group (8.70 ± 1.83) than the conventional priming group (10.38 ± 2.94) ($P = 0.003$) (Table 3).

Left Ventricular Ejection Fraction

The left ventricular EF was compared between the two groups before and after surgery. The differences in preoperative EF (%) (47.50 ± 7.51 vs. 44.13 ± 8.39) and postoperative EF (43.63 ± 5.66 vs. 42.38 ± 6.40) were

not statistically significant between the RAP group and the conventional priming group ($P > 0.05$) (Table 4).

Changes in Blood Gases in Two Groups

Changes in blood gases such as oxygen (mmHg) and carbon dioxide (mmHg), and acidity (PH) in the two groups were investigated in four times, the baseline, half an hour after the onset of the pumps, at the completion of the pump, and after that. The results showed that the amounts of oxygen and carbon dioxide and changes in pH were not significantly different between the two groups ($P > 0.05$).

Table 1. Demographic Features of Patients in Two Groups

Variable	RAP	Conventional priming	P value
Age, year	60.53 ± 9.45	62.35 ± 10.24	0.4
Sex			
Female	15 (37.5)	15 (37.5)	0.5
Male	25 (62.5)	25 (62.5)	0.5
Height, cm	167.5 ± 8.79	164.95 ± 9.31	0.2
Weight, kg	75.38 ± 11.8	74.50 ± 12.47	0.78
Graft number	3.38 ± 0.63	3.23 ± 0.62	0.2
Duration of aortic cross-clamping, min	44.35 ± 17.58	44.35 ± 17.55	1.0
Duration of total bypass, min	80.55 ± 29.72	83.48 ± 26.45	0.6
Base haemoglobin, mg/dl	11.45 ± 1.17	11.61 ± 1.23	0.2

Data in table are presented as No. (%) or Mean ± SD. RAP: Retrograde autologous prime

Table 2. Comparison of Blood transfusions in retrograde autologous priming and conventional Priming groups

	RAP	Conventional priming	P value
Unit of packed cell transfusion (ml)			
During cardiopulmonary bypass	118.75 ± 26.84	275 ± 39.83	0.002
After cardiopulmonary bypass	106.25 ± 26.69	162.5 ± 38.55	0.2
Unit of platelets transfusion (ml)			
During cardiopulmonary bypass	8.75 ± 4.34	13.75 ± 5.06	0.4
After cardiopulmonary bypass	12.5 ± 4.29	18.75 ± 6.2	0.4
Unit of FFP transfusion (ml)			
During cardiopulmonary bypass	41.25 ± 15.18	48.75 ± 18.9	0.7
After cardiopulmonary bypass	49.5 ± 18.9	45 ± 18.76	0.2

Data in table are presented as Mean ± SD. RAP: Retrograde autologous prime; FFP: Fresh frozen plasma

Table 3. Comparison of Ventilator Time in retrograde autologous priming and Conventional priming Priming groups

Variable	RAP	Conventional priming	P value
Ventilator Time (Hour)	8.70 ± 1.83	10.38 ± 2.94	0.003

Data in table are presented as Mean ± SD. RAP: Retrograde autologous prime

Table 4. Comparison of Ejection Fraction in retrograde autologous priming and Conventional priming groups

	RAP	Conventional priming	P value
Ejection Fraction, %			
During cardiopulmonary bypass	47.50 ± 7.51	44.13 ± 8.39	0.06
After cardiopulmonary bypass	43.63 ± 5.66	42.38 ± 6.40	0.3

Data in table are presented as Mean ± SD. RAP: Retrograde autologous prime

DISCUSSION

Increased hemodilution during CPB due to decreased oxygen supply is associated with the dysfunctioning of vital organs. Hemodilution reduces the amount of coagulation-associated proteins and therefore increases bleeding during CPB. The results of this study showed a decrease in transfusions of blood components during surgery in the group that increased with RAP. The number of patients requiring transfusion of PRBC and the mean number of transfused units of PRBCs was significantly different between the RAP and the conventional priming group during the surgery.

Rosengart et al. showed that 3% of patients in the RAP group and 23% in the conventional prime group required a blood transfusion during surgery [15]. Also Shapira et al. showed that RAP caused a reduction in PRB transfusion [16]. Sackowski's meta-analysis investigate the effectiveness of RAP in reducing transfusion of PRBCs in the adult heart surgery concluded that the number of patients receiving PRBC transfusion during operation and the entire hospital stay is reduced by this method [17]. Available findings reported a significant reduction in blood transfusions needed in patients who treated with RAP [18]. There are varying degrees of hemodilution in CPB that may

offer advantages such as decreased peripheral vascular resistance, improved microcirculation perfusion, and reduced blood loss. Therefore, moderate hemodilution is highly essential to manage CPB but excessive hemodilution can affect the perfusion and damage of organs [19].

Decreased hematocrit level causes tissue hypoxia which is the most important mechanism of damage to the body organs and increased mortality [19]. The mean duration of mechanical ventilation was significantly different between the RAP group and the conventional priming group, which is consistent with the results of Foglia [7] and Trapp et al. study reporting RAP reduced the duration of mechanical ventilation, improved the outcome of patients, and reduced pulmonary edema through increasing blood osmotic pressure. Teman et al. showed that difference in longer than ventilation more than 48-h was not statistically significant between intervention and control groups [19]. Trapp et al. comparatively studied RAP, conventional priming, and miniaturized CPB. Their results showed that the duration of mechanical ventilation was not significantly different among the three groups [6].

Heart EFs were compared before and after the surgery in both groups. There was no significant difference in EF between before and after the surgery in both groups, which is consistent with Severdija [9] and Teman [20] studies and inconsistent with Teman study [21].

The changes in blood gases such as oxygen, carbon dioxide and PH in the two groups were investigated four times before the pump, during the pump (30 minutes after starting the pump), at the completion of the pump, and after the pump. The results showed that the changes in oxygen and carbon dioxide and PH in the two groups were statistically significantly different at none of the four intervals [22]. In analyzing lactate levels at different intervals, we could not find any significant difference between the conventional priming group and RAP group [23] which is consistent with Ancheri et al. study [24].

CONCLUSIONS

Because of the more frequent use of allogeneic blood in heart surgery than other surgeries and limitations in banked bloods, the use of lower amounts of such bloods is an essential purpose in cardiac surgery. The use of RAP can help to maintain hematocrit at higher levels, maintain hemodynamic and hemostasis status in good condition, and prevent infections associated with blood transfusions. The results of our study showed that RAP reduced hemodilution, increased hematocrit and, therefore blood transfusion during CPB. In this study, the duration of mechanical ventilation was shorter in the RAP group than the conventional priming group. According to the findings, the amount of blood transfusion, not blood products, is less during surgery. Therefore, it is recommended to consider RAP as an

effective and low-cost technique of priming CPB circuits.

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Conflicting Interest

The authors declare no conflict of interests.

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