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Acute normovolaemic haemodilution with crystalloids in coronary artery bypass graft surgery: a preliminary survey of haemostatic markers

Alireza JALALI[1], Mohammad Hasan NASERI[2], Majid CHALIAN[3], Hasan LAL DOLATABADI[1]

[1] Dept. of Anaesthesiology, Baqiyatallah University of Medical Sciences; [2] Dept. of Cardiovascular Surgery, Baqiyatallah University of Medical Sciences; [3] Nikan Health Researchers Institute, Tehran, Iran.

Introduction — Acute normovolaemic haemodilution (ANH) is a safe and cost-effective blood conservation strategy in procedures with great blood loss. It eliminates the risk of administrative errors and also contaminations that may occur whenever banked blood is used. Classically, haemodilution is regarded as causing coagulopathy. This study was designed to determine the effect of crystalloids on measured coagulation values and perioperative blood loss following ANH in patients undergoing elective coronary revascularization.

Methods — Following a prospective case-control study one hundred candidates for CABG (50 cases in the ANH group and 50 in the control group) were included. Blood samples for coagulation testing haematocrit and platelet levels were collected before ANH, after cardiopulmonary bypass (CPB), and upon arrival at the intensive care unit (ICU). Differences were considered statistically significant with P values < 0.05.

Result — There was no statistically significant difference between chest tube drainage in the two groups. The number of patients using PRBC (packed red blood cell) or FFP (fresh frozen plasma) was significantly higher in the control group in comparison to the ANH group ($P < 0.05$). The PT increased significantly after arrival in the ICU in both groups ($P < 0.001$) but there was no between-group difference ($P = 0.22$). aPTT not only did not change significantly in the ICU relative to the baseline pre ANH values in both groups ($P > 0.05$) but also did not show any between-group difference ($P = 0.69$). There was no statistically significant difference in the aCT of the control and the ANH group after arrival to the ICU ($P = 0.09$). Hct and Plt decreased significantly in both groups after CPB and arrival at ICU.

Conclusion — ANH reduced the need for PRBC and FFP by 58% and 74%, respectively. Regarding the increase in PT and decrease in Plt count, we concluded that performing ANH with saline solution (SS) in patients undergoing CABG surgery may cause a non-clinically significant change in coagulation state.

Keywords: *acute normovolaemic haemodilution – coronary artery bypass graft – coagulopathy – crystalloid.*

Introduction

Coronary artery bypass graft (CABG) surgery 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[1]. Over the last two decades, the potential benefits of avoiding homologous blood transfusion and optimizing oxygen delivery in vital organs have led to a renewed interest for acute normovolaemic haemodilution (ANH) in CABG and other major surgeries[2].

Acute normovolaemic haemodilution (ANH) is a useful and cost-effective blood conservation strategy in procedures with an expected blood loss of more than 1 litre[3-5]. The red blood cell (RBC) loss is decreased in the haemodiluted patient because the blood that is lost during surgery has a reduced haematocrit[5]. This technique effectively reduces the need for allogeneic blood transfusion and the accompanying risk of transfusion-related infection and transfusion reactions[6]. There is

Address for correspondence: Alireza Jalali, M.D., Vanak Square, Mollasadra Ave., 19945-587 Tehran, Iran. P.O. Box: 14155-6437. Postal code: 1435915371. E-mail: alijalali43@hotmail.com

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also evidence that the transfusion of allogeneic blood may induce immunosuppression, which may be detrimental with respect to perioperative infection and patients undergoing surgery for malignancies[7]. ANH is less expensive than preoperative autologous donation (PAD) and eliminates the risk of administrative error that may occur whenever banked blood is used[4,8].

ANH involves the removal of blood from the patient shortly after the induction of anaesthesia and before the start of major surgical blood loss. A replacement fluid is simultaneously infused to maintain intravascular volume. The stored blood is returning to the patient when a threshold haematocrit (Hct) is reached, or sooner, if clinically indicated. Ideally, this is after most of the blood loss has occurred[3].

Both crystalloid and colloid replacement fluids have been successfully used to maintain normovolaemia during ANH[3]. Rapid fluid infusion induces coagulopathy because of haemodilution[9]. Classically, haemodilution is regarded as causing coagulopathy[10,11]. However, colloids such as hetastarch and dextran decrease hypercoagulability in some studies[12-14], whereas crystalloid administration may not[10,11,15,16]. The underlying mechanism of this dilutional coagulopathy may be reduced clot weight, as well as impaired fibrinogen polymerization[17]. However, less is known about the effects of these fluids on haemostasis within the context of ANH. This prospective, randomized study was designed to determine the effect of crystalloids on measured coagulation values and perioperative blood loss following ANH in patients undergoing elective coronary revascularization.

Methods and materials

In a prospective study performed at the Baqiyatallah general hospital, Tehran, Iran, one hundred CAD patients who were scheduled to undergo elective coronary artery bypass graft surgery were included to participate. The study was approved by the Baqiyatallah Ethical Board, and was fully supported and funded by the Baqiyatallah Medical Sciences University. Written informed consent was obtained from the patients. Patients were excluded from participation if they had a history of a known coagulation disorder, platelet count < 100,000/mm^3, preoperative haemoglobin (Hb) < 12 g/dl, anticoagulant therapy within 10 days before surgery, aspirin or non-steroidal anti-inflammatory drug use < 10 days before surgery, or if they had a documented allergy to any of the i.v. fluids used in the protocol. The enrolled patients were randomly assigned to one of the two trial groups [ANH (n = 50) or standard care management (n = 50)] using a computer-generated random numbers table.

All patients were premedicated with midazolam in the preoperative room and received a standardized general anaesthetic induction consisting of lidocaine (1.5 mg/kg), itracuronium (0.5 mg/kg), and fentanyl (5-8 μg/kg). After tracheal intubation, anaesthesia was maintained with midazolam (0.1 mg/kg/h), itracuronium (0.5 mg/kg/h) and a continuous fentanyl infusion (30 μg/kg/h).

Patients in the ANH group underwent moderate haemodilution to a target Hb of 9 g/dl. ANH was performed in conjunction with prepping and draping. Whole blood was collected in standard citrate-phosphate-dextrose (CPDA-1) blood collection bags while simultaneously infusing the replacement fluid [0.9% saline solution (SS)]. SS was administered in a 3:1 volume replacement ratio. The blood collected during haemodilution was returned to the patient when Hb < 8 g/dl or when the attending anaesthesiologist felt it was clinically indicated, primarily for persistent decreases in blood pressure. All haemodiluted blood was returned to the patient before leaving the operation room. If Hb was < 8 g/dl in the operation room or during the hospital stay, PAD was transfused, followed by allogeneic blood, if required. Fresh frozen plasma (FFP) was given only to maintain haemostasis (when aPTT > 70 s). Platelets were infused when the platelet count was $< 30 \times 10^9$ litre^{-1}.

Blood samples for coagulation testing and Hb levels were collected pre ANH, post CPB, and upon arrival to the ICU. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and activated clotting time (aCT) were determined on citrated plasma using an automated coagulation analyzer. Platelets were counted in EDTA-anticoagulated blood. The blood loss was recorded during the first 48 hours of ICU admission and the chest drains were removed with bleeding < 100 ml over 4 hours.

Statistical analysis was performed using SPSS 11.5 for Windows (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. Normally distributed variables were compared between groups with the student's *t*-test (two tailed) and expressed as mean ± SD. Differences were considered statistically significant with P values < 0.05.

Results

Data were obtained from 100 patients [50 in the ANH group and 50 in the control group (standard care management)] who were candidates for elective CABG surgery. Preoperative characteristics of the two groups were similar with regard to age, gender, ejection fraction and concomitant morbidities (table 1). Also, the duration of aortic cross-clamping and CPB were comparable (table 1).

Fluid balance and blood transfusion were compared between the two groups (table 2). There was no

Table 1. – *Preoperative characteristics and operative data of patients undergoing myocardial revascularization with CPB* [a]

Variables	ANH Group [b]	Control Group [b]	*P* value
Number	50(50)	50(50)	NS
Gender (M/F)	49/1	44/6	NS
Age (year)	54.7	58.6	NS
Ejection fraction (%)	46.6	46.5	NS
Hx of hypertension	13(26)	14(28)	NS
Hx of diabetes mellitus	5(10)	7(14)	NS
CPB duration (min)	55.6	56.1	NS
Aortic clamp duration (min)	44.9	45.3	NS

*Significant at $P < 0.05$; NS, not significant.
[a] Cardiopulmonary bypass
[b] Percentages are given in parentheses.

Table 2. – *Intraoperative and postoperative fluid balance and blood transfusion**

Variables	ANH group	Control group	*P* value
Fluid balance (ml)			
Crystalloids	1450	1500	NS
Chest tube drainage	561(300)	536(339)	NS
PRBC infusion (intra or postoperatively)			
Number of patients	17	46	Sig
Mean (ml)	312(117)	381(160)	NS
FFP infusion (intra- or postoperatively)			
Number of patients	10	47	Sig
Mean (ml)	270(134)	300(196)	NS

ANH: acute normovolaemic haemodilution, PRBC: packed red blood cell, FFP: fresh frozen plasma
*Data are presented as mean (± SD).
NS: not significant, Sig: significant ($P < 0.05$).

statistically significant difference between chest tube drainage in the two groups. The number of patients using PRBC (packed red blood cell) or FFP (fresh frozen plasma) was significantly higher in the control group in comparison to the ANH group ($P < 0.05$) but this difference was not significant in the amount of PRBC or FFP used to control the haemostatic or haemodynamic problem. Therefore, ANH reduced the need for PRBC and FFP by 58% and 74%, respectively.

Haematocrit (Hct) and platelet count decreased significantly after cardiopulmonary bypass and also after arrival at the ICU relative to the preoperative baseline in both groups (table 3) but there was no statistically significant difference between the control and the ANH group. ICU measurements of PT and aPTT were compared to the baseline pre ANH values (table 3). The PT increased significantly after arrival at the ICU in both

Table 3. – *Haematocrit and coagulation variables in patient groups**

Variables	Pre ANH	Post CPB	ICU
Hct (%)			
Control group	44.1(2.7)	26.6(3.6) ‡	32.4(3.1) ‡
ANH Group	45.1(2.4)	26.4(3.8) ‡	31.8(3.4) ‡
Plt count (k/mm^3) [140–415]			
Control group	219(57)	146(71) ‡	164(47) ‡
ANH group	208(54)	136(45) ‡	161(48) ‡
PT(s) [10.5–14.0]			
Control group	11.4(0.5)	—	13.7(1.7) ‡
ANH group	11.7(1.2)	—	14.3(3.1) ‡
aPTT(s) [20.0–35.0]			
Control group	36.6(16)	—	37.5(7)
ANH group	34.1(14)	—	38.3(11)

Hct: haematocrit, Plt: platelet, PT: prothrombin time, aPTT: activated partial thromboplastin time.
Pre ANH: before acute normovolaemic haemodilution, Post CPB: after cardiopulmonary bypass, ICU: after intensive care unit arrival.
*Data are presented as mean (± SD). [] indicates normal values.
† $P < 0.05$ between groups.
‡ $P < 0.05$ compared with pre ANH.

groups ($P < 0.001$) but there was no between-group difference. aPTT did not only not change significantly in the ICU relative to the baseline pre ANH values in both groups but also did not have any between-group difference. There was no statistically significant difference in aCT (normal value: 120 ± 10 s) in the control (131.4 ± 20 s) and ANH group (125 ± 18 s) after arrival at the ICU.

Discussion

The results of this analysis demonstrate that ANH can reduce the need for PRBC and FFP by 58% and 74%, respectively. There was no between-group difference in the amounts of Plt, PT, aPTT and aCT; therefore, according to these parameters, acute normovolaemic haemodilution with crystalloids does not influence the coagulation state of patients undergoing CABG surgery and this technique can be used safely in this operation. There was a statistically significant increase in the amount of PT and a dilutional decrease in the platelet level after fluid replacement with crystalloids.

ANH is a technique that comprises the removal of whole blood from a patient while restoring the circulating blood volume with a cellular fluid shortly before an anticipated significant surgical blood loss. The blood is then stored at room temperature, and re-infused in the operation room after major blood loss has ceased, or sooner if indicated. The chief benefit of haemodilution has been recognized to be the reduction of red cell losses when the whole blood is shed perioperatively at lower haematocrit levels after ANH

is complete[18]. A case study analysis of patients who had undergone "minimal" ANH (representing 15% of patients' blood volume) estimates that only 100 ml red cells (the equivalent of 1/2 unit of blood) is "saved" under these conditions[19]. With moderate haemodilution, (target haematocrit levels of 28%), the "savings" become more substantial. The removal of three blood units "saved" 215 ml, or the equivalent of one allogeneic blood unit[20].

The literature which purports to document that ANH efficiently reduces the need for homologous blood transfusion, is extensive[21-25] but little is done in patients undergoing CABG. Or et al. found that ANH in CABG surgery decreases intraoperative requirement of bank blood components including PRBC, FFP and platelets[26]. In another study performed on 100 elective candidates of CABG, ANH reduced the need for homologous blood derivatives by 71% (fresh blood, fresh plasma, RBC concentrates)[27]. Our findings are consistent with these studies and put emphasis on the efficacy of ANH in CABG surgery.

When one analyses the influence that ANH had on the coagulation variables, it is important to remember that the blood was harvested with gentle agitation and then maintained at room temperature while stored in CPDA bags. The influence that ANH may have had on these variables could have been influenced by storage in another substance such as acid citrate dextrose[28]. Because the 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[29,30]. The purpose of this investigation was not to determine which storage medium best suited ANH harvesting but to better understand the influence of one replacement fluid (SS) in an ANH protocol.

Crystalloids are widely used for intravascular volume replacement therapy, most likely because of their low acquisition costs. Additionally, side effects are very rare when using a crystalloid-based intravascular volume replacement strategy. The influence of a crystalloid-based intravascular volume replacement regimen on coagulation is not definitely known. In an *in vitro* study, Ruttman et al.[31] showed that haemodilution *per se* increased coagulability of whole blood most likely as a result of induction of thrombin formation[32]. This hypercoagulability was more frequent in saline-diluted than in gelatin-diluted samples. By contrast, others did not find a hypercoagulability state by haemodilution[33-35]. It is increasingly evident that the pathophysiologic characteristic of *in vitro* studies on coagulation does not always reflect the *in vivo* condition[33,36]. Others also showed a saline-induced increased coagulability *in vivo* and suggested that there might be a correlation between the use of crystalloid solutions and the risk of development of deep vein thrombosis[37].

The definite mechanism that may be responsible for the hypercoagulability after haemodilution with crystalloids is not well defined. In 1959, Monkhouse[38] has shown that diluting plasma with saline increases the thrombin activity of the mixture two- to threefold. This increase in thrombin activity in diluted samples was suggested to be a result of decreasing the antithrombin action rather than because of any real increase in thrombin generation. Similar changes in thrombin generation occur *in vivo* as shown after infusion of large amounts of SS in acute haemorrhage[38].

The influence of different types of crystalloids on coagulation in humans is far from clear. Ng et al.[39] demonstrated increased blood coagulability when surgical blood loss was replaced by crystalloids. In our study, not only did we fail to find any hypercoagulopathy after using crystalloids in both control and ANH groups but we also found an increase in the amount of PT and a dilutional decrease in the platelet level after fluid replacement with crystalloids. Thus, in contrast to some other previous studies, it can be assumed that crystalloids may cause a hypocoagulopathic rather than a hypercoagulopathic effect. These results are compatible with some *in vivo* animal[40] and human[33-35] studies and seems to be due to a greater decrease in circulating procoagulant activity (more dilution in circulating tissue factor activity than tissue factor pathway inhibitor or antithrombin activities, more reduction in factor VIII complex activity than protein C activity, and more dilution in factor X activity rather than antithrombin activity) than anticoagulant activity.

Finally, we concluded that performing ANH with SS in patients undergoing CABG surgery may cause a change in coagulopathic state, which is not clinically significant. Regarding the controversy in the effect of crystalloids on haemostatic status, it seems rational to perform more trials with greater sample sizes to clarify this association.

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