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Acute Normovolemic Hemodilution (ANH) impacts postoperative coagulation profile and bleeding in Adult Cardiac Surgery

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ABSTRACT

Introduction: The coagulation profile of cardiac surgery patients is impacted by pro-inflammatory effects caused by procedures involving cardiopulmonary bypass. In order to counteract these effects, pharmacological therapies and allogeneic blood transfusions are required. The strategy of Acute normovolemic hemodilution also known as "intraoperative autologous donation" is also a viable option to address these negative effects. The theoretical basis for ANH is that the removed blood of a patient's own self is shielded from the inflammatory response of blood cells to the bypass circuit. ANH is an infrequently practiced strategy at various cardiac surgery institutes within Pakistan to enhance coagulation profile, decrease the need for blood transfusions despite being an established approach abroad.

Aims and Objectives: The objective of our study is to compare the effect of ANH on patients undergoing adult cardiac surgery in a sample group versus a control group with the primary endpoint of postoperative drain output as a measure of effectiveness of blood coagulation profile. Blood coagulation profiles were also compared between the two groups as secondary variables.

Place and Duration of study: The study was conducted at the Faisalabad Institute of Cardiology from December 21st, 2023 to February 13th, 2024.

Material and Methods: A randomized controlled trial involving 60 patients over the age of 12 years who were to undergo adult cardiac surgery was conducted. An online research randomizer software randomly selected them into two equal groups, sample and control (n=30). The ANH volume retrieved from the patient's central vein in the sample group was used to fill the CPD blood transfusion bags after administering anesthesia. After the patients in both groups were weaned off CPB and protamine administered to neutralize heparin, ANH blood was infused back into the patients in the sample group whereas the control group received allogenic blood only. Chi square test was applied to all qualitative variables and Independent Samples t-test for all quantitative variables. The results were analyzed using SPSS version 25, and a p-value ≤ 0.05 was considered statistically significant.

Results: Hemoglobin (12.9±0.90 g/dL in ANH and 11.8±1.00 g/dL in non-ANH) and aPTT levels (34.2±6.06 seconds in ANH and 54.2±10.95 seconds in non-ANH) were statistically significant (p-value <0.01). In the ANH group, the mean value (623.3±86.28 mL) of postoperative drain output significantly decreased by approximately 220mL compared to the non-ANH group (842.3±99.26 mL) (p-value <0.01).

Conclusion: ANH positively conserves most of the coagulation profile parameters. It assists in reducing postoperative bleeding and the volume of allogeneic blood required perioperatively in cardiac surgery.

Key Words: Acute normovolemic hemodilution, Cardiopulmonary Bypass, Drain output, Coagulation profile, Cardiac surgery

INTRODUCTION

The risk of cardiac surgery increases by four times with the use of cardiopulmonary bypass (CPB) machines[1]. Every patient has a certain risk which remains regardless of the steps taken. This enhances the need to establish fundamental protocols in diminishing these effects. CPB effects on a patient's coagulation profile and complete blood cell studies is immense which is kept in check with the use of allogeneic blood transfusions. Though it is necessary at some point, routine blood transfusions in itself have physiological and logistic hindrance[2,3]. Amongst these are blood transfusion reactions and the urgency of blood requirements in case of a surgical catastrophe. One such element to tackle these in clinical practice trending at various cardiac surgical institutes is the use of Acute Normovolemic Hemodilution[4-5]. Acute Normovolemic Hemodilution involves the removal of a patient's own whole blood prior to placing the

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patient on CPB. This step can be taken prior to surgical incision, at induction of anesthesia or at any time during surgery but before placing the patient on a CPB machine. Quantity of blood removed is replaced with crystalloid or colloid to maintain normovolemia. Utilizing inotropes to ensure vitally stable patients is also a viable option. This results in lesser RBCs and coagulation factors being lost during the course of CPB duration. Also, the removed blood is spared from inflammatory and hemodilution effects of CPB. Post bypass & after heparin reversal this blood being rich in platelets and coagulation factors is reinfused to the patient. Various researches have proven benefits of ANH on postoperative hemoglobin levels and normalized coagulation profile including aPTT, INR, fibrinogen and platelets[6]. The impact of ANH on postoperative coagulation profile is signified sometimes by the differences in postoperative drain output. It is associated directly with a decrease in drain output. [7]In our country, there has been no study on cardiac surgery setups using ANH in the last 15 years. Most of the research done internationally haven't used the strategy of volume removal based on the nomogram for ANH which we have used. Retrospective studies have usually been done in the past. The objective of our study was to prospectively examine the first 24 hours postoperative drain output between a sample group receiving ANH and the control group not given ANH. Coagulation profiles between the two groups were also compared during the perioperative period i.e. 24-hours before surgery and 24-hours after surgery.

MATERIAL AND METHODS

This randomized controlled trial was conducted at the Cardiac Surgery Department of Faisalabad Institute of Cardiology (FIC), Faisalabad from 21st Dec'23 to 13th Feb '24. It was a single blind study where patients were unaware of their designated groups. This study was approved by the Ethical Review Committee of FIC vide No.45-2023/DME/FIC/FSD. Patients were enrolled in the study after written informed consent. Pre operatively hematological, LFTs and RFts and relevant parameters were measured. All patients enlisted were >12 years old, had no known preoperative deranged hepatic, renal, neurological or coagulation disorder. A total of 60 patients were randomly assigned into two equal groups (ANH and non-ANH) by online research randomizer software. These patients were enlisted to undergo either cardiopulmonary bypass grafting (CABG) or valvular heart surgery (Aortic and Mitral) as per criteria of selection (Table-1). All patients included had a BMI on a normal-overweight scale. Each patient was evaluated for a preoperative coagulation profile. A Hb>11 mg/dL was established as the bare minimum for inclusion in the study. Patients with prior deranged coagulation profiles and Hb<11 mg/dL were excluded from the study. Those patients with a history of hepatitis or chronic kidney disease (CKD) for which they were treated previously, were excluded. No patient was actively smoking preoperatively for at least 03 months. Pulmonology consultation was done for all patients with a history of smoking or respiratory complaints. All patients in our study were receiving Tab Aspirin 75mg preoperatively since their cardiac pathology was diagnosed, as part of institutional practice.

After anesthesia induction, the patient's Central venous line was accessed via the internal jugular vein. Blood was obtained from this central line by gravity-dependent drainage and stored in a CPD transfusion bag at room temperature within the operating theater. The amount of blood that the patient donated depended strictly on the patient's physiologic parameters, estimated blood volume and hematocrit. Intravenous crystalloids and inotropes were used to maintain normovolemia and vitals. Our fluid administration and vasopressor use was influenced by hemodynamic changes in heart rate, electrocardiogram, and mean arterial pressure. 1g tranexamic acid was administered to all patients at induction of anesthesia for hemostasis during surgery[8].

The rationale for transfusing blood both intraoperatively and postoperatively relied upon the anesthetist, who kept it above the minimum level of cutoff values for hemoglobin(>8g/dL) and hematocrit(>24%), which was determined by serial arterial blood gas analysis (ABGs). During cardiopulmonary bypass (CPB), this authority was shifted over to perfusionists. Intraoperatively if it was deemed necessary to transfuse blood, allogeneic whole blood was transfused but the ANH volume was spared. The nomogram that was used to estimate the ANH volume retrieved is shown in Fig-1[22]. The nomogram estimates the amount of ml needed to maintain hematocrit above 24%. The legend in nomogram states exactly the amount of blood that was removed for ANH. As an example, those who fell in yellow boxes had 500ml of blood withdrawn. The subsequent green colored boxes had a larger volume (1000ml, 1500ml etc.) of ANH retrieved. All procedures were performed in conventional cardiac surgery with median sternotomy, aortic (distal ascending aorta) and 2 stage venous cannulation. After the patient was weaned from cardiopulmonary bypass, protamine was administered to neutralize heparin. The patients in the sample group received their pre-donated ANH volume after the Activated Clotting Time (ACT) was determined and found to be in the standard range. ACT measurements signify that heparin has been successfully neutralized by its antidote which is protamine. None of our patients needed extra protamine intraoperatively. A single drain was placed in both mediastinum and right pleura. Post hemostasis sternum was approximated using Surgical Stainless steel wire number 5. Postoperatively, patients were observed for chest drain output for the first 24 hours. Baseline reports were obtained and compared for statistical significance. SPSS version 25 was used to analyze the results and their statistical significance determined via a two-sided test. Chi square test was applied to all qualitative variables and Independent Samples t-test for all quantitative variables. Quantitative variables are stated as mean ±standard deviation. (p≤0.05) was considered significance.

Preop hematocrit% in OR			IAD removal volume mL								
Weight kg	30%	32%	34%	36%	38%	40%	42%	44%	46%	48%	50%
40	338	361	384	406	429	451	474	496	519	541	564
45	418	446	474	502	530	558	585	613	641	669	697
50	498	531	564	598	631	664	697	730	764	797	830
55	578	616	655	693	732	770	809	847	886	924	963
60	658	701	745	789	833	877	921	964	1008	1052	1096
65	737	787	836	885	934	983	1032	1082	1131	1180	1229
70	817	872	926	981	1035	1090	1144	1199	1253	1308	1362
75	897	957	1017	1076	1136	1196	1256	1316	1375	1435	1495
80	977	1042	1107	1172	1237	1302	1368	1433	1498	1563	1628
85	1057	1127	1197	1268	1338	1409	1479	1550	1620	1691	1761
90	1136	1212	1288	1364	1439	1515	1591	1667	1742	1818	1894
95	1216	1297	1378	1459	1541	1622	1703	1784	1865	1946	2000
100	1296	1382	1469	1555	1642	1728	1814	1901	1987	2000	2000
105	1376	1468	1559	1651	1743	1834	1926	2000	2000	2000	2000
110	1456	1553	1650	1747	1844	1941	2000	2000	2000	2000	2000
115	1535	1638	1740	1842	1945	2000	2000	2000	2000	2000	2000
120	1615	1723	1831	1938	2000	2000	2000	2000	2000	2000	2000
125	1695	1808	1921	2000	2000	2000	2000	2000	2000	2000	2000
130	1775	1893	2000	2000	2000	2000	2000	2000	2000	2000	2000
135	1855	1978	2000	2000	2000	2000	2000	2000	2000	2000	2000
140	1934	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
145	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
150	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000

Legend	
0 BAG	No IAD
1 BAG	500 mL
2 BAGS	1000 mL
3 BAGS	1500 mL
4 BAGS	2000 mL

Based on 70 mL/kg BV, RAP, 1000 mL dilution and 24% CPBhct

Fig-1: Nomogram for allowable acute normovolemic hemodilution

Inclusion	Exclusion
Age >12 years	Redo surgery
CABG patients	Pre-op deranged blood reports*
Valvular patients	Pre-op pharmacological inotropes or mechanical IABP requirement
BMI 18.5-29.9	History of Hepatitis CKD
NYHA I-III	Unstable angina
CCS I-III	LVEF<30%

Table-1: Criteria for Selection

Abbreviations: CABG:coronary artery bypass grafting, BMI:body mass index , NYHA:New York Heart Association functional classification grades, CCS Canadian Cardiovascular Society classification grades, IABP: Intra Aortic Balloon Pump, CKD: Chronic Kidney disease, LVEF: Left Ventricle Ejection Fraction

* Baseline blood tests: complete blood count, Renal function tests, Liver function tests, coagulation profile, serum electrolytes, Arterial blood gas analysis, cardiac markers,Troponin I.

RESULTS

Characteristic	ANH	Non-ANH	*p*-value
Age	43.60±13.90	43.27±15.61	0.931
Gender (Male/Female)	18/12	16/14	0.602
Surgery			0.963
AVR	3	3	
MVR	15	14	
CABG	12	13	
Hypertension	8	12	0.273
Diabetes	9	12	0.417
History of Smoking	9	7	0.559
BMI (kg/m^2)	24.1±1.96	24.3±4.55	0.846

Table-2: Preoperative Demographics

AVR: Aortic valve replacement
MVR: Mitral valve replacement
CABG: Coronary artery bypass grafting

Characteristic	ANH	Non-ANH	*p*-value
Hemoglobin (g/dL)	13.1±0.99	13.0±1.19	0.725
Platelets (10^3/uL)	217.0±50.19	231.1±55.19	0.303
Hematocrit (%)	41.8±2.19	41.2±4.09	0.435
aPTT (seconds)	31.1±3.87	30.3±4.10	0.459
PT (seconds)	12.1±1.59	12.1±1.48	0.867
INR	1.2±0.17	1.2±0.18	0.506

Table-3: Preoperative Blood Laboratory analysis
PT: Prothrombin time, aPTT: Activated partial thromboplastin time, INR: International Normalised Ratio

Demographic characteristics of the two groups are shown in Table-2. The number of patients who were preoperatively hypertensive, diabetic or smokers is shown. It did not show any statistical difference (p-value >0.05) in terms of age, gender, type of surgery, history of hypertension, diabetes or smoking. The number of males was more compared to females in both groups. More diabetics and hypertensive patients were present in the control group. Frequency of smokers was higher in the sample population. Preoperative blood baseline reports also did not show any statistical difference though the mean platelet count in the ANH group (217.0) was less than the non ANH group (231.1) with a p-value 0.303 (Table-3).

Characteristic	ANH	Non-ANH	*p*-value
CPB time (min)	72.8±14.76	71.0±15.8	0.662
Hemoglobin (g/dL)	12.9±0.90	11.8±1.00	<0.01*
Platelets (10^3/uL)	209.8±42.91	213.6±74.34	0.809
Hematocrit (%)	35.6±5.42	33.9±2.94	0.137
aPTT (seconds)	34.2±6.06	54.2±10.95	<0.01*
pT (seconds)	18.5±2.84	19.7±4.00	0.186
INR	1.7±0.40	1.6±0.36	0.440
Whole blood Tx(ml)[a]	1633±434	1800±428	0.140
Drain output(ml)	623.3±86.28	842.3±99.26	<0.01*

Table-4: Postoperative Blood Laboratory analysis
*statistically significant
[a] skin incision to 24 hours postoperatively

The CPB time in our sample group (72.8±14.76 minutes) was more than the control group (71.0±15.8 minutes). A prolonged CPB time adversely affects coagulation profile but since it was not statistically significant (*p*-value 0.662) it may not have influenced the results of the research. Our primary variable of study showed a statistically significant difference. The ANH group's mean drain output (623.3±86.28 ml) in the first 24 hours after surgery is approximately 220ml lower than that of the non-ANH group (842.3±99.26 ml). According to postoperative blood laboratory analysis, both groups had differences in their blood baseline reports, but only hemoglobin and aPTT values varied enough to be statistically significant (Table-4). Hemoglobin was about 1.1g/dL higher in mean of ANH (12.9±0.90 g/dL) compared to the non ANH group (11.8±1.00 g/dL). Similar response was seen in our aPTT values with 34.2±6.06 seconds in the ANH group than in the non ANH group (54.2±10.95 seconds).Like the preoperative report, the platelet mean in the ANH group (209.8±42.91×10^3/uL) was again lower than the mean of the non-ANH group (213.6±74.34×10^3/uL).During surgery and in the first 24 hours, the ANH group received a lesser volume of whole blood transfusions (1633±434 ml) than the control group (1800±428 ml). This is the volume of allogeneic blood transfusions and does not include the ANH volume given to the sample group. No reopenings or mortality occurred in our study population.

DISCUSSION

The knowledge of cardiac surgeons about treating patients with blood conservation strategies to prevent significant bleeding is a topic of debate. The blood volume lost from the patient leads to deteriorating vitals signified by tachycardia (>100/min) or hypotension (<90mmHg systolic BP). These changing hemodynamics must be corrected with volume replacement using either crystalloids (normal saline, ringer lactate, 5% Dextrose saline etc.), colloids (hemacil, 10% albumin etc.) or with utilizing inotropes (epinephrine, norepinephrine, dobutamine, dopamine etc.). Failure to act appropriately can lead to a reduction in end organ perfusion, acute kidney injury (AKI) and multiorgan failure (MOF).

The main finding of our study was the decrease in postoperative drain output. The surgical cause (ligature slip, loose anastomoses etc.) of bleeding was not present in our study group as the quantity of blood loss from surgical causes (>200ml/hr) requiring re-operating the patient to achieve hemostasis was not seen. This bleeding volume thus obtained was attributed to a deranged coagulation profile only. Using ANH (623.3±86.28 mL) we could significantly reduce bleeding volume as seen in drain output compared to control (842.3±99.26 mL) with a reduction in mean of approximately 220ml (*p*-value <0.01).

One largest meta-analysis to date and a recent study showed comparable results to our study. In the meta-analysis by Barile L et al. 29 randomized controlled trials were included and the results in terms of experienced postoperative drain output was obtained from the 23 studies which analyzed this variable. From the data gathered from 2043 patients the volume of blood loss was 388 mL in ANH group versus 450 mL in control with a *p*-value <0.01[12]. Similar results were seen in a retrospective study by Takahasi et al. where postoperative bleeding at 24 hours was significantly lower in the ANH group (455±228 and 797±535mL, p<0.01)[7].

The blood coagulation profiles of our study showed different results between the two groups. All of these parameters were better preserved in the ANH group, with Significant differences in Hemoglobin and aPTT values. Non-significant results were seen in the values of platelet count, hematocrit, INR and prothrombin time. Hemoglobin was about 1.1g/dL higher in mean of ANH compared to the non ANH group. Oxygen is transported bound to hemoglobin in red blood cells. A greater amount of hemoglobin in the ANH group (12.9±0.90 g/dL) states that their oxygen carrying capacity is more compared to non ANH group (11.8±1.00 g/dL) (p-value<0.01). The sample group thus had a lower risk towards anemia. This can be seen in the hematocrit levels of both groups as well where the sample group (35.6±5.42 %) had a greater percentage of healthy red blood cells than the control (33.9±2.94 %). The other significant finding in our study was the aPTT time which is a measurement of the intrinsic coagulation pathway that is affected by heparin. The ANH group (34.2±6.06 seconds) experienced a 20 second improvement in mean aPTT (*p*-value <0.01) compared to the control (54.2±10.95 seconds) which resulted in coagulation pathway preservation. The platelet count in the postoperative results though were lesser in number; the percentage decrease was not as much between pre-op and post-op platelet numbers of ANH group (3.31%) than the non ANH group (7.57%). This was a remarkable finding considering the fact that a lesser volume of whole blood transfusions was received by the sample group. This shows that ANH has better preserved the morphology of platelets owing to its autologous nature.

In patients undergoing cardiac surgery requiring CPB, ANH results in significant improvements of aPTT and hemoglobin values[4]. The procoagulant effects which can be achieved by ANH have a superior efficacy compared to the allogeneic blood which is extracted prior to surgery[9]. Frank SM *et al.* showed that the storage of blood led to cell membrane deformability and the presence of spherocytes and echinocytes which are linked with decreased erythrocyte survival. These deformed cells have a lesser affinity to bind with hemoglobin, which leads to decreased levels of hemoglobin in the transfused subject. ANH has a lower drop in hemoglobin levels compared to allogeneic blood. Similar results have been achieved in pediatric cardiac surgery in terms of allogeneic blood product use and preservation of the physiological parameters in blood components[18,19]. Rotational thromboelastometry studies have shown a significantly shorter EXTEM CT and a greater percentage increase in EXTEM A10 in ANH subject studies[14]. Henderson RA et al. proved that this shows a lesser time for clot initiation and greater increase in clot strength when ANH volume is utilized. This enhanced hemostasis at an earlier postoperative stage.

Since the advent of cardiac surgery allogenic transfusion has been used to counteract the pro-inflammatory effects induced by CPB and to maintain normal physiological parameters. ANH proved to have a superior hematological profile to allogeneic blood in our study as only the most essential whole blood transfusions (1633±434 mL were required in the sample group versus 1800±428 mL in control group.

The whole blood volume required in previous studies to maintain normovolemia is also statistically less when the ANH strategy is employed[7,12]. Allogeneic blood is usually stored in blood banks for at least 6-12 hours prior to surgical incision, which can have adverse physiological effects[10]. In an experimental study by Sousa RS, et al., on sheep blood storage of only 6 hours showed metabolic acidemia and deteriorating hematologic, biochemical, and oxidative alterations. In a multi institutional retrospective study by Rhee P et al. of all trauma patients who received an autologous whole blood transfusion from the patient's hemothorax, which was collected from the chest tubes and anticoagulated with citrate phosphorus dextrose, significantly lower packed red blood cell and platelets transfusion were required[13]. ANH when combined with an antifibrinolytic agent, such as tranexamic acid (which we used in our study) assists in hemostasis[20]. Not surprisingly an enhanced hemostasis also decreased the need for allogeneic blood transfusions .

ANH volume is stored at room temperature inside the operation theaters due to logistics. Temperature at which ANH volume is stored is debatable. A colder temperature for this purpose may be more beneficial[11]. In the study done by Kusudo E *et al.* cold storage (4°C) of whole blood compared to room temperature (22°C) provided improved storage conditions for platelet's aggregability, glucose consumption and lactate production. There is an argument over the volume of blood removed for ANH compared to the patient's total circulatory load.[15,16]. Only a fixed volume of blood was removed for ANH in these studies. If the ANH strategy had been employed using an individualized approach towards patients' demographics, such as the use of a nomogram, the results could have been different.

Over time the adverse effects of allogeneic blood transfusions are becoming clearer[2,3,21]. In oncological experiments on primates, allogeneic blood transfusion has a fourfold increase in tumor growth compared to autologous blood transfusions. This likely reflects immunomodulatory effects induced by the introduction of major histocompatibility complex-incompatible antigens with allogeneic blood. This can be countered with the use of ANH in surgery for malignant cardiac neoplasms to prevent recurrence. Additionally, it can be utilized to prevent unnecessary allogeneic transfusions during complex cardiac surgeries like thoracic aorta repair where a significant amount of blood loss is anticipated and insufficient amount of allogeneic blood is present[17].

All the data to date suggests that allogeneic blood transfusions are not ideal in preservation of patients physiologic and blood coagulation parameters. A simpler and readily available technique in the form of ANH is available. Additional investigation should be conducted to determine the feasibility of retrieving a higher volume of ANH. This could result in the complete elimination of allogeneic blood transfusions in the future.

CONCLUSION

The results of our study show that ANH positively conserves most of the coagulation profile parameters. It assists in reducing postoperative bleeding and also decreases the volume of allogeneic blood required perioperatively in cardiac surgery. With further workup it can be one of the fundamental strategies in blood conservation completely obliterating allogeneic blood transfusions.

LIMITATIONS

The sample size in our study and duration of measured variables was small. In future a large sample study over a prolonged period of time with other variables and coagulation tests is needed to determine further uses and implications of ANH.

FINANCIAL ASSISTANCE

None was required as all the equipment and drugs employed are in routine use in our daily surgeries.

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