MODIFIED ULTRAFILTRATION: ROLE IN ADULT CARDIAC SURGICAL HAEMOSTASIS

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Background: During cardiac surgery, cardiopulmonary bypass (CPB) leads to haemodilutional anaemia and activation of inflammatory mediators, affecting haemostasis. Modified Ultrafiltration (MUF) is being increasingly favoured for haemoconcentration without blood transfusion and reducing post operative bleeding. **Methods:** Aim of this study was to record the impact of modified ultrafiltration on haemoconcentration and postoperative bleeding during adult cardiac surgery. This randomized control trial included 100 patients, divided into 2 groups; MUF and control group. Serial blood samples were drawn to evaluate haematological indices. Postoperative chest drainage was recorded for 24 hours. Results were expressed in terms of percentages, means and *p* value ($p<0.05$ was taken as significant). **Results:** Four patients were excluded and 96 patients were analyzed (MUF n=50, control n=46). According to American society of anaesthetist (ASA) classification, MUF group was higher risk group ($p=0.02$) with longer extracorporeal perfusion time ($p<0.001$). Haemoconcentration was successfully achieved in MUF group (final haemoglobin=10.7±1.25, haematocrit=33±3.64%, $p<0.001$) with lower blood loss (MUF=395±153 ml, control=755±435 ml, $p<0.001$) and transfusion requirement ($p<0.001$). Re-exploration rate was 4% and 6.5% in MUF and control group respectively ($p=0.57$). Mortality in both groups was comparable (MUF=4%, control=4.3%, $p=0.94$). **Conclusions:** Modified ultrafiltration is a safe procedure which successfully achieves haemoconcentration, lowers blood loss and transfusion requirement after cardiac surgery in adult population.

Key words: Modified ultrafiltration, haemoconcentration, haemostasis in cardiac surgery

INTRODUCTION

During cardiac operations, cardiopulmonary bypass(CPB) provides systemic perfusion utilizing heparinisation, haemodilution and non-pulsatile blood flow leading to physiologic consequences including haemodilutional anaemia and activation of inflammatory mediators, that affect coagulation.[1] Anaemia at conclusion of CPB is detrimental to recovering myocardium especially after coronary revascularization and delay in myocardial metabolic recovery is observed at haemoglobin levels below 6.0 gram per decilitre (g/dl) and at haematocrit ≤14–17%.[2,3,4] Therefore it is not unreasonable to keep haemoglobin levels above 7 g/dl in patients on CPB (Level of evidence C).[1] Haemoconcentration in cardiac surgery is commonly achieved by transfusing red cell concentrates and studies show that, minority of patients having cardiac procedures (15%–20%) consume >80% of blood products transfused at operation, also carrying with them transfusion related risks[1]. Postoperative haemorrhage not only worsens anaemia, but also necessitates re-exploration with associated morbidity.[5,6,7] Numerous reports identify multivariate predictors of postoperative bleeding after cardiac operations including preoperative antiplatelet drugs, re-operations and emergency surgeries.[1,8] Antifibrinolytic therapies have been widely adopted for perioperative haemostasis in cardiac surgery, but review of most efficacy trials show that they are neither designed nor powered to uncover drug-related morbidity.[1,9] Recently the methods adopted to mitigate inflammatory mediators and post CPB physiology, mainly haemofiltration; are also proving to be effective at haemoconcentration and haemostasis.[10-12]

Use of different haemofiltration techniques during cardiac surgery is well documented[12-17] but modified ultrafiltration(MUF) has increasingly come into favour.[1,10-12] This technique entails removal of water and low molecular weight substances under a hydrostatic pressure gradient after separation from CPB.[10] According to recent guidelines use of modified ultrafiltration is not unreasonable for blood conservation (Class-IIb, Level of evidence B).[1] MUF has been studied extensively in paediatrics[1,18] but there are several studies on adult patients resulting in statistically significant improvement in morbity.[1,10-15] The improved efficacy of MUF relates to the fact that it achieves haemoconcentration without transfusion of blood products leading to significant reduction in post-operative blood loss and transfusion requirement.[10-15,18]

The pioneer work on MUF in Pakistan was started at AFIC/NIHD in January 2006. The present study was undertaken in an effort to define its impact on haemoconcentration and postoperative bleeding in adults undergoing cardiac surgery.

MATERIAL AND METHODS

It was an experimental study (Randomized Control Trial) scheduled to include 100 patients, carried out at AFIC/NIHD Rawalpindi. All the cases above 14 years

age were included. Exclusion criteria were cases having cardiac trauma, Vascular emergencies, American Society of Anaesthetists Class IV or higher cases, Patients in whom Aprotinin is used at any point during hospital stay. Sample was collected using purposive (non-probability) method,[19] Randomization (lottery method) was done using single blind technique to allocate the patients randomly to both groups of 50 each, and were allocated to receive modified ultrafiltration (MUF group) or not (control group).

Primary end points were post cardiopulmonary bypass haemoglobin and haematocrit (laboratory values for haemoglobin gm/dl and haematocrit percentage at the conclusion of bypass), post MUF haemoglobin and haematocrit (laboratory values after muffing for 12–15 minutes), chest drainage(drainage from both pleural and mediastinal drains in first 24 hours postoperatively), re-openings (return to theatre for exploration due to temponade or bleeding; more than 100 ml/hr for more than 5 hours or sudden collection of blood more than 500 ml once) and transfusion of blood products(total amount of red cell concentrates, platelets or fresh frozen plasma transfused during first 24 hours).

Cardiopulmonary bypass was performed with Sarns roller-pump system (Sarns 3M, Terumo, USA). The circuit was primed with 1500–1800 ml of solution containing Lactaed Ringer solution, Mannitol (2 ml/kg bodyweight) and heparin sulphate (300 IU/kg). Anticoagulation was achieved using heparin sulphate (300 IU/kg, intravenous) to maintain activated clotting time (ACT) above 400. Flow rates were regulated at 50–70 ml/kg/min with moderate hypothermia (28–32 °C). Myocardial protection was done by using 10 ml Howards-cardioplegia injection/500 ml warm blood and then 100 ml of this preparation was repeated every 15 minutes. Single mediastinal drain (size, 28Fr) was placed anteriorly and pleural drain placed where indicated. Protamine was given just prior to removal of aortic cannula. Aprotinine was not used during study. Chest was closed after satisfactory haemostasis.

1- Control group:

Upon termination of CPB, venous cannula was removed and heparin was neutralized with protamine sulphate 3 mg/kg for every case. Haemostasis was achieved using conventional means and electrocautery.

2- MUF group:

A Haemofilter (Jostra-Hemofiltration system, BC140 plus, Maquet, Hirrlingen, Germany) was placed in the CPB circuit for every case allocated to the MUF group according to circuit diagram (Figure-1) proposed by perfusionist (Alex Robertson. Great Ormond Street Hospital, London), a modification of original technique described by Naik and colleagues.[20] Circuit design was arterio-venous as inlet was placed close to the arterial cannula and outlet was returned directly to right atrium. On termination of CPB, the patient remained heparinised. The venous line was interrupted temporarily and the venous cannula was left in right atrium. The latter was connected to the haemofilter via MUF-line (Jostra-Purge line for arterial blood filter, Maquet, Hirrlingen, Germany). Blood from arterial line was drawn with the help of an additional roller pump during the ultrafiltration and outlet line of haemofilter was connected to a 3-way stop cock placed on the venous reservoir. MUF was started by allowing the arterial blood to flow from the ascending aortic cannula to the haemofilter, at a rate of 10–15 ml/kg/min. Vacuum was set at 100–150 mm Hg to maintain the desired flow rate. Re-infusion rate to the right atrium was kept less than the MUF rate. The process was carried out for 12–15 minutes and all the concentrated blood was re-infused into the right atrium through the MUF line. All the left over blood in the CPB circuit was chased out with crystalloid solution by the arterial pump to MUF pump in order to salvage CPB circuit volume and to add volume as required. At the conclusion of procedure venous cannula was removed. Protamine sulphate was only given if ACT came higher than the baseline value.

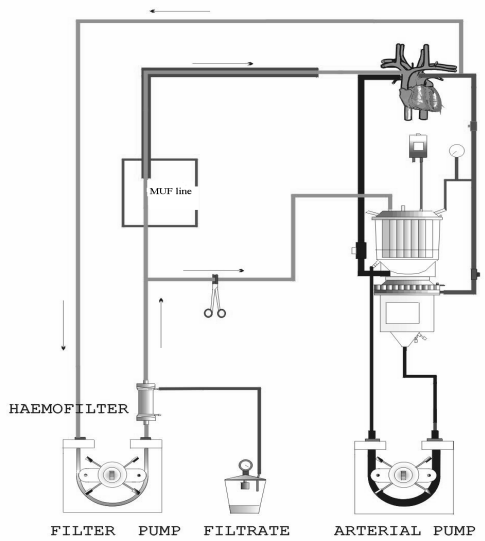

Figure-1: MUF circuit diagram

Intra-operative Monitoring and Sample collection:

Preoperative visit to the cardiac anaesthetic was done in all cases. Single left radial arterial line (20G, Safelet-cath, Nipro, Japan) for perioperative blood pressure monitoring was placed. Anaesthetic agents used were midazolam (0.25 mg/kg), nalbuphine (1 mg/kg), and propofol (1–2 mg/kg). Central venous triple-lumen catheter was placed using right Jugular approach. Throughout the procedure heart rate, ECG, invasive and non-

invasive blood pressure, central venous pressures, temperatures, oxygen saturation, blood gases, ACT and urine output were monitored.

Blood samples for the study were drawn from central venous line at the termination of cardiopulmonary bypass and after MUF for 15 minutes in the MUF group to assess the impact of modified ultrafiltration. 5 ml samples were collected in sterile vacuum tubes and sent to laboratory for assessment.

Post-operative monitoring:

Haemodynamic monitoring, analgesia, sedation and antibiotics administration were carried out according to intensive care protocol. Total chest drainage was recorded for first 24 hours. Red cell concentrates (300 ml/unit) were transfused where haemoglobin fell below 9 gm/dl. Platelets (150 ml/unit) and fresh frozen plasma (100 ml/unit) were transfused if chest drainage exceeded 100 ml/hour for 2 hours. Reopening was carried out with-in 6 hours if indicated.

Statistical analysis:

Database Performa were used to record variables for every patient. All the data was compiled and analysed using SPSS (SPSS-12 for Windows; SPSS-Inc, Chicago, IL). Numeric variables like Post Cardiopulmonary bypass haemoglobin, Post Cardiopulmonary bypass haematocrit, Final haemoglobin, Final haematocrit, Chest drainage in first 24 hours, packed red cells transfused, platelet concentrates transfused and fresh frozen plasma transfused were expressed as Mean±Standard Deviation. Categoric variables like Re-exploration and In-Hospital Status were expressed as frequency and percentages.

Statistical significance was calculated by applying *t-test* to compare numeric variables and *Chi square* test was applied for comparison of categoric variables like Re-exploration and In-Hospital Status in both groups.

RESULTS

The total number of patients was 96 as 4 patients from the control group were excluded because of incomplete data, leaving 50 patients who received modified ultrafiltration (MUF group) and 46 did not (control group). Risk assessment was done according to ASA-classification (Table-1). MUF group was found to be high risk group (ASA-III=16%, p=0.02). Mortality in MUF group was 4% against 4.3% in control group (p=0.94).

Demographic and Operative variables:

Analysis shows that MUF group had higher frequency of females (30%, p=0.04), Diabetes (36%, p=0.009) and congenital heart diseases (6%, p=0.09) being partial atrioventricular septal defect (n=1), Subaortic membrane (n=1) and ventricular septal defect (n=1) leading to more congenital surgical procedures in the MUF group. Age of the patients ranged from 15–70 years and mean age was 50.7±14.7 years in MUF group and 48.7±11.2 years in control group (p=0.4). Rest of the variables were comparable in both groups (Table-2).

Table-1: ASA Classification

ASA class	Definition
Class-I	Normal healthy patient
Class-II	Patient with mild systemic disease, no functional limitation
Class-III	Moderate to severe systemic disease, some functional limitation
Class-IV	Severe systemic disease with constant threat to life, functionally incapacitated
Class-V	Moribund patient not expected to survive with or without surgery
Class-VI	Brain dead patient
Any Class (E)	Emergency procedure

(ASA= American society of anaesthetist)

Table-2: Demographic and Operative Data

Patient Characteristics	MUF	Control	*p* value
Total patients, n	50	46	
ASA Class-III	8	1	0.02
Age, y±SD	50.7±14.7	48.7±11.2	0.46
Female, n	15	6	0.04
Hypertension	15	18	0.34
Diabetes	18	6	0.009
Emergency operation	4	3	0.78
Cardiac Disease			
TVCAD	39	37	0.76
Aortic-valve disease	1	3	0.26
Mitral-valve disease	7	6	0.89
Congenital heart disease	3	0	0.09
Cardiac Procedure			
CABG	40	36	0.83
AVR	0	3	0.06
MVR	5	6	0.64
DVR	1	0	0.33
Redo-MVR	1	0	0.33
CABG+AVR	0	1	0.28
Congenital operations	3	0	0.09

(n=number of patients, y=years, std. dev=standard deviation, TVCAD=triple vessel coronary artery disease, CABG=coronary artery bypass grafting, AVR=Aortic-valve replacement, MVR=Mitral-valve replacement, DVR=Double-valve replacement)

Extracorporeal Perfusion Time:

Extracorporeal perfusion time was assessed by recording CPB time and aortic cross-clamp time. CPB time ranged from 48–187 minutes in MUF group (mean=95.42±27 min), and 45–150 minutes in control group (mean=77.98±21 min). CPB time was longer for MUF group (p<0.001) and so was the aortic cross-clamp time (MUF=56.94±14 min, control=43.67 ± 16 min, p<0.001).

Haemoconcentration:

Haemodilution as a consequence of CPB was recorded in both groups (p>0.05) and post-CPB mean

haemoglobin was 8.9±0.67 g/dl for MUF group and 8.6±0.80 g/dl for control group. Haematocrit was 27±2.95 for MUF group and 26±3.08 for control (Table-3).

Table-3: Haemoconcentration

Haematological index	MUF group (Mean±SD)	Control group (Mean±SD)	*p* value
Post-CPB Haemoglobin (g/dl)	8.9±0.67	8.6±0.80	0.07
Post-CPB Haematocrit (%)	27±2.95	26±3.08	0.10
Final Haemoglobin (g/dl)	10.7±1.25	8.6±0.80	<0.001
Final Haematocrit (%)	33±3.64	26±3.08	<0.001

(CPB= Cardiopulmonary bypass)

Improvement in haematological indices was observed in MUF group (p<0.001) and final haemoglobin and haematocrit values increased to 10.7±1.25 and 33±3.64 respectively (Figure-2).

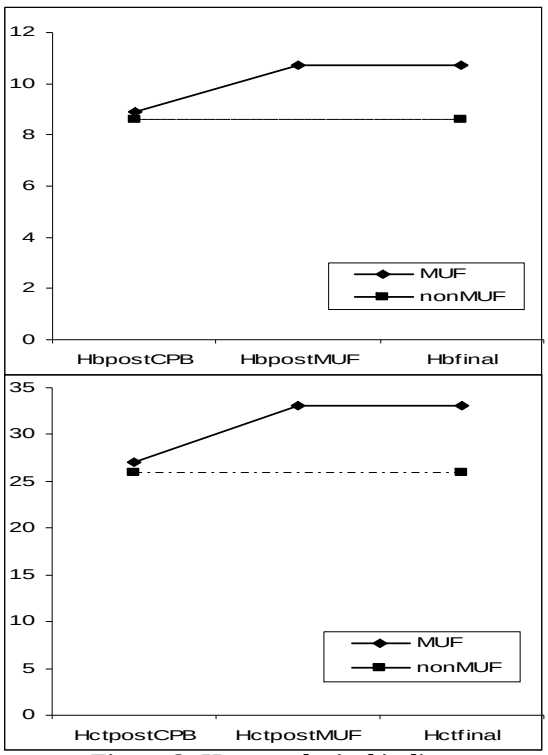

Figure-2: Haematological indices

Haemoglobin (graph i) and Haematocrit (graph ii) improvement in MUF group (solid line) while values stayed at baseline for control group(dotted line)

Blood loss and requirement of blood products:

Post operative blood loss in first 24 hours was significantly lower in MUF group being 395±153 ml against 755±435 ml in the control group (p<0.001). Blood transfusion in the form of packed red cell concentrates was lower for MUF group (140±180 ml vs 508±377, p<0.001) and so was requirement of coagulation factors (p<0.001) including fresh frozen plasma and platelet concentrates (Table-4, Figure-3). Re-exploration rate was 4% in MUF group and 6.5% in control group (p=0.57). Re-exploration for bleeding was 2% for MUF group and 4.3% for control group. Temponade was observed in control group only, being 2.2%.

Table-4: Requirement of Red blood cells and Coagulation factors (Fresh Frozen Plasma and Platelets)

Blood Product	MUF group (Mean±SD)	Control group (Mean±SD)	*p* value
PRBC(ml)	140±180	508±377	<0.001
FFP(ml)	62±160	258±357	0.0012
Platelets(ml)	64±149	212±250	<0.001

(PRBC=Packed red blood cells, FFP=Fresh frozen plasma)

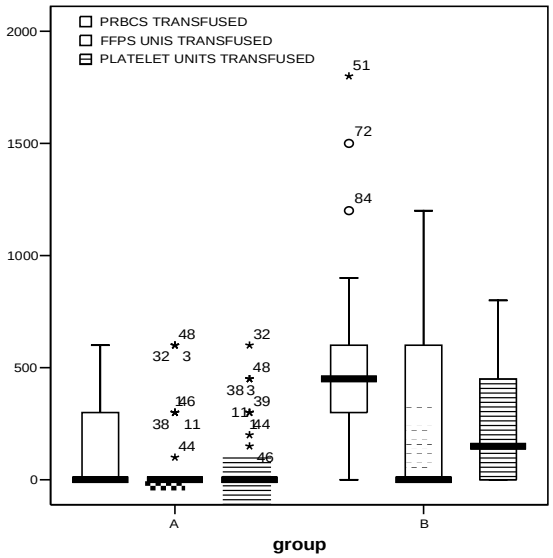

Figure-3: Transfusion requirement

A=MUF group, B=Control-group.
Boxplots represent the amount of red cell concentrates, FFPs and platelets transfused along with range(vertical line arising from boxes) and Mean-values(thick black horizontal lines); showing lower level for MUF group.

DISCUSSION

The pioneer work on MUF in Pakistan was started at AFIC/NIHD in January 2006 in collaboration with international children heart foundation. The circuit design had similar application for both paediatric and adult population. Encouraging results in paediatric population at our institute and international observations[10-15,18] lead us to the application of this technique to our most troubled area being haemostasis during adult cardiac surgery.

Blood and blood products are still scarce, expensive and not completely free from transfusion related complications in developing countries.[1] Efforts at minimizing their usage are encouraged; moreover poor availability and side effects of

Aprotinine in high doses[9] are being increasingly recognized at our institute. The present randomized controlled trial was designed to establish whether modified ultrafiltration has an effect on haemoconcentration and postoperative bleeding in the absence of aprotinine in adult population undergoing cardiac surgery at our institute including redo and emergency surgeries which usually require additional measures for prevention of blood loss in the form of transfusing coagulation factors and antifibrinolytic agents in heavy doses.

Demographic analysis concluded that high risk patients (ASA Class-III, females, diabetics, $p<0.05$) ended up in MUF group including congenital corrective surgeries in adults. MUF group had higher extracorporeal circulation time ($p<0.001$) and expected increased risk for poor outcome compared to control group. Haemodilution was observed in both groups as a consequence of CPB similar to reported observations made by WC. Fang and Habib[3,4] but not at any level during study haemoglobin fell to levels below 6 gm/dl (range=7–10 gm/dl) which is a critical level for myocardial damage.[1-4] Improvement in haematological indices was achieved successfully in MUF group ($p<0.001$) increasing the final haemoglobin from 8.9 to 10.7 gm/dl (1.8 gm/dl) and haematocrit from 27% to 33% without blood transfusion as reported by Ross in children[18] and by Onae M. *et al* and Kamada in adults.[13-15]

Bleeding after open-heart operations is due to variety of factors, including haemodilution, platelet dysfunction, abnormal fibrinolysis.[1,10] The present study showed significantly lower average bleeding in MUF group indicating the success of this technique though only haemoconcentration can be demonstrated as a possible mechanism because platelet functions and cytokine assays were not done due to lack of facilities. Coagulopathy after CPB is critically dependent on haemodilution; it is therefore intuitive how modified ultrafiltration has repeatedly been shown to reduce postoperative bleeding.[10-15] The average volume of packed red blood cells and coagulation factors transfused, was significantly lower than control group demonstrating the favourable impact of modified ultrafiltration on haemostasis. Lower incidence of re-exploration for postoperative haemorrhage in patients undergoing ultrafiltration was also recorded, even though the results failed to reach significance similar to reported by Luciani.[10]

No complications related to use of modified ultrafiltration were recorded in our study representing compliance to the treatment of 100% and allows us to conclude that modified ultrafiltration is safe in any adult cardiac patient. Further trials are also being carried out so that this technique can evolve with wider applicability.

CONCLUSIONS

Modified ultrafiltration is demonstrated as a safe and useful technique for haemoconcentration. The results of present study are highly suggestive of a favourable impact of modified ultrafiltration in reducing postoperative haemorrhage and transfusion requirements after cardiac surgical procedures in adult population.

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REFERENCES

1. Victor A.Ferraris, Suellen P. Ferraris, Sibu P. Saha, Eugene A. Hessel II, Constance K. Haan, B. David Royston *et al*. Perioperative Blood Transfusion and Blood Conservation in Cardiac Surgery: The Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists Clinical Practice Guideline. Annals Thoracic Surgery 2007;83:S27–86.
2. Weisel RD, Charlesworth DC, Mickleborough LL, Fremes SE, Ivanov J, Mickle DA *et al*. Limitations of blood conservation. Journal Thoracic and Cardiovascular Surgery 1984;88:26 –38.
3. Fang WC, Helm RE, Krieger KH, Rosengart TK, DuBois WJ, Sason C. *et al*. Impact of minimum haematocrit during cardiopulmonary bypass on mortality in patients undergoing coronary artery surgery. Circulation 1997;96(2):194 –9
4. Robert H. Habib, Anoar Zacharias, Thomas A Schwann, Christopher J Riordan, Samuel J Durham, Aamir Shah *et al*. Adverse effects of low haematocrit during cardiopulmonary bypass in the adult: should current practice be changed? Journal Thoracic and cardiovascular surgery 2003;125(6):1438-50.
5. Lawrence J. Dacey, John J. Munoz, Yvon R. Baribeau, Edward R. Johnson, Stephen J. Lahey, Bruce J. Leavitt *et al*. Re-exploration for Hemorrhage Following Coronary Artery Bypass Grafting. Incidence and Risk Factors. Archives Surgery 1998;133:442-7
6. Michael J. Moulton, Lawrence L. Creswell, Mary E. Mackey, James L. Cox, Michael Rosenbloom. Re-exploration for bleeding is a risk factor for adverse outcomes after cardiac operations. Journal Thoracic and Cardiovascular Surgery 1996;111:1037-46.
7. Unsworth-White MJ, Herriot A, Valencia O, Poloniecki J, Smith EE, Murday AJ *et al*. Resternotomy for bleeding after cardiac operation: marker for increased morbidity and mortality. Annals Thoracic Surgery 1995;59:664-7.
8. Shishir Karthik, Antony D. Grayson, Emer E. McCarron, D. Mark Pullan, Michael J. Desmond. Re-exploration for bleeding after coronary artery bypass surgery: risk factors, outcomes, and the effect of time delay. Annals of Thoracic Surgery 2004;78:527-34.
9. Mangano DT, Tudor IC, Cynthia Dietzel. The risk associated with aprotinin in cardiac surgery. New England Journal Medicine 2006;354:353-65.
10. Luciani GB, Menon T, Vecchi B, Auriemma S, Mazzucco A. Modified ultrafiltration reduces morbidity after adult cardiac operations: prospective, randomized clinical trial. Circulation 2001; 104(1):I-253-9.
11. Leyh RG, Bartels C, Joubert-Hübner E, Bechtel JF, Sievers HH. Influence of modified ultrafiltration on coagulation,

fibrinolysis and blood loss in adult cardiac surgery. European Journal Cardiothoracic Surgery 2001;19(2):45-51.
12. Munir Boodhwani, Kathryn Wasiams, Andrew Babaev, Gurinder Gill, Nusrat Saleem, Fraser D.Rubens**.** Ultrafiltration reduces blood transfusions following cardiac surgery: a meta-analysis. European Journal Cardio-Thoracic Surgery 2006;30(6):892-7.
13. Onoe M, Magara T, Nojima T, Yamamoto Y, Hong S, Uga H, *et al*. Application of modified ultrafiltration to cardiac surgery in adults. Kyobu Geka 1999;52(6):451-4.
14. Kamada M**,** Niibori K, Akimoto H, Yokoyama H, Tofukuji M, Iguchi A. *et al*. Efficacy of modified ultrafiltration in coronary artery bypass grafting. Kyobu Geka 2001;54(6):463-7.
15. Kamada M**,** Niibori K, Akimoto H, Yokoyama H, Tofukuji M, Iguchi A. *et al*. Efficacy of modified ultrafiltration in reoperation for valvular disease. Kyobu Geka. 2001;54(2):119-24.
16. Kiziltepe U, Uysalel A, Corapcioglu T, Dalva K, Akan H, Akalin H. Effects of combined conventional and modified ultrafiltration in adult patients. Annals Thoracic Surgery 2001;71(2):684-93.
17. Tapan KS, Usha K, Poonam MK, Shiv KC and Minati Choudhury. Effects of combined conventional ultrafiltration and a simplified modified ultrafiltration in adult cardiac surgery. Indian Journal Thoracic and Cardiovascular Surgery 2007;23(2):116-24.
18. Ross M.Ungerleider**.** Effects of Cardiopulmonary Bypass and Use of Modified Ultrafiltration. *Annals Thoracic Surgery* 1998;65:S35-S39.
19. Department of medical education. A guide to Research methodology, Biostatistics and medical writing: College of Physicians and Surgeons Pakistan; 2nd edition 2002.
20. Naik SK, Knight A, Elliott MJ. A successful modification of ultrafiltration for cardiopulmonary bypass in children. Perfusion 1991;6(1):41-50.

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