COMPARATIVE STUDY OF CONVENTIONAL, MODIFIED, AND COMBINED ULTRAFILTRATION DURING PEDIATRIC CARDIAC SURGERY

Thesis

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CONTENTS

	Pages
LIST OF TABLES	
LIST OF FIGURES	
INTRODUCTION	**1**
AIM OF THE WORK	**3**
REVIEW OF LITERATURE	**4**
MATERIAL and METHODS	**62**
RESULTS	**69**
DISCUSSION	**77**
SUMMARY	**81**
REFERENCES	**84**
ARABIC SUMMARY	

LIST OF FIGURES

	Page
Figure A: Technique of Modified Ultrafiltration	**39**
Figure B: Conventional ultrafiltration	**66**
Figure C: Modified ultrafiltration	**67**
Figure 1: Hematocrit value in the three studied groups	**73**
Figure 2: Hemoglobin level in the three studied groups	**73**
Figure 3: Interleukin 6 level before CPB and 30 minutes after CPB.	**75**
Figure 4: Interleukin 8 level before CPB and 30 minutes after CPB.	**75**
Figure 5: TNF level before CPB and 30 minutes after CPB.	**76**

LIST OF TABLE

	Page
Table 1: Demographic data (mean ± SD) or numbers	**69**
Table 2: Hemodynamic data (mean ± SD) before sternotomy (T1), immediately after termination of CPB (T2), 10 minutes after CPB (T3), 30 minutes after CPB (T4)	**70**
Table 3: Transoesophageal echocardiography derived parameters (mean ± SD) before sternotomy (T1), immediately after termination of CPB (T2), 10 minutes after CPB (T3), 30 minutes after CPB (T4)	**71**
Table 4: Intraoperative hematological profile (mean ± SD)	**72**
Table 5: Inflammatory Cytokines levels (pg/ml). Data are mean ± SD	**74**

ABBREVIATIONS

CPB	:	Cardiopulmonory by pass
CUF	:	Conventional Ultrafiltration
MUF	:	Modified Ultrafiltration
TEE	:	Transoesphageal Echo
IL6	:	Interlukin 6
IL 8	:	Interlukin 8
TNF	:	Tissue nectrotizing factor
HB	:	Hemoglobin
HCT	:	Haematocrite
TLC	:	Total leucocytic count
PLC	:	Platelets count
EF	:	Ejection Fraction
FAC	:	Functional area Capacity

INTRODUCTION

To repair most congenital defect in pediatric patients, it is necessary to use cardiopulmonary bypass (CPB), which is not without many risks. One of the challenging problems involved with cardiac surgery is hemodilution during CPB surgery ***(Maehara et al., 1991)***. The CPB circuit is usually partially primed with a crystalloid solution to provide air free circuit during bypass. These crystalloid solutions are introduced into the patient's vascular space causing hemodilution, decreased patient hematocrit level, platelets and clotting factors ***(Elliott, 1993; Thompson et al. 2001)***.

Hemodilution also decreases the colloid osmotic pressure, which causes fluid to move into the extravascular tissues producing edema. This edema affects many organs including the brain, kidney, liver and lung ***(Lonagie et al., 1993)***. Excessive total body water may prolong ventilatory support and contribute to a prolongation of intensive care stay ***(Maluf et al., 2001)***.

Ultrafiltration has become an important strategy for mitigation of the adverse effects of hemodilution associated with the use of CPB ***(Pearl et al., 1999)***. In addition to that, the abnormal conditions to which blood is subjected during CPB trigger an activation of inflammatory response and complement system releasing a number of cytokines which remains one of the major causes of CPB-associated organ injury during pediatric cardiac surgery. There are two basic approaches to ultrafiltration, namely

conventional (CUF) and modified (MUF). Conventional ultrafiltration involves ultrafiltration during the rewarming phase of CPB, whereas modified ultrafiltration is performed after discontinuation of CPB ***(Naik et al., 1991)***.

CUF reduces fluid accumulation associated with CPB, congestive heart failure and diuretic resistant heart failure, induces hemoconcentration, decreases inflammatory, mediators ***(Pearl et al., 1999)***, and reduces blood loss and duration of mechanical ventilation ***(Pearl et al., 1999; Journois et al., 1994)***.

MUF also improves the immediate post-bypass hemodynamics, decreases myocardial edema, reduces pulmonary vascular resistance, induces hemoconcentration, reduces bleeding and thus, the need for blood transfusion ***(Naik et al., 1992; Elliott, 1993; Gaynor et al., 1995; Montenegro & Greeley 1998)***. With MUF, more fluid can be removed than with CUF and this difference may translate into greater efficacy in attenuating the deleterious effects of hemodilution ***(Pearl et al., 1999)***. Care should be taken during MUF to avoid any air embolism and colour of urine should be monitored for hemolysis.

AIM OF THE WORK

This study aimed to evaluate the efficacy of conventional ultrafiltration, modified ultrafiltration, and combined conventional and modified ultrafiltration, in attenuating the deleterious effects of hemodilution and inflammation in pediatric cardiac surgery.

CONSEQUENCES OF CARDIOPULMONARY BYPASS

Cardiopulmonary bypass (CPB) was originally pioneered in children. In 1952, F. John Lewis performed the first open heart operation using fibrillatory arrest ***(Lewis & Taufic, 1953)***. C.W. Lillehei was the first to use cross-circulation and hypothermia to repair an atrial septal defect ***(Lillehei et al., 1955)***. After developing his prototype "heart lung machine," John Gibbon repaired an atrial septal defect in 1953 ***(Gibbon, 1954)***.

In the current practice, cardiopulmonary bypass (CPB) is an essential prerequisite for undertaking corrective cardiac surgery for complex congenital cardiac defects. The advantages of a motionless and bloodless field, however, are undermined by a large number of risks secondary to initiation of the systemic inflammatory response syndrome ***(Raja, 2004)***.

Many consequences of extracorporeal circulation have been implicated in the genesis of the systemic inflammatory state, including exposure of blood components to synthetic surfaces, the fluid overload necessary for priming the circuit, body temperature changes, non-pulsatile flow, ischemia, and reperfusion of end organs ***(Kirklin et al., 1987; Westaby, 1987)***.

It is believed that cellular and humoral factors including cytokines are activated during bypass, which mediate organ damage. The clinical

manifestations of the systemic inflammatory response syndrome include cardiac, respiratory, renal, hepatic, and neurological dysfunction, bleeding diathesis, and even multisystem organ failure ***(Mossent et al., 1992; Moat et al., 1993)***.

Children undergoing cardiopulmonary bypass suffer disproportionate adverse effects because of their size and immature hematopoietic system ***(Mahfood et al., 1991)***. Although children have relatively larger circulating blood volumes when compared with adults (e.g., preterm infants have an estimated blood volume of 90–100 ml/kg compared to 70-80 ml/kg in an adult, their low absolute blood volume accentuates their dilutional coagulopathy. Further, their small blood volume creates practical limitations on the use of certain blood conservation strategies such as autologous donation and cell saver ***(Cote, 1991; Kallos & Smith, 1974)***.

INFLAMMATORY RESPONSE TO CARDIOPULMONARY BYPASS

The damaging effects of cardiopulmonary bypass (CPB) and the subsequent inflammatory response are the result of the extreme conditions encountered during extracorporeal support, including (1) cell activation on contact with the foreign surfaces of the bypass circuit, (2) mechanical shear stress, (3) tissue ischemia and reperfusion, (4) hypotension, (5) nonpulsatile perfusion, (6) hemodilution with relative anemia, (7) blood product administration, (8) heparin and protamine administration, and (9) hypothermia ***(Kozik & Tweddell, 2006)***.

A global inflammatory response ensues with the activation of cellular and humoral cascades, including the activation of the complement, coagulation, and fibrinolytic pathways; endotoxin release; cytokine production; endothelial activation with expression of leukocyte adhesion molecules; activation of leukocytes and platelets; and production and release of oxygen-free radicals, nitric oxide, arachidonic acid derivatives, and proteolytic enzymes ***(Brix-Christensen, 2001; Seghaye, 2003)***.

These inflammatory cascades result in a capillary leak syndrome and multiorgan dysfunction. Younger and smaller patients are more susceptible to the inflammatory response to CPB for several reasons including higher metabolic demands, reactive pulmonary vasculature, and immature organ systems with altered homeostasis. Smaller and younger patients, particularly infants and newborns, are also at increased risk because of the tremendous disparity between the CPB circuit size and the patient, with bypass circuit volumes often 200% to 300% greater than the patient's circulating blood volume. In addition, the greater metabolic demand of infants also requires higher pump flow rates, with neonates being perfused at rates up to 200 $mL \cdot kg^{-1} \cdot min^{-1}$. The combination of a relatively larger CPB circuit and the increased flow rates necessary for younger and smaller patients results in greater exposure of the blood to the foreign surface of the bypass circuit. Immature and developing organ systems place the youngest patients at greatest risk ***(Kozik & Tweddell, 2006)***.

Brain development continues during infancy. Regions of brain development are associated with increased metabolic activity ***(Chugani, 1998)***, specifically oxygen utilization, and these same areas of increased metabolic activity are at increased risk for bypass-related injury including ischemia, reperfusion, increased permeability, and edema formation. The lungs of newborns are also immature. There is a 10-fold increase in the number of alveoli in adults compared with infants, with most of this increase in number of alveoli completed by 8 years of age. This relative pulmonary immaturity predisposes neonates to the development of pulmonary edema and pulmonary hypertension ***(Vidal Melo, 2004)***.

Renal blood flow at birth is lower than later in infancy owing to higher renal vascular resistance. Renal blood flow increases during the first week of life, but does not reach adult values until 2 years of age. Furthermore, neonates have less renal autoregulatory function than adults, which leads to limited sodium reabsorption and excretion, concentrating, and diluting mechanisms, and decreased ability to regulate acid–base homeostasis ***(Bestic & Reed, 2005)***.

The immune system in neonates is also immature, with neutrophils showing functional deficits, including decreases in adhesiveness, deformability, and chemotaxis, as well as impaired complement generation ***(Ulrichs & Speer, 2004)***.

Components of the Systemic Inflammatory Response

Complement Activation

Complement activation occurs through both the alternative (stimulated by foreign surface contact, endotoxin, and kallikrein) and classical (protamine) pathways. The exposure of blood to extracorporeal circuits activates the alternative pathway, leading to the formation of C3a and C5a, whereas reversal of heparin with protamine activates the classical pathway with an associated rise in C4a levels and further rise in C3a levels ***(Chenoweth et al., 1981; Kirklin et al., 1983; Kirklin et al., 1986; Steinberg et al., 1993)***.

The anaphylatoxins C3a and C5a cause activation, degranulation, and adhesion of neutrophils, and activation of basophils and mast cells with histamine release, as well as platelet aggregation ***(Wachtfogel et al. 1989; Moat et al., 1993; Wachtfogel et al., 1993)***.

Seghaye et al. (1993) found that children who developed CPB-related complications had persistently higher C3 conversion than those without postoperative complications, but the same group failed to demonstrate a correlation between complement activation and adverse outcomes in neonates ***(Seghaye et al., 1994)***.

Neutrophil Activation

Neutrophils are activated by a wide variety of stimuli, including foreign surface contact, endotoxin, cytokines, complement, platelet-activating factor, and ischemia–reperfusion. Once activated, neutrophils

begin the process of endothelial adherence and migration with subsequent release of proteases and oxygen-derived free radicals. Endothelial cell barrier dysfunction is impaired, with resultant fluid extravasation ***(Boyle et al., 1997)***.

Studies in pediatric patients have shown a decrease in circulating leukocytes with initiation of CPB and a simultaneous rise in circulating neutrophil elastase and myeloperoxidase, indicating neutrophil adhesion, activation, and degranulation ***(Ashraf et al., 1997; Chew et al., 2001)***.

Plasma levels of adhesion molecules have been shown to be higher in children undergoing open heart surgery compared with adults ***(Boldt et al., 1995)***. Increased levels of adhesion molecules have been correlated with adverse outcomes in children undergoing open heart surgery, suggesting a central role of leukocyte activation in CPB-related injury ***(Paret et al., 2000)***.

Kinin Production

Kinin peptides are potent vasodilators that also participate in inflammation, leading to increased vascular permeability and neutrophil chemotaxis. The biologic effects of kinins are mediated through B1 and B2 receptors. B2 receptors are expressed in many cell types and have a high specific affinity for bradykinin ***(Campbell et al., 2001)***. Activation of B2 receptors leads to the release of calcium, nitric oxide, eicosanoids, free radicals, and cytokines ***(Hellal et al., 2003)***. Mediated by activation of the B2 receptor, bradykinin can increase the permeability of the blood–