Original Article

Effect of combined Conventional Ultrafiltration and Modified Ultrafiltration on Serum Interleukin-6 and TNF-α Levels in Pediatric Cardiac Surgery Patients

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Abstract

Background: Water retention occurs in most of the congenital heart surgery patients, especially in pediatrics. Ultrafiltration excretes water, electrolytes, many free radicals and inflammatory mediators. The aim of this study was to investigate the effect of modified ultrafiltration (MUF) on the serum levels of TNF-α and IL-6 in pediatrics patients undergoing congenital heart surgeries.

Methods and Materials: A total of 91 pediatric congenital heart disease patients candidate for total correction were selected and divided randomly in two groups: CUF (Conventional Ultrafiltration) and CUF+MUF; 40 patients were allocated to CUF group and 51 patients to CUF+MUF group. Serum levels of TNF-α and IL-6 were assessed before CPB and 6 hours after the end of the operation in ICU. Postoperative levels of TNF-α and IL-6 were compared between the two groups.

Results: In the MUF+CUF group, the preoperative and postoperative TNF-α levels were 2.5±5.6 and 1.4±3.0 respectively. However, IL-6 serum levels before and after operation were 4.8±8.9 and 41±56. In the CUF only group, the TNF-α level before and after surgery was 3.1±6.2 and 1.0±0.44; respectively; similarly, IL-6 serum levels were 3.3±8.2 and 34.8±37.7.

Conclusion: MUF in congenital heart surgery could filtrate excess water and elevate hematocrit but does not have a definitive role in reducing TNF-α and IL-6 serum levels.

Keywords: Ultrafiltration; TNF-α; IL-6; Cardiopulmonary Bypass

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Introduction

Throughout congenital heart surgery with cardiopulmonary bypass (CPB), the contact between blood and nonself surfaces, hemodilution and hypothermia causes production of free radicals, development of inflammatory responses and inflammatory mediators (1). Conventional ultrafiltration (CUF) and modified ultrafiltration (MUF) are two hemofilteration methods during cardiac surgery, to excrete excess water, free radicals and inflammatory mediators such as TNF-α and IL-6 from circulation (2). The hemofilter in CPB functions similar to kidneys in the body, eliminating water and waste products from the blood. The CUF is applicable for CPB. However, after weaning from CPB, blood filtration can be continued; known as MUF; these two methods have a number of technical differences (3).

The aim of this study was to evaluate the effect of CUF+MUF on reduction of TNF-α and IL-6 inflammatory mediators compared to those treated with CUF alone in children undergoing congenital heart surgery with CPB.

Methods

In a prospective clinical randomized trial, a total of 91 patients among 1 month to 14 years old undergoing congenital heart surgery with CPB were selected and divided randomly into two groups (CUF+MUF and CUF). In each group, after the induction of anesthesia, 1 mL of the patient blood was sent to the laboratory to determine the mean serum levels of TNF-α and IL-6 before surgery. It should be noted that CUF was done for all patients and 51 patients underwent MUF after surgery. Activated clotting time (ACT) was maintained throughout the CPB over 480 seconds. In MUF usually, the volume of filtered liquid is 10 mL per kg of patients' body weight.

After a patient was transferred to pediatric cardiac ICU and 6 to 8 hours after the end of the operation, a second blood sample was sent to the laboratory to assay the serum levels of TNF-α and IL-6. In the laboratory, the samples were centrifuged at 3000 rpm and serum levels of mentioned cytokines were assessed by specific kits. Then the results of these two groups were compared before and after the operation in the two groups: CUF+MUF and CUF

In this study, we tried to compare the similar cases with different destructive factors, such as the difference between pump time and clamp time, the type of operation, blood and plasma consumption and age of the patients.

Cytokines assay: throughout the sample collection, was attempted to use the same equipment for everyone in the experiment. The oxygenator used in this experiment was Dideco 902, 901, Sorin Hemofilter, TNF-α ELISA kit and interleukin-6 ELISA kit (IBL international GmbH, Germany) was purchased. The test was done in the Modarres Hospital lab in Tehran, Iran. All samples centrifuged and their serum was frozen after collecting at -18°C before test.

Anesthesia: anesthesia induction was performed with intravenous Ketamine (1 mg/Kg), Atracurium (1 mg/Kg) and Fentanyl (1 μg/Kg); then, continued with Isoflurane. The patients were cooled up to 30-28° C with the onset of CPB. After surgical procedure, the patients were warmed up to 36.5–37°^{C}; then, transferred to the ICU.

Data analysis: the results were analyzed using Chi Square test and paired t-test. SPSS statistical software, version 16.0 (SPSS Inc., Chicago, IL, USA) was used for data entry and analysis.

Results

The study results demonstrated smaller weight and age in CUF+MUF group; however, other parameters were not statistically different. Also, preoperative levels of TNF-α and IL-6, and hematocrit were similar in both groups and the "Male/Female gender" ratio was relatively similar between the two groups (Table 1).

In addition, 16 patients had Tetralogy of Fallot (17.6%), 44 had ventricular septal defect (48.8%), 15 patients had atrial septal defect (16.5%) and 16 patients had (17.6%) other types of congenital heart disorder. Disease type was not analyzed between groups.

Table 1: Demographic and preoperative data in study groups

	CUF+MUF group (N = 51)	CUF group (N = 40)	P. value
Age (month)	28/7±32/9	46/9±43/3	0.03
Male/Female gender (Chi square test)	0.92	1.13	0.09
Weight (Kg)	10.4 ± 5.8	14.9 ± 8.2	0.005
Hematocrit %	38.7 ± 7.0	40.2 ± 8.3	0.3
Lactate (mmol/l)	1.2 ± 0.6	1.1 ± 0.5	0.6
TNFα (pg/ml)	2.5 ± 5.6	3.1 ± 6.2	0.6
IL6 (pg/ml)	4.8 ± 8.9	3.3 ± 8.2	0.4

Table 2: Intraoperative data in study groups

	CUF+MUF group (N = 51)	CUF group (N = 40)	P. value
Pump time (min)	100 ± 21	80 ± 25	0.000
Clump time (min)	61 ± 25	43 ± 20	0.000
Final Hematocrit %	30 ± 5	28 ± 5	0.2
Receiving Blood Unit	1.4 ± 0.6	1.2 ± 0.7	0.09
Receiving FFP unit	0.5 ± 0.9	0.3 ± 0.7	0.2
Final lactate mmol/L	4 ± 1.6	4.4 ± 2	0.2
Hemofilter volume mL	1012 ± 412	1108 ± 360	

Operating room parameters including CPB time, aortic clamp time, transfused units of blood, blood gas and electrolyte parameters, etc. were all similar in both groups without a statistically significant difference.

The mean values of TNF-α and IL-6 between two groups did not show a significant difference during the pre- and postoperative assessments; however, both mediators increased inside the group in postoperative assays; compared with preoperative levels. There was no significant difference in other parameters of the study, such as lactate and hematocrit, before and after surgery.

Discussion

Increased level of inflammatory mediators during congenital heart surgery is inevitable. In some studies, MUF has improved blood pressure and hematocrit, and has had beneficial effects on mechanical ventilation by removing excess water. Our expectation of MUF was to decrease the mean serum TNF-α and IL-6 levels. The results of this study indicated that, contrary to our expectations, there was no significant difference in the reduction of inflammatory mediators in the two groups, and the MUF volume was not sufficiently low, for example, if it were 15 mL/Kg or more would be effective and reduce inflammatory mediators. HCT was also expected to be higher after MUF, the mean HCT before surgery was 37% in the MUF+CUF group and 30% in the postoperative period, while in the CUF group preoperative HCT was before surgery 40% and after surgery was 28%, indicating that the MUF improves hematocrit after surgery and reducing the need for blood transfusion.

Table 3: Postoperative data of the study groups

	CUF+MUF group (N = 51)	CUF group (N = 40)	P. value
TNFα (pg/L)	1.4 ± 3	1.09 ± 0.4	0.4
IL6 (pg/L)	41 ± 56	34 ± 37	0.5
Lactate in ICU (mmol/L)	4.8 ± 2	5.4 ± 2.3	0.1
Blood units transfused in ICU	0.3 ± 0.4	0.3 ± 0.5	

During CPB, blood from a reservoir is directed to the oxygenator by a roller pump, and after oxygenation, it will pushed to the patient with positive pressure through the arterial line. During CUF by separating a subordinate pathway, the patient's blood flows into the hemofilter, filtered, and then returns to the oxygenator (4).

On the other hand, in MUF, the patient is isolated from the pump, the blood passes through the arterial cannula with hydrostatic pressure to the hemofilter, and after filtration, it returns to the right atrium (5).

Ultrafiltration may excrete excess water and consequent improvement in hematocrit as well as the removal of additional electrolytes (like potassium), reducing free radicals and inflammatory mediators such as TNF-α and IL-6 (1-3).

Recognized in early 1960s, TNF-α is an inflammatory mediator with 17 kDa molecular weight and one of the two products of macrophages. Its main function is to ignite cellular signaling of inflammation, malignancy or infection to other body cells; then, cells in other body organs, like macrophages, B and T lymphocytes, monocytes, neutrophils, endothelial, and malignant cells continue the inflammatory cascade; fever is one of its clinical presntations (1). The most important task of TNF-α is to regulate the function of immune system cells and act as a tumor necrosis agent. Excessive TNF-α production may cause fever, inflammation, and cell death. Although TNF-α has an anti-tumor effect, however, if its filed of action stays unlimited, carcinogenesis, tumor invasion and metastasis may also ensue. Therefore, TNF-α induces both tumor necrosis and tumor replication. This is why assessment of TNF-α could be useful guide in both diagnostic and therapeutic approaches (6).

IL-6 is another inflammatory mediator that has several roles in inflammation phase and immune responses. Its level rises in some autoimmune diseases and has an important role in the development of fever (7).

MUF did not play a significant role in reducing inflammatory mediators in our assessments. Several factors (age, pump time, ischemic time, surgical conditions, type of oxygenator and hemofilter) may have a role in inflammatory mediators' production. It certainly needs more time or maybe a larger population size that is the main limitations of this study. Maybe patients undergoing longer procedure time (up to 90 minutes of ischemic time and up to 120 minutes of pump time), would benefit more from MUF. In such patients, inflammatory mediators, addition of blood and blood products, others inflammation provoking factors like suction and vent (which constantly inflict destructive and devastation power on the patient's blood components) would possibly create a wider space for the effects of MUF (8).

Inflammatory factors cause permeability of the vascular wall and cause electrolytes and proteins such as albumin to leak into the interstitial space. As a result, oncotic pressure increases and fluid starts flowing from the vascular bed to the interstitial spaces, leading to tissue edema. With MUF, this maybe somewhat overcome (6-8).

There were a number of limitations in this study; the following are among the most important ones:

- limited study population
- the differences in age and weight between the two study groups
- plurality of destructive factors
- limited sampling frequency

Some of the above factors were mainly due to financial limitations; however, they may have affected the results of our study.

Conclusion

Inflammatory mediators (TNF-α, and IL-6) were increased in both study groups; however, there was no significant difference between CUF+MUF and CUF groups. This may demonstrate that MUF does not exert a clear effect on the reduction or elimination of inflammatory mediators in pediatric cardiac surgeries undergoing CPB. More complementary studies are suggested in this respect.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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