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Dynamics of NT-proBNP and sST2 Biomarker Levels in Children with Congenital Heart Defects at Various Periods of Cardiac Surgery

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Abstract Congenital heart defects (CHD) occur in 0.5–0.9% of newborns and survival is substantially improved in the last decades [1-5]. From a pathophysiologic standpoint, CHD may be characterized by (1) increased volume overload (i.e., defects characterized by left-to-right shunt, such as ventricular septal defect, patent ductus arteriosus, truncus arteriosus, atrial septal defect, and atrioventricular septal defects); (2) pressure overload involving the left ventricle (i.e., aortic stenosis and aortic coarctation) or the right ventricle (i.e., tetralogy of Fallot and pulmonary stenosis); (3) complex cyanotic CHD (i.e., univentricular heart and transposition of the great arteries) [1,7]. The N-terminal-pro-type B natriuretic peptide (NT-proBNP) is 76 amino acids derived from cleavage of a prohormone of 108 amino acids synthesized and released by cardiomyocytes. NT-proBNP can be used as an adjunctive marker in the integrated screening, diagnosis, management, and follow-up of children with heart failure caused by various acquired and congenital heart diseases [6]. The natriuretic peptides, NT-proBNP and BNP, correlate with various indexes of disease severity in children with congenital heart defects. The measurement of the circulating cardiac biomarkers BNP and NT-proBNP is now recommended by international guidelines [2,10].

Keywords Congenital heart defects, Biomarkers, NT - proBNP protein, sST2 protein, Artificial circulation, Ultrafiltration

1. Introduction

The study of molecular markers of myocardial damage, such as NT-proBNP and sST2, in the perioperative period of cardiac surgery in children with congenital heart defects is an important area of clinical and laboratory diagnostics. [1,2,4,6,8.11]. These biomarkers reflect the degree of stress and damage to cardiomyocytes and can also be used to monitor the severity of the condition, the effectiveness of intervention and the early detection of complications [3,5,7,9,10].

The aim of the study: to analyze the level of NT-proBNP and sST2 proteins in children with congenital heart defects at different periods of cardiac surgery.

2. Material and Methods of the Study

Clinical studies were conducted in the cardiac surgery departments of the Tashkent Pediatric Medical Institute and the Era Med Multidisciplinary Medical Center from 2021 to 2024. The study involved 232 children, including 202 patients with a confirmed diagnosis of congenital heart disease. These patients were divided into two groups.

The first group included 92 children (47.4%) with cyanotic forms of CHD, which were divided into 2 subgroups. Subgroup 1a consisted of 47 children who underwent CPB with classical ultrafiltration. Subgroup 1b consisted of 45 children who underwent CPB with modified ultrafiltration. The second group consisted of 110 children (39.7%) with acyanotic forms of CHD, which were also divided into 2 subgroups. Subgroup 2a consisted of 57 children who underwent CPB with classical ultrafiltration. Subgroup 2b consisted of 53 children who underwent CPB with modified ultrafiltration.

The control group consisted of 30 (12.9%) practically healthy children. The criteria for exclusion from the study were: children with severe genetic diseases and stigmas of dysembryogenesis, the presence of infectious and inflammatory diseases. The diagnosis of congenital heart disease and the type of defect were established according to echocardiography data.

To quantify the concentration of N-terminal fragment of brain natriuretic propeptide (NT-proBNP) in serum, chemiluminescence immunoassay (CLIA) was used using an

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automated analyzer (e.g. Elecsys 2010, Roche Diagnostics). To measure the level of soluble form of interleukin-1 receptor ST2 (sST2) enzyme-linked immunosorbent assay (ELISA) was used using a commercial kit (e.g. Presage® ST2 Assay, Critical Diagnostics, USA).

3. Research Results

In this study, we analyzed the dynamics of NT-proBNP and sST2 concentrations in the perioperative period in children with CHD, divided into two main groups: the first (n=92) and the second (n=110), each of which was further divided into subgroups depending on the perfusion technique used (1a, 1b; 2a, 2b).

The control group of children was characterized by an initial sST2 level of 35.2±0.4 ng/ml, which corresponds to the norm for healthy children.

In children of the 1st group, before the start of artificial circulation (AC), the sST2 level was significantly increased (1a: 57.8±0.4 ng/ml; 1b: 59.4±0.4 ng/ml, $p<0.001$), which may indicate chronic myocardial overload before surgery.

During IR and especially after ultrafiltration (1a) and modified ultrafiltration (1b), a further increase in protein concentration was observed, reaching a maximum: in subgroup 1a: 68.5±0.4 ng/ml; in subgroup 1b: 64.9±0.4 ng/ml. By the end of the operation, the sST2 level had decreased slightly, but remained significantly higher than the control values: 1a: 58.6±0.4 ng/ml; 1b: 48.6±0.4 ng/ml.

It should be noted that by the end of the operation, the sST2 level in children of subgroup 1b was statistically significantly lower than in children of subgroup 1a ($p<0.001$), which indicates a more pronounced clearance of the mediator when using MUF.

In children of the 2nd group, with less pronounced hemodynamic disorders, the initial level of sST2 was also higher than the control, but to a lesser extent than in the 1st group: 2a: 45.9±2.82 ng/ml; 2b: 42.4±0.9 ng/ml ($P<0.001$). After IR and ultrafiltration, the sST2 level increased, reaching: 2a: 52.5±1.0 ng/ml; 2b: 51.9±0.9 ng/ml. By the end of the operation, the values decreased to 48.7±0.9 and 40.6±0.9 ng/ml, respectively. The sST2 level in children of subgroup 2b was significantly lower than in 2a ($P<0.01$), similar to the trends identified in the first group (Table 1).

Thus, the use of modified ultrafiltration in both groups resulted in a more pronounced reduction in sST2 by the end of surgery, compared with traditional ultrafiltration, reflecting more effective removal of proinflammatory mediators and myocardial injury proteins.

Dynamics of NT-proBNP level. In the control group, the NT-proBNP level was 92.4±1.3 pg/ml, which also corresponds to the age norm.

In children of the 1st group, the NT-proBNP level was already significantly elevated before the start of the operation (1a: 167.3±1.1; 1b: 159.5±1.1 pg/ml, $p<0.001$), which indicates volume and pressure overload in the conditions of congenital heart disease. During the IR stage and after filtration, the concentration of NT-proBNP increased, reaching a peak: 1a: 182.7±1.1 pg/ml; 1b: 168.2±1.0 pg/ml. By the end of the operation, the NT-proBNP level decreased, but remained above baseline values: 1a: 159.9±0.9 pg/ml; 1b: 135.1±1.0 pg/ml.

Thus, in children of subgroup 1b (MUF), there was a tendency for a more rapid decrease in the level of NT-proBNP, which may indicate less functional stress of the myocardium.

In children of the 2nd group, the initial NT-proBNP values were lower than in the first group, but also exceeded the norm: 2a: 137.2±1.1 pg/ml; 2b: 128.5±0.9 pg/ml. Following surgical intervention, the NT-proBNP level increased moderately and reached: 2a: 142.5±1.0 pg/ml; 2b: 136.3±2.1 pg/ml. By the end of the operation, there was also a decrease in: 2a: 139.7±1.0 pg/ml; 2b: 132.1±2.0 pg/ml. The indicators in subgroup 2b remained lower than in 2a, which confirms the more gentle nature of the intervention with MUF and a lower degree of surgical stress (Table 1).

sST2 and NT-proBNP levels at all time points were higher in children in group 1 compared to group 2, indicating a more severe initial condition and a more pronounced inflammatory -hemodynamic response to surgery.

The use of modified ultrafiltration (MUF) in both groups resulted in a greater reduction in both sST2 and NT-proBNP levels at the end of surgery compared with conventional ultrafiltration.

The difference between the subgroups was particularly evident in the final stages of the operation, indicating the importance of choosing the method of perfusion support to minimize myocardial damage.

The conducted analysis of the dynamics of NT-proBNP and sST2 in children with congenital heart defects in the perioperative period showed that these markers are sensitive indicators of myocardial stress and can be used to assess the severity of the condition, as well as the effectiveness of surgical intervention and perfusion protection methods. The use of modified ultrafiltration is accompanied by better dynamics of reducing sST2 and NT-proBNP levels, which confirms its advantages in the correction of CHD.

Analysis of the dynamics of NT-proBNP and sST2 levels in children with congenital heart defects in the perioperative period showed that both markers are informative indicators of the degree of functional overload and myocardial damage.

NT-proBNP and sST2 levels were significantly higher in patients with CHD compared to the control group, especially in children with severe hemodynamic impairment.

At all stages of the operation, an increase in the concentrations of these biomarkers was observed, reflecting the activation of the inflammatory and stress-reactive cascade in response to cardiac surgery.

Table 1. Indicators of biomarkers NT-proBNP and sST2 in examined children of groups 1 and 2 with CHD at different periods of cardiac surgery (M ± m)

Indicators	KG	1 group (n = 92)							
		1a subgroup (n = 47)				1b subgroup (n =45)			
		Before IR	During IR	After UV	End of operation	Before IR	During IR	After MUF	End of operation
sST2 protein, ng/ml	35.2 ± 0.21	57.8 ± 0.4 ***	68.5 ± 0.4 ***	58.6 ± 0.4 ***	71.6 ± 0.4 ***	59.4 ± 0.4 ***	64.9 ± 0.4 ***	48.6 ± 0.4 ***	39.2 ± 0.4 ***
NT-proBNP, pg/ml	92.4 ±1.3	167.3 ± 1.1 ***	182.7 ± 1,1 ***	159,9 ± 0,9 ***	145,3 ± 1,2 ***	159.5 ± 1.1 ***	168.2 ± 1.0 ***	135.1 ± 1.0 ***	126,1±1,1
Indicators	KG	Group 2 (n = 110)							
		2a subgroup (n = 53)				2b subgroup (n = 57)			
		Before IR	During IR	After UV	End of operation	Before IR	During IR	After MUF	End of operation
sST2 protein, ng/ml	35.2 ± 0.4	45.9 ± 2.82 ***	52.5 ± 1.0 ***	48.7 ±0,9 ***	42.7 ± 1.0 ***	42.4 ± 0.9 ***	51.9 ± 0.9 ***	40.6 ± 0.9 ***	37.2 ± 1.0
NT-proBNP, pg/ml	92.4 ±1.3	137.2 ±1.1 ***	142.5 ± 1,0 ***	139.7 ± 1,0 ***	132.3 ± 0,9 ***	128.5 ± 0.9 ***	136.3 ± 2.1 ***	132.1± 2,0 ***	118.1 ± 2,0 ***

Note: * - differences relative to the control group data are significant (* - P <0.05, ** - P <0.01, *** - P <0.001)

4. Conclusions

The use of modified ultrafiltration (MUF) contributed to a more effective reduction in NT-proBNP and sST2 levels at the end of surgery compared with conventional ultrafiltration (UF), indicating its greater effectiveness in limiting the inflammatory response and myocardial stress. The results confirm the diagnostic and prognostic significance of NT-proBNP and sST2 in assessing the condition of patients with CHD and the validity of using MUF as part of myocardial protection protocols in surgical correction of heart defects in children.

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