

On the changes of NT-proBNP level in children having undergone radical operation of tetralogy of Fallot and the clinical significance

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Abstract. – OBJECTIVE: To explore changes of plasma N-terminal pro-brain natriuretic peptide (NT-proBNP) level in children having undergone radical operation of tetralogy of Fallot (TOF) and its clinical significance.

PATIENTS AND METHODS: 52 cases of children with TOF hospitalized in our hospital from October 2011 to April 2013 were chosen, and they were all treated with radical operation of TOF. Levels of plasma NT-proBNP in these children were measured before the operation, and 3h, 12h, 48h, 1 week, 1 months, and 3 months after the operation. The cardiac color supersonic diagnostic set was used to examine pulmonary artery transvalvular pressure gradient, right ventricular end-diastolic volume (RVEDV), left ventricular ejection fraction (LVEF), and right ventricular Tei index.

RESULTS: (1) 3h after the operation, the level of NT-proBNP gradually rose and reached its peak 48h after the operation, which was markedly higher than the level before the operation ($p < 0.01$), yet the levels measured 1 month and 3 months after the operation were lower than the level before the operation ($p < 0.05$). (2) 1 week after the operation, NT-proBNP level, pulmonary artery transvalvular pressure gradient, and RVEDV of the group with right ventricular dysfunction were markedly higher than those of the group with normal right ventricular function ($p < 0.05$). (3) 3 months after the operation, levels of plasma NT-proBNP of children in the severe reflux group and moderate reflux group were markedly higher than those in the slight reflux group ($p < 0.05$); levels of plasma NT-proBNP of children in the severe reflux group were markedly higher than those of the slight reflux group ($p < 0.05$) 1 week or 3 months after the operation.

CONCLUSIONS: Changes of the NT-proBNP level during early stage after radical operation of children's TOF were in line with changes of the right ventricular function and could be regarded as an objective indicator for evaluating the right ventricular function.

Key Words:

Tetralogy of Fallot, Plasma, N-terminal pro-brain natriuretic peptide (NT pro-BNP), Right ventricular function.

Introduction

Congenital tetralogy of Fallot (TOF), one of the most common cyanotic congenital heart disease, accounts for 10% of the occurrences of all congenital heart diseases^{1,2}. It is a serious congenital heart malformation, and operation is the only solution to cure it³. In recent years, as technology advances, the success rate of TOF operation constantly rises and even reaches as high as 98%~99%, yet the long-term effects are still far from perfect^{4,5}. Particularly, after operations, children may have pulmonary regurgitation, pulmonary insufficiency, right ventricular dilation, and congestive heart-failure, which may seriously affect curative affects and their living quality^{6,7}. NT-proBNP is generated when proBNP is split into BNP. Mainly secreted by ventricles, it can reflect changes in ventricular functions⁸⁻¹⁰ and holds a great predicting value for TOF clinical prognosis. Here, we report results of the relevant studies conducted to explore changes in the level of plasma NT-proBNP of children after TOF radical operation and its clinical significance.

Patients and Methods

Patients

52 cases of children with TOF treated in our hospital from October 2011 to April 2013 were chosen, which included 31 males and 21 females. Their ages varied from 2 months to 2.5 years old, the average being (7.3 ± 5.1) months. The inclusion criteria was as following: cardiac function of II-III class before the operation; no primary diseases related to the liver and kidney; normal liver function; no infection or allergy; no attacks of serious anoxia. When patients with old myocardial infarction, dilated cardiomyopathy, tumor, valvulopathy, renal insufficiency, and

thrombotic diseases were excluded, there were 8 cases of atrial septal defect and 5 of serious pulmonary stenosis. All the children were treated by TOF radical operation under general anesthesia and cardiopulmonary bypass, the duration for extracorporeal circulation being (84 ± 59) min and the duration for aorta occlusion being (56 ± 41) min.

Methods

Venous blood was drawn from all the children when their stomachs were empty before the operation, and 3h, 12h, 48h, 1 week, 1 month and 3 months post operation. The blood was put in anticoagulative tubes and photoelectric immune luminescence instrument from Roche (Roche Diagnostic, Penzberg, Germany) was used to measure the level of NT-proBNP in children's plasma. One week after the operation, cardiac color ultrasound examination was conducted, and the cardiac color ultrasound machine (Philips IE33; Philips Medical Systems, Andover, MA, USA) was used to check pulmonary transvalvular gradient, right ventricular end-diastolic volume (RVEDV), left ventricular ejection fraction (LVFE) and right ventricular Tei index. In terms of the Tei index, patients were divided into a group of 45 cases with normal right ventricular function (right ventricular Tei index < 0.52) and another group of 7 cases with right ventricular dysfunction (right ventricular Tei index ≥ 0.52). Changes in the indexes of the groups were analyzed.

Statistical Analysis

All the data were represented by mean \pm standard deviation ($\pm s$). SPSS 17.0, a statistical software, was adopted, and the enumeration data were tested by *t*, $p < 0.05$ meaning that the difference was of statistical significance.

Results

Changes of Plasma NT-proBNP Level in Children with TOF Before and After the Operation

The levels of plasma NT-proBNP in children with TOF were (583.4 ± 72.3) pg/ml, (622.8 ± 78.6) pg/ml, (706.4 ± 88.7) pg/ml, (805.6 ± 92.2) pg/ml, (781.3 ± 88.1) pg/ml, (455.4 ± 73.6) pg/ml, (327.8 ± 68.4) pg/ml before the operation, and 3h, 12h, 48h, 1week, 1 month and 3 months after the operation, respectively. 3h after the operation, the level of NT-proBNP increased and reached its peak 48h after the operation, which was markedly higher than the level before operation ($p < 0.01$). Levels 1 month and 3 months after the operation were markedly lower than those before the treatment ($p < 0.05$).

Observation Indexes of Children with Different Right Ventricular Functions

Cardiac color ultrasound examination was conducted 1 week after the operation, and the patients were divided into a group of 45 cases with normal right ventricular function (right ventricular Tei index < 0.52) and a group of 7 cases with right ventricular dysfunction (right ventricular Tei index ≥ 0.52). The plasma NT-proBNP level, pulmonary transvalvular gradient, and RVEDV of patients with right ventricular dysfunction were higher than those of patients in the group with normal right ventricular function, while the LEVF of the group with right ventricular dysfunction was obviously lower than that of patients in the normal group ($p < 0.05$) (Table I).

Levels of Plasma NT-proBNP of Children Varying in Pulmonary Artery Regurgitation

3 months after the operation, cardiac ultrasonography was conducted again. As a result, there were 22 cases of no or slight regurgitation,

Table I. Observation of indexes in children with different right ventricular functions.

Groups	Cases (n)	NT-proBNP (pg/ml)	Pulmonary transvalvular gradient (mmHg)	REDV (mmHg)	LEVF
Normal right ventricular function group	45	682.4 ± 82.9	12.8 ± 2.1	8.8 ± 1.2	0.63 ± 0.02
Right ventricular dysfunction group	7	$1029.3 \pm 228.4^{**}$	$38.6 \pm 21.3^{**}$	$12.6 \pm 1.5^*$	$0.54 \pm 0.03^*$

Note: Compared with the normal right ventricular function group, $p < 0.05$, $^{**}p < 0.01$.

20 cases of moderate regurgitation, and 10 cases of serious regurgitation in the patients' pulmonary arteries. Patients in the groups of serious and moderate regurgitation had higher levels of plasma NT-proBNP than those in the group of slight regurgitation 48h, 1 week and 3 months post operation ($p < 0.05$); the plasma NT-proBNP levels of patients in the group of serious regurgitation had obviously higher levels of plasma NT-proBNP, 1 week and 3 months post operation ($p < 0.05$) (Table II).

Discussion

TOF, the most common cyanotic congenital heart disease, accounts for 10% of all congenital heart diseases and for more than 50% of all cyanotic congenital heart diseases in terms of morbidity. So far, operation remains the only way to treat TOF. In recent years, the success rate of TOF operation keeps rising with developing technology, reaching as high as 98%-99%¹¹⁻¹³. The vast majority of children can undergo radical operation. However, some children with ill-developed pulmonary vasculatures have to undergo palliative operation instead of radical operation. Nevertheless, as TOF has 4 kinds of malformation, namely, ventricular septal defect, dextropositioned aorta, pulmonary stenosis, and right ventricular hypertrophy¹⁴, dissection is subject to many changes and the curative effects of operations can vary a lot. Thus, the long-term effects are still not ideal. Particularly, pulmonary artery regurgitation, pulmonary valvular insufficiency, right ventricular dilation, congestive heart failure and other symptoms occurring post operation will seriously affect curative effects and the quality of life of patients.

NT-proBNP, produced when pro-BNP gets split into BNP, is mainly secreted by heart ventricles and can reflect functional changes in heart ventricles¹⁵. Compared with BNP, NT-proBNP has no bioactivity, longer half-life period, higher plasma concentration, and better stability; thus, it is more suitable for clinical tests^{16,17} and more valuable in predicting patient's cardiac function and clinical prognosis. A large number of researches in recent years have shown that NT-proBNP level is closely related to the left ventricular function, and an unusual rise in the NT-proBNP level in patients of chronic left ventricular failure indicates bad prognosis¹⁸⁻²². Currently, the relation between NT-proBNP and left ventric-

Table II. Plasma NT-proBNP levels of children with different arterial valve regurgitation (pg/ml).

Group	Cases (n)	Preoperative						
		Preoperative	Preoperative 3h	Preoperative 12h	Preoperative 48h	Preoperative 1 week	Preoperative 1 month	Preoperative 3 months
No or slight regurgitation group	22	587.2 ± 73.3	626.3 ± 81.2	703.1 ± 92.3	742.6 ± 83.3	645.3 ± 81.3	327.2 ± 71.7	185.6 ± 52.3
Moderate regurgitation group	20	580.1 ± 70.1	621.5 ± 73.6	705.3 ± 85.3	851.6 ± 92.2*	788.3 ± 82.1*	468.1 ± 82.1*	327.1 ± 72.2**
Severe regurgitation group	10	582.8 ± 78.6	624.2 ± 83.3	710.6 ± 112.3*	873.7 ± 112.3*	852.3 ± 91.4** ^Δ	557.7 ± 81.8** ^Δ	398.8 ± 86.6** ^Δ

Note: Compared with slight regurgitation group, * $p < 0.05$, ** $p < 0.01$; compared with the moderate regurgitation group, ^Δ $p < 0.01$.

ular function is widely accepted by scholars, and adopted as auxiliary diagnosis of heart diseases in clinics²³. However, reports concerning the changes in NT-proBNP levels that occur in children who have undergone radical operation are still limited²⁴.

This research was conducted by monitoring the plasma NT-proBNP levels of children before and after operations and combining ultrasonic cardiogram. As a result, the NT-proBNP levels of children started to rise 3h after operation; reached peaks after 48h and retained a relatively high level; which gradually dropped after 1 week. The levels 1 month or 3 months after the operation were lower than levels before the operation. The major reason may be damages to myocardial cells caused by traumas brought by operations and children's stress after operations²⁵. NT-proBNP experienced a transient increase. The gradual increase 1 week after the operation and the lower levels observed after 1-3 months post operation compared with those before operations indicate that children's heart malformation got corrected after the operation, haemodynamics became better and cardiac function got gradual recovery. Thus, the NT-proBNP level dropped.

1 week after the operation, cardiac color ultrasound examination was conducted. As a result, the plasma NT-proBNP level, pulmonary transvalvular gradient, RVEDV of children in the group with right ventricular dysfunction were markedly higher than those of children in the group with normal right ventricular function; yet the LEVF in the former group was markedly lower than that in the latter group. Such a result manifested that NT-proBNP level was closely related to children's right ventricular function after operations. Nevertheless, the rise of pulmonary transvalvular gradient and RVEDV and the reduction of LEVF indicated bad prognosis²⁶; thus, it was shown that NT-proBNP level was closely related to the operation prognosis of children after operations.

The research also found that pulmonary regurgitation could largely influence the NT-proBNP level of TOF children after operations. The plasma NT-proBNP of children in the severe regurgitation group and moderate regurgitation group was markedly higher than that of children in the slight regurgitation group 48h, 1 week and 3 months after operations, indicating that pulmonary artery regurgitation was an important factor for cardiac insufficiency after TOF radical operations and an

important factor influencing children's prognosis. Therefore, in TOF radical operation, enough emphasis should be given to the treatment of pulmonary artery to reduce the occurrence of pulmonary artery regurgitation after operations. Changes of NT-proBNP levels in children after operations, indicated that measurement of plasma NT-proBNP levels of TOF children before operations could help understand their prognosis and guide their treatment.

Conclusions

The changes in NT-proBNP levels during initial period in children with TOF who underwent radical operations, were in line with changes in the right ventricular function and, thus, could serve as an objective indicator for evaluating right ventricular function.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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