CLINICAL RESEARCH / KLİNİK ÇALIŞMA

VAN TIP DERGİSİ Medical Journal

Van Tıp Derg 24(4): 316-321, 2017
DOI: 10.5505/vtd.2017.62207

Effects of Adenotonsillectomy on N-Terminal Pro-Brain Natriuretic Peptide (NT-ProBNP) Levels in Children with Adenotonsillar Hypertrophy

Adenotonsiller Hipertrofi Olan Çocuklarda Adenotonsillektominin N-Terminal Pro-Beyin Natriüretik Peptid (NT-ProBNP) Düzeylerine Etkileri

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ABSTRACT

Objective: Adenotonsillar hypertrophy (ATH) is the most common cause for obstructive sleep apnea syndrome (OSAS) and adenotonsillectomy is used in treatment. Children with OSAS experience cardiovascular complications. N-terminal pro-brain natriuretic peptide (NT-proBNP) is one of the critical markers used for cardiovascular diseases. The present study aimed to determine the effects of adenotonsillectomy on NT-proBNP levels in patients with ATH.

Materials and Methods: The study has been designed as a single center clinical study. Children with ATH were included in the study, who were complaining from snoring, breathing from the mouth and breathing pauses during sleep. Measurements of arterial oxygen saturation (SaO_2), complete blood cell count, routine biochemical blood tests, chest radiography, electrocardiography, and a complete ear, nose and throat examination were performed. Upper airway obstruction and snoring were graded. NT-proBNP level was measured quantitatively by electrochemiluminescence method. Adenotonsillectomy was performed by curettage and cold dissection methods under general anesthesia.

Results: The study included 25 patients with ATH. Snoring or apnea was not observed in any of the patients at the post-operative 6 month. The median pre- and post-operative NT-proBNP levels were 10.01 pg/mL and 7.13 pg/mL, respectively and the difference was significant. There were no significant differences among the subgroups of gender, pre-operative snoring, pre-operative apnea, tonsil size, and adenoid size regarding the difference of NT-ProBNP level between the post- and pre-operative periods.

Conclusion: Adenotonsillectomy provided airway patency, and thereby led to an improvement in unfavorable effects on cardiovascular system.

Key Words: Adenotonsillar hypertrophy, obstructive sleep apnea syndrome, adenotonsillectomy, N-terminal pro-brain natriuretic peptide

ÖZET

Amaç: Adenotonsiller hipertrofi (ATH), obstrüktif uyku apne sendromuna (OSAS) yol açan en önemli neden olmakla birlikte, tedavisinde adenotonsillektomi kullanılır. OSAS'lı çocuklar kardiyovasküler komplikasyonlar yaşarlar. N-terminal pro-beyin natriüretik peptid (NT-proBNP), kardiyovasküler hastalıklar için kullanılan kritik belirteçlerden biridir. Bu çalışmada ATH'li hastalarda adenotonsillektominin NT-proBNP düzeyleri üzerine etkilerini araştırmayı amaçladık.

Gereç ve Yöntem: Çalışma tek merkezli bir klinik çalışma olarak dizayn edilmiştir. Uyku sırasında horlama, ağız solunumu ve nefes darlığı şikayetleri ile başvuran ATH'li çocuklar çalışmaya dâhil edildi. Arteryel oksijen satürasyonu (SaO_2), tam kan sayımı, rutin biyokimyasal kan testleri, göğüs radyografisi, elektrokardiyografi ve tam bir kulak-burun-boğaz muayenesi yapıldı. Üst hava yolu obstrüksiyonu ve horlama derecelendirildi. NT-proBNP düzeyi, elektrokemilüminesans yöntemi ile nicel olarak ölçüldü. Adenotonsillektomi, genel anestezi altında küretaj ve soğuk disseksiyon yöntemleri kullanılarak gerçekleştirildi.

Bulgular: Çalışmaya ATH'li 25 hasta dâhil edildi. Post-operatif 6 aydaki hastaların hiçbirinde horlama veya apne görülmedi. Ameliyat öncesi ve ameliyat sonrası NT-proBNP düzeyleri medyan sırasıyla 10.01 pg/mL ve 7.13 pg/mL arasında idi ve fark anlamlıydı. Pre-operatif horlama, pre-operatif apne, bademcik boyutu ve adenoid boyut arasında NT-ProBNP düzeyinin post-operasyon öncesi ve pre-operatif dönem arasındaki fark bakımından anlamlı fark bulunmadı.

Sonuç: Adenotonsillektomi solunum yollarında açıklık sağladığı için kardiyovasküler sistem üzerindeki olumsuz etkilerin düzelmesine neden oldu.

Anahtar Kelimeler: Adenotonsiller hipertrofi, obstrüktif uyku apne sendromu, adenotonsillektomi, N-terminal pro-beyin natriüretik peptit

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Geliş Tarihi: 25.05.2017, **Kabul Tarihi:** 24.06.2017

Introduction

Adenotonsillectomy is traditionally performed for recurrent tonsillitis and its sequels; however, nowadays, it has become the primary indication for obstructive sleep apnea syndrome (OSAS) (1). OSAS is a quite common disorder with prevalence rates reported between 1% and 5% depending on diagnostic criteria and population (2). The most common cause for OSAS is adenotonsillar hypertrophy (ATH) (3). Children with OSAS have chronic airway obstruction and pulmonary hypertension and severe cases develop cor pulmonale (4). Additionally, snoring and sleep disorders that are encountered in children with OSAS lead to neurocognitive and behavioral disturbances and poor school performance (5). Hypercarbia and hypoxemia resulting from mechanical airway obstruction induce respiratory acidosis and pulmonary vasoconstriction develops, which in turn leads to reversible or lifetime changes in pulmonary vasculature, pulmonary hypertension, and right ventricular dysfunction (4). Early adenotonsillectomy in such children would prevent the development of many pathological conditions.

N-terminal pro-brain natriuretic peptide (NT-proBNP) is a critical marker used in the diagnosis, risk stratification and decision making in the treatment of cardiovascular diseases. Myocardial wall stress is the main stimulator that enhances NT-proBNP synthesis (6). NT-proBNP may be beneficial as a marker for the risk of cardiopulmonary disease that may occur due to OSAS in children with ATH. This study aims to determine the effects of adenotonsillectomy treatment on NT-proBNP levels in patients with ATH.

Materials and Methods

Children with ATH, who were complaining from snoring, breating from the mouth and breathing pauses during sleep, were included in the study. On the examination, all the patients were determined to have clinically obvious symptoms and signs of obstructive sleep apnea which lasted for more than 8 months. Patients who had heart or renal failure or severe lung disease and those who had upper airway obstruction due to other reasons, including presence of nasal polyps, in their medical history, physical examination or laboratory data were excluded since these patients would have a high probability of having an elevated baseline or variable circulating NT-proBNP level unrelated to OSAS. Data regarding the patients' snoring and apnea symptoms were obtained from the parents. Arterial oxygen saturation (SaO_2) measurements were performed using an oximetry monitor (Hewlett Packard M 3046 A, Viridia M3, Germany), which simultaneously measures oxyhemoglobin concentration, cardiac rhythm, and breath rate. Complete blood cell count, routine biochemical blood tests, chest radiography, and electrocardiography were pre-operatively performed with a complete ENT examination supported by nasal and nasopharyngeal endoscopy in prosperous cases to additionally assess nasal patency and adenoid size. In all patients, lateral skull radiography was used for air column imaging. Adenotonsillectomy was performed by curettage and cold dissection methods under general anesthesia.

Same as the literature, we have pre-operatively graded upper airway obstruction as Grade I, Grade II, Grade III, and Grade IV. We have defined Grade I upper airway obstruction as tonsils in tonsillar fossa which are hardly apparent behind the anterior pillars; Grade II upper airway obstruction is the tonsils which are easily apparent behind the anterior pillars; Grade III upper airway obstruction is the tonsils extending to the midline and Grade IV upper airway obstruction is the tonsils completely congesting the airway (7). Grading of the adenoid hypertrophy was based on the severity of the airway obstruction: mild (1°) indicating <25% obstruction; moderate (2°) indicating 25%-50% obstruction; moderately severe (3°) indicating 50%-75% obstruction; and severe (4°) indicating >75% obstruction (8).

Snoring was graded as: mild, snoring just in the supine position at some nights; moderate, snoring observed each night but disappears by changing the sleeping position; severe, snoring observed every night but does not disappear after the changes in sleeping positions (9).

For determination of NT-proBNP, blood samples were taken from the antecubital vein at night prior to adenotonsillectomy and at the post-operative 6 months. Blood samples were centrifuged and the plasma obtained was kept frozen for the analysis. NT-proBNP level was measured quantitatively by the electrochemiluminescence method (Roche Diagnostics GmbH, Mannheim, Germany).

This study has been approved by the Ethics Committee of Erzurum Ataturk University and informed consents of the patients were obtained from their parents or legal representatives.

Statistical Analysis: The data was analyzed using the Predictive Analytics Software (PASW) 18.0 for Windows program (SPSS Inc., Chicago, IL, USA). Number and percentage were used as categorical variables while mean, standard deviation, median, and minimum and maximum (min-max) were used as numerical variables. For non-normally distributed numerical variables, two independent groups were compared using Mann Whiney U test and multiple groups were compared using Kruskal-Wallis test. For non-normally distributed numerical variables, the relation between the variables was analyzed by Spearman's Rho test and the change in time was assessed by Wilcoxon signed-rank test. Statistical significance was determined as $p<0.05$.

Results

25 patients with ATH (mean age, 8.5±2.9 years), including 8 girls (mean age, 9.4±2.7 years) and 17 boys (mean age, 8.2±3.0 years) were included. The data regarding the patients are shown in Table 1.

None of the patients showed the presence of neither snoring nor apnea in the re-evaluation at the post-operative 6th month. The median (min-max) post-operative NT-proBNP level was 7.13 pg/mL (3.01-91.75 pg/mL). The decrease in the post-operative NT-proBNP level as compared to the pre-operative NT-proBNP level was significant (Table 2, Figure 1).

Table 1. Characteristics of patients with adenotonsillar hypertrophy

Characteristics	
Gender	
Girl	8 (32.0)
Boy	17 (68.0)
Age, year	8.0 (2.5-13.0)
Tonsil size	
Grade I	3 (12.0)
Grade II	10 (40.0)
Grade III	11 (44.0)
Grade IV	1 (4.0)
Adenoid size	
1°	0 (0.0)
2°	9 (36.0)
3°	7 (28.0)
4°	9 (36.0)
Snoring	
None	1 (4.0)
Mild	2 (8.0)
Moderate	11 (44.0)
Severe	11 (44.0)
Apnea	16 (64)
Arterial oxygen saturation (SaO_2), %	97 (95-99)
Respiratory rate, respiration/min	25 (18-32)
Pulse rate, beat/min	98 (84-154)
Systolic blood pressure, mmHg	90 (80-100)
Diastolic blood pressure, mmHg	60 (50-60)
NT-ProBNP, pg/Ml	10.01 (3.08-63.58)

NT-ProBNP, N-terminal pro-brain natriuretic peptide.
Values are presented as number (%) or median (minimum-maximum).

Table 2. Preoperative and post-operative N-terminal pro-brain natriuretic peptide levels in children with adenotonsillar hypertrophy

	Pre-operative period Median (Min-Max)	Post-operative period Median (Min-Max)	p
NT-ProBNP, pg/mL	10.01 (3.08-63.58)	7.13 (3.01-91.75)	0.023

NT-ProBNP, N-terminal pro-brain natriuretic peptide; Min-Max, minimum-maximum.

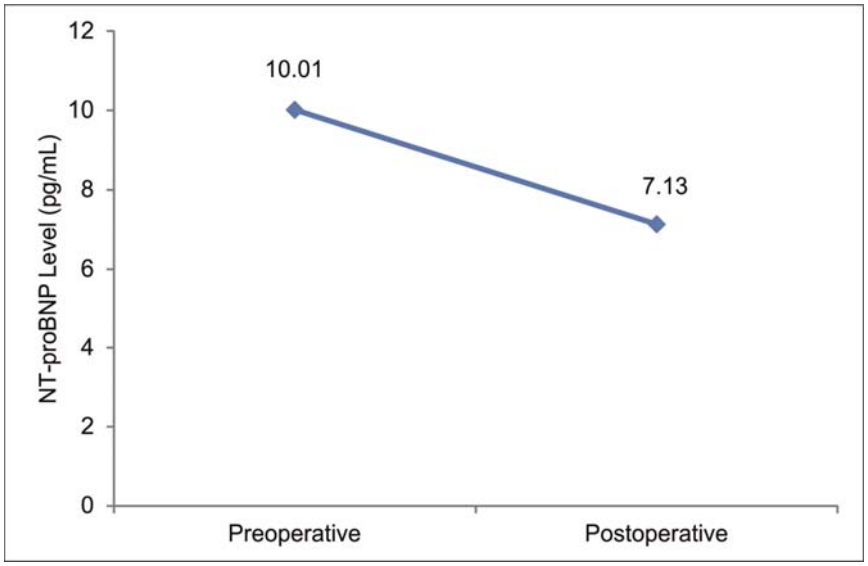

Fig. 1. Change in the N-terminal pro-brain natriuretic peptide (NT-proBNP) level between the preoperative and post-operative periods in children with adenotonsillar hypertrophy.

In our study, the factors that affect the decrease in NT-proBNP levels after surgery were assessed. Sub-groups of gender, pre-operative snoring, pre-operative apnea, tonsil size, and adenoid size did not differ significantly regarding the post- and pre-operative changes in NT-ProBNP level (Table 3).

The relation of the change in NT-proBNP level between post- and pre-operative periods with age, preoperative values of SaO_2, respiratory rate, pulse rate, and systolic and diastolic blood pressures, and the differences of these parameters between post- and pre-operative periods was not significant (Table 4).

Discussion

Adenotonsillar hypertrophy can cause cardiovascular complications in children. Adenotonsillectomy is commonly used to treat adenotonsiller hypertrophy. However, timing is important and in making the surgical decision can be difficult. Brain natriuretic peptide (BNP) and NT-proBNP are used either alone or in combination as diagnostic and prognostic markers in cardiovascular diseases. BNP scores and NT-proBNP concentrations of 71 children were measured by Zhang et al. (15). The measurement was performed on children with congenital heart disease in congestive heart failure (HF) group and non-congestive HF group. Higher BNP and NT-proBNP values were determined in both groups compared to the control group and these variables in the congestive HF group were determined to have increased. Compared to BNP, NT-proBNP is more stable *in vitro* with a longer plasma half-life (10). In this study, NT-proBNP levels are evaluated and adenotonsillectomy has been demonstrated to significantly reduce NT-proBNP levels.

In our study, exclusion of the patients having diseases such as heart and renal failure, severe lung disease, or upper airway obstruction caused by other reasons like nasal polyps, which are likely to influence NT-proBNP levels, allowed elimination of confounding factors. In their study, Lee et al. (11) reported that, children with ATH (n=21) who had no echocardiographic right ventricular dysfunction and had similar echocardiographic parameters with the control group (n=21), had significantly higher NT-proBNP levels than the controls (66.44±37.63 pg/mL vs. 27.85±8.89 pg/mL, p=0.001). In their study on 90 children with OSAS and age- and gender-matched controls (n=45), Goldbart et al. (12) reported higher NT-proBNP levels in OSAS children than in the controls (189.1±112.7 pg/mL vs. 104.8±49.5 pg/mL, p=0.006). Moreover, they determined a significant decrease in NT-proBNP levels after adenotonsillectomy (86±32.6 pg/mL vs. 187.8±114 pg/mL, p=0.002). Oran et al. (13) conducted a study on 20 children with ATH and 20 healthy children and found significantly higher pre-operative BNP levels in the ATH group (median BNP: 59.42 pg/mL vs. 37.79 pg/mL, p=0.03). Additionally, they observed a significant

Table 3. Difference of the N-terminal pro-brain natriuretic peptide level at the post- and pre-operative periods in the groups of gender, snoring, apnea, tonsil size, and adenoid size

	Difference of the NT-ProBNP level post- and preoperatively Median (Min-Max)	p
Gender		
Girl	-5.94 (-30.99-6.31)	0.560
Boy	-5.50 (-58.65-82.08)	
Preoperative snoring		
None	-2.65 (-2.65-(-2.65))	0.200*
Mild	-5.87 (-6.16-(-5.57))	
Moderate	-0.34 (-30.99-82.08)	
Severe	-9.50 (-58.65-12.02)	
Preoperative apnea		
Absent	-5.57 (-30.99-6.31)	1.000
Present	-3.94 (-58.65-82.08)	
Tonsil size		
Grade IV	-5.50 (-5.50-(-5.50))	0.725*
Grade III	-4.83 (-30.99-82.08)	
Grade II	-1.36 (-58.65-12.02)	
Grade I	-10.18 (-24.04-(-8.31))	
Adenoid size		
4°	-4.83 (-30.99-82.08)	0.694
3°	-8.31 (-23.10-6.31)	
2°	-2.38 (-58.65-12.02)	

NT-ProBNP, N-terminal pro-brain natriuretic peptide; Min-Max, minimum-maximum.

*Since the number of patients is limited, p values were calculated by excluding 'no snoring' and 'mild snoring' subgroups from the preoperative snoring group and by excluding 'grade I' and 'grade IV' subgroups from the tonsil size group.

Table 4. Relation of the difference of the N-terminal pro-brain natriuretic peptide level at the post- and pre-operative periods with other parameters

Difference of the NT-proBNP level post- and pre-operatively		
Variables	Rho	p
Age	-0.052	0.805
Pre-operative SaO_2	-0.038	0.856
Difference of the SaO_2 level post- and pre-operatively	0.017	0.938
Pre-operative respiratory rate	-0.046	0.828
Difference of the respiratory rate post- and pre-operatively	-0.135	0.521
Preoperative pulse rate	-0.130	0.534
Difference of the pulse rate post- and pre-operatively	0.320	0.119
Preoperative SBP	-0.283	0.171
Difference of the SBP post- and pre-operatively	0.281	0.173
Preoperative DBP	-0.143	0.496
Difference of the DBP post- and pre-operatively	0.066	0.754

NT-proBNP, N-terminal pro-brain natriuretic peptide; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

decrease in the BNP levels post-operatively and that the BNP level reached to a similar level to that of the control group. Kaditis et al. (14) determined a significant reduction in log-transformed BNP values after adenotonsillectomy in 21 children with OSAS (1.9±0.3 vs. 2.2±0.7, p=0.035). They reported the untransformed BNP levels to be 11.4±9.7 pg/mL and 6.6±2 pg/mL before and after adenotonsillectomy, respectively. In the multivariable analysis, they showed that there was a significant relation between change in BNP concentrations after adenotonsillectomy and change in obstructive apnea-hypopnea index following surgery; however, change in BNP concentrations after adenotonsillectomy was not associated with gender or age before surgery. In our study, the change in NT-proBNP levels between post- and pre-operative periods did not significantly differ among the subgroups of gender, pre-operative snoring, pre-operative apnea, tonsil size, and adenoid size. In addition, the change in NT-proBNP level between post- and pre-operative periods was not found to be related to the pre-operative values of SaO_2, respiratory rate, pulse rate, systolic and diastolic blood pressures and the changes in these parameters between the post- and pre-operative periods. The absence of snoring and apnea in any of the patients and a significant decrease in NT-proBNP level at the post-operative 6th month suggested that adenotonsillectomy provided airway patency, and thereby led to an improvement in unfavorable effects on cardiovascular system.

In conclusion, according to the findings of our study, NT-proBNP can rise before related other clinical and laboratory findings in children with ATH. We found no significant difference in SO_2, respiratory rate, pulse rate, systolic and diastolic blood pressures between post- and pre-operative periods. Thus, we concluded that NT-proBNP level can provide extra benefit in the decision of adenotonsillectomy. However, we suppose that larger-scale studies may contribute revealing the data on this subject.

References

1. Ramos SD, Mukerji S, Pine HS. Tonsillectomy and adenoidectomy. Pediatr Clin North Am 2013; 60(4): 793-807.
2. Tan HL, Gozal D, Kheirandish-Gozal L. Obstructive sleep apnea in children: a critical update. Nat Sci Sleep 2013; 5: 109-123.
3. Chang SJ, Chae KY. Obstructive sleep apnea syndrome in children: Epidemiology, pathophysiology, diagnosis and sequelae. Korean J Pediatr 2010; 53(10): 863-871.
4. Blum RH, McGowan FX Jr. Chronic upper airway obstruction and cardiac dysfunction: anatomy, pathophysiology and anesthetic implications. Paediatr Anaesth 2004; 14(1): 75-83.
5. Brown KA. Outcome, risk, and error and the child with obstructive sleep apnea. Paediatr Anaesth 2011; 21(7): 771-780.
6. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart 2006; 92(6): 843-849.
7. Kumar DS, Valenzuela D, Kozak FK, Ludemann JP, Moxham JP, Lea J, et al. The reliability of clinical tonsil size grading in children. JAMA Otolaryngol Head Neck Surg 2014; 140(11): 1034-1037.
8. Modrzyński M, Mierzwinski J, Zawisza E, Piziewicz A. Acoustic rhinometry in the assessment of adenoid hypertrophy in allergic children. Med Sci Monit 2004; 10(7): 431-438.
9. Ogretmenoglu O. Horlama ve obstruktif sleep apne sendromu (OSAS). Aktuel Tıp Dergisi 2000; 5: 33-39.
10. Clerico A, Vittorini S, Passino C. Measurement of the pro-hormone of brain type natriuretic peptide (proBNP): methodological considerations and pathophysiological relevance. Clin Chem Lab Med 2011; 49(12): 1949-1954.
11. Lee JH, Yoon JM, Lim JW, Ko KO, Choi SJ, Kim JY, et al. Effect of adenotonsillar hypertrophy on right ventricle function in children. Korean J Pediatr 2014; 57(11): 484-488.
12. Goldbart AD, Levitas A, Greenberg-Dotan S, Ben Shimol S, Broides A, Puterman M, et al. B-type natriuretic peptide and cardiovascular function in young children with obstructive sleep apnea. Chest 2010; 138(3): 528-535.
13. Oran B, Ozturk K, Çimen D, Vatansev H, Bulut S, Arslan D. Release of NT-pro brain natriuretic peptide in children before and after adenotonsillectomy. Int J Pediatr Otorhinolaryngol 2013; 77(5): 666-669.
14. Kaditis AG, Chaidas K, Alexopoulos EI, Varlami V, Malakasioti G, Gourgoulianis K. Effects of adenotonsillectomy on R-R interval and brain natriuretic peptide levels in children with sleep apnea: a preliminary report. Sleep Med 2011; 12(7): 646-651.
15. Zhang SR, Zhang YH, Xu Q, Qiu HX, Chen Q. Values of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide in evaluation of cardiac function in children with congenital heart disease. Article in Chinese] Zhongguo Dang Dai Er Ke Za Zhi 2009; 11(6): 429-432.