Hassan Motamed[1, 2], Arash Forouzan[1, 2], Habib Heybar[3], Mohammad Javad Khorasani[1], Saeed Hesam[4]

[1]Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Air Pollution and Respiratory Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Cardiology Department, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4]Biostatistics Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Khouzestan, Iran

Bronchodilatory effects of B-type natriuretic peptide in acute asthma attacks: a randomized controlled clinical trial

Abstract

Introduction: B-type natriuretic peptide (BNP) regulates different physiological processes such as blood pressure, cardiac growth, and neural and skeletal development. Thus, the aim of this study w as to evaluate the effect of BNP in the treatment of acute asthma attacks.

Material and methods: In this randomized clinical trial, patients with acute asthma attacks were enrolled. The patients were divided randomly into two groups. Patients in the interventional group received BNP via intravenous infusion. Two μg/kg of BNP was injected as a bolus in 60 seconds. Then, infusion of BNP immediately began and was given in 0.01, 0.02, and 0.03 μg/kg/min doses every 30 minutes for the first 1.5 hours. The patients in the control group received nebulized salbutamol. Afterwards, peak flow meter findings, hemodynamic parameters, and estimation of the clinical severity of asthma in both groups were checked every 30 minutes.

Results: In total, 40 patients were included in this study. The values of PEFR in the 60th and 90th minutes in the control group were lower than those in the interventional group. In the 60th minute, the mean of PEFR was 377.3 in the BNP group but 335.95 in the control group ($P = 0.049$). Moreover, this difference remained significant in the 90th minute ($P = 0.021$). However, forced expiratory volume in one second (FEV_1) did not differ between the groups at any time ($p > 0.05$).

Conclusion: Although a large experimental study is needed to verify our hypothesis, it seems that BNP might be a therapeutic option in asthma exacerbations, particularly in those with β2 agonist receptor polymorphism.

Key words: bronchodilator agents, asthma, B-type natriuretic peptide, emergency medicine

Adv Respir Med. 2020; 88: 531–538

Introduction

Today, chronic lung diseases such as asthma are one of the most common causes of disability and death in human societies. Asthma is the most common chronic disorder of the respiratory tract and, in 2011 alone, resulted in 51% of 26 million US adults diagnosed with the disease reporting an asthma attack [1]. The burden caused by severe asthma results in a greater number of resonances, healthcare utilization, and expenditures [2] which increase the frequency of hospital admissions by nearly 50% [3].

High dose β2 agonists, inhaled anticholinergics, and oral corticosteroids are often recommended to manage acute exacerbations [4–8]. However, these are not always effective [9] because of the resistance due to β2 adrenoreceptor gene polymorphism in 30% of patients [10, 11–15] which also impacts the frequently delayed response to corticosteroids [16–18]. Therefore, finding other drugs which are also effective in controlling signs and symptoms in this high-risk population is necessary.

Natriuretic peptides (NPs), which include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP), regulate different physiological processes such as blood pressure, cardiac growth, and neural and skeletal development [19–21]. Moreover, BNP influences a variety of animal and human respiratory cells by NP receptors such

Address for correspondence: Hassan Motamed, Emergency Medicine Department, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran; e-mail: hasan_motamed@yahoo.com
DOI: 10.5603/ARM.a2020.0178
Received: 24.04.2020

ISSN 2451–4934

as type II alveolar cells, airway epithelial cells, and airway smooth muscle (ASM) cells [22–25]. Therefore, the administration of BNP can cause bronchorelaxation in patients with asthma. Calzetta et al. demonstrated that BNP stimulated the release of acetylcholine (210.7 ± 11.1%) from human bronchial epithelial (BEAS-2B) cells. This resulted in increased myosin phosphatase target subunit 1 and nitric oxide synthase gene/protein expression which enhanced nitric oxide levels in asthmatic airway smooth muscle supernatant (35.0 ± 13.0%). This shows that BNP protects against bronchial hyperresponsiveness via an interaction between the respiratory epithelium and airway smooth muscle in subjects with asthma [26]. To the best of our knowledge, there are hardly any sufficient prospective studies on this subject. Therefore, the present study was designed to evaluate the clinical efficacy of BNP in alleviating acute asthma attacks in asthmatic patients.

Material and methods

Study design and target group

This prospective, double-blind clinical trial was conducted in the Emergency Department of Ahvaz Golestan Hospital in Ahvaz, a city in the southwest of Iran, from March 2015 to June 2016. The asthma symptoms and peak flow meter findings in patients receiving BNP combined with standard treatment (intervention group) were compared to those of patients receiving just standard treatment (control group). The inclusion criteria consisted of being referred to the Emergency Department of Ahvaz Golestan Hospital with a diagnosis of asthma which was confirmed based on clinical and para-clinical British guidelines on the management of asthma [12% or 200cc increase in forced expiratory volume in one second (FEV_1) levels after 15 min following administration of inhaled short-acting beta-2-agonists such as salbutamol], having a history of asthma symptoms (i.e. wheezing, shortness of breath, and cough), signing a consent form to participate in the study, being aged between 18–55, not consuming bronchodilators 6 hours before admission to the emergency department, and having the ability to perform peak flow meter tests.

Exclusion criteria consisted of having an underlying pulmonary disease (i.e. cancer or laryngeal edema), left ventricular dysfunction (diastolic dysfunction with preserved ejection fraction), eosinophilic pneumonia, systemic vasculitides (i.e. polyarteritis nodosa), chronic obstructive pulmonary disease (i.e. chronic bronchitis or emphysema), interstitial lung disease, a lung mass, history of chronic bronchitis, coronary artery disease, a cardiac arrhythmia, pregnancy, lactation, and/or a mild or severe asthma exacerbation (predicted $FEV_1 < 25\%$) that occurred in patients with a known asthma diagnosis in response to a "trigger" (i.e. a viral upper respiratory infection, allergen or irritant exposure, lack of adherence to medication, or an unknown stimulus). Patients were also excluded in the case that they were critically ill and required CPR, had a lack of favorable response to treatment and a deteriorating clinical condition requiring the use of other complementary therapies for the treatment of asthma (i.e. magnesium sulfate/epinephrine, intubation, or intermittent positive pressure ventilation), blood pressure < 100 mm Hg at admission, an allergic history to BNP, a history of smoking (10 packs per year), age either below 18 years or more than 55 years, and/or a dissatisfaction to continue participation in the study. We also excluded patients with uncompleted data.

Participants

The participants were randomly allocated into two groups using a block randomization procedure with matched subjects in each block based on age and sex. The study received ethics approval from the Ethics Committee of Ahvaz University of Medical Sciences. All participants gave written informed consent.

After obtaining informed consent, eligible patients were enrolled. The peak flow meter and estimation of clinical severity of asthma were performed in both the control and interventional groups before administering any drug. Then, based on the severity of the asthma attack, asthma treatment was performed according to standard protocols. Patients with a mild to moderate severity of attacks were treated with 2.5 mg of nebulized racemic salbutamol over 20 minutes in three doses, as well as 0.5 mg of inhaled ipratropium in 3 doses within 20 minutes. Patients with extremely severe attacks were treated with 5 mg of inhaled racemic salbutamol via an inhaler in three doses over 20 minutes, 0.5 mg of inhaled ipratropium in three doses over 20 minutes, and 50 mg of oral prednisolone.

Patients in the interventional group received BNP via intravenous infusion. For this purpose, 2 μg/kg of BNP was injected as a bolus over 60 seconds. Standard treatment was the base treatment in both groups, but BNP infusion was the additive adjunctive treatment for the case group. BNP infusion consisted of 0.01, 0.02, and 0.03 μg/kg/min

each for 30 minutes in the first 1.5 hours. If the patient had a systolic blood pressure < 100 mm Hg on two separate readings, the infusion was discontinued and the patient was excluded from the study. Also, if the systolic blood pressure decreased to 20 mmHg, the infusion was interrupted. If the patient's systolic blood pressure improved, infusion was resumed and the patient was included in the study. Throughout the study, all patients underwent cardiac monitoring and pulse oximetry. The patients' blood pressure was measured by monitors approximately every 10 minutes. For all patients, drugs were injected through a catheter inserted in the elbow. Patients were treated in a semi-upright position at an angle of 45 degrees. The patients in the control group received standard treatment (nebulized salbutamol). Then, peak flow meter findings (peak expiratory flow rates [PEFR] and FEV_1), hemodynamic parameters, and estimation of the clinical severity of asthma in the both groups were checked every 30 minutes.

Sample size

The sample sized used in these studies was justified in previous similar studies [29, 30]. For our study, we determined the sample size according to other reviews in literature which showed that the minimum size for every group was to be no less than 20 patients.

Data analysis

Data were analyzed and reported only for patients who completed the trial. Statistical analysis of the data was performed using SPSS. To compare qualitative variables between groups, analysis of non-independent observations were used which included variance with repeated measurements (parametric), the Friedman test (non-parametric), and ANOVA with repeated measurements for multifactorial, separately for each group. The two-tailed p-value of < 0.05 was considered significant.

Results

Forty patients completed the study. Five patients were removed because they declined to participate and did not meet the inclusion criteria. 20 patients were placed into the interventional group and 20 were placed into the control group (Figure 1). The mean age of the patients in the interventional and control groups was 42.7 ± 10.38 and 36.65 ± 11.25, respectively. 19 patients (47.5 %) were male (Table 1). Before intervention,

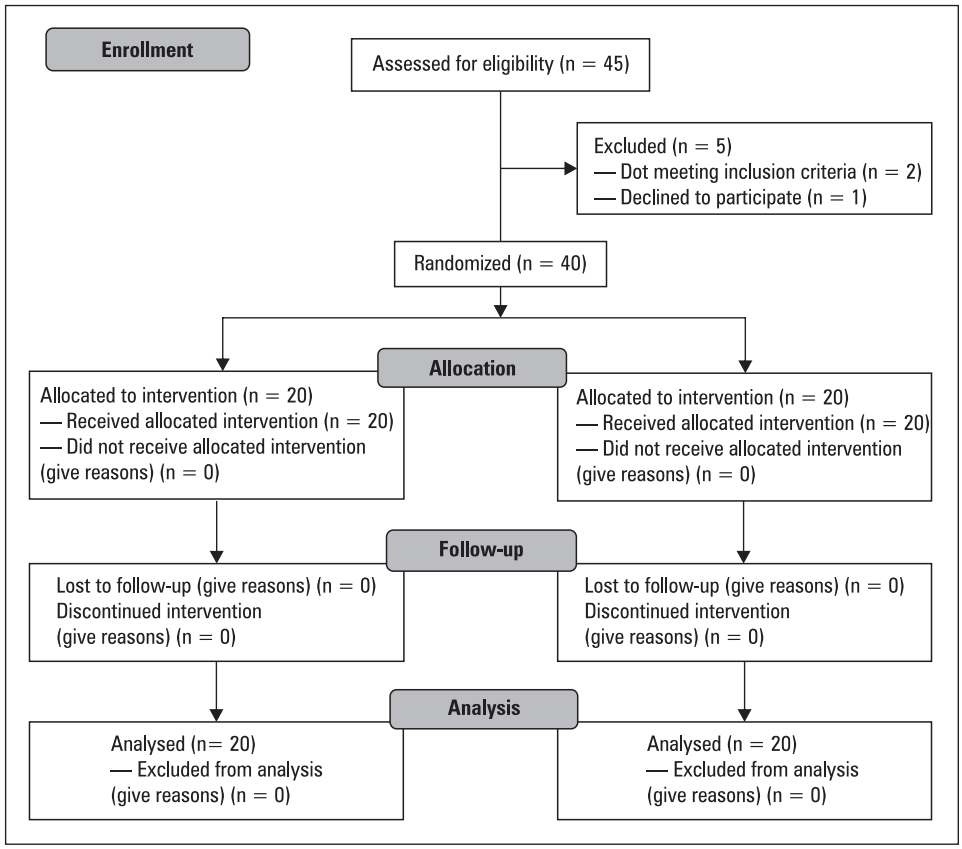

Figure 1. Flow diagram

Table 1. Studied variables during different periods of time in both control and B-type natriuretic peptide group

Group variables			BNP (n = 20)	Control (n = 20)	P-value
Age, year [mean ± SD]*			42.7 ± 10.38	36.65 ±11.25	0.085
Sex, male [N (%)]*			9 (45)	10 (50)	0.752
Asthma duration, year [mean ± SD]*			3.7 ± 1.68	3.95 ±2.06	0.677
FEV_1 [mean ± SD]		Before intervention	1.67 ± 0.43	1.67 ± 0.33	0.955
30th min		2.04 ± 0.44	1.96 ± 0.34	0.54	
60th min		2.36 ± 0.43	2.29 ± 0.44	0.596	
90th min		2.7 ± 0.45	2.58 ± 0.47	0.4	
PEFR [mean ± SD]		Before intervention	289.95 ± 66.99	279.15 ± 54.05	0.578
30th min		335.15 ± 66.26	302.45 ± 53.82	0.095	
60th min		377.3 ± 73.62	335.95 ± 53.05	0.049	
90th min		427.7 ± 78.2	376.9 ± 53.42	0.021	
PR, per min [mean ± SD]		Before intervention	89.25 ± 7.05	91.4 ± 5.16	0.278
30th min		95.9 ± 3.07	95.45 ± 2.21	0.598	
60th min		99.3 ± 4.06	98.45 ± 2.85	0.498	
90th min		95.9 ± 2.16	95.45 ± 1.46	0.598	
RR, per min [mean ± SD]		Before intervention	28.65 ± 2.47	28.85 ± 2.13	0.786
30th min		22 ± 1.58	22.2 ± 1.5	0.685	
60th min		19.65 ± 1.3	19.35 ± 0.81	0.39	
90th min		15.1 ± 0.78	15.05 ± 0.75	0.839	
SBP [mm Hg] [mean ± SD]		Before intervention	121.25 ± 5.59	118.5 ± 7.45	0.195
30th min		120.5 ± 4.26	121.5 ± 6.09	0.551	
60th min		118.75 ± 6.85	119.25 ± 4.06	0.781	
90th min		118.3 ± 6.57	118.65 ± 6.99	0.871	
DBP, mm Hg [mean ± SD]		Before intervention	79.5 ± 12.55	79.5 ± 10.5	0.99
30th min		75 ± 11.35	79 ± 4.7	0.158	
60th min		75.25 ± 9.24	79.5 ± 9.3	0.156	
90th min		78.75 ± 12.96	80.75 ± 9.77	0.585	
O_2 saturation [%], [mean ± SD]		Before intervention	90.8 ± 0.76	91.05 ± 0.88	0.347
30th min		93.45 ± 1.14	93.75 ± 1.16	0.417	
60th min		95.75 ± 0.91	95.25 ± 1.61	0.236	
90th min		96.75 ± 0.85	96.8 ± 0.89	0.857	
Dyspnea [mean ± SD]		Before intervention	4 ± 0.79	4.25 ± 0.5	0.241
At discharge			0.72 ± 0.59	0.75 ± 0.57	0.893
Speaking, N [%]	Before intervention	Sentence	3 (15 %)	3 (15 %)	0.667
		Phrase	13 (65 %)	15 (75 %)	
		Word	4 (20 %)	2 (10 %)	
	At discharge	Sentence	16 (80%)	16 (80%)	0.99
		Phrase	4 (20 %)	4 (20 %)	
Wheezing, N [%]	Before intervention	Mild	2 (10 %)	0	0.127
		Moderate	16 (80 %)	14 (70 %)	
		Severe	2 (10 %)	6 (30 %)	
	At discharge	Mild	18 (90 %)	18 (90 %)	0.99
		Moderate	2 (10 %)	2 (10 %)	

*Parametric. DBP —diastolic blood pressure; , FEV1 — forced expiratory volume in one second; PEFR — peak expiratory flow rates RR — respiratory rate; PR — pulse rate; SBP — systolic blood pressure;

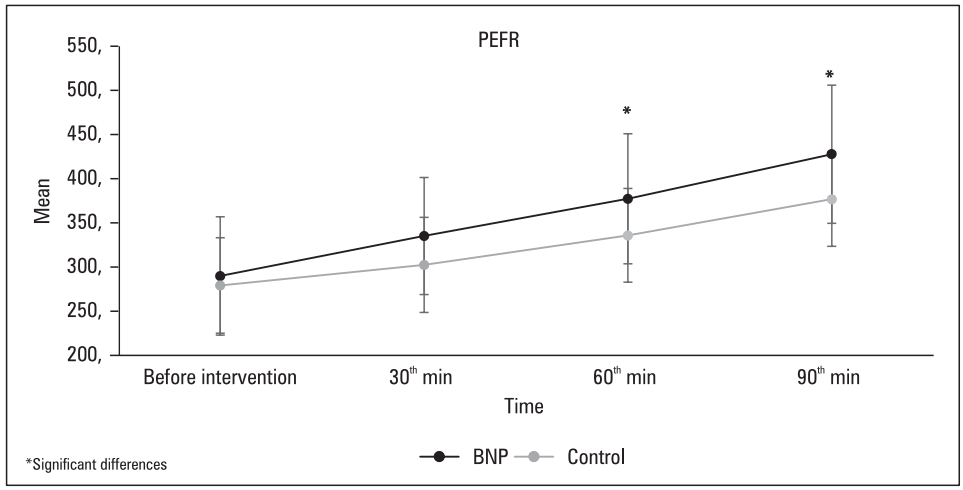

Figure 2. Peak expiratory flow rate (PEFR) trend during the study

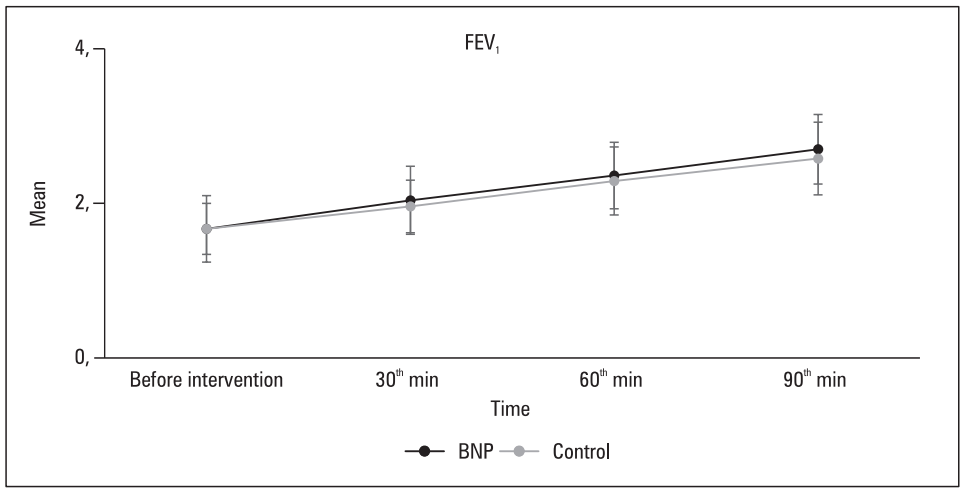

Figure 3. Forced expiratory volume in one second (FEV_1) trend during the study

the studied variables including peak flow meter readings, hemodynamic measurements, and clinical findings did not show a significant difference between the groups ($P > 0.05$).

Results showed that the means of PEFR in the 60^{th} and the 90^{th} minutes in the control group were lower than those in the interventional group. In the 60^{th} minute, the mean of PEFR was 377.3 in the BNP group but 335.95 in the control group ($P = 0.049$). Moreover, this difference remained significant in the 90^{th} minute ($P = 0.021$) (Figure 2). However, FEV1 did not differ between the groups at any time ($p > 0.05$) (Figure 3). Hemodynamic parameters such as respiratory rate, pulse rate, and systolic and diastolic blood pressures did not differ between the two groups in different periods of time ($p > 0.05$) (Figure 4–7). Furthermore, we found that clinical findings such as speaking and wheezing were similar in both groups at discharge ($p > 0.05$). Finally, the severity of dyspnea was not different between the two groups at discharge (0.72 *vs* 0.75, $P = 0.893$).

Discussion

According to our results, administering BNP increased PEFR significantly without having serious side effects or changing hemodynamic parameters. However, the severity of dyspnea at discharge did not differ in comparison with the control group.

Akerman *et al.* showed that intravenous (IV) nesiritide (BNP) is an effective bronchodilator in patients with asthma. They found that after 180 min of nesiritide infusion, FEV_1 and FVC expanded to 2.41 L and 3.65 L, respectively [27]. Orlandi *et al.* showed that the effect of BNP on relaxing bronchial smooth muscle cells is mediated from the epithelium and is associated with rapid changes in EGFR and

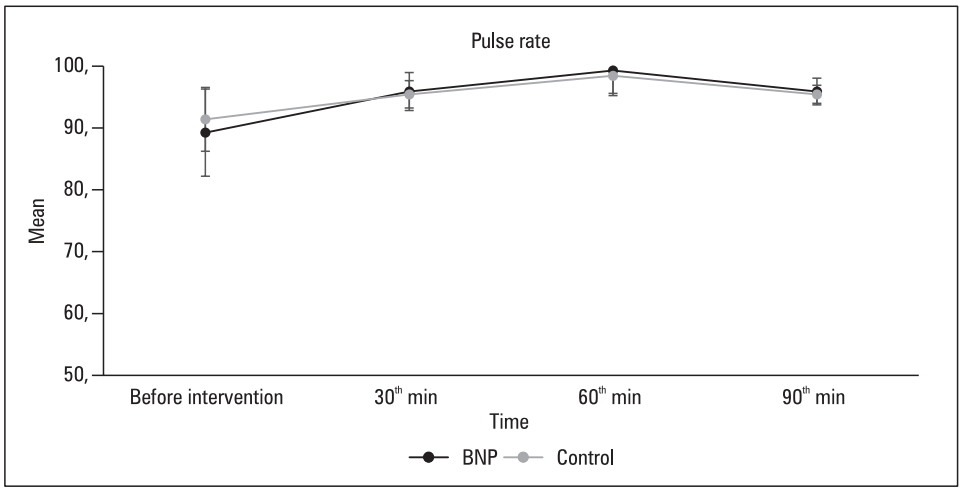

Figure 4. Pulse rate (PR) trend during the study

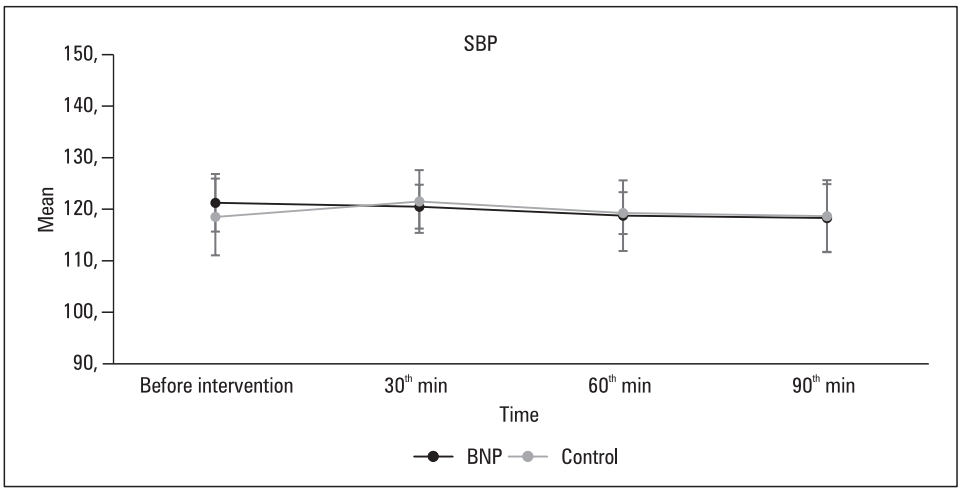

Figure 5. Systolic blood pressure (SBP) trend during the study

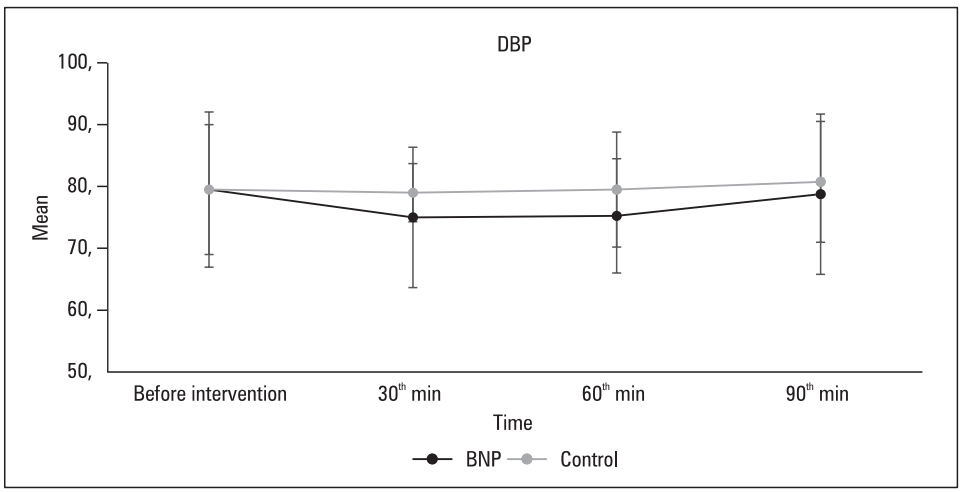

Figure 6. Diastolic blood pressure (DBP) trend during the study

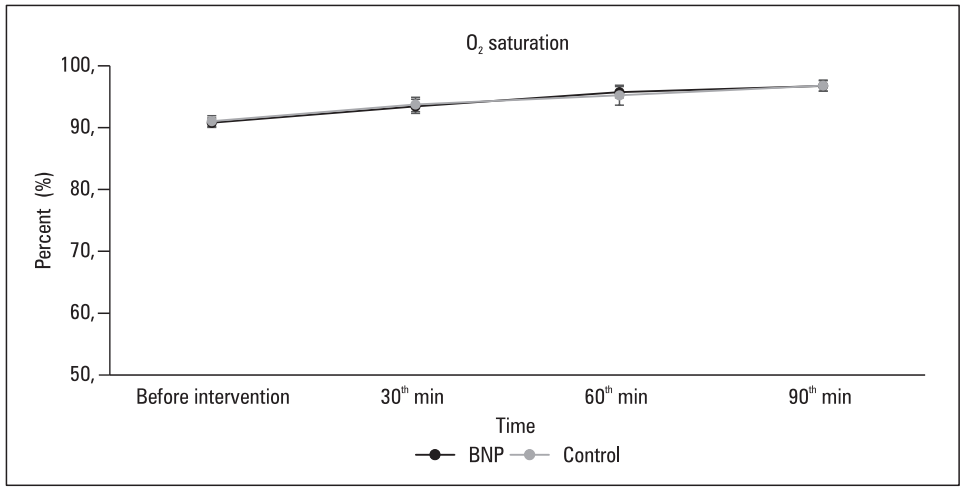

Figure 7. Percent of O_2 saturation trend during the study

calcium homeostasis-associated gene levels [28]. Calzetta *et al.* demonstrated that supernatant from BEAS-2B cells treated with BNP reduced the hyperreactivity of asthmatic smooth muscle cells by shifting the potency of histamine by 1.19-fold but had no effect in healthy smooth muscle cells. BNP did not have a direct effect on smooth muscle cells. Blocking muscarinic M2-receptors and iNOS abolished the protective role of supernatant from BEAS-2B treated with BNP. BNP stimulated the release of acetylcholine (210.7 ± 11.1%) from BEAS-2B cells that, in turn, increased MYPT1 and iNOS gene/protein expression and enhanced NO levels in asthmatic ASM supernatant (35.0 ± 13.0%) [26]. Another study conducted by Matera *et al.* showed that BNP induced a weak relaxant activity on carbachol-contracted bronchi in non-sensitized (relaxation: 4.23 ± 0.51%) and passively sensitized bronchi (relaxation: 11.31 ± 2.22%). On the other hand, BNP induced a relaxant activity on his-contracted bronchi in non-sensitized (relaxation: 42.52 ± 9.03%) and in passively sensitized bronchi (relaxation: 60.57 ± 9.58%). Finally, they acknowledged the modest relaxant role of BNP in asthma and, possibly, COPD [29]. These four studies confirmed our results.

However, Nishimura *et al.* showed a modest elevation of plasma BNP during acute exacerbations of chronic obstructive pulmonary disease. It appears that acute exacerbations of chronic obstructive pulmonary disease may have an impact on plasma BNP levels that are not attributable to heart failure [30].

Study limitation

The results of this study are in contrast with other studies. This may be due to different sample sizes, different races with different demographic features with different chief complaints, and a lack of controlling for risk factors common in both conditions.

Conclusions

Although a large experimental study is needed to verify our hypothesis, it seems that BNP could be a therapeutic option in the treatment of asthma exacerbations, particularly in those with $\beta 2$ agonist receptor polymorphism.

Acknowledgment

This study was financially supported by the Office of Vice-chancellor for Technology and Research Development of Jundishapur Medical Sciences University, Ahvaz, Southwest Iran as part of Mohammad Javad Khorasani's thesis under the research code U-94070. We gratefully acknowledge the dedicated efforts of the investigators, the coordinators, the volunteer patients who participated in this study, and the Clinical Research Development Units (CRDU) of Ahvaz Golestan Hospital.

Conflict of interest

None declared.

References:

1. American Lung Association Epidemiology and Statistics Unit, Research and Program Services Division 2012.
2. National Asthma Education and Prevention Program. Third Expert Panel on the Diagnosis and Management of Asthma. Expert panel report 3: guidelines for the diagnosis and management of asthma. Bethesda: National Heart, Lung, and Blood Institute. 2007.

3. Ivanova JI, Bergman R, Birnbaum HG, et al. Effect of asthma exacerbations on health care costs among asthmatic patients with moderate and severe persistent asthma. J Allergy Clin Immunol. 2012; 129(5): 1229–1235, doi: 10.1016/j.jaci.2012.01.039, indexed in Pubmed: 22326484.
4. National Heart, Lung and Blood Institute. Global Initiative for asthma. Global strategy for asthma management and prevention. NHLBI/WHO workshop report. Bethesda, Md: NIH. 2002.
5. National Institutes of Health and National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma–update on selected topics 2002. Washington, DC: US Dept of Health and Human Services. 2002.
6. National Asthma Council. Asthma Management Handbook 2002. National Asthma Council Australia, Ltd, Melbourne 2002.
7. British Thoracic Society. Scottish Intercollegiate Guidelines Network British Guideline on the Management of Asthma. Thorax. 2003; 58(Suppl 1): i1–94.
8. Becker A, Lemière C, Bérubé D, et al. Summary of recommendations from the Canadian Asthma Consensus guidelines, 2003. CMAJ. 2005; 173(6 Suppl): S3–11, indexed in Pubmed: 16157733.
9. Kercsmar CM, McDowell KM. Love it or lev it: levalbuterol for severe acute asthma--for now, leave it. J Pediatr. 2009; 155(2): 162–164, doi: 10.1016/j.jpeds.2009.03.062, indexed in Pubmed: 19619747.
10. Fischl MA, Pitchenik A, Gardner LB. An index predicting relapse and need for hospitalization in patients with acute bronchial asthma. N Engl J Med. 1981; 305(14): 783–789, doi: 10.1056/NEJM198110013051402, indexed in Pubmed: 7266631.
11. Hall IP. Pharmacogenetics of asthma. Eur Respir J. 2000; 15: 449–451.
12. Drazen JM, Silverman EK, Lee TH. Heterogeneity of therapeutic responses in asthma. Br Med Bull. 2000; 56(4): 1054–1070, doi: 10.1258/0007142001903535, indexed in Pubmed: 11359637.
13. Palmer LJ, Silverman ES, Weiss ST, et al. Pharmacogenetics of asthma. Am J Respir Crit Care Med. 2002; 165(7): 861–866, doi: 10.1164/ajrccm.165.7.2109096, indexed in Pubmed: 11934710.
14. Koga T, Kamimura T, Oshita Y, et al. Determinants of bronchodilator responsiveness in patients with controlled asthma. J Asthma. 2006; 43(1): 71–74, doi: 10.1080/02770900500448662, indexed in Pubmed: 16448969.
15. Tsai HJ, Shaikh N, Kho JY, et al. Beta 2-adrenergic receptor polymorphisms: pharmacogenetic response to bronchodilator among African American asthmatics. Hum Genet. 2006; 119(5): 547–557, doi: 10.1007/s00439-006-0169-2, indexed in Pubmed: 16596417.
16. Tantisira KG, Hwang ES, Raby BA, et al. TBX21: a functional variant predicts improvement in asthma with the use of inhaled corticosteroids. Proc Natl Acad Sci U S A. 2004; 101(52): 18099–18104, doi: 10.1073/pnas.0408532102, indexed in Pubmed: 15604153.
17. Tantisira KG, Lake S, Silverman ES, et al. Corticosteroid pharmacogenetics: association of sequence variants in CRHR1 with improved lung function in asthmatics treated with inhaled corticosteroids. Hum Mol Genet. 2004; 13(13): 1353–1359, doi: 10.1093/hmg/ddh149, indexed in Pubmed: 15128701.
18. Tantisira KG, Silverman ES, Mariani TJ, et al. FCER2: a pharmacogenetic basis for severe exacerbations in children with asthma. J Allergy Clin Immunol. 2007; 120(6): 1285–1291, doi: 10.1016/j.jaci.2007.09.005, indexed in Pubmed: 17980418.
19. Pandey KN, Pandey KN. Stoichiometric analysis of internalization, recycling, and redistribution of photoaffinity-labeled guanylate cyclase/atrial natriuretic factor receptors in cultured murine Leydig tumor cells. J Biol Chem. 1993; 268(6): 4382–4390, indexed in Pubmed: 8095048.
20. Potter LR, Abbey-Hosch S, Dickey DM. Natriuretic peptides, their receptors, and cyclic guanosine monophosphate-dependent signaling functions. Endocr Rev. 2006; 27(1): 47–72, doi: 10.1210/er.2005-0014, indexed in Pubmed: 16291870.
21. Potter LR, Yoder AR, Flora DR, et al. Natriuretic peptides: their structures, receptors, physiologic functions and therapeutic applications. Handb Exp Pharmacol. 2009(191): 341–366, doi: 10.1007/978-3-540-68964-5_15, indexed in Pubmed: 19089336.
22. Hellermann G, Kong X, Gunnarsdóttir J, et al. Mechanism of bronchoprotective effects of a novel natriuretic hormone peptide. J Allergy Clin Immunol. 2004; 113(1): 79–85, doi: 10.1016/j.jaci.2003.10.009, indexed in Pubmed: 14713911.
23. Bianchi C, Gutkowska J, Thibault G, et al. Radioautographic localization of 125I-atrial natriuretic factor (ANF) in rat tissues. Histochemistry. 1985; 82(5): 441–452, doi: 10.1007/BF02450479, indexed in Pubmed: 3161851.
24. Kawaguchi S, Uchida K, Ito T, et al. Immunohistochemical localization of atrial natriuretic peptide receptor in bovine kidney and lung. J Histochem Cytochem. 1989; 37(11): 1739–1742, doi: 10.1177/37.11.2553804, indexed in Pubmed: 2553804.
25. Matera MG, Calzetta L, Passeri D, et al. Epithelium integrity is crucial for the relaxant activity of brain natriuretic peptide in human isolated bronchi. Br J Pharmacol. 2011; 163(8): 1740–1754, doi: 10.1111/j.1476-5381.2011.01339.x, indexed in Pubmed: 21410689.
26. Calzetta L, Passeri D, Kanabar V, et al. Brain natriuretic peptide protects against hyperresponsiveness of human asthmatic airway smooth muscle via an epithelial cell-dependent mechanism. Am J Respir Cell Mol Biol. 2014; 50(3): 493–501, doi: 10.1165/rcmb.2013-0119OC, indexed in Pubmed: 24074453.
27. Akerman MJ, Yaegashi M, Khiangte Z, et al. Bronchodilator effect of infused B-type natriuretic peptide in asthma. Chest. 2006; 130(1): 66–72, doi: 10.1378/chest.130.1.66, indexed in Pubmed: 16840384.
28. Orlandi A, Calzetta L, Doldo E, et al. Brain natriuretic peptide modulates calcium homeostasis and epidermal growth factor receptor gene signalling in asthmatic airways smooth muscle cells. Pulm Pharmacol Ther. 2015; 31: 51–54, doi: 10.1016/j.pupt.2015.02.005, indexed in Pubmed: 25722070.
29. Matera MG, Calzetta L, Parascandolo V, et al. Relaxant effect of brain natriuretic peptide in nonsensitized and passively sensitized isolated human bronchi. Pulm Pharmacol Ther. 2009; 22(6): 478–482, doi: 10.1016/j.pupt.2009.04.005, indexed in Pubmed: 19393327.
30. Nishimura K, Nishimura T, Onishi K, et al. Changes in plasma levels of B-type natriuretic peptide with acute exacerbations of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis. 2014; 9: 155–162, doi: 10.2147/COPD.S55143, indexed in Pubmed: 24523584.