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Original Article

Comparison of High and Low Doses of Captopril in the Treatment of Neonates with Left-to-Right Shunt

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ABSTRACT

Introduction: Due to the significant differences between the physiology and pathology of adults and neonates, clinical guidelines for adults are not directly applicable to children. This study was performed to evaluate the effects of high- and low- dose captopril on the neonates with large left-to-right shunts.

Methods: The study was conducted on 20 neonates with congenital heart disease, left-to-right shunt, and cardiac failure. Based on the Ross scoring system, the neonates were clinically evaluated by measuring renin, aldosterone, and B-type natriuretic peptide, and performing echocardiography.

For each neonate, the treatment of heart failure started with digoxin and frusemide, and reevaluation was conducted 3 days after the treatment. Afterwards, the neonates were randomly divided into 2 groups; low- (0.03mg/kg) and high-doses (0.5mg/kg) of captopril were administered, and the reevaluation was carried out, after one week of therapy.

Results: The study revealed higher reduction of the Ross score in the high-dose group; however, the change was not statistically significant (*P*=0.56). B-type natriuretic peptide and aldosterone reduced further in the high-dose group; again the changes were not statistically significant (*P*=0.4). Moreover, the treatment with captopril increased the pulmonary blood flow (QP), and pulmonary-to-systemic blood flow (QP/QS) in both groups; though the changes were not significant.

Conclusion: According to the present study, although high-dose captopril can decrease B-type natriuretic peptide and the neonates' clinical symptoms, the resultant changes are not statistically significant. Therefore, clinical decision making should follow a case-by-case basis for each neonate, in order to select the effective dose of captopril.

Keywords: Angiotensin-converting enzyme inhibitors, Congenital heart disease, Heart failure, Left-to-right shunt, Neurohormones

Introduction

Congenital Heart Disease (CHD) is one of the most common congenital malformations, affecting 0.8% of all live births. It accounts for nearly one-third of all the major congenital anomalies, which are the prominent cause of heart failure (1-4). CHD accounts for 4% of all neonatal mortality, and is associated with several substantial morbidities, such as neuro-developmental delay and functional limitations (1).

The etiology of heart failure differs greatly for adults and infants. A large percentage of children with heart failure have an underlying CHD; although in contrast with the adult patients, ischemic heart disease is rarely found among children (5). Therefore, due to the heterogeneity of the underlying causes of heart failure, and the difference between the pathophysiology of adults and children, the large and rapidly-growing literature on adults' heart failure treatments, is not directly applicable to infants.

Heart failure primarily involves the function and structure of myocardium; although, other organs, such as the kidneys, and the musculoskeletal, nervous, and neurohormonal systems are also affected.

The chronic stimulation of these homeostatic mechanisms can deteriorate the cardiac function; hence, the treatment of heart failure should focus on alleviating these adverse effects (6).

First-line therapies for heart failure have not changed in the recent years, and the appropriate drug therapy is determined based on the underlying causes, and the severity of heart failure (7). Recently, angiotensin-converting enzyme inhibit-

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ors (ACE-I) are recommended for heart failure therapy in neonates; however, a limited number of studies have concentrated on the proper dose or the adverse effects of these medications. Thus, the present study aims to compare the therapeutic effects of low-dose and high-dose captopril, in the neonates with significant left-to-right shunts.

Materials and Methods

The patients

The present study was conducted on 20 neonates in the neonatal intensive care unit of Namazi Hospital, Shiraz, Iran (December 2011-April 2012). All the neonates suffered from left-to-right shunts, among whom, 10 had large ventricular septal defects and 10 were diagnosed with patent ductus arteriosus.

The study protocol

All the neonates were evaluated for neonatal sepsis and other congenital anomalies. The purpose, benefits, and the adverse effects of this interventional study were clarified for the parents, and the written consents were obtained. According to Ross scoring system, the echocardiographic and clinical evaluations were performed, on the first day of admission to the neonatal intensive care unit. The patients with congestive heart failure received medications with digoxin and diuretics for three days, and then the reevaluation was carried out.

After this phase, the neonates were randomly divided into two groups. During all the phases of this study, the echocardiographer and the neonatologist were not informed about the study groups. The second phase started on the third day; one group received low-dose captopril (0.03 mg/kg), while the other received high-dose captopril (0.3 mg/kg). Also, 4 cc blood samples were obtained for determining the renin, aldosterone, B-type natriuretic peptide, and NT-pro B-type natriuretic peptide serum levels. After seven days, the last evaluation was performed, and the second blood samples were drawn for the hormonal assay.

The exclusion criteria were as follows: the adverse effects of captopril such as hypotension, cyanosis, renal dysfunction, neutropenia, angioedema, allergic reactions, and rash; trisomy 21, and congenital defects which interfered with the neonate's feeding (e.g. cleft palate and esophageal atresia).

Echocardiographic examination

The neonates underwent comprehensive 2-dimensional, M-mode, and Doppler echocardiography, using a General electric Vivid 3 machine (7 MHz probe). The echocardiograms were interpreted at the echocardiography core laboratory by a single reader, to minimize the bias and the inter-observer errors. In M-mode echocardiography, ejection fraction, fractional shortening, end systolic dimension, and end diastolic dimension were measured. Besides, velocity time integral and pulmonary and aortic annulus diameters were measured in short and long axis views, for the calculation of the blood flow in the pulmonary and systemic circulation, respectively.

The hormonal assay

Plasma samples were collected from 4 ml of whole blood, and were stored at -80°C for assay. B-type natriuretic peptide and NT-pro B-type natriuretic peptide were assayed by the Ramp (TM) company kit (A Rapid, Quantitative Whole Blood Immunochromatographic Platform for Point-of-Care Testing). In addition, aldosterone concentrations were determined via a (commercially available) direct quantitative enzyme immunoassay (IBL International Institute), and the renin serum level was measured using DiaSorin kits.

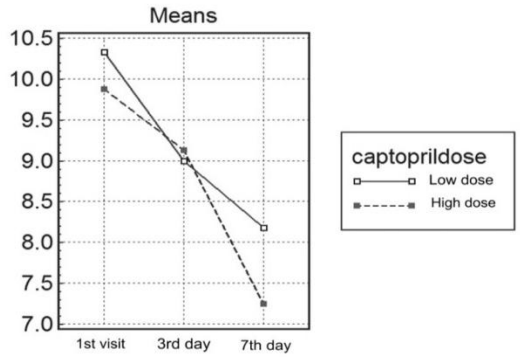

Figure 1. Ross score of the neonates receiving low and high doses of captopril in the first, third, and seventh day visits

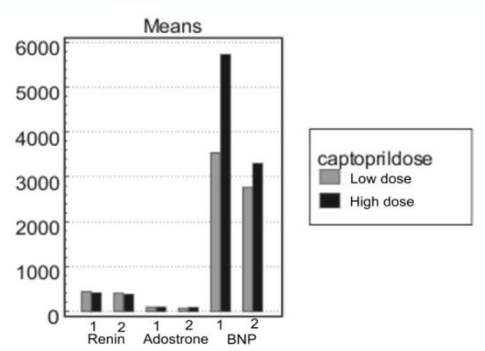

Figure 2. The serum levels of rennin, aldosterone, and B-type Natriuretic Peptide before (1) and after (2) the treatment with low and high doses of captopril

Table 1. Difference of Ross scores in the two groups of neonates

Total score difference	Captopril dose	Difference	*P*-value
First and second visit	Low dose	-1.00	0.45
	High dose	-1.2	
Second and third visit	Low dose	-0.88	0.56

Table 2. The percent of changes of renin, aldosterone, and BNP serum levels before and after the treatment with low and high doses of captopril

Serum level difference of neurohormones	Captopril dose group	Percent of changes	P-value
Renin	Low dose	-6±16	0.7
	High dose	-9±16	
Aldosterone	Low dose	-18±21	0.4
	High dose	-10±11	
BNP	Low dose	-2±11	0.4
	High dose	-40±20	

Ross scoring system

The severity of the congestive heart failure was estimated by Ross Score (8), which is based on the amount of formula consumed per feeding, time of feeding, the respiratory rate and pattern, heart rate, peripheral perfusion, and the presence of hepatomegaly. The scoring system is categorized into four classes, based on the scores: I (0–5), II (6–10), III (11–15), and IV (16–20) (9, 10). Hepatomegaly was measured as the distance below the right costal margin with abdominal situs solitus (11). Besides, the heart, and respiratory rates were recorded when the neonates were in a calm state (11). It should be mentioned that the volume of formula per feeding, is assigned to the bottle-fed babies. Regarding the breastfed infants, the taken volume has to be subjectively rated as normal, reduced, or non-oral feeding.

Statistical analysis

All the data are expressed as mean ± one standard deviation (SD). The data before and after the therapy were compared by Wilcoxon signed-ranks tests, and $P < 0.05$ was considered statistically significant. All the statistical analyses were performed using SPSS version 16.

Results

The treatment of heart failure was performed on 20 neonates, using high and low doses of oral captopril. The median age at the time of diagnosis was 4.5 days in the high-dose group, and 4.2 days in the low-dose group. All the patients had a gestational age of 36 weeks or more, and their median weight was 2,420 g.

Ross clinical scoring system

No statistically significant difference was found between the Ross scores of the groups, at the beginning of the analysis (10.4±1.8 and 9.9±1.7 in the low- and high-dose groups, respectively; *P*=0.5). However, the scores decreased in the 2nd visit (low-dose group: 9.4 ± 1.2, high-dose group: 8.7±1.7; *P*=0.8). In the 3rd visit, the Ross scores reduced further in the high-dose group (8.5±1.2 and 7.1±1.6 in the low- and high-dose groups, respectively; *P*=0.2) (Figure 1). The reduction of Ross scores in the first and second visits was -1.00±1.63 in the low-dose group, and -1.2±1.22, in the high-dose group (*P*=0.45). Also, the score reductions found in the second and third visits were -0.88 ± 1.05 and -1.6±1.26, respectively (*P*=0.56).

The hormonal assay

The effectiveness of captopril was evaluated by measuring the changes of renin, aldosterone, and B-type natriuretic peptide serum levels. The mean value of these markers is shown in Figure 2. B-type natriuretic peptide and aldosterone reduced further in the high-dose group; however, the changes were not statistically significant (Table 1).

Table 3. Assessment of 1st, 2nd, and 3rd echocardiographic indices in the low and high dose captopril groups

variable	group	1st echocardiography	2nd echocardiography	3rd echocardiography	P 1st and 2nd	P 2nd and 3rd	P low and high dose group¥
EF*	Low dose	68.5±6.8	73.1±7.4	74.5±10	0.009	0.002	0.68
	High dose	65.44±14.9	66.3±15.9	67.3±15.9			
SF	Low dose	35.7±5.1	39.3±6.2	41.1±7.9	0.004	0.044	0.75
	High dose	34.11±10.9	35±12.2	37.1±12.3			
EDD	Low dose	1.6±0.5	1.5±0.5	1.7±0.3	0.001	0.003	0.29
	High dose	1.5±0.4	1.4±0.32	1.6±0.4			
ESD	Low dose	1±0.27	0.94±0.32	1.03±0.2	0.002	0.016	0.19
	High dose	0.9±0.3	0.91±0.24	1±0.3			
QP	Low dose	8.6±4.2	6.2±2.8	10.3±6.6	0.401	0.944	0.167
	High dose	8.7±5.1	7.4±3.4	13.4±12			
QS	Low dose	5.6±2.7	4.8±2.1	5.5±2.4	0.1	0.367	0.167
	High dose	4.5±1.9	4.6±3.5	4.2±1.9			
QP/QS ratio	Low dose	2.2±2	1.4±0.6	1.4±0.6	0.68	0.725	0.752
	High dose	2.08±1.6	2.1±1	2.1±1.05			

*EF , Ejection fraction ; SF, Shortening fraction; EDD, End diastolic dimension ; ESD , End systolic dimension. Data are expressed as mean ±SD.¥ P of low and high dose group in 1st and 2nd echocardiography.

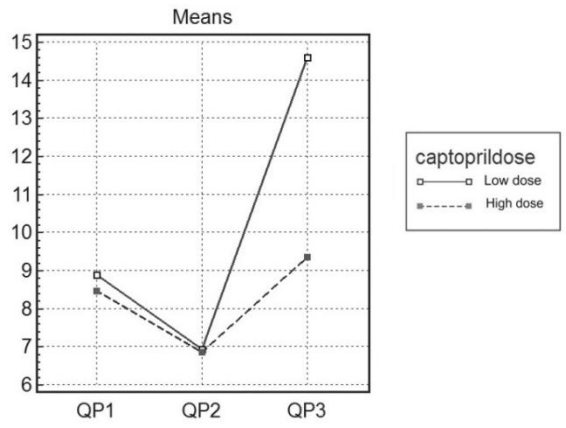

Figure 3. The serial changes of QP in 3 different visits during the study

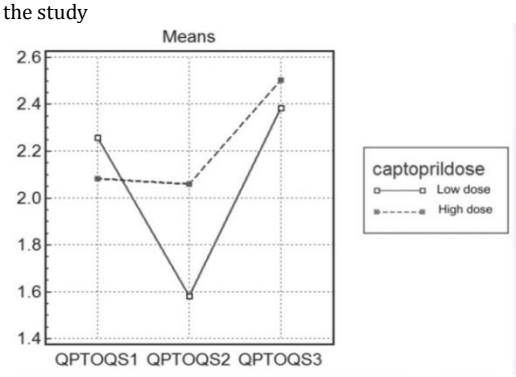

Figure 5. The serial changes of QP to QS ratio in 3 visits during the study

Echocardiography

Ejection fraction (66.81±11.8%, 68.94±13.7%, *P*=0.009), shortening fraction (*P*=0.004), end systolic diameter (1.02±0.27, 0.96±0.29, *P*=0.002), and end diastolic diameter (1.6±044, 1.53±0.4, *P*=0.001) changed significantly, after the treatment with digoxin and furosemide. M-mode echocardiographic indices are presented in Table 2 and 3.

Treatment with captopril increased pulmonary blood flow (QP), systemic blood flow (QS), and QP/QS ratio in both groups; the results are depicted in Figures 3, 4 and 5.

Discussion

Several advanced monographs provide a comprehensive overview of the adults' experience with therapeutic strategies for heart failure. Many aspects of heart failure treatment for children are extrapolated from adult medicine, due to the insufficient evidence regarding the children's treatments (12). Several large-scaled clinical trials have shown that angiotensin-converting enzyme inhibitors reduce the mortality and morbidity in the patients with heart failure (13). Although there are some studies on the use of angiotensin-

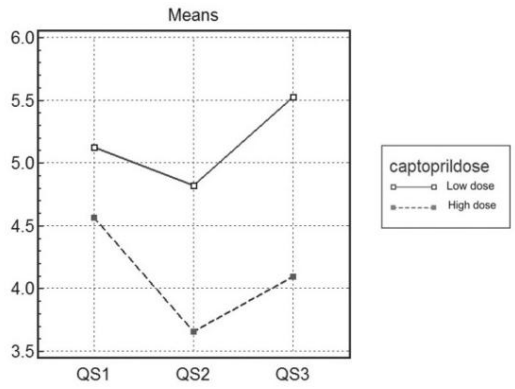

Figure 4. The serial changes of QS in 3 different visits during the study

converting enzyme inhibitors in pediatrics, the hormonal effects of angiotensin-converting enzyme inhibition, the efficacy and safety of this category of drugs, and the proper dose for neonates and children have not been clearly asserted for the treatment of ventricular dysfunction (14-16).

New evidence has shown that in addition to the signs and symptoms of heart failure, the data from echocardiography and biomarkers, such as N-terminal pro-brain natriuretic peptide, are all useful in stratifying the outcomes for children with heart failure (11).

Initially, the Ross classification (Ross *et al*, 2012) was used for grading the presence and severity of heart failure signs and symptoms, in infants and children; recently, several modifications of the system have been applied (11). By performing standard therapy and administering the angiotensin-converting enzyme inhibitors, after 3 visits the findings were in favor of clinical improvement. The differences found in the current study were not statically significant, due to the small number of patients; however, the Ross score reduced further in the high-dose captopril group.

Cardiac and vascular biomarkers are used in the diagnosis, assessment, and prognosis of a variety of cardiovascular diseases in both adults and children (17). The levels of Brain natriuretic peptide and the N-terminal fragment of the prohormone of B-type natriuretic peptide are associated with the severity and the outcomes of heart failure in adults (8). Regarding the children, cardiac biomarkers are most often used to assess cardiomyopathy or congenital cardiovascular malformations (17).

Reiner Buchhorn *et al* analyzed the neurohormonal, clinical, and hemodynamic data in two groups of infants with heart failure, who underwent treatment with either low-dose

captopril or propranolol. Compared with the patients on low captopril dosage, the infants who underwent propranolol treatment showed improvement in clinical heart-failure score, and diastolic ventricular function; they also had shorter lengths of hospital stay, along with lower plasma renin activities. Nevertheless, high-dose captopril was not evaluated in the aforementioned study (18).

In the present study, neurohormonal analysis was performed at baseline before starting the captopril, and 7 days after the treatment with high or low doses of captopril. After this period of treatment, aldosterone changes were in favor of the effectiveness of angiotensin-converting enzyme inhibitors, in both groups; although the difference among the two groups was not statically significant. Changes of renin in our laboratory evaluation were in an inverse relation to the aldosterone level and B-type Natriuretic Peptide; consequently, it can be considered as a predictor of heart failure. A study by Ratnasamy *et al* showed that the reduction of this neurohormonal marker is a valuable prognostic factor (10). In the current study, the changes of this marker showed better improvement in the high-dose group; although, due to the small number of the study subjects, the difference was not statistically significant.

Ratnasamy *et al* also evaluated the associations between neurohormonal and inflammatory activation and heart failure in children. They divided the children with heart failure into 3 symptom-severity groups, based on The New York Heart Association (NYHA) classification for <6 year-old children, and the Ross classification for infants and younger children. They found that N-terminal fragment of the prohormone of B-type natriuretic peptide (NT-pro B-type natriuretic peptide), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α), and soluble tumor necrosis factor receptor II (sTNF-RII), were associated with the echocardiographic parameters. NT-pro B-type natriuretic peptide and hs-CRP were also associated with the symptom severity (10).

In the present study, the echocardiographic indices were obtained in three steps: the baseline, after the treatment with furosemide and digoxin, and after the treatment with captopril in low- and high-dose groups. The comparison of the first and second echocardiographies showed significant improvements in some indices, such as ejection fraction (P<0.009), shortening fraction (P<0.004), end systolic dimension (P<0.002), and end diastolic dimension (P<0.001). Moreover, the comparison of the second and third echocardiographies showed better improvements in the mean ejection fraction in the low-dose group, while other indices, such as shortening fraction and end systolic and diastolic dimensions, improved better in the high-dose group.

The study findings revealed an increase in pulmonary and systemic blood flows, after starting captopril, in both groups. In the two study groups, while captopril increased the pulmonary to systemic flow ratio, frusemide and digoxin had an inverse effect. Our study results were in contrast with those of Boucek MM *et al*, who evaluated the effect of captopril on the ovine's hemodynamic pathology with ventricular septal defects. They showed increased systemic blood flow and decreased pulmonary blood flow, after starting captopril in the animal models (19). They also evaluated the effects of captopril on the distribution of the left ventricular output with the ventricular septal defect in the animals, and showed that the captopril caused dose-dependent changes in the distribution of the left ventricular output in the lambs with ventricular septal defects; therefore it caused a reduction in the total pulmonary flow and preserved the organ blood flow (20). These differences may indicate the pulmonary vasodilatory effect of captopril in the neonatal period.

Limitations of the study

Due to the small sample size, we could not use statistical techniques to adjust all the possible confounding factors. In addition, it was difficult to measure the hemodynamic parameters in the pediatric patients, since these measurements often require invasive monitoring.

Conclusion

This study showed that although high dose captopril can decrease B-type natriuretic peptide and the clinical symptoms in neonates, these changes are not statistically significant. Therefore, clinical decision making should follow a case-by-case basis for each neonate, in order to select the effective dose of captopril.

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References

1. Aschera SB, Smitha PB, Clarkc RH, Cohen-Wolkowieza M, et al. Sepsis in young infants with congenital heart disease.Early Human Development.2012; 88S2, S92–S97.
2. Cox GF, Sleeper LA, Lowe AM, Towbin JA, Colan SD, Orav EJ, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. Pediatrics. 2006; 118:15-19.
3. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003; 348:1647-1655.
4. Jeffrey A. Towbin,April M. Lowe,Steven D. Colan, Lynn A. Sleeper,E. John Orav, et al. Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children. JAMA. 2006; 296: 1867-1876.
5. Rosenthal D, Chrisant M, Edens E, Mahony L, Canter CH, Colan S, Ross R, et al. International society for heart and lung transplantation: practiceguidelines for management of heart failure in children.The Journal of Heart and Lung Transplantation.2004; 23(12).
6. Gradman AH, Papademetriou V. Combined renin-angiotensin-aldosterone system inhibition in patients with chronic heart failure secondary to left ventricular systolic dysfunction. American Heart Journal. 2009; 157(6):-18-21.
7. James N, Smith M. Treatment of heart failure in children. Current Paediatrics. 2005; 15: 539–8.
8. Rodeheffer RJ. Measuring Plasma B-Type Natriuretic Peptide in Heart Failure. JACC. 2004; 44(54):740–9.
9. Buchhorn R, Hulpke-Wette M, Hilgers R, Bartmus D, Wessel A, Bursch J. Propranolol treatment of congestive heart failure in infants with congenital heart disease: The CHF-PRO-INFANT Trial. International Journal of Cardiology. 2001; 79: 167–73.
10. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi P. Associations between neurohormonal and inflammatory activation and heart failure in children. Am Heart J. 2008; 155:527–33.
11. Ross RD. The Ross Classification for Heart Failure in Children after 25Years: A Review and an Age-Stratified Revision. Pediatr Cardiol. 2012; DOI 10.1007/s00246-012-0306-8.
12. Auslender M. New drugs in the treatment of heart failure. Progress in Pediatric Cardiology. 2000; 12:119-124.
13. Brunner-La Rocca HP, Vaddadi G, Esler MD. Recent insight into therapy of congestive heart failure: focus on ACE inhibition and angiotensin-II antagonism.JACC.1999; 33(5): 1163–73.
14. Cichoka E, Kawalec W, Januszewicz P, Wyszynska T. The effect of ACE inhibition on left ventricular function and structure in hypertensive adolescents. J Hypertens. 1994; 12:143.
15. Grenier MA, Fioravanti J, Truesdell SC, Mendelsohna AM, Vermiliona RP, Lipshultz SE. Angiotensin-converting enzyme inhibitor therapy for ventricular dysfunction in infants, children and adolescents: a review. Progress in Pediatric Cardiology.2000; 91:111-12.
16. Watanabe M, Kawaguchi H, Onozuka H ,et al. Chronic effects of enalapril and amlodipine on cardiac remodeling incardiomyopathic hamster hearts. J Cardiovasc Pharmacol. 1998; 32:248-59.
17. Wilkinson JD, Diamond M, Miller TL. The promise of cardiovascular biomarkers in assessing children with cardiac diseaseand in predicting cardiovascular events in adults. Progress in Pediatric Cardiology.2011; 32:25–34.
18. Buchhorn R, Ross RD, Hulpke-Wette M, Bartmus D, WesselA, Schulz R. Effectiveness of low dose Captopril versus Propranolol therapy in infants with severe congestive failure due to left-to-right shunts. International Journal of Cardiology.2000; 76:227–33.
19. Boucek MM, Chang R. Effects of Captopril on the Distribution of Left Ventricular Output with Ventricular Septal Defect Pediatric Research1988; 24: 499–503.
20. Boucek MM, Chang R, Synhorst DP. Renin-angiotensin II response to the hemodynamic pathology of ovines with ventricular septal defect. Circ Res. 1989; 64(3): 524-31.