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Original Article

Comparison of Captopril with Enalapril on Improvement of Systolic and Diastolic Heart Functions in Asymptomatic Patients Over 10 Years Old with Beta-Thalassemia Major

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Abstract

Background: Beta-thalassemia major is a severe and lethal hemolytic anemia. Regular transfusion is necessary for avoidance of its complications but it may end to cardiac involvement secondary to iron overload. Angiotensin converting enzyme inhibitors (ACEIs) are useful medications even in early stages of heart failure. We studied the effects of two common ACEIs on improvement of heart function in asymptomatic patients with beta thalassemia.

Methods: Of 300 patients over 10 years old with beta-thalassemia, 62 asymptomatic patients were divided into two groups. Captopril (1mg/kg/d in 2-3 divided doses) was started for patients in group one and enalapril (0.1 mg/kg once daily) was started for patients in group two. Six months later, systolic and diastolic parameters were assessed and compared with those before treatment with ACEIs in each group and after treatment between the two groups.

Results: In group one, left myocardial performance index, ejection fraction and fractional shortening were improved significantly **(**P<0.001). Decrease in peak atrial velocity and increase in early maximum filling velocity/atrial velocity (E/A) ratio of mitral valve were also significant (P=0.04 and P=0.01 respectively). In group two, a significant improvement in myocardial performance index, ejection fraction, and fractional shortening was seen compared with before treatment (P<0.001). Also peak early maximum filling velocity of mitral valve and peak atrial velocity of tricuspid valve were improved. Comparison of the two groups after treatment with ACEIs did not show any difference, although both of them showed significant improvement.

Conclusion: In patient with beta-thalassemia major early administration of ACEIs is recommended**.** Since the difference between the efficacy of captopril and enalapril was not significant, both drugs seem to be suitable in these patients.
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Keywords ● Major beta thalassemia ● iron overload ● heart insufficiency

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Introduction

Thalassemia was first described in 1925 by Cooley and Lee. George Whipple and William Bradford published few pathologic aspects of the disease in 1932. Whipple named it thalassic anemia or thalassemia.[1] Thalassemia is the most common genetic disorder worldwide.[2] Most patients with hemoglobin level 4 g% or less are in uncompensatory heart function state.[2]

Frontal bossing, bone deformities, organomegaly, hyperpigmentation of skin, spontaneous bone fracture, leukopenia, thrombocytopenia, infection, growth retardation, and bleeding are features of the disease.[3] To avoid these complications, regular blood transfusion is necessary.[2,3] Although blood transfusion decreases complications and increases survival, it leads to iron overload and deposition in the vital organs such as the heart.[2-4] In fact, organ degeneration secondary to iron deposition is the main cause of mortality in thalassemic patients.[5] Iron deposition in cardiac muscles leads to cardiomyopathy,[6] a disease of cardiac muscles with dysfunction.[7] Iron deposition in myocardium causes cardiac dysfunction in the late years of the first decade that renders diastolic dysfunction before systolic dysfunction. Angiotensin converting enzyme inhibitors (ACEIs) are effective medications that improve heart function.[8] Renin angiotensin-aldosterone system is activated in patients with heart insufficiency.

Angiotensin brings about heart failure severity by different ways. Growth factors activation that leads to intensive growth out of fibroblasts, cardiomyocytes, and myocardial fibrosis is one important effect of angiotensin that leads to left ventricular remodeling.[9]

Bengur et al. showed a significant increase in cardiac index and stroke volume in patients with dilated cardiomyopathy after captopril consumption.[7] Stern and colleagues also reported a significant decrease in end systolic and diastolic volume in patients with cardiomyopathy after captopril administration,[7] However, similar studies in pediatric patients are limited.[9] Compared with enalapril, captopril has been in use for a longer time and has been investigated more extensively. Enalapril is a newer drug, which has been less experienced in pediatric cardiology. Captopril is used three times daily while enalapril is used only once a day. Consumption of captopril concomitant with food can reduce its absorption from the gastrointestinal tract while this is not true with enalapril. Complications with the use of captopril are more common in comparison with enalapril.[10,11]

The aim of the present study was to compare the effects of captopril and enalapril on cardiac function in thalassemic patients older than 10 years old.

Subjects and Methods

This study was a double blind clinical trial. There are 1800 registered thalassemic patients in Sistan and Baloochestan province of Iran. Of these patients 650 have records in Special Diseases Center of Ali Asghar hospital of Zahedan and almost half of them are older than 10 years. In this group, those who were asymptomatic and had no apparent signs of heart disease were chosen. Patients with valvular heart diseases, hypertension, anemia, and renal or endocrine disorders were excluded from the study.

The patients with similar hemoglobin level, echocardiographic parameters, and cardiovascular physical examination, divided randomly into two groups. The study population in each group included 31 patients. Written informed consent was obtained from the parents. Physical examination, chest radiography, and electrocardiography were normal and primary echocardiographic parameters [left myocardial performance index (MPI), fractional shortening (FS), ejection fraction (EF), peak early maximum filling velocity (PEV), peak atrial velocity (PAV), early maximum filling velocity/atrial velocity (E/A) proportion, and deceleration time (DT)] were similar in the two groups. Packed cell transfusion interval and Desferal consumption were similar too. The mean age of the patients in group one was 13.7±3.8 years old, and in the patients in group two, it was 15.1±3.1 years old without significant difference (P=0.4). Group one, included 18 males and 13 females and group two, included 21 males and 10 females.

Captopril (1 mg/kg/day, 2-3 divided doses) was started for patients in group one and enalapril (0.1 mg/kg / once daily) was administered in another group. Captopril was manufactured by Daropakhsh factory (Iran) in the form of 25 mg tablets and enalapril was manufactured by the same factory in the form of 5 mg tablets. Six months later, the patients in the two groups were evaluated by echocardiography (Echo-challenge 7000 with transducer No.2.5, 3.5 and 5, Italy). Systolic and diastolic parameters (FS, EF, MPI, DT, Peak E and A-velocity - PEV, PAV - of mitral and tricuspid, and E/A proportions, and DT of mitral and tricuspid) were evaluated before and after treatment and compared between the two groups

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by *t* test using SPSS software version 11.

Results

Six months after treatment, MPI, EF and FS changed significantly in the two groups; (P<0.001) in group one and (P<0.001) in group two. The results have been shown in tables 1 and 2.

In group one, decrease in PAV and increase in E/A ratio of mitral valve were significant (P value= 0.04 and 0.01 respectively). Despite positive effects of captopril on the other diastolic parameters, the results were not statistically significant (table1). Table 2 shows the improvement of echocardiographic parameters in group 2 six months after treatment. Comparison of the two groups after 6 months revealed no statistically significant difference. The results have been shown in table 3.

Discussion

While in patients with beta-thalassemia major, diastolic function is primarily disturbed and leads to systolic dysfunction and heart failure,[12] evaluation of both systolic and diastolic functions are necessary. Because of iron deposition in myocardium, firstly restrictive cardiomyopathy is appeared even though systolic function is intact or minimally disturbed.[12] In diastolic dysfunction, PEV increases and DT will be short. These conditions are seen especially in early stage of cardiomyopathy in thalassemia and it is a marker for diastolic dys-

Table 1: Comparison of the effects of captopril on heart ventricular parameters before and after treatment (paired *t* test)**.**

	T	P value	mean Before treatment	mean after treatment	mean period difference
Left MPI	7.23	0.00	0.6187	0.5703	0.0484
Ejection fraction	- 12.16	0.00	57.9	61.4	-3.5
Fractional Shortening	-12.17	0.00	30.2	33.3	-3.1
PEV of mitral	1.13	0.27	98.4	92.8	5.6
PAV of mitral	2.1	0.04	54.1	49	5.1
Proportion of E/A (mitral)	-2.6	0.013	1.7	1.96	0.27
PEV of tricuspid	1.1	0.27	65.9	62	3.85
PAV of tricuspid	1.35	0.19	47.1	43.5	3.6
Proportion of E/A (tricuspid)	-0.13	0.90	1.45	1.46	0.01
DT of mitral	-1.8	0.08	124.2	132	-8.5
DT of tricuspid	1	0.30	142.8	135.6	7.3

MPI: Myocardial performance index, PEV: Peak early maximum filling velocity, PAV: Peak atrial velocity, E/A: Early maximum filling velocity/atrial velocity, DT: Deceleration time

Table 2: Comparison of the effects of enalapril on heart ventricular parameters before and after treatment (paired *t* test).

	T	P Value	mean Before treatment	mean after treatment	Mean period difference
Left MPI	10.1	0.00	0.61	0.57	0.004
Ejection fraction	-5.1	0.00	54.1	60.5	-6.4
Fractional Shortening	-4.6	0.00	28.4	32.7	-4.35
PEV of mitral	1.96	0.05	98.3	89.8	8.6
PAV of mitral	1.7	0.09	53.6	48.1	5.47
Proportion of E/A (mitral)	-0.43	0.66	1.87	1.92	-0.05
PEV of tricuspid	1.46	0.16	62.7	56.0	6.7
PAV of tricuspid	2.26	0.03	49.26	42.26	6.99
Proportion of E/A (tricuspid)	-1.0	0.29	1.28	1.37	-0.09
DT of mitral	-1.9	0.07	122.25	132.4	-10.1
DT of tricuspid	-1.1	0.28	122.0	127.9	-5.9

MPI: Myocardial performance index, PEV: Peak early maximum filling velocity, PAV: Peak atrial velocity, E/A: Early maximum filling velocity/atrial velocity, DT: Deceleration time

Table 3: Comparison of ventricular parameters between two studied groups 6 months after treatment (paired *t* test).

	T	P value	Mean in group 1 (Captopril)	Mean in group 2 (Enalapril)
Left MPI	-0.02	0.98	0.57 ± 14	0.57 ± 0.03
Ejection fraction	0.47	0.66	60.5 ± 8.2	61.4 ± 6.3
Fractional Shortening	0.44	0.64	32.7 ± 5.8	33.3 ± 4.6
PEV of mitral	0.7	0.5	89.8 ± 15.8	92.8 ± 18.5
PAV of mitral	0.3	0.76	1.92 ± 0.44	1.96 ± 0.47
Proportion of E/A (mitral)	0.4	0.09	56 ± 13	62.4 ± 14.5
PEV of tricuspid	0.5	0.63	0.57 ± 14	61.4 ± 8.2
PAV of tricuspid	1.35	0.19	42.3 ± 9.6	43.5 ± 10.8
Proportion of E/A (tricuspid)	0.9	0.4	1.4 ± 0.43	1.5 ± 0.31
DT of mitral	0.08	0.93	132.4 ± 19.2	132.8 ± 17.3
DT of tricuspid	1.8	0.07	127.9 ± 14.1	135.6 ± 18.6

MPI: Myocardial performance index, PEV: Peak early maximum filling velocity, PAV: Peak atrial velocity, E/A: Early maximum filling velocity/atrial velocity, DT: Deceleration time

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function.[12] The results of the present study showed that captopril and enalapril are effective on improvement of both systolic and diastolic functions. PAV and E/A proportion of mitral had a significant improvement after 6 months of treatment with captopril (P=0.04 for PAV and P=0.013 for E/A) (table 1).

PEV of mitral valve showed 6.5 m/s decrease (improvement) but it was not statistically significant. An improvement in PEV of tricuspid was also obvious (5.83 m/s decrease) but it was not statistically significant either. Despite no significant difference between PAV of tricuspid before and after treatment with captopril, this parameter had an improvement numerically. MPI, FS, and EF had improved significantly (table 1). In group two, systolic parameters had an obvious improvement (P<0.001). Except for MPI that is a representative for both systolic and diastolic functions in spite of positive effects of enalapril on diastolic parameters, only the effects on PAV of tricuspid (P=0.03) were statistically significant. Overall, enalapril affected systolic and diastolic functions (table 2). Sharp et al. showed a significant improvement of EF in patients with cardiac dysfunction treated by enalapril for 6 months.[13] Nicholas et al. showed positive effects of ACEIs on systolic function.[14] The effect of enalapril on systolic and diastolic functions in asymptomatic thalassemic patients has been studied, which revealed positive results.[12] The results of the present study, showed similar results.

Hirsch et al. described similar effects of captopril and enalapril on cardiac function.[9] Another study on the effects of captopril and enalapril in patients with heart insufficiency showed similar results.[15] Karl Josef Osterziel et al. also showed similar effects of captopril and enalapril on the improvement of heart function and hemodynamic.[16] Our study also showed that captopril and enalapril had similar effects on systolic and diastolic function improvement.

Based on the above studies, captopril and enalapril are effective on the heart function of patients with beta thalassemia but according to literature captopril is used three times a day but enalapril can be used only once a day. Consumption of captopril concomitant with food can reduce its absorption from the gasterointestinal tract while this is not true for enalapril. Complications with the use of captopril are more common and severe in comparison with enalapril.[10-11] so it might be concluded that enalapril may be better than captopril in pediatric patients, however further studies are needed to approve this conclusion.

Conclusion

Our study revealed that from eight studied diastolic parameters, six parameters improved in both groups; although only two parameters showed significant improvement. This can be due to some physiological factors. For example an increase in heart rate even in normal range (80±10 beats/min) causes significant increase in PAV and decrease in E/A without any effect on PEV. Inspiration also causes decrease in PEV and E/A of mitral without any change of PAV.[17] Control of these conditions is impossible during a clinical study especially in children.

Finally in order to early detection of cardiac dysfunction even in asymptomatic patients with thalassemia, serial echocardiography and prophylactic treatment with ACEIs are recommended.

This study showed that the differences between clinical beneficial effects of captopril and enalapril were not significant and both could be used similarly in patients with beta thalassemia major.

Conflict of Interest: None declared

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