

The effect of metoprolol succinate on the cardiac function of patients with thalassaemia cardiomyopathy: a double-blind randomised study

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ABSTRACT

Background Heart failure is the most common cause of mortality in β -thalassaemia major. However, the management of this disease, apart from chelation therapy, is largely empirical. Therefore, we decided to evaluate the effect of metoprolol succinate on patients with thalassaemia cardiomyopathy (TCM).

Materials and methods In this clinical trial, 45 patients with TCM were randomised to receive either metoprolol (n=26) or placebo (n=19). Echocardiography and a 6 min walk test were performed at baseline and repeated after 6 months and the values compared.

Results In the metoprolol group, left ventricular ejection fraction (LVEF) rose from 38.65% to 42.84% ($p<0.001$), while it decreased in the placebo group from 37.89% to 35.84% ($p=0.01$); the difference between the two groups was significant ($p<0.001$). Left ventricular (LV) mass in the metoprolol group decreased from 154.31 to 144.26 g ($p=0.02$), while in the placebo group it increased from 174.32 to 200.15 g ($p=0.68$); the difference between the two groups was significant ($p<0.001$). End systolic volume (ESV) decreased in the metoprolol group from 42.19 to 36.73 cm³ ($p<0.001$) but increased from 47.37 to 57.42 cm³ in the placebo group ($p=0.144$); the difference between the groups was significant ($p<0.001$). No differences in exercise capacity or pulmonary capillary wedge pressure were seen between the two groups ($p=0.268$ and $p=0.535$, respectively).

Conclusions Metoprolol succinate as a β -blocker may have the potential to significantly improve systolic function in patients with TCM and reverse LV remodelling to the same extent as in other types of cardiomyopathy.

Trial registration number NCT01863173.

INTRODUCTION

Thalassaemia is one of the most common monogenic disorders internationally. It is estimated that about 5% of the world population carry globin variants.¹ β -Thalassaemia is the most frequent variant, affecting 1.5% of the global population.² β -Thalassaemia major (BTM) is the typical presentation in affected individuals and arises from either homozygous or compound heterozygous defects. It usually manifests during the first year of life and is fatal if not managed subsequently with regular blood transfusions and iron chelation therapy.^{1,2} Despite recent advances in the therapeutic management of BTM patients and the resulting increased survival, congestive heart failure (CHF), usually in the form of dilated cardiomyopathy, is still the primary cause of mortality,

accounting for 71% of deaths even in recent series.¹

The pathophysiology of cardiomyopathy in patients with BTM is complex and not yet completely understood (volume or iron overload alone are not sufficient to explain the entire process) but varying combinations of the above-mentioned factors interact to produce a unique cardiomyopathy called thalassaemia cardiomyopathy (TCM).^{1,3–5} Fortunately, the outcome for patients with CHF has improved dramatically in recent years. In 1964 half of all patients with CHF died within 3 months of diagnosis, but 5-year survival is now 48%, which is comparable with other types of heart failure.^{1,5–7} The observed improvement in survival is attributed to frequent blood transfusions and intensive chelation therapy. Although chelation therapy is effective in preventing TCM and improving survival once heart failure is established, it is less effective when the patient becomes symptomatic and even after sufficient chelation, no firm evidence of reverse left ventricular (LV) remodelling has been yet demonstrated.^{5,8–10} Some studies have noticed abnormal heart structure in the majority of patients even after intensive chelation due to the effects of fibrosis and hypertrophy.⁵ Despite the well-established role of blockers of angiotensin, aldosterone and β -adrenergic pathways in the management of patients with ischaemic and non-ischaemic cardiomyopathies, only a minority of patients with TCM are currently using β -blockers.^{5,7,9,11}

In light of the lack of data on the efficacy of β -blockers in the management of TCM, we decided to perform a randomised clinical trial study to evaluate the effect of the long-acting β -blocker agent metoprolol succinate on the cardiac systolic and diastolic function and symptoms of patients with TCM.

MATERIAL AND METHODS

Patient selection

From January 2012 to May 2012, all patients with BTM referred to the thalassaemia clinic of Shahid Dastgheib Hospital, Shiraz were interviewed. The diagnosis of BTM was based on clinical evaluation and confirmed by a complete blood count and haemoglobin electrophoresis. All patients were receiving regular blood transfusions and iron chelation therapy. A total of 63 patients with documented left ventricular ejection fraction (LVEF) $<50\%$ by echocardiography were identified and were included if they had shown no signs or symptoms of decompensated heart failure for at least the previous 4 weeks (hospitalisation for CHF, worsening



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lower extremity oedema, worsening dyspnoea on exertion, and orthopnea), did not have acute myocarditis, and had a haemoglobin level >7 g/dL. Exclusion criteria were a pulse rate <60 /min, systolic blood pressure <90 mm Hg, evidence of peripheral vascular disease, major depression, a history of asthma, a PR interval >240 ms, second or third degree AV block, and major diseases including diabetes mellitus requiring insulin injection, hypothyroidism, hypoparathyroidism, chronic renal failure (glomerular filtration rate <30 mL/min), hepatic cirrhosis, hepatitis B and hepatitis C, a positive HIV test, and other haemoglobinopathies. All patients received diuretics and ACE inhibitors.^{11–13}

Study design

This study was approved by the Ethical Committee of Shiraz University of Medical Sciences under agreement CT-P-91-3502. Five of the 63 patients with LVEF were excluded due to insulin dependent diabetes, seven due to severe or uncontrolled CHF, three due to refusal to enter the study, one due to hepatitis and one due to hypothyroidism, leaving 45 patients for inclusion in the study. Written informed consent from the patients or their caregivers was obtained. All patients underwent a complete transthoracic echocardiography examination with tissue Doppler using a Siemens Acuson CV 70 machine (Siemens Medical Solutions, Issaquah, Washington, USA) according to published guidelines and recommendations. LVEF was recorded using Simpson's method and tissue Doppler data were recorded from the septum medial to the mitral valve annulus.^{5 10 14–16} Thereafter, a 6 min walk test (6MWT) was performed according to published protocols under the supervision of a trained nurse.^{17 18} The patients were then randomly assigned to receive either metoprolol succinate (MetoHexal Retard, 47.5 mg tablets; Hexal, Holzkirchen, Germany) or placebo (provided by the Department of Pharmacology, School of Medicine, Shiraz University of Medical Sciences). Randomisation was carried out by a trained nurse blinded to the patient's data who randomly selected a card labelled 1 or 2, thereby allocating the patient to the therapy or placebo group. There was a 2-month dose titration period during which the patients attended a cardiologist unaware of the patient's allocation once every 2 weeks; if the patient showed no evidence of decompensated heart failure (worsening lower extremity oedema, dyspnoea or orthopnea) and no side effects of β -blocker therapy (symptomatic hypotension, symptomatic bradycardia), the medication was titrated upwards to a maximum dose of 95 mg/day (about 2 mg/kg body weight). After this initial 2-month stage, the patients continued on the maximum medication dose for 4 months and visited their cardiologist once a month. At each visit the patients were provided with their monthly medication by the same nurse and compliance was checked by counting any remaining tablets. The patients were instructed to continue taking their previous routine medications including anti-failure therapy and attend their scheduled visits to the thalassaemia clinic. At the end of the 6-month period, the patients underwent transthoracic echocardiography by the same cardiologist who had performed the initial echocardiography and was blind to patient allocation and clinical course. Each patient then underwent a 6MWT in the same location and under the same protocol as previously. The patient's serum ferritin level before and after the study was also obtained from the thalassaemia clinic and is expressed as ng/mL in this study.

Statistical analysis

All data were analysed using SPSS v.15.0 (Chicago, Illinois, USA). Continuous data are presented as means \pm SD. The

independent t test was used to determine differences in the age of the participants in the two study groups and also differences in the continuous variables within groups before and after treatment. Fisher's exact test was used to determine differences between the genders of participants in the two study groups and the Mann–Whitney test to evaluate differences in measurements between the two groups after treatment. Pearson's correlation coefficient was used for correlation studies. A p value <0.05 was considered statistically significant for all tests.

RESULTS

Patient characteristics

A total of 45 patients with a mean age of 19.22 ± 6.24 years (range 6–43 years) consisting of 27 females (60%) and 18 males (40%) fulfilled the criteria for study inclusion and were randomised to the placebo (n=19) or metoprolol succinate group (n=26). The mean ages in the placebo and metoprolol groups were 19.53 ± 6.97 years and 19.00 ± 5.79 years, respectively, which were not significantly different ($p=0.78$). The placebo group consisted of nine females (47.4%) and 10 males (52.6%), while the metoprolol group consisted of 18 females (69.2%) and eight males (30.8%), which was not significantly different ($p=0.21$). There were also no differences between the two groups regarding other baseline characteristics (table 1), but there was a significant difference in their 6MWT distance at baseline (placebo: 242.50 ± 68.1 m vs metoprolol: 347.20 ± 69.2 m; $p<0.001$).

Patient compliance and side effects

All patients in the study group successfully completed the 6-month period of investigation. During the initial 2-month period, three patients in the metoprolol group and one patient in the placebo group experienced increased lower extremity oedema which was managed by raising their diuretics dosage; in two of these patients (one in each group) the oedema did not recur after downward titration of the diuretics dosage. All patients in the metoprolol group achieved the pre-specified maximum dose of 95 mg per day except for two patients with low bodyweight for whom 47.5 mg per day was considered sufficient. None of the patients experienced symptomatic bradycardia, and only two patients experienced symptomatic hypotension, which was successfully managed by decreasing the diuretics dosage. The ferritin level in the placebo group increased during the study from 2392.5 ± 1409.7 ng/mL to 2613.1 ± 1511.0 ng/mL, which was significant ($p=0.002$). The same increase was observed in the metoprolol group (from 3125.1 ± 2035.4 ng/mL to 3439.6 ± 2045.3 ng/mL; $p=0.003$).

Table 1 Comparison of baseline characteristics between the placebo and metoprolol group

	Placebo group	Metoprolol group	p Value
Age (years)	19.53 ± 6.97	19 ± 5.97	0.78
Weight (kg), mean (range)	44.8 (39–61)	45.5 (35–58)	0.84
Blood pressure (mm Hg), median (range)	100/70 (90–115/65–80)	105/75 (90–135/60–80)	0.4
Pulse rate per minute, mean (range)	95 (83–113)	93 (85–110)	0.78
Haemoglobin (mg/dL), mean (range)	8.5 (7.5–9)	8.3 (7–9.5)	0.63
Ferritin (ng/dL), mean	2392.5 ± 1409.7	3125.1 ± 2035.4	0.48
6 Min walk test (m)	242.5 ± 68.1	347.2 ± 69.1	<0.001

Table 2 Changes in LV mass, and systolic and diastolic function in the study groups

	Placebo group		Metoprolol group		p Value
	Before	After	Before	After	
LVEF (%)	37.89±5.08	35.84±5.26*	38.65±5.27	42.84±4.92**	<0.001
LV mass (g)	174.32±60.16	200.15±86.8*	154.31±41.29	144.26±39.6	<0.001
ESV (cm ³)	47.37±27.31	57.42±55.29	42.19±9.14	36.73±7.11**	<0.001
ESD (mm)	31.53±9.29	30.47±8.70	28.88±4.09	29.88±4.91	0.267
EDD (mm)	44.95±9.08	48.57±8.98*	42.85±6.11	44.03±6.19	0.268
S velocity (m/s)	0.150±0.035	0.138±0.038	0.138±0.037	0.142±0.038	0.067
Tei index	0.53±0.161	0.59±0.108	0.607±0.181	0.615±0.187	0.206
PCWP (mm Hg)	6.43±1.72	6.97±1.78	7.04±2.56	7.25±3.93	0.535
E velocity (m/s)	0.23±0.039	0.22±0.046	0.22±0.051	0.23±0.061	0.506
LA size (mm)	32.53±7.0	35.84±9.2	30.04±4.4	31.34±3.8	0.519

*p<0.05; **p<0.01.

EDD, end diastolic dimension; ESD, end systolic dimension; ESV, end systolic volume; LA, left atrium; LVEF, left ventricular ejection fraction; LV, left ventricle; PCWP, pulmonary capillary wedge pressure; S velocity, peak systolic velocity.

but the difference in ferritin level at the end of the study was not statistically significant between the two groups (p=0.379).

Exercise capacity

Three of the patients did not fully cooperate for the 6MWT and so their results were not recorded (two in the metoprolol group and one in the placebo group). At the end of the study, the patients in the placebo group had decreased exercise capacity (242.5±68.1 m vs 234.2±59.2 m), while those in the metoprolol group had a small but non-significant increase in exercise capacity as measured by the 6MWT (347.2±69.2 m vs 349.0±68.3 m), which was not significant (p=0.268).

LV mass, and systolic and diastolic function

As shown in table 2, there was a significant difference between the two treatment groups in terms of LVEF, LV mass and end systolic volume (ESV) (p<0.001). Systolic and diastolic function (other indices of LV mass) did not show significant differences at the end of the study.

Correlation study

A study was performed in the metoprolol group to detect any correlations between baseline characteristics and changes in LVEF, LV mass or ESV. As shown in table 3, the only significant and meaningful correlation was between initial ESV and final ESV and LV mass. A weak correlation was also found between peak systolic velocity (S velocity) and changes in ESV, but was not meaningful. No correlation was found between patient gender and changes in LVEF, LV mass or ESV (p=0.129, p=0.160 and p=0.644, respectively).

DISCUSSION AND CONCLUSION

As far as we know, this is the first study to evaluate the efficacy of long-acting metoprolol succinate in patients with TCM. In this randomised, double-blind, placebo-controlled clinical trial, we demonstrated the efficacy of metoprolol to favourably alter LVEF, LV mass and ESV in these patients. Moreover, the fact that the pre-specified maximum dose was reached in all patients and no patient discontinued the drug demonstrated its acceptable safety profile and satisfactory patient compliance.

It was first suggested in 1975 that β -blockade might be beneficial in patients with CHF.¹¹ Subsequent reports consistently confirmed this finding, demonstrating that although treatment with a β -blocker may initially have deleterious effects resulting

in myocardial depression, LVEF gradually rises after 3–6 months.^{11 19–21} β -Blockers along with ACE inhibitors are now the mainstay of CHF therapy.²² They reverse the process of LV remodelling, improve patient symptoms, reduce hospitalisation and prolong life.^{11 19–21}

Patient compliance

It is well documented that patients with BTM have reduced blood pressure because of chronic anaemia and decreased systemic vascular resistance and may not tolerate the hypotensive effects of drugs.²³ Moreover, worsening heart failure, especially in the first few days after initiation of a β -blocker, may result in non-compliance.¹¹ During the run-in period of the carvedilol heart failure study in the USA, seven deaths occurred and an additional 17 patients (1.4%) were not randomised because of worsening heart failure.¹¹ In another trial, seven of 56 patients died or could not tolerate the drug and an additional 37% had worsening heart failure while the dosage was being increased.¹¹ In a trial of carvedilol in TCM, only one patient out of eight tolerated an increasing dose of carvedilol, while others were

Table 3 Correlation coefficients between changes in LVEF, LV mass and ESV versus baseline characteristics of the patients in the metoprolol group

	Change in LVEF	Change in LV mass	Change in ESV
Age	−0.062	0.039	0.255
LVEF	−0.357	0.314	0.151
EDD	0.288	−0.046	0.256
LV mass	0.350	−0.332	−0.028
ESD	0.219	0.016	0.202
ESV	−0.129	−0.515**	−0.633**
E velocity	0.223	−0.137	−0.194
S velocity	0.054	−0.211	−0.434*
Tei index	−0.006	0.070	0.065
6MWT distance	−0.112	−0.074	0.188
LA mass	0.101	−0.297	−0.208
Ferritin level	0.261	−0.002	−0.0266

*p<0.05; **p<0.01.

EDD, end diastolic dimension; ESD, end systolic dimension; ESV, end systolic volume; LA, left atrium; LVEF, left ventricular ejection fraction; LV, left ventricle; 6MWT, 6-min walk test; PCWP, pulmonary capillary wedge pressure; S velocity, peak systolic velocity.

kept on the minimum dosage of the medication.²⁴ As carvedilol because of its α -blocking as well as β -blocking properties may cause profound hypotension especially in patients with TCM, we decided to use metoprolol succinate which has only selective β -blocking activity and good patient compliance.^{11 19–21} Only three patients (11.5%) experienced worsening lower extremity oedema, which was successfully managed by increasing the dosage of their diuretics. Interestingly, this complication did not recur upon downward titration of diuretics in two of three patients, which suggests that the phenomenon might only be temporary. During the study, only two patients (7.6%) developed symptomatic hypotension, which was successfully managed by lowering their diuretic dosage. No patients experienced symptomatic bradycardia. All these data suggest that metoprolol succinate, especially in the setting of TCM with low blood pressure, is well tolerated by patients, a finding suggested by earlier studies of metoprolol succinate.¹⁹

Effect on systolic function

TCM is a distinct type of cardiomyopathy with different opposing mechanisms exerting their effects on the myocardium. On the one hand, patients have chronic anaemia, leading to high cardiac output, dilated ventricles and a supernormal ejection fraction (EF), while on the other hand they have iron overload due to regular blood transfusions which leads to restrictive cardiomyopathy, pulmonary hypertension and finally systolic dysfunction.^{1 9 25–27} Although chelation therapy has improved survival in these patients, they still lag behind those with other types of cardiomyopathy.^{1 6} Moreover, it is unclear whether chelator agents reverse cardiomyopathy in these patients.⁹ In this study, we clearly demonstrated that metoprolol succinate compared with placebo not only protects against the progressive fall in LVEF but actually increases LVEF. It is well known that in patients with TCM, death is more common in those with LVEF <45% or a fall of >10% in LVEF in serial measurements compared with those with LVEF >45% or a fall of <10% in serial measurements.²⁸ Therefore, every attempt to increase and maintain the EF is valuable in patients with TCM. It was also demonstrated in this study that metoprolol improves LV contractility as evidenced by increased LVEF, and also favourably affects LV anatomical indices as evidenced by decreased LV mass and ESV in patients with TCM, which can be interpreted as a reversal of LV remodelling, an outcome only rarely reported in previous studies with dual intensive chelation therapy.⁹ Our study contradicts an earlier report which found that a β -blocker (carvedilol) was not effective in increasing LVEF in patients with TCM. However, in that study the maximum dose of carvedilol was not reached because significant hypotension developed in the majority of patients and the sample size was small (eight patients in the carvedilol group and six patients in the placebo group).²⁴ This highlights the importance of reaching the maximum tolerated dosage of medication, which seems to be more achievable with metoprolol than with carvedilol. In our study not all anatomical indices were favourably altered as shown by the lack of change in end diastolic dimension and end systolic dimension, which may be due to the lower sensitivity of these markers compared to LV mass and ESV.

Metoprolol was previously reported to increase LVEF and to have favourable effects on LV geometry in patients with other types of heart failure, but this is the first report of such outcomes in patients with TCM with its unique and distinct pathophysiology.^{11 19–21} Interestingly, this increase in LVEF was seen on the background of a significant increase in serum ferritin level during the course of the study. Although it is well known

that serum ferritin level may not accurately reflect myocardial iron levels, the significant increase of ferritin levels in both groups, associated with a decrease in LVEF in the placebo group, suggests that myocardial iron stores may have also increased during the study period.^{8 29} The reason for this increase is not known but is probably related to a shortage of chelator agents as implied by the high ferritin levels at baseline. This observation suggests that metoprolol may protect against cardiomyopathy even in the context of increasing iron overload, which is proposed as the main underlying factor of cardiomyopathy in patients with BTM.^{1 9 23} This observation if repeated in other studies may be very important for preventing the development of cardiomyopathy in patients with BTM. After we identified significant changes in LVEF, LV mass and ESV in the metoprolol group, we performed a correlation study between these parameters and the patients' baseline characteristics (table 2) but only found a negative correlation between baseline ESV and final ESV and LV mass, which might indicate that metoprolol has a larger effect in patients with lower initial ESV.

Although patients in the metoprolol group had a higher EF at the end of the study, the Doppler derived mitral annulus S velocity did not show significant improvement. Although S velocity is a sensitive measurement of systolic function and has good correlation with LVEF, it only represents longitudinal subendocardial fibres of the myocardium which are mainly affected by infiltrative diseases of the myocardium while LVEF is affected by changes in longitudinal and radial fibres. Therefore the improvement in LVEF might have been influenced by increased radial fibre contractility,^{30 31} which we might have been able to determine had we chosen to use echocardiographic strain imaging.

Effect on diastolic dysfunction

In our study, diastolic function slightly and non-significantly worsened in both treatment groups although there was a trend toward less deterioration in the metoprolol group. In contrast, an earlier study of carvedilol in TCM patients revealed an improvement of diastolic function in the carvedilol group compared with placebo.²⁴ In our study we selected E velocity, pulmonary capillary wedge pressure and left atrium (LA) mass as markers for diastolic function, while the study of Ajami *et al* used changes in the proportion of early and late transmitral flow velocities even though tissue Doppler velocities did not show significant improvement. In another study of metoprolol in patients with non-thalassaemic cardiomyopathy, although metoprolol significantly improved systolic function, no such improvement was noted for diastolic function.¹¹ There are several reasons why it is unclear whether or not metoprolol protects against diastolic dysfunction. First, study duration is generally limited to a few months and may not be long enough for improvements in diastolic function to become apparent as systolic function seems to be more sensitive to heart failure management in clinical trials. Second, different studies have considered different parameters for diastolic function, but the advent of more sensitive markers of diastolic dysfunction may result in improvements. Third, multiple mechanisms may be responsible for the diastolic dysfunction of patients with TCM and these should be addressed separately; while serum iron level normalises during chelation therapy and systolic function improves, diastolic dysfunction persists, emphasising the need for more research into the pathophysiology of TCM.^{5 32} Fourth, sample size should also be considered as larger studies may reveal diastolic improvement not achieved with current study designs.

Limitations of the study

One of the limitations of our study is that we could not document any improvement in patients' symptoms in the metoprolol group. We used the 6MWT as an objective measure of patient's symptoms as recommended, but at the end of the study there was no significant difference between the two treatment groups.³³ It has been suggested that positive changes in the 6MWT are seen with cardiac resynchronisation therapy, positive airway pressure and following cardiac rehabilitation, but not after β -blocker or ACE inhibitor therapy, as was the case in our study.³⁴ As we did not record the New York Heart Association (NYHA) classification of patient symptoms, as this index is relatively subjective, we do not have an endpoint for symptom improvement in our study.

Conclusion

In this study we showed that metoprolol succinate compared with placebo increases LVEF, and decreases LV mass and ESV in patients with TCM, but there was no improvement in diastolic function or the 6MWT.

Contributors JK: main researcher, writing, design and data gathering; AZ: main researcher, writing and statistical evaluation; MK: co-operation with the haematology department and gathering the data of thalassaemia patients; SN: organising supply of the placebo and providing pharmacological guidance; MB: writing and design.

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Competing interests None.

Patient consent Obtained.

Ethics approval The Ethics Committee of Shiraz University of Medical Sciences approved this study under agreement CT-P-91-3502.

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