

A randomized controlled trial evaluating the effects of amlodipine on myocardial iron deposition in pediatric patients with thalassemia major

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Background: Mortality rates increase due to iron deposition in the cardiac muscles of thalassemia major (TM) patients. Iron overload cardiomyopathy could be treated with a combination therapy of an iron chelator and an L-type calcium channel blocker. We designed a randomized controlled study to assess the potential of amlodipine, alongside chelation, in reducing myocardial iron concentration in TM patients compared with a placebo.

Objectives: This study aims to estimate the change in myocardial iron concentration (MIC) determined by magnetic resonance imaging after 6 months of treatment with amlodipine, as well as measuring the changes in the secondary outcomes (liver iron concentration (LIC), serum ferritin level (SF), and left ventricle ejection fraction (LVEF)) of study participants.

Methods: A single, randomized, placebo-controlled trial was performed in 40 β -Thalassemia major patients aged between 6 and 20 years old, who received either oral amlodipine 2.5–5 mg/day or a placebo, in addition to a Deferasirox chelation regimen in a 1:1 allocation ratio.

Results: After 6 months, a significant reduction was noted in the MIC of patients receiving amlodipine ($n=20$), compared with the patients receiving the placebo ($n=20$). At baseline, the mean was 0.76 ± 0.11 mg/g dry weight, while at 6 months, the mean was 0.51 ± 0.07 mg/g dry weight ($p<0.001$). Also, there was a significant change in the myocardial T2* after 6 months; the amlodipine increased the myocardial T2* from 40.63 ± 5.45 ms at baseline to 43.25 ± 5.35 ms ($p<0.001$). However, amlodipine did not significantly affect the secondary outcomes by the end of the study.

Conclusion: The addition of amlodipine to the standard chelation therapy in transfusion-dependent thalassemia major patients improves myocardial iron overload without increasing the adverse effects.

Keywords: thalassemia major, amlodipine, magnetic resonance imaging, myocardial iron concentration

Introduction

Thalassemia syndromes are a heterogeneous group of hemoglobin disorders which exhibit decreased or absent production of normal globin chains.¹

Chronic hemolytic anemia results from a defect in hemoglobin synthesis, which leads to the reduced synthesis of β -globin chains. Hemolytic anemia is characterized by its severity, its development during the first year of life and its requirement of life-long transfusion therapy.² This hemoglobin disorder leads to β -Thalassemia, one of the most common inherited blood disorders of thalassemia births.¹ Two clinical forms of β -thalassemia have been distinguished, depending on clinical severity: thalassemia major

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and thalassemia intermedia. β -Thalassemia major is the typical phenotype, arising either from homozygous or compound heterozygous defects.^{3,4} Transfusion-dependent Thalassemia patients receive more iron than is normal. This iron accumulation causes damage to various body organs, mainly the heart, which is very sensitive to iron toxicity,⁵ but also the liver and endocrine organs.⁶ Heart failure due to myocardial siderosis is a result of the heart tissues' slow removal of excess iron.^{7–10} this is the major cause of death in transfusion-dependent thalassemia major patients.⁷

Therefore, myocardial iron measurement is an important step in determining the risk of cardiac complications.¹¹ and in tailoring the appropriate iron-chelation treatment for transfused thalassemia major patients.^{4,12} Cardiac T2* magnetic resonance imaging (MRI), using an intense magnetic field, can successfully assess iron deposition in cardiac muscles. The values derived from "T2*MRI" are inversely proportional to tissue iron levels. Most recorded cases of heart failure in thalassemia patients to date have occurred in patients with very low T2* values.^{11,13,14} In particular, myocardial T2* values less than 20 milliseconds (ms) indicate cardiac iron overload, while in severe cardiac iron overload, the T2* value is less than 10 ms.^{4,15} Subsequently, the accuracy and reproducibility of T2*MRI measurements are important for the management of patients with iron overload cardiomyopathy.

Despite the availability of iron chelation therapy, iron-mediated cardiac toxicity remains the leading cause of death in thalassemia major patients¹⁶ Although intense chelation can help many patients, depletion of the cardiac iron burden often takes years and mortality is high with incomplete compliance.¹⁷

Myocardial iron overload occurs when transferrin becomes saturated and iron is free rather than being regulated by transferrin-mediated uptake mechanisms under normal iron homeostasis.¹⁸ Previous studies in mice demonstrated that calcium channel blockers could be a means to remove iron from cardiac muscles.^{19–21}

Amlodipine (AML) is a dihydropyridine calcium channel blocker that competitively inhibits the calcium channel to prevent calcium influx into the cell²² Its antioxidant property has been proven in various studies.^{23,24} fortunately, it is available at an affordable price that allows maximum compliance, which makes the drug highly suitable for our study. It is an orally administered drug with a known safety profile in both children and adults.

Amlodipine's pharmacokinetic properties differ from the other nondihydropyridine CCBs, since amlodipine

has a long half-life (35–50 hr.) compared with verapamil (3–7 hrs) or nitrendipine (2–5 hrs). The long half-life of Amlodipine decreases the time between dosage intervals and minimizes the large differences in peak to trough plasma concentration for a longer time.²⁵

A limited number of human studies have shown a significant reduction in MIC after using amlodipine.^{26–28} Hence, we conducted a randomized, controlled-placebo study to demonstrate the efficacy of amlodipine, in addition to chelation therapy, in reducing myocardial iron concentration.

Methods

The study was designed as a single center, prospective randomized, placebo-controlled trial with allocation of a 1:1 ratio. The study was carried out in Beni-Suef University Hospital, Egypt. Thalassemia is prevalent in this city, as it serves neighboring villages where the disease is also common. Ethical committee approval (Ethical committee code: FWA00015574) and written informed consent from parents or caregivers were obtained before the start of the study. The clinical trial registry number is PACTR201902478249291. The trial was conducted in accordance with the Declaration of Helsinki.

Patients eligible for enrollment at baseline were male or female aged between 6 and 20 years old with β -Thalassemia major. Potential participants had been diagnosed with thalassemia major (TM), due to the presence of microcytic hypochromic anemia and hemoglobin electrophoresis. Additionally, patients who had been receiving regular blood transfusions during the past two years, with a serum ferritin (SF) level more than 1000 ng/ml, were also considered. Participants were excluded if they were more than 20 years old, their SF was less than 1000 ng/ml, they experienced heart failure (ejection fraction (EF) less than 30%), they were contraindicated to undergo the MRI scan, or they were expected to change their chelation therapy regimen during the next 6 months.

Patients were invited to participate during a visit to the outpatient hematology clinic at Beni-Seuf University Hospital (BUH). Once they met the inclusion criteria and signed the consent form, blood samples were collected for hematological and chemical analysis, and MRI scans were performed.

After doing the MRI scans and other laboratory tests, patients were allocated into either the iron chelator (Deferasirox) plus amlodipine group (Norvasc; Pfizer 2.5 mg/day for patients weighing less than 30 kg and 5 mg/day for patients weighing more than 30 kg)²⁵ or the iron

chelator Deferasirox placebo group (Exjade; Novartis 20–40 mg/kg/day) for 6 months.²⁹ The clinical pharmacist generated a computer list to randomly allocate the patients to either the drug or placebo group. The study medications were dispensed at each monthly visit and the patients were informed as to the group to which they were assigned.

Magnetic resonance imaging (MRI)

While all 40 TM patients were admitted to Beni-Suef University Hospital, the MRI scan were conducted at Al Kasr El-Aini Hospital, Egypt, where a four-element cardiac phased-array coil was used. Scans were synchronized to the cardiac cycle using standard ECG gating, according to a specific protocol for the measurement of heart T2*, liver T2*, MIC, and LIC.¹⁵

Participants were asked to take a single breath and hold it while a single 10 mm mid-ventricular slice was placed precisely mid-point between the base of the short axis and the head of the left ventricle (TE=2.6–18.8 ms, with 2.02 ms accretion).

For T2* and MIC analysis, a homogeneous full-thickness region of interest (ROI) was chosen in the septum.³⁰ The signal intensity of this region was measured for each of the images and the data were plotted against the TE to form an exponential decay curve. Cut-off points in this MRI instrument are as follows: Cardiac: normal >20ms, mild: 14–20 ms, moderate: 10–14 ms, severe <10 ms; Liver: normal >6.3 ms, mild: 2.8–6.3 ms, moderate: 1.4–2.7 ms, severe <1.4 ms.¹²

The analysis was carried out on a PC using Thalassaemia-Tools software. The measurements of the heart T2* and MIC were done according to the protocol developed by Carpenter et al,⁶ while the measurements of the liver T2* and LIC followed that of MW Garbowski.³¹

Serum ferritin

Serum was separated, labeled, and stored frozen at –20°C and was measured by micro-particle enzyme immunoassay (Abbott AXSYM System).

Efficacy assessment

The primary trial endpoint was the change in the MIC and cardiac T2* after 6 months in either the placebo or treatment group. Efficacy data were analyzed as changes from core baseline to month 6.

However, we considered the drug effective if there was a change in the MIC, rather than the T2*, after the publication of a study done by Carpenter et al which showed a nonlinear correlation between T2* and MIC.⁶ The use of

both MIC and LIC allow for a precise measurement of the iron concentration in the tissues.^{29,32}

The secondary trial endpoint noted potential changes in the LIC, liver T2*, SF, and LVEF after 6 months of treatment in either group.

Safety assessment

Participants and their parents were informed of the expected side effects of amlodipine, such as edema, dizziness and swollen ankles. Participants in both groups were monitored for adverse effects by a complete blood count (CBC) and physical examination during their routine visits to the hematology clinic. A minor change in the chelation therapy regimen was allowed during the study, particularly for participants with excess iron concentration. Participants were also educated about the importance of compliance with the medication.

Statistical analysis

Using G*Power software version 3.1.9.2 (Post hoc detection of power), we conducted a one-sided two sample Wilcoxon-Mann-Whitney *t*-test using the major variables. We calculated a sample size of 20 in each group (Amlodipine and placebo) achieving nearly 100%, depending on effect size, with a significance level (α) of 0.05, normality of data and 2-tailed analysis.

All the data were expressed as mean \pm SD, with differences among the groups from baseline to 6 months compared for all continuous parameters. Independent *t*-tests were performed for the parametric variables and a Mann-Whitney test for the non-parametric variables (particularly MIC, serum ferritin, LIC, liver T2*, myocardial T2*). The respective changes in the MIC, LIC and serum ferritin within each group were not normally distributed, so we compared them using the Wilcoxon rank test and paired sample *t*-test for the normally distributed parameters. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) computer software (version 22), IBM software, USA. Differences were considered statistically significant at $p < 0.05$.

Results

The baseline demographic and clinical characteristics

The baseline demographic characteristics showed no significant differences between the amlodipine and the placebo groups, with the exception of the age at onset, liver

T2* and liver iron concentration (LIC), with more iron deposition found in the livers of the placebo group patients (Table 1). Cardiac iron overload defined by $T2^* \leq 35$ ms ($MIC \leq 0.59$ mg/g)^{33,34} was observed in 50% of both the amlodipine and placebo group members at baseline. Patients flow-through is shown in Figure 1.

The initial MIC showed no statistically significant differences in the patients allocated to placebo or amlodipine treatment, with a mean \pm SD of 0.74 ± 0.11 mg/g vs 0.76 ± 0.11 mg/g, respectively ($P=0.87$). The clinical characteristics of the study patients are shown in Table 1.

Myocardial iron concentration

The addition of amlodipine to the standard chelator therapy showed a significant reduction in the MIC, from 0.76 ± 0.11 mg/g at baseline to 0.51 ± 0.07 mg/g after 6 months ($p < 0.001$) Figure 2. Also, a significant change in the myocardial T2* was noted after 6 months; the addition of amlodipine increased the myocardial T2* from 40.63 ± 5.45 ms at baseline to 43.25 ± 5.35 ms ($p < 0.001$) (Table 2).

The MIC significantly increased in patients receiving the placebo after 6 months of the trial, from 0.74 ± 0.11 mg/g to 0.8 ± 0.11 mg/g ($p < 0.001$). Additionally, the myocardial T2* significantly decreased, from 53.23 ± 6.61 ms at baseline to 52.99 ± 6.6 ms after 6 months ($p=0.009$) (Figure 3). The differences between the groups were significantly in favor of the amlodipine treatment group (Table 3).

Serum ferritin

The serum ferritin level did not change significantly in either of the two groups by the end of the study, measuring 1929 ± 421.06 ng/ml for the amlodipine group and 2759 ± 340.73 ng/ml for the placebo group ($p=0.925$).

Liver iron concentration

The absolute changes in LIC were not significant in either the placebo or the amlodipine groups. However, a significant difference was found in the relative liver T2* after 6 months, as the liver T2* decreased in the placebo group from a mean of 20.19 ± 2.21 ms to 20.00 ± 2.23 ms ($p=0.004$) (Table 4), while no significant change in the relative LIC was noted after 6 months.

Left ventricular ejection fraction

The mean \pm SD left ventricular ejection fraction remained stable and within the normal range after 6 months of treatment for both groups. The amlodipine group baseline measure was $62.28 \pm 0.79\%$, while at month 6, it was 62.40

$\pm 0.76\%$, an absolute change of -0.125 ± 0.64 ($p=0.398$). For the placebo group, the baseline was $63.40 \pm 0.55\%$, while at month 6, it was $63.10 \pm 0.57\%$, with an absolute change of 0.3 ± 1.12 ($p=0.249$).

Adverse effects

A significant difference was noted between the amlodipine and placebo groups regarding side effects. More patients in the placebo group experienced gastro-intestinal (G.I) upset—a total of 14 patients (70%) compared to six patients (30%) in the amlodipine group. Four (20%) of the amlodipine participants complained of dizziness and 3 (15%) experienced swollen ankles. No cases of palpitation or hypotension were reported in the treatment group (Figure 4).

Minor changes in chelation therapy were allowed during the study, particularly for patients with severe iron overload or those who experienced side effects from the treatment. This consisted of minor adjustments in the Deferasirox dose. No patients switched to other chelators during the 6 months of the study.

Discussion

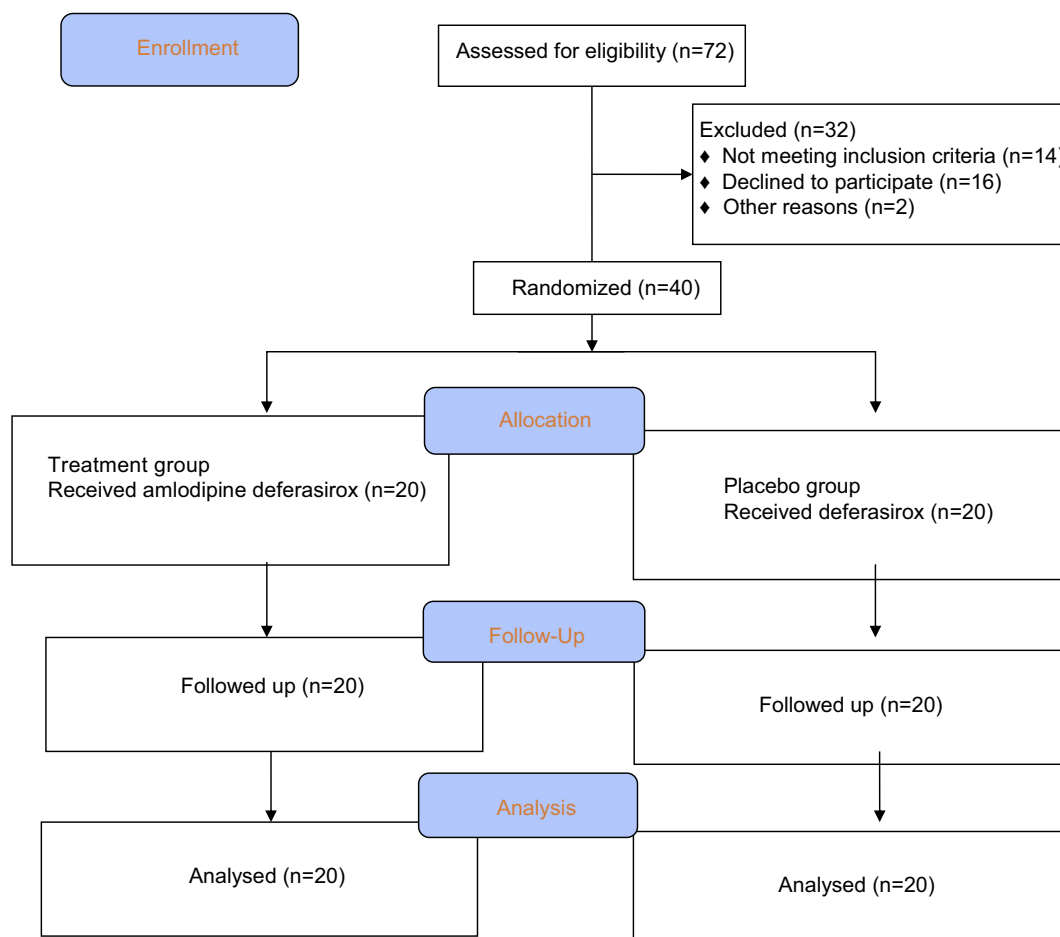
Cardiomyopathy resulting from iron overload is still a common cause of morbidity and mortality in transfusion-dependent TM patients.^{2,35} Despite treatment with the most commonly used iron chelators and regular blood transfusions, a significant proportion of β -TM patients have myocardial iron loading. Moreover, chronic iron overload can lead to several diseases, including cirrhosis, diabetes, neurodegenerative disease, and endocrine disorders³⁶ Therefore, a logical step toward reducing cardiac mortality is optimizing the treatment of myocardial siderosis.

In this study, we found that the addition of oral Amlodipine to the standard chelation therapy reduced the myocardial iron concentration in transfusion-dependent thalassemia major patients. This combination is more effective than iron chelators alone. After 6 months of treatment, the myocardial iron concentration decreased significantly (p -value < 0.001). This is explained by the mechanism of iron uptake in the heart tissues, which is mediated by the L-type calcium channels. The relative improvement of MIC in the amlodipine patients was consistent with a previous study by Fernandes et al (2016), also indicating a significant reduction in the MIC and improvement in the heart T2* after treatment with amlodipine in 57 patients older than 6 years of age.^{26,37}

Table 1 Baseline demographic and clinical characteristics

Variable		Placebo	Amlodipine	Base line characteristic	
				t. or z or X ² values	P-value
Age (years)		13.40±1.01	12.50±1.02	<u>0.627</u>	0.535
Weight/kg		38.08±2.53	36.23±2.80	<u>0.490</u>	0.627
Height/m		1.39±0.03	1.35±0.04	<u>0.888</u>	0.380
Pretransfusional.Hg (g/dl)		7.47±0.37	7.24±0.27	<u>0.510</u>	0.613
No. of blood transfusion/life		159.85±15.16	181.90±17.46	<u>0.953</u>	0.346
Deferasirox dose mg/kg/day		1151.25±111.72	1200.00±115.21	<u>0.304</u>	0.763
BMI		19.17±0.61	19.48±0.72	0.027	0.978
Age at onset (months)		12.85±2.37	8.25±1.41	2.032	0.042
Duration of disease (years)		12.39±1.03	11.91±1.02	0.352	0.725
Gender	Male	9 (45%)	8 (40%)	<i>0.102</i>	0.749
	Female	11 (55%)	12 (60%)		
Splenectomy	No	18 (90%)	17 (85%)	<i>0.230</i>	0.632
	Yes	2 (10%)	3 (15%)		

Note: The italic numbers are X². The underlined values refer to the t-test. The other numbers are z values.

**Figure 1** Consort diagram detailing the study subjects.

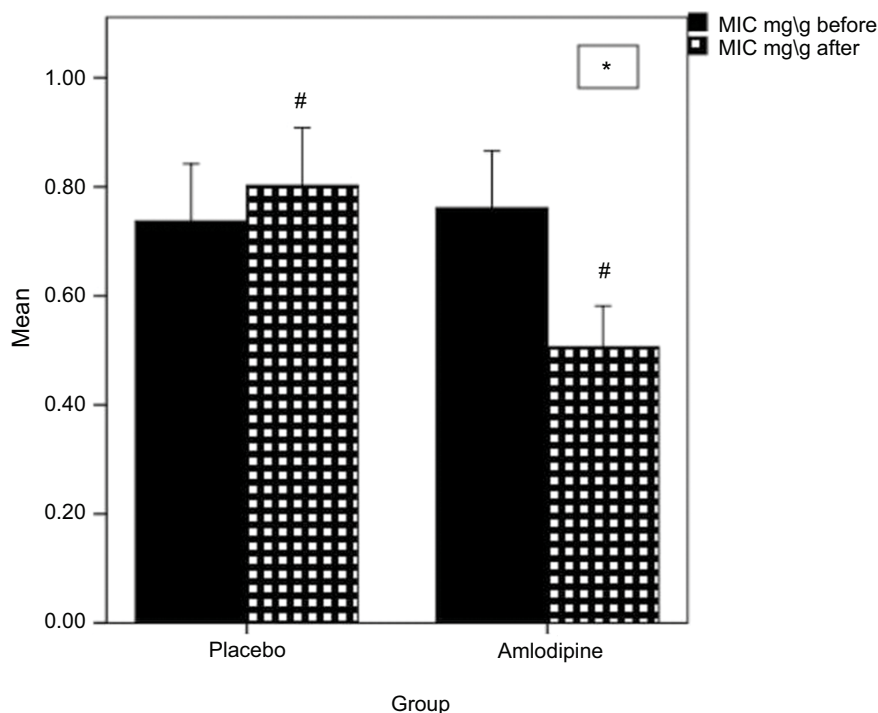


Figure 2 Mean change in MIC.

Note: *Significantly different from placebo (significant difference between Amlodipine and placebo). #Significantly different from before or baseline (significant difference between before and after).

Table 2 Comparison between placebo and amlodipine in before (Base line characteristics) and after treatments

Variable	Placebo	Amlodipine	t. or z values	P-value	Amlodipine + or – by % regarding Placebo
S.F before, ng/ml	2752.20±342.47	2949.85±420.90	0.027	0.978	7.18
S.F after, ng/ml	2759.00±340.73	1929.00±421.06	0.095	0.925	-30.08
Liver T2* before, ms	20.19±2.21	35.25±5.57	2.340	0.019	74.59
Liver T2* after, ms	20.00±2.23	35.38±5.59	2.381	0.017	76.90
MIC before, mg/g	0.74±0.11	0.76±0.11	<u>0.162</u>	0.872	2.70
MIC after, mg/g	0.80±0.11	0.51±0.07	<u>2.282</u>	0.028	-36.25
LIC before, mg/g	2.74±0.34	1.64±0.55	3.395	0.001	-40.15
LIC after, mg/g	2.77±0.34	1.63±0.55	3.423	0.001	-41.16
Myocardial T2* before, ms	53.23±6.61	40.63±5.45	1.894	0.058	-23.67
Myocardial T2* after, ms	52.99±6.60	43.26±5.35	1.447	0.148	-18.36
LVEF before,%	63.40±0.55	62.28±0.79	<u>1.171</u>	0.249	-1.70
LVEF after, %	63.10±0.57	62.40±0.76	<u>0.737</u>	0.466	-1.11

Note: The underlined values refer to the t-test. The other numbers are z values.

Abbreviations: MIC, myocardial iron concentration; LIC, liver iron concentration; MRI, magnetic resonance imaging; ms, milliseconds; SF, serum ferritin; LVEF, left ventricle ejection fraction.

In addition, our results revealed a significant improvement in myocardial T2* after treatment with amlodipine, from 40.63±5.45 ms at baseline to 43.26±5.35 ms. This finding is in accordance with the recent work by Eghbali et al, which indicated that myocardial T2* significantly changed after 1 year of treatment, from 21.9 ms to 24.5 ms.²⁸ Another study conducted by Fernandes et al (2014) found an increase

of 30% in the myocardial T2* after 1 year of treatment with amlodipine.^{27,37}

However, no change was noted in the LIC and hepatic T2* after 6 months of treatment with amlodipine. We suggest this is due to the fact that iron deposition in the liver tissues does not depend on active uptake by voltage-gated calcium channels; therefore, blocking or opening the calcium channels would not

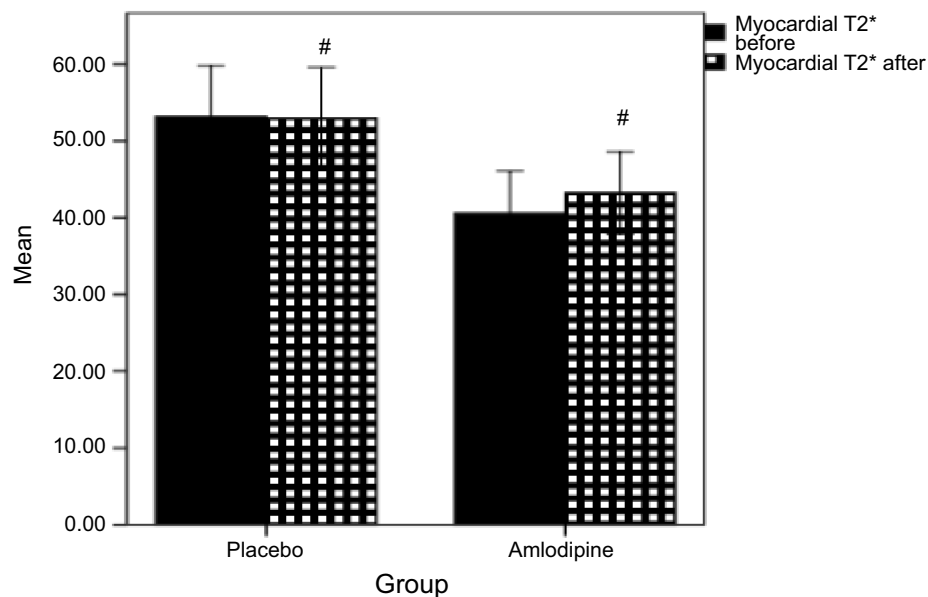


Figure 3 Mean change in Myocardial T2*.

Note: *Significantly different from placebo (significant difference between Amlodipine and placebo). #Significantly different from before or baseline (significant difference between before and after).

Table 3 Outcomes at 6 months (Amlodipine group)

Variable	Before	After	t. or z values	p-value	After + or – by % regarding base line
MIC mg/g	0.76±0.11	0.51±0.07	<u>7.532</u>	<0.001	–32.8947
Myocardial T2* MRI, ms	40.63±5.45	43.26±5.35	3.811	<0.001	6.473,049
LIC, mg/g	1.64±0.55	1.63±0.55	1.123	0.261	–0.61
Hepatic T2* MRI, ms	35.25±5.57	35.38±5.59	1.427	0.154	0.37
SF, ng/ml	2949.85±420.90	1929.00±421.06	1.364	0.172	–34.6068
LVEF,%	62.28±0.79	62.40±0.76	<u>0.865</u>	0.398	0.19

Note: The underlined values refer to the t-test. The other numbers are z values.

Table 4 Outcomes at 6 months (placebo group)

Variable	Before	After	t. or z values	p-value	After + or – by % regarding base line
MIC, mg/g	0.74±0.11	0.80±0.11	<u>4.429</u>	<0.001	8.108,108
Myocardial T2* MRI, ms	53.23±6.61	52.99±6.60	2.599	0.009	–0.45,087
LIC, mg/g	2.74±0.34	2.77±0.34	1.1312	0.190	1.094891
Hepatic T2* MRI, ms	20.19±2.21	20.00±2.23	2.917	0.004	–0.94,106
SF, ng/ml	2752.20±342.47	2759.00±340.73	0.946	0.344	0.247,075
LVEF, %	63.40±0.55	63.10±0.57	<u>1.189</u>	0.249	–0.47,319

Note: The underlined values refer to the t-test. the other numbers are z values.

Abbreviations: MIC, myocardial iron concentration; LIC, liver iron concentration; MRI, magnetic resonance imaging; ms, milliseconds; SF, serum ferritin; LVEF, left ventricle ejection fraction.

affect the iron uptake into the liver tissue. This is in accordance with the studies done by Fernandes et al (2016) and Eghbali et al (2017).^{26,28}

Although no significant change was found in the serum ferritin level by the end of the study, the median of SF was kept below 2500 ng/ml, which is associated with increased morbidity and mortality.^{38,39} Thus, the serum ferritin level

is not a good indicator of myocardial iron deposition. This is supported by many previous studies which have demonstrated a weak correlation between plasma ferritin levels and cardiac T2*MRI.^{12,40}

Only 12.5% of our patients underwent a splenectomy. This low rate may be due to the early diagnosis of the disease and the availability of blood products in Egypt.

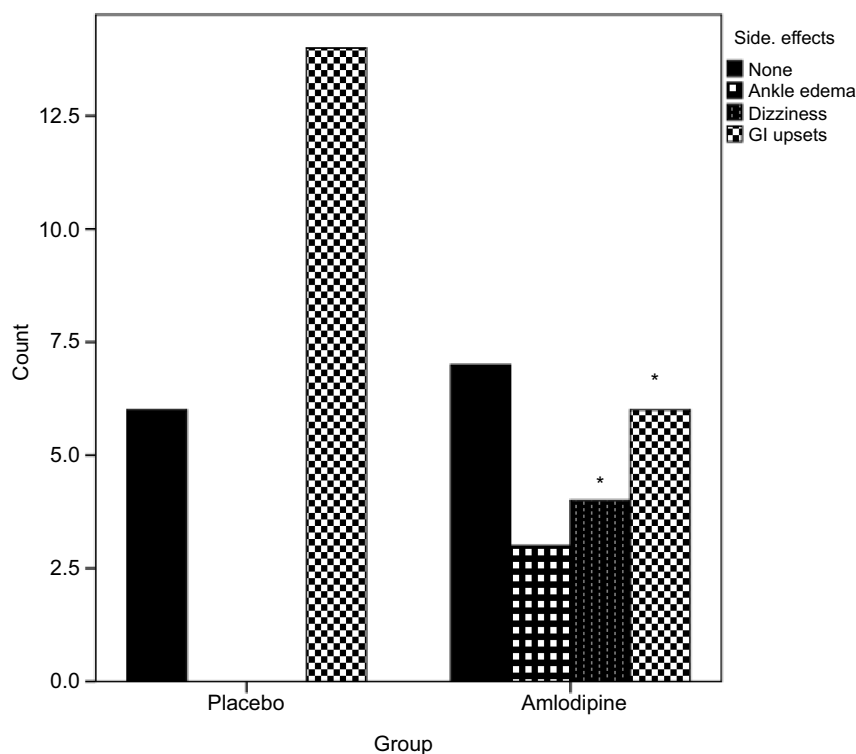


Figure 4 Untoward effects of treatments; gastrointestinal upset was the most common adverse effect in both groups*.

Note: *Significantly different from placebo (significant difference between Amlodipine and placebo).

In this study, the amlodipine had no serious adverse effects (Figure 4), which is consistent with the known safety profile of amlodipine in previous studies.^{41,42}

A limited number of clinical trials in our country have demonstrated the efficacy of amlodipine in reducing myocardial iron concentration. Therefore, this study focused on the efficacy of amlodipine on myocardial iron deposition in pediatric patients with thalassemia major in Egypt.

Study limitations

Although our findings indicated that the addition of amlodipine to the standard chelator therapy results in a significant reduction in the myocardial iron concentration, our study included a short observation period and a small sample size. The effects of long-term treatment with amlodipine and the use of different iron chelators should be assessed by other studies with larger sample sizes. Since the removal of the accumulated iron from heart tissues is a slow process, we suggest long-term controlled studies be established to strengthen the evidence demonstrating the clinical benefits of amlodipine alongside an iron chelation regimen.

We did not find any significant clinical change in the LVEF after six months of treatment with amlodipine. This

outcome may also require a longer-term study or the recruitment of patients with reduced ejection fraction from the start of the study.

Conclusion

In conclusion, it is clinically beneficial to add amlodipine to the standard chelation therapy in patients with transfusion-dependent thalassemia major, as the amlodipine results in a significant reduction in the myocardial iron concentration.

Disclosure

The authors report no conflicts of interest in this work.

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