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Comparison of the effects of calcium channel blockers plus iron chelation therapy versus chelation therapy only on iron overload in children and young adults with transfusion-dependent thalassemia: A randomized double-blind placebo-controlled trial

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Abstract

Background: Myocardial iron deposition is a significant cause of morbidity and mortality in patients with transfusion-dependent thalassemia (TDT). Amlodipine, L-type calcium channel blocker with regular chelation therapy may reduce myocardial iron overload. Lack of randomized trials prompted this study to assess the effect of calcium channel blocker (amlodipine) in combination with iron chelation therapy on iron overload in patients with TDT.

Methods: Sixty-four eligible patients were randomized to receive either amlodipine and chelation (group A) or chelation alone (group B) in double-blind placebo-controlled trial. Myocardial iron concentration (MIC) using T2* magnetic resonance imaging (MRI), liver iron concentration (LIC), left ventricular ejection fraction (LVEF), and serum ferritin were measured at baseline and 12 months.

Results: In the amlodipine group, mean cardiac T2* value significantly increased from 18.11 ± 8.47 to 22.15 ± 7.61 ($p = .002$) at 12 months, whereas in control group, there was a nonsignificant increase ($p = .62$) in cardiac T2* value from 19.50 ± 8.84 to 20.03 ± 9.07. There was a significant decrease in MRI-derived MIC in the amlodipine group compared to control group (1.93 ± 1.61 to 1.29 ± 0.90, $p = .01$). Changes in the LVEF ($p = .45$), MRI-derived LIC ($p = .09$), and serum ferritin ($p = .81$) were not significant between the two groups.

Conclusion: Amlodipine is safe and when combined with chelation therapy appears to be more effective in reducing cardiac iron overload than chelation only in children and young adults with TDT.

KEYWORDS
calcium channel blocker, chelation, iron overload, myocardial iron concentration, thalassemia

Abbreviations: LIC, liver iron concentration; LTCC, L-type calcium channel blocker; LVEF, left ventricular ejection fraction; MIC, myocardial iron concentration; MRI, magnetic resonance imaging; TTCC, T-type calcium channel blocker.

1 | INTRODUCTION

Thalassemia refers to a group of genetic disorders in which there is an imbalance between α-globin and β-globin chain production. Ineffective erythropoiesis is the hallmark leading to anemia, erythroid hyperplasia, and increased absorption of iron from the gut.[1] The combination of hemolysis, increased iron absorption, and repeated blood transfusions culminate in a state of iron overload. Myocardial iron deposition is a significant problem and major cause of morbidity and mortality in these patients.[2] Monotherapy and combination chelation therapy have been used to reduce iron deposition in different organs.[3] However, these measures may be insufficient to remove iron deposits in the tissues, especially in the heart. In vitro studies have demonstrated the role of L-type (LTCC) and T-type calcium channel (TTCC) blockers in uptake of iron by cardiomyocytes and reduction of myocardial iron overload by LTCC (nifedipine, amlodipine, verapamil) and TTCC blockers (efonidipine).[4,5] A pilot study carried out in patients with thalassemia major reported a significant reduction in serum ferritin levels with the use of amlodipine in conjunction with standard chelation therapy.[6]

There are studies from India that have used combination chelation therapy in patients with thalassemia major, but none in combination with amlodipine.[7,8] A double-blind placebo-controlled trial was planned to evaluate the efficacy and safety of a calcium channel blocker, amlodipine, in addition to standard chelation therapy in reducing iron levels in patients with thalassemia major. The primary outcome of the study was change in myocardial iron concentration (MIC) at 12 months from baseline as defined by T2* magnetic resonance imaging (MRI) values. Secondary outcomes were change in liver iron concentration (LIC) at 12 months as defined by T2*MRI values, change in serum ferritin levels at 6 and 12 months, change in left ventricular ejection fraction (LVEF) at 12 months from baseline, and adverse events at the initiation of study and 3, 6, and 12 months.

2 | PATIENTS AND METHODS

This randomized double-blind placebo-controlled trial was carried out in the thalassemia unit of the division of pediatric hematology oncology, department of pediatrics in collaboration with the department of radiodiagnosis and imaging and department of cardiology of a university teaching hospital in north India from June 2019 to October 2020. Study was approved by institute ethics committee. The study was registered with Central Trial Registry of India (CTRI) - CTRI/2019/06/019787.

Objective of the study was to assess the effect of amlodipine, LTCC blocker, in addition to the standard chelation therapy in reducing myocardial iron overload in patients with thalassemia major. We hypothesized that amlodipine plus chelation therapy is more efficacious than chelation therapy alone in reducing myocardial iron deposition in patients with thalassemia with iron overload. Patients with transfusion-dependent thalassemia (TDT) registered in the thalassemia unit were enrolled for the trial. Inclusion criteria were patients in the age group of 6–20 years with serum ferritin >1000 ng/ml, history of having received ≥10 transfusions, and being on stable chelation for >6 months. Exclusion criteria were patients with known congenital or acquired heart disease (valvular, cardiomyopathy), or significant renal disease (serum creatinine more than three times normal/estimated glomerular filtration rate [eGFR] <30 ml/min/m^2) or having hepatic disease (alanine transferase [ALT]/aspartate transferase [AST] more than three times upper limit of normal), or cardiac T2* value <4 milliseconds, and not willing to giving written informed consent.

2.1 | Calculation of sample size

In a pilot study done on 16 patients with thalassemia major where myocardial T2* value was estimated, T2* value of <20 milliseconds was observed in seven (43.8%) patients, implying increased myocardial iron. Remaining nine (56.2%) patients had myocardial T2* ≥20 seconds. We hypothesized that there would be 50% reduction in the incidence of myocardial iron overload with the use of intended drug (amlodipine) in the intervention arm.

Using a one-sided test for two proportions, with α error of 5%, power of study 80%, and level of confidence 95%, the sample size was calculated as 64. With a dropout rate of 5%, the final proposed sample size was 68. In 1:1 ratio, 34 patients were planned to be randomized into each arm.

2.1.1 | Randomization

Children fulfilling the inclusion criteria were randomized to one of the two groups (intervention vs. control group) using computer-generated randomization tables. The randomization sequence was prepared by an independent person. Allocation of children was done using serially numbered opaque and sealed envelopes.

2.2 | Intervention

2.2.1 | Intervention group (group A)

Children in this group received regular iron chelation and amlodipine (5 mg/day for ≥30 kg bodyweight and 2.5 mg/day for <30 kg bodyweight).

2.2.2 | Control group (group B)

Children in this group received regular iron chelation and placebo.

2.3 | Data collection

Eligible patients meeting the inclusion/exclusion criteria were recruited over a period of 6 months. Recruitment was done among

the patients who were registered in the thalassemia unit and were receiving regular blood transfusions. Each patient was randomized into either of the two groups. All patients were subjected to thorough clinical examination, including assessment of nutritional status. They underwent routine investigations, including complete blood count (CBC), renal function tests (RFT), liver function tests (LFT), thyroid function tests (TFT), electrocardiogram (ECG), etc. They had following specific investigations pertaining to the study:

1. MIC at baseline and at 12 months using T2*MRI.
2. LIC at baseline and at 12 months using signal-intensity ratios on gradient echo images.
3. Echocardiography for LVEF at baseline and 12 months.
4. Serum ferritin at baseline, 6, and 12 months.

2.4 | Magnetic resonance imaging (MRI)

MRI was done on a 1.5-T (Siemens Avanto, Erlangen, Germany) system. LIC was measured by the method developed by Gandon et al.[9] A set of five breath-hold gradient echo sequence with fixed TR and different TE and flip angles prescribed for 1.5-T scanner was used, and a free, online worksheet provided by University of Rennes was employed to obtain LIC.

Cardiac imaging was performed using body matrix coil and prospective ECG triggering. A short breath-hold coaching session was performed for each patient prior to the scan. Quantitative T2* relaxation maps (MapIt, Siemens Healthcare, Erlangen, Germany) were obtained in a single 10-mm midventricular short-axis view and four-chambered view using a single breath-hold gradient echo sequence with eight TEs (2.4–16 milliseconds). Acquisition time per slice was 8–12 seconds. The addition of a four-chambered sequence added less than 1 minute to the overall scan time. MRI of all patients was done by a single technician and analyzed by a single radiologist.

MIC was calculated from T2* using the equation MIC = 45.0 × (T2*)$^{-1.22}$, according to Carpenter formula.[10]

2.4.1 | Severity index

Grading	Cardiac T2* (ms)	MIC (mg/g)	LIC (μmol/g)
Normal	>20	<1.16	<36
Mild	15–20	1.16–1.65	36–126
Moderate	10–14	1.65–2.71	126–270
Severe	<10	>2.71	>270

2.5 | Serum ferritin

Values were obtained after sending adequate amount of pretransfusion blood sample in plain vial to central investigation laboratory where analysis was done by using ferritin-kit method.

2.6 | Two-dimensional echocardiography

ACUSON CV70 cardiovascular system (Siemens) was used for the assessment of LVEF. Biplane Simpson's method was used to quantify LVEF.

2.7 | Study drug: Amlodipine

Tablets of generic amlodipine were made available from Pradhan Mantri Jan Aushadhi Kendra (PMJK) located in the hospital and given to patients according to their weight (2.5 mg/day for children <30 kg and 5 mg/day for children ≥30 kg). Placebo was prepared in the Department of Pharmaceutics of the university. Both drug and placebo were dispensed in plain opaque envelopes by a third person. Both patients and treating physicians were unaware of the type of medication given to the patients.

Patients received care with regular blood transfusions and standard chelation therapy. Majority of the patients were receiving deferasirox, dose 20–40 mg/kg/day in single dose. Only two patients, one patient in each group, were receiving a combination of deferasirox and deferiprone (dose 75 mg/kg/day in three divided doses). The chelation drugs were available free of cost from the hospital supported by National Health Mission and compliance was very good. They had follow-up appointments as directed by the need for transfusions. They were checked for any kind of adverse effect of drugs (hypotension, abdominal pain, nausea, ankle edema, headache, flushing, palpitation, dizziness, somnolence, and cough) during the follow-up and also through phone calls, and managed accordingly.

2.8 | Statistical analysis

The statistical program SPSS version 16.0 was used for data entry and analysis. Independent sample *t*-test/Mann–Whitney *U* test, chi-square test/Fisher exact test, and analysis of variance (ANOVA) were used to compare parametric and nonparametric variables. One-way repeated measured ANOVA was conducted to evaluate the difference between amlodipine group and placebo group before and after therapy values of T2*, MIC, ejection fraction, and serum ferritin. A *p*-value of <.05 was considered statistically significant.

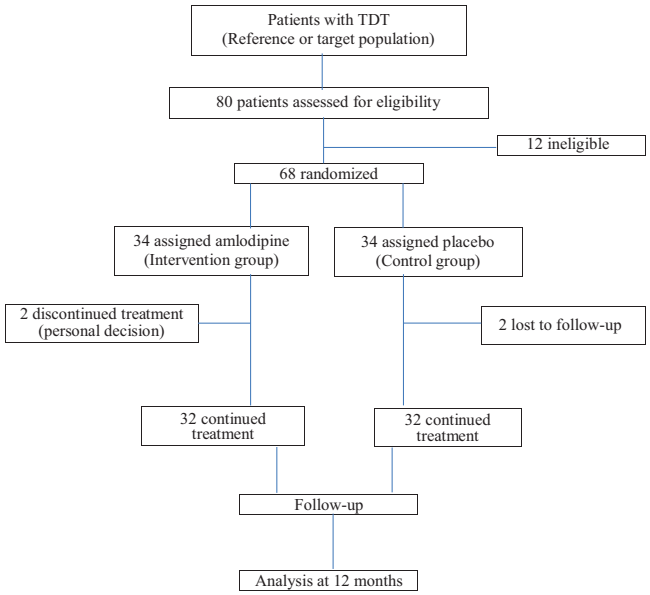

FIGURE 1 The flow of participants in the study

3 | RESULTS

Eighty patients were assessed for eligibility, of which 12 were ineligible. Finally, 68 patients were randomized into groups A and B. Patients in group A received amlodipine and standard chelation therapy (intervention group), whereas patients in group B (placebo group) received only chelation therapy. Flow of the patients has been presented in Figure 1. Sixty-two patients were receiving deferasirox (dose: 30.50 ± 5.75; range: 25–40 mg/kg/day) and one patient in each group was receiving a combination of deferasirox and deferiprone. Compliance was checked by counting the empty boxes of the drug that had been dispensed. Placebo was composed of sucrose.

Majority of patients were in the age group of 6–10 years, who contributed to more than half of the study population (53%), followed by 22 patients (34%) in the 11–15 years age group. Eight patients (13%) were more than 15 years of age. Male patients (80%) outnumbered female patients (20%) with a male-to-female ratio of 3.9:1. Patient population consisted of 45 patients (70%) with homozygous beta thalassemia and 19 patients (30%) with E-beta thalassemia. All were transfusion dependent and had received more than 20 transfusions at the time of entry into the study. Nutritional status of the patients was assessed as per the WHO criteria. Majority of the patients (87.5%) had normal weight for age and only two patients (3.1%) had severe undernutrition. However, less than half of the patients (46.8%) had normal height for age and 16 (25%) had severe stunting.

Patient characteristics in groups A (amlodipine) and B (placebo) at baseline have been presented in Table 1. Both groups were compared with respect to age, gender, nutritional status (body mass index), mean serum ferritin, and the nature of chelation therapy. Patients in the two groups were comparable in relation to various variables, such as cardiac T2* (18.11 ± 8.47 vs. 19.50 ± 8.84, p = .52), MIC (1.93 ± 1.61 vs. 1.95 ± 1.92), LIC (463.22 ± 210.00 vs. 410.06 ± 215.38), and LVEF (65.31 ± 4.99 vs. 65.16 ± 3.25). All the variables were compared again at 12 months (Table 2). Cardiac T2* and LIC had decreased (22.15 ± 7.61 to 20.03 ± 9.07; 430.97 ± 200.39 to 396.00 ± 218.12, respectively) and MIC had increased in group B compared to group A. However, the differences were not statistically significant. LVEF also decreased in the group B (63.06 ± 4.96 to 61.91 ± 4.58) but the difference was again statistically not significant (p = .34). The response rates of various parameters were also compared in relation to age 6–10, 11–15, and >15 years (Table 3). Changes were more pronounced in age group <10 years and homozygous β thalassemia.

Cardiac T2*, MIC, LIC, and LVEF were compared within the groups A and B at 12 months from their baseline values (Table 4). In group A, there was significant increase in cardiac T2* (18.11 ± 8.47 to 22.15 ± 7.61, p = .002) and decrease in MIC (1.93 ± 1.61 to 1.29 ± 0.9, p = .017) at 12 months. No significant difference was observed in group B for cardiac T2* (19.50 ± 8.84 to 20.03 ± 9.07, p = .62) and MIC (1.95 ± 1.92 to 1.80 ± 1.77, p = .35) values. The LVEF decreased in both the groups, but in group B, the decrease was highly significant. The serum ferritin values did not show any significant change within the two groups. Repeated measures analysis revealed significant changes in MIC in the amlodipine group compared to placebo group, with Wilks' lambda = .89 (p = .01). Change in T2* was accordingly significant, with Wilks' lambda = .88 (p = .037). Change in the LVEF (p = .45), LIC (p = .099), and serum ferritin (p = .81) was not significant between the two groups (Figure 2).

In our study, we had hypothesized that there would be 50% reduction in the incidence of myocardial iron overload with the use of intended drug (amlodipine) in the intervention arm (group A). In group A, significantly higher number of patients had T2* value of >20 seconds at 12 months (38% vs. 66%), whereas in group B, no significant change was observed (53% vs. 47%, p = .024).

4 | DISCUSSION

Iron overload poses a significant challenge in patients receiving regular transfusions. It can be managed effectively by iron chelation therapy. However, there are patients who continue to be iron overloaded even with maximal doses of single chelation drug. These patients benefit from combination chelation therapy, where deferasirox may be combined with deferrioxamine or deferiprone.[11] Recently, potential novel therapeutic strategies in the treatment of these patients have focused on LTCC and TTCC blockers. These two channels have been reported as being the main route for cardiac iron uptake under conditions of iron overload.[12] In recent years, some studies have shown the benefit of addition of oral amlodipine, an LTCC blocker, to standard chelation therapy in improving the cardiac T2* in TDT patients.[6,13] Two systematic reviews have suggested that there is need for more randomized controlled trials to provide more evidence in supporting the role of amlodipine in reducing iron overload in patients with thalassemia major.[14,15]

In the present study, the cardiac T2* improved significantly from 18.11 ± 8.47 at baseline to 22.15 ± 7.61 after 12 months in the

TABLE 1 Patient characteristics and comparison of variables at baseline between the groups

Characteristics	Amlodipine ($n = 32$)	Placebo ($n = 32$)	p-Value
Gender, *n* (%)			.76
Male	25 (78)	25 (78)	
Female	7 (22)	7 (22)	
Age (year)	10.66 ± 3.54	10.62 ± 3.99	.98
Mean BMI (kg/m^2)	16.15 ± 1.69	16.18 ± 1.49	.94
Hepatitis C, *n* (%)	1 (3.1)	–	
Splenectomy, *n* (%)	12 (38)	6 (19)	.09
Chelation therapy, *n* (%)			
Deferasirox (DFX)	31 (97)	31 (97)	
DFX + deferiprone (DFP)	1 (3.1)	1 (3.1)	
Mean serum ferritin (ng/ml)	2527.00 ± 1558.97	2307.00 ± 1209.23	.53
Myocardial T2* (milliseconds)	18.11 ± 8.47	19.50 ± 8.84	.52
MIC (mg/g)	1.93 ± 1.61	1.95 ± 1.92	.96
LIC (μmol/g)	463.22 ± 210.00	410.06 ± 215.38	.32
LVEF (%)	65.31 ± 4.99	65.16 ± 3.25	.88
Myocardial T2* categories, *n* (%)			.61
>20 milliseconds	12 (38)	17 (53)	
15–20 milliseconds	8 (25)	5 (16)	
10–15 milliseconds	4 (13)	4 (13)	
<10 milliseconds	8 (25)	6 (19)	
MIC categories (mg/g), *n*			.93
<1.16	12	17	
1.16–1.65	8	4	
1.65–2.71	4	4	
>2.71	8	7	
LIC categories (μmol/g), *n* (%)			.11
<36	–	–	
36–126	3 (9.4)	3 (9.4)	
126–270	2 (6.3)	8 (25)	
>270	27 (84)	21 (66)	

amlodipine group. However, there was no significant change observed in patients in control group. This observation is in accordance with a recent study, where a significant improvement was observed in myocardial T2* from 40.63 ± 5.45 milliseconds at baseline to 43.25 ± 5.35 milliseconds after 6 months in patients treated with amlodipine.[16] The relative improvement of myocardial T2* in the patients who received amlodipine was also consistent with a randomized controlled trial, which indicated that myocardial T2* changed significantly after 1 year of treatment, from 21.9 ± 8.0 to 24.5 ± 7.6 milliseconds.[17] Significant reduction in MIC in amlodipine-treated group (1.93 ± 1.61 at baseline to 1.29 ± 0.90 after 12 months) in our study was also similar to the observations of two previous studies.[13,16]

In an early pilot study carried out on 15 patients, it was observed that myocardial T2* increased significantly in comparison to baseline at 6 and 12 months (21.7 ± 7.2 to 28.2 ± 7.9 and 28.3 ± 8.0 milliseconds, with $p = .007$ and .03, respectively) in amlodipine-treated group, whereas no differences were observed in the control group (25.1 ± 8.8 to 24.7 ± 7.8 and 26.2 ± 11.4 milliseconds, $p = .99$ and .95, respectively).[6] Significant differences between groups were also observed at 6 months (28.2 ± 7.9 vs. 24.7 ± 7.8 milliseconds in the control group, $p = .03$). However, the difference was not significant at 12 months.

No significant change was noted in LIC in both amlodipine group and placebo group after 12 months of treatment in the present study. This can be explained by 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 affect the iron uptake into hepatocytes. This is in accordance with the earlier studies.[6,16,17] Second, we have used signal-intensity ratios on gradient echo images to determine LIC, which has not been validated in

TABLE 2 Comparison of variables between the groups at 12 months

Characteristics	Amlodipine ($n = 32$)	Placebo ($n = 32$)	p-Value
Mean serum ferritin (ng/ml)	2353.03 ± 1435.50	2242.00 ± 982.87	.72
Myocardial T2* (milliseconds)	22.15 ± 7.61	20.03 ± 9.07	.32
MIC (mg/g)	1.29 ± 0.70	1.80 ± 1.77	.14
LIC (μmol/g)	430.97 ± 200.39	396 ± 218.12	.52
LVEF (%)	63.06 ± 4.96	61.91 ± 4.58	.34
Myocardial T2* categories, *n* (%)			.39
>20 milliseconds	21 (66)	15 (47)	
15–20 milliseconds	5 (16)	8 (25)	
10–15 milliseconds	4 (13)	4 (13)	
<10 milliseconds	2 (06.3)	5 (16)	
MIC categories (mg/g), *n*			.31
<1.16	20	15	
1.16–1.65	6	7	
1.65–2.71	4	5	
>2.71	2	5	
LIC categories (μmol/g), *n* (%)			.33
<36	–	–	
36–126	1 (3.1)	4 (13)	
126–270	7 (22)	8 (25)	
>270	24 (75)	20 (63)	

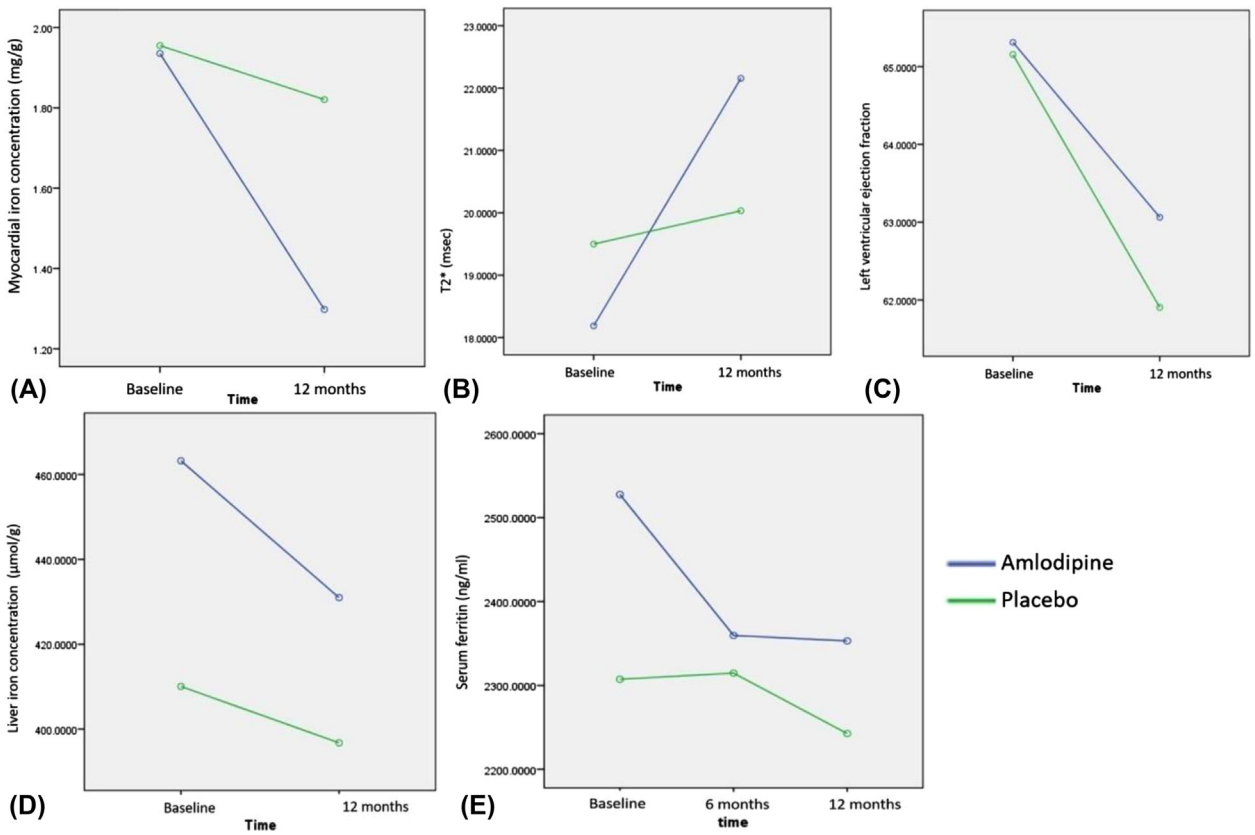

FIGURE 2 Diagrammatic representation of changes in variables at baseline and 12 months between the groups

TABLE 3 Response rates of various parameters in relation to age and type of thalassemia

	Amlodipine (group A)			Placebo (group B)		
	0 Months	12 Months	*p*-Value	0 Months	12 Months	*p*-Value
Comparison between age groups6–10 years (group A = 17 patients; group B = 17 patients)11–15 years (group A = 12 patients; group B = 10 patients) >15 years (group A = 3 patients; group B = 5 patients)						
LIC (μmol/g)						
6–10 years	407.2 ± 214.5	383.7 ± 202.6	.46	426.3 ± 219.2	383.11 ± 219	.15
11–15 years	498 ± 206.2	470.1 ± 197.0	.24	392.1 ± 208.5	391.9 ± 210.1	.98
>15 years	641.0 ± 8.8	542.0 ± 183.3	.45	390.6 ± 258.9	442.8 ± 272.4	.45
MIC (mg/g)						
6–10 years	2.1 ± 2.0	1.3 ± 0.85	.03	1.3 ± 085	1.4 ± 0.85	.74
11–15 years	1.6 ± 0.95	1.3 ± 1.2	.33	2.0 ± 2.2	1.6 ± 1.7	.18
>15 years	2.1 ± 1.3	2.0 ± 1.3	.25	3.9 ± 2.6	3.6 ± 3.0	.67
T2* (milliseconds)						
6–10 years	18.2 ± 8.6	22.2 ± 5.7	.02	22.2 ± 7.8	21.3 ± 7.8	.58
11–15 years	18.5 ± 8.1	22.9 ± 8.3	.07	18.8 ± 8.5	21.4 ± 10.1	.17
>15 years	16.66 ± 12.4	18.66 ± 15.0	.32	11.6 ± 8.8	13 ± 9.3	.29
LVEF (%)						
6–10 years	65.5 ± 3.7	64 ± 5.8	.34	65.88 ± 3.3	64.2 ± 3.8	.12
11–15 years	66.9 ± 5.2	62.6 ± 3.5	.09	63.9 ± 3.3	57.3 ± 3.1	.01
>15 years	57.3 ± 4.0	59.33 ± 3.7	.7	65.2 ± 2.1	63.2 ± 2.3	.15
Ferritin (ng/ml)						
6–10 years	1942.7 ± 1042.1	1972.1 ± 1236.6	.91	2196.6 ± 1226.2	2199.9 ± 926.7	.99
11–15 years	2853.1 ± 1771	3049.4 ± 1643.4	.70	2270.3 ± 914.8	2335 ± 718.8	.76
>15 years	4538.3 ± 1455.22	1725.66 ± 343.07	.09	2757.8 ± 1768.33	2202.6 ± 1690.5	.58
Comparison between homozygous beta thalassemia (group A = 26 patients; group B = 19 patients) and E-beta thalassemia (group A = 6 patients; group B = 13 patients)						
LIC (μmol/g)						
HbE-β	385.8 ± 248.5	358.6 ± 221.8	.57	376.3 ± 218.7	363.7 ± 206.0	.60
Homozygous β	481.1 ± 201.4	447.6 ± 195.9	.16	433.15 ± 215.8	419.4 ± 228.7	.60
MIC (mg/g)						
HbE-β	2.1 ± 3.0	0.99 ± 0.58	.31	1.2 ± 0.72	1.1 ± 0.47	.87
Homozygous β	1.8 ± 1.17	1.3 ± 0.95	.025	2.4 ± 2.3	2.2 ± 2.2	.491
T2* (milliseconds)						
HbE-β	22.66 ± 10.9	26.0 ± 7.77	.22	22.4 ± 7.8	22.7 ± 7.2	.9
Homozygous β	17.2 ± 7.7	21.2 ± 7.4	.006	17.4 ± 9.0	18.2 ± 9.9	.605
LVEF (%)						
HbE-β	66.33 ± 6.1	64.0 ± 5.3	.36	64.5 ± 2.8	61.3 ± 4.2	.4
Homozygous β	65.0 ± 4.8	62.8 ± 4.9	.087	65.5 ± 3.5	62.3 ± 4.8	.09
Serum ferritin (ng/ml)						
HbE-β	2017.8 ± 910	1975 ± 487.3	.87	1886.6 ± 800.2	2488 ± 1006.3	.007
Homozygous β	2645 ± 1664.6	2440.2 ± 1570.2	.56	2595.2 ± 1369.8	2074.6 ± 956.7	.12

TABLE 4 Comparison of variables at baseline and 12 months within the groups

	Amlodipine (group A)			Placebo (group B)		
Variables	Baseline	12 Months	*p*-Value	Baseline	12 Months	*p*-Value
Cardiac T2* (milliseconds)	18.11 ± 8.47	22.15 ± 7.61	.002	19.50 ± 8.84	20.03 ± 9.07	.62
Myocardial iron concentration (mg/g)	1.93 ± 1.61	1.29 ± 0.90	.017	1.95 ± 1.92	1.80 ± 1.77	.36
Liver iron concentration (μmol/g)	463.22 ± 210.00	430.97 ± 200.39	.125	410.06 ± 215.38	396.00 ± 218.12	.47
Left ventricular ejection fraction (%)	65.31 ± 4.99	63.06 ± 4.96	.048	65.16 ± 3.25	61.91 ± 4.58	<.001
Serum ferritin (ng/ml)	2527.00 ± 1558.97	2353.03 ± 1435.50	.64	2307.00 ± 1209.23	2242.00 ± 982.87	.81

transfusional siderosis. Most of our patients had LIC values well outside the established calibration range for this technique. Thus, lack of effect on treatment on LIC could reflect insensitivity of our MRI technique in this range of iron burden.

Serum ferritin levels did not show a significant change in either of the groups from baseline to 6 months, from 6 to 12 months, and from baseline to 12 months in our study. Similar findings were observed in the two other studies.[13,16] However, one study observed a significant reduction in serum ferritin levels in both combined treatment and control groups,[17] but the difference was not significant between the groups. Present study population comprised of relatively young patients, as 53% of patients were in the age group of 6–10 years. Still they had a high iron overload inspite of good compliance with chelation and adequate dosing. One of the possible reasons could be start of chelation at a late age, as many patients had delayed diagnosis.

In our study population, all patients had normal LVEF (≥55%) at baseline, which decreased after 12 months in both the groups but remained within the normal range. In this study, only one patient in amlodipine group suffered from hypotension (blood pressure <50th centile), where the dose of amlodipine was reduced to half of the initial dose. No other adverse effects were found with amlodipine. Other studies have also confirmed the safety profile of amlodipine.[13,17] Some of the other advantages of using amlodipine in TDT are once daily oral route, affordable price, which allows maximal compliance, and global availability, rendering its use feasibility in countries with limited resources.

One of the limitations of our study was not using MRI to calculate the LVEF. This was done to save time. Another limitation was the use of signal-intensity ratios on gradient echo images to determine LIC, which is not a very accurate technique to measure high iron overload. Also T2* values from 20 to 25 milliseconds reflect mild iron overload. But in our study we used the cutoff 20 milliseconds, as was used in a previous study.[16]

5 | CONCLUSION

Amlodipine is safe, and when combined with chelation therapy, appears to be more effective in reducing cardiac iron overload than chelation only in children and young adults with TDT.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Vineeta Gupta conceived the project, wrote and critically reviewed the paper. Ishan Kumar analyzed the radiology data and helped in writing the paper. Vibhesh Raj and Priyanka Aggarwal helped in data collection and analysis. Vikas Agrawal helped with cardiology aspect.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

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