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Low-cost matched sibling bone marrow transplant for standard-risk thalassemia in a limited-resource setting

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ABSTRACT

Thalassemias are the most common inherited genetic disorder in India and a major public health burden with bone marrow transplant (BMT) considered the only established curative therapy. We describe outcomes for patients (n = 71) with standard-risk thalassemia (liver size < 2 cm and age <15 years), receiving BMT in 6 low-cost start up BMT centers in the Indian sub-continent from August-2013 to July-2016. Patients received HLA-matched sibling donor unmanipulated BMT. Conditioning was with busulfan (14 mg/kg oral total over days −10 to −7, serum levels not measured), cyclophosphamide (200 mg/kg total over days −5 to −2) and anti-thymocyte globulin (Genzyme 4 mg/kg or Fresenius 16 mg/kg over days −12 to −10). Kaplan Meier survival analysis revealed thalassemia free survival (TFS) of 83% with overall survival (OS) of 93% with a median follow up of 17.5 months (IQR 13.4–22.6). Twelve percent of the patients rejected, 12% had severe GVHD (7% acute grade 3–4 GVHD and 4% had moderate/severe chronic GVHD). All 3 patients with acute GVHD Grade 3 are off immunosuppression, and those with chronic GVHD are well with Lansky score >80 at the last follow up. 5 patients (7%) died, mortality related to transplant. Enough data existed for 2 centers in India (36/71 transplants) to analyze overall costs from admission up to one-year post-BMT which revealed a median cost of Rs 7,30,445 ($11519) [Range Rs 4,52,821–10,32,842 ($ 7079–16147)]. In conclusion, children with thalassemia in resource limited settings can achieve good outcomes with BMT at a reasonable cost.

1. Introduction

Thalassemias are the most common inherited genetic disorder in India with carrier rates of around 5–17% with carrier frequency even higher among some groups [1]. About 10,000 children are born in India each year with thalassemia [2,3]. Conservative management of thalassemia consists of lifelong blood transfusions and iron chelation and has improved over the years but is very expensive in the long run and is a major public health burden [4–6]. In spite of all the advances made in iron chelation, iron overload and the resulting complications cannot be completely prevented [7] nor can other problems unrelated to iron overload

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such as pulmonary hypertension, osteopenia, thrombophilia, pain and blood-borne infections. At present blood or marrow transplant (BMT) is the only established curative therapy [8,9].

BMT is a highly specialized expensive medical procedure needing expertise, good support systems and resources in order to achieve optimal outcomes. Myelo-ablative stem cell transplant costs in the range of $80,499 to $137,564 in Western countries whereas the same procedure can be performed in India at a fraction of the cost [3–11]. Even in developing countries BMT in thalassemia major seems to be more cost-effective than life-long transfusion, chelation and investigations [3,12,13]. BMT is shown to achieve equal or even superior outcomes in the long run [14–16]. The cost of BMT in India and other countries is roughly the cost of 3–5 years of regular blood transfusion and iron chelation [6,17]. Hence transplant programmes, especially matched sibling donor transplants, are particularly relevant in a developing country like India where resources are limited, as long as good outcomes are ensured. To optimize good outcome, BMT should be performed at a young age, before major irreversible disease- or iron overload-related organ damage sets in.

Even though the long-term cost efficacy of BMT is well established the short-term expense are high and unaffordable for most families in low-middle income countries (LMIC) [18]. In spite of BMT being less expensive compared to higher income countries, in LMIC the per-capita income is proportionally much lower and most patients have to pay for BMT out of their pocket. In contrast, blood transfusion and chelation, is often supported by local governments or NGO's. So it is essential that BMT programmes in resource-limited settings are not only sound scientifically but also cost-conscious without compromising on safety and efficacy [19]. Expenses, that are not clearly proven to be of medical benefit should be eliminated and frugal innovation principles applied, i.e. there should be a constant strive to detect cost-saving opportunities translating into improved affordability and value delivery without compromising on safety and efficacy [20]. In limited-resource setting financial constraints directly influence access to care and hence probability of survival [21].

2. Methods

2.1. Study design and procedures

We defined severe thalassemia as a thalassemia syndrome with inability to spontaneously maintain hemoglobin levels ≥7 g/dl [22]. We used the above definition rather than the standard categories of thalassemia major and intermedia as these categories are based on number of transfusions per year in a well-resourced setting whereas most patient in developing countries are inadequately transfused [23] and can be misleading. Standard-risk thalassemia was defined as age less than 15 years with liver size ≤2 cm below costal margin. Liver biopsy was not part of the evaluation. Pesaro classification was not used in view of difficulty in applying it directly in a low-middle income country where initial liver size and iron overload status can be modified by aggressive pre-BMT intervention [24].

All transplants were among standard risk thalassemia using fully HLA-matched sibling donors. All BMTs were carried out in 6 newly developed BMT units in the Indian subcontinent: The Children's Hospital of the Pakistan Institute of Medical Sciences, Islamabad, Pakistan (CHPIMS), the South-East Asia Institute for Thalassemia, Jaipur, India (SEAIT), the Asiri Central Hospital, Colombo, Sri Lanka (ACH), Nawaloka Hospital, Colombo, Sri Lanka (NH), Kokilaben Dhirubhai Ambani Hospital, Mumbai (KDAH), India and People Tree Hospital, Bangalore, India (PTH). Institutional partnerships and collaboration methodology is summarized elsewhere [25]. The great majority of patients included in this report were fully supported by organizations mentioned in the acknowledgment section so that patients were purely selected on medical grounds rather than on funding availability. An information technology platform facilitating interaction among BMT professionals and promoting continuing quality improvement, was employed by each participating center and data was entered prospectively on a daily basis by local physicians and nurses (BMTPlus, Jagritiy Innovations, Bangalore, India) [25]. Computer-generated (Microsoft Excel) individualized treatment plans developed according to good clinical practices and providing clear and simple operating instructions to point-of-care professionals were generated for each patient and double checked by BMT consultants. Written informed consent was obtained from patients and donors or their respective parents or guardians if less than 18 years old for participation in the study including sharing data on the online database the use of which was approved by institutional review boards at each participating center.

All patients and their caretakers were hosted in single rooms with split air conditioning but no centralized HEPA filtration with positive pressure gradients, strict hand washing and sanitation of all personnel and visitors was enforced and BMT units were thoroughly cleaned daily by dedicated personnel. Bathrooms were not attached to facilitate cleaning and reduce humidity within patient single rooms. Care-takers were given robust education regarding hand hygiene and safe disposal of the biological waste. Infusion pumps and monitors were installed outside the rooms with pass-through cables and IV lines, use of large glass windows facilitating maximum observation from outside and minimizing staff trafficking inside the rooms.

Neutrophil recovery was defined as the first of three consecutive days with an absolute neutrophil count (ANC) greater than 500/μL, platelet recovery as the first day of a stable platelet count above 20,000/μL without platelet transfusions in the preceding week. Toxicity was graded according to ECOG common toxicity criteria [26]. Hypertension was categorized using standard criteria [27]. Sinusoidal obstructive syndrome (SOS) was defined and graded according to the Seattle criteria [28], acute graft *vs.* Host disease (aGVHD) according to Consensus criteria [29], and chronic GVHD (cGVHD) according to NIH guidelines [30]. Only acute GVHD > grade 2 and moderate/severe chronic GVHD were included in survival as severe GVHD (sGVHD). Persistent pancytopaenia is defined as no engraftment by day 30 in case of primary graft failure or neutrophils below <500 for more than 30 days and or low platelets needing transfusion more than 30 days with secondary graft failure. Mixed chimerism was categorized according to % of donor cells detected (level 1: 90%–99%, level 2: 75%–89% and level 3: 5%–74%) [31].

2.2. Patient characteristics and transplant procedure

To receive BMT, patients need to have a) a diagnosis of severe thalassemia defined as a thalassemia syndrome with the inability to spontaneously maintain hemoglobin levels ≥ 7 g/dl; b) liver ≤ 2 cm below the costal margin on abdominal palpation; c) availability of a suitable HLA genoidentical sibling; d) clear understanding of BMT risks and benefits, including parental/caretaker informed consent for transplantation; e) age less than 12 years, with no active severe infectious diseases (HIV, hepatitis B, tuberculosis, malaria) or other conditions affecting transplant outcome; f) creatinine, bilirubin and SGPT less than three times normal values (SGPT up to 10 times normal values was accepted in case of hepatitis C virus positivity), normal chest x-ray and echocardiogram (shortening fraction ≥35%), normal age-appropriate performance scale; g) Institutional commitment to sharing patient data

according to privacy regulations: h) minimum 1 year of follow up from the date of transplant to ensure capture of most chronic GVHD and graft rejection.

A total of 71 consecutive standard risk thalassemia patients met these criteria and received first BMT from August 2013 and July 2016 and were conditioned with ATG, busulfan (oral) and cyclophosphamide (ATG-BuCy) (Fig. 1b). ATG-BuCy protocol consisted of ATG (Rabbit- Thymoglobulin) 4 mg/kg total dose on day −12 to −10 (at CHPIMS Rabbit-Fresenius was used at 16 mg/kg total dose because Thymoglobulin was not available), oral busulfan 3.5 mg/kg day in 4 divided doses on days −10 to −7 (total dose 14 mg/kg), and cyclophosphamide 50 mg/kg/day once daily on days −5 to −2 (total dose 200 mg/kg) followed by the infusion of G-CSF primed freshly harvested HLA-compatible marrow on day 0. Busulfan levels were not checked. Donor marrow was G-CSF-primed in 77% of the patients by treating the donor with filgrastim 5 mcg/kg/dose twice daily for either 3 (21 patients) or 5 days (34 patients) prior to harvest. GVHD prophylaxis consisted of cyclosporin A in two daily doses aiming at trough levels of 150–250 ng/mL for up to day +180 after which it was tapered by −5%/week and discontinued at 12 months post-BMT unless otherwise indicated. A methotrexate course consisting of 10 mg/m^{2}IV on day +1 (24 h after marrow infusion), and 8 mg/m^{2}IV +3, +6, and +11 (the latter dose only in the absence of severe mucositis) with folinic acid rescue at 24 h after each methotrexate with 3 doses of 10 mg/m^2 IV at 8 h intervals was used in 58 patients and Mycophenolate 10 mg/kg/dose TID from day 0 to +45 was used in 13 patients.

Erythrocyte depletion from marrow harvest was required in 6 patients due to major ABO mismatch with isohemagglutinin titers >1:32. All patients received mebendazole 100 mg twice daily for three days before conditioning for anti-helmintic empirical therapy regardless of stool examination result. No antibacterial prophylaxis was employed. Antifungal prophylaxis consisted of fluconazole 6 mg/kg once daily from day +4 until ANC >500/μL. Acyclovir 250–500 mg/m^2/dose three times daily from day +1 to +90 was used for herpes varicella-zoster and simplex prophylaxis. Peripheral blood weekly CMV DNA copy was monitored by qualitative PCR from day +30 up to day +100 in uncomplicated cases, quantitative real-time PCR was employed if the former was positive, ganciclovir pre-emptive therapy was administered for DNA copies greater than 1000/mL. For *pneumocystis jiroveci* prophylaxis, co-trimoxazole at 5 mg/kg/dose twice daily on alternate days three times a week was administered from the day the total white count reached >1.000/μL to day +100. Post-BMT all blood products except for the allograft were irradiated with ≥25Gy. Immunoglobulin prophylaxis was not employed. No Autologous back up marrow was collected. Engraftment was monitored at least at 1, 2, 4, and 8 months by molecular (STR) analysis or Y chromosome cytogenetics or fluorescent in-situ hybridization in case of gender mismatch. Table 1 summarizes patient distribution by center. All patients have at least 12 months follow up post-BMT.

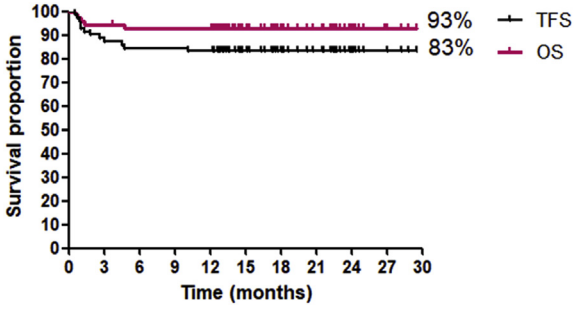

Fig. 1. Overall survival (OS) and Thalassemia Free Survival (TFS). All patients who survived free of thalassemia had a Lansky score >80 at 1 year hence GVHD free Thalassemia free survival (GFRS) is essentially same as TFS.

For cost-analysis we have restricted our analysis to Indian centers as there are likely to many variables that affects the costs between different countries. The costs were estimated from the day of admission for transplant, inpatient stay up to one year post transplant and follow up including any complications in the 1 year period post-transplant. Pre-transplant preparation costs such as hydroxyurea or transfusion were not included in the calculations. The final cost analysis was restricted to Bangalore and Jaipur centers where accurate internal cost figures were available.

2.3. Statistics

Data were collected and analyzed in August 2017. Patient characteristics were summarized through the use of medians and ranges. Kaplan- Meier survival curves were used to describe the survival figures. Height-for-age and body mass index-for-age z-score were calculated based on World Health Organization anthropometric data [32].

3. Results

In our cohort PTH-Bangalore, India and SEAIT-Jaipur, India contributed 18 (25.4%) patients each, 26 (36.6%) of the patients were from CHPIMS, Pakistan, 6 (8.4%), 2 (2.8%) and 1 (1.4%) were from ACH-Colombo, Sri Lanka, KDAH-Mumbai, India and NH-Colombo, Sri Lanka respectively. CHPIMS represents slightly earlier cohort of patients compared to the rest of the centers hence had more patients without G-CSF priming and had low-resolution HLA typing. Patient characteristics which are expected to influence transplant outcomes are summarized in Table 1. All children were under 15 years and there was a slight preponderance for males in this cohort. Majority of the donors were Thalassemia carriers (75%) and were CMV positive (65.5%). Nearly half of the patients (46%) had hydroxyurea prior to transplant as it became our standard practice towards the later years.

Complications related to transplant are summarized in Table 2. Median day of neutrophil engraftment was day +18, median day of platelet recovery above 20,000/cu.mm without platelet transfusion was day +21.5. One patient with primary graft failure recovered the neutrophil counts after day 48. All children had minimum of 12 months follow up to ensure we captured majority of the late complications. Hypertension was the most common complication affecting more than 1/3 of the children followed by CMV reactivation but majority were controlled by antivirals and only 1 out 10 patients had a manifest CMV disease. Of the total 11.2% of the patients had graft rejection, 7% had acute grade 3–4 GVHD and 4.2% had moderate or severe chronic GVHD. Five patients died due to Treatment Related Mortality (TRM). Two of the five children died due to acute severe GVHD (grade 4), one child died to due primary graft failure with persistent pancytopenia with secondary sepsis, another child died due intracranial hemorrhage at day +11 post-transplant and yet another child died due to severe pseudomonas sepsis resulting in multi-organ failure. Of the total 71 patients 59 were cured giving a thalassemia free survival (TFS) of 83% by Kaplan-Meier method and overall survival (OS) of 93%. GVHD and rejection free survival (GRFS) was 74.6%. The survival curves are depicted in Figs. 1 and 2.

The cost analysis was done for 2 centers covering 36 transplants (50.7% of total) where we had accurate itemized data. All these transplants were performed under supported programs on a non-profit basis. Accommodation costs included hospital stay, food, medical and nursing care which accounted for just under half of the

Table 1
Patient characteristics relevant to transplant.

	Value	
No. of patients	71	
Follow up (months)	Median 17.5 months (IQR 13.4–22.6)	
Age at BMT (years)	Median 5 years (IQR 2.7–7.5)	
Sex ratio (Male/Female)	M:F 1.29:1	
Height-for-age z-score	Median (- 1.70) (IQR -2.6 to −1)	
Body mass index-for-age z-score*	Median (−0.45) (IQR -1.4 to 0.4)	
Consanguinity	Yes 39 (55%)	
	No 25 (35%)	
	Status unknown 7 (10%)	
Matched-sibling donor type	No Sibling gender mismatch	28 (39%)
	Sister donor to brother	26 (37%)
	Brother donor to sister	17 (24%)
High resolution 12/12 HLA typing	Yes	41 (58%)
	No	30 (42%)
Donor thalassemia minor	Thalassemia carrier	50 (70%)
	Normal	17 (24%)
	Unknown	4 (6%)
ABO mismatch	Major	7 (10%)
	Minor	8 (11%)
	Bidirectional	48 (68%)
	No ABO mismatch	8 (11%)
CMV status	Donor and Recipient CMV status available for 52 patients	
	Donor and Recipient positive	42 (80.7%)
	Donor positive Recipient negative	4 (7.7%)
	Donor negative and Recipient positive	4 (7.7%)
	Donor and Recipient negative	2 (3.8%)
Pre-BMT ferritin (ng/mL)	Median 1700 (IQR 1104–2288)	
No of transfusions prior to transplant	Median 39 (IQR 24–80.5)	
Hydroxyurea therapy prior to BMT	33 (46%)	
Splenectomy	None	
Hepatitis C positive	None	
Median nucleated cell dose	6.9×10^8 cells/kg IQR (4.6–8.0)	
Immunosuppressive treatment	CSA and MTX 58 (82%)	
	CSA and MMF 13 (18%)	
G-CSF priming	Yes	55 (77%)
	No	16 (23%)
Neutrophil recovery > 500/μL	Median 18 (IQR 16–21) day post transplant	
Platelet recovery > 20,000/μL	Median 21.5 (IQR 19–29) day post transplant	

Table 2
Complications associated with transplant.

Central line associated skin infection	1	1.4%
Central associated bacteremia or sepsis	6	8.5%
Clostridium difficile enterocolitis	0	0%
CMV infection (total)	10	14.1%
CMV disease	1	1.4%
CMV subclinical reactivation	9	12.7%
Fungal infection	2	2.8%
Hypertension	26	36.6%
PRES	1	1.4%
Haemorrhagic cystitis > ECOG grade 2 (gross haematuria with clots)	4	5.6%
TPN usage	0	0%
VOD/SOS	5	7%
TA-TMA	1	1.4%
Auto-immune cytopaenias	1	1.4%
Rejection		8
Primary graft failure (all had persistent pancytopaenia)		3
Secondary graft failure (all had autologous recovery)		5
Acute GVHD Grade 3-4		5
Moderate or severe chronic GVHD		3
Death related to BMT		5
Death Unrelated to BMT		0a

total costs; Median stay was 56 days (Range: 28–93 days); Four patients needed re-admission with average length of stay 13.5 days (7–23 days); medication and investigation costs accounted for the majority of the remaining costs. Readmission costs are included in the cost analysis. The technology platform employed (BMTPlus) in the day to day patient management tracked the ongoing costs for each patient throughout the treatment and follow up [25]. Details of expenses are reported in Table 3, and even though this is only for half the patients, with all the centers using the same Cure2Children protocols, and having similar supportive care arrangements in place, we do not think the costs from other centers are likely to be significantly different.

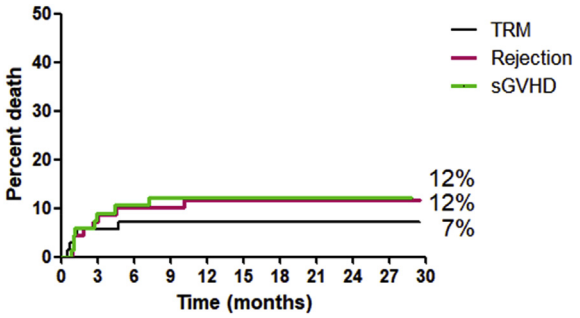

Fig. 2. Treatment Related Mortality (TRM), Rejection, Severe GVHD (sGVHD) considered acute GVHD grade 3 and 4 and chronic GVHD moderate and severe.

4. Discussion

Our BMT programme was designed with an aim to deliver low-cost transplants with assured quality to provide good clinical outcome to children with standard risk thalassemia in developing countries [33]. Where financial resources are limited it is important to understand the costs and benefits of interventions in order to evaluate whether these interventions provide good value [34,35]. In LMIC the choice of conditioning regimen is crucial as outcomes such as graft rejection, and graft-versus-host disease (GVHD) will negatively impact both cost-containment and patient outcomes [36]. Previous studies have demonstrated that decreasing the risk of severe complications can reduce the overall costs [35].

Six-loci high-resolution sequence-based HLA typing was employed in the majority of our patients as low resolution typing, even in related donors, can miss relevant mismatches potentially affecting transplant outcomes [37]. Most of the pre-transplant preparation took place in the thalassemia day care centers in collaboration with the transplant physicians and on day +60 post-transplant patients were referred back to the thalassemia day care centerin liaison with the transplant team. Soon after engraftment patients were shifted to a step-down facility close to the BMT center, i.e. a non-hospital environment with easy and fast access to appropriate medical care whenever required. Our units were not fitted with HEPA filtration systems as there is no convincing evidence that they are necessary in low-risk transplants [38]. We used oral busulfan instead of intravenous (iv) busulfan as the potential advantage of iv busulfan over oral busulfan in standard-risk thalassemia transplant is not well established [39]. Very few cases developed sinusoidal obstructive syndrome and all responded to standard supportive care. We used unmanipulated bone marrow as the stem cell source as the risk of chronic GVHD is reported to be much lesser with bone marrow compared to peripheral blood stem cells (PBSC) [40,41] as chronic GVHD has implication for long term quality of life and secondary malignancies post-BMT [14]. Sourcing PBSC is a high-cost procedure needing apheresis equipment which would drive up cost in a limited resource setting. Bone marrow as a source of stem cells not only has superior long term clinical outcome but lower cost implication for short and long term [10]. Most of our sibling donors received G-CSF priming of the marrow prior to harvest for more rapid engraftment [42]. We routinely used irradiated random donor platelets for correction of platelet counts prior to engraftment, and used single donor platelets only if clinically indicated.

Our results suggest that good outcomes can be achieved at lower cost even in resource limited settings. BMT cost-containment greatly depends on minimizing treatment-related toxicities such as severe mucositis, fungal infections and severe GVHD. None of our patients needed parenteral nutrition, no proven or probable fungal infections were observed and severe GVHD (acute > grade 2 or moderate/severe chronic GVHD) rates where low. Basic and simple measures such as strict hand hygiene, regular and thorough room cleaning, infection control measures to prevent cross infection and good training on central line handling, was effective in controlling infection in standard risk thalassemia BMT. The absence of expensive measures like HEPA filtration and positive-pressure air-control systems did not negatively impact our outcomes.

In order to provide an accurate estimate of cost we included expenses up to 1 year post-transplant in our description. The costs of BMT in US and Europe are significant: Majhail et al., in 2009 reported 67 matched related donor myeloablative transplants in the US among adult patients cost $137,112 (interquartile range [IQR], 97,658–225,430) for the first 100 days excluding the cost of procuring the stem cells [43]. Although costs in LMIC are much lower, they are still substantial: Ngamkiatphaisan et al., in 2007 reported the 1 year cost of allogeneic BMT done for 67 adult patients with AML as $ 22,593 [44]. Chandy et al. from CMC Vellore, India reported in 2001 that the cost of BMT for admission to discharge varied from $6500 for an uncomplicated transplant in a child to $40,000 for complicated transplant in an adult [6]. More recently, Sharma et al., in 2014 reported a median BMT cost of $17914 (range $10832–44701) from admission to discharge after

Table 3
Cost analysis*.

Center	Investigations expenses	Medicines expenses	Accommodation expenses	Procedure expenses	Blood Product expenses	Total expenses
SEAIT, Jaipur, India						
Median INR (US dollars)	Rs. 170901 ($ 2672)	Rs. 167654 ($ 2621)	Rs. 295000 ($ 4611)	Rs. 101500 ($ 1587)	Rs. 17000 ($ 266)	Rs. 754691 ($ 11798)
Range INR (US dollars)	Rs. 112225–200210 ($ 1754–3130)	Rs. 108723–281350 ($ 1700–4399)	Rs. 240000–420500 ($ 3752–6574)	Rs. 75000–111500 ($ 1173–1743)	Rs. 8500–59500 ($ 133–930)	Rs. 677350–999385 ($ 10589–15624)
PTH, Bangalore, India						
Median INR (US dollars)	Rs. 162000 ($ 2532)	Rs. 124072 ($ 1938)	Rs. 311453 ($ 4869)	Rs. 69776 ($ 1091)	Rs. 8000 ($ 125)	Rs. 676833 ($ 10581)
Range INR (US dollars)	41396–219485 ($ 647–3431)	50416–289345 ($ 788–4524)	170694-475505 ($ 2669–7434)	10200–22138 ($ 159–3461)	2900-67100 ($ 45–1049)	452821-1032842 ($ 7079–16147)
Combined data						
Median INR (US dollars	Rs. 165000 ($ 2579)	Rs. 144518 ($ 2259)	Rs. 295000 ($ 4611)	Rs. 95263 ($ 1489)	Rs. 12000 ($ 188)	Rs. 730445 ($ 11519)
Range INR (US dollars)	41396–219485 ($ 647–3431)	50416–289345 ($ 788–4524)	170694–475505 ($ 2669–7434)	10200–221384 ($ 159–3461)	2900–67100 ($ 45–1049)	452821–1032842 ($ 7079–16147)

* As per exchange rates on 1st Sep 2017 (1 dollar – 63.9645 rupees)

studying 162 consecutive allogeneic transplants [11].

Our costs are lower compared to previous reports from India, possibly because we only transplanted standard-risk children with thalassemia whereas other reports included malignancies and adult patients which are likely to push the costs up. We performed our transplants on a non-profit basis and have negotiated low tariffs for hospital charges, investigations and medicines. In spite of a low cost, our outcomes were comparable to those reported internationally [45,46].

5. Conclusions

Our results suggest that it is possible to achieve good outcomes without significant long-term morbidity with simplified and cost-conscious BMT in children with thalassemia. We believe that patient selection unbiased by financial background and purely based on medical criteria, emphasis on simple and well-proven infection control measures, judicious use of antibiotics, intensive use of information and communication technology-assisted quality assurance, and close collaboration with thalassemia centers during down staging, pre- and post-transplant as well as continued effective follow up support, are critical components to the delivery of good outcomes with reduced overall costs.

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