RESEARCH PAPER

Quality Matters – Hematopoietic Stem Cell Transplantation *versus* Transfusion and Chelation in Thalassemia Major

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Objective: To compare quality of life of children with thalassemia major who have undergone stem cell transplantation with those on regular transfusion. **Methods**: The study included 40 children who underwent transplantation and 40 children and 20 adults on regular transfusion and iron chelation therapy. The quality of life assessment was done using the Pediatric Quality of Life Inventory 4.0 Generic Core Scale. **Results**: The mean total summary score, psychosocial summary score and physical score was 92, 91 and 92.8, respectively in transplant group and 83, 82.7 and 83.6, respectively in children in transfusion group. The adult group on transfusion showed overall poorer scores of 74.9, 76 and 73.9, respectively. The average scores in all domains were significantly (P<0.05) lower and drop steeply in second decade in transfusion group. **Conclusion**: Allogeneic stem cell transplantation improves quality of life in thalassemia major.

Keywords: *Children, Quality of life, Stem cell transplantation.*

Thalassemia major is a major public health problem in India with 10,000 new births of affected children added each year [1]. Regular blood transfusions lead to iron overload that causes morbidity in the form of growth retardation, endocrinal problems, cardiomyopathy, transfusion transmitted infections and osteoporosis, and hence decreasing overall quality of life. Provision of safe lifelong monthly transfusions and optimal chelation therapy is a challenging task in our country. Allogeneic hematopoietic stem cell transplantation (HSCT) from a HLA-matched donor is the only potential cure [2], albeit with a small but significant mortality, morbidity and cost. Recent advances in the field of HSCT have made this option more safe and feasible. In the present study, we aim to compare the health related quality of life of children suffering from thalassemia major who have undergone HSCT from HLA-identical donor with those on regular transfusion and iron chelation.

Methods

We performed a cross-sectional observation study at a tertiary care center in Southern India. Written informed consent was sought from parents and patients; child's assent was obtained where necessary. Ethical clearance was obtained from the hospital review board.

We included 40 children aged 5-18 years who underwent HSCT from HLA identical donor between 2007 and 2015. The children included in the study had completed at-least 2 years post transplantation, and they were not receiving any immunosuppressant drugs. All children who had undergone transplantation had received myeloablative conditioning with fludarabine, thiotepa and treosulfan; antithymocyte globulin was added in those who underwent matched unrelated transplantation. The GVHD prophylaxis consisted of methotrexate, tacrolimus and steroids. The transfusion group included 40 age-matched children and 20 adults who were on regular transfusion and iron chelation therapy.

The quality of life assessment was performed using the Pediatric Quality of Life Inventory (Peds QoL) 4.0 Generic Core Scale. A user agreement was signed with the MAPI research Institute, Lyon, France, prior to its use. We used this questionnaire validated in three languages: UK-English, Hindi and Tamil. Three separate questionnaires were administered for children aged 5-7 years, 8-12 years and 13-18 years, and the adult version of Peds QoL was used for those more than 18 years of age. The patients were interviewed over telephone or in person. For children between age 5-7 years, parents' proxy report was used. This scale includes the essential core domains, which include Physical Functioning (8 items), Emotional Functioning (5 items), Social Functioning (5 items) and School Functioning/Work functioning (5 items) [3,4]. Peds QoL

items ask how much of a problem a particular thing has been for patients during the past month. Item responses are measured on a five-point Likert scale ranging from 0 (never a problem) to 4 (almost always a problem). Raw scores are transformed into standardized scores on a scale from 0 to 100 with higher scores representing higher functioning levels.

Statistical analysis was performed using SPSS version 25.0 (IBM, New York). Continuous variables for the two groups were compared with an unpaired t-test for normally distributed data. A difference was considered statistically significant when two-tailed p value was less than 0.05.

RESULTS

In the post-transplant group, the median age of children was 10 years (range 5-18 y). The median age at which the transplantation was done was 5 years. The median time-point of assessment post HSCT was 5 years (range 2 y to 10 y). Out of 40 children, 34 underwent matched related donor transplantation and 6 had matched unrelated transplantation. Four (10%) patients had chronic graft *versus* host disease.

The median age of transfusion group was also 10 years (range 5-18 y). The median age of adult group was 22 years (range 18 to 39 y) with equal number of males and females.

***Table* I** presents mean scores of Peds QoL subscales (Physical, Emotional, Social and School/Work functioning) as well as Psychosocial Health Summary score and Total Summary score for both post transplantation group and transfusion group. The average score in all domains except social functioning were significantly (P<0.001) lower in transfusion group as compared to children who were transplanted. The quality of life index dropped steeply in the patients over 18 years on regular transfusion and chelation therapy. The age at which transplantation was done and type of transplantation (matched related donor *versus* alternative donor) did not have significant impact on quality of life. Though children who had chronic graft *versus* host disease had lower quality of life scores as compared to others, its impact on QoL was not analyzed separately. In both the post-transplant and transfusion group the most affected domain was school/ work functioning.

DISCUSSION

With advances in transfusion and iron chelation, though survival has improved in patients with thalassemia major, the quality of life worsens with age even with optimal transfusion and chelation therapy. Early hematopoietic stem cell transplantation can ensure a better quality of life. The 5-year probabilities of overall survival (OS) and thalassemia-free survival (TFS) are currently estimated as 95% and 90%, respectively with HSCT [5]. The patients scored lowest in school functioning/work functioning in all the three groups, as they have to visit the hospital for transfusions or frequent medical check-ups and hence miss school or work.

The patients on transfusion and chelation have poor QoL scores in our study. It was observed that children have better quality of life with optimal transfusion and chelation but as they grow older it worsens due to various complications related to iron overload and repeated transfusions. This was consistent with the findings of previous studies [6-8] on quality of life in transfusion dependent thalassemia. A study conducted in UK by Clarke, *et al.* [9] shows similar HRQoL in both transplanted children and those on transfusions. This is possibly due to availability of free medical care and resources. However, similar recommendations cannot be made in our country, where access to safe blood transfusion and optimal chelation is a huge challenge. The result from a recent study from Hong Kong [10] is similar to our study which shows a significant improvement in QOL in patients who have undergone transplantation. HSCT is associated with significant

TABLE I PEDS QOL QUALITY OF LIFE SCORES IN VARIOUS DOMAINS IN POST-HEMATOPOIETIC STEM CELL TRANSPLANT (HSCT) AND TRANSFUSION GROUP

	Post HSCT Mean (SD) (95% Confidence Interval)	*Transfusion (<18 y) Mean (SD) (95% Confidence Interval)*	*P value*	*Transfusion (>18 y) Mean (SD) (95% Confidence Interval)*	*P value*
Physical	92.8 (9.6)	83.6 (13.6)	<0.001	73.5 (18.6)	<0.001
Emotional	93.5 (10.9)	84.4 (14.3)	<0.001	74.5 (17.7)	<0.001
Social	92.9 (11)	89.4 (15.5)	0.24	86.5 (11.8)	0.08
School	88.6 (14.8)	74.8 (17.3)	<0.001	67 (14.6)	<0.001
Psychosocial summary	91.6 (8.9)	82.7 (12.9)	<0.001	76 (10.2)	<0.001
Total summary	92 (8.3)	83 (11.8)	<0.001	74.9 (12)	<0.001

WHAT THIS STUDY ADDS?

- Allogeneic stem cell transplantation improves overall quality of life in patients with thalassemia major.

morbidity and mortality and long term complications in those who have significant pre-transplant co-morbidities and organ dysfunction. A long-term study [11] has shown-that HRQoL and lifestyles of patients who were well-managed pre-transplant are similar to general population. Hence, careful selection of patients and donors can improve overall outcome. The cost of HSCT in India from a matched sibling donor is approximately INR 10-15 Lakh, which is lower than the West and almost equivalent to the cost of 3 to 5 years of transfusion and chelation [12]. The immediate financial impact of HSCT is very high but the cost of care of regular transfusion and chelation increased exponentially over time with age. Hence, HSCT has a clear advantage over transfusion and chelation in terms of providing cost effective care.

The current study has several limitations. There was a possibility of selection bias and children who have undergone HSCT might have been healthier without co-morbidities. Also, there was no healthy control to say whether post-transplant QoL is comparable to general population.

This study suggests quality of life benefits of early HSCT for children with thalassemia major.

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