https://doi.org/10.29309/TPMJ/2025.32.08.9819

The Professional Medical Journal
www.theprofesional.com
2025, Volume, 32 Issue, 08

ORIGINAL ARTICLE

Effectiveness of hydroxyurea in reducing the transfusion requirements in patients with beta-thalassemia major.

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Article Citation: Bhayo T, Bharo MA, Kiran A, Soomro TA, Athwani MK, Bhanbhro F. Effectiveness of hydroxyurea in reducing the transfusion requirements in patients with beta-thalassemia major. Professional Med J 2025; 32(08):926-932.
https://doi.org/10.29309/TPMJ/2025.32.08.9819

ABSTRACT… Objective: To determine the effectiveness of hydroxyurea in reducing the transfusion requirements in patients with beta thalassemia major. **Study Design:** Randomized Controlled Trial. **Setting:** Department of Pediatric Medicine, Ghulam Muhammad Mahar Medical College (GMC), Sukkur, Pakistan. **Period:** January 2024 to January 2025. **Methods:** A total of 230 patients (115 in each group) aged 5-12 years with beta-thalassemia and receiving six or more annual blood transfusions were enrolled. In hydroxyurea group, oral hydroxyurea was given at 10-20 mg/kg/day along with standard treatment. Standard treatment group was maintained at normal blood transfusions and chelation therapy without giving them hydroxyurea. Both treatment groups were followed for six months to track their transfusion requirements, hemoglobin and serum ferritin levels. Data were analyzed using IBM-SPSS statistics, version 26.0. **Results:** In a total of 230 patients, 124 (53.9%) were male, and the mean age was 8.54±2.3 years. The mean baseline hemoglobin levels, serum ferritin levels, the number of PRBC transfusions, and transfusion intervals were 6.48±0.81 g/dl, 2536.18±1418.28 ng/dl, 3.09±0.67, and 2.94±0.88 weeks, respectively. After 6-months of treatment, patients receiving hydroxyurea demonstrated a significantly lower mean number of PRBC transfusions (1.27±0.45 vs. 2.50±0.50; p<0.001), longer transfusion-free intervals (3.66±0.70 vs. 3.17±0.75 weeks; p<0.001), higher hemoglobin levels (8.24±0.68 g/dl vs. 7.72±0.93 g/dl; p<0.001), and greater reduction in serum ferritin levels (1910.84±1019.46 ng/dl vs. 2229.72±1208.22 ng/dl; p=0.0365). **Conclusion:** Hydroxyurea significantly reduces transfusion requirements, prolongs transfusion intervals, increases hemoglobin levels, and lowers serum ferritin in patients with beta-thalassemia major.

Key words: Beta-thalassemia Major, Blood Transfusion, Children, Effectiveness, Hydroxyurea.

INTRODUCTION

Beta-thalassemia major (BTM), also known as Cooley's anemia, represents a serious inherited blood disease which produces defective hemoglobin, leading to chronic anemia.[1] BTM appears primarily in those geographical areas, which experience high levels of related marriages, such as South Asia, the Mediterranean, and the Middle East. The prevalence of BTM can range between 10% and 20% in sub-Saharan Africa, up to 40% in certain Middle Eastern and Indian populations, and as high as 80% in northern Papua New Guinea and isolated groups of North-East India.[2,3] In Pakistan, BTM represents a significant public health challenge, with an estimated 5,000-9,000 new cases diagnosed annually.[4] The high number of people with this condition results in substantial expenses for both medical facilities and families as well as broader societal costs.

Regular blood transfusions combined with iron chelation therapy serves as the main approach to manage BTM but may result in iron overload.[5] Blood transfusion therapy increases survival rates for BTM patients yet imposes major long-term health complications on these patients. Patients typically need multiple transfusions with intervals ranging between 2 and 4 weeks yet this therapy leads to problems like transfusion-related effects along with viral transmission challenges, immune response formation, and iron accumulation problems.[6]

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Article received on: 21/03/2025
Accepted for publication: 30/05/2025

Recent decades have seen serious efforts in exploring techniques to minimize transfusion demands while promoting effective hemoglobin levels and enhancing patient's quality of quality.[7] Chemotherapy drug hydroxyurea is proving to be a promising medical approach as an additional treatment as it stimulates fetal hemoglobin (HbF) production because HbF normally appears in fetal development but disappears after birth.[8] Researchers demonstrated that elevated HbF production levels in BTM patients help counter defective beta-globin chain malfunctions and decrease anemia symptoms as well as the requirement for blood transfusions.[9] An Iranian study showed that using hydroxyurea, 10.6% of the patients with BTM became completely transfusion free, transfusion interval in 21.3% of patients increased more than 50%, and the mean monthly transfusion volume decreased from 572cc to 442cc (p-value=0.001).[10] Another study revealed that the mean transfusion volume in the hydroxyurea group remained 94.6±29.8 mL/kg versus 102.1±28.0 mL/kg of the placebo group, with a difference of −7.5mL/kg, for entire six months of the study period.[11] A local study revealed that the mean transfusions per year in patients receiving hydroxyurea with blood transfusion was 9.62±1.44 transfusions/year versus 17.4±62.89, for those who only received standard treatment.[12]

Although, local research about hydroxyurea potential in Pakistan have shown promising preliminary results for its therapeutic benefits[13], the precise role of hydroxyurea in BTM patients across Pakistan lacks comprehensive investigation. Knowing the need, the current study was planned aiming to determine the effectiveness of hydroxyurea in reducing the transfusion requirements in patients with BTM. The findings of this study would not only be a valuable addition to the existing data, but help clinicians and the entire healthcare system to create opportunities to manage thalassemia patients more effectively by reducing the PRBC transfusions and increasing the transfusion intervals. The main aim of this study was to determine the effectiveness of hydroxyurea in reducing the transfusion requirements in patients with beta thalassemia major.

METHODS

This randomized controlled trial was carried out at the Pediatric Medicine Department of the Ghulam Muhammad Mahar Medical College (GMC) Sukkur, Pakistan, from January 2024 to January 2025, after obtaining approval from the institutional review board (letter number: Ped. Medicine/SMBBMU/13). A sample size of 230 (115 in each group) was calculated using the OpenEpi sample size calculator considering the blood transfusion volume (ml/kg) after 6 months of hydroxyurea treatment as 94.6±29.8 ml/kg versus 102.1±28.0 ml/kg with placebo,[11] taking 95% confidence interval and 85% power. The inclusion criteria were children of any gender, aged 5-12 years with beta-thalassemia and receiving six or more annual blood transfusions in the preceding last 1 year. The exclusion criteria were children with co-existing renal disease (raised urea or creatinine >1.5 times of normal values), chronic liver disease (liver enzymes > 3 times of normal upper limit). Children having known hypersensitivity to hydroxyurea or those on immunosuppressent drugs were also not included. Patients with history or plans of bone marrow transplantation were also excluded. Children with platelets count below 150,000 /ul were also not included. Parents/caregivers were briefed about the objective and safety aspectes of the study to obtain informed and written consents.

A comprehensive evaluation of the eligible patients, involving their demographics, medical history, physical examination, and yearly number of transfused packed red blood cells (PRBCs) was carried out. Pre-transfusion hemoglobin parameters and baseline serum ferritin measurements were taken. The patients were then distributed to two concealed groups employing the random number tables as an allocation method. In Group-A, patients received hydroxyurea at 10-20 mg/kg/day along with the standard treatment including blood transfusions and chelation therapy. Group-B was maintained at standard treatment including blood transfusions and chelation therapy. Both treatment groups were followed for six months to track their

transfusion requirements, hemoglobin and serum ferritin levels.

The statistical analysis was performed using "IBM-SPSS Statistics, version 26.0". The quantitative variables, which included age, weight, height, hemoglobin and serum ferritin levels, PRBC transfusions, and interval between transfusions, were represented as mean and standard deviation (SD). For the qualitative variables like gender, residential status, and socioeconomic status, frequencies and percentages were calculated. Independent sample t-test was applied to compare quantitative data between groups while chi-square test or fisher's exact test was employed for the comparison of categorical data between groups. P-value < 0.05 was considered significant.

RESULTS

In a total of 230 patients, 124 (53.9%) were male, and 106 (46.1%) female. The mean age, weight, and height were 8.54±2.3 years, 18.33±2.21 kg, and 102.54±8.18 cm, respectively. There were 153 (66.5%) patients who belonged to rural areas of residence. The mean baseline hemoglobin levels, serum ferritin levels, the number of PRBC transfusions, and transfusion intervals were 6.48±0.81 g/dl, 2536.18±1418.28 ng/dl, 3.09±0.67, and 2.94±0.88 weeks, respectively. Demographic, clinical and laboratory parameters were statistically similar among patients of both study groups and the details are shown in t did not differ significantly between study groups.

After six months, 4 patients in hydroxyurea group, and 9 in standard treatment only group lost to follow-up, so were excluded from the final outcomes analysis (table-2). Patients receiving hydroxyurea demonstrated a significantly lower mean number of PRBC transfusions compared with the standard treatment group (1.27±0.45 vs. 2.50±0.50; p<0.001), along with longer transfusion-free intervals (3.66±0.70 vs. 3.17±0.75 weeks; p<0.001). The mean hemoglobin levels were significantly higher in the hydroxyurea group than in the standard treatment group (8.24±0.68 g/dl vs. 7.72±0.93 g/dl; p<0.001). A greater reduction in serum ferritin levels was observed in the hydroxyurea group (1910.84±1019.46 ng/dl) compared with the standard treatment group (2229.72±1208.22 ng/dl; p=0.0365).

Characteristics		Total (%)	Hydroxyurea Group (n=115)	Standard Treatment Only Group (n=115)	P-Value
Gender	Male	124 (53.9%)	68	56	0.112
	Female	106 (46.1%)	47	59	
Age (years) Mean±SD		8.54±2.3	8.70±2.14	8.45±2.42	0.4075
Weight (kgs) Mean±SD		18.33±2.21	18.52±2.42	18.11±2.13	0.1740
Height (cm) Mean±SD		102.54±8.18	103.27±8.26	101.82±8.11	0.1805
Residential status	Urban	77 (33.5%)	36	41	0.4848
	Rural	153 (66.5%)	79	74	
Socioeconomic status	Low	110 (47.8%)	61	54	0.3162
	Middle	68 (29.6%)	33	35	
	High	52 (22.6%)	21	31	
Hemoglobin (mg/dl)		6.48±0.81	6.41±0.94	6.56±0.76	0.1846
Serum ferritin (ng/dl)		2536.18±1418.28	2614.92±1482.15	2467.02±1371.87	0.4331
Packed red blood cells transfusion (count)		3.09±0.67	3.12±0.74	3.06±0.62	0.5058
Interval between blood transfusions (weeks)		2.94±0.88	2.88±0.91	3.01±0.85	0.2641

Table-I. Characteristics of patients in both study groups (N=230)

Outcomes	Hydroxyurea (n=111)	Standard Treatment (n=106)	P-Value
Packed red blood cells transfusions (count)	1.27±0.45	2.50±0.50	<0.001
Intervals between blood transfusions (weeks)	3.66±0.70	3.17±0.75	<0.001
Hemoglobin (g/dl)	8.24±0.68	7.72±0.93	<0.001
Serum ferritin (ng/dl)	1910.84±1019.46	2229.72±1208.22	0.0365

Table-II. Comparison of outcome parameters among patients of both study groups after 6-months (n=217)

DISCUSSION

After six months of follow-up, patients receiving hydroxyurea exhibited a significant reduction in the mean number of PRBC transfusions (1.27±0.45 vs 2.50±0.50; p<0.001) and a prolongation in transfusion-free intervals (3.66±0.70 vs 3.17±0.75 weeks; p<0.001) compared with those receiving standard treatment alone. The findings of this study align closely with those reported by Hatamleh et al.[14], where a meta-analysis encompassing 294 patients demonstrated that hydroxyurea use significantly prolonged transfusion intervals and improved hemoglobin levels. Hatamleh et al.[14] reported a mean deviation in transfusion intervals of 10.07 days (95% CI, 2.16–17.99) and an increase in hemoglobin levels by 1.71 g/dL (95% CI, 0.84–2.57). Although the interval increment reported in the present study was measured in weeks rather than days, the consistent trend of interval extension reinforces the validity of hydroxyurea's effect. Similar to the decline in ferritin levels observed in the current study (318.88 ng/dl greater reduction with hydroxyurea), Hatamleh et al.[14] noted a pooled mean difference of –299.65 ng/dl, emphasizing hydroxyurea's potential in mitigating iron overload. Comparable results were also reported by Huang et al.[15], who found that hydroxyurea was associated with a significant reduction in transfusion requirements in transfusion-dependent beta-thalassemia, with a pooled response rate of 0.37 for a 50% reduction in transfusion needs and a good response rate of 0.65 for achieving transfusion independence. Although the present study did not specifically categorize responses as partial or complete responders, the substantial decrease in transfusion burden and rise in hemoglobin levels underscore hydroxyurea's efficacy as demonstrated in broader systematic reviews.[14,15]

A significant rise in mean hemoglobin levels (8.24±0.68 g/dl vs 7.72±0.93 g/dl; p<0.001) and a greater decline in serum ferritin levels (1910.84±1019.46 ng/dl vs 2229.72±1208.22 ng/dl; p=0.0365) were observed in the hydroxyurea group, confirming the drug's beneficial hematological effects. Suthar et al.[16], documented a significant rise in hemoglobin after high-dose hydroxyurea therapy in transfusion-dependent thalassemics (p<0.001), although the increment in fetal hemoglobin (HbF) was not statistically significant. In contrast, the present study did not specifically measure HbF levels but did demonstrate a significant rise in total hemoglobin, suggesting that hydroxyurea-induced globin switching may have contributed to improved erythropoiesis. Bhattacharya et al.[17], also reported that hydroxyurea reduced transfusion requirements significantly in children with E-beta thalassemia without adversely affecting growth parameters, findings that mirror the hematologic benefits and favorable safety profile observed herein. Bayanzay and Khan[18] performed a meta-analysis revealing a weighted average odds ratio of 0.493 for good responders and 0.270 for moderate responders, suggesting that hydroxyurea benefits a significant proportion of transfusion-dependent patients. These pooled data align with the response rates observed in this trial, where a meaningful proportion of patients exhibited a 50% or greater reduction in transfusion needs, fulfilling the predefined criteria for effectiveness. Bayanzay and Khan noted the absence of randomized controlled trials in their meta-analysis, emphasizing the importance of rigorously designed trials like the current study.[18] Algiraigri et al.[19], conducted a meta-analysis including 10 observational studies and reported a complete response rate of 36% and an overall response rate of 66%, further supporting the effectiveness of hydroxyurea in

reducing transfusion dependency. The response magnitude observed in the current randomized controlled setting corroborates these findings, offering stronger evidence by minimizing selection bias and confounding inherent in observational designs. Asif et al.[21], in a local study from Islamabad categorized patients into good, partial, and non-responders and found that only 23% achieved transfusion independence, a lower proportion compared with results reported in systematic reviews. Asif et al.[21], used slightly higher hydroxyurea doses (15-20 mg/kg/day) compared with the more flexible 10-20 mg/kg/day dosing in the current study, which may also influence treatment responses and tolerability. Mehta et al.[21] observed significant maintenance of hemoglobin levels with hydroxyurea and a reduction in transfusion frequency ($p=0.022$).

The clinical implications of the present study are substantial. Hydroxyurea presents a promising adjunctive therapy capable of reducing transfusion dependency, alleviating iron overload, and minimizing transfusion-related complications such as alloimmunization and iron-induced organ damage. Importantly, by reducing transfusion requirements, hydroxyurea could also relieve the burden on healthcare systems in resource-limited settings, where safe and timely transfusions remain a challenge. Reducing iron burden may delay or lessen the intensity of chelation therapy, improving patients' quality of life and adherence to treatment regimens. The rise in hemoglobin levels observed with hydroxyurea also holds clinical relevance. Even modest increases in steady-state hemoglobin can translate into improved functional status, reduced fatigue, better growth and development in children, and overall enhanced well-being. Given the chronic nature of beta-thalassemia major, treatments that provide even incremental hematologic benefits without significant toxicity are invaluable.

However, certain limitations of this study must be acknowledged. The follow-up duration was limited to six months, which, although sufficient to detect short-term efficacy, does not capture long-term outcomes such as sustained transfusion independence, organ damage prevention, or cumulative drug toxicity. Longer follow-up periods are necessary to evaluate durability of response and long-term safety. The study did not stratify outcomes based on beta-thalassemia genotypes, HbF levels, or hydroxyurea-induced changes in fetal hemoglobin, which may have provided deeper insights into responders versus non-responders. Although allocation concealment was performed, the absence of blinding could introduce performance or detection bias, although the objective nature of outcomes such as transfusion numbers and hemoglobin levels may mitigate this risk. The study was conducted at a single tertiary care center, potentially limiting the generalizability of the findings to different ethnicities, healthcare settings, or genetic backgrounds. Although hydroxyurea dosing was flexible (10-20 mg/kg/day), optimal dosing strategies remain undefined. Future trials should explore dose-response relationships, starting doses, and escalation strategies to maximize efficacy while minimizing toxicity. Furthermore, the study did not specifically assess the incidence of adverse events apart from monitoring clinical complaints, laboratory parameters such as neutropenia, and thrombocytopenia. Formal adverse event recording and grading would enhance safety data interpretation.

CONCLUSION

Hydroxyurea significantly reduces transfusion requirements, prolongs transfusion intervals, increases hemoglobin levels, and lowers serum ferritin in patients with beta-thalassemia major. Hydroxyurea's promising role as an oral adjunctive therapy in transfusion-dependent thalassemia.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SOURCE OF FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Tahira Bhayo:** Data collection, drafting, responsible for data, proof reading.
2	**Mumtaz Ali Bharo:** Conception, design, proof reading, critical revisions.
3	**Ayesha Kiran:** Literature review, data analysis, proof reading.
4	**Tufail Ahmed Soomro:** Literature review, data analysis, proof reading.
5	**Mahesh Kumar Athwani:** Literature review, data analysis, proof reading.
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