E-ISSN 2250-0944

ISSN 2250-1150
doi: 10.48047/ijprt/15.02.206

Pediatric Beta-Thalassemia Major: Chronic Transfusion, Oxidative Stress, and the Overlooked Surgical Burden

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Abstract

Association between chronic transfusion therapy, oxidative stress biomarkers, and surgical interventions in pediatric patients with beta-thalassemia major was evaluated in a prospective cohort of 200 children aged 5–16 years receiving regular transfusions and chelation therapy. Serum markers including malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), and ferritin were measured. Incidence of surgical interventions—splenectomy, central line placement, gallbladder surgery—were recorded over two years. Children included both splenectomized (n = 60) and non-splenectomized groups. Baseline oxidative stress was significantly higher in splenectomized compared to non-splenectomized (MDA: 4.2 ± 0.9 vs. 3.1 ± 0.7 μmol/L; $p < 0.001$), with elevated SOD and CAT activities and depressed GSH ($p < 0.01$). Ferritin levels were markedly elevated in all participants (mean ± SD: 2,800 ± 950 ng/mL) and correlated with MDA ($r = 0.65$; $p < 0.001$). Surgical burden analysis revealed splenectomy associated with increased central line–related thrombotic events (25% vs. 8%; $p = 0.002$) and gallstones requiring cholecystectomy (30% vs. 12%; $p = 0.001$). Multivariate logistic regression identified elevated MDA and high ferritin as predictors of surgical complications (OR ~ 2.3 and 1.8 respectively, both $p < 0.01$). These findings reveal a trifecta of transfusion-related oxidative damage, iron overload, and surgical morbidity in pediatric beta-thalassemia major, pointing to the need for refined chelation protocols, antioxidant support and surgical risk mitigation.

Keywords

Beta-thalassemia major; chronic transfusion; oxidative stress; ferritin; splenectomy; pediatric surgical burden

Introduction

Beta-thalassemia major in children presents as severe anemia requiring lifelong regular transfusion therapy starting in infancy. Each unit of transfused packed red blood cells delivers approximately 200–250 mg of iron. Since the human body lacks mechanisms to excrete excess iron, chronic transfusion results in progressive iron overload. This leads to accumulation of non-transferrin-bound iron, catalyzing free radical formation and lipid peroxidation, and promoting multiorgan damage—particularly to the liver, heart, endocrine glands, and bone marrow. Oxidative stress arises as an early and central pathogenic factor in transfusion-dependent beta-thalassemia, reflected in elevated biomarkers such as malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), and depleted glutathione (GSH) reserves. Iron overload, as indicated by serum ferritin, correlates robustly with oxidative indices and tissue damage.1-5

Surgical interventions constitute a frequently overlooked burden in pediatric beta-thalassemia major. Hypersplenism often necessitates splenectomy, typically performed when transfusion requirements exceed 200 mL/kg per year. Splenectomy, while reducing transfusion dependency, carries risks including thromboembolism, infections, and complications related to central venous access. Central line placement for frequent transfusions introduces risks of line-associated thrombosis and infection. Cholelithiasis secondary to chronic hemolysis and iron deposition frequently leads to gallbladder surgery in this population. Despite recognition of these procedures, few studies quantify their incidence relative to biochemical and oxidative stress markers.6-8

Oxidative imbalance has been explored in pediatric cohorts: elevated MDA, SOD, and CAT, with reduced GSH and total antioxidant capacity (TAC) compared to healthy controls, indicating persistent redox disturbance. A randomized trial of vitamin E supplementation demonstrated reductions in MDA and improvements in antioxidant enzyme activities among transfusion-dependent children. Studies also show that higher serum ferritin associates with greater

oxidative damage and may predispose to surgical morbidity. Nevertheless, prospective studies integrating biochemical, oxidative stress and surgical outcome data remain sparse.9-10

The current study examines the interplay between chronic transfusion-induced iron overload, oxidative stress biomarkers, and the cumulative surgical burden in pediatric beta-thalassemia major. Hypothesized outcomes include higher oxidative stress in splenectomized children, correlation of ferritin with oxidative markers, and elevated surgical morbidity associated with elevated oxidative stress. A comprehensive understanding could inform optimization of chelation protocols, antioxidant supplementation and surgical risk mitigation strategies.

Methodology

A prospective cohort of 200 pediatric patients (ages 5–16) with transfusion-dependent beta-thalassemia major was enrolled at Post Graduate Institute, Quetta. Sample size was calculated via Epi Info targeting detection of surgical complications incidence of 25% in high-ferritin/high-MDA subgroup versus 10% in lower levels, with $\alpha = 0.05$ and power = 0.80. All participants received regular packed RBC transfusions every 3–4 weeks and standard iron chelation therapy (deferoxamine, deferiprone or deferasirox). Baseline assessment included demographic data, transfusion history, spleen status, hemoglobin, serum ferritin, and oxidative markers—plasma MDA, erythrocyte SOD and CAT activities, and GSH levels. Salivary or urine antioxidant capacity was also measured. Over two years participants were monitored for surgical interventions: splenectomy (if not yet performed), central line placement and removal, cholecystectomy, or other surgery. Verbal informed consent was obtained from guardians and assent from children when appropriate, with documentation per institutional ethical protocols. Inclusion criteria comprised confirmed beta-thalassemia major diagnosis, regular transfusion dependency, and adherence to chelation. Exclusion criteria included other hemoglobinopathies, prior bone marrow transplant, malignancy, antioxidant supplement use within preceding three months, or chronic inflammatory conditions. Oxidative stress assays were performed in standardized laboratory settings using spectrophotometric and enzymatic methods. Surgical events were adjudicated by pediatric hematologists and surgeons blinded to oxidative marker levels. Statistical analysis used t-tests and chi-square tests for group comparisons, Pearson correlation for ferritin-MDA relationships, and multivariate logistic regression (adjusting for age, sex, transfusion

volume, chelation regimen) to identify predictors of surgical complications. Significance threshold $p < 0.05$.

Results

Table 1: Baseline Oxidative Stress and Iron Overload by Splenectomy Status

Marker	Splenectomized (n=60)	Non-splenectomized (n=140)	p-value
MDA (µmol/L)	4.2 ± 0.9	3.1 ± 0.7	< 0.001*
SOD (U/mg Hb)	12.5 ± 3.2	9.8 ± 2.6	< 0.001*
CAT (U/mg Hb)	85 ± 20	65 ± 15	< 0.001*
GSH (µmol/g Hb)	180 ± 25	210 ± 30	< 0.01*
Ferritin (ng/mL)	3,100 ± 1,050	2,600 ± 900	< 0.01*

Table 1 indicates significantly higher oxidative stress and iron burden in splenectomized patients.

Table 2: Surgical Events Over Two-Year Follow-Up

Procedure	Splenectomized (n=60)	Non-splenectomized (n=140)	p-value
Central line–related thrombosis (%)	15/60 (25%)	11/140 (8%)	0.002*
Cholecystectomy for gallstones (%)	18/60 (30%)	17/140 (12%)	0.001*
Other surgical interventions (%)	9/60 (15%)	10/140 (7%)	0.07

Table 2 shows higher rates of line-related thrombosis and gallbladder surgery in splenectomized group.

Table 3: Multivariate Predictors of Surgical Complications

Predictor	Odds Ratio (OR)	95% CI	p-value
MDA (per 1 µmol/L increase)	2.3	1.5–3.5	< 0.001*

Predictor	Odds Ratio (OR)	95% CI	p-value
Ferritin (per 500 ng/mL)	1.8	1.2–2.6	0.003*
Splenectomy status	2.4	1.4–4.2	0.002*

Table 3 confirms that elevated MDA, higher ferritin, and splenectomy independently predict surgical complications.

Discussion

Chronic blood transfusion in pediatric beta-thalassemia major results in inevitable iron overload and oxidative stress. Elevated MDA, SOD, and CAT with depleted GSH indicate persistent redox imbalance. Splenectomized children exhibited more pronounced oxidative stress and iron burden compared to non-splenectomized peers, underscoring the impact of splenic removal on red blood cell turnover and oxidative dynamics.11-13

High serum ferritin correlated significantly with MDA levels ($r \approx 0.65$), supporting the mechanistic linkage between iron overload and lipid peroxidation. Multivariate analysis confirmed both ferritin and MDA as independent predictors of surgical complications, indicating that oxidative damage may predispose toward complications such as thrombotic central lines or gallstone formation.14-16. Surgical burden—including line-associated thrombosis and gallbladder surgery—was significantly higher among splenectomized children. Splenectomy, while beneficial in reducing transfusion frequency, appears to increase susceptibility to vascular and biliary complications. This may relate to altered red cell physiology, increased hemolysis, and disturbed iron metabolism.17-18. These findings highlight the need for augmented antioxidant strategies in children undergoing splenectomy or those with persistently elevated oxidative stress. Vitamin E supplementation has been shown to reduce MDA and improve antioxidant enzyme levels in similar cohorts, suggesting therapeutic potential for modulating oxidative injury alongside chelation optimization.19-20

Prospective integration of oxidative biomarkers into routine monitoring could allow stratification of surgical and vascular risks. Personalized chelation regimens tailored to reduce iron burden rapidly, accompanied by antioxidant interventions, may mitigate the downstream surgical morbidity seen in this vulnerable population.

Limitations include single-center design, lack of long-term outcome beyond two years, and absence of direct measurement of advanced oxidative markers such as peroxiredoxin-2 or DNA oxidation. Residual confounding by nutritional status or infection cannot be excluded.

Future studies should evaluate interventions aimed at reducing oxidative load in high-risk children, test minimal invasive vascular access protocols, and examine whether earlier splenectomy timing correlates with lower oxidative markers and surgical events.

Conclusion

Oxidative stress and iron overload in pediatric beta-thalassemia major, particularly among splenectomized patients, are associated with elevated rates of surgical complications including central line thrombosis and gallstone surgery. Integration of oxidative biomarkers into clinical practice could inform targeted antioxidant and chelation strategies to reduce surgical burden. Future research is needed to validate interventional protocols and optimize long-term outcomes.

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