

Pain Intensity in Beta-Thalassemia Major Patients and Its Related Factors: A Cross-Sectional Study in the South of Iran

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ABSTRACT

Background and Objective: Beta-thalassemia is an autosomal recessive hemoglobinopathy that is thought to be the most common genetic mutation. Complications of iron overload and treatment processes are the most common cause of pain in these patients. Children with chronic diseases like thalassemia deal with a lot of pain during the diagnostic process, treatment and management of their disease. The aim of the present study was to evaluate pain in patients with thalassemia major.

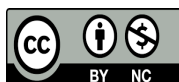
Methods: The present descriptive-analytical study was performed on 211 patients with beta-thalassemia major, referred to Ali Asghar Clinic in Zahedan in 2017. A brief pain inventory (BPI) questionnaire was used to collect patients' information analyzed using Chi-square t-test and Pearson correlation coefficient.

Findings: The mean pain intensity was 1.72 ± 2.60 score and 2.15 ± 3.33 score in patients ≤ 15 years and > 15 years, respectively ($p=0.011$). The mean pain intensity was 2.37 ± 1.49 score and 3.52 ± 2.33 score in patients receiving oral and injectable iron chelators, respectively ($p=0.004$). However, no significant relationship was found between pain intensity with gender and presence of cardiomyopathy.

Conclusion: Since the mean pain intensity is associated with increasing age and the type of iron depletion, these factors should be considered as the main pain generator factors in these patients.

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Introduction

Thalassemia major is a hereditary condition, affecting children everywhere in the world like Iran. It results from a defect in globin chain synthesis, leading to a shorter lifespan of the erythrocytes. The chronic nature of this disease has negative impacts on the patients' physical and mental health [1-4]. A sequela of this disease is severe anemia, which disrupts these children's growth and development. Furthermore, the excessive energy and caloric intake required for the hematopoiesis of these kids predispose them to general weakness, physical frailty and recurrent infections. Without blood transfusions, these kids will inevitably die within the first decade of their lives [5-7]. The most important concept of this treatment is regular blood transfusions as the anemia can lead to many complications such as slower growth and increased bone marrow activity which can lead to deformities in the skeletal system and extramedullary hematopoiesis which can cause hepatosplenomegaly [1, 8].

The most accepted protocol is blood transfusions which should be aimed at maintaining a hemoglobin level of 9- 10 mg/dl, which for children who keep up with this regimen within the first decade of their lives can lead to iron overload, cardiomyopathies, hepatic fibrosis, and endocrine issues. These complications are the leading cause of pain in these children [2, 9, 10]. Pain is a common manifestation of thalassemia major, leading to a series of complaints of headaches, fatigue, weakness, hair loss, and musculoskeletal pains [11]. Caytemel et al. studied these severely painful foot ulcers in thalassemia patients which had severely affected their quality of life [12].

Pain is an ever-increasing complaint of thalassemia patients, and many studies have indicated this as a noteworthy subject [13]. Scalone et al. studied the presence of pain in thalassemia and while 62% of their thalassemia patients reported pain only 1% stated it as severe pain, meaning an increased tolerance to pain in these patients [12, 14].

Pakbaz et al. reported pain in thalassemia patients too as a comparison between thalassemia major and intermedia. In their study, 21% of patients reported intermediate pain and 14% of patients reported severe pain [15]. The rise in pain is in direct

correlation with age. Studies show musculoskeletal and joint pains in the lower extremities and the vertebrae not only exist but are severe enough to affect the quality of life in these patients [11].

Kids with thalassemia generally have negative thoughts about their own lives, they feel guilt, anxiety and, low confidence. They also feel different from their peers. Psychological findings such as; complaint of their physical symptoms and separation anxiety may indicate their fear of the future and the emotional toll the disease has taken on them. The pain, disease and, quality of life in these patients have an integrated relationship which in addition to the physical signs and symptoms affects all aspects of their lives, meaning one of the most important aims of treatment is alleviating the burdens these patients lives [16].

Nowadays, with the existing treatments, many reports express an increased life expectancy of thalassemia major patients. In addition to the physical and mental health issues they face, social obstacles such as; starting families, getting a higher education and jobs leave another impact and burden on their lives. These issues will eventually lead to frustration and social avoidance, further reducing their quality of life [17]. To improve the quality of life of these patients, it is necessary to pay particular attention to the complications of either the disease or its treatment, especially the pain [18]. Given the high prevalence of thalassemia major in Sistan and Baluchestan province (southeast of Iran), the painful complications of this disease including; iron overload, extramedullary hematopoiesis, and multiple blood transfusions as their treatment regimen, we decided to study the extent of the pain thalassemia major patients suffer from.

Methods

Design and participant

This descriptive-analytical study was conducted on 211 patients with thalassemia major referred to Ali-Asghar clinic in Zahedan in 2017. The population pool was measured with 95% confidence interval, with an alpha score <0.5 and a power of 80% (1-beta=0.8, beta=0.2).

The population in this study consisted only of patients previously diagnosed with β Thalassemia Major by a pediatrics hematologist, who were referred to Ali-Asghar clinic in Zahedan, capital of Sistan and Baluchistan in 2017. All participants had already provided their consent to be included in this study. The exclusion criteria included participants who were already treated with a bone marrow transplant.

Data collection

The patients' information including age, gender, iron chelation (agents and routines), and their history of cardiomyopathy confirmed through requesting echocardiography was gathered.

Brief pain inventory (BPI) is a standard index for evaluating the extent of pain in patients with chronic conditions including thalassemia; it contains 4 sections each of which evaluate pain in a unique way dating only to recent events. This index is made based on two criteria; 1- the intensity of pain and 2- the extent to which this pain disrupts the patients' daily life. There are different subsections within the questionnaire, one of which is the sensory evaluation, scored from 0-10, where an increase indicates more severe pain. Another part evaluates how much the pain has affected the patient's quality of life and is made up of 7 questions [19, 20] the intensity of pain correlates directly with the score. The second section evaluates the effect of pain on the patient's quality of life [14]. The questionnaire was filled by the patients during their pack cell transfusion appointments in the thalassemia ward of Ali-Asghar clinic in Zahedan, the process of which was supervised by the researchers involved in this study, and necessary guides would be given to patients if needed. The data was then gathered by the physician and the hematologist. The questionnaire of this study was a translated version of the one provided (figure 1) in Cleeland's article from 2006. The patients selected their location of pain based on the picture in figure 1, which we have taken from Cleeland's article [20].

Data analysis

The required data were analyzed with SPSS 22.0 for descriptive statistics (frequency distribution

tables, correlation coefficient) and analytical statistics methods (ANOVA and independent t-test)

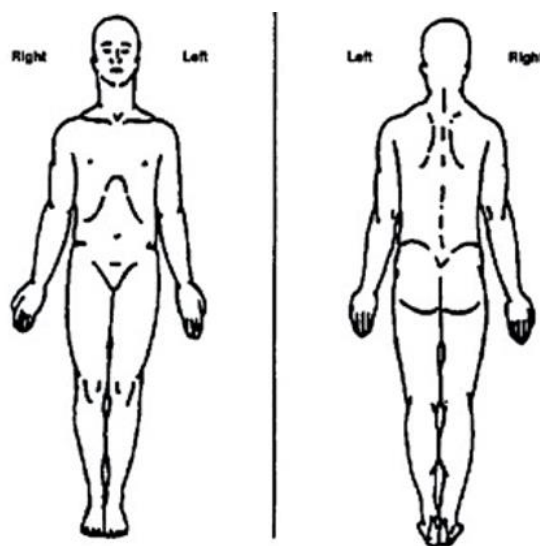


Figure 1. The picture we gave patients to identify the painful regions on their bodie

Results

This study was conducted on 211 patients (82=males and 129=females). The patients were categorized based on their age groups as follows: 1- 13 Children aged between 5-10 years old (6.2%) 2- 58 patients aged between 10-15 years old (27.5%) and 3- 139 patients ≥ 15 years old (65.9%).

In Table 1, the location of pain in patients with β Thalassemia Major is shown. The most common painful locations are in the thorax, legs and the least common painful location are in the head, hands and, feet.

Table 2 shows the painful regions too, but in different age groups and genders with β thalassemia major. Data analysis using Chi-Square resulted in a P-Value of more than 0.05 indicating a statistically insignificant finding. (P-Values for age and gender are 0.56 and 0.055 respectively.)

Table 3 shows the mean pain intensity of β thalassemia major patients of different ages, sex, type of iron chelation and, cardiomyopathy groups. Analysis was performed by independent t-test, revealing a significant relationship between age and pain intensity (P-Value=0.011). However, an existing relationship between gender and pain was proven statistically insignificant (P-Value=0.6). The relationship between the mean of pain intensity and

iron chelation turned out statistically significant using one-way analysis of variance (ANOVA) with a P-Value of 0.004, meaning patients who were also treated with oral iron chelator agents reported less

severe pains. Lastly, there were no statistically significant correlations between pain and cardiomyopathy using an independent t-test (P-Value=0.68).

Table 1: Location of pain in Beta-thalassemia major patients

Location	Number	Percent
No response	33	15.6
No pain	2	0.9
Head	2	0.9
Head and Thorax	9	3/4
Head, Thorax, Hand and, Feet	8	3.8
Head, Thorax and, Feet	14	6.6
Head, Hand and, Feet	1	0.5
Head and, Feet	3	1.4
Thorax	38	18
Thorax and, Hand	5	2.4
Thorax, Hand and, Feet	12	5
Thorax and, Feet	46	21.8
Hand	6	2.8
Hand and, Feet	10	4.7
Feet	22	10.4
Total	211	100

Table 2: Prevalence of pain in the more common locations in Beta-thalassemia patients

Variable	Location	Head		Thorax		Upper Extremities		Lower Extremities		Combined		P-Value
		Numbers	Percent	N	%	N	%	N	%	N	%	
Age (year)	5-10	0	0	2	5.3	0	0	2	9.1	0	6.3	0.56
	10-15	1	50	8	21	4	66.7	5	22.7	40	28.2	
	>15	1	50	28	73.7	2	33.3	15	68.2	93	65.5	
	Total	2	100	38	100	6	100	22	100	142	100	
Sex	Male	1	50	8	21.2	4	66.7	7	31.8	62	43.4	0.066
	Female	1	50	30	78.9	2	33.3	15	68.2	81	56.6	
	Total	100	143	100	22	100	6	100	38	100	2	

Table 3: Comparison of the intensity of pain in Beta-thalassemia major patients categorized by the patients' age, sex, iron chelation methods, and cardiomyopathy

Variables	Intensity of pain	Numbers	The mean and standard deviation of pain intensity	P-Value
Age (years)	15≥	64	2.6±1.72	0.011
	15<	136	3.33±2.15	
Sex	Male	76	3.19±1.98	0.6
	Female	125	3.03±2.09	
Types of iron Chelation	Oral	57	2.37±1.49	0.004
	Injection	66	3.52±2.33	
	Combined	73	3.31±2.005	
Cardiomyopathy	Yes	65	3.18±2.03	0.68
	No	146	3.05±2.06	

Discussion

The aim of the current study was to evaluate pain in patients with β thalassemia major referred to Ali-Asghar Clinic in Zahedan in 2017. In this study, the results showed that the severity of pain in patients with β thalassemia major increased with age but had no statistically significant relationship with gender. There was no statistically significant relationship between common pain points and age and gender. Patients who had cardiomyopathy did not experience pain as intensely as those with cardiomyopathy. In a 2013 study by Dru Haines et al. of the 252 thalassemia patients aged from 12-71 years old, 64% reported pain within the past 4 weeks with 22% reporting daily pain. The patients in this study were cared for at 12 research centers and the pain evaluation system was with a BPI questionnaire just like our study. This retrospective descriptive study showed that there is a significant relationship between aging an increase in pain intensity regardless of the time of diagnosis, transfusion status, sex, type of iron chelation and, iron overload [13]. Eighty-one percent of patients experienced pain for a year or more and 31 percent experienced pain for five years or more.

Pain is a major cause of disability and an unknown problem in thalassemia patients. The strongest predictor of pain intensity and frequency in thalassemia patients is age [13]. Other causes are little-known predictors of pain in these patients. The findings of this study closely resemble ours.

Another study looked at the prevalence and severity of pain in patients who received regular transfusions compared with those who received irregular blood transfusions. There were 115 males and 137 females participating, of which 201 had regular transfusions, 14 had irregular transfusions and 37 had no transfusions. 75 patients with regular transfusions, 7 patients with intermittent transfusions, and 11 patients without blood transfusions reported pain. Totally, 93 patients were analyzed for common pain points, of which 76 reported pains in the lower back, 52 in both legs, 45 headaches, 44 in the back, 36 in the pelvis, 29 in both upper limbs, 26 in the abdomen, and 25 patients reported chest pains. The findings of this

study also associate headaches and dysfunction increase with age [21]. The findings of this study also match ours in the presence of a direct correlation between age and pain intensity.

Bagherian et al. evaluated the severity of venipuncture pain in children with thalassemia before blood transfusion. They studied 120 children aged 3 to 6 years old. Moreover, 50.8% were girls and 49.2% were boys, and the mean age of the children was 4.1 ± 1.1 years old. In addition, 18.3% of kids suffered from mild pain, 32.5% moderate pain and 49.2% severe pain. The mean score of pain was 2.4 ± 6.8 score. Girls and younger children reported significantly more pain [22]. This finding is quite different than ours, which could be explained by the younger population of this study.

In this study, we found that the severity of pain is more related to age and iron chelation methods. The other factors we studied had no significant relationship with pain (i.e., sex and cardiomyopathy). Due to the high prevalence of thalassemia in Sistan and Baluchestan province, these patients suffer from pain due to complications of iron overload and extracellular hematopoiesis, as well as venipuncture for blood transfusion, therefore; to the aims of the ongoing study were to find the common points of pain in patients and the relationship between different factors and the intensity and frequency of pain and to evaluate pain in β thalassemia patients. Therefore, we pinpointed the different sources of pain (venipunctures for example), complications causing pain (iron overload and extramedullary hematopoiesis) and, the most common locations of pain in our patients. This enabled us to find the relationships between different factors and the intensity and frequency of pain. The high prevalence of thalassemia in this region meant a higher number of participants which given the 95% confidence interval of this study, yields fairly accurate results.

Of the limiting and confounding factors that could have affected the results of this study, the patient's response to the questionnaire comes to mind. Given that this was entirely the patients' response to the questions on a 0-10 scale of their pain, this could have been affected by the

individual's logical and emotional preferences. To this end, we strongly advise future studies to use a larger population with a wider variety of different ages and complications. Finally, since pain increases with age, it is only fair to provide the necessary recommendations and counsel on this subject at the time of the diagnosis by educating the patients on this condition and its management. In short, this study shows that children with thalassemia need help to adapt to their condition and society, thus, employing routine psychiatric care for children with thalassemia with the aims of educating patients with coping mechanisms for the pains and helping them with any psychiatric or behavioral issues is beneficial to improving their quality of lives.

Limitations of the study

These items may be considered as the limitations of this study:

1. Emotional and logical preferences of patients in responding to the questionnaire.
2. Dialectical differences and barriers between care-takers and patients which was solved by translators.
3. A sample size which may not be suitable to conclude exactly, which a larger population pool may be required for further study.

Conclusion

According to the results of this study, the intensity of pain is more related to the age and iron chelation than the gender and any pre-existing cardiomyopathies. Therefore, these factors should be considered as the main pain generator factors in these patients.

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Ethical approval

This study was certified by the Ethics Committee of Zahedan University of Medical

Sciences under the code: IR.ZAUMS.REC.1392.1057.

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Conflict of interests

The authors disclose no conflicting interests.

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