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Original Article

Pain Assessment among Egyptian Children with Transfusion-Dependent Hemoglobinopathies: Pilot Study

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ABSTRACT

Background: Hemoglobinopathies that require transfusions are among the most prevalent hereditary disorders in the world. Transfusion-dependent hemoglobinopathies cause unpredictable, recurrent, and frequently permanent pain, making them distinct from other pain syndromes. **Objective: -** This paper aims to evaluate the experience of pain in children diagnosed with transfusion dependent hemoglobinopathies. Additionally, it seeks to explore the associations between pain and various sociodemographic and clinical factors in the sample of children under study. **Methodology:** This cross-sectional, descriptive study comprised a sample of children between the ages of 8 and 18 years who had transfusion-dependent hemoglobinopathies. The data was obtained from the hematology clinic located at Children's Hospital, affiliated with Mansoura University in Egypt. The data was collected by the utilization of a semi-structured interview form and the implementation of the revised-Face, Leg, Activity, Cry, and Consolability scale (r-FLACC). **Results:** Of the children who participated in the research, two-thirds (66%) were female, and 76% had been diagnosed with beta-thalassemia. Of the children who participated in the study, over half (56%) experienced significant pain symptoms. Children with sickle cell disease who undergo twice-monthly blood transfusions and have been studied report experiencing severe pain. **Conclusion:** Of the children who participated in the study, over half experienced severe pain symptoms. Types of transfusion-dependent hemoglobinopathies, particularly sickle cell disease, and twice-monthly blood transfusions, have been linked with severe pain levels. **Recommendations: -** Regular evaluations and improved pain management programs aimed at pain reduction, would significantly enhance the well-being of pediatric patients diagnosed with transfusion-dependent hemoglobinopathies.

Keywords: *Hemoglobinopathies Pain, Transfusion-dependent,*

Introduction:

Hemoglobinopathies are hereditary conditions marked by structural alterations in hemoglobin. The two most well-known illnesses in this category are thalassemias and sickle cell disease (SCD) **(Khandros & Kwiatkowski, 2022).** Approximately 2.4% of infants are homozygotes or compound heterozygotes with globin defects that cause symptoms. Among these individuals, 0.44 have thalassemia and 1.96 have SCD **(Indrák, et al, 2018).**

Children with transfusion-dependent hemoglobinopathies are living longer with the help of advancements in treatment, which has revealed presently undiagnosed issues such chronic pain **(Van Veelen et al., 2023).** Many physicians who treat children with transfusion-dependent hemoglobinopathies have encountered patients who experience chronic pain that can occasionally be excruciating and unmanageable. Pain has been identified as an increasing consequence and a substantial cause of morbidity in transfusion-dependent hemoglobinopathies, despite the fact that it is not a symptom that is often associated with these conditions **(Ballas & Darbari 2020).**

Poor hemoglobin levels, iron overload, and poor bone mass have all been suggested as possible reasons of the pain associated with transfusion-dependent hemoglobinopathies, while the precise mechanism of pain is still unclear **(Karlson et al, 2023)**. Lower hemoglobin levels, which occur at the conclusion of a transfusion cycle, are thought to be associated with children with transfusion-dependent hemoglobinopathies experiencing greater pain. Furthermore, children who postpone blood transfusions are more likely to experience prolonged pain due to alterations in their skeleton and increased bone marrow **(Williams et al, 2020)**.

Children with transfusion-dependent hemoglobinopathies are emotionally, intellectually, physically, and socially impacted by chronic pain, and their medical care is frequently provided in healthcare facilities that may not be fully aware of their complex needs **(Sidhom et al., 2023)**. Counseling professionals must take into account

the different stages of development of children they are working with who suffer from chronic pain in order to help them recognize the complex issues they are confronting **(Darbari et al, 2020)**.

Aim of the study:-

This paper aims to:-

1) Evaluate children with hemoglobinopathies that require transfusions for their level of pain.
2) Analyze the associations between the clinical and sociodemographic characteristics of the children under study and pain.

Materials and Method

The proposed cross-sectional descriptive research was approved by the Research Ethics Committee. Fifty children were included in the research study, based on information found in their medical files at the Children Hospital of Mansoura University's Haematology Clinic. Hemoglobinopathies that depend on transfusions had been identified in these children. The age range for participation was 8 to 18 years old, and participants had to be diagnosed with hemoglobinopathies that were transfusion-dependent. To obtain these data, the entire population was counted as part of the survey. In the six months between March 2021 and May 2021, 50 children were referred to the clinic for a clinical follow up.

These subjects was meet the following criteria:

a) Age range from 8 to 18 years.
b) Gender: The study will encompass individuals of both male and female sexes.
c) Children should attend consistently frequent either the out-patient clinic or the in-patient department of the Children Hospital at Mansoura University.
d) Children who are dependent on blood transfusions

Exclusion criteria:

a) Non-compliance with participation in the research.
b) Adverse clinical circumstances that may result in the patient decline from the program.
c) Specific mental health conditions which may affect the child participation on the study.

Data collection tools:-

Information for the study was gathered via semi-structured interview questionnaires:

Tool (1) Socio-demographic characteristics and clinical data of the children:

Age, sex, education, disease, blood transfusion, Splenic, cardiac, kidney, bone, and arthritic complications related to the disorder were all included in the demographics and clinical section of the questionnaire.

Tool (2) The Revised-Face, Leg, Activity, Cry, and Consolability scale (r- FLACC):-

The r-FLACC is a pain assessment instrument that is derived from the FLACC tool, which has been extensively examined and frequently utilized for assessing pain in preverbal individuals **(Voepel-Lewis et al., 2002)**. The reliability and validity of the FLACC scale were examined in a study conducted by **von Baeyer and Spagrud (2007)**, focusing on its application in children and young individuals up to the age of 18. A 3-point scale (ranging from 0 to 2) is utilized to assign values of intensity in five distinct categories, including face, legs, activity, cry, and Consolability. The total scores encompass a spectrum of values from 0 to 10, with a higher score indicating a greater degree of pain. The categorizations of pain severity are as follows: mild pain is represented by scores ranging from 0 to 3, moderate pain falls within the range of 4 to 6, and severe pain is denoted by scores ranging from 7 to 10. The Arabic translation of this tool was conducted by **Shabana and Ibrahim in 2018.**

Procedure

Candidates have been interviewed and chosen to participate in the research at the Hematology Clinics and Hematology Ward of the Children's Hospital of Mansoura University. All potential participants and their families were provided with comprehensive information and explanations regarding the research. During routine clinic or hospital visits, children and their families submitted written consent subsequent to being aware of the objective of the study.

Data analysis

SPSS version 26 (Statistical Package for the Social Sciences, version 26, SPSS Inc. Chicago, IL, USA) statistical analysis software was used to process the data. Descriptive statistics such as frequency, mean, and standard deviation were used for the calculations. To determine if the variables followed a normal distribution, the Kolmogorov-Smirnov test was performed. Mean pain scores were compared across categorical and clinical factors using ANOVA. The F value of the analysis of variance (ANOVA) test was computed to facilitate the comparison of means for parametric

data involving two groups or more. The level of significance for all statistical tests is set at the "5%" level (p smaller than 0.05). Results are considered significant when the chance of errors is "less than 5% (p 0.05)" and non-significant when the probability of errors is "greater than 5% (p > 0.05)". When the margin of error is less than 0.01% (p 0.001), the result is considered highly significant. The significance of the findings increases as the p-value decreases.

Ethical Considerations:-

Each caregiver and child orally consented to participate in the study. The right to refuse or revoke consent at any moment was explained to all the children and the people who were in charge of them. The right to privacy was respected for the children. The study's ethical review board came from Mansoura University's Faculty of Nursing's Research Ethics Committee.

Results

Table 1 presents the characteristics of the sample under study. Aged between 15 and 18 years, 54% of the researched sample took part in the study, with a mean and S.D. of 11.4 ± 1.94. In terms of levels of education, near to half 48% of the participants completed their secondary education. Three quarters (75%) of the study participants had a diagnosis of beta-thalassemia, and two-thirds (66%) were girls.

Nearly two-thirds (64%) of the study population experienced cardiac problems as a direct result of transfusion-dependent hemoglobinopathies. Hepatic problems affected nearly three-quarters of the sample (72%), bone and joint complications affected nearly three-quarters (74%), and splenomegaly affected more than three-quarters (78.4%) of the sample.

The statistics presented in Table 2 are of an illustrative and descriptive nature, and they are related to the evaluation of pain. In terms of the clinical symptoms of pain, greater than half (56%) of the sample children that was investigated and evaluated suffer from severe pain.

With regards to Table 3, labeled "Relationship between the average pain scores among the children under study and their socio-demographic and clinical characteristics," In relation to the age range of the children under study, it was observed that the age group ranging from 15 to 18 years had the highest mean pain score, which was recorded as 9.27 ± 0.45. In relation to the variable of gender, the analysis revealed that females had the highest mean score (M = 7.43, SD = 1.35). The individuals with a Secondary educational level obtained the highest score (9.28 ± 0.46) in this study. The data presented in the table indicates that the group of children diagnosed with Sickle Cell Anemia exhibited the highest average score (7.79 ± 1.34). Furthermore, individuals who underwent twice monthly blood transfusions achieved the highest mean score (8.07 ± 0.80).

When examining children with further complications associated to the primary condition, it was discovered that those with splenomegaly had the highest mean pain score (7.54 ± 1.17). Furthermore, individuals with cardiomegaly had the highest mean pain score (7.70 ± 1.28). Those with hepatomegaly, osteoporosis, and bone deformities had the highest mean pain score. For bone and joint problems (7.89 ± 1.11), and for hepatomegaly (7.84 ± 1.27).

Table 1: Demographic and clinical characteristics of studied sample

Demographic profile	Category	Frequency N = 50	%
Age	8 – 12	9	18
	12 – 15	14	28
	15 – 18	27	54
	Mean ± S.D = 11.4 ± 1.94		
Gender	Girls	33	66
	Boys	17	34
Educational level	Primary School	10	20
	Preparatory school	16	32
	Secondary School	24	48
Type of disease	Beta Thalassemia	38	76
	Sickle cell disease	12	24

Transfusion times per Month	**Once Monthly**	28	56
	Twice Monthly	22	44
Complications related to transfusion-dependent hemoglobinopathies			
Splenomegaly	No	11	22
	Yes	39	78
Cardiac complications	No	18	36
	Yes	32	64
Hepatic Complications	No	14	28
	Yes	36	72
Bone and joint complications	No	13	26
	Yes	37	74

Table 2: Frequency distribution of the studied sample according to pain assessment:-

Variable	**Mean ± SD**	**Level**		
		Mild No (%)	**Moderate No (%)**	**Severe No (%)**
Pain	7.19 ± 1.32	10 (20)	12 (24)	28 (56)

Table 3:- Relationship between total mean scores of pain among studied children and the socio-demographic and clinical characteristics

Characteristics	**Pain Mean ± S.D**	**Test of significance**
Age 8 yrs : < 12 yrs 12 yrs : < 15 yrs 15 yrs : 18 yrs	 6.34 ± 0.90 8.11 ± 0.32 9.27 ± 0.45	 **F**= 486.24 **P** = < 0.001**
Gender Boys Girls	 6.89 ± 1.19 7.43 ± 1.35	**F**= 20.39 **P** = < 0.001**
Educational Level Primary Preparatory Secondary	 6.34 ± 0.90 8.13 ± 0.36 9.28 ± 0.46	 **F** = 470.99 **P** = < 0.001**
Medical Diagnosis Beta Thalassemia Major Sickle Cell Anemia	 7.13 ± 1.29 7.79 ± 1.34	**F** = 7.48 **P** = 0.007*
Transfusion times per Month Once Monthly Twice Monthly	 6.51 ± 1.23 8.07 ± 0.80	**F** = 213.26 **P** = < 0.001**
Complications related to hematological disorder:-		
Splenomegaly:- No Yes	 6.66 ± 1.35 7.54 ± 1.17	**F** = 47.64 **P** = < 0.001**

Cardiomegaly:-		
No	7.11 ± 1.31	**F** = 8.61
Yes	7.70 ± 1.28	**P** = 0.004*
Hepatomegaly:-		
No	6.88 ± 1.22	**F** = 57.61
Yes	7.84 ± 1.27	**P** = < 0.001**
Bone and joint complications:-		
No	6.95 ± 1.30	**F** = 41.98
Yes	7.89 ± 1.11	**P** = < 0.001**

*Statistical Significant at P < 0.05 ** High Statistical Significant at P < 0.001

Discussion

This study offers novel details on the frequency, severity, and interference caused by pain in children with hemoglobinopathies that need on transfusions. The current study's findings indicate that more than half of the participants under investigation experienced significant pain. The underlying scientific cause of sickle cell disease (SCD) and β-thalassemia patients is a mutation in the gene responsible for producing adult hemoglobin. Red blood cells in sickle cell disease (SCD) clump together, take on a characteristic sickle form, and obstruct the flow of oxygen and blood through small blood arteries, leading to severe consequences. **Anoosheh & Keikhaei's** study from 2022, which discovered that almost half of the children they observed experienced acute pain crises, supported these findings. These findings contradict those of a 2018 study by **Batta et al.,** which indicated that 48.75 percent of the children in the study had experienced the least amount of pain in the previous seven days. Only 10.5% of them, however, experience the worst pain.

The relationship between the children's clinical and sociodemographic traits and the revised Face, Leg, Activity, Cry, and Consolability scale (r-FLACC) that was explored. Regarding the age range of the children under study, it was discovered that the group with the greatest mean pain score was the 15–18 year old age group; also, those in secondary education had the highest score.

Initially, as the age of children with hematological disorders increases, they develop presbyalgos, which is a diminished capacity to perceive detrimental signals caused by impairments in the structure and function of pathways in the peripheral and central nervous systems that are involved in the processing of painful stimuli. This is caused by a reduction in the number of delta nerve fibers that detect signals of intense localized pain and a proliferation of non-neuronal glial cells that replace pain-transmitting neurons. Additional alterations, such as diminished proprioception and modified conductivity of peripheral nerves, heighten the likelihood of injury, thereby increasing the probability of experiencing pain. This observation could indicate a diminished capacity to endure pain of greater intensity, possibly due to the discovery that endogenous pain inhibitory systems are less efficient. Furthermore, as age increases and hematological disorder treatment durations prolong, neuroplasticity—the capacity to recuperate from injury and alleviate pain—appears to decelerate. Hematological disorder in older children is associated with prolonged episodes of hyperalgesia in response to painful stimuli. This, in conjunction with a sluggish recovery from injury, could result in extended episodes of pain and functional limitations. Furthermore, it is worth noting that as the age of a child with a hematological disorder increases, there is also a higher incidence of complications associated with the disease or its treatment. Such complications encompass osteoporosis, hepatomegaly, splenomegaly, hepatomegaly, and hepatomegaly. One prevalent symptom of these complications is pain, which is present in conjunction with the pain caused by the disease and the treatment regimen that necessitates regular cannulation.

Similarly, **Bakshi et al. 2023** found that there is an inequality in mean scores between age groups. The average pain ratings of children older than 12 years old were significantly higher than those of children younger than that age. However, **Pizzinato et al.'s 2022** findings indicated a high mean pain score in the 9-year-old male and preparatory school age groups.

It was shown that girls had the greatest mean pain score when it related to gender. According to the study, girls experience nearly all chronic pain disorders to a far larger degree than do boys.

The body releases a plethora of pain-relieving chemicals in response to injury, most notably the natural opioid beta-endorphins. This explains the gender disparities in pain levels

observed in children with hematological disorders. However, compared to male bodies, the bodies of many females release fewer beta-endorphins. Less natural painkillers may cause a female victim of the same injury to experience greater pain **(Flegge, Barr, and Craner, 2022).**

Females may be more sensitive to pain due in part to hormones. It was discovered that recurring pain in females was connected with changes in estrogen plasma levels. Additionally, women may experience pain more intensely than men due to their higher nerve density—more nerves in a given location of the body.

Moreover, there are distinct variations in the psychological perception of pain between females and males. For instance, it has been observed that females exhibit a greater likelihood to experience concern regarding pain and perceive a heightened sense of helplessness in relation to it. Additionally, females are more prone to developing anxiety and depression, both of which have been associated with elevated levels of pain. In contrast, males possess a wider array of pain coping mechanisms compared to females, potentially offering utility in some conditions.

The children with sickle cell anemia in the study had the highest average pain score. Vaso-occlusion (VOC)-related pain in sickle cell disease is frequently characterized as having a rapid, throbbing, and acute start. The joints, extremities, and lower back are common places to experience pain. Vaso-occlusive crises frequently have a one to two day prodromal phase before the pain peaks on day three and lasts until day six or day seven, at which point it resolves. Increased blood viscosity, erythrocyte adhesion, HbS formation, and heterocellular aggregate formation can physically obstruct small blood vessels, disrupting oxygen flow and limiting oxygen supply to tissues that need it. These factors can lead to sickle cell pain crises. This causes a sickle cell pain crisis, which is characterized by abrupt, intense pain that typically needs medical attention. The combination of ischemic tissue damage, hypoxia/reperfusion injury, and inflammation distinguishes SCD pain from that of thalassemia.

Consistent with our findings, a study conducted by **Harris et al. (2021)** corroborated the presence of elevated pain scores among individuals diagnosed with Sickle Cell Anemia. Soliman, Alaaraj, and **Yassin (2021)** observed a significant presence of elevated pain levels among the children who participated in the study and were diagnosed with Sickle Cell Anemia.

Those who received a transfusion of blood twice monthly also had the highest average score. Anemia, in which hemoglobin levels are abnormally low, is the primary symptom of hematological illnesses because it reduces the delivery of oxygen to tissues that need it. This causes instant, excruciating pain. In children with hematological problems, this process results in twice as much pain as in children with the same disorder who receive blood transfusions once a month. Patients who reported receiving a blood transfusion more frequently (every 2 weeks) than those who reported receiving a transfusion less frequently (every 4 weeks or every 2 months) had higher pain intensity scores **(Fung et al, 2022).**

In relation to the association between r-FLACC and socio-demographic and clinical characteristics, the findings of this study indicate that among the children with complications related to hematological disorders, those who presented with splenomegaly, cardiomegaly, hepatomegaly, osteoporosis, and bone deformity exhibited the highest scores for pain as assessed by the r-FLACC scale. Hepatomegaly, osteoporosis, and bone deformities are conditions that warrant attention. The study posited that the enlargement of the organ exerts pressure on veins and other organs.

High degrees of pain were reported by the children with splenomegaly studied by **Suttorp and Classen (2021)**. **Mohakud et al.'s (2022)** study found the same thing; patients with Sickle Cell Anemia who also experienced organ enlargement reported higher pain scores. Pain and cardiomyopathy were also found to have statistically significant relationships **(Naderi et al., 2022)**.

Conclusion

In total, greater than fifty percent of the children who participated in the study and had transfusion-dependent hemoglobinopathies experienced severe pain complaints. The findings of this study suggest that pain symptoms, along with sociodemographic and clinical variables, have a significant relationship to one another.

High levels and sensations of pain are reported by girls aged 15 to 18 who have been diagnosed with sickle cell disease, who transfuse blood twice monthly, and who suffer from complications associated to the disease.

Recommendations:-

It is highly recommended that children with transfusion-dependent hemoglobinopathies regularly undergo pain assessments and any other therapies that can help reduce their pain levels.

More study is required to identify pain's dynamics and the factors that shape it.

Children with hemoglobinopathies that require transfusions have special needs in terms of nursing care, including patient education, psychological support, and pain relief. It would be helpful to conduct research on children's pain treatment that focuses on the perspectives of both medical professionals and their patients. Care for patients should be based on professional impartiality rather than the provider's own values, attitudes, and beliefs.

Limitations:-

When doing an analysis of the research, it is essential to keep in mind that there are some restrictions. Due to the study's cross-sectional design, it was difficult to determine how much pain had accumulated throughout the course of the study. Second, because these data are solely from a single hospital, it is difficult to extrapolate them to other children who suffer from transfusion-dependent hemoglobinopathies and live in other surroundings. Third, there was no healthy control group that could be utilized to compare the levels of pain experienced by the two different groups.

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