Research, Society and Development, v. 9, n. 10, e6949109046, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i10.9046

Relationship between painful manifestations and the use of hydroxyurea in children and adolescents with sickle cell disease

Relação entre manifestações dolorosas e o uso da hidroxiuréia em crianças e adolescentes com doença falciforme

Relación entre las manifestaciones dolorosas y el uso de hidroxiurea en niños y adolescentes con enfermedad de células falciformes

Received: 10/04/2020 | Reviewed: 10/11/2020 | Accept: 10/13/2020 | Published: 10/14/2020

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Abstract

To analyze the profile of pain, its triggering factors, and the relationship with the use of hydroxyurea in children and adolescents with sickle cell disease. This was an analytical cross-sectional study of 80 patients with sickle cell disease, both male and female, aged 6 to 18 years, seen at the Center for Hematology and Hemotherapy of Pernambuco, Brazil. To assess the pain profile, forms with the adapted visual scale from the “Fear of Dental Pain Questionnaire – Short Form” were used. Fisher's exact test was used to evaluate the

association between pain manifestations and the use of hydroxyurea. Pain was reported by 68.7% of the patients and 52.7% of them reported severe pain, which eventually affected their daily routines. Physical triggers presented the highest rate (78.2%). The most frequent sites of pain were the trunk (80%) and lower extremities (54.5%), and constricting (40%) and deep (40%) pain were the most frequent types. Thirty percent of the patients reported being treated with hydroxyurea for prevention of painful events. It is concluded that the patients with sickle cell disease showed a high rate of painful events and physical factors, such as cold temperature, trauma and physical effort, were considered to be the most prevalent. There was no association between the use of hydroxyurea and pain improvement.

Keywords: Pain; Sickle cell disease; Child; Adolescent.

Resumo

Analisar o perfil da dor, os seus fatores desencadeantes e a sua relação com o uso da hidroxiuréia em crianças e adolescentes com a doença falciforme. Trata-se de um estudo transversal analítico realizado com 80 pacientes com doença falciforme, de ambos os sexos, na faixa etária de 6 a 18 anos, atendidos no Centro de Hematologia e Hemoterapia de Pernambuco, Brasil. Para avaliação do perfil da dor foram utilizados formulários que possuíam a escala visual adaptada de *Fear of Dental Pain Questionnaire-Short Form*. Foi utilizado o teste Exato de Fisher, para avaliar a associação entre o relato de dor e o uso da hidroxiuréia. Verificou-se que 68,7% dos pacientes relataram dor e destes 52,7% de intensidade forte com repercussões na sua rotina diária. Em relação aos fatores desencadeantes, os físicos apresentaram maior percentual (78,2%). Os locais mais comuns de relato de dor foram o tronco (80%) e os membros inferiores (54,5%); os tipos de dores mais frequentes foram em forma de aperto (40%) e profunda (40%). Trinta por cento dos pacientes faziam uso da hidroxiuréia como medicamento para prevenção das crises dolorosas. Conclui-se que pacientes com doença falciforme apresentaram percentual elevado de crises dolorosas e os fatores físicos, como temperatura fria, trauma e esforço, foram considerados os mais prevalentes pelo seu desencadeamento. Não houve associação entre o uso da hidroxiuréia e melhora da dor.

Palavras-chave: Dor; Doença falciforme; Criança; Adolescente.

Resumen

Analizar el perfil del dolor, sus factores desencadenantes y la relación con el uso de hidroxiurea en niños y adolescentes con enfermedad de células falciformes. Se trata de un

estudio transversal analítico de 80 pacientes con enfermedad de células falciformes, de ambos sexos, con edad de 6 a 18 años, atendidos en el Centro de Hematología y Hemoterapia de Pernambuco, Brasil. Para evaluar el perfil de dolor se utilizaron formularios con la escala visual adaptada del *Fear of Dental Pain Questionnaire-Short Form*. Por medio de la prueba Exacta de Fisher se evaluó la asociación entre las manifestaciones de dolor y el uso de hidroxiurea. El 68,7% de los pacientes manifestaron dolor, de los cuales el 52,7% indicaron dolor severo que eventualmente afectó a sus rutinas diarias. Los desencadenantes físicos tuvieron la tasa de dolor más alta (78,2%), siendo más frecuente en el tronco (80%) seguido por las extremidades inferiores (54,5%). Los tipos de dolores más recurrentes fueron constrictivo (40%) y profundo (40%). El treinta por ciento de los pacientes hizo uso de hidroxiurea para prevenir crisis de dolor. Para concluir, los pacientes con enfermedad de células falciformes manifestaron un alto porcentaje de eventos dolorosos y factores físicos como el frío, traumatismos y el esfuerzo físico, fueron los más prevalentes. No hubo asociación entre el uso de hidroxiurea y la mejoría del dolor.

Palabras clave: Dolor; Enfermedad Falciforme; Niño; Adolescente.

1. Introduction

Sickle cell disease (SCD) is a single-gene genetic and inherited disorder. It is caused by a mutation in the gene that produces hemoglobin A, converting it to sickle hemoglobin (HbS). Sickle cell anemia (SCA) is considered the most common type of SCD (Campelo *et al.*, 2018).

SCD is recognized by the World Health Organization (WHO) as a serious public health problem, having a large impact on the morbidity and mortality of affected individuals if it is left undiagnosed or is not treated properly (McGann, 2014). It has been estimated that 2 million Brazilians carry the HbS gene and 25,000 to 50,000 are believed to have the homozygous form. The distribution of SCD in Brazil is quite heterogeneous, but the northern and northeastern regions have the highest prevalence rates (6 to 10%) owing to the predominance of the African American ethnic group, a risk factor that is well established in the literature (Jesus, 2010).

Acute or chronic recurrent pain is the most frequent clinical manifestation, resulting from the occlusion of small blood vessels by sickle-shaped red blood cells (Ballas, 2007; Sorkin, 1997; Felix *et al.*, 2010). Other causes may also contribute to painful events, including endothelial activation, erythrocyte and leukocyte adhesion, vasoconstriction, coagulation

activation, cellular dehydration, inflammatory response, reperfusion injury, and impaired blood flow due to lower nitric oxide bioavailability (Brunetta *et al*., 2010).

Painful vaso-occlusive crisis, a marker of SCD, is the main cause of morbidity and the most common reason for emergency care and hospital admission. It may occur at a very early age, in the first months of life (Sousa *et al*., 2015; Fixler & Styles, 2002; Dumaplin, 2006).

To date, there is no specific treatment for SCD. The available drugs help relieve the symptoms, improving the patient's quality of life. One of these drugs, hydroxyurea, improves blood flow, increases fetal hemoglobin levels, and acts as an exogenous source of nitric oxide, reducing HbS concentration and the frequency of painful episodes (Silva-Pinto *et al.*, 2013). The aim of this study was to assess the profile of pain, its triggering factors and its response to hydroxyurea in children and adolescents with SCD.

2. Methods

This is an analytical cross-sectional study. The census sample was compound of 80 male and female patients aged 6 to 18 years with clinical and laboratory diagnosis of SCD, seen between February and June 2019 at the Center for Hematology and Hemotherapy of Pernambuco (HEMOPE), a referral center for the treatment of these patients. As a result of the specificity of the study population and the difficulty associated with random selection of patients with SCD, we used a nonprobability (convenience) sample. Patients diagnosed with attention deficit disorder and/or cognitive disorders were excluded from the study because these conditions might bias its results.

A form validated by the face validity method was applied to ensure the reliability of the data. A single researcher applied it so as to ensure the reliability of the collected data (Anastasi, 1982). This validation was conducted with 20% of the parents and/or legal guardians. The visual scale adapted from the *Fear of Dental Pain Questionnaire – Short Form* (S-FDPQ) was used to assess pain intensity. S-FDPQ was translated and validated for use with Brazilian children and adolescents (Ferreira & Colares, 2011). The visual scale consists of five faces that represent: 1- no pain, 2- mild pain, 3- moderate pain, 4- severe pain, and 5- unbearable pain.

All of the children/adolescents and their parents/legal guardians answered questions about the presence and site of pain experienced in the past 3 months. A drawing of a doll with segments of human body parts was used for easier identification of the site of pain, and

patients were asked to point to the affected region. Data were collected to determine the frequency and duration of pain; possible triggering factors such as cold temperature, trauma, and physical effort; psychological factors; fever and infection; type of pain; interference of pain with the daily routine; the approach to pain relief; and treatment used.

This study was approved by the Research Ethics Committee of HEMOPE (process number: 2.934364). The parents or legal guardians and the adolescents were informed about the research methodology and only those who signed the free informed consent form were eligible to participate.

Statistical analysis

Absolute and relative frequencies were estimated for the categorical variables, whereas mean, standard deviation, and median were calculated for the numerical variables. Fisher's exact test was used to assess the association between variables. Statistical significance was set at 5%. The data were typed into an Excel spreadsheet and the statistical calculations were made using SPSS (Statistical Package for the Social Sciences) version 23.

3. Results

Eighty patients were assessed and 55% were male, 57.5% were aged 6 to 11 years, and 81.2% were of mixed ancestry. With respect to SCD, 95% of the patients had SCA and 5% had some subtype of hemoglobinopathy such as HbS-beta+thalassemia. History of stroke was found in 15.0% of the patients, and spleen and liver disorders accounted for 28.8% and 18.8%, respectively. Table 1 shows the frequency of painful events in SCD patients.

Table 1. Assessment of the history of pain in patients with sickle cell disease. Recife, Brazil, 2019.

Variables	*n*	*%*
Presence of pain in the past 3 months?		
Yes	55	68.7
No	25	31.3
Have you felt this pain before?		
A few times	32	40.0
Many times	23	28.7
No	25	31.3
Interval between painful events		
Monthly	4	5.0
Bimonthly	11	13.7
Semiannually	25	31.3
Annually	15	18.7
No painful events	25	31.3

Source: Authors.

Regarding hydroxyurea, 30% of the patients had been using it for over 6 months. All of the patients reported that pain was related to SCD and the triggering factors were mostly physical (78.2%). The most commonly affected sites were the trunk (80%) and lower extremities (54.5%); the most common types of pain were constricting (40%) and deep (40%); and 23.6% of the patients reported that the pain was very frequent (Table 2).

Table 2. Assessment of pain profile in patients with sickle cell disease. Recife, Brazil, 2019.

Variables	*n*	*%* [a]
Pain intensity		
Mild	5	9.1
Moderate	15	27.3
Severe	29	52.7
Unbearable	6	7.5
Triggering factors [b]		
Physical	43	78.2
Biological	17	30.9
Not associated with any triggering factor	9	16.4
Site of pain [b]		
Head	6	10.9
Trunk	44	80.0
Upper extremities	13	23.6
Lower extremities	30	54.5
Type of pain		
Burning	4	7.3
Constricting	22	40.0
Deep	22	40.0
Other	7	12.7

[a] The percentage was obtained from 55 patients who had reported pain in the past 3 months.
[b] Given the possibility of more than one answer choice, the sum of frequencies is greater than the total number (55) of patients who reported pain.
Source: Authors.

Most children/adolescents stated that pain would interfere in their daily routines. When asked about what they did to relieve the pain, only one (1.8%) patient said the pain had gone away on its own and 98.2% mentioned taking some pain medication (Table 3).

Table 3. Assessment of the interference of pain in daily routine and approach used for pain relief in patients with sickle cell disease. Recife, Brazil, 2019.

Variables	*N*	*%*
Total	55	100.0
Has the pain kept you from:		
Sleeping?		
Yes	45	81.8
No	10	18.2
Eating/Drinking?		
Yes	38	69.1
No	17	30.9
Walking?		
Yes	21	38.2
No	34	61.8
Playing?		
Yes	39	70.9
No	16	29.1
Strolling?		
Yes	8	14.5
No	47	85.5
Going to school?		
Yes	44	80.0
No	11	20.0
Doing school work?		
Yes	5	9.1
No	50	90.9
Watching TV?		
Yes	6	10.9
No	49	89.1

What did you do to relieve the pain?		
The pain went away on its own		
Yes	1	1.8
No	54	98.2
You took some medicine		
Yes	54	98.2
No	1	1.8
You did something else		
Yes	20	36.4
No	35	63.6
Saw a doctor		
Yes	33	60.0
No	22	40.0
Were you hospitalized?		
Yes	34	61.8
No	16	29.1
Not informed	5	9.1

Source: Authors.

No significant associations were observed between hydroxyurea and pain intensity and frequency ($p>0.05$) (Table 4).

Table 4. Assessment of pain intensity and frequency based on the use of hydroxyurea by patients with sickle cell disease. Recife, Brazil, 2019.

Variables	Use of hydroxyurea						p value
	Yes		No		Group total		
	N	%	N	%	n	%	
Pain intensity							$p^a = 0.674$
Mild	2	9.1	3	9.1	5	9.1	
Moderate	7	31.8	8	24.2	15	27.3	
Severe	12	54.5	17	51.5	29	52.7	
Unbearable	1	4.5	5	15.2	6	10.9	
Pain frequency							$p^a = 0.820$
Rarely	1	4.5	3	9.1	4	7.3	
Sometimes	15	68.2	23	69.7	38	69.1	
Very frequently	6	27.3	7	21.2	13	23.6	

[a]Fisher's exact test. Source: Authors.

4. Discussion

Pain was an apparent symptom among the children and adolescents who participated in the present study and it is an important clinical manifestation of SCD. The analysis of the perception of painful events associated with SCA among children and their caregivers demonstrated that assessing pain in terms of its characteristics, impact, and coping and management strategies is a protective measure, as such assessment allows adopting approaches that could minimize the potential detrimental effect of pain on child development (Dias *et al*., 2013).

All participants considered that pain was closely related to SCD, but the type and intensity of pain varied considerably. Deep and constricting pain were the most prevalent types. As for pain intensity, severe pain accounted for 52.7%. As with the results found in the present study, other studies revealed that pain is regarded as severe by most children and that constricting pain is reported by them quite frequently (Dias *et al.*, 2013; National Institutes of Health, 2002; Yaster *et al.*, 2000).

The presence of pain was related to triggering factors, and physical triggers were the most prevalent. Previous studies have referred to painful events as frequently spontaneous, possibly triggered by infections, dehydration, acidosis, hypoxia, physical stress, fatigue, changes in temperature, and high altitude (Steinberg, 1999; Shapiro, 1989).

In relation to the pain site, most indicated that the trunk and lower extremities were mostly affected. A study has shown that preschool children with SCD felt pain predominantly in their extremities, whereas school-aged children and young adults complained of pain in the trunk (Shapiro, 1989).

Pain was considered a limiting factor for activities of daily living and for leisure activities, confirming the hypothesis that pain associated with SCD may cause physical and emotional imbalance (Schneider & Medeiros, 2012; Freire *et al.*, 2015; Marques *et al.*, 2015). Also, this study demonstrated that 61.1% of the patients needed hospital admission, predisposing them to a higher risk of infections and to deterioration of their clinical picture, thus affecting their social life and their quality of life.

Some studies have shown changes in the quality of life of children and adolescents with SCD as a result of systemic involvement (spleen and liver disorders and stroke) (Araujo *et al*., 2013; Taryn *et al*., 2016; Roberti *et al*., 2010). In the present study; however, these changes were unremarkable.

Manifestations of pain in individuals with hemoglobinopathies include episodes that require drug treatment as an attempt to ameliorate symptoms and improve the clinical picture (Tostes *et al*., 2008; Voskaridou *et al.*, 2010; Silva & Shimauti, 2006; Figueiredo, 2007). With the purpose of improving the quality of life of these patients, reducing the frequency of painful events, 30% of the children and adolescents in the present study were treated with hydroxyurea for prevention of painful events, showing a good treatment response, even though no significant association has been found between this medication and the intensity and frequency of pain. A study showed a reduction in the number of hospital admissions, painful events, and need of blood transfusions, but there was also no significant association with the use of hydroxyurea (Bandeira *et al*., 2004). Therefore, further studies with other designs should be conducted to assess the use of hydroxyurea in children and adolescents with SCD and the use of other drugs with the same benefits of hydroxyurea but without its toxicity, permitting a more comprehensive assessment of painful events.

5. Conclusion

The patients with SCD investigated showed a high rate of painful events, most of which were found to be associated with physical factors. Notably, the painful manifestation of SCD is characterized by multiple adverse effects that affect children and adolescents and also their families, with several consequences for their daily lives. Strategies for the implementation of public policies aimed at the prevention of painful events are necessary in order to change positively the course of the disease and improve the quality of life of patients.

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