The Use of Analgesic Drugs in Patients with Sickle Cell Painful Crisis

I Boyd[1], M Gossell-Williams[1], MG Lee[2]

ABSTRACT

Objective: *To determine the drug options used for pain in patients with acute sickle cell painful crisis at the University Hospital of the West Indies (UHWI), Jamaica.*
Method: *This retrospective study assessed all patients admitted to the UHWI between January 1, 2006, and December 31, 2010, with acute sickle cell anaemia painful crisis and the data obtained regarding site, severity, outcome and drug options selected for pain.*
Results: *There were 101 patients with a mean age (± SD) of 18.6 (± 14.3) years; there was no difference in gender (42 females, 59 males). Eight sites of pain were reported, with the most common site being the lower limbs (44.6%) and 60.3% experienced pain in more than one site. Most of the patients (75.2%) were diagnosed with severe pain. Drug options included opioid, non-opioid or a combination, with pethidine (76) and paracetamol (79) being the most common chosen opioid and non-opioid drugs selected for therapy. There was low correlation between pain severity and appropriate first-line treatment (Spearman's rho = 0.344;* $p < 0.000$*). All patients with "mild" and "mild to moderate" pain were initially treated and obtained resolution of pain with non-opioid based therapy. However, most of the patients with severe pain (55.3%) required a second-line and some third line (14.5%) of therapy for resolution at the time of discharge from the hospital.*
Conclusion: *Painful crisis in patients with sickle cell anaemia is associated with severe pain in 75% and most will require second-line therapy for adequate resolution. Physicians need to provide adequate pain relief to decrease morbidity in these patients.*

Keywords: Drugs, pain, painful crisis, sickle cell anaemia, sickle cell disease

El Uso de Analgésicos en Pacientes con Crisis Dolorosas por Células Falciformes

I Boyd[1], M Gossell-Williams[1], MG Lee[2]

RESUMEN

Objetivo: *Determinar las opciones de medicamentos usados para el dolor en pacientes con crisis de dolor agudo debido a las células falciformes, en el Hospital Universitario de West Indies (HUWI), Jamaica.*
Método: *Este estudio retrospectivo evaluó todos los pacientes ingresados en el HUWI entre el 1ero de enero de 2006 y el 31 de diciembre de 2010, con crisis dolorosas agudas por anemia de células falciformes, así como los datos obtenidos en relación con el lugar, gravedad, resultado y opciones de medicamentos seleccionados para el dolor.*
Resultados: *El estudio comprendió 101 pacientes con una edad media (± SD) de 18.6 (± 14.3) años. No hubo diferencias de género (42 hembras, 59 varones). Se notificaron ocho lugares de dolor, siendo las extremidades inferiores el sitio más común (44.6%), y el 60.3% experimentó dolor en más de un sitio. La mayor parte de los pacientes (75.2%) fueron diagnosticados con dolor severo. Las opciones de medicamentos incluyeron opiáceos, no opiáceos o una combinación, con petidina (76) y paracetamol (79), siendo los opiáceos y los no opiáceos los fármacos más seleccionados para la terapia. Hubo una baja correlación entre la severidad del dolor y el tratamiento adecuado de primera línea (rho de Spearman = 0.344;* $p < 0.000$*). Todos los pacientes con dolor "leve" y "leve a moderado" fueron tratados inicialmente, y alcanzaron la resolución del dolor con terapia basada en los no opiáceos. Sin embargo, la mayoría de los pacientes con dolor severo (55.3%) necesitaron*

From: [1]Department of Basic Medical Sciences, Pharmacology Section and [2]Department of Medicine, The University of the West Indies, Kingston 7, Jamaica, West Indies.

Correspondence: Professor MG Lee, Department of Medicine, Faculty of Medical Sciences, The University of the West Indies, Kingston 7, Jamaica, West Indies. E-mail: michael.lee@uwimona.edu.jm

 DOI: 10.7727/wimj.2012.272

terapia de segunda línea, y algunos terapia de tercera línea (14.5%) de terapia para la resolución en el momento del alta del hospital.

Conclusión: *La crisis de dolor en pacientes con anemia de células falciformes está asociada con dolor severo en el 75% de los casos, y la mayoría de ellos requerirá tratamiento de segunda línea para la resolución adecuada. Los médicos necesitan proporcionar alivio adecuado del dolor a fin de disminuir la morbilidad en estos pacientes.*

Palabras claves: Medicamentos, dolor, crisis dolorosas, anemia de células falciformes, enfermedad de células falciformes

West Indian Med J 2014; 63 (2): 480

INTRODUCTION

Sickle cell disease is a group of hereditary blood disorders affecting haemoglobin. Sickle cell anaemia (SCA) is inherited when both parents of the affected offspring carry the sickle cell trait and have the heterozygous genotype, HbAS. Patients with SCA therefore inherit a homozygous HbSS genotype (1). Sickle cell anaemia is characterized by the deformation of normal erythrocytes which causes them to appear sickled. This characteristic sickle shape results from the substitution of a valine residue for glutamic acid at position 6 in the beta-subunit of haemoglobin which causes distortion of haemoglobin fibres, thus changing the biconcave disc structure of red blood cells (2–4). Due to the distortion, the haemoglobin molecules aggregate into a foci and cause the cell membrane to collapse to give the red blood cells a 'C' shape under the microscope (5).

Patients with SCA may experience complications such as sickle cell painful crises. The prolonged interaction of sickled and endothelial cells along with plasma constituents is responsible for painful crisis in these patients (6). The pain experienced may be classified as either chronic – a mild prolonged pain due to destruction of bones, joints and visceral organs, or acute – severe pain due to the destruction of microvascular beds (6). While the severity and duration of pain vary among patients suffering from sickle cell painful crisis, there are some predictable patterns that most patients present with. In Jamaica, the most frequent sufferers of sickle cell painful crises range in age from five to 30 years. Patients most frequently experience pain in long bones and joints, but can also experience pain in the sternum, back and abdomen (5). Based on the pain pathophysiology, physicians frequently choose non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol and opiates to treat sickle cell painful crisis. These are the three main classes of analgesics that prove to be most effective in painful crisis.

This study explores the management of pain in sickle cell painful crises with analgesics in patients admitted to the University Hospital of the West Indies (UHWI), Jamaica. Trends in treatment will help to determine if the management and outcome of pain in sickle cell painful crisis is directly influenced by the severity of pain experienced by patients.

SUBJECTS AND METHODS

Patients admitted to the UHWI, Jamaica, between January 1, 2006 and December 31, 2010, with acute sickle cell anaemia painful crises, were reviewed. Hospital charts were obtained using the International Classification of Diseases (ICD) codes for sickle cell disease with acute crisis. Patients were included based on the following inclusion criteria: (a) patients admitted to hospital or seen as outpatients, specifically for pain related to sickle cell painful crisis, (b) patients treated with NSAIDs, paracetamol, narcotic analgesics or a combination of two or more of the three and (c) all the relevant patient data were available. Data collected included: gender, date of birth, severity of pain, duration of hospital stay, treatment received and outcome of treatment.

This study was approved by the University Hospital of the West Indies/University of the West Indies/Faculty of Medical Sciences Ethics Committee. The data obtained in the study were uploaded to SPSS (Statistical Package for the Social Sciences), version 16 to facilitate assessment of data with descriptive and inferential statistics. Therapy was grouped as 'first line' (received as initial treatment), 'second line' and 'third line' (first and second adjustments made to initial treatment). Association between pain severity and appropriate first-line management was assessed using Spearman rank correlation.

RESULTS

One hundred and one patients with acute sickle cell painful crisis were reviewed. The mean age (± SD) of the study population was 18.6 (± 14.3) years and median (interquartile range; IQR) was 13.0 (24). Most patients were between the ages of zero and nine years (37.7%) and 60.4% of the patients were between the ages of zero and 18 years. The study population distribution by gender was 59 (58.4%) males and 42 (41.6%) females with no significant difference in gender distribution ($\chi^2 = 2.861$; $p = 0.091$).

Pain was reported at eight sites (Table 1): generalized (patients who denoted their site of pain as generalized were not listed under any other category of site of pain to avoid counting the data more than once), abdomen, chest, back, lower limbs, upper limbs, joints (the joints were not counted as either upper or lower limbs) and penile (priapism). The most common site of pain was the lower limbs with 44.6% of

Table 1: Sites of pain and hospitalization days

Characteristics of pain	**Frequency (%)**							
Site of pain	**Generalized**	**Abdomen**	**Chest**	**Back**	**Lower limbs**	**Joints**	**Upper limbs**	**Penis (priapism)**
	11 (10.9)	42 (41.6)	25 (24.8)	20 (19.8)	45 (44.6)	22 (21.8)	25 (24.8)	2 -(2.0)
Number of pain sites	**1** 50 (49.5)	**2** 25 (24.8)	**3** 16 (15.8)	**4** 7 (6.9)	**5** 2 (2.0)	**6** 1 (1.0)		
Days of hospitalization	**1** 35 (34.7)	**2–3** 14 (13.9)	**4–7** 26 (25.7)	**8–14** 21 (20.8)	**> 14** 5 (5)			

patients reporting this site. The cumulative sites of pain showed that 1% of the patients experienced pain in six sites, with 49.5% of the patients experiencing pain in only one site. The days of hospitalization ranged from one day to greater than 14 days (Table 1). Most patients were hospitalized for one day (34.7%) and four to seven days (25.7%). There was no association between days of hospitalization and pain severity ($\chi^2 = 24.206$; $p = 0.234$). The pain scale used to assess the severity of pain in most patients was not recorded. Some charts contained a brief pain inventory questionnaire, filled out by the physician, while others showed evidence of the use of analogue pain scales that might have been verbally communicated to the patients. The results of pain assessment led to five categories of pain severities (Table 2). The most reported pain severity was severe, 75.2%, and 18.8% reported moderate pain. The least reported were: mild, mild to moderate and moderate to severe, 2% each.

The analgesic treatments consisted of non-opioid based (NSAIDs, aspirin, paracetamol, combination of two of these) and opioid based [opioid or opioid combined with one or two non-opioids analgesics] (Table 3). All patients experiencing mild and mild to moderate pain were treated initially with non-opioid based therapy and obtained resolution (Table 2). Of patients with moderate and moderate to severe pain (n = 21), most received non-opioid therapy (n = 16) and 12 obtained resolution of the pain, however, nine required second-line therapy. Of the patients with severe pain (n = 76), 34 resolved with first-line therapy; 42 required additional therapy while 11 required third-line of therapy. Further assessment of initial therapy for patients with severe pain showed that most (n = 62) initially received opioids as part of first-line therapy; however, 14 were initially given non-opioid based therapy. Most patients (n = 94; 93.1%) had resolved pain on discharge from the hospital. Two of the

Table 2: Pain severity and therapy

	Initial pain severity on presentation (frequency)					
	Mild	Mild to moderate	Moderate	Moderate to severe	Severe	Total
First line (n = 101)	**2**	**2**	**19**	**2**	**76**	
Non-opioid	2	2	16	–	14	34
Opioid	–	–	1	–	18	19
Opioid + non-opioid	–	–	2	2	44	48
Second line (n = 51)			**7**	**2**	**42**	
Non-opioid	–	–	5	2	12	19
Opioid	–	–	1	–	7	8
Opioid + non-opioid	–	–	1	–	23	24
Third line (n = 11)					**11**	
Non-opioid	–	–	–	–	5	5
Opioid	–	–	–	–	1	1
Opioid + non-opioid	–	–	–	–	5	5
Pain resolution						
Unresolved	–	–	–	–	7	7

Table 3: List of analgesics given to patient, grouped as non-opioid and opioids

Analgesic	Dose (route)	Number of patients
Non-opioids		
Paracetamol	250–1000 mg (O)	79
Diclofenac	25–75 mg (IM)	28
	6–50 mg (O)	38
Ibuprofen	400 mg (O)	4
Aspirin	325 mg (O)	1
Opioids		
Pethidine	15–100 mg (IM)	66
	20–75 mg (IV)	5
	50–100 mg (O)	5
Codiene	7.5–20 mg (O)	11
Morphine	1.5–10 mg (IM)	11
	5–20 mg (O)	5
Tramadol	100 mg (O)	1

O = orally, IM = intramuscularly, IV = intravenously

patients who experienced severe pain had unresolved pain upon discharge; five patients received a prescription to be treated as outpatients because their symptoms no longer required hospitalization.

Assessment of the association between pain severity and use of opioid or non-opioid based therapy for initial treatment using Spearman's rank correlation coefficient showed low, but significant correlation between these variables (0.344, $p < 0.000$). Assessment of the association between the therapy used and other lines of therapy could not be examined, as data on the pain severity at the time of changing to second line or third line were not noted.

DISCUSSION

About 5% of the world's population carries the genes responsible for haemoglobinopathies. There are 200 000 babies born with sickle cell anaemia in Africa each year (7). In Jamaica, sickle cell disease is the commonest genetic disorder, with the HbS gene present in 10% of the population and it is estimated that one in 300 babies is born with the HbSS genotype while one in 500 is born with the HbSC genotype (1).

Sickle cell painful crisis is one of the serious complications of sickle cell anaemia. It commonly manifests as pain in the back, abdomen, extremities and chest (5). The eight reported sites of pain in this study included: abdomen, chest, back, upper limbs, lower limbs, joints, penile and "generalized" pain. Many patients experienced pain in multiple sites simultaneously. Painful crisis is associated with vaso-occlusion and it is theorized that some precipitating factors of pain are: dehydration, hypoxia, emotional stress and increased viscosity (5, 8). These factors may prolong interaction of sickled and endothelial cells along with plasma constituents and thus trigger painful crisis (6).

The severity of pain in this study covered the entire range from mild to severe, which is typical of the wide range of pain severities expected from patients with crisis. While the quality of pain was not well documented in the patient data, other studies have described it as "deep-seated" and "boring" (8). Most patients in the study experienced severe pain (75.2%). Although acute pain crises are relatively common in patients with SCA, the pain is commonly incompletely treated (6).

The World Health Organization (WHO) ladder for cancer pain is used globally for the treatment of several types of pain conditions, including sickle cell crisis, and consists of a three-step ladder (9). Step 1, located at the bottom of the ladder, recommends treatment for persisting or increasing pain with non-opioid analgesics including paracetamol, aspirin, NSAIDS with or without the use of adjuvant therapy (medications that help to relieve pain but are not classified as analgesics). Step 2 of the ladder recommends treatment for mild to moderate pain with the addition of opioids, with or without non-opioid analgesics or adjuvant therapy. Step 3 of the ladder recommends treatment for moderate to severe pain with opioids, with or without non-opioid analgesics or adjuvant therapy**.** Treatment is given around the clock. This approach to pain therapy coupled with pain scales allows physicians to gain insight into how to treat pain conditions accurately. The ladder applies a step-up or step-down approach *ie* increasing pain severity requires a step-up approach while decreasing pain severity requires a step-down approach. Severe pain was experienced by 75.2% of patients in the study and hence they would have been treated with a step-down approach, where treatment would start with opioids and end with NSAIDs or paracetamol.

The treatment options identified in this study were divided into first, second and third lines because some patients received more than one round of treatment, where the pain was not resolved with the initial medications given. The lines of treatment also facilitated categorizing the possible combinations of medications that were given to some patients. In the present study, patients with mild pain were treated with paracetamol only or a combination of paracetamol and NSAIDs. Patients with moderate pain were treated with all medications in the study, except opioid based combination. Treatment for patients with moderate, moderate to severe and severe pain suggest some inconsistency with Step 3 on the WHO ladder which recommends the use of opioids as primary treatment for this group of pain. The Spearman's rank correlation coefficient (Spearman's rho) was used to assess the correlation between the severities of pain and the first line of treatment. The correlation between pain severity and first-line treatment (non-opioid based *versus* opioid based) suggests that there was a significant association. However, it was low; this is possibly related to the number of patients presenting in these categories who should have been managed initially with opioid based therapy (30 of 97 patients). Additionally, the incon-

sistence seemed to be more among the patients with moderate pain (only three out of 19 receiving opiate based therapy) than it was in patients with severe pain (62 out of the 76 received opioid based therapy). The outcome of pain showed that only patients with severe pain experienced unresolved outcomes. Opiate analgesics work centrally to relieve pain by acting on opiate receptors to inhibit the opening of the voltage-gated calcium channel and are very effective in rapid pain relief, especially in those patients who may not have had multiple exposures to this class of drugs (10). Unfortunately, over time, the use of opiates results in tolerance, dependence and severe adverse reactions such as respiratory depression (10). Physicians are often reluctant to give adequate dosages of analgesics because of concerns about addiction, tolerance and side effects (6). The Ministry of Health in Jamaica also identified reservations among physicians in Jamaica to prescribe opiates (11).

It is unclear if physicians in the study applied the WHO ladder for cancer pain in their treatment approach. However, there was a seemingly step-up or step-down approach used by the physician according to the severity of the pain. The low correlation between the reported severity of pain and the lines of treatment given may be due to other factors that influence pain treatment and its subsequent outcome. Those other factors may be the patients' response to pain, specialized treatment and alternative treatments.

There were several limitations in the present study. Although the patient charts recorded pain severity, the actual pain scale used was not documented. The labelling of patient pain site as general rather than pointing to a specific site could lead to overlap with other sites, hence causing some sites of pain to be counted multiple times.

In conclusion, the majority of patients in the study were young, below age 20 years and there was no difference in gender. Patients with mild and mild to moderate pain had only one line of treatment before resolution of pain and showed evidence of correct application of the WHO pain management ladder. There were, however, inconsistencies in the management of patients with more severe pain. The significant influence that pain can have on the quality of life request further studies focussing on how these inconsistencies can be reduced and thus ensure adequate pain relief.

REFERENCES

1. Asnani MR, Reid ME, Ali SB, Lipps G, Williams-Green P. Quality of life in patients with sickle cell disease in Jamaica: rural-urban differences [serial on the Internet]. Rural Remote Health 2008; **8:** 890. Available from: http://www.rrh.org.au/publishedarticles/article_print_890.pdf
2. Ingram VM. A specific chemical difference between globins of normal and sickle-cell anaemia haemoglobin. Nature 1956; **178:** 792–4.
3. Christoph GW, Hofrichter J, Eaton WA. Understanding the shape of sickled red cells. Biophys J 2005; **88:** 1371–6.
4. Guyton AC, Hall JE. Textbook of medical physiology. Philadelphia, PA: Elsevier; 2005.
5. Serjeant GR, Serjeant BE. Sickle cell disease. 3rd ed. New York: Oxford University Press; 2001.
6. Yale SH, Nagib N, Guthrie T. Approach to the vaso-occlusive crisis in adults with sickle cell disease. Am Acad Fam Phys 2000; **61:** 1349–56.
7. World Health Organization. Sickle-cell anaemia. Report by the Secretariat. Fifty-ninth World Health Assembly; A59/9. Geneva: World Health Organization; 2006. Available from: http://apps.who.int/gb/archive/pdf_files/WHA59/A59_9-en.pdf
8. Diggs LW. Sickle cell crises. Am J Clin Pathol 1965; **44:** 1–19.
9. World Health Organization. Cancer pain relief: with a guide to opioid availability. 2nd ed. Geneva: WHO; 1996.
10. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's pharmacology. Philadelphia: Churchill Livingston Elsevier; 2000.
11. Ministry of Health, Jamaica. Ministry of Health increases advocacy for improved pain management and palliative care. Kingston: Ministry of Health; 2010 Nov 15. Available from: http://www.moh.gov.jm/index.php?option=com_content&view=article&id=363:ministry-of-health-increases-advocacy-for-improved-pain-management-a-palliative-care&catid=1:latest-news&Itemid=80