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Pain Relief in the Sickle-Cell Crisis: Intravenous Morphine Versus Ketorolac; A Double-Blind, Randomized Clinical Trial

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Abstract

Background: Sickle cell disease (SCD) is a congenital hemoglobinopathy. A low Hb level and high hemoglobin-to-hematocrit ratio may lead to the vaso-occlusive crisis in patients, for the management of which hyperbaric oxygen, hydration, and pain relief therapy are proposed.

Objectives: In this study, we sought to compare the effects of morphine and ketorolac on relieving painful sickle cell crisis.

Methods: In this double-blind, randomized clinical trial, we recruited 92 SCD patients who referred to the Emergency Department of a university-affiliated hospital, in Mashhad, Iran, from December 2016 to May 2017. The patients were randomly assigned to two groups of ketorolac and morphine injections for relieving pain crisis according to the clinical conditions of the patients. Pain severity was measured by the visual analogue scale before and after the intervention. Data were analyzed using SPSS software.

Results: A total of 92 SCD patients were evaluated, while, 19 (21%) were female and 73 (79%) were male, with the mean age of 20.77 ± 8.6 years. At the pre-injection phase, the mean pain scores were 9.1 ± 0.4 and 9.1 ± 0.7 in the ketorolac and morphine groups, respectively. After the intervention, the mean pain scores were 3.7 ± 1.2 and 4.9 ± 2.1 in the ketorolac and morphine groups, respectively. A significant association was found between the pain score after drug injection and the administered drug (P = 0.006).

Conclusions: The management of pain crisis with ketorolac injection yielded the same results as the morphine injection in SCD patients. However, ketorolac was found to be associated with fewer side effects than morphine; thus, it can be beneficial for managing SCD patients suffering pain crisis.

Keywords: Anemia, Congenital, Hemoglobinopathies, Ketorolac, Morphine, Pain, Sickle Cell, Vaso-Occlusive Crisis

1. Background

Globally, sickle cell disease (SCD) is the most common genetic hematologic disorder (1). Pain is the most frequent symptom of SCD that often occurs in the form of sudden, severe episodes called a crisis. Vaso-occlusive crisis (VOC) of sickle cell anemia is a common, principal cause of hospitalization, and the major cause of mortality in affected adults (2). Patients with pain crisis frequently refer to Emergency Departments (EDs) for pain relief. The routine ED management of VOC consists of hydration, hyperbaric oxygen therapy, and analgesia, which requires using acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), or mild oral narcotic agents such as codeine for the treatment of mild pain. Patients with more severe pain are usually hospitalized and treated with parenteral narcotics (3). Most researchers propose the intramuscular administration of meperidine as the most common parenteral analgesic while others recommend other analgesics (4, 5).

Today, morphine is the most common drug used for pain management in EDs; however, the long-term use of parenteral narcotics may lead to drug addiction (6). Therefore, NSAIDs such as ketorolac are proposed as analgesics in patients with postoperative or dental pain (7). Ketorolac is the first injectable NSAID approved by the Food and Drug Administration (8). Lottenberg and Hassell reported that NSAIDs might be beneficial for the treatment of adults with SCD (9). The British and other therapeutic guidelines have proposed the use of NSAIDs to control mild-to-moderate and severe pain in SCD patients (10). In this study, we attempted to compare the injection of morphine as a narcotic with the injection of ketorolac as an NSAID for the treatment of painful sickle cell crisis in Emergency Departments.

2. Methods

2.1. Study Population

This study was a double-blind, randomized clinical trial performed among 120 patients with sickle cell anemia who visited the Edalatian Emergency Department, Imam Reza Hospital, from December 2016 to May 2017. The study setting was a general teaching hospital with approximately 65000 admissions per year, affiliated to Mashhad University of Medical Sciences, Mashhad, Iran. The exclusion criteria included the lack of any drug use for pain crisis relief, addiction to injectable morphine, and the use of other analgesics two hours before the intervention (Figure 1).

2.2. Sample Size

According to the study objectives, using the Mann-Whitney U test, the power of 90% for normal distribution, the non-inferiority set at three, the significance level of 0.05, and standard deviation of 1.5 for the population under study, the sample size for each group was calculated to be 42. Finally, 92 SCD patients were enrolled in the study.

2.3. Study Protocol

The patients were randomly assigned to two groups of ketorolac injection (n = 50; 30 mg/kg IV; group I) and morphine injection (n = 45; 4 - 10 mg diluted in 4 - 5 mL distilled water; group II). First, the pain intensity for each patient was determined using the visual analog scale (VAS; 0: no pain, 5: moderate pain, and 10: worst pain imaginable). Then, according to the peak effect of each drug, the onset of drug action was determined to be less than 5 min with the peak effect reaching after 20 min and the maximum duration of 7 h. The pain was assessed again in both groups using the VAS five min after the intervention (the peak effect of both drugs was less than 20 min) by another colleague who was blinded to the type of injected drug. No other analgesic was administered during the study period.

Complications and side effects associated with the administered drugs were recorded in both groups, including nausea and vomiting, dizziness, respiratory depression, addiction, skin rash in the injection area, bleeding from the injection site, hypotension, seizure, drowsiness, and allergic reactions.

2.4. Statistical Analysis

The per-protocol analysis was the comparison of treatment groups. The descriptive data were summarized as means, standard deviation, and/or percentages. The normality of the data was checked prior to data analysis using the One-Sample Kolmogorov-Smirnov test. To analyze the data including descriptive statistics, such as frequency and relative frequency, student's *t*-test and chi-square test were used. The Mann-Whitney U test was run for nonparametric data and the nominal data were analyzed using the Fisher's exact test. All analyses were performed using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA). The P values of less than 0.05 were considered statistically significant.

3. Results

In total, 92 SCD patients with pain crisis visited the ED setting during the trial, 50 (54.3%) of whom received ketorolac injection and 42 (45.7%) morphine injection. The mean age was 20.16 $\pm$ 9.1 and 21.5 $\pm$ 8.1 years in the morphine and ketorolac groups, respectively. The *t*-test reflected no significant difference between the two groups in the mean age (P = 0.186; Table 1).

3.1. Pain Severity Before the Intervention

The pain intensity was measured using the VAS, which showed the mean pain score of 9.1 $\pm$ 0.5 (range: 6 - 10) before administering the analgesics. In the ketorolac group, the mean pain score was 9.1 $\pm$ 0.4 (range: 8 - 10), while in the morphine group, the mean pain score was 9.1 $\pm$ 0.7 (range: 6 - 10; Table 1).

3.2. Pain Severity After the Intervention

The total mean pain score was 4.2 $\pm$ 1.8 (min: 2, and max: 9) after receiving the analgesics. The mean post-injection pain scores were 3.7 $\pm$ 1.2 (min: 3, and max: 9) and 4.9 $\pm$ 2.1 (min: 2, and max: 9) in the ketorolac and morphine groups, respectively (Table 1). The total pain score decreased in both groups after 5 minutes. The total relief of pain was statistically equal in the ketorolac (3.7 $\pm$ 1.2) and morphine (4.9 $\pm$ 2.1) groups (P = 0.000). The Mann-Whitney U test reflected a significant relationship between the type of drug and the pain score (P = 0.002).

3.3. Side Effects

Our results indicated that 86 (93.5%) patients showed no complications or side effects and six (6.5%) cases only showed side effects after drug injection. Fisher's exact test revealed a significant association between the type of drug and side effects (P = 0.007; Table 2).

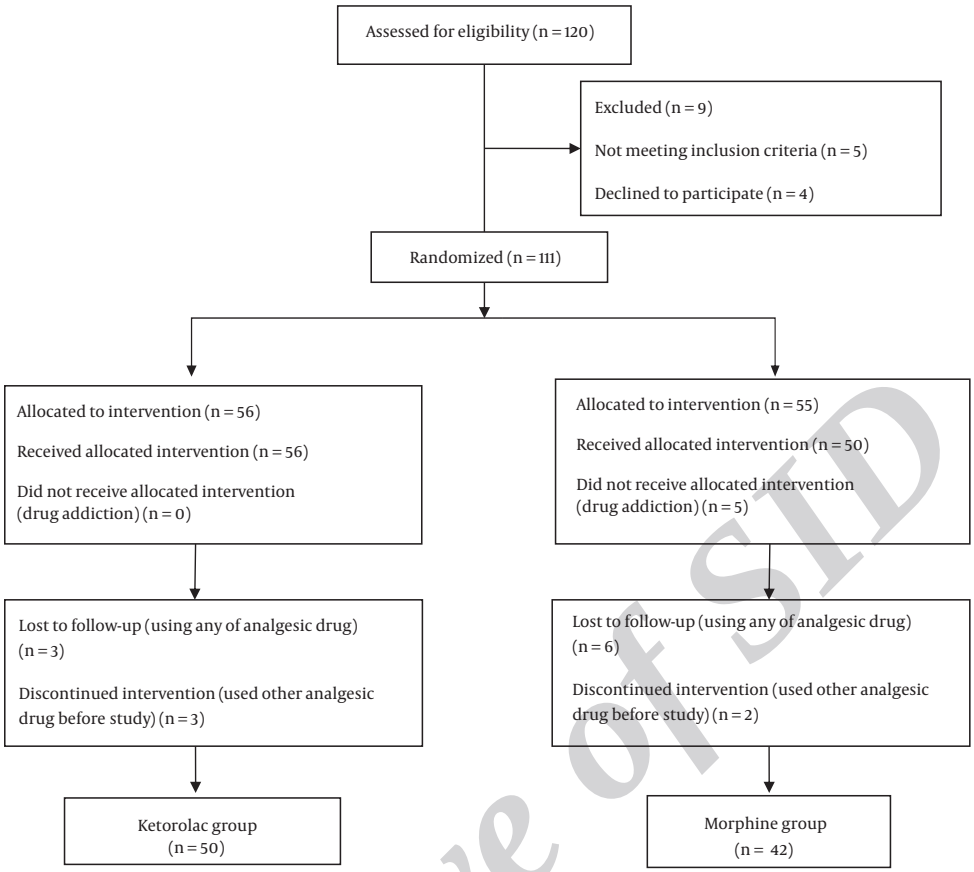

Figure 1. Flow diagram of the patients

Table 1. Comparison of Patient Characteristics[a]

Variable	Gender		Mean Age, y	Mean Pain[b] Score Before Intervention	Mean Pain Score After Intervention
	Male	Female			
Ketorolac injection (n = 50)	44 (88)	6 (12)	21.5 ± 8.1	9.1 ± 0.4	3.7 ± 1.2
Morphine injection (n = 42)	29 (68)	13 (31)	20.16 ± 9.1	9.1 ± 0.7	4.9 ± 2.1
Total (n = 92)	73 (21)	19 (79)	20.77 ± 8.6	9.1 ± 0.5	4.2 ± 1.8
P value	0.0001		0.0001	0.0001	0.0001

[a] Values are expressed as mean ± SD or No. (%).
[b] Visual Analogue Scale.

Table 2. Distribution of Drug Side Effects

Groups	Nausea and Vomiting, No. (%)		Drowsiness, No. (%)	
	Yes	No	Yes	No
Ketorolac injection	-	50 (100)	-	50 (100)
Morphine injection	6 (14.3)	36 (85.7)	4 (9.5)	38 (90.5)
P value	0.007		0.007	

4. Discussion

The results of this study indicated that the prevalence of SCD was higher among men than in women. The mean score of pain significantly decreased in SCD patients in both groups before using the drugs. The study of the side effects showed that patients who received ketorolac had no

complications after injecting the drug, but patients who received morphine showed nausea, vomiting, and drowsiness.

Pain crisis management is one of the most important health challenges in SCD patients visiting EDs. In this study, we injected morphine as a narcotic and ketorolac as an NSAID for the management of these patients. The international pain guidelines, such as those put forth by the World Health Organization, propose opioid agonists (e.g., fentanyl, morphine, pethidine, hydrocodone, and oxycodone) as the main agents for the treatment of moderate-to-severe pain (11, 12). Seya et al. reported narcotic analgesics consumption in the top 20 countries of the Human Development Index, measured as morphine equivalents (13). Since opioid agonists may have side effects or cause addiction, researchers are seeking to find suitable alternative analgesics for opioid agonists with better effects and fewer side effects (14, 15). Numerous guidelines pointed out that paracetamol, could be a proper treatment for pain relief in SCD patients (12).

Givens et al. showed that 43% of patients were given morphine as an analgesic for one month with no need to recall for four years (16). Bartolucci et al. reported that pain reduced in 71% of patients 24 to 48 h after receiving morphine, and no pain was reported until 30 h later. In 29% of patients, the pain did not reduce after taking morphine, leading to hospitalization (17). Campos et al. demonstrated that the pain of patients reduced about 30 min after receiving morphine and severe pain decreased immediately after taking the drug (18). Earlier studies reported that among SCD patients who visited EDs for pain crisis and used morphine either orally or intravenously for pain relief, pain decreased about 24 h after receiving the drug, and none of the patients was hospitalized.

Ketorolac is an NSAID with potent analgesic, anti-inflammatory, and antipyretic properties, which can be used for painful sickle cell crisis. Studies demonstrated that ketorolac is comparable with morphine in relieving pain (19, 20). Wright et al. (21), Ender et al. (14), Jacob and Mueller (22), Perlin et al. (23), and Udeza and Herrera (6) reported that anti-inflammatory agents such as ketorolac do well in treating pain crisis in SCD patients.

Herdwick et al. compared the effects of ketorolac and morphine on relieving pain crisis. The effects of the two drugs were similar, but in a number of SCD patients who used morphine, the medication was repeated after 2 h due to the high severity of pain. In severe pain management, in 53% of cases, ketorolac was more effective than morphine (24).

The results of our study indicated that ketorolac had the same effects as morphine for relieving pain crisis. Our results showed that ketorolac and morphine caused a significant difference in the mean pain scores before and after drug injection. According to these results and those of previous studies, both drugs have similar effects on relieving pain crisis. However, choosing more effective analgesics with fewer side effects should be considered for pain management in EDs.

Ketorolac is preferred to morphine in managing acute pain because, contrary to morphine, it does not have adverse effects on the central nervous system and does not cause respiratory depression and hypotension. Moreover, morphine reduces the movement of the digestive tract and may cause itching or allergic reactions; furthermore, the chronic use of morphine can lead to drug dependence (25). In addition, research has shown that ketorolac has proper efficacy in 25 to 50% of cases when compared to opiate drugs. In this study, we found no side effects for ketorolac while in the morphine group, nausea, vomiting, and drowsiness were observed in six patients.

Sickle cell crisis is a major cause of hospitalization among SCD patients. The use of narcotics for a long time can cause dependence while ketorolac, as an NSAID, can relieve pain crisis in patients, like morphine, but with fewer side effects. In this study and other studies, it was noted that ketorolac relieves acute pain, but the comparison of ketorolac and placebo for patients with severe pain can be unethical. Ketorolac as a drug that can relieve pain in the shortest possible time may be used for emergency patients. However, further studies with larger sample sizes are needed to determine the best pain crisis management strategy.

4.1. Conclusion

The classification of pain based on its severity can be effective in developing management plans for the pain crisis. It can be concluded that morphine and ketorolac yielded comparable results for relieving pain crisis in SCD patients. However, ketorolac had fewer side effects than morphine. On the other hand, given that ketorolac is an NSAID, it can be used as a good alternative to narcotic drugs in patients with pain, especially pain crisis in SCD patients. The use of an appropriate clinical approach to reducing pain crisis can lead to better pain management and improvement in these patients.

Footnotes

Authors' Contribution: Morteza Talebi Doluee: Designed and performed the experiments; Behrang Rezvani Kakhki: Collected and analyzed the data; Hamid Heidarian Mir: Performed analyses and edited the paper; Mahsa Fateminayyeri and Farideh Madanitorbati: Collected the data and co-

wrote the paper; Somayyehalsadat Hosseini: Designed the study and wrote the paper.

Clinical Trial Code: The study was registered at the Iranian Registry for Clinical Trials (IRCT20160725119 56N6).

Conflicts of Interests: The authors have no conflicts of interest.

Ethical Approval: The study protocol was reviewed and approved by the Ethics Committees of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1395.222).

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References

1. Brandow AM, Zappia KJ, Stucky CL. Sickle cell disease: A natural model of acute and chronic pain. *Pain*. 2017;**158 Suppl 1**:S79–84. doi: 10.1097/j.pain.0000000000000824. [PubMed: 28221286]. [PubMed Central: PMC5350013].
2. Ware RE, de Montalembert M, Tshilolo L, Abboud MR. Sickle cell disease. *Lancet*. 2017;**390**(10091):311–23. doi: 10.1016/S0140-6736(17)30193-9. [PubMed: 28159390].
3. Hoppe C, Jacob E, Styles L, Kuypers F, Larkin S, Vichinsky E. Simvastatin reduces vaso-occlusive pain in sickle cell anaemia: a pilot efficacy trial. *Br J Haematol*. 2017;**177**(4):620–9. doi: 10.1111/bjh.14580. [PubMed: 28369718]. [PubMed Central: PMC5435522].
4. Sokol E, Obringer E, Palama B, Hageman J, Peddinti R. Outpatient management of febrile children with sickle cell disease. *Clin Pediatr (Phila)*. 2016;**55**(3):268–71. doi: 10.1177/0009922815594345. [PubMed: 26149843].
5. Evensen CT, Treadwell MJ, Keller S, Levine R, Hassell KL, Werner EM, et al. Quality of care in sickle cell disease: Cross-sectional study and development of a measure for adults reporting on ambulatory and emergency department care. *Medicine (Baltimore)*. 2016;**95**(35). e4528. doi: 10.1097/MD.0000000000004528. [PubMed: 27583862]. [PubMed Central: PMC5008546].
6. Udezue E, Herrera E. Pain management in adult acute sickle cell pain crisis: A viewpoint. *West Afr J Med*. 2007;**26**(3):179–82. [PubMed: 18399330].
7. Arhami Dolatabadi A, Memary E, Kariman H, Nasiri Gigloo K, Baratloo A. Intranasal desmopressin compared with intravenous ketorolac for pain management of patients with renal colic referring to the Emergency Department: A randomized clinical trial. *Anesth Pain Med*. 2017;**7**(2). e43595. doi: 10.5812/aapm.43595. [PubMed: 28824859]. [PubMed Central: PMC5556593].
8. Steinberg AC, Schimpf MO, White AB, Mathews C, Ellington DR, Jeppson P, et al. Preemptive analgesia for postoperative hysterectomy pain control: Systematic review and clinical practice guidelines. *Am J Obstet Gynecol*. 2017;**217**(3):303–13. doi: 10.1016/j.ajog.2017.03.013. [PubMed: 28351670].
9. Lottenberg R, Hassell KL. An evidence-based approach to the treatment of adults with sickle cell disease. *Hematology Am Soc Hematol Educ Program*. 2005:58–65. doi: 10.1182/asheducation-2005.1.58. [PubMed: 16304360].
10. Olujohungbe A, Bennett L, Chapman C, Davis B, Howard J. *Standards for the clinical care of adults with sickle cell disease in the UK*. London, UK: Sickle Cell Society; 2008.
11. World Health Organization. *WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses*. WHO; 2012.
12. Solomon LR. Treatment and prevention of pain due to vaso-occlusive crises in adults with sickle cell disease: an educational void. *Blood*. 2008;**111**(3):997–1003. doi: 10.1182/blood-2007-07-089144. [PubMed: 17940207].
13. Seya MJ, Gelders SF, Achara OU, Milani B, Scholten WK. A first comparison between the consumption of and the need for opioid analgesics at country, regional, and global levels. *J Pain Palliat Care Pharmacother*. 2011;**25**(1):6–18. doi: 10.3109/15360288.2010.536307. [PubMed: 21426212].
14. Ender KL, Krajewski JA, Babineau J, Tresgallo M, Schechter W, Saroyan JM, et al. Use of a clinical pathway to improve the acute management of vaso-occlusive crisis pain in pediatric sickle cell disease. *Pediatr Blood Cancer*. 2014;**61**(4):693–6. doi: 10.1002/pbc.24864. [PubMed: 24249617].
15. Deloee MT, Zarmehri B, Pishbin E, Najafi MN, Salehi M. Intravenous acetaminophen versus intravenous morphine sulfate for isolated diaphyseal long bone fractures: A randomized clinical trial. *Trauma Mon*. 2017;**22**(4).
16. Givens M, Rutherford C, Joshi G, Delaney K. Impact of an Emergency Department pain management protocol on the pattern of visits by patients with sickle cell disease. *J Emerg Med*. 2007;**32**(3):239–43. doi: 10.1016/j.jemermed.2006.07.022. [PubMed: 17394984].
17. Bartolucci P, El Murr T, Roudot-Thoraval F, Habibi A, Santin A, Renaud B, et al. A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults. *Blood*. 2009;**114**(18):3742–7. doi: 10.1182/blood-2009-06-227330. [PubMed: 19717646].
18. Campos J, Lobo C, Queiroz AM, do Nascimento EM, Lima CB, Cardoso G, et al. Treatment of the acute sickle cell vaso-occlusive crisis in the Emergency Department: A Brazilian method of switching from intravenous to oral morphine. *Eur J Haematol*. 2014;**93**(1):34–40. doi: 10.1111/ejh.12293. [PubMed: 24571671].
19. Porta A, Aiolfi A, Musolino C, Antonini I, Zappa MA. Prospective comparison and quality of life for single-incision and conventional laparoscopic sleeve gastrectomy in a series of morbidly obese patients. *Obes Surg*. 2017;**27**(3):681–7. doi: 10.1007/s11695-016-2338-2. [PubMed: 27686234].
20. Son JS, Doo A, Kwon YJ, Han YJ, Ko S. A comparison between ketorolac and nefopam as adjuvant analgesics for postoperative patient-controlled analgesia: A randomized, double-blind, prospective study. *Korean J Anesthesiol*. 2017;**70**(6):612–8. doi: 10.4097/kjae.2017.70.6.612. [PubMed: 29225744]. [PubMed Central: PMC5716819].
21. Wright SW, Norris RL, Mitchell TR. Ketorolac for sickle cell vaso-occlusive crisis pain in the emergency department: Lack of a narcotic-sparing effect. *Ann Emerg Med*. 1992;**21**(8):925–8. [PubMed: 1497158].
22. Jacob E, Mueller BU. Pain experience of children with sickle cell disease who had prolonged hospitalizations for acute painful episodes. *Pain Med*. 2008;**9**(1):13–21. doi: 10.1111/j.1526-4637.2006.00252.x. [PubMed: 18254762].
23. Perlin E, Finke H, Castro O, Rana S, Pittman J, Burt R, et al. Enhancement of pain control with ketorolac tromethamine in patients with sickle cell vaso-occlusive crisis. *Am J Hematol*. 1994;**46**(1):43–7. [PubMed: 7514356].
24. Hardwick WE Jr, Givens TG, Monroe KW, King WD, Lawley D. Effect of ketorolac in pediatric sickle cell vaso-occlusive pain crisis. *Pediatr Emerg Care*. 1999;**15**(3):179–82. [PubMed: 10389953].
25. Maslin B, Lipana L, Roth B, Kodumudi G, Vadivelu N. Safety considerations in the use of ketorolac for postoperative pain. *Curr Drug Saf*. 2017;**12**(1):67–73. doi: 10.2174/1574886311666160719154420. [PubMed: 27440142].