

What is the optimal opioid analgesic in the management of sickle cell pain crisis?

Eze Onyegbule Okubuiro (FWACS, FHEA (UK))^{1*}, Chimaobi Tim Nnaji (FMCA, FWACS)² and Chinwe Edith Okoli (FMCA, FWACS)³

¹Centre for Evidence-Based Medicine, University of Oxford, United Kingdom

²Department of Anaesthesia, Federal Medical Centre, Owerri, Imo State – Nigeria

³Department of Anaesthesia, Federal Medical Centre, Umuahia, Abia State – Nigeria

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Abstract

Sickle cell disease is an autosomal recessive disorder that is common in people of African, Middle-Eastern and Mediterranean ancestry and its incidence varies from 10 to 40% of the population across equatorial Africa. The homozygous sickle cell disease affects about 2% of neonates in Nigeria and accounts for 25% of deaths in children under 5 years in Africa annually. The most common clinical manifestations are pain and anaemia. Pain associated with sickle cell pain crisis is usually severe, requiring treatment with strong opioids in addition to other interventions such as oxygen therapy and hydration with isotonic solutions. In order to accommodate the complex biopsychosocial components of this condition, pharmacotherapy, psychotherapy, functional restoration and other non-opioid pharmacotherapies need to be integrated in a multidisciplinary protocol for optimal outcome. There is a dearth of studies on the ideal analgesic regimen in the management of sickle cell crisis. Adoption of morphine PCA as the Gold standard in this condition is derived from studies on acute pain management protocols that are non-specific for sickle cell pain crisis. More research is needed to identify the most appropriate opioid analgesic protocol in the management of sickle cell pain crisis. Such study requires exploration of alternative methods of opioid administration as PCA equipment may not be universally accessible in places (especially, resource-limited settings) where sickle cell disease is most endemic.

Keywords: Sickle-cell-disease, management, pain-crisis, analgesia opioids.

Introduction

Sickle cell disease is an autosomal recessive disorder that is common in people of African, Middle-Eastern and Mediterranean ancestry [1]. Its incidence varies from 10 to 40% of the population across equatorial Africa [2]. Homozygous sickle cell disease (sickle cell anaemia) affects about 2% of new-borns in Nigeria and accounts for 25% of deaths in children under 5 years in Africa annually [3]. Although sickle cell anaemia patients have been credited with a mean life expectancy of 53 years in males and 58 years in females respectively, this period is characterised by innumerable hospital visits/admissions arising from complications of this condition [4].

Heterozygous sickle cell disease (carrier state) is usually asymptomatic and confers protection against falciparum malaria, which is endemic in the tropics [1]. "Sickle cell anaemia is the commonest severe inherited disorder of humans" [5]. The signs and symptoms of homozygous sickle cell disease do not manifest in a child until about 4 to 6 months of age. The most common clinical manifestations are pain (pain crisis) and anaemia (sequestration crisis) [3]. These are due to vascular occlusion by aggregation of deformed, sickle cell haemoglobin containing red blood cells. The acute vaso-occlusive painful episodes, which mostly affect the long bones of the extremities, back, sternum and abdomen are frequently recurrent, unpredictable and continue through life. Other sources of pain are priapism, avascular necrosis of the heads of femur and humerus and acute chest syndrome [6]. Pain associated with sickle cell pain crisis is usually severe, requiring treatment with strong opioids in addition to other interventions such as oxygen therapy and aggressive hydration with isotonic solutions. Morphine, because of its global availability and widespread

*Correspondence

Eze Onyegbule Okubuiro

Centre for Evidence-Based Medicine, University of Oxford, United Kingdom

E-Mail: raag.mishra@gmail.com

experience with its use, remains the most popular agent in the management of these episodes.⁷ It can be administered orally or parenterally (including patient controlled systems), depending on the patient's clinical state. Other potent opioids that have been used in the treatment of sickle cell pain crisis include; fentanyl, oxycodone, hydromorphone and meperidine with or without non-steroidal anti-inflammatory drugs (NSAIDs)[1,5,7]

National Institute for Health and Clinical Excellence (NICE) and the American Pain Society guidelines recommend opioids for the management of moderate to severe sickle cell vaso-occlusive pain[8,9] In order to accommodate the complex bio-psychosocial components of this condition, these bodies also recommend the integration of psychotherapeutic interventions, interdisciplinary therapy, functional restoration and other non-opioid pharmacotherapies. Although opioids have been proven to be effective in the management of sickle cell disease pain crises, they are associated with some debilitating side effects such as respiratory depression, drowsiness, constipation, tolerance, and dependence[7,9] The objective of this review is to determine the optimal opioid analgesic for the management of sickle cell pain crisis. It will utilize evidence from clinical research to compare the analgesic efficacy, side effects and quality of life of patients following the use of the respective opioids in the management of this crisis.

Literature review and critical analysis

Sickle cell haemoglobin (HbS) arises due to mutation of the haemoglobin gene[10]. The difference between normal adult haemoglobin (HbA) and HbS is the substitution of glutamic acid with valine at the 6th position of the β -chain of HbS. By six months of age, adult haemoglobin (HbA) predominates in the circulation of the infant. This heralds the onset of signs and symptoms in patients with homozygous sickle cell disease[11]

Sickle cell crisis may be triggered by infection, cold, dehydration or any hypoxic state. Following deoxygenation, HbS crystallizes and polymerizes with other similarly affected haemoglobins. This polymer grows and fills the red blood cell, disrupting its architecture and flexibility[10] As it is difficult for the deformed erythrocytes to navigate through the arterioles, there is aggregation with other deformed erythrocytes. This results in the blockage of the microcirculation leading to hypoxia of affected tissues. Such hypoxia and hypoxaemia, triggers further de-

oxygenation and crystallization of other aberrant haemoglobins thereby setting off a vicious cycle (vaso-occlusive crisis). The rate and extent of HbS crystallization is proportional to the extent and duration of haemoglobin deoxygenation[10]. Pain occurs in sickle cell vaso-occlusive crisis due to ischaemic tissue injury and local release of inflammatory neuromodulators[1,10]

The pain of sickle cell vaso-occlusive crisis has been described as worse than postoperative pain and as intense as cancer pain[11]. It is the most common and debilitating complication of sickle cell disease[12]. Usually, painful episodes last between 3 and 14 days. In children, there is involvement of the hands, feet, fingers and toes (hand and foot syndrome)[13]. Hospital management of this crisis includes oxygen therapy, aggressive rehydration, potent opioids with/without adjuncts and the identification/management of precipitating factors. On admission, opioids are administered via the fastest and most reliable route (intravenously), either as a continuous infusion or via patient-controlled systems[8,13] Traditionally, once pain is controlled, parenteral opioids are converted to oral medications, which are eventually weaned down before patient is discharged home on simple analgesics.

Opioids that have been employed in the treatment of sickle cell pain crises include morphine, fentanyl, pethidine, oxycodone, hydromorphone. Although the intravenous route is generally preferred, intramuscular, subcutaneous, transdermal and transmucosal regimens have also been used.¹³ However, systemic absorption via the later routes is unpredictable, affected by local circulation and tissue vascularization. Some side effects of opioids include respiratory depression, drowsiness, constipation, nausea and vomiting and hypotension. Others, associated with chronic use of opioids are dependence, tolerance, addiction, immunosuppression, gonado-suppression and opioid induced hyperalgesia[7,11]

Morphine is a pure opioid agonist that exerts its analgesic effect via excitation of the mu, kappa and delta and zeta opioid receptors in the body. It may be given orally, rectally, subcutaneously, intramuscularly or intravenously to relieve severe pains of sickle cell crisis[7] It undergoes extensive 1st pass metabolism (40 – 50%) in the liver following oral administration. Active metabolites of morphine are morphine-3-glucuronide and morphine-6-glucuronide; they are excreted in urine. These metabolites possess similar side effects but are twice as potent as morphine[14] Hepatic and renal impairments lead to accumulation of

morphine and its metabolites in the body and contribute to the prolonged side effects of the drug. However, studies have shown that glomerular filtration, renal and hepatic blood flow is increased in homozygous sickle cell disease as a consequence of chronic anaemia[7,15] This results in rapid clearance of morphine and its metabolites from the body requiring higher doses of the drug in order to maintain adequate analgesia during painful crises[7]

In 2007, Van Beers et al conducted a randomised controlled study that compared the effects of patient-controlled analgesia with continuous intravenous infusion of morphine during vaso-occlusive crises in 25 adults with sickle cell disease[16]. The study reported no significant difference in average pain relief after 2 days of morphine PCA (mean VAS = 5.3 cm) compared with morphine infusion (mean VAS = 4.9 cm), p -value=0.09. Assessments in quality of life remained unchanged in both groups. The mean daily morphine consumption was significantly less in the PCA group (0.5mg/hr) compared to the infusion group (2.4mg/hr), p -value=0.01. Incidence of nausea/vomiting was significantly greater in the continuous infusion group (p =0.045). One patient in the continuous infusion group suffered severe hypoxia that was treated with naloxone; none of such was encountered in the PCA group. This study affirms the analgesic efficacy and 'opioid sparing' potentials of morphine PCA in sickle cell vaso-occlusive crisis. It also showed that morphine PCA was safer and offered better patient satisfaction with fewer side effects than morphine continuous infusion.

The indifference in quality of life post-intervention in both groups may be related to the psycho-socio-economic effects of the recurrent crises on the life of patients. Morphine PCA equipment is more expensive than continuous infusion consumables, but, it requires less health personnel involvement and gives cognitively unimpaired patients some degree of control (self-confidence) over their pain management. However, this study is flawed by a lack of power calculation. The small study population ($n=25$) exposed the trial to a high risk of type-2 error. Also, there was no mention of the method of randomisation, inclusion/exclusion criteria and the statistical tools used in the analysis of data obtained. These adversely affect the credibility of the study.

Morphine is the gold standard in the management of sickle cell vaso-occlusive crisis (VOC)[7,11] However it is associated with dose related undesirable side effects. NSAIDS decrease the need for opioids with which it

acts synergistically[9]. With the aim of comparing the effects of ketoprofen and placebo as adjuncts to morphine, Bartolucci et al. (2009), recruited 66 adult sickle cell disease patients with VOC, who received continuous intravenous morphine infusion (2mg/hr) after initial 0.1mg/kg bolus dose on admission. In addition, they received either continuous intravenous infusion of ketoprofen 300mg/day or physiological saline (placebo). The primary outcome was pain relief assessed with VAS and categorical pain score (CPS). Other outcome measures were total consumption, treatment failure, side effects and toxicity of morphine.

Seven patients in each group (21%) were withdrawn from the study due to treatment failure (uncontrolled anaemia or vaso-occlusive crisis lasting >5 days or sepsis). This signifies that ketoprofen offers no protection against treatment failure that may occur using this regimen. There was no significant difference in pain relief between the two groups as assessed by VAS ($p=0.64$) and CPS ($p=0.46$). Opioid consumption ($p=0.64$) and side effects were similar in both groups. This study suggests that, although continuous intravenous infusion of morphine is effective in VOC pain management, co-administration of ketoprofen offers no additional benefit. This position is contrary to the expected synergy between NSAIDS and opioids[9] This is also contrary to the expected suppression of nociception transmission associated with the use of NSAIDS in this condition[9,11]

Routine infusion of full doses of morphine at pre-determined rates in both groups may have masked the effects of ketoprofen in this study. Assessment of NSAIDS as adjuncts to morphine PCA in vaso-occlusive crises may yield more accurate results. The high attrition rate in each group (7/33;21%), may have adversely affected the power of this study (90%), which was otherwise adequate. Also, categorical pain scale used in co-assessment of analgesic effects of the interventions may not have been sensitive enough to discern the pain experienced by the patients. VAS score of 0, allocated to sleeping patients might not have reflected these patients' true pain state

Fentanyl, a synthetic opioid that acts primarily at the mu opioid receptor is another opioid that has been used in this condition[18]. It is associated with fewer side effects than morphine. It also has a low molecular weight, high potency (100 times greater than morphine), and high lipid solubility[18]. These qualities enable trans-mucosal and trans-dermal administration. It has a short half-life, making it suitable for acute pain states where it may be given via

continuous infusion or patient controlled systems. In sickle cell pain crisis, fentanyl can be administered via transdermal or trans-mucosal (buccal and nasal) routes. The latter routes become attractive when there is difficulty in securing intravenous access. Drug bioavailability is 92%, with elimination half-life of 13-22 hours following transdermal application. However, absorption may be affected by skin temperature and local blood circulation. Also, delayed achievement of steady plasma concentration (>12 hours), difficulty in titrating the dose of transdermal fentanyl to patients' fluctuating vaso-occlusive pain, generate concerns regarding its use during such period[11].

The most common side effect of fentanyl is respiratory depression hypoventilation[18]. It causes less constipation than morphine. However, erythema, papules, itching and oedema have been reported at the site of application in some patients[18]. Unlike morphine, fentanyl does not cause dramatic hypotension or bronchospasm (does not cause histamine release). Its degradation by cytochrome P₄₅₀ in the liver yields inactive metabolites that are excreted in the urine.

In 1996, ten adolescents with sickle cell disease pain crisis were recruited into a study that aimed to determine the effects of transdermal fentanyl[19]. Seven and three of the patients had 25µg/hr and 50µg/hr transdermal fentanyl respectively based on body weight, while all of them received background morphine PCA (<2.5mg/hr). The outcome measures were pain and sedation status, vital signs and oxygen saturation. They reported a delay of 48 hours before achievement of minimum effective analgesic concentration of fentanyl in all the patients. Also, they reported no adverse effects in any of the patients. There was no reduction in the amount of supplemental morphine used during the 1st 48 hours in all the patients. This amount was noticed to be less after 48 hours of transdermal fentanyl administration, although, there was no test of significance. The trial demonstrates the unpredictable onset of action of transdermal fentanyl that makes this route unsuitable in acute pain management. However, the study is flawed by a small sample size, non-randomisation, lack of control group and power calculation. These methodological inadequacies challenge the clinical relevance of the findings.

A related randomised, double blind, placebo controlled clinical trial compared the effects of intranasal fentanyl with intravenous morphine in 67 children who presented to the emergency department with post limb

fracture pain.²⁰ They noticed that intranasal fentanyl (150µg/ml) at a dose of 1.7µg/kg, was equi-analgesic with bolus intravenous morphine 0.1mg/kg (p=0.753). Pain was measured with VAS before and 5 minutes after either of the interventions and, every 10 minutes thereafter for 30 minutes. The side effect profiles of both interventions were similar. However, the VAS used in pain assessment may have been too complex for these young children/adolescents. A numerical rating scale (although less sensitive) might have been more appropriate.

Intranasal fentanyl had an onset of 5 to 10 minutes while intravenous morphine had immediate effect. This study shows that intranasal fentanyl can be given during pain episodes before establishment of intravenous access. The duration of this study (30 minutes) may be considered too short to determine the effects of these interventions on clinical states with longer duration such as sickle cell disease pain crises.

Pethidine is another opioid agonist that has been used in sickle cell pain crisis management. It is administered intramuscularly or intravenously due to its poor oral bioavailability. With a half-life of 3 to 4 hours, it is metabolised by hydrolysis and N-demethylation in the liver to pethidinic acid and norpethidine respectively. Pethidine is the least potent and has the narrowest therapeutic window among synthetic opioids of clinical relevance.²¹ Its side effects include dysphoria, addiction, dependence, tolerance, sedation, nausea/vomiting, constipation and respiratory depression²⁰. Norpethidine is neurotoxic and has been implicated in seizures, coma and mortality following pethidine use[21-23].

A randomised control trial by Ozun et al. (2010) compared the effects of pethidine and tramadol on 68 adult sickle cell disease patients in pain crises[24]. The patients received either pethidine (1mg/kg) or tramadol (1.5mg/kg) on arrival at the emergency room. Analgesic effects and side effects of these drugs were monitored continuously for 2 hours. Patients in pethidine group recorded significantly better analgesia than the tramadol group (p<0.05). Side effect profiles in both groups were not significantly different. There was no incidence of neurotoxicity. No patient received more than 2 doses of either medication. The study suggests that pethidine is effective in the initial management of sickle cell pain crisis. It did not assess the effect of pethidine throughout the period of the pain crisis, which usually lasts between 3 to 14 days. Also, there was no mention of the method of randomisation or the statistical tools used in the analysis of results.

Absence of power calculation further diminished the clinical relevance of the study.

A Cochrane systematic review in 2009, identified only nine randomised control trials on management of sickle cell pain crisis[25]. These studies included clinical trials that employed opioid and non-opioid analgesics. The review could not be completed due to small patient population and lack of relevant data amongst other methodological drawbacks. However, the opioid sparing effects of NSAIDs was recognized in the management of sickle cell pain crisis. The report suggests the use of existing evidence based acute pain management protocols in the management of sickle cell pain crisis.

Conclusion

Sickle cell disease is the commonest severe genetic disorder of mankind [5]. Heterozygous sickle cell disease (carrier state) is usually asymptomatic and offers some protection against falciparum malaria that is endemic in the tropics [1]. However, homozygous sickle cell disease presents with symptoms of the disease. Unfortunately, this condition is associated with poor quality of life occasioned by lifelong recurrence of sickle cell crisis. There is no known cure for sickle cell disease although recent advances in stem cell therapy provide hope in the management of this condition. Aggressive management of sickle cell crisis, lifestyle modification (to avoid triggers) and genetic counselling are helpful measures adopted so far.

Pain is the commonest cause of visit/admission to the emergency department in sickle cell disease[11]. There is no study till date that has compared the analgesic efficacy of the opioids in the treatment of sickle cell pain crises[7,25]. Randomised control trials on opioids in the management of pain episodes in sickle cell disease are few and flawed by small sample population, lack of statistical power calculation and other methodological inadequacies[16-17,19,23]. These RCTs also lacked uniform outcome measures and employed diverse assessment and analytical tools that impairs fair comparison.

Morphine PCA is adopted as the gold standard in management of sickle cell pain crises. It provides adequate analgesia while delivering optimal doses required for the management of each sickle cell acute pain episode. Evidence from literature reviewed so far, favours its use in sickle cell pain crisis.[7,16,17,19,23] However, close patient monitoring is necessary because of associated dose dependent sedation,

drowsiness, respiratory depression, nausea and vomiting. Respiratory depression following its use responds to low dose naloxone. Immuno-suppression, gonado-suppression, headache and opioid hypersensitivity that can occur with chronic use of morphine calls for caution. However, none of these were reported in any of the studies analysed.

Fentanyl is about 100 times more potent and has fewer side effects than Morphine[18]. Fentanyl is associated with respiratory depression and tissue accumulation due to its high lipid solubility[18]. Whereas transdermal administration of fentanyl proved unsatisfactory due to prolonged and unpredictable onset of action, intravenous route has not been reported in the treatment of sickle cell pain crisis[19]. Intranasal use was as effective as intravenous morphine infusion in acute post fracture pain management[20]. However, this regimen has not been reported in sickle cell pain crisis management. Pethidine is unpopular in sickle cell pain management due to its associated adverse side effects, especially addiction and neurotoxicity[21-23]. Norpethidine, its neurotoxic metabolite is believed to competitively antagonise pethidine. It reduces analgesic potency of pethidine[21]. However, pethidine may be useful as initial treatment in sickle cell pain crisis[24]. It continues to receive patronage, especially in resource poor settings because it is cheap and readily available.

Although other opioids such as diamorphine, methadone, oxycodone and hydromorphone might be effective in management of acute sickle cell pain episodes, there are no RCTs that have assessed their use in this condition.

Recommendations

Due to the dearth of RCTs using opioids in the management of sickle cell pain crises, more randomised controlled trials that are sufficiently powered to assess the effects of different opioids/methods of administration in sickle cell pain crisis management is recommended. Uniform outcome measures and validated assessment tools need to be employed in such RCTs to ensure fair comparison. Results from such trials should be analysed using standard tools to ensure their credibility. The challenge of small study population may be overcome by performance of multicentre trials, which will also enhance credibility of the findings.

Psychosocial, economic and spiritual aspects of life of a sickle cell patient in painful crises are adversely

affected. Therefore, management of the patient should involve a multidisciplinary team comprising Physicians (Haematologists, Pain Physicians, Intensivists), Pharmacists, Nurse specialists, Psychologists, Occupational therapists, Social Workers and Priests in order to ensure favourable outcome. Family and group therapies are encouraged to initiate and reinforce positive coping strategies and lifestyle in patients and their family. Multimodal analgesia (with opioids, simple analgesics and NSAIDS) is recommended in the management of this condition to reduce opioid consumption and side effects.

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