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Review

The acute pain crisis in sickle cell disease: What can be done to improve outcomes?

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ABSTRACT

The acute pain crisis (APC) is the commonest complication of sickle cell disease (SCD). Severe episodes may require treatment in hospital with strong opioid analgesic drugs, combined with additional supportive care measures. Guidelines for APC management have been produced over the past two decades gathering evidence from published studies, expert opinion, and patient perspective. Unfortunately, reports from multiple sources indicate that guidelines are often not followed, and that acute care in emergency departments and on acute medical wards is suboptimal. It is important to understand what leads to this breakdown in health care, and to identify evidence-based interventions which could be implemented to improve care. This review focuses on recently published articles as well as information about on-going clinical trials.

Aspects of care which could potentially make a difference to patient experience include availability and accessibility of individual care plans agreed between patient and treating specialist, innovative means of delivering initial opioids to reduce time to first analgesia, and availability of a specialist unit away from the ED, where expert care can be delivered in a more compassionate environment. The current evidence of improved outcomes and health economic advantage with these interventions is inadequate, and this is hampering their implementation into health care systems.

1. Introduction

The acute pain crisis (APC) is the commonest complication of sickle cell disease (SCD). These episodes of pain are unpredictable in onset and duration and can progress to life-threatening complications, including acute chest syndrome, acute fat embolism syndrome and multi-organ failure. Severe episodes may require treatment in hospital with strong opioid analgesic drugs, combined with additional supportive care measures. Careful monitoring of pain score and vital signs is essential to ensure adequate pain control, to avoid adverse effects of analgesic drugs, and to expedite intervention to manage complications [1].

Guidelines for APC management have been produced over the past two decades gathering evidence from published studies, expert opinion, and patient perspective. Unfortunately, reports from multiple sources indicate that guidelines are often not followed, and that acute care in emergency departments and on acute medical wards is suboptimal, leading to patient dissatisfaction, anxiety, and sometimes to avoidable harm. In the UK, this was recently highlighted in the report 'No one's listening' prepared by the All Party Parliamentary Group on Sickle Cell Disease and Thalassaemia (APPG) [2]. This identified a wide range of deficiencies in services, and highlighted that the National Health Service (NHS) core values of respect and dignity, compassionate care, quality, and inclusion are not being consistently applied to people living with SCD.

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It is important to understand what leads to this breakdown in health care, and to identify evidence-based interventions which could be implemented to address these problems. This applies not just in the UK, but to most other high income countries in Europe and North America where SCD patients are being managed in increasing numbers. For countries with very high prevalence in indigenous populations, and with less well developed health care systems, such as Sub-Saharan African countries, and India, the standard practice for managing APC is less well documented, and other solutions may be needed, requiring a broader public health approach.

2. Methodology

This review focuses on interventions which might improve the management of pain in an acute health care setting, and does not address home management of pain, management of chronic pain, or pharmacological therapies to abort or attenuate APC. We identified four current guidelines which included literature reviews and robust methodology in formulating recommendations:

1) The National Institute of Health Care Excellence (NICE) guideline, first published in 2012 for the UK National Health Service (NHS) [3]. This was based on a systematic review of literature up to 2012. A follow-up surveillance report was published in 2016 without any new publications or major on-going studies identified which would alter the recommendations in the original document.
2) The National Heart Lung and Blood Institute (NHLBI) USA published an expert panel report entitled 'Evidence based management of Sickle Cell Disease' in 2014 based on a literature review covering the period June 2010 and July 2014. The panel made 17 recommendations around the management of an APC, including introduction of individualized care plans, rapid initial administration of analgesia, and proactive re-assessment and re-administration of analgesia [4].
3) The ASH guideline undertook a thorough review of literature up to 2017 and used validated methodology to develop and appraise important questions relating to pain management [1]. The ASH panel noted that optimal pain management is interdisciplinary and the panel focused on specific topics, including opioid therapy, non-opioid pharmacological therapies, non-pharmacological and integrated approaches to interdisciplinary care that incorporates both pharmacological and non-pharmacological interventions.
4) A Cochrane review on pain management for children and adults with SCD based on a literature search up to September 2019 [5]. This was described as the first systematic review encompassing the search of all drugs implemented during a VOC, and replaced a previous Cochrane review on pain which had a slightly broader remit [6]. The authors concluded that the amount and quality of evidence around the use of pharmacological treatments for acute pain in SCD is very low, and they were not able to determine whether one pharmacological treatment is more effective than any other, nor make judgement about adverse events. They suggested that treatment decisions are largely based on clinical experience and advice from respected authorities.

These guidelines have helped in establishing a consensus on the important metrics which determine the quality of care of APC, and which can be used to develop end points for use in comparative clinical trials. Although there is clearly some overlap, we have listed these as 'patient-centred' and 'health service' metrics in Table 1.

As a starting point, we reflected on the conclusions contained in these guidelines, and then reviewed articles which had been published from 2018 until August 2023 as well as information about on-going clinical trials. Search terms included were 'Sickle' plus 'pain', 'VOC', 'analgesia', 'crisis'. We initially searched PubMed and Clinical trials.gov, and subsequently interrogated Scopus and Web of Science over the same time period to verify we had not missed any relevant articles.

3. General observations

The majority of observational and interventional studies have been undertaken in the USA. Thus, conclusions should be applied cautiously in other countries with different health care systems, and consideration should be given to different demographic and socio-economic profiles, access to health care, and previous exposure to SCD disease modifying therapies and analgesic drugs. There is a substantial body of literature around management of APC in the UK, but very little from the rest of Europe. While patient numbers in France are comparable to UK, numbers in many European countries comparatively small, but increasing rapidly due to immigration. Going forward. it will be important to evaluate models of APC care and patient reported outcomes, perhaps integrated through organizations such as EuroBloodNet [7].

One important consideration is that chronic exposure to strong

Table 1
Metrics for evaluating and comparing analgesia protocols and models of care for APC.

Patient-centred metrics
• Reduction in pain score
• Rate of adverse effects, particularly related to opioid therapy
• Analgesia dosage (usually expressed in morphine equivalents)
• Adherence to agreed care plan
• Time to 'Readiness for discharge".[1]
• Patient satisfaction
• Quality of life
• Loss of schooling or employment for patient and carer
Health service metrics
• Time to first analgesia
• Time to second and subsequent analgesia doses
• Admission to hospital bed versus discharge from ED/Ambulatory care
• Length of hospital stay
• *Re*-admission rate
• Overall cost to health care system of delivering service
• Cost of social care
• Overall societal costs of managing APC in the SCD population

[1] A composite of reduced pain score, no further need for parenteral analgesics, and judgement by physician and patient.

opioids may induce tolerance which would attenuate their analgesic effect, as well as contributing to the development of central sensitization and hyperalgesia, which may be confused with acute vaso-occlusive pain, and is less likely to respond to standard analgesia. There is some evidence that exposure of SCD patients to chronic opioid therapy may be higher in the USA compared to Europe [8–11].

The increase in opioid use, dependence, and overdose deaths in the general (non-SCD) population of the US has been named the "opioid crisis". This opioid crisis has heightened problems and raised concerns about over prescription and balance between pain control and adverse effects of opioids in SCD patients. Overwhelming pain is a frequent experience for patients with sickle cell disease, and pain management is crucial. They are therefore affected by the ongoing opioid crisis, particularly in the USA. Increasing restrictions make it difficult for patients to access the opioids they need, and a focus on reducing opioid use without a pain management plan has also affected the quality of patient care. In February 2022, the US Centers for Disease Control and Prevention published their proposed clinical practice guideline for prescribing opioids, reversing some prescribing limits and suggesting prescribing healthcare providers use their best judgement. However, it was made clear that these guidelines will not apply to sickle cell disease, although they do reinforce a role for opioids and suggest that specific guidelines are forthcoming. The lack of clear guidance for opioid use in sickle cell disease will no doubt add to the frustration of patients who continue to suffer [10,12].

4. Individualized care plans (ICP's)

4.1. Design and implementation of ICP's

Individualized care plans (ICP's) are documents that contain information about an individual's particular SCD history and tailored recommendations for management of APCs, co-designed and agreed in advanced by the patient. There is a broad consensus that ICP's are an important first step to ensuring consistent, safe, and effective treatment. ICP's should be developed in consultation between the patient, together with the acute and SCD-care providers and should include medications and doses that are effective for a given patient. Plans can be embedded in the electronic medical record [1,4].

The problems with practical implementation and adherence to ICP's have been well documented in different settings [13,14]. The 'No One's Listening' report highlighted the failure to comply with ICP's even when jointly agreed between the patient and their haematology consultant [2]. In this report, patients stated that healthcare professionals in ED would still question the validity of their care plan.

Observational studies in paediatric services show that when ICP's are accessible and adhered to, they increase the likelihood that initial opioid dosing and follow-up doses are given within the recommended timeframe, and can contribute to a reduced rate of hospitalization length of stay in hospital [15–19]. From the adult care perspective, Welch-Coltrane et al. conducted a health care improvement project in which ICP's were introduced for high utilizing subjects. The initiative took place in a single academic health centre in the USA, where ICP's were developed by a multidisciplinary team including haematologists, ED physicians and pain specialists. ICP components included individualized opioid dosing (with specific opioid selected from a range of options), non-opioids and non-pharmacological agents as well as an in-patient pain specialist consultation. During implementation there was a reduction in opioid usage, as well as lower admission and 7-day readmissions rates and reduced health care costs [20].

The UK National Health Service Race & Health Observatory found inconsistencies in provision, due to wide variations in format and interpretation by healthcare professionals or patients and concluded that digitalizing care plans might address some of these issues [21]. This has led to a project to make digital universal health care plans (UCP's) available for all SCD patients treated in the NHS. The UCP will be accessible to health care providers in primary care, ambulance and ED settings, as well as the patient and will include the individualized pain management protocol. [22] In the USA, ALIGN is a multi-centre study to evaluate a structured, framework-informed approach for implementing electronic health record-embedded ICP's with both patient and provider access in routine ED practice. This study will be the first to report on individual pain plans available in the electronic medical record patient portal in the United States [23].

4.2. Opioid dosing in ICP's

With regard to the specific dosing schedules within the ICP, the ASH guideline and NHLBI expert report recommended tailored opioid dosing based on consideration of baseline opioid therapy and prior effective therapy. To evaluate this approach, Tanabe et al. randomized 52 patients to a standard weight-based dosing of intravenous (IV) opioid (starting opioid dose based only on weight e.g. hydromorphone 0.02 mg/kg, morphine sulfate 0.1 mg/kg) or individualized dose (ID) determined by the SCD team and based on maximal home opioid usage. The study took place in two urban academic medical centers with emergency medicine residency programs. Reduction in pain score from arrival to discharge was significantly improved, and there was an 18% absolute reduction in the rate of admission to hospital in the ID group. The initial opioid dose was higher in the ID group compared to weight-based dosing (12 mg vs 8.5 mg IV morphine equivalent), and the latter was a relatively low dose compared to standard protocols [24]. A follow-up analysis of data from this study showed a more rapid reduction in pain (time to achieve an absolute 13 mm, or 30% reduction from baseline measured by visual analogue score) in the ID group [25].

Subsequently, a larger trial was undertaken in which an ID protocol was compared with weight-based opioid dosing in 6 sites across the USA. This trial took place during the COVID19 pandemic and closed early without reaching the target sample number. 96 episodes were evaluable, where, in contrast to the previous study, there was no difference in pain score associated with individualized dosing. This was probably due to prescription of very similar opioid doses in both weight based and individualized protocol groups [26].

The investigators concluded that the benefits of individualized protocols are worth the logistical investment. However, it is not clear how much difference individualized opioid dosing plans would make in different health care settings outside of the USA, where there is less use of chronic oral opioids for home management of pain. In these settings, ED staff may prefer more standardized approach to opioid dosing which might avoid logistic difficulties in prescribing on an individual level. One potential compromise would be the use of standardized dosing for those SCD patients who have relatively low opioid requirements outside of hospital and do not attend regularly, with individualized dosing reserved for the minority of patients with high opiate use at home. These suggestions could be evaluated by undertaking trials of similar design in a range of different health care settings, and including a more detailed health economic evaluation.

5. Alternatives routes of opioid administration

Trans mucosal (e.g. sublingual, buccal or intranasal) drug administration has potential advantages over IV and oral routes, enabling direct access to the blood stream without the need for IV cannulation and avoiding gastrointestinal and hepatic first pass metabolism. Several trials of trans mucosal opioids for acute pain have shown that time to analgesia can be improved with acceptable safety compared to IV opioid alone [27]. There has been recent interest in using these formulations as a means of optimizing time to first analgesic dose for SCD patients [28–32].

Pilot studies from one institution have shown that a single immediate dose of intranasal diamorphine (0.1 mg/kg single dose) given at the same time as the first dose of oral morphine in an oral morphine protocol

resulted in rapid analgesia for children [33,34]. Fein et al. conducted a single centre randomized controlled trial comparing a single immediate dose of intranasal fentanyl (INF, 2μg/kg, maximum dose 100μg) with saline placebo in children presenting with acute pain [29]. Subjects in both arms went on to receive standard IV morphine and non-steroidal anti-inflammatory agents from 20 min after receiving study drug. The design of the study necessitated patients randomized to INF receiving opioids at least 20 min before those in the placebo group, and perhaps not surprisingly had a significant improvement in pain score at 20 min compared to placebo. In a multicenter retrospective review of treatment of children presenting to ED in academic centres in North America, 19% had been given INF, and these children had a 9-fold increased probability of being discharged home form ED rather than admission [35].

Sublingual fentanyl has also been evaluated in adolescents and adults when used as initial analgesia combined with oral oxycodone. The first stage of the study was a dose finding protocol using metrics of opioid toxicity (reduced respiratory rate, increased sedation score) as end points. The study found that a 400μg dose of sublingual fentanyl was safe and effective in patients weighing less than 50 kg and 600μg in patients weighing more than 60 kg, irrespective of previous opioid exposure [36]. A trial in 20 adults using a crossover design evaluated the addition of one or more doses of fentanyl buccal tablet to a standard multimodal analgesia intravenous infusion of ketorolac (a non-steroidal anti-inflammatory agent) with tramadol 7.2 mg/kg/day for 72 h. Buccal fentanyl at 100μg up to a total of 400μg over a 24-h period was administered three hours into the analgesia protocol. Addition of fentanyl did not result in toxicity and improved overall pain scores [30].

In conclusion, there is accumulating data on use of a limited number of doses of trans mucosal fentanyl for initial analgesia, suggesting that this might provide an alternative to IV opioid and enable more rapid administration after arrival in the acute care setting. Further studies are needed to compare intranasal and sublingual routes, to establish the range of safe dosing, and to clarify how trans mucosal fentanyl can be combined with other opioids to sustain analgesia during the course of the APC. Bioavailability of transmucosal fentanyl differs between children and adults [37], and since the majority of the published data in acute sickle pain management is from paediatric populations, it is important to conduct more studies in adult populations to explore questions of dosage, efficacy and safety.

6. Background opioid analgesia

Severe pain during an acute pain episode may persist for days or even weeks, and some form of supplementary continuous or background analgesia may be needed to avoid fluctuations in analgesia with intermittent boluses. One therapeutic approach is to use continuous opioid infusion via a patient-controlled analgesia (PCA) pump. The ASH guideline reported that addition of a continuous IV opioid infusion to the on-demand dosing schedule via PCA is a widespread practice, but found insufficient evidence on efficacy and safety to make a recommendation. The authors were concerned about the possibility of harm through excessive opioid dosing via continuous infusion if patients were not monitored carefully and dose adjusted in the case of respiratory suppression or over-sedation.

Another approach to background analgesia is the use of modified-release (MR) oral opioid. The only controlled trial comparing oral MR opioid versus continuous IV infusion was a small study in children, concluding that MR morphine could be used as an alternative to continuous IV morphine for the management of painful episodes in children [38]. In this study the dose of MR morphine was high (1.9 mg/kg twice daily) and may have contributed to the increased rate of acute chest syndrome in the oral group [39]. One centre has developed oral protocols using a lower dose of oral MR morphine, or MR oxycodone. Although uncontrolled, studies involving these oral background protocols show the oral MR opioids can be used with acceptable efficacy and safety in children and adults [34,36].

In conclusion, although background analgesia is often required for adequate control of pain in the hospital setting, it is not clear whether to recommend a continuous opioid infusion, or use of oral MR opioid for background analgesia. The latter may allow a more flexible approach to ambulating a patient and enable earlier discharge from hospital. Potential harms include the risk of adverse opioid effects through continuous administration, prolonged hospital stay while doses are weaned down, and the potential of increasing the risk of opioid tolerance and dependency. A randomized study comparing these two approaches in adult patients would help to clarify these issues.

7. Non-opioid analgesics in multi-modal analgesia plans

A multimodal analgesic approach, using adjuvant analgesics with different mechanisms of action might enhance pain-receptor targeting and reduce adverse effects, thus improving pain control and reducing opioid exposure. Multimodal analgesia is becoming more widespread in chronic pain management, and there is increasing interest in using this approach in managing SCD-related pain [40]. There have been a number of studies exploring the role of non-steroidal inflammatory drugs (NSAIDs) given in combination with opioids, and these have been reviewed in the ASH guideline, leading to a recommendation to include a short course (5 to 7 days) of NSAIDs in addition to opioids for adults and children with acute pain.

The role of routine IV fluids to improve outcomes during an APC is not clear [1]. One recent retrospective study found that IV fluid administration was associated with a worse outcome, however, this probably related to selection bias in patients administered IV fluid bolus [41]. With regard to oxygen administration, there are on-going prospective studies which may help to define the role of high-flow oxygen (NCT03976180) or hyperbaric oxygen (NCT03412045) given routinely during management of APC. Emerging evidence related to other potential non-opioid agents is discussed below.

7.1. Sub-anaesthetic ketamine

Ketamine binds to the *N*-methyl-D-aspartate (NMDA) receptor and produces dissociative anaesthesia characterised by catalepsy, amnesia, and analgesia at anaesthetic dose (1–4.5 mg/kg). Ketamine also interacts with several other binding sites, including mu-opioid receptors, but the clinical contribution of these interactions has not been clearly elucidated [42]. At low (sub-anaesthetic) dose, ketamine has been used as a non-opioid adjunct with analgesic and opioid-sparing effects. Furthermore, activation of the NMDA receptor is thought to be important in inducing and maintaining central sensitization to pain, and ketamine may therefore have a role in managing complex pain in SCD associated with central sensitization. Based on very limited data in SCD [43–48] the ASH guideline recommended a sub-anaesthetic (analgesic) ketamine infusion as adjunctive treatment of pain that is refractory or not effectively treated with opioids.

There have been two randomized controlled studies of early administration of ketamine in place of IV morphine. Lubega et al. conducted a single institution randomized controlled study comparing IV ketamine 1 mg/kg and IV morphine 0.1 mg/ kg in the setting of a paediatric day care unit in Kampala, Uganda [46]. They concluded that ketamine and morphine provided similar analgesia efficacy, however, ketamine was associated with a high incidence of side effects which were described as transient, and mild.

Alsharani et al. conducted a randomized controlled study in 250 adult patients in a large centre in Saudi Arabia, comparing low dose (1 mg/kg) ketamine and 1 mg/kg single dose of IV morphine [43]. Participants were allowed to receive IV paracetamol or IV or injected bolus of non-steroidal anti-inflammatory before receiving first study dose, and rescue doses of IV morphine following administration of study drug. There was no significant difference in the primary end point - the mean difference in pain score up to 180 min. Overall morphine usage was less

in the ketamine arm, but there were adverse effects related to ketamine.

Current limited evidence suggests that early ketamine may provide an alternative to IV opioid for initial analgesia, but would need to be combined with opioids for sustained analgesia. This would require a more complex care protocol and would likely be associated with increased adverse effects. Ketamine can have negative connotations for some patients due to its status as a recreational drug, and particular attention should be given to patient counselling and shared decision making.

7.2. Gabapentinoids

These bind to presynaptic neurons at the alpha2-delta subunit of voltage-gated calcium channels and reduce calcium influx into presynaptic terminals, thereby reducing excessive release of excitatory neurotransmitters. They have been shown to be effective in control of neuropathic pain as well as reducing central sensitization and hyperalgesia, symptoms which may contribute to the pain experienced during an acute pain crisis of SCD. Currently, the evidence on utility of this class of drugs is limited to a single-centre randomized placebo-controlled trial in children and young adults with SCD [49]. Subjects were randomized to a single high oral dose (15 mg/kg) of gabapentin or placebo, given in combination with a standard IV opioid protocol. The study was terminated after the first interim analysis, where there was no significant effect on the primary outcome (33% reduction in pain score between $t =$ 0 and 2 h), and also no difference in a range of secondary end points including opioid usage and proportion admitted to hospital. A larger study in the adult population may be warranted, as any gabapentin effect is more likely in the adult population with a higher prevalence of complex pain.

7.3. IV Paracetamol

Paracetamol is widely distributed in the body and readily penetrates the cerebrospinal fluid. It has been successfully used in postoperative pain in children and is well tolerated when used at therapeutic doses. The IV form provides higher serum levels with a more rapid and predictable analgesia over other routes of administration and lasts four to six hours.

Baichoo et al. conducted a retrospective before-and-after analysis of outcomes in a single US paediatric centre after introducing IV paracetamol as part of a multi-modal analgesia protocol for children [50]. Doses could be repeated 4 hourly. The mean number of doses per patient was 7, and pain score reduced by a mean of 2.4 points on a 1–10 scale when paracetamol was given. They also demonstrated an opioid-sparing effect. Subsequently, Dhebaria conducted a single-center, randomized, double-blinded, placebo-controlled study comparing the cumulative morphine dosing in 71 paediatric patients with APC randomized to receive either 15 mg/kg IV acetaminophen or placebo [51]. This is currently the only randomized prospective study, and in this study there was no difference in morphine usage, pain score, admission rate or patient satisfaction between the two groups.

7.4. Conclusions

The data currently available from clinical trials using non-opioid analgesic agents suggests there may be a moderate effect in controlling acute sickle pain and reducing opioid exposure. It is unclear how any of these agents should be combined, whether they can be given in repeated doses to sustain the opioid-sparing and analgesia effect, and whether the resources and logistics involved in formulating more complex individual management plans which include multimodal analgesia result in a net benefit in health economics and patient satisfaction. Further prospective randomized controlled studies, including adult populations, will help to resolve these uncertainties.

8. Non-pharmacological therapies for acute SCD pain

Pharmacological treatment is the usual approach to managing acute SCD pain, however non-pharmacological therapies have also been shown to be effective. The ASH guidelines classified non-pharmacological therapies into three categories: psychological, physical, and integrative medicine. The panel recognized the paucity of data available to support recommendations, but suggested massage, yoga, transcutaneous electrical nerve stimulation (TENS), virtual reality (VR), and guided audiovisual (AV) relaxation in addition to standard pharmacological management. This was mostly based on direct evidence from patients with SCD and indirect evidence from postoperative adult surgical populations [1]. Recently, small, single-centre studies have shown potential benefit for progressive muscle relaxation [52], music therapy [53], hypnosis [54] and there are on-going studies in acupuncture (NCT04122378) and virtual reality (NCT03353584).

Additional evidence indicates that cognitive behavioral therapy (CBT) reduces SCD pain [55]. Specifically, guided imagery included in CBT [56] and smartphone-assisted CBT [57] are effective in children. Moreover, it should be noted that there are ongoing studies incorporating CBT into digital health interventions.

9. Optimization of the acute care pathway

For acute pain which cannot be managed at home, the hospital emergency department is the default location for health care intervention. This is because ED is open 24 h per day and provides access to trained medical, nursing and allied health care professional staff who can provide urgent assessment and treatment. Problems with ED care are well-described and generally difficult to resolve. These include lack of continuity and connection with the patient's SCD treatment team, poor guideline adherence, delays in triage and assessment, reassessment, and repeat analgesia dosing. The environment is often overcrowded, noisy and stressful, and does not encourage biofeedback techniques for self-management of pain, such as relaxation and distraction. Furthermore, problematic staffing attitudes in the non-specialist setting can generate a feeling of stigma and discrimination. Patients may be labeled as drug seeking, obstructive or difficult.

9.1. Specialist hospital-based ambulatory care units (ACU's)

Potential alternatives to current ED care include specialized units providing care in an alternative hospital-based setting. These are variously described as ambulatory units, day care units or infusion centres. The ASH guideline terminology for such units is an 'SCD-specific hospital-based acute care facility'. For the purposes of this review we refer to them as Ambulatory Care Units (ACU's). The ASH guideline specified that patients on these units should be managed by a team specialized in acute SCD pain management, and should be located in a hospital with easy access to acute and intensive care facilities, recognizing that occasionally patients present with acute pain together with life-threatening complications including acute chest syndrome and sepsis. This type of care provision is generally available during working hours only (Monday to Friday, 9 am to 5 pm), although there are some examples of extended opening hours [58,59]. The unit could be entirely dedicated to SCD, or alternatively, with smaller patient populations or insufficient dedicated staff and space, the service could be embedded in a larger multi-specialty unit, such as a hospital-based haemato-oncology unit [58,60].

Currently, there are no randomized studies comparing standard ED care with ACU's, and observational studies are predominantly from a US health care perspective. Reports in the 1990's from Montefiore Medical Centre, New York, USA [61], and the Day Centre at Birmingham City Hospital, UK [62], demonstrated satisfactory pain control, and reduction in hospital admissions, leading to significant cost savings for the service. These finding have subsequently been replicated in other

centres, including the infusion clinic at Johns Hopkins Medical Centre and in various paediatric settings [58,59,63]. A report from a day care unit in Jamaica where the unit was not located in a hospital setting highlighted the potential for harm. Fatal events were reported in a small number of patients who had been discharged home, with causes of death including acute chest syndrome and sepsis [64].

More recently, Lanzkrom et al. have published a study attempting to compare outcomes in infusion centres (IC) with ED. [58] The ESCAPED (Examining Sickle Cell Acute Pain in the Emergency Versus Day Hospital) study was a prospective observational study in four US cities. The investigators considered that randomly assigning to ED or IC was not possible because patients are reluctant to be assigned to ED-only care, and also because of the practical challenges of randomizing during an acute event. The usual arrangement is for patients to be treated in an IC during working hours, but out of hours and in unfavourable daytime circumstances (low staffing, non-availability of beds, additional complications) might be allocated to care in ED. In order to account for potential bias in the type of patient and type of presentation, a propensity score was applied to each event. Patients treated in IC received parenteral pain medication substantially faster than those seen in the ED, were more likely to have their pain reassessed 30 min after the initial dose and were substantially less likely to be hospitalized, compared to those who received care in an ED. A subsequent health economic analysis of this study suggested large savings in medical and societal costs in the US, largely driven by reduction in hospital admissions in those attending IC [65].

One potential concern is whether opening an ACU might encourage increased usage of hospital services and enhance opioid exposure, rather than supporting patients to develop longer term holistic pain coping strategies. It is also not clear how the facility would be made available to patients in low-prevalence areas, with more limited specialist service provision. One proposed solution is provision of a centralized 'hyper-acute unit' providing acute care for all service users in the region, and open 24 h a day [66]. This may be suitable for service users who live nearby, but will entail prolonged travel for those living in more remote parts of the region. There have been concerns that this model of care may result in increased bed occupancy in the central hospital as a consequence of admitting patients who would normally attend their local hospital. Furthermore, such a scheme could dis-incentivize investment in the necessary service improvements in ED care.

Although SCD-specific ACU's appear to have advantages over ED, they are not yet standard of care and there are challenges and significant resource implications for health care providers in setting up these services. The current data is largely retrospective and observational, and both the NICE and ASH guidelines have recommended further research in this area to compare clinical outcomes, patient satisfaction and health economic implications. A true randomized trial comparing outcomes in ED and ACU, including different types and size of service and a more comprehensive evaluation of health economics and patient satisfaction might resolve some of the uncertainties. Although there would be significant practical challenges, this trial design might be feasible in a universal public funded health care setting such as the National Health Service in the UK.

9.2. Enhanced ED care

Although ACU's appear to offer better quality of care compared to ED, it is not possible to provide this care continuously, and ED care will always be needed as a default. Improving pain management and patient satisfaction in the ED model of care remains a high priority. Examples of modifications to ED care pathways include:

(1) *"Fast-tracking"* patients in the ED into a treatment unit [58,67].

(2) *Delivery of the care protocol in ED by an acute sickle pain nurse specialist.* Evidence for this role includes experience in a clinical trial of acute pain management in ED, where continued communication, reassurance and support sustained over the first 6 h of management in ED and, if admitted, on transfer to the hospital ward were highly valued and contributed to the overall patient-reported outcome [36]. Similar staffing and competencies are used routinely in other health care environments (e.g. theatre recovery), Further prospective studies including health care outcomes, health economic impact and patient satisfaction would help in evaluating whether such a role is feasible outside of the research study setting.

(3) *Regular education of ED providers around management of APC.* This could be mandated by training and revalidation schemes organized by professional bodies representing acute and emergency medicine specialists.

(4) *Quality control reporting.* To further provide insight in the efficacy and efficiency of care provided in the ED, it would be helpful to ensure standardized outcome reporting for all ED's within a healthcare system. This would enable comparison between EDs and highlight where improvements are needed.

10. Patient perspective

Patients, carers and organizations continue to campaign for equitable access to treatment, timely administration of effective pain relief and an improvement to the care pathway, recognizing the profound impact of APC on the quality of life for sickle cell patients.

10.1. Patient-reported experiences

In the UK, a series of reports over the past 30 years document harrowing first hand testimonies from patients and parents regarding poor care. The common themes of inadequate knowledge and experience on the part of acute health care providers, lapses in compassionate care, and evidence of racism have not changed (Maxwell and Streetley, NCEPOD report) [2,68,69]. The APPG report took evidence from patients receiving care in a variety of UK health care institutions and highlighted the role of racism in the negative attitudes towards sickle cell patients. These experiences are not unique to adults and may have a very damaging effect on the long-term welfare of adolescents during transition to adult care. Renedo et al. conducted a co-produced longitudinal qualitative study with young people with SCD aged 13–21 living in two UK cities [70]. Participants reported significant problems with the care they received in ED and in hospital ward, stating that pain relief and their basic care needs were not always met. Participants said that non-specialist healthcare staff did not seem to know enough about SCD and often seemed not prepared to listen to them or act on what they said. Because of their experiences, they tried to avoid being admitted to hospital, attempting to manage their painful episodes at home.

10.2. Challenges of biases due to racial or ethnic disparities between providers and users of healthcare

In most of Europe and North America, people with SCD are of African or African-Caribbean ancestry. Whilst people with SCD have varied ancestry across the world (compare for example India or Saudi Arabia), racialized associations between being Black and having SCD are important in many regions because of anti-Black racism. Whilst racism is often thought of as something happening between individuals, far-reaching inequalities across and beyond healthcare demonstrate the reality of *structural* racism within institutions. Racial discrimination impacts at multiple levels for those living with SCD: a) individual practitioners may be biased (consciously or unconsciously); b) patients may have experienced racialized discrimination in their sickle cell care, and in other aspects of care; and c) healthcare systems are built unfairly and need challenging [71,72].

These observations emphasize the need for an institutional approach to address health care failings. Institutions need to monitor for these issues by ensuring regular evaluation of patient-satisfaction with the service, as well as prompt investigation of reported incidents and

complaints. It should also be mandatory for health care workers to have periodic training and refresher training in diversity, inclusivity and racial bias awareness.

10.3. Specific aspects of care

Decisions regarding the route of analgesia needs further discussion with patients. Most agreed that IV analgesia had a quicker response rate than other methods, but there is also a general consensus that the sooner the pain is addressed the faster the patient can be discharged leading to an increase in patient satisfaction and experience.

In the No One's Listening enquiry, many patients and carers felt that the care received within haematology services or ambulatory units addressed their care needs much more comprehensively as they understood the patient and were knowledgeable about the condition. Patients are prepared to travel further, in order to attend hospitals that they trust and feel they will receive better care and tailored treatment for their condition [2,73].

Patients acknowledged that self-management can happen alongside medical management. Commonly used approaches were Mind-Body Approaches (massage therapy, thermotherapy, relaxation, Biological Approaches (Herbal Medicines, Homeopathy, Diet, Cannabis), and Energy-Based Approaches (Prayer, Spiritual Healing e.g. Reiki, Yoga). Whatever therapies work for an individual can be added to their care plan, which should be regularly reviewed and updated to reflect what works [74].

10.4. Measuring patient satisfaction

Satisfaction with care provided by specialist and non-specialist teams in hospital is an important metric of care quality, enabling comparison of different health care settings and across different institutions, and identification aspects of the care pathway which need improvement. Although there are relatively few studies in which patient satisfaction has been included as a study end point, several questionnaires have been developed which are specifically designed and validated for measuring satisfaction with SCD pain management in hospital. Going forward, it will be important to further evaluate these or other similar questionnaires so that patient reported satisfaction can be used as a robust end point in future clinical trials of APC management.

11. Conclusions

It is clearly difficult to provide acceptable care and to adhere to standards contained in existing guidelines. Aspects of care which could potentially make a difference to patient experience include availability and accessibility of individual care plans agreed between patient and treating specialist, innovative means of delivering initial opioids to reduce time to first analgesia, and availability of a specialist unit away from the ED, where expert care can be delivered in a more compassionate environment.

12. Future considerations

The current evidence of improved outcomes and health economic advantage with the above care interventions is inadequate, and this is hampering their implementation into health care systems. Further prospective randomized controlled trials should be conducted to address the lack of evidence. It will be important to conduct these trials in a variety of health care setting to address the dearth of evidence outside of the USA.

Practice points

- Individual care plans generally improve outcomes (reduced risk admission, reduction in pain scores, and reduced length of stay). These should be formulated by the SCD team in consultation with the patient and made easily accessible to ED and pre-hospital carers, ideally through an electronic record format.
- Patients should be prioritized for triage through ED to ensure rapid assessment and administration of first analgesia.
- Alternative routes of opioid administration should be considered to improve time to first analgesia. For example, intranasal or sublingual fentanyl as an alternative to the first IV opioid dose.
- Managing patients with APC in a setting that provides direct access to care (bypassing ED) is associated with a shorter time to initiation of pain relief, shorter duration of treatment, more effective pain relief and fewer hospital admissions than care in emergency departments. Implementation of an ambulatory care model should be considered, especially in hospitals serving large SCD populations.

Research agenda

- The uncertainties identified in previous guidelines (e.g. ASH, NICE) remain important topics for research. These include (i) alternative routes of opioid administration, (ii) further defining the role of non-opioid analgesics and non- pharmacological methods of improving APC management and (iii) comparison of ambulatory care vs ED care including health economic evaluation and evaluation of patient satisfaction. Prospective randomized controlled studies are needed, particularly in the adult population, and including a variety of different health care systems.

- There is a continued need to develop new and effective therapeutic approaches to prevent acute pain episodes, which would supplement or supplant the current use of hydroxycarbamide and chronic transfusion. These studies will need to define inclusion criteria carefully to avoid enrolment of patients with acute exacerbations of chronic pain, and those who are accessing acute health care to manage problems which are predominantly psychosocial rather than acute pain crisis.

Declarations

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Declaration of competing interest

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