Appendix A: Summary of evidence from surveillance

2023 surveillance of sickle cell disease: managing acute painful episodes in hospital (2012) NICE guideline CG143

Summary of evidence from surveillance

Studies were considered for inclusion using criteria defined by the guideline review protocols and are summarised from the information presented in their abstracts.

We searched for new evidence that relates to primary analgesia (including timing) for acute painful sickle cell episodes in hospital, which is covered by 3 areas of the guideline: individualised assessment at presentation, primary analgesia and reassessment and ongoing management.

Individualised assessment at presentation

NICE guideline CG143 recommendations that we included in this review:

1.1.3 Assess pain and use an age-appropriate pain scoring tool for all patients presenting at hospital with an acute painful sickle cell episode.

1.1.4 Offer analgesia within 30 minutes of presentation to all patients presenting at hospital with an acute painful sickle cell episode (see also the recommendations on primary analgesia).

Surveillance decision

This section of the guideline should not be updated.

Review question and evidence

Review question: How should an acute painful sickle cell episode be managed using pharmacological interventions?

2016 surveillance evidence

In previous surveillance, no studies relevant to this section of the guideline were identified.

2023 surveillance evidence

We found 1 secondary analysis of an RCT relevant to this section of the guideline.

Time of treatment

A secondary analysis (Brandow et al., 2016) of the Magnesium for children in Crisis RCT (aged 4 to 21 years, n=204 across 8 sites) assessed whether length of stay (LOS) in emergency department (ED) and change in health-related quality of life (HRQL) are affected by initial opioid dose and time to administration. Earlier initiation of oral opioids was strongly correlated with shorter LOS (r=0.61, P < 0.01). Higher initial opioid dose was weakly correlated with longer LOS (r=0.34, P<0.01). Higher initial opioid doses (6 vs -2.2; P=0.01) and oral opioids initiated within 24 hr (5.7 vs -1.7, P = 0.04) were associated with larger mean change in HRQL at discharge.

Intelligence gathering

There was no additional information gathered for this section of the guideline.

Impact statement

When developing the guideline, the committee agreed by consensus that the prompt availability of analgesia is very important to patients and that treatment should not be delayed when they present at hospital. The committee agreed that 30 minutes should be the maximum length of time a patient should wait, as the episode should be treated as an acute medical emergency.

There was no direct evidence to support or contradict the guideline recommendation to offer analgesia within 30 minutes of presentation to all patients presenting at hospital with an acute painful sickle cell episode. The only available evidence from a secondary analysis of an RCT (Brandow et al., 2016) provides support for earlier initiation of oral opioids to reduce LOS and patient quality of life. However, there was a wide variation in time to the start of the first oral opioid limiting any specific conclusions.

New evidence is unlikely to change guideline recommendations.

Primary analgesia

NICE guideline CG143 recommendations:

- 1.1.7 When offering analgesia for an acute painful sickle cell episode:
  - ask about and take into account any analgesia taken by the patient for the current episode before presentation
  - ensure that the drug, dose and administration route are suitable for the severity of the pain and the age of the patient
  - refer to the patient's individual care plan if available.

- 1.1.8 Offer a bolus dose of a strong opioid by a suitable administration route, in accordance with locally agreed protocols for managing acute painful sickle cell episodes, to:
  - all patients presenting with severe pain
  - all patients presenting with moderate pain who have already had some analgesia before presentation.
- 1.1.9 Consider a weak opioid as an alternative to a strong opioid for patients presenting with moderate pain who have not yet had any analgesia.
- 1.1.10 Offer all patients regular paracetamol and NSAIDs (non-steroidal anti-inflammatory drugs) by a suitable administration route, in addition to an opioid, unless contraindicated.

  The use of NSAIDs should be avoided during pregnancy, unless the potential benefits outweigh the risks. NSAIDs should be avoided for treating an acute painful sickle cell episode in women in the third trimester. See the BNF for details of contraindications.
- 1.1.11 Do not offer pethidine for treating pain in an acute painful sickle cell episode.

Surveillance decision

This section of the guideline should not be updated.

Review question and evidence

Review question: How should an acute painful sickle cell episode be managed using pharmacological interventions?

2016 surveillance evidence

In previous surveillance, no studies relevant to this section of the guideline were identified.

2023 surveillance evidence

We found 5 RCTs and 5 systematic reviews relevant to this section of the guideline.

Of the 5 RCTs, 4 included children and young people with 1 included an adult population.

Primary analgesia in children and young people

A systematic review and meta-analysis (Alghamdi & Al-Shahrani, 2020) investigated the efficacy and safety of ketamine in treating pain crises in both children and adults with SCD (sickle cell disease). Fourteen mixed study types (n=581) were included in the analysis. The authors identify that evidence from case reports and case series showed that ketamine significantly reduced pain scales and opioid utilisation in children and adults with sickle cell crises (vaso-occlusive crises) when compared with opioids. The only pooled results provided from 2 studies (study types not specified) in children identified no significant difference between ketamine and control group (not specified) in pain scale measures (mean difference

(MD) 0.42, 95% CI -0.25 to 1.09, P= 0.22). Ketamine was associated with more adverse events than the control group (odds ratio (OR) 15.9, 95% CI 5.85 to 43.33, P<0.0001).

A randomised, non-inferiority trial (Lubega et al., 2018) compared intravenous (IV) ketamine (1 mg/kg) versus IV morphine (0.1 mg/kg) in children with severe painful sickle cell crisis (aged 7 to 18 years, n=240). Patients were treated in a tertiary care centre. For the primary outcome, Numerical Rating Scale (NRS) pain score, treatments were comparable: 66.4% ketamine versus 61.3% morphine (MD 5.5, 95% CI −2.2 to −13.2). Ketamine patients were more likely to develop side effects than morphine patients, 37.5% versus 3.3%, though they were transient, anticipated and non-life threatening. Morphine had significantly more treatment failures 40% versus 28.3% (RR 0.7, 95% CI 0.5 to 1.03, p=0.07).

A placebo controlled RCT (Fein et al., 2017) of children and young people with SCD and in pain crises (aged 3 to 20 years, n=49) sought to establish if intranasal fentanyl (2 µg/kg, maximum 100 µg) was effective in decreasing pain after 20 minutes. Children were presenting at an ED and assessed using a modified Wong–Baker FACES pain scale before and after administration of the drug or placebo. Children treated with intranasal fentanyl had a greater decrease in median pain score at 20 minutes compared to placebo (2 (interquartile range, (IQR) 0.5 to 4) versus 1 (IQR 0 to 2), P=0.048), but not at 10 or 30 minutes.

An RCT (Panda et al., 2021) aimed to compare the efficacy of 8 hourly doses of IV acetaminophen (paracetamol, 10mg/kg) and IV diclofenac sodium (NSAID, 10mg/kg) in the management of pain crisis among children with SCD (mean age 8.3 years (SD 3.2), n=104). Patients were treated in a tertiary care centre. For the main outcome (score tool not specified) a 50% reduction in pain score was achieved in 35 (77.3%) and 10 (21.7%) children among acetaminophen and diclofenac sodium groups respectively (RR 3.6, 95% CI 2.02-6.33, P< 0.001). The mean (SD) fall in pain score at 1 hour was significantly higher among the acetaminophen group (1.51 (0.5) and 1.06 (0.5); P<0.001). Neither group experienced major side effects, though the 8 patients receiving IV diclofenac developed local phlebitis at the site of infusion.

An RCT (Dhebaria et al., 2021) aimed to determine whether 15 mg/kg IV acetaminophen (paracetamol) versus placebo had an opioid-sparing effect by comparing the cumulative amount of morphine between 2 groups of children (aged 4 to 16 years, n=71). Patients were treated in an ED and received a 0.1 mg/kg dose of IV morphine, 0.5 mg/kg ketorolac, or both. The mean total amount of morphine given was 8.6 mg (95% CI 6.5 to 10.8) in the acetaminophen group and 8.0 mg (95% CI 5.9 to 10.2) in the placebo group, difference 0.6 (−2.3 to 3.5). There was no significant difference in the morphine received between the 2 groups.

Primary analgesia in adults

A Cochrane systematic review (Cooper et al., 2019) assessed RCT evidence of pharmacological interventions, compared to placebo or any active comparator, for treating pain crises in adults with SCD (17 to 42 years) who received treatment in hospital EDs (9 studies, n=594 patients). Only 3 studies were included in quantitative synthesis, due to lack of available data. For non-steroidal anti-inflammatory drugs (NSAID) compared with placebo

there was no difference in Patient Global Impression of Change (PGIC) 'very much improved' (1 study, 21 participants, risk ratio (RR) 7.64 (0.44 to 131.75)). For opioids compared with active comparator there was no difference in PGIC 'very much improved' (1 study, 18 participants, 33% of the opioids group versus 19% comparator group). Side effects were rare and were generally mild. Overall, there was insufficient data for analysis and uncertainty regarding the efficacy or harm from pharmacological interventions for treating SCD pain crises.

A Cochrane systematic review (Abboursheid et al., 2022) assessed RCT evidence comparing inhaled nitric oxide (iNO) with placebo for treating pain crises in people with SCD in hospital (3 studies, n=188 patients). Only 1 trial reported median time to pain resolution, which was 73.0 hours versus 65.5 hours in the iNO and placebo group respectively (n=150). Only 1 trial reported on the frequency of pain crises in the follow-up period and found there may be little or no difference between the iNO and placebo groups for return to the ED (RR 0.73, 95% CI 0.31 to 1.71) and rehospitalisation (RR 0.53, 95% CI 0.25 to 1.11) (n=150).

An RCT (Alshahrani et al., 2022) of adults (n=278) with SCD presenting to ED with pain crises sought to evaluate the efficacy and safety of single, low-dose ketamine infusion (0.3 mg/kg) when compared with standard dose morphine infusion (0.1 mg/kg). For the primary outcome mean difference in the numerical pain rating scale (NPRS) score over 2 hours, the reduction in NPRS score did not differ significantly in the ketamine and morphine treatment groups: 5.7 versus 5.6 respectively (MD 0.13 (95% CI, -0.34 to 0.60)). The ketamine treatment was associated with significantly reduced cumulative dose of opioids compared to morphine group (an opioid-sparing effect): 0.07 mg/kg versus 0.13 mg/kg (MD 0.061 (95% CI 0.038 to 0.083, p <0.001). There were no significant differences in adverse outcomes.

Adjuvant therapy

A systematic review and network meta-analysis (NMA) (Sridharan & Sivaramakrishnan, 2020) considered RCTs of interventions adjunctive to opioids for pain crises in people with SCD (11 studies, patient number not reported). The analysis included evidence on ketorolac, magnesium sulfate, ketoprofen, ibuprofen, methadone, inhalational nitric oxide, methylprednisolone, and arginine with morphine. Using pain reduction scores (not specified) pooled analysis favoured arginine (-2 (-3.39, -0.61)) followed by ibuprofen (-1.7 (-3.26, -0.14)) for producing additional analgesic effects when combined with morphine alone. No significant differences were observed in adverse events.

A Cochrane systematic review (Okomo & Meremikwu, 2017) aimed to assess RCT evidence on fluid replacement therapy adjunctive to analgesics for acute episodes of pain in people with SCD. No relevant trials were identified.

Intelligence gathering

There was no additional information was gathered for this section of the guideline.

Impact statement

Evidence gathered on pharmacological interventions for acute painful sickle cell episodes was limited to 5 RCTs and 5 systematic reviews. The systematic reviews were all limited by a small number of included studies. There was also heterogeneity across the available evidence base with respect to populations, interventions and settings. Additionally, most studies were small and none of the RCTs were from UK settings.

Evidence on analgesics recommended in CG143.

We didn't identify evidence that supports or refutes current recommendations. The available Cochrane review (Cooper et al., 2019) of pharmacological interventions identified very limited evidence and was unable to make any conclusions about efficacy or harms of interventions.

A systematic review and NMA (Sridharan & Sivaramakrishnan, 2020) considered a range of agents and identified arginine and ibuprofen as producing additional analgesic effects when combined with morphine. Arginine is not licensed for use in the UK, whereas adjunctive NSAIDs are currently recommended in the guideline.

An RCT (Dhebaria et al., 2021) aimed to determine whether 15 mg/kg IV acetaminophen (paracetamol) versus placebo in children had an opioid-sparing effect. It did not demonstrate any sparing effect. When developing the original recommendations the committee, however, agreed that the use of NSAIDs has an opioid-sparing effect. A separate recommendation was made to ensure that NSAIDs and paracetamol are offered to all patients in addition to an opioid and that this is not delayed. The current evidence is insufficient to change this recommendation.

At the time of guideline development in 2012 the committee noted that there were very few RCTs comparing different opioids, and the committee agreed that it was not possible to recommend a specific opioid for treating acute painful sickle cell episodes. A recommendation for research was made to help fill this gap in the evidence, but new research does not appear to have materialised.

In addition to there being limited new evidence on different opioid formulations and adjunct pain therapies, there was no new evidence to confirm the best mode of analgesic delivery on pain relief and acute sickle cell complications.

Evidence of analgesics that are not currently recommended.

A systematic review and 2 trials on the use of ketamine in both adults and children (Alghamdi & Al-Shahrani, 2020; Alshahrani et al., 2022; Lubega et al., 2018) offer limited evidence on the efficacy of ketamine, when compared with opioids, for treating episodes of pain crises in people with SCD. In addition, these trials were conducted outside the UK and ketamine is not licensed for treating acute pain in the UK. This new evidence on an unlicensed drug does not provide a basis for updating the guideline.

In the RCT (Panda et al., 2021) which didn't include opioids and compared the efficacy of 8 hourly doses of IV acetaminophen (paracetamol) and IV diclofenac sodium, intravenous

acetaminophen was a better alternative to unlicensed intravenous diclofenac in children with SCD pain crisis. However, this study provided no comparison with interventions recommended by the guideline and therefore offers insufficient evidence to change guideline recommendations.

The RCT (Fein et al., 2017) which considered the use of intranasal fentanyl in children provides very limited evidence to support an unlicensed use of the drug for acute pain and does not impact the guideline.

At the time of developing the guideline the committee discussed nitric oxide for managing SCD pain crises but did not feel that there was enough evidence of a beneficial effect to support a recommendation. A recent Cochrane systematic review (Abboursheid et al., 2022) assessed RCT evidence of iNO but found no evidence to support its use.

A Cochrane systematic review (Okomo & Meremikwu, 2017) found no evidence on fluid replacement therapy adjunctive to analgesics for acute episodes of pain in people with SCD.

Overall, the Cochrane reviews on iNO and fluid replacement therapy identified no new evidence which would trigger an update of the guideline.

New evidence is unlikely to change guideline recommendations.

Reassessment and ongoing management

NICE guideline CG143 recommendations:

1.1.12 Assess the effectiveness of pain relief:

- every 30 minutes until satisfactory pain relief has been achieved, and at least every 4 hours thereafter
- using an age-appropriate pain scoring tool
- by asking questions, such as:
    - How well did that last painkiller work?
    - Do you feel that you need more pain relief?

1.1.13 If the patient has severe pain on reassessment, offer a second bolus dose of a strong opioid (or a first bolus dose if they have not yet received a strong opioid).

1.1.14 Consider patient-controlled analgesia if repeated bolus doses of a strong opioid are needed within 2 hours. Ensure that patient-controlled analgesia is used in accordance with locally agreed protocols for managing acute painful sickle cell episodes and/or acute medical emergencies.

1.1.15 Offer all patients who are taking an opioid:

- laxatives on a regular basis
- anti-emetics as needed
- antipruritics as needed.

1.1.16 Monitor patients taking strong opioids for adverse events, and perform a clinical assessment (including sedation score):

- every 1 hour for the first 6 hours
- at least every 4 hours thereafter.

1.1.17 If the patient does not respond to standard treatment for an acute painful sickle cell episode, reassess them for the possibility of an alternative diagnosis.

1.1.18 As the acute painful sickle cell episode resolves, follow locally agreed protocols for managing acute painful sickle cell episodes to step down pharmacological treatment, in consultation with the patient.

Surveillance decision

This section of the guideline should not be updated.

Review question and evidence

Review question: How should an acute painful sickle cell episode be managed using pharmacological interventions?

2016 surveillance evidence

In previous surveillance, no studies relevant to this section of the guideline were identified.

2023 surveillance evidence

We found no studies to this section of the guideline.

Intelligence gathering

There was no additional information gathered for this section of the guideline.

Impact statement

There was no evidence and therefore no impact on this section of the guideline.

No evidence identified.

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