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Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults.

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Cooper TE, Hambleton IR, Ballas SK, Cashmore BA, Wiffen PJ

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[Intervention Review]

Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults

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ABSTRACT

Background

Sickle cell disease (SCD) is a group of inherited disorders of haemoglobin (Hb) structure in a person who has inherited two mutant globin genes (one from each parent), at least one of which is always the sickle mutation. It is estimated that between 5% and 7% of the world's population are carriers of the mutant Hb gene, and SCD is the most commonly inherited blood disorder.

SCD is characterized by distorted sickle-shaped red blood cells. Manifestations of the disease are attributed to either haemolysis (premature red cell destruction) or vaso-occlusion (obstruction of blood flow, the most common manifestation). Shortened lifespans are attributable to serious comorbidities associated with the disease, including renal failure, acute cholecystitis, pulmonary hypertension, aplastic crisis, pulmonary embolus, stroke, acute chest syndrome, and sepsis.

Vaso-occlusion can lead to an acute, painful crisis (sickle cell crisis, vaso-occlusive crisis (VOC) or vaso-occlusive episode). Pain is most often reported in the joints, extremities, back or chest, but it can occur anywhere and can last for several days or weeks. The bone and muscle pain experienced during a sickle cell crisis is both acute and recurrent.

Key pharmacological treatments for VOC include opioid analgesics, non-opioid analgesics, and combinations of drugs. Non-pharmacological approaches, such as relaxation, hypnosis, heat, ice and acupuncture, have been used in conjunction to rehydrating the patient and reduce the sickling process.

Objectives

To assess the analgesic efficacy and adverse events of pharmacological interventions to treat acute painful sickle cell vaso-occlusive crises in adults, in any setting.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid, Embase via Ovid and LILACS, from inception to September 2019. We also searched the reference lists of retrieved studies and reviews, and searched online clinical trial registries.

Selection criteria

Randomized, controlled, double-blind trials of pharmacological interventions, of any dose and by any route, compared to placebo or any active comparator, for the treatment (not prevention) of painful sickle cell VOC in adults.

Data collection and analysis

Three review authors independently assessed studies for eligibility. We planned to use dichotomous data to calculate risk ratio (RR) and number needed to treat for one additional event, using standard methods. Our primary outcomes were participant-reported pain relief of 50%, or 30%, or greater; Patient Global Impression of Change (PGIC) *very much* improved, or *much or very much* improved. Our secondary outcomes included adverse events, serious adverse events, and withdrawals due to adverse events. We assessed GRADE and created three 'Summary of findings' tables.

Main results

We included nine studies with data for 638 VOC events and 594 participants aged 17 to 42 years with SCD presenting to a hospital emergency department in a painful VOC. Three studies investigated a non-steroidal anti-inflammatory drug (NSAID) compared to placebo. One study compared an opioid with a placebo, two studies compared an opioid with an active comparator, two studies compared an anticoagulant with a placebo, and one study compared a combination of three drugs with a combination of four drugs.

Risk of bias across the nine studies varied. Studies were primarily at an unclear risk of selection, performance, and detection bias. Studies were primarily at a high risk of bias for size with fewer than 50 participants per treatment arm; two studies had 50 to 199 participants per treatment arm (unclear risk).

Non-steroidal anti-inflammatory drugs (NSAID) compared with placebo

No data were reported regarding participant-reported pain relief of 50% or 30% or greater.

The efficacy was uncertain regarding PGIC *very much* improved, and PGIC *much or very much* improved (no difference; 1 study, 21 participants; very low-quality evidence).

Very low-quality, uncertain results suggested similar rates of adverse events across both the NSAIDs group (16/45 adverse events, 1/56 serious adverse events, and 1/56 withdrawal due to adverse events) and the placebo group (19/45 adverse events, 2/56 serious adverse events, and 1/56 withdrawal due to adverse events).

Opioids compared with placebo

No data were reported regarding participant-reported pain relief of 50% or 30%, PGIC, or adverse events (any adverse event, serious adverse events, and withdrawals due to adverse events).

Opioids compared with active comparator

No data were reported regarding participant-reported pain relief of 50% or 30% or greater.

The results were uncertain regarding PGIC *very much* improved (33% of the opioids group versus 19% of the placebo group). No data were reported regarding PGIC *much or very much* improved.

Very low-quality, uncertain results suggested similar rates of adverse events across both the opioids group (9/66 adverse events, and 0/66 serious adverse events) and the placebo group (7/64 adverse events, 0/66 serious adverse events). No data were reported regarding withdrawal due to adverse events.

Quality of the evidence

We downgraded the quality of the evidence by three levels to very low-quality because there are too few data to have confidence in results (e.g. too few participants per treatment arm). Where no data were reported for an outcome, we had no evidence to support or refute (quality of the evidence is unknown).

Authors' conclusions

This review identified only nine studies, with insufficient data for all pharmacological interventions for analysis.

The available evidence is very uncertain regarding the efficacy or harm from pharmacological interventions used to treat pain related to sickle cell VOC in adults. This area could benefit most from more high quality, certain evidence, as well as the establishment of suitable registries which record interventions and outcomes for this group of people.

PLAIN LANGUAGE SUMMARY

Medicines for treating painful sickle cell crises in adults

Bottom line

We are uncertain which medicines provide the best pain relief for adults experiencing a painful sickle cell crisis.

Background

People with sickle cell disease have abnormally shaped red cells in their blood. Sickle cell disease is the most common inherited blood disorder around the world. It is estimated globally that 367 million to 500 million people are carriers. People with sickle cell disease have a higher chance of life-threatening complications, such as infection, severe chest pain and stroke in early life, and kidney or liver damage in adulthood.

A pain crisis is the most common problem of sickle cell disease and can require several treatments at once, usually in an emergency situation. The first priority is to control the pain, using medicines (such as opioids, non-steroidal anti-inflammatories, paracetamol, and blood thinners) or relaxation, hypnosis, heat, ice, or acupuncture.

Study characteristics

In September 2019, we searched for clinical trials that used medicines in any setting to treat painful sickle cell crises. We found nine trials, with 594 adults (aged 17 to 42 years) who had sickle cell disease, experiencing a combined total of 638 painful episodes.

Key results

The studies looked at different comparisons of the medicines butorphanol, cetiedil, fentanyl, ketoprofen, ketorolac, metoclopramide, morphine, paracetamol, placebo, tinzaparin, and tramadol. Only three studies compared the same two drugs (non-steroidal anti-inflammatory drugs such as ibuprofen, aspirin, or naproxen, with a placebo (pretend treatment)) and we had very limited data to be able to investigate the effects on pain scores from these medicines.

Side effects were rare and were generally mild.

Quality of the evidence

We rated the quality of the evidence from studies using four levels: very low, low, moderate, or high. Very low-quality evidence means that we are very uncertain about the results. High-quality evidence means that we are very confident in the results. For pain relief and side effects, we rated the quality of evidence as very low.

We downgraded the quality of the evidence to very low because there were not enough data (e.g. too few participants). For some outcomes the quality of the evidence is unknown because there was no evidence available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Non-steroidal anti-inflammatory drugs (NSAID) compared with placebo for painful sickle cell vaso-occlusive crises

NSAIDs compared with placebo for painful sickle cell vaso-occlusive crises

Patient or population: adults with sickle cell disease in a vaso-occlusive crises

Settings: emergency departments

Intervention: NSAIDs (ketorolac or ketoprofen)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	NSAIDs				
Participant-reported pain relief of 50% or greater	No data	No data	No data	No data	No data ^a	Quality of the evidence is unknown
Participant-reported pain relief of 30% or greater	No data	No data	No data	No data	No data ^a	Quality of the evidence is unknown
PGIC <i>very much</i> improved (Follow-up: up to 5 days)	0/11	3/10	RR 7.64 (0.44 to 131.75)	21 participants, 21 VOC events (1 study)	⊕⊕⊕⊕ Very low^b	—
PGIC <i>much or very much</i> improved (Follow-up: up to 5 days)	4/11	6/10	RR 1.65 (0.65 to 4.19)	21 participants, 21 VOC events (1 study)	⊕⊕⊕⊕ Very low^b	—
Any adverse event (Follow-up: up to 5 days)	19/45	16/45	N/A	72 participants, 90 VOC events (2 studies)	⊕⊕⊕⊕ Very low^b	—
Serious adverse events (Follow-up: up to 5 days)	2/56	1/55	N/A	93 participants, 111 VOC events (3 studies)	⊕⊕⊕⊕ Very low^b	—
Withdrawals due to adverse events	1/56	1/55	N/A	93 participants, 111 VOC events (3 studies)	⊕⊕⊕⊕ Very low^b	—

(Follow-up: up to 5 days)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **N/A:** not applicable; **NSAID:** non-steroidal anti-inflammatory drug; **PGIC:** Patient Global Impression of Change; **RR:** risk ratio; **VOC:** vaso-occlusive crisis.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^a No data available, therefore no GRADE rating has been performed for this outcome and the quality of the evidence is unknown.

^b Downgraded three levels; too few data (limited number of participants per treatment arm) to have confidence in results.

Summary of findings 2. Opioids compared with placebo for painful sickle cell vaso-occlusive crises

Opioids compared with placebo for painful sickle cell vaso-occlusive crises

Patient or population: adults with sickle cell disease in a vaso-occlusive crisis

Settings: emergency departments

Intervention: opioids

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo	Opioids				
Participant-reported pain relief of 50% or greater	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Participant-reported pain relief of 30% or greater	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown



PGIC very much improved	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
PGIC much or very much improved	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Any adverse event	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Serious adverse event	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Withdrawals due to adverse events	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **N/A:** not applicable; **PGIC:** Patient Global Impression of Change; **RR:** risk ratio.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect;

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^a No data available, therefore no GRADE rating has been performed for this outcome and the quality of the evidence is unknown.

Summary of findings 3. Opioids compared with active comparator for painful sickle cell vaso-occlusive crises

Opioids compared with active comparator for painful sickle cell vaso-occlusive crises

Patient or population: adults with sickle cell disease in a vaso-occlusive crisis

Settings: emergency departments

Intervention: opioids (morphine)

Comparison: active comparator (butorphanol or paracetamol)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Active comparator	Opioids				
Participant-reported pain relief of 50% or greater	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Participant-reported pain relief of 30% or greater	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
PGIC very much improved (Follow-up: within 1 day)	19.1 per 100	33.3 per 100	N/A	18 participants, 24 VOC events (1 study)	⊕⊕⊕⊕ Very low^b	—
PGIC much or very much improved	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown
Any adverse event (Follow-up: within 1 day)	7/64	9/66	N/A	124 participants, 130 VOC events (2 studies)	⊕⊕⊕⊕ Very low^b	—
Serious adverse event (Follow-up: within 1 day)	0/64	0/66	N/A	124 participants, 130 VOC events (2 studies)	⊕⊕⊕⊕ Very low^b	—
Withdrawals due to adverse events	No data	No data	N/A	N/A	No data ^a	Quality of the evidence is unknown

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **N/A:** not applicable; **PGIC:** Patient Global Impression of Change; **RR:** risk ratio; **VOC:** vaso-occlusive crisis.

GRADE Working Group grades of evidence

High quality: we are very confident that the true effect lies close to that of the estimate of the effect;

Moderate quality: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different;

Low quality: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect;

Very low quality: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

^a No data available, therefore no GRADE rating has been performed for this outcome and the quality of the evidence is unknown.

^b Downgraded three levels; too few data (limited number of participants per treatment arm) to have confidence in results.

BACKGROUND

A previous review, entitled 'Pain management for sickle cell disease in children and adults' was withdrawn as it was out of date (Dunlop 2014). This is a completely new review focusing only on the treatment of painful vaso-occlusive crises (VOC; or episodes) of sickle cell disease and it excludes the paediatric population.

Description of the condition

Sickle cell disease is a generic term for a group of inherited disorders of haemoglobin (Hb) structure in which the affected person inherits two mutant globin genes (one from each parent), at least one of which is always the sickle mutation (WHO 2010). The latter results from a single nucleotide change (GAT→GTT) in the sixth codon of exon 1 of the β -globin gene responsible for the synthesis of the β -globin chain. The resulting replacement of the normal glutamic acid by valine at position 6 in the β chain leads to the formation of sickle Hb (Hb S). Sickle cell anaemia is the homozygous state, in which the sickle gene is inherited from both parents. Other sickle cell syndromes result from the coinheritance of the sickle gene and a non-sickle gene, such as in Hb C, Hb OArab, Hb D, β +thalassaemia or β 0-thalassaemia (NIH 2014).

JB Herrick first described the abnormally shaped red blood cell in 1910 (Herrick 1910). Sickle cell originated in Sub-Saharan Africa and the Indian subcontinent (Martí-Carvajal 2009; Stuart 2004; Weatherall 2006), and has persisted as a recessive trait due to the survival advantage against malaria experienced by people with the heterozygote form (Weatherall 2001). In recent years, the United Nations and the World Health Organization have recognized sickle cell disease as a global public health problem due to population mobility, with increased migration from high- to low-frequency sickle Hb areas (WHO 2010). Combined with the global increase in population size, reduction in child mortality and improved adult survival, the worldwide burden of sickle cell disease is predicted to increase (Al Hajeri 2007; Martí-Carvajal 2009; Piel 2013).

Sickle cell disease is the most common inherited blood disorder globally. Epidemiologically, it is estimated that between 5% (approximately 367 million people) (WHO 2011) and 7% (approximately 500 million people) (Weatherall 2001) of the world's population are carriers of the mutant Hb gene.

Worldwide, the African region has the highest prevalence with an estimated 200,000 babies born with sickle cell disease every year (Diallo 2002). In 2010, approximately 75% of the globally estimated homozygous sickle cell disease newborns were from Sub-Saharan Africa (Piel 2013). In the US, the number of people living with sickle cell disease is approximately 100,000 and it predominantly affects Americans of African descent (NIH 2015). In addition to this, 3.5 million African-Americans have the sickle cell trait HbAS genotype (i.e. are heterozygote carriers of sickle Hb) (Yawn 2014). The UK reports an estimated prevalence of 12,500 people with the disease (National Screening Committee 2006).

Shortened lifespans are attributable to serious comorbidities associated with the disease. People with sickle cell disease have a higher chance of life-threatening complications, such as sepsis, acute chest syndrome and stroke in early life, and end organ damage in adulthood (Tanabe 2012). For example, in the 1990s, African-Americans with sickle cell disease had a life expectancy of less than 50 years, compared with the life expectancy of African-

Americans without sickle cell disease of more than 70 years (Platt 1994).

Sickle cell disease is characterized by the presence of distorted sickle-shaped red blood cells in the bloodstream. These sickle-shaped cells arise as a result of the "polymerization (gelling of the molecules) of the abnormal Hb in the red blood cells when they release their combined oxygen" (Al Hajeri 2007). Many manifestations of the disease are attributed to either haemolysis (premature red cell destruction) or vaso-occlusion (obstruction of blood flow), which is the most common manifestation (Al Hajeri 2007). Red cell dehydration contributes to vaso-occlusion: dehydrated red cells adhere to vascular endothelium, which results in blockage of blood flow (Lutz 2015). Other severe outcomes of the manifestations of sickle cell disease can include acute chest syndrome (chest crisis), priapism, acute cholecystitis, acute stroke and aplastic crisis (NIH 2014).

Vaso-occlusion can lead to acute, painful crisis. This is also known as a sickle cell crisis, VOC or vaso-occlusive episode. Pain is most often reported in the joints, extremities, back or chest, but it can occur anywhere and can last for several days or weeks. The frequency and severity of the painful episodes vary widely within and between individuals. The peak incidence is in late adolescence and early adulthood (Ballas 2007). The bone and muscle pain experienced during a sickle cell crisis is both acute (sudden onset of severe intensity) and recurrent (reoccurring unpredictably and intermittently over long periods while fluctuating in frequency and quality) (Serjeant 1994; Thienhaus 2002).

This review focused on the vaso-occlusive manifestation of the disease, which causes the acute and painful crises (episodes), VOC. It excluded the other possible outcomes in people with sickle cell disease.

Description of the intervention

A VOC can require several interventions, depending on the person and situation. Treatment is primarily symptomatic and aims to stabilize pain. As well as pharmacological agents, non-pharmacological approaches, such as relaxation, hypnosis, heat, ice and acupuncture, have been used to rehydrate the person and reduce the sickling process (Ballas 2005; Ballas 2007; De Ceulaer 1982; Gaston 1986; Lane 2001; Okomo 2015).

In this review, we assessed pharmacological interventions used to treat VOC in adults living with sickle cell disease. These included (but were not limited to) opioid and non-opioid analgesics, as well as partial agonists, mixed agonists-antagonists, antagonists and adjuvants (Ballas 2007).

In context, a VOC is the hallmark of sickle cell disease and is the most common cause of hospitalization (up to 90%) (Ballas 2005; Dampier 2013). Therefore, treatment for adults with VOC is usually on presentation to an emergency healthcare facility, requiring immediate treatment for acute and debilitating pain. In addition, some people with sickle cell disease often self-medicate at home with pharmacological agents. In both settings, primary management should focus on rapid pain control, whereby fluids and analgesics should be administered immediately (Gillis 2012).

VOC can be treated with various drugs (described below). As with all pharmacotherapies, the risk of adverse effects can be minimized

by prescribing the lowest dose for the shortest duration possible to control the symptoms (NICE 2015).

For all analgesia, the person's respiratory rate, pain and sedation are assessed at 20-minute intervals until pain control is reached, then monitored with analgesia readministered every four hours (NICE 2015; Rees 2003). Patient-controlled administration (PCA) is an option used in adolescents transitioning into adult care (Telfer 2014).

Opioid analgesics

Opioid analgesics are recommended as the primary choice of pain relief in VOC management (NICE 2015). They include (but are not limited to): codeine, hydrocodone/paracetamol (hydrocodone/acetaminophen), hydrocodone/ibuprofen, oxycodone (and with codeine), morphine, hydromorphone, oxymorphone, methadone, diamorphine and fentanyl (Ballas 2007). Opioids are generally available in healthcare settings in most Western countries and are often delivered as intravenous (IV) morphine every four to six hours. In addition, oral opioids are prescribed as PCA after a VOC episode (NICE 2015).

Most analgesic opioids have a half-life of two to four hours, with the exception of methadone, propoxyphene and meperidine, for which this can be one to several days (Trescot 2008). Although the standard dosing is generally every four to six hours, some people develop tolerance to opioids, thus requiring doses every two hours (Okpala 2002). Combination with diclofenac or paracetamol (which have different mechanisms of action) helps keep opioid use to a minimum (Okpala 2002).

The adverse effects of analgesic opioids include: (short-term) respiratory depression, constipation, vomiting, nausea, pruritus and hives (Ballas 2007), addiction, and withdrawals (Rosenblum 2008).

Non-opioid analgesics

Non-opioid analgesics are the other drugs of choice for managing a VOC (NICE 2015). These include: paracetamol, non-selective cyclooxygenase (COX) inhibitors (aspirin (acetylsalicylic acid), ibuprofen, naproxen and ketorolac) and selective COX-2 inhibitors (celecoxib) (Ballas 2007).

The most commonly used drugs from this family are non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, diclofenac and ketorolac. They are commonly used for mild-to-moderate pain either alone or in combination with opioid analgesia (Rees 2003).

NSAIDs are available in most countries. The adverse effects of NSAIDs include gastrointestinal complications and they should be administered with caution in people with a history of renal failure, bleeding tendencies, asthma or peptic ulcers (Rees 2003).

Paracetamol is also widely available in Western countries and is administered orally at a dosage of 200 mg to 500 mg every four to six hours until satisfactory pain relief has been achieved. The adverse effects of paracetamol are influenced by the dosage and duration of use and can include liver failure (Rees 2003).

Other pharmacotherapeutic drugs

Other pharmacotherapeutic drugs to be considered for analysis in this review include partial agonists (e.g. buprenorphine

and buprenorphine/naloxone), mixed agonist-antagonists (e.g. pentazocine, nalbuphine and butorphanol) and hydroxyurea (Ballas 2007). Finally, we will also consider any other pharmacotherapeutic drugs that we find, which are used to treat VOC.

How the intervention might work

Analgesics work in several ways to treat VOC, thus the key factor is whether the drugs provide relief of participant-reported pain. Therefore, we were interested in gathering a comprehensive list of all pharmacotherapeutic treatments that have been trialed in a clinical setting to treat a new or recurrent painful crisis in people with sickle cell disease. We were also interested in combination drug therapies.

Why it is important to do this review

Globally, sickle cell disease is one of the four most common autosomal-recessive disorders, along with thalassaemia, Tay-Sachs disease and cystic fibrosis (Hussein 2015). In many countries, there has been an improvement in the survival rate of children with sickle cell disease who now live on into adulthood, thus increasing the adult population living with this condition (Quinn 2010; Sasongko 2013).

We are unaware of any recent or up-to-date systematic reviews that draw on comparisons of a full range of pharmacotherapies used specifically to treat VOC in adults. Therefore, this review aimed to address and analyse all available pharmacotherapies, including drug combinations.

This systematic review also addressed the issue of tolerance or habituation to opioids where this was reported in people with sickle cell disease (Tanabe 2012; Waldrop 1995). Regular analgesia should be given for acute pain when presenting in the emergency setting. Due to people developing a tolerance and requiring more frequent doses of opioids, it has been suggested that efforts should be made to prevent such tolerance developing in new patients because there is a limited choice of injectable opioids that can be used in acute painful episodes (Okpala 2002).

A systematic review of the current evidence on the reported benefits and harms is required to clarify the most effective pharmacotherapeutic options (and combinations) for effective pain relief interventions in adults with acute painful sickle cell VOC.

OBJECTIVES

To assess the analgesic efficacy and adverse events of pharmacological interventions to treat acute painful sickle cell vaso-occlusive crises in adults, in any setting.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) with double-blind assessment of participant outcomes following immediate treatment for acute painful sickle cell vaso-occlusive episodes. We considered studies of parallel and crossover trial designs. We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical

trials and extended abstracts of otherwise unpublished clinical trials if sufficient data could be analysed. We excluded studies that were non-randomized, case reports and clinical observations.

Types of participants

Studies included adults, aged 18 years and above, diagnosed with sickle cell disease and who had an acute painful sickle cell VOC (new or recurring).

We anticipated that some studies would contain some participants below 18 years of age (such as adolescents mixed with adults over 18 years of age). In the protocol, we planned to extract the data on participants aged 18 years and above and to contact the study authors for the separate adult data if necessary. At review stage, we changed this approach to include the study and data on all its participants if less than 20% of the participants were aged 17 or under. If greater than 20% of the participants were aged 17 years or under, we planned to extract the data on the participants aged 18 years and above, and contact the authors of the studies for separate adult data if necessary. However, this did not occur.

Types of interventions

Any pharmacological intervention at any dose, by any route, administered for the relief of acute pain associated with a sickle cell vaso-occlusive episode or event (new or recurring) and compared to placebo or any active comparator.

We included studies treating the crisis in any healthcare setting, as well as combination drug regimens. IN fluid replacement therapy is a primary step in both the National Institute of Health and Care Excellence (NICE) and National Institutes of Health (NIH) guidelines for managing a sickle cell crisis (NICE 2015; NIH 2014), and was, therefore, considered standard practice and not an active comparator for the purpose of this review. We excluded studies using agents to treat pain resulting from other causes and studies using agents to attempt to treat the cause of sickle cell disease, chronic pain or non-painful symptoms of the disease.

Types of outcome measures

Studies had to report pain assessment as either a primary or secondary outcome to be eligible for this review.

We anticipated that studies would use a variety of outcome measures, with the majority of studies using standard subjective scales (numerical rating scale (NRS) or visual analogue scale (VAS)) for pain intensity or pain relief, or both (Dworkin 2008).

We used the following dichotomous measures of pain: at least 50% pain relief over baseline (substantial), at least 30% pain relief over baseline (moderate), *very much* improved on the Patient Global Impression of Change (PGIC) (substantial), and *much or very much* improved on the PGIC (moderate). These outcomes are different from those used in most earlier reviews (Wiffen 2005), and we recognize that continuous responses to chronic pain generally do not follow a normal (Gaussian) distribution. People with chronic pain desire high levels of pain relief, ideally more than 50% and ideally leading to no more than mild pain (Moore 2013; O'Brien 2010). For the purpose of this review, we considered it appropriate to adapt these measurements of chronic pain to acute painful episodes, as the outcomes used to measure the end points of chronic pain are the same outcomes used to measure end points of acute pain.

We included three 'Summary of findings' tables. The 'Summary of findings' tables included outcomes of at least 50% and at least 30% pain intensity reduction, PGIC, serious adverse events (which included death) and withdrawals due to adverse events. We used the GRADE approach to assess the quality of the evidence related to each of the key outcomes listed in here (Higgins 2011a), as appropriate (see [Data synthesis](#)).

Primary outcomes

- Participant-reported pain relief of 50% or greater at 6, 12, 24, 48 hours and at the end of treatment.
- Participant-reported pain relief of 30% or greater at 6, 12, 24, 48 hours and at the end of treatment.
- Patient global impression of change (PGIC) *very much* improved.
- Patient global impression of change (PGIC) *much or very much* improved.

Secondary outcomes

- Opioid consumption.
- Time to pain resolution.
- Length of hospitalization.
- Participants experiencing any adverse or serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, was an 'important medical event' that may have jeopardized the person, or may have required an intervention to prevent one of the above characteristics or consequences. Acute chest syndrome is well documented as a reported adverse event of VOC and we planned to assess the issues around tolerability of the drugs.
- Any pain-related outcome indicating some improvement, such as sleep quality or activities of daily living.
- Withdrawals due to lack of efficacy, adverse events and for any cause.
- Reports of tolerance or habituation to opioids.

Search methods for identification of studies

The Information Specialist carried out the searches.

Electronic searches

We searched the following databases without language restrictions:

- Cochrane Central Register of Controlled Trials (CENTRAL; via the Cochrane Library) searched 16 September 2019;
- MEDLINE and MEDLINE in Process (via Ovid) searched 1947 to 16 September 2019;
- Embase (via Ovid) searched 1974 to 2019 week 38;
- LILACS (via BIRME) searched 1982 to September 2019.

We used MeSH or equivalent and text-word terms. We tailored the searches to the individual databases.

The search strategies for CENTRAL, MEDLINE, Embase and LILACS are in [Appendix 1](#).

Searching other resources

We searched the metaRegister of controlled trials (mRCT) (www.isrctn.com/), ClinicalTrials.gov (www.clinicaltrials.gov/), and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. We also checked the reference lists of reviews and retrieved articles for additional studies and performed citation searches on key articles.

Data collection and analysis

Selection of studies

Three review authors (TC SB, and BJ) independently determined the eligibility of each study identified by the search by reading the title and abstract. The review authors then independently eliminated studies that clearly did not satisfy the inclusion criteria and obtained full copies of the remaining studies.

Three review authors (TC SB, and BJ) independently read these reports to select relevant studies. In the event of disagreement, a fourth review author (PW) adjudicated. We did not anonymize the studies before assessment. We included a PRISMA flow chart, which shows the status of identified studies ([Moher 2009](#)), as recommended in Part 2 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). We included studies in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Data extraction and management

Two review authors (TC and IH) independently extracted data using a standard piloted form, and checked for agreement before entry into Review Manager 5 ([Review Manager 2014](#)).

We included information about the pain condition, number of participants treated, drug and dosing regimen, study design (placebo or active control), study duration and follow-up, analgesic outcome measures and results, withdrawals and adverse events (participants experiencing any adverse event or serious adverse event).

We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review.

We collected characteristics of the studies in sufficient detail to complete the [Characteristics of included studies](#) table.

Assessment of risk of bias in included studies

Two review authors (TC and IH) independently assessed the risk of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)), adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We completed a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager 5 ([Review Manager 2014](#)).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not

clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomization; consecutively numbered, sealed, opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind the participants and personnel from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that the participants and personnel involved were blinded to treatment groups); unclear risk of bias (study did not state whether or not participants and personnel were blinded to treatment groups); or high risk of bias (participants or personnel were not blinded) (as stated in [Types of studies](#), we included trials with or without blinding, and participant- or observer-reported outcomes).
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, e.g. identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk of bias (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Selective reporting (checking for possible reporting bias). We assessed the methods used to report the outcomes of the study as: low risk of bias (if all planned outcomes in the protocol or methods were reported in the results); unclear risk of bias (if there was no clear distinction between planned outcomes and reported outcomes); or high risk of bias (if some planned outcomes from the protocol or methods were clearly not reported in the results).
- Size of study (checking for possible biases confounded by small-study size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).
- Other bias, such as multiple publications, financial declarations, participants with conflicts of interest. We assessed studies for any additional sources of bias as low, unclear or high risk of bias, and provided rationales.

Measures of treatment effect

We used dichotomous data to calculate risk ratios (RR) with 95% confidence intervals (CI) using a fixed-effect model unless there was significant statistical heterogeneity (see [Assessment of heterogeneity](#)).

We calculated numbers needed to treat for an additional beneficial outcome (NNTB) as the reciprocal of the absolute risk reduction (ARR; [McQuay 1998](#)). For unwanted effects, the NNTB becomes the number needed to treat for an additional harmful outcome (NNTH) and is calculated in the same manner. We planned to use the term number needed to treat to prevent an additional outcome (NNTp) where the unwanted effect is less common with treatment than control.

For our primary outcomes measuring pain, we planned not to use continuous data in analyses because it is inappropriate where there is underlying skewed distribution, as is usually the case with analgesic response. For our secondary outcomes, we used continuous data for the meta-analysis where appropriate.

Unit of analysis issues

We expected that the unit of analysis would be at the participant level, with each participant providing one pain episode per trial. It was possible that a trial may have included multiple pain events per participant, introducing a statistical clustering effect with two pain events in the same participant likely to be more similar than two independent pain events from two different participants; however, this did not occur in any of our included studies. We had planned to use the number of trial clusters and an estimate of the intraclass correlation coefficient to inflate the standard errors associated with each clustered trial in this scenario.

We had planned for the unit of analysis to be each participant from the first phase of treatment before crossing over (who, where randomised, took at least one dose of study, and provided at least one outcome score) if any included studies were crossover studies. We would include the second phase of treatment if there was a sufficient washout period and results were reported clearly and separately. If not, and the results appeared unclear from which phase they were taken, we would contact the authors and attempt to gain access to the original data. Otherwise, we would not use the data.

Dealing with missing data

We used intention-to-treat analysis where the intention-to-treat population consisted of participants who were randomized, received at least one dose of the assigned study treatment and provided at least one post-baseline assessment. We assigned missing participants zero improvement wherever possible.

Assessment of heterogeneity

We dealt with clinical heterogeneity (variation in participants, interventions or outcomes) by combining studies that examined similar conditions when possible. We assessed statistical heterogeneity visually ([L'Abbé 1987](#)), and with the I^2 statistic. We considered the possible reasons when the I^2 value was greater than 50%.

Assessment of reporting biases

The aim of this review was to use dichotomous outcomes of known utility and of value to patients ([Hoffman 2010](#); [Moore 2010a](#); [Moore 2010b](#); [Moore 2010c](#); [Moore 2013](#)). The review did not depend on what the authors of the original studies chose to report or not, though difficulties arose in studies failing to report any dichotomous results. We extracted and used continuous data where possible, which poorly reflected efficacy and utility but was useful for illustrative purposes only.

We assessed publication bias using a method designed to detect the amount of unpublished data with a null effect required to make any result clinically irrelevant (usually taken to mean an NNTB of 10 or higher; [Moore 2008](#)).

Data synthesis

We planned to meta-analyse data from similar comparisons using a fixed-effect model in Review Manager 5 ([Review Manager 2014](#)). Due to the lack of available data, we used Review Manager 5 to undertake a summary of effects from individual studies, fixed-effects and without group totals ([Analysis 1.1](#); [Analysis 1.2](#); [Analysis 1.3](#); [Analysis 1.4](#)).

We planned to have used a random-effects model for meta-analysis if there was significant clinical heterogeneity and it was considered appropriate to combine studies. This did not occur.

Quality of the evidence

Two review authors (TC, PW) independently rated the quality of the evidence for each outcome. We used the GRADE system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software ([GRADEpro GDT](#)), and the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning the grade of evidence.

- High: further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- Low: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very low: any estimate of effect is very uncertain.

Reasons for decreasing grade are due to:

- serious (–1) or very serious (–2) limitation to study quality;
- important inconsistency (–1);
- some (–1) or major (–2) uncertainty about directness;
- imprecise or sparse data (–1);
- high probability of reporting bias (–1).

In addition, we anticipated there may have been circumstances where the overall rating for a particular outcome would need to

be adjusted per GRADE guidelines (Guyatt 2013a; Guyatt 2013b). For example, if there were so few data that the results are highly susceptible to the random play of chance, or if studies used last observation carried forward imputation in circumstances where there were substantial differences in adverse event withdrawals, or where there were a small number of participants per treatment arm, one would have no confidence in the result, and would need to downgrade the quality of the evidence by three levels to very low quality.

In circumstances where no data were reported for an outcome, the quality of the evidence is unknown and we reported this as 'no evidence to support or refute'.

Subgroup analysis and investigation of heterogeneity

We planned no subgroup analyses since experience from previous reviews suggests a limited chance of sufficient data. We would have

considered subgroup classification between genotypes should the data be available; however, the available data proved to be insufficient for this purpose.

Sensitivity analysis

We planned no sensitivity analysis because the evidence base is known to be too small to allow reliable analysis. We did not plan to pool results from sickle cell pain of different origins in the primary analyses.

R E S U L T S

Description of studies

Results of the search

A PRISMA flow diagram of the search results is shown in [Figure 1](#).

Figure 1. Study flow diagram.

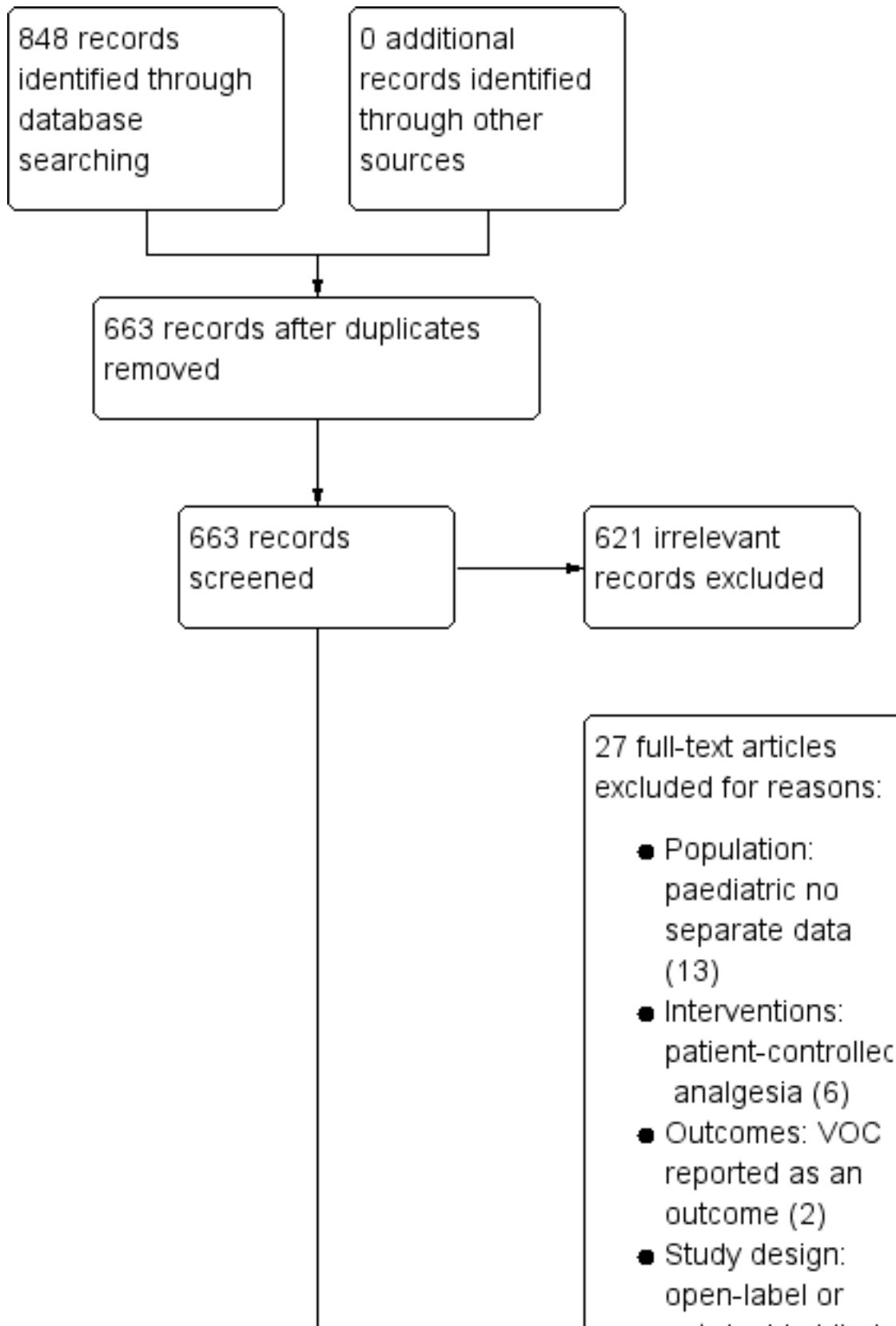
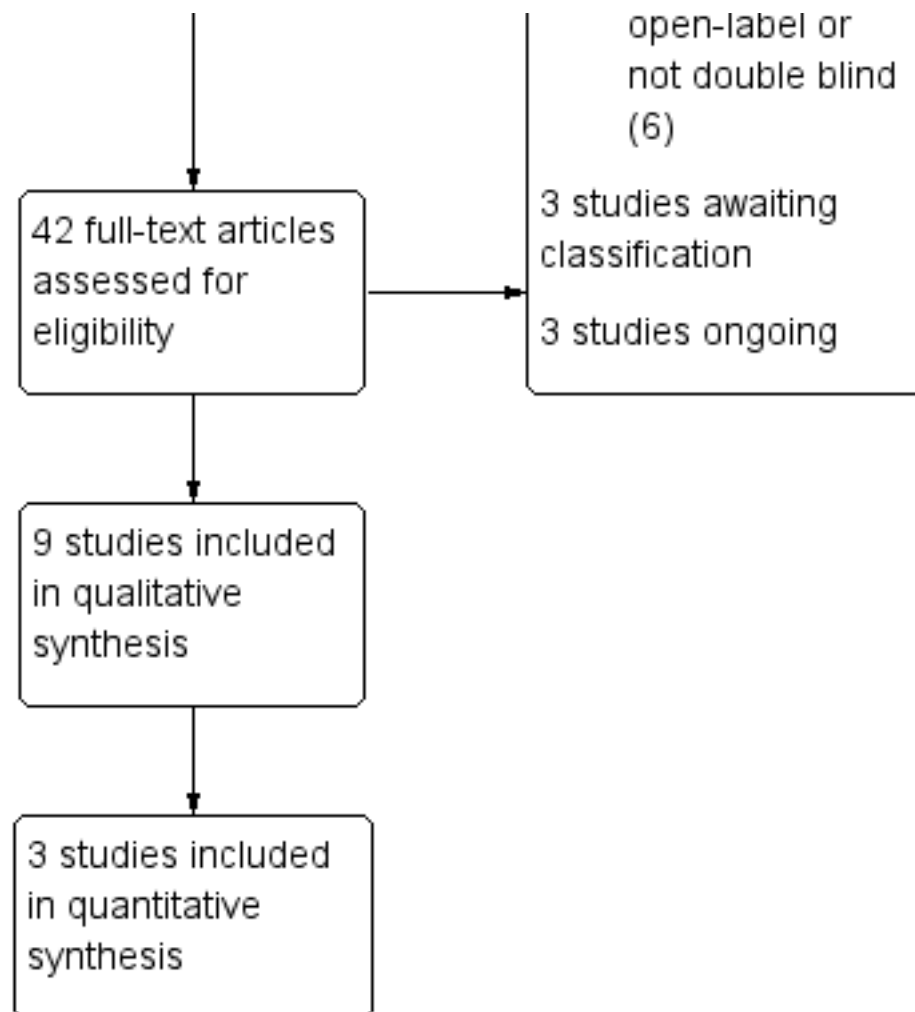


Figure 1. (Continued)



The three main database searches found 848 records, of which we removed 185 duplicates. We also searched clinicaltrials.gov and app.who.int/trialsearch/ and found no additional eligible studies.

We screened the remaining 663 titles and abstracts for eligibility, of which we removed 621 as clearly irrelevant studies.

We retrieved the full-text reports of the 42 remaining studies. Twenty-seven were ineligible and excluded ([Characteristics of excluded studies](#) table). Three studies are awaiting classification ([Characteristics of studies awaiting classification](#) table), and three studies are ongoing ([Characteristics of ongoing studies](#) table).

Nine studies fulfilled the eligibility criteria, which we included in the qualitative synthesis. We entered three of these studies into a quantitative analysis.

Included studies

We included nine studies in this review. See [Characteristics of included studies](#) table.

Design

All nine studies were randomized double-blind placebo-controlled trials with two arms. Eight studies were parallel groups and one study had crossover arms.

Sample sizes

The sample sizes of the studies ranged from 18 participants ([Gonzalez 1988](#); [Wright 1992](#)) to 253 participants ([Qari 2007](#)).

Setting

Two studies were multicentre studies and seven were single-centre studies. All studies were based in emergency departments of hospitals from France, Italy, Saudi Arabia, and the USA. No included studies were based in home or other settings.

Participants

The age ranges were adults from 17 to 42 years old. Gender ratios were roughly equal between women and men across all studies. All nine studies had inclusion criteria of pre-existing diagnosis of sickle cell disease and presenting to the emergency department in a VOC.

Interventions

Analgesic interventions varied including butorphanol, cetiedil, fentanyl, hydromorphone, ketamine, ketoprofen, metoclopramide, morphine, paracetamol, tinzaparin and tramadol.

Six studies administered IV bolus injections (Arambasik 2013; Benjamin 1986; Gonzalez 1988; Qari 2007; Rehmani 2013; Wright 1992), three administered IV infusions (Bartolucci 2009; De Franceschi 2016) and one administered an IV bolus followed by an IV infusion (Perlin 1994). Two studies were a single dose of the drug only and seven administered multiple doses of the treatments (Rehmani 2013; Wright 1992).

Outcomes

All nine studies reported pain outcomes using a validated pain scale or global assessment scores. Four studies reported opioid consumption (Bartolucci 2009; Perlin 1994; Rehmani 2013; Wright 1992). Two studies reported time to pain resolution (Bartolucci 2009; Qari 2007). Two studies reported the duration of time spent in hospital (Perlin 1994; Qari 2007). All but two studies reported adverse events and withdrawals (Arambasik 2013; Qari 2007).

Excluded studies

We excluded 27 studies in this review. See [Characteristics of excluded studies](#) table.

Thirteen studies were in paediatric or combined paediatric-adult populations, with no separate data available for adults. Six studies implemented patient-controlled analgesia (PCA). In two studies, pain was not measured as an outcome but VOC was measured as the outcome. Six studies were either not double-blind or were an open-label trial.

Studies awaiting classification

See [Studies awaiting classification](#) table.

De Castro 2013 and Perlin 1988 are conference abstracts which currently meet eligibility criteria but require outcome data. We contacted the study authors for further information so these remain in studies awaiting classification. In Teuscher 1989, it was unclear whether pain was reported as a primary or secondary outcome. We contacted the study author for further information but this has not been received.

Ongoing studies

We identified three ongoing studies (IRCT2016072511956N6; NCT03431285; NCT03978156). See [Characteristics of ongoing studies](#) table.

Risk of bias in included studies

A summary of the risk of bias assessment is available in [Figure 2](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Size	Other bias
Arambasik 2013	?	?	?	?	?	?	-	?
Bartolucci 2009	?	?	?	?	-	+	-	?
Benjamin 1986	+	+	+	?	?	+	-	+
De Franceschi 2016	+	?	?	+	+	+	-	+
Gonzalez 1988	?	?	+	+	?	+	-	-
Perlin 1994	+	+	+	+	?	+	-	+
Qari 2007	?	?	?	?	?	-	?	+
Rehmani 2013	?	?	?	?	?	-	?	+
Wright 1992	+	+	+	?	+	+	-	+

Full details of risk of bias assessments are available in the [Characteristics of included studies](#) table.

Allocation

Random sequence generation

Four studies adequately described the methods used to randomize participants (computer-generated randomization) and were at low risk of selection bias for random sequence generation (Benjamin 1986; De Franceschi 2016; Perlin 1994; Wright 1992). Five studies did not adequately describe the methods used to randomize participants and were at unclear risk of selection bias for random sequence generation (Arambasik 2013; Bartolucci 2009; Gonzalez 1988; Qari 2007; Rehmani 2013). No studies displayed a high risk of selection bias for random sequence generation.

Allocation concealment

Three studies adequately described the methods used to conceal allocation of treatment to each group and were at low risk of selection bias for allocation concealment (Benjamin 1986; Perlin 1994; Wright 1992). Six studies did not adequately describe the methods used to conceal allocation of treatment to each group and were at unclear risk of selection bias for allocation concealment (Arambasik 2013; Bartolucci 2009; De Franceschi 2016; Gonzalez 1988; Qari 2007; Rehmani 2013). No studies displayed a high risk of selection bias for allocation concealment.

Blinding

Performance bias

Four studies adequately described the methods to blind both participants and study personnel from knowledge of the treatment groups and were at low risk of performance bias (Benjamin 1986; Gonzalez 1988; Perlin 1994; Wright 1992). Five studies did not adequately describe the methods to blind both participants and study personnel from knowledge of the treatment groups and were at unclear risk of performance bias (Arambasik 2013; Bartolucci 2009; De Franceschi 2016; Qari 2007; Rehmani 2013). No studies displayed a high risk of performance bias.

Detection bias

Three studies adequately described the methods used to conceal and blind the outcome assessors from knowledge of the treatment groups and were at low risk of detection bias (De Franceschi 2016; Gonzalez 1988; Perlin 1994). Six studies did not adequately describe the methods used to conceal and blind the outcome assessors from knowledge of the treatment groups and were at unclear risk of detection bias (Arambasik 2013; Bartolucci 2009; Benjamin 1986; Qari 2007; Rehmani 2013; Wright 1992). No studies displayed a high risk of detection bias.

Incomplete outcome data

Two studies adequately accounted for all participants from the recruitment stage, through randomization until follow-up, including counting all withdrawals and were at low risk of attrition bias (De Franceschi 2016; Wright 1992). Six studies did not adequately account for all participants from the recruitment stage, through randomization until follow-up, including counting all withdrawals and were at unclear risk of attrition bias (Arambasik 2013; Benjamin 1986; Gonzalez 1988; Perlin 1994; Qari 2007; Rehmani 2013). One study reported 20% attrition, the outcome reporting ignored these randomized participants and analyses did not appear to be by intention to treat (Bartolucci 2009). This was at high risk of attrition bias.

Selective reporting

Six studies adequately reported in their results all the outcomes that were planned in the methods sections and were at low risk of reporting bias (Bartolucci 2009; Benjamin 1986; De Franceschi 2016; Gonzalez 1988; Perlin 1994; Wright 1992). One study displayed an unclear risk of reporting bias and was at unclear risk of reporting bias (Arambasik 2013). Two studies, planned to measure outcomes in their methods, but did not mention them when reporting results and were at high risk of reporting bias (Qari 2007; Rehmani 2013). Qari 2007 did not report on adverse events or opioid consumption, as planned. Rehmani 2013 did not report on the VRS, as planned.

Other potential sources of bias

Size

Two studies investigated between 50 and 200 participants per treatment arm and were at unclear risk of bias in relation to size (Qari 2007; Rehmani 2013).

Seven studies investigated fewer than 50 participants per treatment arm and were at high risk of bias in relation to size (Arambasik 2013; Bartolucci 2009; Benjamin 1986; De Franceschi 2016; Gonzalez 1988; Perlin 1994; Wright 1992). No studies investigated more than 200 participants per treatment arm.

Other

Gonzalez 1988 displayed a high risk of bias in relation to a unit of analysis issue, 12 events per treatment arm. However, the unit of randomization was the painful crisis (45 randomized crises events among 18 participants), random-effects analysis took this unit of analysis issue appropriately into account. This was judged at high risk of 'other' bias.

Bartolucci 2009 displayed some unclear risk of bias in relation to a unit of analysis error. The unit of randomization was the painful crisis (66 randomized crises among 54 participants), but the unit of analysis ignored the clustered nature of the data which were analysed as if all randomized events were independent. This was judged at unclear risk of 'other' bias.

Arambasik 2013 displayed some unclear risk of bias as we could not conclude there was low risk of bias due to only the abstract being available. This was judged at unclear risk of 'other' bias.

For the remaining six studies, we found no other potential sources of bias and they were at low risk of 'other' bias.

Effects of interventions

See: **Summary of findings for the main comparison** Non-steroidal anti-inflammatory drugs (NSAID) compared with placebo for painful sickle cell vaso-occlusive crises; **Summary of findings 2** Opioids compared with placebo for painful sickle cell vaso-occlusive crises; **Summary of findings 3** Opioids compared with active comparator for painful sickle cell vaso-occlusive crises

For results and adverse events of individual studies, see [Appendix 2](#) (primary outcome data: pain outcomes); [Appendix 3](#) (secondary outcome data); and [Appendix 4](#) (adverse events and withdrawals).

Table 1 displays the types of pharmacological intervention comparisons by study.

Table 1: types of drug comparisons

Study	Interventions	Comparison pair
Arambasik 2013	Ketamine + hydromorphone vs placebo + hydromorphone	Opioid vs placebo
Bartolucci 2009	Ketoprofen vs placebo	NSAID vs placebo
Benjamin 1986	Cetiedil vs placebo	Vasodilator (anti-sickling) vs placebo
De Franceschi 2016	Ketorolac + tramadol + metoclopramide + fentanyl vs ketorolac + tramadol + metoclopramide	Combination vs combination
Gonzalez 1988	Butorphanol vs morphine	Opioid vs opioid
Perlin 1994	Ketorolac vs placebo	NSAID vs placebo
Qari 2007	Tinzaparin vs placebo	Anticoagulant vs placebo
Rehmani 2013	Morphine vs paracetamol	Opioid vs paracetamol
Wright 1992	Ketorolac vs placebo	NSAID vs placebo

Comparison 1: non-steroidal anti-inflammatory drugs versus placebo

Three studies compared an NSAID with placebo ([Bartolucci 2009](#); [Perlin 1994](#); [Wright 1992](#)). See [Summary of findings for the main comparison](#).

Primary outcomes

Participant-reported pain relief of 50% or greater

None of the studies reported participants-reported pain relief of 50% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participant-reported pain relief of 30% or greater

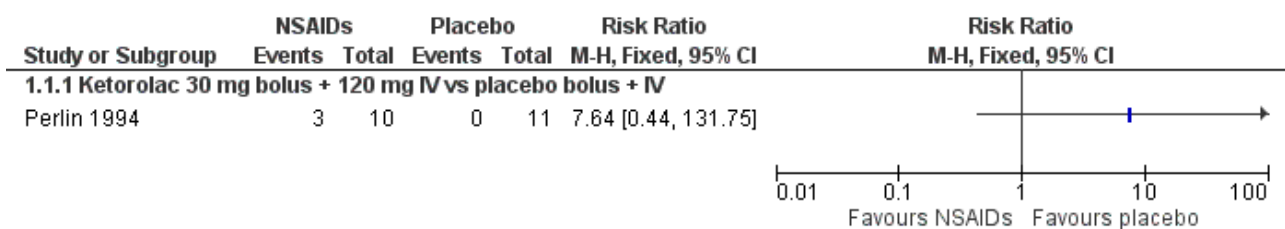
None of the studies reported participant-reported pain relief of 30% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change very much improved

One study reported PGIC *very much* improved ([Perlin 1994](#)). As there was only one study reporting this comparison, we did not undertake a meta-analysis but provided a summary of effects from the individual study (RR: risk ratio); [Analysis 1.1](#); [Figure 3](#).

Figure 3. Forest plot of comparison: 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, outcome: 1.1 Patient Global Impression of Change very much improved.

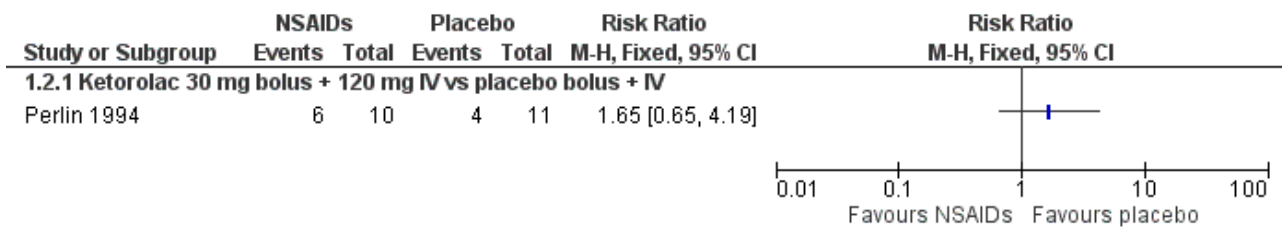


[Perlin 1994](#) reported *very much* improved for 3/10 participants in the ketorolac group, and for 0/11 participants in the placebo group (RR 7.64, 95% CI 0.44 to 131.75; P = 0.16; [Analysis 1.1](#); [Figure 3](#)). As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Patient Global Impression of Change much or very much improved

One study reported PGIC *much or very much* improved ([Perlin 1994](#)). As there was only one study reporting this comparison, we did not undertake a meta-analysis but provided a summary of effects from the individual study (RR: risk ratio); [Analysis 1.2](#); [Figure 4](#).

Figure 4. Forest plot of comparison: 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, outcome: 1.2 Patient Global Impression of Change *much or very much* improved.



Perlin 1994 reported the combination of *much or very much* improved for 6/10 participants in the ketorolac group, and 4/11 participants in the placebo group (RR 1.65, 95% CI 0.65 to 4.19; P = 0.29; Analysis 1.2; Figure 4).

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Secondary outcomes

Opioid consumption

Three studies reported opioid consumption (Bartolucci 2009; Perlin 1994; Wright 1992).

Bartolucci 2009 reported the use of additional rescue morphine. The overall median (interquartile range (IQR)) consumption of morphine was 110 mg (IQR 46 to 195) in the ketoprofen group and 88 mg (IQR 52.5 to 262.5) in the placebo group (33 participants per group).

Perlin 1994 reported the use of additional rescue meperidine. The mean daily dose of meperidine was 523.6 mg (standard deviation (SD) 222.1) in the ketorolac group (10 participants) and 662.4 mg (SD 68.6) in the placebo group (11 participants). The overall mean consumption of meperidine was 1866.7 mg (SD 1112.4) in the ketorolac group and 2804.5 mg (SD 795.1) in the placebo group.

Wright 1992 reported the use of additional rescue meperidine. The overall mean consumption of meperidine was 231 mg (SD 92) in the ketorolac group and 250 mg (SD 85) in the placebo group (12 participants per group).

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Time to pain resolution

One study reported time to pain resolution (Bartolucci 2009).

Bartolucci 2009 reported median time to participants' resolution of pain as 51 hours (IQR 35.5 to 87) in the ketoprofen group and 50 hours (IQR 36 to 103) in the placebo group (33 participants per group). As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Length of hospitalization

One study reported length of hospitalization (Perlin 1994).

Perlin 1994 reported mean length of hospitalization as 3.3 days in the ketorolac group (10 participants) and 7.2 days in the placebo group (11 participants) (P < 0.05). As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Participants experiencing any adverse or serious adverse event

Two studies reported adverse events (Bartolucci 2009; Wright 1992).

Bartolucci 2009 reported any mild adverse events in 16/33 participants in the ketoprofen group and 19/33 participants in the placebo group.

Wright 1992 reported adverse events in 0/12 participants in the ketorolac group and 0/12 participants in the placebo group.

Three studies reported serious adverse events (Bartolucci 2009; Perlin 1994; Wright 1992).

Bartolucci 2009 reported serious adverse events in 1/33 participants in the ketoprofen group, and 2/33 participants in the placebo group.

Perlin 1994 reported serious adverse events in 0/10 participants in the ketorolac group and 0/11 participants in the placebo group.

Wright 1992 reported serious adverse events in 0/12 participants in the ketorolac group and 0/12 participants in the placebo group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Any pain-related outcome indicating some improvement

Three studies reported additional pain related outcome data (Bartolucci 2009; Perlin 1994; Wright 1992).

Bartolucci 2009 reported the mean daily scores on a categorical pain scale (0 to 3) as median 0.4 (IQR 0.2 to 0.7) in the ketoprofen group and 0.4 (IQR 0.2 to 0.7) in the placebo group. The authors also reported mean daily scores on a VAS (0 mm to 100 mm, where 0 = no pain) as median 12.6 (IQR 4.8 to 23.2) in the ketoprofen group and 9.6 (IQR 5.8 to 33.2) in the placebo group.

[Perlin 1994](#) reported the pain scores at baseline on a VAS (0 mm to 100 mm), as mean 77.7 (95% CI 69.1, 86.2) in the ketorolac group and 79.1 (95% CI 72.1 to 86.0) in the placebo group. Pain scores at 24 hours on a VAS (0 mm to 100 mm) were mean 58.6 (95% CI 48.6 to 68.5) in the ketorolac group and 72.6 (95% CI 62.4 to 82.8) in the placebo group ($P < 0.05$). Mean pain scores at baseline on a visual categorical scale (0 to 3) were 2.5 in the ketorolac group and 2.6 in the placebo group. Mean pain scores at 24 hours on a visual categorical scale (0 to 3) were 2.0 in the ketorolac group and 2.4 in the placebo group. Mean pain scores at 24 hours on a VRS (0 to 4) were 1.8 in the ketorolac group and 1.9 in the placebo group.

[Wright 1992](#) reported mean pain scores at baseline on a VAS (0 mm to 100 mm) were 70.3 in the ketorolac group and 79.3 in the placebo group ($P = 0.26$). Mean pain scores at four hours on a VAS (0 mm to 100 mm) were 44 (SD 34) in the ketorolac group and 37 (SD 31) in the placebo group ($P = 0.49$).

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Withdrawals: due to lack of efficacy, adverse events and for any cause

Two studies reported all-cause withdrawals ([Perlin 1994](#); [Wright 1992](#)).

[Perlin 1994](#) reported total all-cause withdrawals in 1/10 participants in the ketorolac group and 0/11 participants in the placebo group.

[Wright 1992](#) reported total all-cause withdrawals in 0/12 participants in the ketorolac group and 0/12 participants in the placebo group.

Three studies reported withdrawals due to adverse events ([Bartolucci 2009](#); [Perlin 1994](#); [Wright 1992](#)).

[Bartolucci 2009](#) reported withdrawals due to adverse events in 1/33 participants in the ketoprofen group and 1/33 participants in the placebo group.

[Perlin 1994](#) reported withdrawals due to adverse events in 0/10 participants in the ketorolac group and 0/11 participants in the placebo group.

[Wright 1992](#) reported withdrawals due to adverse events in 0/12 participants in the ketorolac group and 0/12 participants in the placebo group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Reports of tolerance or habituation to opioids

None of the studies reported tolerance or habituation to opioids.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Comparison 2: opioids versus placebo

One study compared ketamine plus hydromorphone with placebo plus hydromorphone ([Arambasik 2013](#)). See [Summary of findings 2](#).

Primary outcomes

Participant-reported pain relief of 50% or greater

The study did not report participant-reported pain relief of 50% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participant-reported pain relief of 30% or greater

The study did not report participant-reported pain relief of 30% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change *very much* improved

The study did not report PGIC *very much* improved.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change *much* or *very much* improved

The study did not report PGIC *much* or *very much* improved.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Secondary outcomes

Opioid consumption

The study did not report opioid consumption.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Time to pain resolution

The study did not report time to pain resolution.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Length of hospitalization

The study did not report length of hospitalization.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participants experiencing any adverse or serious adverse event

The study did not report any adverse event or serious adverse event.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Any pain-related outcome indicating some improvement

[Arambasik 2013](#) reported mean pain scores on a VAS (1 to 10, where 1 implies none or minimal pain), on arrival, of 8.7 (95% CI

8.07 to 9.29) in the ketamine plus hydromorphone group and 8.5 (95% CI 7.90 to 9.05) in the placebo plus hydromorphone group. At administration of the study drugs, mean pain scores were 6.0 (95% CI 4.71 to 7.29; a 31% decrease from arrival) in the ketamine plus hydromorphone group and 7.0 (95% CI 6.20 to 7.85; a 17.6% decrease from arrival) in the placebo plus hydromorphone group. Once doses were administered, the mean pain scores were 5.2 (95% CI 4.01 to 6.46; a 40.2% decrease from arrival) in the ketamine plus hydromorphone group and 5.6 (95% CI 4.27 to 6.93; a 34.1% decrease from arrival) in the placebo plus hydromorphone group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Withdrawals: due to lack of efficacy, adverse events and for any cause

The study did not report withdrawals.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Reports of tolerance or habituation to opioids

The study did not report tolerance or habituation to opioids.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Comparison 3: opioids versus active comparator

Two studies compared an opioid with an active comparator: [Gonzalez 1988](#): morphine versus butorphanol; [Rehmani 2013](#): morphine versus paracetamol. See [Summary of findings 3](#).

Primary outcomes

Participant-reported pain relief of 50% or greater

Neither study reported participant-reported pain relief of 50% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participant-reported pain relief of 30% or greater

Neither study reported participant-reported pain relief of 30% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change very much improved

One study reported PGIC *very much* improved ([Gonzalez 1988](#)).

[Gonzalez 1988](#) reported an equivalent scale of *very much* improved as 'excellent' for 19.1% of events in the butorphanol group and 33.3% of events in the morphine group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Patient Global Impression of Change much or very much improved

One study reported PGIC *much or very much* improved ([Gonzalez 1988](#)).

[Gonzalez 1988](#) reported equivalent scales of 'good' and 'excellent'. The study reported 'good' improvement from 47.6% in the butorphanol group and 38.1% in the morphine group. The study reported 'excellent' improvement from 19.1% in the butorphanol group and 33.3% in the morphine group. The study did not report a combination of 'good and excellent' (equivalent scale of *much and very much* improved) and the available percentages did not seem to match the raw data, so it was not possible to calculate a combined percentage for this outcome.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Secondary outcomes

Opioid consumption

One study reported opioid consumption.

[Rehmani 2013](#) reported the use of additional rescue morphine 0.1 mg/kg at 30 minutes for 27/54 participants in the morphine group, and 24/52 participants in the paracetamol group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Time to pain resolution

Neither study reported time to pain resolution.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Length of hospitalization

Neither study reported length of hospitalization.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participants experiencing any adverse or serious adverse event

Both studies reported adverse events and serious adverse events.

[Gonzalez 1988](#) reported nausea and vomiting in 4/12 participants in the butorphanol group and 4/12 participants in the morphine group.

[Rehmani 2013](#) reported mild adverse events in 5/54 participants in the morphine group and 3/52 participants in the paracetamol group.

[Gonzalez 1988](#) reported serious adverse events in 0/12 participants in the morphine group and 0/12 participants in the butorphanol group.

[Rehmani 2013](#) reported serious adverse events 0/54 participants in the morphine group and 0/52 participants in the paracetamol group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Any pain-related outcome indicating some improvement

Both studies reported mean pain scores, at different time points.

[Gonzalez 1988](#) reported adjusted mean overall pain scores, on a VAS (0 mm to 100 mm, where 0 = no pain) of 46.08 in the morphine group and 44.42 in the butorphanol group. Adjusted mean overall pain scores, on a Pain Relief Scale (0 mm to 100 mm, where 0 = no pain) were 55.50 in the morphine group and 43.79 in the butorphanol group.

[Rehmani 2013](#) reported mean pain scores, on a VAS (0 mm to 100 mm, where 0 = no pain), at 30 minutes, of 44 (95% CI 33 to 56) in the morphine group and 41 (95% CI 32 to 49) in the butorphanol group. This was not statistically significant ($P = 0.72$).

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Withdrawals: due to lack of efficacy, adverse events and for any cause

Neither study reported withdrawals.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Reports of tolerance or habituation to opioids

Neither study reported tolerance or habituation to opioids.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Comparison 4: 'other' active comparators versus placebo

Two studies investigated an active comparator compared with a placebo: [Benjamin 1986](#): vasodilator (cetiedil) versus placebo; [Qari 2007](#): anticoagulant (tinzaparin) versus placebo.

Primary outcomes

Participant-reported pain relief of 50% or greater

Neither study reported participant-reported pain relief of 50% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participant-reported pain relief of 30% or greater

Neither study reported participant-reported pain relief of 30% or greater.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change *very much* improved

Neither study reported PGIC *very much* improved.

See [Appendix 2](#) for further details reported by [Benjamin 1986](#).

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change *much or very much* improved

One study reported PGIC *much or very much* improved ([Benjamin 1986](#)).

[Benjamin 1986](#) reported 'good + excellent' (an equivalent scale to *much or very much* improvement) for 9/16 participants in the cetiedil 0.2 mg/kg group, 10/18 participants in the cetiedil 0.3 mg/kg group, 11/13 participants in the cetiedil 0.4 mg/kg group and 4/16 participants in the placebo group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Secondary outcomes

Opioid consumption

Neither study reported opioid consumption.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Time to pain resolution

One study reported time to pain resolution.

[Qari 2007](#) reported mean time to participants' resolution of pain as 61.68 hours in the tinzaparin group (127 participants) and 104.4 hours in the placebo group (126 participants).

We considered the available data for this outcome to be low-quality evidence, downgraded once for sparse data, and once for high probability of reporting bias.

Length of hospitalization

One study reported length of hospitalization.

[Qari 2007](#) reported mean length of hospitalization as 7.08 days hours in the tinzaparin group (127 participants) and 12.06 in the placebo group (126 participants).

We considered the available data for this outcome to be low-quality evidence, downgraded once for sparse data, and once for high probability of reporting bias.

Participants experiencing any adverse or serious adverse event

One study reported adverse events and serious adverse events.

[Benjamin 1986](#) reported headache, nausea, vomiting and dry mouth in 2/17 participants in the cetiedil 0.2 mg/kg group, 9/18 participants in the cetiedil 0.3 mg/kg group, 8/14 participants in the cetiedil 0.4 mg/kg group and 8/18 participants in the placebo group.

[Benjamin 1986](#) reported no serious adverse events in the cetiedil 0.2 mg/kg group (0/16 participants), cetiedil 0.3 mg/kg group (0/18 participants), cetiedil 0.4 mg/kg group (0/13 participants) and the placebo group (0/16 participants).

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the

results and we downgraded the quality of evidence by three levels to very low quality.

Any pain-related outcome indicating some improvement

Neither study reported any pain-related outcome indicating some improvement.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Withdrawals: due to lack of efficacy, adverse events and for any cause

Neither study reported withdrawals.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Reports of tolerance or habituation to opioids

Neither study reported tolerance or habituation to opioids.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Comparison 5: combination pharmacotherapy versus combination pharmacotherapy

One study compared ketorolac plus tramadol plus metoclopramide plus fentanyl (KTMF) with ketorolac plus tramadol plus metoclopramide (KTM) (De Franceschi 2016).

Primary outcomes

Participant-reported pain relief of 50% or greater

De Franceschi 2016 reported participant-reported pain relief of 50% or greater at six hours for 12/20 participants in the KTMF group and 0/20 participants in the KTM group.

De Franceschi 2016 reported participant-reported pain relief of 50% or greater at 12 hours for 18/20 participants in the KTMF group and 4/20 participants in the KTM group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Participant-reported pain relief of 30% or greater

De Franceschi 2016 reported participant-reported pain relief of 30% or greater at six hours for 20/20 participants in the KTMF group and 1/20 participants in the KTM group.

De Franceschi 2016 reported participant-reported pain relief of 30% or greater at 12 hours for 20/20 participants in the KTMF group and 4/20 participants in the KTM group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Patient Global Impression of Change very much improved

The study did not report PGIC *very much* improved.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Patient Global Impression of Change much or very much improved

The study did not report PGIC *much or very much* improved.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Secondary outcomes

Opioid consumption

The study did not report opioid consumption.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Time to pain resolution

The study did not report time to pain resolution.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Length of hospitalization

The study did not report length of hospitalization.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Participants experiencing any adverse or serious adverse event

De Franceschi 2016 reported adverse events as 0/20 in the KTMF group and 0/20 in the KTM group.

De Franceschi 2016 reported serious adverse events as 0/20 in the KTMF group and 0/20 in the KTM group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Any pain-related outcome indicating some improvement

The study did not report any pain-related outcome indicating some improvement.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

Withdrawals: due to lack of efficacy, adverse events and for any cause

De Franceschi 2016 reported total all-cause withdrawals as 0/20 in the KTMF group and 0/20 in the KTM group.

De Franceschi 2016 reported withdrawals due to adverse events as 0/20 in the KTMF group and 0/20 in the KTM group.

As there were too few data for this outcome (limited number of participants per treatment arm), we had no confidence in the results and we downgraded the quality of evidence by three levels to very low quality.

Reports of tolerance or habituation to opioids

The study did not report tolerance or habituation to opioids.

As there were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

DISCUSSION

Summary of main results

We included nine studies in this review with data for 638 VOC events and 594 participants aged 17 to 42 years with sickle cell disease presenting to a hospital emergency department in a painful VOC.

Three studies compared NSAID with placebo for which we were unable to undertake a meta-analysis. One study compared an opioid with a placebo, two studies compared an opioid with an active comparator, two studies compared an anticoagulant with a placebo, and one study compared a combination of three drugs with a combination of four drugs.

Risk of bias across the nine studies varied. For randomization and allocation concealment, studies were mostly at an unclear risk of bias, with only three studies adequately describing their randomization methods (low risk). For blinding, studies primarily displayed an unclear risk of bias, with only two studies clearly describing blinding methods of participants, personnel and outcome assessors methods (low risk). For attrition, studies primarily displayed an unclear risk of bias, with only two studies clearly accounting for all participants (low risk), and one study not at all (high risk). For reporting, studies primarily displayed a low risk of bias, with two studies poorly reporting planned outcomes (high risk) and one study unclearly reporting planned outcomes (low risk). For size, studies primarily displayed a high risk of bias with fewer than 50 participants per treatment arm, and two studies with 50 to 199 participants per treatment arm (unclear risk). For other risks of bias, studies primarily displayed a low risk of bias, with two studies showing uncertainties in their procedures (unclear risk) and one study displaying a high risk of bias.

Pain outcomes: only one study (under comparison 5: Combination pharmacotherapy versus combination pharmacotherapy) reported participant-reported pain relief of 50% or greater and 30% or greater; so due to a lack of available data we were unable to undertake a meta-analysis (De Franceschi 2016). Three studies reported Patient Global Impression of Change *very much* improved, and *much* or *very much* improved, however, due to lack of data, we were unable to undertake a meta-analysis.

1: Non-steroidal anti-inflammatory drugs (NSAID) compared with placebo

For **PGIC very much improved**, we found no differences between ketorolac and placebo (RR 7.64, 95% CI 0.44 to 131.75; $P = 0.16$; Analysis 1.1; Figure 3), or for **PGIC much or very much improved** (RR 1.65, 95% CI 0.65 to 4.19; $P = 0.29$; Analysis 1.2; Figure 4) (one study, 21 participants, very low-quality evidence).

For **opioid consumption (rescue morphine)**, we found no differences between ketoprofen (overall median consumption 110 mg, IQR 46 to 195) and placebo (88 mg, IQR 52.5 to 262.5) (one study, very low-quality evidence). The same for **rescue meperidine**, no differences were reported between ketorolac (1866.7 mg, SD 1112.4) compared with placebo (2804.5 mg, SD 795.1), and ketorolac (231 mg, SD 92) compared with placebo (250 mg, SD 85) (two non-comparable RCTs, very low-quality evidence).

For **median time to participants' resolution of pain**, we found no differences between ketoprofen (51 hours, IQR 35.5 to 87) and placebo (50 hours, IQR 36 to 103) (33 participants per group, one study, very low-quality evidence).

For **mean length of hospitalization**, we found a difference between ketorolac (3.3 days) and placebo (7.2 days) ($P < 0.05$) (21 participants, one study, very low-quality evidence).

Mild adverse events were reported in the ketoprofen (16/33), placebo (19/45), and ketorolac (0/12) study arms (two studies, very low-quality evidence). Serious adverse events (not specified) were reported in the ketoprofen (1/33), placebo (2/56), and ketorolac (0/22) study arms (three studies, very low-quality evidence).

For **any pain-related outcome indication some improvement**, we found a difference in mean change in pain scores between ketorolac and placebo, from baseline to 24 hours, on a VAS 0 to 100 mm: ketorolac baseline (77.7, 95% CI 69.1, 86.2) to 24 hours (58.6, 95% CI 48.6 to 68.5), and placebo baseline (79.1, 95% CI 72.1 to 86.0) to 24 hours (72.6, 95% CI 62.4 to 82.8) ($P < 0.05$) (one study, very low-quality evidence). However, other scales used to measure pain (VCS 0 to 3, VRS 0 to 4, VAS at 4 hours) reported no differences between ketorolac and placebo, the same for ketoprofen compared with placebo (three studies, very low-quality evidence).

Withdrawals due to adverse events were reported in ketoprofen (1/33), ketorolac (0/22), and placebo (1/56) (three studies, very low-quality evidence).

2: Opioids compared with placebo

For **any pain-related outcome indication some improvement**, we found no difference in mean pain scores between ketamine/hydromorphone and placebo/hydromorphone on a VAS (1 to 10 cm): ketamine/hydromorphone (5.2 cm; 95% CI 4.01 to 6.46; 40.2% decrease from baseline), placebo/hydromorphone (5.6 cm; 95% CI 4.27 to 6.93; 34.1% decrease from baseline) (one study, very low-quality evidence).

3: Opioids compared with active comparator

For **PGIC very much improved**, the outcome was reported as 'excellent' in 19.1% of butorphanol and 33% of morphine events (one study, very low-quality evidence).

For **opioid consumption (rescue morphine 0.1 mg/kg taken at 30 minutes)**, we found no difference between morphine (27/54) and paracetamol participants (24/52) (one study, very low-quality evidence).

Mild **adverse events** (nausea and vomiting) were reported in butorphanol (4/12), morphine (9/66), and paracetamol (3/52). No **serious adverse events** were reported in any treatment group (0/132 participants) (two studies, very low-quality evidence).

For **any pain-related outcome indication some improvement**, we found no difference between the adjusted mean pain scores using: VAS (0 to 100 mm) morphine (46.08 mm) and butorphanol (44.42 mm); or PRS (0 to 100 mm) morphine (55.50 mm) and butorphanol (43.79 mm) (one study, very low-quality evidence).

4: Other active comparator compared with placebo

For **PGIC much or very much improved**, we found no differences between cetiedil 0.2 mg/kg (9/16 participants), cetiedil 0.3 mg/kg (10/18), cetiedil 0.4 mg/kg (11/13), and placebo (4/16) (one study, very low-quality evidence).

For **mean time to participants' resolution of pain**, we found no differences between tinzaparin (61.68 hours, 127 participants) and placebo (104.4 hours, 126 participants) (one study, low quality evidence).

For **mean length of hospitalization**, we found no differences between tinzaparin (7.08 days, 127 participants) and placebo (12.06 days, 126 participants) (one study, low quality evidence).

Any **adverse events** (headache, nausea, vomiting and dry mouth) were reported in cetiedil 0.2 mg/kg (2/17), cetiedil 0.3 mg/kg (9/18), cetiedil 0.4 mg/kg (8/14), and placebo (8/18) (one study, very low-quality evidence). No **serious adverse events** were reported in any groups (one study, very low-quality evidence).

5: Combination pharmacotherapy compared with combination pharmacotherapy

For **participant-reported pain relief of 50% or greater**, we found no differences between ketorolac plus tramadol plus metoclopramide plus fentanyl (KTMF) (12/20) and ketorolac plus tramadol plus metoclopramide (KTM) (0/20) at six hours, and no differences between KTMF (18/20) and KTM (4/20) at 12 hours (one study, very low-quality evidence).

For **participant-reported pain relief of 30% or greater**, we found this was reported in 20/20 participants for KTMF and in 1/20 participants for KTM (at six hours), and in 20/20 participants for KTMF and in 4/20 participants for KTM (at 12 hours) (one study, very low-quality evidence).

Adverse events, serious adverse events, and total all-cause **withdrawals** were reported in KTMF (0/20) and KTM (0/20) (one study, very low-quality evidence).

Overall completeness and applicability of evidence

This review identified only nine studies, with insufficient data for all pharmacological interventions for analysis.

As we were unable to undertake a meta-analysis for each drug comparison (only a summary of effects from individual studies), we were unable to comment about efficacy or harm from the use of pharmacological interventions to treat painful sickle cell VOC in adults. Similarly we could not comment on our remaining secondary outcomes: opioid consumption, time to pain resolution, length of hospitalization and opioid tolerance.

Quality of the evidence

Of the nine included studies, only four adequately described randomization methods, and only three adequately described single- or double-blinding methods. One study displayed a high risk of attrition bias and two studies displayed a high risk of selective reporting bias. Seven studies displayed a high risk of size bias with study samples fewer than 50 participants per treatment arm, and the remaining two were unclear risk of size bias. Only seven

studies provided sufficient information about adverse events, and four studies about withdrawals.

The studies recruited participants with adequate baseline pain in a VOC, but not all reported clinically useful outcome measures.

The studies themselves were of moderate quality; however, the number of studies and sample sizes for some comparisons were limited, given what is known about study size and estimates of effect for outcomes derived from studies with few participants and events (Dechartres 2013; Dechartres 2014; McQuay 1998; Nüesch 2010; Thorlund 2011).

We downgraded the quality of the evidence for our primary outcomes to very low quality for the reason:

- Due to too few data for these outcomes (limited number of participants per treatment arm) as we had no confidence in the results.

In some comparisons, and for some outcomes, there were no data available, so we reported this as:

- There were no data for this outcome, the quality of evidence is unknown, and there is no evidence to support or refute.

We applied the same approach to our secondary outcomes.

Potential biases in the review process

We used a comprehensive and highly sensitive search strategy in the major databases, in addition to two large clinical trial registries. We consider it unlikely that we missed relevant studies.

We followed standard Cochrane methods and there were no contestable decisions relating to the inclusion or exclusion of studies, data analyses, or assessing risk of bias. There were no contestable decisions relating to the synthesis of studies.

Agreements and disagreements with other studies or reviews

This is the first Cochrane Review, and the first systematic review that we are aware of that encompasses the search of all drugs implemented during a VOC.

AUTHORS' CONCLUSIONS

Implications for practice

For people with sickle cell disease

The amount and quality of evidence around the use of any pharmacological treatment for painful sickle cell vaso-occlusive crises (VOC) is very low. This means treatment is based on clinical experience and advice from respected authorities. We could make no judgement about which pharmacological treatment is more effective than any other to reduce the painful crisis. We could make no judgement about adverse events or withdrawals.

Sickle cell pain should be treated by specialists in this area.

For clinicians

The amount and quality of evidence around the use of any pharmacological treatment for painful sickle cell VOC is very low. This means treatment is based on clinical experience and advice

from respected authorities. We could make no judgement about which pharmacological treatment is more effective than any other to reduce the painful crisis. We could make no judgement about adverse events or withdrawals.

Clinicians who do not have expertise in this field should defer to clinicians with specialist knowledge.

For policy makers and funders of the intervention

The amount and quality of evidence around the use of any pharmacological treatment for painful sickle cell VOC is very low. This means treatment is based on clinical experience and advice from respected authorities. We could make no judgement about which pharmacological treatment is more effective than any other to reduce the painful crisis. We could make no judgement about adverse events or withdrawals.

Specialist services treating people with sickle cell disease will need to be supported (by clinical expertise and multi-factorial service models) to provide adequate treatment.

Implications for research

The results of this review are disappointing with fewer than 600 participants included in relevant randomized controlled trials. While it would be easy to suggest more trials are needed, and they probably are, it may be that a different approach is necessary. One possible route is the establishment of suitable registries for this group of people which records interventions and outcomes. To achieve any progress, thought needs to be given to relevant outcomes for this patient group.

With the advent of precision medicine, the use of analgesics in general and opioids in particular should be based on recent

advances in the pharmacodynamics and pharmacokinetics of opioids. Pharmacodynamically, opioids are ligands that bind and activate specific receptors that modulate the transmission of painful stimuli in the central nervous system. Accordingly, the analgesic potential of a specific opioid depends on the number of receptors and the ability of the opioid to bind to these receptors. Since these factors vary among people, so does the analgesic potential. In addition, pharmacokinetically, opioids are metabolized by specific enzymes into metabolites that could be analgesically active or inactive depending on the opioid being used. These enzymes could be duplicated, triplicated, mutated or deleted in different people thus causing significant variation in pain relief among patients. Hopefully, these pharmacological markers could be determined for each person in the future which allows the choice of the best opioid compatible with the person in question.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Arambasik 2013

Methods	<p>Allocation: randomized</p> <p>Controlled: placebo and active comparator</p> <p>Blinding: double-blind</p> <p>Arm: 2-arm, parallel treatment group, pilot study</p> <p>Centre: single centre</p> <p>Study dates and duration: 16-month period trial (June 2011 to October 2012)</p>
Participants	<p>Inclusion criteria: not reported</p> <p>Exclusion criteria: not reported</p> <p>Baseline characteristics</p> <p>N: 37 participants; 37 VOC episodes</p> <p>Age (mean): 29.9 years</p> <p>Gender: F 13, M 24</p> <p>Number randomized: 17 intervention, 20 control</p> <p>Number completed: number of participants at each follow-up time not explicitly stated</p> <p>Setting of recruitment and treatment: not reported</p> <p>Country and sites: Akron General Medical Centre, Akron, OH, USA</p>
Interventions	<p>Duration of treatment: individual time to resolution of crisis</p> <p>Follow-up period: not reported</p> <p>Treatment group (17 participants; 17 VOC episodes):</p> <ul style="list-style-type: none"> • IV hydromorphone 2 mg

Arambasik 2013 (Continued)

- 15 minutes later: IV hydromorphone 2 mg + IV ketamine 6.2 mg/kg

Control group (20 participants; 20 VOC episodes):

- IV hydromorphone 2 mg
- 15 minutes later: IV hydromorphone 2 mg + IV saline placebo 6.2 mg/kg

Cointerventions/additional analgesia: not reported

Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain score (VAS 0–10) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Not reported
Notes	<p>Abstract only, sufficient data on pain scores</p> <p>Sources of funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "this pilot study was randomised, prospective, double-blinded trial."</p> <p>Comment: unclear details of randomization.</p>
Allocation concealment (selection bias)	Unclear risk	<p>Quote: "this pilot study was randomised, prospective, double-blinded trial."</p> <p>Comment: unclear details of concealment.</p>
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	<p>Quote: "this pilot study was... double-blind..."</p> <p>Comment: insufficient information, unclear method of blinding.</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information from abstract.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information from abstract.
Selective reporting (reporting bias)	Unclear risk	Comment: primary outcome was reported in methods and results. However, unclear what other outcomes were from this abstract alone.
Size	High risk	Comment: total 37 participants, fewer than 50 participants per treatment arm.
Other bias	Unclear risk	Comment: unclear due to only abstract available.

Bartolucci 2009

Methods	<p>Allocation: randomized</p> <p>Controlled: placebo and active comparator</p>
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Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (Review)

Bartolucci 2009 (Continued)

Blinding: double-blind

Arm: 2-arm, parallel treatment groups

Centre: single centre

Study duration: 39-month period trial (August 2000 to March 2003)

Participants

Inclusion criteria: homozygous SCD participants' who had a severe VOC requiring hospitalization in the internal medicine department.

Exclusion criteria: VOC lasting > 72 hr or < 24 hr; parenteral hydration > 24 hr; blood transfusion during the previous month; any NSAID intake during the previous 7 days; pregnancy; history of drug abuse; hypertension; leukocyte count > $30 \times 10^9/L$ or < $4 \times 10^9/L$; presence at inclusion of an acute chest syndrome, defined as the association of 2 criteria among chest pain, radiological infiltrate and auscultatory abnormality; severe anaemia requiring a blood transfusion at inclusion; psychiatric disorder or progressive visceral disease; and ketoprofen allergy or NSAID contraindication; peptic ulcer or treated with 1 of the following drugs the week before enrolment: aspirin, valproic acid, macrolides, anti-H2, imidazole, rifampicin, phenobarbital, carbamazepine, phenytoin, heparin, vitamin K antagonist, ticlopidine, lithium, methotrexate, interferon- α , diuretics or antihypertensive agents

Baseline characteristics

N: 54 participants; 66 VOC episodes

Gender: F 20, M 34

Age (mean): ≥ 15 years overall: 27 (SD 7) years intervention; 26 (SD 7) years control

Number randomized: 33 intervention; 33 control (VOC episodes)

Number completed: 26 intervention; 26 control (VOC episodes)

Setting and location: Adult Sickle Cell Referral Centre, Paris University Hospital, France

Interventions

Treatment group (33 VOC episodes):

Days 1 and 2:

- IV infusion ketoprofen 300 mg, 2 days
- IV morphine 0.1 mg/kg every 5 minutes until pain relief achieved, followed by continuous morphine infusion at initial dose of 2 mg/hr with repeated pulses until pain was well controlled

Days 3–5:

- oral ketoprofen 100 mg, every 8 hr

Control group (33 VOC episodes):

Days 1 and 2:

- continuous IV physiological saline (placebo), for 2 days
- IV morphine 0.1 mg/kg every 5 minutes until pain relief achieved, followed by continuous morphine infusion at initial dose of 2 mg/hr with repeated pulses until pain was well controlled

Days 3–5:

- oral placebo, every 8 hr

Duration of treatment: 5 days

Follow-up period: up to 14 days postdischarge

Bartolucci 2009 (Continued)

Cointerventions/additional analgesia: adjunctive standardized treatment: bed rest, < 3 L of 5% glucose infusion, 1 L/day oral alkaline water, 20 mg/day folic acid, morphine dose not reported and IV paracetamol 2 g every 8 hr for 48 hr, then 1 g every 8 hr)

Outcomes	Primary outcomes <ul style="list-style-type: none"> Duration of VOC from inclusion (in hr); when at least ¾ were met: absence of fever for 8 hr, absence of pain progression and no requirement of IV infusion of opioid analgesics for the last 8 hr Secondary outcomes <ul style="list-style-type: none"> Morphine consumption during VOC Pain intensity by VAS; at baseline, every 4 hr Severity of pain assessed by CPS to grade pain at 7 body sites; at baseline and 12 hr Treatment failure, toxicity and adverse effects; reported on a standardized case report form 	
Notes	Sources of funding: Inserm was the trial promoter. Publication costs of the article were defrayed in part by page charge payments. The article was marked as advertising.	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned in a 1:1 ratio to either the intervention or control group." Comment: no details of randomization method.
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information of concealment.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information of details of the blinding process for either IV saline or oral placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no statement of outcome assessment of blinding.
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote: "7 VOCs each group were excluded from the analysis because of treatment failures." Comment: 20% attrition, and similar in each group. But outcome reporting ignored these randomized participants, and analyses did not seem to be ITT.
Selective reporting (reporting bias)	Low risk	Comment: all end points listed in the methods were reported in the results.
Size	High risk	Comment: total participants 54 (66 events), < 50 participants per treatment arm.
Other bias	Unclear risk	Comment: unit of analysis error. Unit of randomization was the painful crisis (66 randomized crises among 54 participants), but unit of analysis ignored the clustered nature of the data; analysed as if all randomized events were independent.

Benjamin 1986

Methods	<p>Allocation: randomized</p> <p>Controlled: placebo</p> <p>Blinding: double-blind</p> <p>Arm: 4 arms, parallel treatment groups</p> <p>Centre: multicentre (5 centres)</p> <p>Study dates and duration: not reported</p>
Participants	<p>Inclusion criteria: known history of SCD (SS, SB/Thal), in a crisis lasting 4–24 hr. 1 crisis per participant</p> <p>Exclusion criteria: pregnant, women of childbearing potential, incarceration, drug abuse history, transfusion 90 days prior to trial, acute cerebrovascular accident, overt infection, renal failure with a serum creatinine concentration > 2 mg percent (0.18 mmol/L), clinical or roentgenographic evidence of pulmonary oedema, glaucoma, urinary retention, high sensitivity to anticholinergic or atropine-like drugs</p> <p>Baseline characteristics</p> <p>N: 67 participants; 67 VOC episodes</p> <p>Age: ≥ 19 years (67% aged 20–29) years</p> <p>Gender: F 27, M 36</p> <p>Setting and location: 5 state and university hospitals, and clinical centres, USA</p> <p>Number randomized: 16 cetiedil 0.2 mg/kg group; 18 cetiedil 0.3 mg/kg group; 13 cetiedil 0.4 mg/kg group; 16 control group</p> <p>Number completed: 16 cetiedil 0.2 mg/kg group; 18 cetiedil 0.3 mg/kg group; 13 cetiedil 0.4 mg/kg group; 16 control group</p> <p>(63 included in efficacy analysis, 4 high haemoglobin A, all 67 included in safety analysis)</p>
Interventions	<p>Treatment group A (16 participants; 16 VOC episodes):</p> <ul style="list-style-type: none"> • IV cetiedil 0.2 mg/kg body weight in normal saline, every 8 hr, total of 12 doses <p>Treatment group B (18 participants; 18 VOC episodes):</p> <ul style="list-style-type: none"> • IV cetiedil 0.3 mg/kg body weight in normal saline, every 8 hr, total of 12 doses <p>Treatment group C (13 participants; 13 VOC episodes):</p> <ul style="list-style-type: none"> • IV cetiedil 0.4 mg/kg body weight in normal saline, every 8 hr, total of 12 doses <p>Control group (16 participants; 16 VOC episodes):</p> <ul style="list-style-type: none"> • 0.9 mg/mL normal IV saline, every 8 hr, total of 12 doses <p>Duration of treatment period: 4 days</p> <p>Follow-up period: not reported</p> <p>Cointerventions/additional analgesia: additional analgesics if required – limited to parenteral meperidine hydrochloride 1.2 mg/kg, or oral paracetamol 300 mg with codeine phosphate 30 mg. Standard fluid replacement therapy</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain intensity scale (numerical 0–3)

Benjamin 1986 (Continued)

Secondary outcomes

- Number of painful sites
- Duration of crisis (when 4 criteria met)
- Need for analgesic medication
- Investigator's overall evaluation of the participant's responses to study medication

Notes

Sources of funding: supported by Johnson and Johnson Baby Products, McNeil Pharmaceutical, Inc and by General Clinical Research Center Grants (RR 00102 and RR 00046) from the National Institutes of Health and by the Veterans Administration Medical Service Research Fund.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomly assigned at a central data centre." "The randomization plan specified a coded ampule and a volume dosage for each patient."
Allocation concealment (selection bias)	Low risk	Quote: "Drug, active or placebo, was presented in identically appearing ampules. The investigators were aware of the volume of medication but were not aware of the ampule's contents."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The study was double-blind." "The investigators were aware of the volume of medication but were not aware of the ampule's contents."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The investigators were aware of the volume of medication but were not aware of the ampule's contents." Comment: not entirely clear whether this was extended to the pain evaluators or research nurses being blind to the treatment groups when assessing pain.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "Sixty-seven patients were entered in the trial. Sixty-three patients were included in the analysis of efficacy. Four patients were found retrospectively to have high hemoglobin." Comment: reasonable retroactive application of exclusion criteria. Likely to be fairly small attrition bias effect, but small numbers per treatment group, so this randomization 'error' was unfortunate.
Selective reporting (reporting bias)	Low risk	Comment: no protocol available, but all planned end points were reported in results.
Size	High risk	Comment: total participants 67, < 50 participants per treatment arm.
Other bias	Low risk	Comment: no other possible sources of bias.

De Franceschi 2016
Methods

Allocation: randomized

Controlled: active comparators - combination pharmacotherapy

Blinding: double-blind

De Franceschi 2016 (Continued)

Arm: 2-arm crossover treatment

Centre: single centre

Study duration: January 2010 to July 2013

Participants	<p>Inclusion criteria: adults (aged 18–45 years) prior diagnosis of SCD, presenting to emergency department with severe VOC (VAS 7+).</p> <p>Exclusion criteria: opioid consumption in prior 2 weeks; history of opioid consumption (VOC or non-SCD related); altered conscious state; pregnancy or lactating; hepatic or renal failures (or both); gastritis; peptic ulcer; allergies to study drugs; cardiopulmonary disease, psychiatric conditions which may compromise study responses.</p> <p>Baseline characteristics</p> <p>N: 20 participants; 40 VOC episodes</p> <p>Gender: F 11, M 9</p> <p>Age (median): 22 years (range 17–28 years)</p> <p>Number randomized: 10 intervention; 10 control (VOC episodes)</p> <p>Number completed: 10 intervention; 10 control (VOC episodes)</p> <p>Setting and location: Department of Medicine, University of Verona, Italy</p>
Interventions	<p>Treatment group VOC₁ (10 participants; 20 VOC episodes):</p> <ul style="list-style-type: none"> continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day, for maximum of 72 hr <p>Treatment group VOC₂ (10 participants; 20 VOC episodes):</p> <ul style="list-style-type: none"> continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day + fentanyl buccal single tablet 100 µg after 3 hr from beginning of multimodal analgesia, for maximum of 72 hr
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Time-weighted-sum pain intensity differences (SPID24) (VAS 0–10) <p>Secondary outcomes</p> <ul style="list-style-type: none"> Pain intensity difference (VAS 0–10) Total pain relief (NRS 0–10) Time-weighted-sum of anxiety (SAID24) (NRS 0–10) Mood level (NRS 0–10) Sedation level (NRS 0–10) Adverse effects Participant satisfaction (NRS 0–4)
Notes	<p>Sources of funding: not reported</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	Low risk Comment: not applicable, crossover trial.

De Franceschi 2016 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "data were collected by blinded physicians and nurses." Comment: insufficient information.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "data were collected by blinded physicians and nurses."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for from randomization through allocation, results and follow-up.
Selective reporting (reporting bias)	Low risk	Comment: study authors reported all of the outcomes planned in their methods.
Size	High risk	Comment: total participants 20, < 50 participants per treatment arm.
Other bias	Low risk	Comment: we found no other potential sources of bias.

Gonzalez 1988

Methods	<p>Allocation: randomized</p> <p>Controlled: active comparator</p> <p>Blinding: double-blind</p> <p>Arm: 2-arm, parallel treatment groups</p> <p>Centre: single centre</p> <p>Study duration: not reported</p>
Participants	<p>Inclusion criteria: adults aged 18–65 years with SCD treated in the emergency department</p> <p>Exclusion criteria: history of drug or alcohol abuse; opioid tolerance; hypersensitivity; allergy to morphine or butorphanol; pregnancy; breastfeeding; acute myocardial infarction within 6 months; daily use of narcotic analgesic during the last week</p> <p>Baseline characteristics</p> <p>N: 18 participants</p> <p>Gender: F 6, M 12</p> <p>Age (mean): 29.3 (SD 7.7) years</p> <p>Number randomized: 9 butorphanol; 9 morphine</p> <p>Number completed: 9 butorphanol; 9 morphine</p> <p>Setting and location: primary emergency department, Medical College of Virginia Hospital, USA</p>
Interventions	<p>Duration of treatment: not explicitly stated</p> <p>Follow-up period: not explicitly stated</p>

Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (Review)

Gonzalez 1988 (Continued)

Treatment group (9 participants; 12 VOC episodes):

- IM butorphanol 2 mg, repeated within 30–60 minutes if needed until initial pain relief obtained. Dose repeated every 2–4 hr to maintain a pain relief rating of ≤ 50 mm until discharge

Control group (9 participants; 12 VOC episodes):

- IM morphine 6 mg, repeated within 30–60 minutes if needed until initial pain relief obtained. Dose repeated every 2–4 hr to maintain a pain relief rating of ≤ 50 mm until discharge

Standard treatments to all groups: dextrose 5% and 0.45% saline IV infusion 150 mL/hr

Cointerventions: IM prochlorperazine 5–10 mg as needed for nausea or vomiting

Cointerventions/additional analgesia: standard IV hydration

Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain (LAS, VAS) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Global assessment of treatment as decided by nurse • Level of alertness • Vital signs
Notes	<p>Sources of funding: supported by a grant from Bristol-Meyers United States Pharmaceutical Group, Evansville, IN, USA.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned on each visit to receive either 2 mg IM butorphanol or 6 mg IM morphine."
Allocation concealment (selection bias)	Unclear risk	Comment: no technical details of allocation concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the patient and the medical and nursing staff were blinded to the identity of the assigned drug."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the patient and the medical and nursing staff were blinded to the identity of the assigned drug" Comment: nursing staff made patient assessments, so likely to be adequate.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: all participants were accounted for from randomization, through treatment, to follow-up. However, see 'Size' and 'Other Bias' domains below.
Selective reporting (reporting bias)	Low risk	Comment: no protocol available, but all planned outcomes were reported in results.
Size	High risk	Comment: total 18 participants (45 events), some randomized twice, < 50 participants per treatment arm.
Other bias	High risk	Comment: unit of analysis issue, 12 events per treatment arm. However, unit of randomization was the painful crisis (45 randomized crises events among 18

Gonzalez 1988 (Continued)

participants), random-effects analysis took this unit of analysis issue appropriately into account.

Perlin 1994

Methods	<p>Allocation: randomized</p> <p>Controlled: placebo</p> <p>Blinding: double-blind</p> <p>Arm: 2-arm, parallel-group design</p> <p>Centre: single centre</p> <p>Study Duration: unclear</p>
Participants	<p>Inclusion criteria: aged ≥ 15 years, people with SCD admitted to emergency department with pain of VOC</p> <p>Exclusion criteria: active peptic ulcer disease; systemic bleeding disorders; impaired renal function (urea > 20 mg/dL /or serum creatinine > 1 mg/dL, or both); other medical condition; history of hypersensitivity to NSAIDs; pregnant women</p> <p>Baseline characteristics</p> <p>N: 21 participants; 21 VOC episodes</p> <p>Gender: F 10, M 11</p> <p>Age (range): 19–41 years</p> <p>Number randomized: 10 intervention; 11 control</p> <p>Number completed: 9 intervention; 9 control</p> <p>Setting and location: Howard University Hospital, Washington, DC, USA</p>
Interventions	<p>Treatment group (10 participants; 10 VOC episodes):</p> <ul style="list-style-type: none"> loading dose ketorolac 30 mg continuous IV infusion ketorolac 120 mg, 5 mg/hr, total dose 150 mg on the first day, then maximum 120 mg/day for up to 5 days <p>Control group (11 participants; 11 VOC episodes):</p> <ul style="list-style-type: none"> loading dose saline continuous IV infusion saline, dose each/hr, for up to 5 days <p>Duration of treatment: duration of crisis, 5-day infusion period</p> <p>Follow-up period: not stated</p> <p>Cointerventions/additional analgesia: supplemental IM meperidine 100 mg as needed, frequency no more than 3 hr</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Quantity of meperidine required over 5-day period <p>Secondary outcomes</p>

Perlin 1994 (Continued)

- Pain intensity Verbal Categorical Scale, VAS (0–100, Pain Relief Verbal Scale (0–4))
- Duration of hospital stay (measured from the day of enrolment to the day of discharge)
- Global Assessment (1–5: 1 = much worse, 5 = much better)
- Adverse events

Notes **Sources of funding:** supported in part by a grant from Syntex Research, a division of Syntex (USA), Inc, who manufacture ketorolac as Toradol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "the study was randomized," "The study drugs were prepared by a designated hospital pharmacist (J.P.) and allocated according to a predetermined, computer generated random code, balanced in blocks of four."
Allocation concealment (selection bias)	Low risk	Comment: preparations by a hospital pharmacist, not study investigators.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study drugs were prepared by a designated hospital pharmacist (J.P.) and allocated according to a predetermined, computer generated random code, balanced in blocks of four." Comment: not explicitly stated, but likely that investigators remained blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: not explicitly stated, but likely that investigators remained blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "3 participants withdrawn prematurely (1-active, 2-control)...ITT analysis to account for withdrawals." Comment: effect not likely to be small, but appropriate ITT analysis to cope with withdrawals.
Selective reporting (reporting bias)	Low risk	Comment: no protocol available, but all planned outcomes were reported in results
Size	High risk	Comment: total participants 21, fewer than 50 participants per treatment arm.
Other bias	Low risk	Comment: no other potential sources of bias. General comment: ITT analysis performed.

Qari 2007

Methods

Allocation: randomized

Controlled: placebo

Blinding: double-blind

Arm: 2-arm, parallel-group design

Centre: multicentre (3 centres)

Qari 2007 (Continued)

Study duration: 48 months

Participants	<p>Inclusion criteria: participants aged ≥ 12 years with acute SCD/SCA crisis and no other complications; pain severe enough to require more than paracetamol; SCA participants with homozygous sickle cell (SS) disease; participants admitted through the emergency department with painful VOC severe enough to require narcotic analgesia</p> <p>Exclusion criteria: presence of medical or surgical contraindication to LMWH; pregnancy; low platelet counts ($< 100,000/dL$) or impaired haemostasis on admission in the form of $INR > 1.4$ or prolonged aPTT > 5 seconds of the hospital normal range; complicated SCA; history of cerebrovascular accident; current aplasia; acute chest syndrome; exchange transfusion; sequestration; anticoagulants therapy for other aetiology; participants with painful crises within the month before this admission; women receiving hormonal contraception</p> <p>Baseline characteristics</p> <p>N: 253 participants; 253 VOC episodes</p> <p>Gender: F 132, M 121</p> <p>Age (mean): 22.8 (SD 4.5) years intervention; 21.6 (SD 3.8) years control</p> <p>Number randomized: 127 intervention; 126 control</p> <p>Number completed: 127 intervention; 126 control</p> <p>Setting and location: King Abdulaziz University Hospital, King Abdulaziz Oncology Centre, Jeddah, Saudi Arabia</p>				
Interventions	<p>Treatment group (127 participants; 127 VOC episodes):</p> <ul style="list-style-type: none"> subcutaneous tinzaparin 175 IU/kg, once daily, for 7 days <p>Control group (126 participants; 126 VOC episodes):</p> <ul style="list-style-type: none"> subcutaneous placebo, once daily, for 7 days <p>Duration of treatment: 7 days</p> <p>Follow-up period: not reported</p> <p>Cointerventions/additional analgesia: (preintervention) supportive analgesia: IV morphine 1 mg/hr + hydration IV fluids</p>				
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Total number of hospitalized days <p>Secondary outcomes</p> <ul style="list-style-type: none"> Rate of decline of the pain intensity over study days Number of days experienced with severest/highest pain score (NPS) Occurrence of complications during hospitalization 				
Notes	<p>Sources of funding: not reported</p>				
Risk of bias					
Bias	<table border="1"> <thead> <tr> <th>Authors' judgement</th> <th>Support for judgement</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top;">Random sequence generation (selection bias)</td> <td style="vertical-align: top;"> <p>Unclear risk</p> <p>Quote: "patients were randomized consecutively into either study group."</p> <p>Comment: no method of randomization provided.</p> </td> </tr> </tbody> </table>	Authors' judgement	Support for judgement	Random sequence generation (selection bias)	<p>Unclear risk</p> <p>Quote: "patients were randomized consecutively into either study group."</p> <p>Comment: no method of randomization provided.</p>
Authors' judgement	Support for judgement				
Random sequence generation (selection bias)	<p>Unclear risk</p> <p>Quote: "patients were randomized consecutively into either study group."</p> <p>Comment: no method of randomization provided.</p>				

Qari 2007 (Continued)

Allocation concealment (selection bias)	Unclear risk	Comment: no technical details of allocation concealment provided.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "Tinzaparin and placebo were provided by the manufacturer. All drug supplies were appropriately packaged, labelled, and kept in a locked, safe area under appropriate storage conditions with access limited to persons authorized by the investigator and those who directly involved in the study." Comment: no technical details.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no technical details.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information, not reported on withdrawals or treatment failures.
Selective reporting (reporting bias)	High risk	Comment: no available protocol, some outcomes listed in the methods were not reported in the results: adverse effects, opioid consumption.
Size	Unclear risk	Comment: total participants 253, 50 to 199 participants per treatment arm.
Other bias	Low risk	Comment: no other possible sources of bias.

Rehmani 2013

Methods	Allocation: randomized Controlled: active comparator Blinding: double-blind Arm: 2-arm, parallel-group design Centre: single centre Study duration: not reported
Participants	Inclusion criteria: participants presenting to emergency department with acute painful crisis of SCD Exclusion criteria: not reported Baseline characteristics N: 106 participants; 106 VOC episodes Gender: not reported in abstract Age: not reported Number randomized: 54 intervention; 52 control Number completed: not reported Setting and location: King Abdulaziz Hospital, Al Ahsa, Saudi Arabia
Interventions	Treatment group (54 participants; 54 VOC episodes): <ul style="list-style-type: none"> single IV morphine 0.1 mg/kg

Rehmani 2013 (Continued)

Control group (52 participants; 52 VOC episodes):

- single IV paracetamol 1 g

Duration of treatment: duration of painful crisis

Follow-up period: not reported

Cointerventions/additional analgesia: rescue analgesics

Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain intensity (VAS 100 mm) • Pain intensity (VRS 1–4) • Change in pain intensity after 30 minutes <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Rescue analgesia (morphine) • Adverse effects
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Notes	Sources of funding: not reported
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "106 patients were randomised to treatment, morphine or paracetamol."</p> <p>Comment: no clear method of randomization.</p>
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient information.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: insufficient information.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: insufficient information.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: insufficient information.
Selective reporting (reporting bias)	High risk	Comment: not all outcomes listed in methods were reported in the results, e.g. VRS; however, unclear due to abstract only.
Size	Unclear risk	Comment: total participants 106, 50–199 participants per treatment arm.
Other bias	Low risk	Comment: no other possible sources of bias.

Wright 1992

Methods	Allocation: randomized
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Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (Review)

Wright 1992 (Continued)

	<p>Controlled: placebo</p> <p>Blinding: double-blind</p> <p>Arm: 2-arm, parallel-group trial (single dose)</p> <p>Centre: multicentre</p> <p>Study duration: 10 months</p>
Participants	<p>Inclusion criteria: men and women presenting to emergency department with chief complaint of crisis pain, must have self-rated moderate or severe pain intensity on a categorical scale</p> <p>Exclusion criteria: allergy to study drugs; active peptic ulcer; bleeding disorders; analgesics or central nervous system-active drugs during the 3-hr period before administration of study medication</p> <p>Baseline characteristics</p> <p>N: 18 participants; 24 events</p> <p>Gender: F 15, M 9</p> <p>Age (mean): 29.8 years intervention; 31.9 years control</p> <p>Number randomized: 12 events intervention; 12 events control</p> <p>Number completed: unclear</p> <p>Setting and location: Vanderbilt University Hospital or Metropolitan Nashville General Hospital, USA</p>
Interventions	<p>Treatment group (12 VOC episodes):</p> <ul style="list-style-type: none"> • IM ketorolac 60 mg <p>Control group (12 VOC episodes):</p> <ul style="list-style-type: none"> • IM saline placebo <p>Duration of treatment: 4 hr</p> <p>Follow-up period: not reported</p> <p>Cointerventions/additional analgesia: both groups received IV meperidine 50 mg and IV promethazine 12.5 mg on presentation and a standardized dose of meperidine every 30 minutes during 4-hr observation.</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain intensity (VAS 100 mm) <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Pain intensity on categorical scale – mild, moderate, severe • 40% reduction in total narcotic requirement over 4 hr • Total relief pain score: 240 minutes – baseline scores
Notes	<p>Sources of funding: study was supported by Biomedical Research Support Grant RR-05424.</p>
Risk of bias	
Bias	<p>Authors' judgement Support for judgement</p>

Wright 1992 (Continued)

Random sequence generation (selection bias)	Low risk	Quote: "the study medication was assigned in accordance with a computer-generated randomization schedule, and the drugs were administered in identical syringes."
Allocation concealment (selection bias)	Low risk	Quote: "patients were enrolled in a prospective double-blind fashion. They were randomly assigned to receive either ketorolac 60 mg IM or saline placebo IM."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the drugs were administered in identical syringes."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "a single nurse observer was responsible for all data collection and drug administration for all enrolled patients." Comment: unclear role and knowledge of the study drugs.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for from randomization, through intervention, to follow-up.
Selective reporting (reporting bias)	Low risk	Comment: all planned outcomes in the methods were reported in the results.
Size	High risk	Comment: total participants 18, 12 events per treatment arm, < 50 participants per treatment arm.
Other bias	Low risk	Comment: no other possible source of bias.

aPTT: partial thromboplastin time bleeding test; CPS: categorical pain score; F: female; hr: hour; IM: intramuscular; INR: international normalized ratio; ITT: intention to treat; IV: intravenous; LAS: lung allocation score; LMWH: low-molecular-weight heparin; M: male; NSAID: non-steroidal anti-inflammatory drugs; N: number of sample size; NPS: numerical pain score; NRS: numerical rating scale; SB/Thal: sickling beta-thalassaemia; SCA: sickle cell anaemia; SCD: sickle cell disease; SD: standard deviation; SPID24: sum of the pain intensity difference in 24 hours; VAS: visual analogue scale; VOC: vaso-occlusive crisis; VRS: verbal rating scale.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Al-Jam'a 1999	Participants: children and adults aged ≥ 2.5 years. Age data not reported separately.
Ataga 2018	Participants: VOC (crisis event) as an outcome, not the condition/population.
Ballas 2010	Outcomes: did not report on pain as an outcome as per eligibility criteria.
Cho 2016	Intervention: patient-controlled analgesia.
Dampier 2010	Participants: aged ≥ 10 years, no separate data reported for ≥ 18 years (no full-text publication available).
Dampier 2013	Study design: not double-blind (single blind with participants knowing the treatment and assessors blinded). Notes: terminated early due to low accrual.

Study	Reason for exclusion
Desai 2013	Outcomes: did not report on pain as an outcome as per eligibility criteria.
Euctr 2008	Intervention: patient-controlled analgesia.
Euctr 2011	Participants: paediatric population aged < 18 years.
Gonzalez 1991	Intervention: patient-controlled analgesia.
Isrctn 2006	Intervention: patient-controlled analgesia.
Isrctn 2009	Participants: paediatric population aged < 18 years.
Morris 2009	Participants: paediatric population aged < 18 years (age range 3–19 years).
Nct 2019a	Participants: paediatric population aged < 18 years.
Nct 2019b	Study design: open-label study design, not blinded as per eligibility criteria.
Niihara 2018	Participants: VOC (crisis event) as an outcome, not the condition/population.
Orringer 2001	Participants: children and adults (age range 8–60 years). Pain data available for < 15 years but not adults.
Pactr 2018	Study design: open-label trial, not blinded as per eligibility criteria.
Puri 2019	Participants: paediatric population aged 1–21 years. No separate data available for 18–21 years in the full-text publication.
Rousseau 2015	Participants: paediatric population (age range 6–21 years).
Sandoval 2013	Study design: open-label case series, no evidence of controls or randomization. Not a randomized controlled trial.
Shah 2019	Participants: VOC (crisis event) as an outcome, not the condition/population.
Smith 2011	Intervention: patient-controlled analgesia.
Tanabe 2018	Study design: open-label trial, not blinded as per inclusion criteria.
Telen 2015	Participants: 54 adults, 20 children. Data not reported separately.
Uzun 2010	Study design: not double-blind as per eligibility criteria.
van Beers 2007	Intervention: patient-controlled analgesia.

VOC: vaso-occlusive crisis.

Characteristics of studies awaiting assessment [ordered by study ID]

De Castro 2013

Methods	Allocation: randomized
	Controlled: placebo
	Blinding: double-blind

Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (Review)

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De Castro 2013 (Continued)

	Arm: 2-arm parallel group Centre: multicentre Study dates and duration: not reported
Participants	Diagnostic criteria/inclusion criteria: people hospitalized for VOC Exclusion criteria: not reported in abstract Number: not reported in abstract Age: 12–60 years Gender: not reported Setting of recruitment and treatment: not reported in abstract Country and sites: not reported in abstract
Interventions	Treatment group (number not reported): multiple IV doses of GMI 1070 Loading dose to achieve steady state drug level was followed by maintenance doses every 12 hr. Study dose was doubled per protocol after interim pharmacokinetic analysis. Control group (number not reported): not reported in abstract
Outcomes	Primary <ul style="list-style-type: none"> VAS pain intensity (10 cm) Secondary <ul style="list-style-type: none"> Time to resolution of VOC Opioid utilization
Notes	Conference abstract only. Insufficient data to analyse. Attempted to contact authors.

Perlin 1988

Methods	Allocation: randomized by unclear method Controlled: placebo Blinding: double-blind
Participants	Number: not reported Age: not reported Gender: not reported Inclusion criteria: not reported Exclusion criteria: not reported
Interventions	Study period: 5 days Both groups: IM meperidine or hydroxyzine (or both), dose not reported, every 3–4 hr as needed. Intervention group (number not reported): oral diflunisal 1000 mg loading dose + oral diflunisal 500 mg every 12 hr

Perlin 1988 *(Continued)*

	Control group (number not reported): oral placebo, loading dose + oral placebo, every 12 hrs
Outcomes	Primary <ul style="list-style-type: none"> • Pain score according to a categorical pain scale
Notes	Conference abstract only. Insufficient data to analyse. Attempted to contact authors

Teuscher 1989

Methods	Allocation: randomized by unclear method Controlled: placebo Blinding: not reported Arm: 2-arm, parallel group Centre: single Study duration: not reported
Participants	Inclusion criteria: not reported Exclusion criteria: not reported Baseline characteristics 36 participants Gender: not reported in abstract Ages: not reported in abstract Number randomized: not reported Number completed: not reported Setting and location: rural hospital, Togo, West Africa
Interventions	Duration of treatment: not reported Follow-up period: not reported Treatment group (number not reported): not reported Control group (number not reported): placebo not reported Cointerventions/additional analgesia: not reported
Outcomes	Primary: not reported Secondary: not reported
Notes	Unclear from abstract whether the study reported on pain as an outcome as per eligibility criteria.

hr: hour; IM: intramuscular; IV: intravenous; VAS: visual analogue scale; VOC; vaso-occlusive crisis.

Characteristics of ongoing studies *[ordered by study ID]*

IRCT2016072511956N6

Trial name or title	To relieve crisis pain in sickle cell anemia patients
Methods	<p>Allocation: randomized</p> <p>Controlled: active comparator</p> <p>Blinding: double-blind</p> <p>Arm: 2 parallel</p> <p>Centre: single</p> <p>Study duration: February 2017 (recruited, ongoing, data not published)</p>
Participants	<p>Inclusion criteria: adults with sickle cell anemia; no prior history of cardiovascular or respiratory disease; no hypertension; not using other analgesic drugs</p> <p>Exclusion criteria: known major side effects of trial medications; addiction, especially to morphine</p> <p>Baseline characteristics</p> <p>N: target sample size 84, recruitment complete</p> <p>Gender: female and male</p> <p>Ages: no age limit (if included, need separate adult data only)</p> <p>Setting and location: Emam Reza Hospital, Mashhad University of Medical Sciences, Iran</p>
Interventions	<p>Treatment group: 30 mg injection ketorolac</p> <p>Control group: 4-10 mg injection morphine at 4 to 5 ml injection water solution</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> Pain relief (VAS) 5 minutes before and 5 minutes after injection <p>Secondary outcomes</p> <ul style="list-style-type: none"> Side effects
Starting date	19 February 2017
Contact information	Somaye Sadat Hosseiny, Emam Reza Hospital, Emam Reza Square, Ebne Sina Avenue Mshhad Iran Email: somaye_2004a@yahoo.com
Notes	If study is included in future updates, need to separate adult data only

NCT03431285

Trial name or title	Ketamine for acute painful crisis in sickle cell disease patients
Methods	<p>Allocation: randomized</p> <p>Controlled: active comparator</p> <p>Blinding: triple</p> <p>Arm: 3 arm, parallel groups</p>

Pharmacological interventions for painful sickle cell vaso-occlusive crises in adults (Review)

NCT03431285 (Continued)

	<p>Centre: single</p> <p>Study duration: 1 January 2018 (recruiting, ongoing)</p>
Participants	<p>Inclusion criteria: known diagnosis of sickle cell disease based on sickle cell tests and haemoglobin electrophoresis; acute onset of painful crises, defined as having an onset within 7 days</p> <p>Exclusion criteria: healthy volunteers; other comorbidities; allergies to study medication; pregnancy or breastfeeding</p> <p>Baseline characteristics</p> <p>N: 264 participants, still recruiting</p> <p>Gender: men and women</p> <p>Ages: 18–60 years</p> <p>Setting and location: Dammam University, Saudi Arabia</p>
Interventions	<p>Treatment group: morphine</p> <p>Control group: ketamine</p> <p>Other group: standard intravenous hydration</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Pain <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Length of stay in emergency department • Cumulative use of opioids • Rate of hospital admission • Adverse effects
Starting date	1 January 2018
Contact information	Mohammed SS Alshahrani, MD, Dammam, Eastern, Saudi Arabia, 31952
Notes	

NCT03978156

Trial name or title	Dronabinol for pain and inflammation in adults living with sickle cell disease
Methods	<p>Allocation: randomized</p> <p>Controlled: placebo</p> <p>Blinding: double-blind</p> <p>Arm: 2 crossover</p> <p>Centre: single</p> <p>Study duration: June 2019 (recruiting). Estimated completion June 2020.</p>

NCT03978156 (Continued)

Participants	<p>Inclusion criteria: adults over 18 clinical diagnosis of SCD; baseline score <60 ACQ-Me 7-day pain domain</p> <p>Exclusion criteria: intolerance to dronabinol, sesame oil, or marijuana; psychiatric disorder; concomitant medical condition; pregnant</p> <p>Baseline characteristics</p> <p>N: 30</p> <p>Gender: female and male</p> <p>Ages: 18 years or older</p> <p>Setting and location: Yale New Haven Hospital, USA</p>
Interventions	<p>Treatment group: 2.5 mg dronabinol oral tablet (titrated to 10 mg twice daily)</p> <p>Control group: placebo oral tablet</p>
Outcomes	<p>Primary outcomes</p> <ul style="list-style-type: none"> • Feasibility • Adherence to study medication and study procedures • Avoidance of other cannabinoid substances <p>Secondary outcomes</p> <ul style="list-style-type: none"> • Patient reported 7-day pain interference (Adult Sickle Cell Quality of Life Measurement Information System ASCQ-Me) • Patient reported emotional impact (Adult Sickle Cell Quality of Life Measurement Information System ASCQ-Me) • Patient reported sleep impact (Adult Sickle Cell Quality of Life Measurement Information System ASCQ-Me) • Patient reported stiffness impact (Adult Sickle Cell Quality of Life Measurement Information System ASCQ-Me) • Patient reported social functioning (Adult Sickle Cell Quality of Life Measurement Information System ASCQ-Me) • Pain severity (Numerical Rating Scale 0-10) • Nociceptive Pain Severity (Patient Reported Outcomes Measurement Information System PROMIS) • Neuropathic Pain Severity (Patient Reported Outcomes Measurement Information System PROMIS) • Gastrointestinal Nausea short form (Patient Reported Outcomes Measurement Information System PROMIS) • Emotional distress anxiety 8a (Patient Reported Outcomes Measurement Information System PROMIS) • Opioid utilization • Markers of inflammation: white blood cell count, C-reactive protein, serum tryptase, serum pro-inflammatory cytokines, serum measure of Substance P
Starting date	6 June 2019
Contact information	Susanna Curtis, Yale New Haven Hospital Smilow Cancer Centre, New Haven, Connecticut, 06510, USA. Yale University School of Medicine Oncology Section. Email: susanna.curtis@yale.edu
Notes	

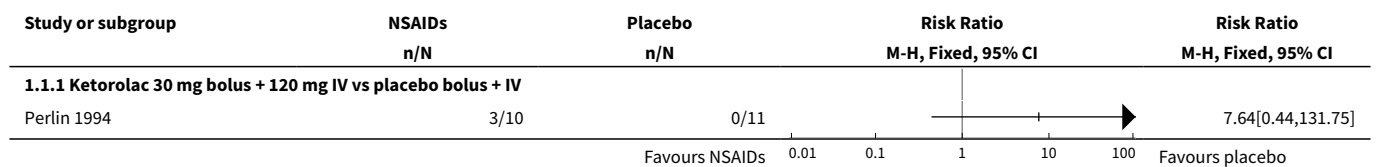
mg: milligrams; ml: millilitres; N: number of participants; SCD: sickle cell disease; VAS: visual analogue scale

DATA AND ANALYSES

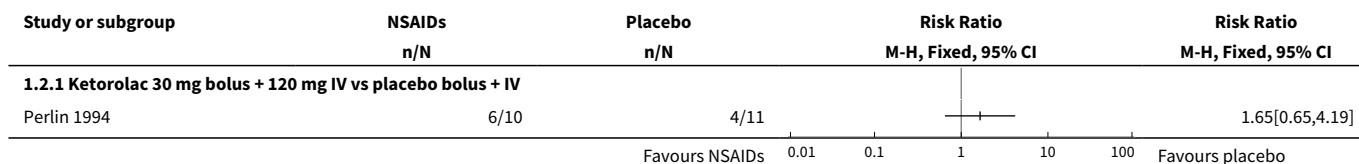
Comparison 1. Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient Global Impression of Change very much improved	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Ketorolac 30 mg bolus + 120 mg IV vs placebo bolus + IV	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Patient Global Impression of Change much or very much improved	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 Ketorolac 30 mg bolus + 120 mg IV vs placebo bolus + IV	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Opioid consumption	3		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Ketoprofen 300 mg IV + 100 mg oral vs saline IV + oral	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Ketorolac 30 mg bolus + 120 mg IV vs placebo bolus + IV	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Ketorolac 60 mg IM vs saline IM	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Time to pain resolution (hours)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Ketoprofen 300 mg IV + 100 mg oral vs saline IV + oral	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

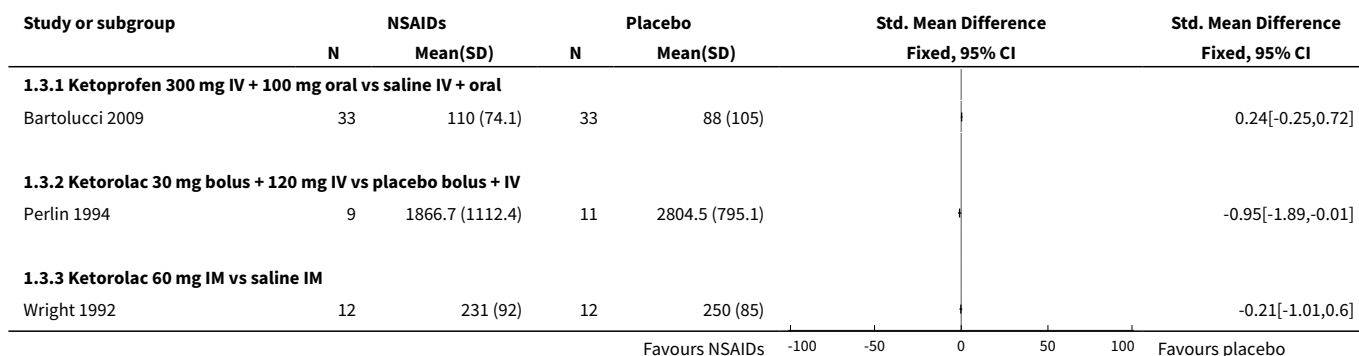
Analysis 1.1. Comparison 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 1 Patient Global Impression of Change very much improved.



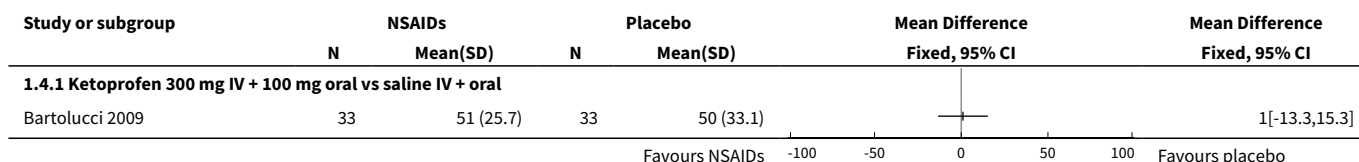
Analysis 1.2. Comparison 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 2 Patient Global Impression of Change *much or very much* improved.



Analysis 1.3. Comparison 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 3 Opioid consumption.



Analysis 1.4. Comparison 1 Non-steroidal anti-inflammatory drugs (NSAIDs) versus placebo, Outcome 4 Time to pain resolution (hours).



APPENDICES

Appendix 1. Database search strategies

CENTRAL search strategy (via CRSO)

#1 MeSH DESCRIPTOR Anemia, Sickle Cell EXPLODE ALL TREES

#2 (sickle cell):TI,AB,KY

#3 "SCD":TI,AB,KY

#4 ("sickling disorder"):TI,AB,KY

#5 "HBS":TI,AB,KY

#6 ((haemoglobin near1 disease)):TI,AB,KY

#7 ((haemoglobin near1 disease)):TI,AB,KY

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 30

#9 MeSH DESCRIPTOR Pain EXPLODE ALL TREES

#10 pain*:TI,AB,KY

#11 #9 OR #10

#12 ((acetaminophen or "acetylsalicylic acid" or "alendronic acid" or alfentanil or amitriptyline or aspirin or baclofen or benzocaine or bupivacaine or buprenorphine or butorphanol or carbamazepine or chlorprocaine or "choline magnesium trisalicylate" or clonazepam or clonidine or codeine or dexamethasone or dexmetomidine or dextroamphetamine or dextropropoxyphene or diamorphine or diazepam or diclofenac or dihydrocodeine or domperidone or fentanyl or fluoxetine or gabapentin or hydrocodone or hydromorphone or "hyoscine hydrobromide" or ibuprofen or ketamine or ketoprofen or ketorolac or "levo bupivacaine" or lidocaine or loperamide or lorazepam or mefenamic acid or meperidine or methadone or methylphenidate or midazolam or morphine or naproxen or nitrous oxide or nortriptyline or oxycodone or pamidronate or paracetamol or paroxetine or pentazocine or pethidine or phenobarbital or "phenytoin" or piroxicam or pregabalin or propoxyphene or "risedronate sodium" or "sodium clodronate" or tetracaine or tramadol or "valproic acid")):TI,AB,KY

#13 MeSH DESCRIPTOR Analgesics EXPLODE ALL TREES

#14 MeSH DESCRIPTOR Anesthesia, Local

#15 MeSH DESCRIPTOR Anti-Inflammatory Agents, Non-Steroidal EXPLODE ALL TREES

#16 #12 OR #13 OR #14 OR #15

#17 #8 AND #11 AND #16

MEDLINE search strategy (via Ovid)

1 exp Anemia, Sickle Cell/

2 sickle cell.tw.

3 "SCD".tw.

4 "sickling disorder".tw.

5 "HBS".tw.

6 (hemoglobin adj1 disease).tw.

7 (haemoglobin adj1 disease).tw.

8 or/1-7

9 exp Pain/

10 pain*.tw.

11 or/9-10

12 (acetaminophen or "acetylsalicylic acid" or "alendronic acid" or alfentanil or amitriptyline or aspirin or baclofen or benzocaine or bupivacaine or buprenorphine or butorphanol or carbamazepine or chlorprocaine or "choline magnesium trisalicylate" or clonazepam or clonidine or codeine or dexamethasone or dexmetomidine or dextroamphetamine or dextropropoxyphene or diamorphine or diazepam or diclofenac or dihydrocodeine or domperidone or fentanyl or fluoxetine or gabapentin or hydrocodone or hydromorphone or "hyoscine hydrobromide" or ibuprofen or ketamine or ketoprofen or ketorolac or "levo bupivacaine" or lidocaine or loperamide or lorazepam or mefenamic acid or meperidine or methadone or methylphenidate or midazolam or morphine or naproxen or nitrous oxide or nortriptyline or oxycodone or pamidronate or paracetamol or paroxetine or pentazocine or pethidine or phenobarbital or "phenytoin" or piroxicam or pregabalin or propoxyphene or "risedronate sodium" or "sodium clodronate" or tetracaine or tramadol or "valproic acid").tw.

13 exp Analgesics/

14 Anesthesia, Local/

15 exp Anti-Inflammatory Agents, Non-Steroidal/

16 or/12-15

17 8 and 11 and 16

18 randomized controlled trial.pt.

19 controlled clinical trial.pt.

20 randomized.ab.

21 placebo.ab.

22 drug therapy.fs.

23 randomly.ab.

24 trial.ab.

25 groups.ab.

26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25

27 exp animals/ not humans.sh.

28 26 not 27

29 17 and 28

Embase search strategy (via Ovid)

1 exp Anemia, Sickle Cell/

2 sickle cell.tw.

3 "SCD".tw.

4 "sickling disorder".tw.

5 "HBS".tw.

6 (hemoglobin adj1 disease).tw.

7 (haemoglobin adj1 disease).tw.

8 or/1-7

9 exp Pain/

10 pain*.tw.

11 or/9-10

12 (acetaminophen or "acetylsalicylic acid" or "alendronic acid" or alfentanil or amitriptyline or aspirin or baclofen or benzocaine or bupivacaine or buprenorphine or butorphanol or carbamazepine or chlorprocaine or "choline magnesium trisalicylate" or clonazepam or clonidine or codeine or dexamethasone or dexmetomidine or dextroamphetamine or dextropropoxyphene or diamorphine or diazepam or diclofenac or dihydrocodeine or domperidone or fentanyl or fluoxetine or gabapentin or hydrocodone or hydromorphone or "hyoschine hydrobromide" or ibuprofen or ketamine or ketoprofen or ketorolac or "levo bupivacaine" or lidocaine or loperamide or lorazepam or mefenamic acid or meperidine or methadone or methylphenidate or midazolam or morphine or naproxen or nitrous oxide or nortriptyline or oxycodone or pamidronate or paracetamol or paroxetine or pentazocine or pethidine or phenobarbital or "phenytoin" or piroxicam or pregabalin or propoxyphene or "risedronate sodium" or "sodium clodronate" or tetracaine or tramadol or "valproic acid").tw.

13 exp Analgesics/

14 Anesthesia, Local/

15 exp Anti-Inflammatory Agents, Non-Steroidal/

16 or/12-15

- 17 8 and 11 and 16
- 18 Randomized controlled trial/
- 19 Controlled clinical study/
- 20 18 or 19
- 21 Random\$.ti,ab.
- 22 randomization/
- 23 intermethod comparison/
- 24 placebo.ti,ab.
- 25 (compare or compared or comparison).ti.
- 26 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
- 27 (open adj label).ti,ab.
- 28 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.
- 29 double blind procedure/
- 30 parallel group\$1.ti,ab.
- 31 (crossover or cross over).ti,ab.
- 32 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant \$1)).ti,ab.
- 33 (assigned or allocated).ti,ab.
- 34 (controlled adj7 (study or design or trial)).ti,ab.
- 35 (volunteer or volunteers).ti,ab.
- 36 human experiment/
- 37 trial.ti.
- 38 or/20-37
- 39 17 and 38

LILACS search strategy (via BIRME)

(sickle cell) or SCD or (sickling disorder) or HBS or (haemoglobin disease) or (haemoglobin disease) [Words] and pain\$ [Words] and (acetaminophen or (acetylsalicylic acid) or (alendronic acid) or alfentanil or amitriptyline or aspirin or baclofen or benzocaine or bupivacaine or buprenorphine or butorphanol or carbamazepine or chloroprocaine or (choline magnesium trisalicylate) or clonazepam or clonidine or codeine or dexamethasone or dexmetetomidine or dextroamphetamine or dextropropoxyphene or diamorphine or diazepam or diclofenac or dihydrocodeine or domperidone or fentanyl or fluoxetine or gabapentin or hydrocodone or hydromorphone or (hyoscine hydrobromide) or ibuprofen or ketamine or ketoprofen or ketorolac or (levo bupivacaine) or lidocaine or loperamide or lorazepam or mefenamic acid or meperidine or methadone or methylphenidate or midazolam or morphine or naproxen or nitrous oxide or nortriptyline or oxycodone or pamidronate or paracetamol or paroxetine or pentazocine or pethidine or phenobarbital or (phenytoin) or piroxicam or pregabalin or propoxyphene or (risedronate sodium) or (sodium clodronate) or tetracaine or tramadol or (valproic acid)) [Words]

Appendix 2. Primary outcome data

Study	Treatment	Partici- pant-re- ported pain re-	Partici- pant-re- ported pain re-	Patient Glob- al Impression of Change: both 'much	Additional pain data report- ed by study
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(Continued)

		lief of 50% or greater	lief of 30% or greater	improved' & 'much or very much improved'	
Aram- basik 2013	Treatment group (17 participants; 17 VOC episodes):	Ketamine: no data	Ketamine: no data	Ketamine: no data	VAS (1–10); mean (% decrease from arrival)
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV ketamine 6.2 mg/kg 	Placebo: no data	Placebo: no data	Placebo: no data	At arrival
	Control group (20 participants; 20 VOC episodes):				Ketamine: 8.7 (95% CI 8.07 to 9.29)
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV saline placebo 				Placebo: 8.5 (95% CI 7.90 to 9.05)
					At administration
					Ketamine: 6.0 (95% CI 4.71, to 7.29); 31%
					Placebo: 7.0 (95% CI 6.20 to 7.85); 17.6%
					At disposition
					Ketamine: 5.2 (95% CI 4.01 to 6.46); 40.2%
					Placebo: 5.6 (95% CI 4.27 to 6.93); 34.1%
Bartolucci 2009	Ketoprofen (33 VOC episodes):	Ketoprofen: no data	Ketoprofen: no data	Ketoprofen: no data	CPS (0–3) daily mean scores; <i>median</i>
	Days 1 and 2: continuous IV ketoprofen infusion, 300 mg/day, 2 days				Ketoprofen: 0.4 (IQR 0.2–0.7)
	Days 3–5: oral ketoprofen 100 mg, every 8 hr, 3 days	Placebo: no data	Placebo: no data	Placebo: no data	Placebo: 0.4 (IQR 0.2–0.7)
	Placebo (33 VOC episodes):				VAS (0–100) daily mean scores; <i>median</i>
Days 1 and 2: physiological saline con- tinuous IV infusion, 2 days.				Ketoprofen: 12.6 (IQR 4.8–23.2)	
Days 3–5: oral placebo tablet, every 8 hr, 3 days				Placebo: 9.6 (IQR 5.8–33.2)	
Benjamin 1986	Cetiedil 0.2 (16 participants; 16 VOC episodes): 0.2 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.2 mg: no data	Cetiedil 0.2 mg: no data	Overall evalu- ation of treat- ment (good)	Cetiedil 0.2 mg: no data
	Cetiedil 0.3 (18 participants; 18 VOC episodes): 0.3 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.3 mg: no data	Cetiedil 0.3 mg: no data		Cetiedil 0.3 mg: no data
	Cetiedil 0.4 (13 participants; 13 VOC episodes): 0.4 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.4 mg: no data	Cetiedil 0.4 mg: no data	Cetiedil 0.2 mg: 5/16	Cetiedil 0.4 mg: no data
	Placebo (16 participants; 16 VOC episodes): saline IV infusion, every 8 hr, 4 days, total 12 doses	Placebo: no data	Placebo: no data	Cetiedil 0.3 mg: 4/18	Placebo: no data
				Cetiedil 0.4 mg: 4/13	
			Placebo: 2/16		

(Continued)

Overall evaluation of treatment (good + excellent)

Cetiedil 0.2 mg: 9/16

Cetiedil 0.3 mg: 10/18

Cetiedil 0.4 mg: 11/13

Placebo: 4/16

De Franceschi 2016	<p>Treatment group VOC₁ (KTM) (10 participants; 20 VOC episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day, for maximum of 72 hr</p>	At 6 hr	At 6 hr	KTM: no data	KTM: no data
		KTM: 0/20	KTM: 1/20	KTMF: 12/20	KTMF: 20/20
	<p>Treatment group VOC₂ (KT MF) (10 participants; 20 VOC episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day + fentanyl buccal single tablet 100 µg after 3 hr from beginning of multimodal analgesia, for maximum of 72 hr</p>	At 12 hr	At 12 hr		
		KTM: 4/20	KTM: 4/20	KTMF: 18/20	KTMF: 20/20
Gonzalez 1988	<p>Butorphanol (9 participants; 12 VOC episodes): IM butorphanol 2 mg, repeated within 30–60 min until pain relief obtained, repeat every 2–4 hr, until discharge.</p>	Butorphanol: no data	Butorphanol: no data	Good	VAS (0–100 mm); <i>adjusted means overall</i>
		Morphine: no data	Morphine: no data	Butorphanol: 47.6%	Butorphanol: 44.42
	<p>Morphine (9 participants; 12 VOC episodes): IM morphine 6 mg, repeat within 30–60 min until pain relief obtained, repeated every 2–4 hr, until discharge</p>			Morphine: 38.1%	Morphine: 46.08
				Excellent	Pain relief (0–100 mm); <i>adjusted means overall</i>
				Butorphanol: 19.1%	Butorphanol: 43.79
				Morphine: 33.3%	Morphine: 55.50
Perlin 1994	<p>Ketorolac (10 participants; 10 VOC episodes): ketorolac 30 mg bolus; continuous IV infusion ketorolac 120 mg, 5 mg/hr, total dose 150 mg (on first day), maximum 120 mg/day, up to 5 days</p>	Ketorolac: no data	Ketorolac: no data	Better	VAS (0–100 mm); <i>mean</i>
		Placebo: no data	Placebo: no data	Ketorolac: 3/10	At baseline
	<p>Placebo (11 participants; 11 VOC episodes): bolus saline; continuous IV infusion saline, up to 5 days</p>			Placebo: 4/11	Ketorolac: 77.7 (95% CI 69.1 to 86.2)
					Placebo: 79.1 (95% CI 72.1 to 86.0)
					At 24 hr
					Ketorolac: 58.6 (95% CI 48.6 to 68.5)

(Continued)

					Placebo: 72.6 (95% CI 62.4 to 82.8)
					P < 0.05
				Much better	VCS (0–3); <i>mean</i>
				Ketorolac: 3/10	At baseline
				Placebo: 0/11	Ketorolac: 2.5
					Placebo: 2.6
					At 24 hr
					Ketorolac: 2.0
					Placebo: 2.4
				Better + much better	VRS (0–4) at 24 hr; <i>mean</i>
				Ketorolac: 6/10	Ketorolac: 1.8
				Placebo: 4/11	Placebo: 1.9
Qari 2007	Tinzaparin (127 participants; 127 VOC episodes): subcutaneous tinzaparin 175 IU/kg, once daily, 7 days	Tinzaparin: no data	Tinzaparin: no data	Tinzaparin: no data	Tinzaparin: no data
	Placebo (126 participants; 126 VOC episodes): subcutaneous placebo, once daily, 7 days	Placebo: no data	Placebo: no data	Placebo: no data	Placebo: no data
Rehmani 2013	Morphine (54 participants; 54 VOC episodes): IV morphine 0.1 mg/kg, single dose	Morphine: no data	Morphine: no data	Morphine: no data	VAS (0–100 mm) at 30 min; <i>mean</i>
	Paracetamol (52 participants; 52 VOC episodes): IV paracetamol 1 g, single dose	Paracetamol: no data	Paracetamol: no data	Paracetamol: no data	Morphine: 44 (95% CI 33 to 56)
					Paracetamol: 41 (95% CI 32 to 49)
					P = 0.72
Wright 1992	Ketorolac (12 VOC episodes): IM ketorolac 60 mg, single dose	Ketorolac: no data	Ketorolac: no data	Ketorolac: no data	VAS (0–100 mm) at baseline; <i>mean</i>
	Placebo (12 VOC episodes): IM saline, single dose	Placebo: no data	Placebo: no data	Placebo: no data	Ketorolac: 70.3
					Placebo: 79.3
					P = 0.26
					VAS (0–100 mm) at 4 hr; <i>mean</i>
					Ketorolac: 44 (SD 34)
					Placebo: 37 (SD 31)
					P = 0.49

(Continued)

CI: confidence interval; **CPS:** categorical pain scale; **hr:** hour; **IM:** intramuscular; **IQR:** interquartile range; **IV:** intravenous; **KTM:** ketorolac + tramadol + metoclopramide; **KTMF:** ketorolac + tramadol + metoclopramide + fentanyl; **min:** minute; **SD:** standard deviation; **VAS:** visual analogue scale; **VCS:** visual categorical score; **VOC:** vaso-occlusive crisis; **VRS:** verbal rating scale.

Appendix 3. Secondary outcome data

Study	Treatment	Opioid consumption	Time to pain resolution (hours)	Length of hospitalization (days)	Tolerance to opioids
Aram-basik 2013	Treatment group (17 participants; 17 VOC episodes):	Ketamine: no data	Ketamine: no data	Ketamine: no data	Ketamine: no data
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV ketamine 6.2 mg/kg 	Placebo: no data	Placebo: no data	Placebo: no data	Placebo: no data
	Control group (20 participants; 20 VOC episodes):				
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV saline placebo 				
Bartolucci 2009	Ketoprofen (33 VOC episodes):	<i>Median, mg</i>	<i>Median, hours</i>	Ketoprofen: no data	Ketoprofen: no data
	Day 1 and 2: continuous IV infusion ketoprofen, 300 mg/day, 2 days	Ketoprofen: 110 (IQR 46–195)	Ketoprofen: 51 (IQR 35.5–87)	Placebo: no data	Placebo: no data
	Days 3–5: 100 mg oral ketoprofen, every 8 hr, 3 days	Placebo: 88 (IQR 52.5–262.5)	Placebo: 50 (IQR 36–103)		
	Placebo (33 VOC episodes):				
	Day 1 and 2: physiological saline continuous IV infusion, 2 days				
	Days 3–5: oral placebo tablet, every 8 hr, 3 days				
Benjamin 1986	Cetiedil 0.2 (16 participants; 16 VOC episodes): 0.2 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.2 mg: no data	Cetiedil 0.2 mg: no data	Cetiedil 0.2 mg: no data	Cetiedil 0.2 mg: no data
	Cetiedil 0.3 (18 participants; 18 VOC episodes): 0.3 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.3 mg: no data	Cetiedil 0.3 mg: no data	Cetiedil 0.3 mg: no data	Cetiedil 0.3 mg: no data
	Cetiedil 0.4 (13 participants; 13 VOC episodes): 0.4 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.4 mg: no data	Cetiedil 0.4 mg: no data	Cetiedil 0.4 mg: no data	Cetiedil 0.4 mg: no data
	Placebo (16 participants; 16 VOC episodes): saline IV infusion, every 8 hr, 4 days, total 12 doses	Placebo: no data	Placebo: no data	Placebo: no data	Placebo: no data
		P > 0.05	Placebo: no data	Placebo: no data	Placebo: no data
		P > 0.05			
De Franceschi 2016	Treatment group VOC₁ (KTM) (10 participants; 20 VOC episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day, for maximum of 72 hr	KTM: no data	KTM: no data	KTM: no data	KTM: no data
		KTMF: no data	KTMF: no data	KTMF: no data	KTMF: no data

(Continued)

Treatment group VOC₂ (KTMF) (10 participants; 20 VOC
episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day + fentanyl buccal single tablet 100 µg after 3 hr from beginning of multimodal analgesia, for maximum of 72 hr

Gonzalez 1988	Butorphanol (9 participants; 12 VOC episodes): IM butorphanol 2 mg, repeated within 30–60 min until pain relief obtained, repeat every 2–4 hr, until discharge Morphine (9 participants; 12 VOC episodes): IM morphine 6 mg, repeat within 30–60 min until pain relief obtained, repeated every 2–4 hr, until discharge	Morphine: no data butorphanol: no data	Butorphanol: no data Morphine: no data	Butorphanol: no data Morphine: no data	Butorphanol: no data Morphine: no data
Perlin 1994	Ketorolac (10 participants; 10 VOC episodes): bolus ketorolac 30 mg; continuous IV infusion ketorolac 120 mg, 5 mg/hr, total dose 150 mg (on first day), maximum 120 mg/day, up to 5 days Placebo (11 participants; 11 VOC episodes): bolus saline; continuous IV infusion saline, up to 5 days	<i>Meperidine mg mean total dose</i> Ketorolac: 1866.7 (SD 1112.4) Placebo: 2804.5 (SD 795.1) <hr/> <i>Mean daily dose</i> Ketorolac: 523.6 (SD 222.1) Placebo: 662.4 (SD 68.6)	Ketorolac: no data Placebo: no data	Ketorolac: 3.3 Placebo: 7.2 <i>P < 0.05</i>	Ketorolac: no data Placebo: no data
Qari 2007	Tinzaparin (127 participants; 127 VOC episodes): subcutaneous tinzaparin 175 IU/kg, once daily, 7 days Placebo (126 participants; 126 VOC episodes): subcutaneous placebo, once daily, 7 days	Morphine Tinzaparin: unclear Placebo: unclear	<i>Mean hours</i> Tinzaparin: 61.68 Placebo: 104.4	<i>Mean days</i> Tinzaparin: 7.08 Placebo: 12.06	Tinzaparin: no data Placebo: no data
Rehmani 2013	Morphine (54 participants; 54 VOC episodes): IV morphine 0.1 mg/kg, single dose Paracetamol (52 participants; 52 VOC episodes): IV paracetamol 1 g, single dose	<i>Rescue morphine (0.1 mg/kg) at 30 min:</i> Morphine: 27/54 Paracetamol: 24/52	Morphine: no data Paracetamol: no data	Morphine: no data Paracetamol: no data	Morphine: no data Paracetamol: no data
Wright 1992	Ketorolac (12 VOC episodes): IM ketorolac 60 mg, single dose Placebo (12 VOC episodes): IM saline, single dose	<i>Mean (SD) meperidine mg</i> Ketorolac: 231(92) Placebo: 250(85)	Ketorolac: no data Placebo: no data	Ketorolac: no data Placebo: no data	Ketorolac: no data Placebo: no data

(Continued)

P = 0.61

CPS: categorical pain scale; **hr:** hour; **IM:** intramuscular; **IQR:** interquartile range; **IV:** intravenous; **KTM:** ketorolac + tramadol + metoclopramide; **KTMF:** ketorolac + tramadol + metoclopramide + fentanyl; **min:** minutes; **SD:** standard deviation; **VAS:** visual analogue scale; **VCS:** visual categorical score; **VOC:** vaso-occlusive crisis; **VRS:** verbal rating scale.

Appendix 4. Adverse events and withdrawals

Study	Treatment	Total number of participants reporting ≥ 1 adverse event	Serious adverse events	Total all-cause withdrawals	Withdrawals due to adverse events
Aram-basik 2013	Treatment group (17 participants; 17 VOC episodes):	Ketamine: no data	Ketamine: no data	Ketamine: no data	Ketamine: no data
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV ketamine 6.2 mg/kg 	Placebo: no data	Placebo: no data	Placebo: no data	Placebo: no data
	Control group (20 participants; 20 VOC episodes):				
	<ul style="list-style-type: none"> IV hydromorphone 2 mg 15 min later: IV hydromorphone 2 mg + IV saline placebo 				
Bartolucci 2009	Ketoprofen (33 VOC episodes):	Ketoprofen: 16/33	Ketoprofen: 1/33	Ketoprofen: unclear	Ketoprofen: 1/33
	Days 1 and 2: continuous IV infusion ketoprofen 300 mg/day, 2 days Days 3–5: 100 mg oral ketoprofen, every 8 hr, 3 days	Placebo: 19/33	Placebo: 2/33	Placebo: unclear	Placebo: 1/33
	Placebo (33 VOC episodes):				
	Days 1 and 2: physiological saline continuous IV infusion, 2 days Days 3–5: oral placebo tablet, every 8 hr, 3 days				
Benjamin 1986	Cetiedil 0.2 (16 participants; 16 VOC episodes): 0.2 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.2 mg: 2/17	Cetiedil 0.2 mg: 0/16	Cetiedil 0.2 mg: unclear	Cetiedil 0.2 mg: unclear
	Cetiedil 0.3 (18 participants; 18 VOC episodes): 0.3 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.3 mg: 9/18	Cetiedil 0.3 mg: 0/18	Cetiedil 0.3 mg: unclear	Cetiedil 0.3 mg: unclear
	Cetiedil 0.4 (13 participants; 13 VOC episodes): 0.4 mg/kg IV infusion, every 8 hr, 4 days, total 12 doses	Cetiedil 0.4 mg: 8/14	Cetiedil 0.4 mg: 0/13	Cetiedil 0.4 mg: unclear	Cetiedil 0.4 mg: unclear
	Placebo (16 participants; 16 VOC episodes): saline IV infusion, every 8 hr, 4 days, total 12 doses	Placebo: 8/18	Placebo: 0/16	Placebo: unclear	Placebo: unclear
	"The incidence of adverse effects was similar for the cetiedil 0.3, 0.4 and placebo groups, and significantly lower for the				

(Continued)

cetiedil 0.2 group (p = 0.04). The most commonly reported AE were headache and nausea and committing, and dry mouth."

De Franceschi 2016	<p>Treatment group VOC₁ (KTM) (10 participants; 20 VOC episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day, for maximum of 72 hr</p> <p>Treatment group VOC₂ (KT MF) (10 participants; 20 VOC episodes): continuous IV infusion ketorolac 0.86 mg/kg/day + tramadol 7.2 mg/kg/day + metoclopramide 0.57 mg/kg/day + fentanyl buccal single tablet 100 µg after 3 hr from beginning of multimodal analgesia, for maximum of 72 hr</p>	KTM: 0/20 KTMF: 0/20	KTM: 0/20 KTMF: 0/20	KTM: 0/20 KTMF: 0/20	KTM: 0/20 KTMF: 0/20
Gonzalez 1988	<p>Butorphanol (9 participants; 12 VOC episodes): IM butorphanol 2 mg, repeated within 30–60 min until pain relief obtained, repeat every 2–4 hr, until discharge.</p> <p>Morphine (9 participants; 12 VOC episodes): IM morphine 6 mg, repeat within 30–60 min until pain relief obtained, repeated every 2–4 hr, until discharge</p>	Butorphanol: 4/12 (nausea and vomiting) Morphine: 4/12 (nausea and vomiting)	Butorphanol: 0/12 Morphine: 0/12	Butorphanol: no data Morphine: no data	Butorphanol: no data Morphine: no data
Perlin 1994	<p>Ketorolac (10 participants; 10 VOC episodes): bolus ketorolac 30 mg; continuous IV infusion ketorolac 120 mg, 5 mg/hr, total dose 150 mg (on first day), maximum 120 mg/day, up to 5 days</p> <p>Placebo (11 participants; 11 VOC episodes): bolus saline; continuous IV infusion saline, up to 5 days</p>	Ketorolac: unclear Placebo: unclear	Ketorolac: 0/10 Placebo: 0/11	Ketorolac: 1/10 Placebo: 0/11	Ketorolac: 0/10 Placebo: 0/11
Qari 2007	<p>Tinzaparin (127 participants; 127 VOC episodes): subcutaneous tinzaparin 175 IU/kg, once daily, 7 days</p> <p>Placebo (126 participants; 126 VOC episodes): subcutaneous placebo, once daily, 7 days</p>	Tinzaparin: no data Placebo: no data	Tinzaparin: no data Placebo: no data	Tinzaparin: no data Placebo: no data	Tinzaparin: no data Placebo: no data
Rehmani 2013	<p>Morphine (54 participants; 54 VOC episodes): IV morphine 0.1 mg/kg, single dose</p> <p>Paracetamol (52 participants; 52 VOC episodes): IV paracetamol 1 g, single dose</p>	Morphine: 5/54 Paracetamol: 3/52	Morphine: 0/54 Paracetamol: 0/52	Morphine: no data Paracetamol: no data	Morphine: no data Paracetamol: no data
Wright 1992	<p>Ketorolac (12 VOC episodes): IM ketorolac 60 mg, single dose</p> <p>Placebo (12 VOC episodes): IM saline, single dose</p>	Ketorolac: 0/12 Placebo: 0/12	Ketorolac: 0/12 Placebo: 0/12	Ketorolac: 0/12 Placebo: 0/12	Ketorolac: 0/12 Placebo: 0/12

CPS: categorical pain scale; **hr:** hour; **IM:** intramuscular; **IQR:** interquartile range; **IV:** intravenous; **KTM:** ketorolac + tramadol + metoclopramide; **KTMF:** ketorolac + tramadol + metoclopramide + fentanyl; **VAS:** visual analogue scale; **VCS:** visual categorical score; **VOC:** vaso-occlusive crisis; **VRS:** verbal rating scale.

WHAT'S NEW

Date	Event	Description
18 February 2020	Amended	Clarification added to Declarations of interest .
22 November 2019	Review declared as stable	See Published notes .

HISTORY

Protocol first published: Issue 5, 2016

Review first published: Issue 11, 2019

Date	Event	Description
18 July 2017	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

TC registered the title.

TC, IH, SB and PW wrote the 2016 protocol.

TC, IH, SB, PW and BJ screened, extracted, analysed and graded the data, and wrote the full review.

TC will be responsible for updates.

DECLARATIONS OF INTEREST

TC: none known.

IH: none known.

SB is an internist specializing in basic and clinical haematology with an emphasis on the management of adult and children with sickle cell disease and pain. SB has been in the Speakers Bureau of Novartis with an emphasis on Deferasirox (both Exjade and Jadenu formulations) in September 2016.

BJ: none known.

PW undertakes work for GSK under the auspices of his company Oxford Systematic Review Services. The work is related to over-the-counter analgesics.

The protocol for this review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. A new author team fully compliant with the 2014 policy completed the review. As with all reviews, new and updated, at update this review will be revised according to 2020 policy update.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of participants: in the protocol, for any studies we identified that included participants aged 17 years and under, we planned to extract the data on participants aged 18 years and above and to contact the study authors for the separate adult data if necessary. We changed this approach to include the study and data on all its participants if less than 20% of the participants were aged 17 years or under. The reason for this change was because we felt that less than 20% would not make a significant impact on the results.

If greater than 20% of the participants were aged 17 years or under, we planned to extract the data on the participants aged 18 years and above, and contact the authors of the studies for separate adult data if necessary.

Outcomes planned: in the protocol, we expressed that death would be sought as a secondary outcome. This was not the intention and we have not investigated it as an outcome. The implication is that the outcome, 'serious adverse events' includes death. This has been amended in the 'Methods' section.

Risk of bias domains: in the protocol, we unintentionally omitted three domains (blinding of participants and personnel, selective reporting bias, other). These are now outlined in the 'Methods' section.

GRADE quality of the evidence: we unintentionally omitted a final reason for downgrading to very low quality in one step (by three levels). This is now outlined in the 'Methods' section.

Measures of treatment effect: we clarified that we planned not to use continuous data for our primary outcomes measuring pain. For our secondary outcomes, we used continuous data for the meta-analysis where appropriate.

NOTES

The research area is not active and we do not expect new RCTs to be published. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be assessed for updating in five years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.