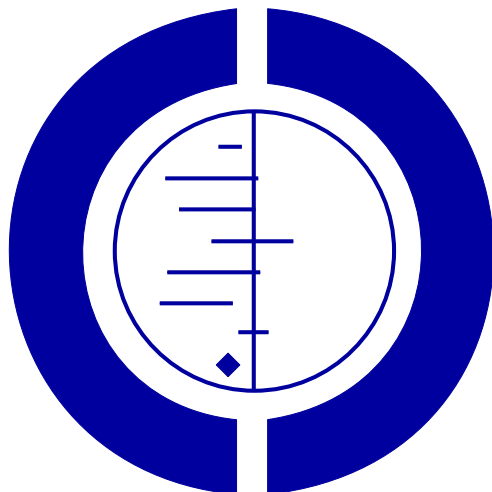


Drug treatments for pain in sickle cell disease (Protocol)

Bennett KCLB, Dunlop R, Lau J, Benjamin LJ, Carr DB



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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the efficacy of pharmacological interventions for pain management in sickle cell disease, we will address the following questions:

- 1) which drugs are most effective to treat acute painful crisis in children and adults?
- 2) are there differences in drug efficacy between children and adults?

If sufficient trials are retrieved to warrant doing so, we will examine the efficacy of drugs for chronic pain of any cause in sickle cell disease.

BACKGROUND

Sickle cell disease is characterized by production of abnormal (sickle) hemoglobin, resulting in chronic hemolytic anemia; susceptibility to pneumococcal and other infections; pain; stroke; and multiple organ dysfunction. Sickle cell disease is an autosomal recessive disorder common among people of African descent and also found in the Caribbean, the Middle East, the Mediterranean and South Europe. The most common types include hemoglobin SS (homozygous) disease, sickle cell-hemoglobin C disease, and the sickle beta-thalassemia syndromes (APS 1999). Repeated vaso-occlusive episodes predispose patients to multiple organ dysfunction (e.g., spleen, liver, brain, kidneys) and shortened survival (Platt 1991). The acute chest syndrome, commonly precipitated by fat embolism or infection, is the leading cause of death (Vichinsky 2000).

Sickle cell pain is primarily nociceptive due to tissue ischaemia and vaso-occlusion of the microcirculation by sickled or less deformable red blood cells (Ballas 1998). The origin of acute bone pain appears to be avascular necrosis of bone marrow. The commonest sites of bone pain are lumbar (48.6%), femur (29.5%) and the knees (20.8%) (Serjeant 1994). Pain syndromes in sickle cell disease may be acute or chronic. Patients who experience three or more acute painful episodes per year that require treatment with parenteral opioids in a medical facility are considered to have severe disease (Charache 1995). Leg ulcers, avascular necrosis of

humeral or femoral heads and bone infarcts cause chronic pain. Major characteristics of chronic sickle pain include emotional, behavioral, affective and psychological responses.

The acute painful crisis that is the hallmark of sickle cell disease is unpredictable. It may follow exposure to cold, or in uncommon cases emotional stress, exercise or alcohol (Ballas 1998, Serjeant 1994). Over 90% of hospital admissions of patients with sickle cell disease are for the treatment of acute pain (Brozovic 1987). The acute painful episode is characterized by four distinct phases. In the first, prodromal phase (pre crisis) patients develop symptoms of numbness, aches and paresthesia in the sites subsequently affected by pain. This phase can last up to two days. Following the prodromal phase, the initial infarctive phase is characterized by the onset of typical crisis pain that increases gradually to a peak by the second or third day. This pain is secondary to infarction due to sickling of red blood cells. In the following, post infarctive phase there is persistent severe pain. Signs and symptoms of inflammation are predominant in this phase (Ballas 1998). In the resolving (post crisis) phase pain gradually remits over one to two days. The number of painful sites can vary but is usually two or three.

OBJECTIVES

To assess the efficacy of pharmacological interventions for pain

management in sickle cell disease, we will address the following questions:

- 1) which drugs are most effective to treat acute painful crisis in children and adults?
- 2) are there differences in drug efficacy between children and adults?

If sufficient trials are retrieved to warrant doing so, we will examine the efficacy of drugs for chronic pain of any cause in sickle cell disease.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised and quasi randomised controlled trials. Inpatient and outpatient study settings will be included.

Types of participants

Children and adults with acute or chronic pain due to sickle cell disease regardless of setting (developed versus developing world), phenotype, age, gender, race and ethnic origin.

Types of intervention

All interventions that include the use of analgesics (opioids and NSAIDs) by the following routes will be eligible for inclusion:

- oral
- intravenous
- intramuscular
- subcutaneous
- spinal (epidural).

Other drugs such as corticosteroids, NSAIDs, and drugs with potential anti-sickling properties (actidil and pentoxifylline) will also be examined provided that they are given primarily for pain relief. Because an existing review in the Cochrane Library (Davies 2001) focuses on the use of hydroxyurea for sickle disease and includes pain intensity as an outcome measure, the present review will not address this treatment.

Types of outcome measures

The following outcomes will be assessed:

- patient rated pain intensity or pain relief
- duration of pain
- number of painful sites.

If reported, we will also assess data on the following:

- the number of emergency department visits
- number of hospitalizations and the length of stay

- total amount of drug(s) consumed
- the reported adverse events

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: Pain, Palliative and Supportive Care Group search strategy

MEDLINE will be searched from 1966 to the present using a search strategy as follows:

(a"/" at the end of a term indicates that it is a Medical Subject Heading (MeSH) term; "exp" indicates that the term is exploded meaning that all MeSH terms nested under the exploded MeSH term are included in the search; "tw" indicates that the term is a text word meaning the entire reference, not just the MeSH terms are searched; "\$" is a wildcard character used to search for multiple forms of word; "pt." indicates a publication type).

- 1.follow-up studies/
- 2.follow-up.tw.
- 3.exp Case-Control Studies/
- 4.case control.tw.
- 5.exp Longitudinal Studies/
- 6.longitudinal.tw.
- 7.exp Cohort Studies/
- 8.cohort.tw.
- 9.(random\$ or rct).tw.
- 10.exp Randomized Controlled Trials/
- 11.exp random allocation/
- 12.exp Double-Blind method/
- 13.exp Single-Blind method/
- 14.randomized controlled trials.pt
- 15.clinical trials.pt.
- 16.(clin\$ adj trial\$.tw.
- 17.((singl\$ or doubl\$ or trebl\$ or tripl\$) adj(blind\$ or mask\$)).tw.
- 18.exp Placebos/
- 19.placebo\$.tw.
- 20.exp Research Design/
- 21.Comparative Study/
- 22.exp Evaluation Studies/
- 23.exp Prospective Studies/
- 24.1 or 2 or 3 or 4or 5or 6 or 7or 8 or 9 or 10 or 11or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
- 25.(treatment or control\$ or intervention).tw.
- 26.longitud\$.tw.
- 27.24 or 25 or 26
- 28.exp pain/
- 29.exp Pain Measurement/
- 30.exp Pain Clinics/
- 31.exp Pain Threshold/
- 32.exp Nociceptors/

- 33.exp pain, intractable/
- 34.exp chest pain
- 35.pain.af.
- 36.28 or 29 or 30 or 31 or 32 or 33 or 34 or 35
- 37.exp analgesia/
- 38.analgesi\$.tw.
- 39.parenteral analgesi\$.tw.
- 40.intravenous analgesi\$.tw.
- 41.intramusc\$.tw.
- 42.patient controlled analgesi\$.tw.
- 43.systematic analgesi\$.tw.
- 44.exp analgesia, epidural/
- 45.(cse or combined spinal-epidural anesthesia).tw.
- 46.continuous epidural analgesia.tw.
- 47.exp Anesthesia, Epidural/
- 48.extradur\$ analgesi\$.tw.
- 49.epidur\$ analgesi\$.tw.
- 50.spinal epid\$.tw.
- 51.peridur\$ analgesi\$.tw.
- 52.spinal epid\$.tw.
- 53.exp anesthetics/
- 54.(anaesthe\$ or anesthe\$.tw.
- 55.37 or 38 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or
- 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
- 56.36 or 55
- 57.exp Anemia, Sickle Cell/
- 58.sickle cell.af.
- 59.(painful crisis or chest crisis).af.
- 60.57 or 58 or 59
- 61.27 or 56 or 60
- 62.56 or 60
- 63.exp alternative medicine/
- 64.60 and 63
- 65.61 or 64

The Cochrane Controlled Trials register will be searched using the text word "sickle cell". EMBASE will also be searched using similar search strategy as in MEDLINE.

Bibliographies of identified reviews and study reports will be examined for references to other trials.

METHODS OF THE REVIEW

Two reviewers will independently screen the titles and abstracts of trials retrieved in the literature search for eligibility for inclusion in this review. Reviewers will not be blinded to authors, institutions, journal of publication or study results. Disagreement concerning inclusion will be resolved by discussion and, if needed, a third reviewer.

DATA EXTRACTION

Data extraction will be performed by two reviewers using a data extraction form designed specifically for this review. Information tabulated on this form includes number of subjects, their condition, study design, duration and follow up, dosing regimen outcome measures including analgesic outcomes, subject withdrawals and adverse effects. Additional information will be entered concerning age and gender of subjects; pain intensity and prior duration upon entry into the study; and location and number of painful sites. Disagreement about extracted data will be resolved by discussion and, if needed, a third reviewer.

Outcomes reported in each retrieved trial will be summarized. Meta-analysis using continuous data methods such as weighted mean difference using the random effects model will be performed for interventions in which more than one report has combinable outcome data by virtue of similar or identical assessment at comparable times in comparable populations. Where there is a sufficient number of trials, we intend to conduct a subgroup analysis to evaluate the efficacy of treatments during acute versus chronic pain episodes. Where possible and appropriate, we will calculate the number-needed-to-treat (NNT) for the interventions under review.

STUDY QUALITY

Each report will be scored for quality by two reviewers using the scale devised by Jadad et al (Jadad 1996). This scale employs the following five questions which can give a maximum score of 5 points. 0 or 1 point can be given for each question:

- 1) Is the study randomised? If 'yes', add 1 point.
- 2) Is the randomisation procedure reported and is it appropriate? If 'yes', add 1 point. If 'no' deduct 1 point
- 3) Is the study double blind? If 'yes', add 1 point.
- 4) Is the blinding procedure appropriate and adequate? If 'yes', add 1 point. If 'no' deduct 1 point
- 5) Are withdrawals and dropouts described? If 'yes', add 1 point.

If there is disagreement between reviewers, the opinion of a third reviewer will be sought to resolve the issue.

The quality scores derived will not be used to weight the studies in any way.

POTENTIAL CONFLICT OF INTEREST

None known.

ACKNOWLEDGEMENTS

Mandy Bryant, Trials Search Co-ordinator for the Cochrane Cystic Fibrosis and Genetic Disorders Group, for her assistance with searching their specialised register for trials relevant to this review.

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REFERENCES

Additional references

APS 1999

American Pain Society. Guideline for the management of acute and chronic pain in sickle cell disease. Acute and chronic pain in sickle cell disease August 1999; (1):1–98.

Ballas 1998

Ballas SK. *Sickle cell pain*. Vol. II, Seattle: International Association for the Study of Pain, 1998.

Brozovic 1987

Brozovic M, Davies SC, Brownell AI. Acute admissions of patients with sickle cell disease who live in Britain. *British Medical Journal* 1987;**249**:1206–8.

Charache 1995

Charache S, Terrin ML, Moore RD, et al. Effects of hydroxyurea on frequency of painful crisis in sickle cell anemia. *N Engl J Med* 1995; **332**:1317–22.

Davies 2001

Davies S, Olujuhungbe A. Hydroxyurea for sickle cell disease (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2001. Oxford: Update Software.

Jadad 1996

Jadad A, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clin Trials* 1996;**17**:1–12.

Platt 1991

Platt OS, Thoringhton BD, Brambilla DJ, et al. Pain in sickle cell disease: rates and risk factors. *N Engl J Med* 1991;**325**:11–6.

Serjeant 1994

Serjeant GR, Ceulaer CDE, Lethbridge R, Morris J, Singhal A. The painful crisis of homozygous sickle cell disease. *British Journal of Haematology* 1994;**87**(3):586–91. 95085957.

Vichinsky 2000

Vichinsky EP, Neumayr LD, Earles A, Williams R, Lennette ET. Causes and outcomes of the acute chest syndrome in sickle cell disease. *N Engl J Med* 2000;**342**:1855–65.

* Indicates the major publication for the study

COVER SHEET

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