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Fluid replacement therapy for acute episodes of pain in people with sickle cell disease (Review)

Okomo U, Meremikwu MM

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[Intervention Review]

Fluid replacement therapy for acute episodes of pain in people with sickle cell disease

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ABSTRACT

Background

Treating vaso-occlusive painful crises in people with sickle cell disease is complex and requires multiple interventions. Extra fluids are routinely given as adjunct treatment, regardless of the individual's state of hydration with the aim of slowing or stopping the sickling process and thereby alleviating pain. This is an update of a previously published Cochrane Review.

Objectives

To determine the optimal route, quantity and type of fluid replacement for people with sickle cell disease with acute painful crises.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register which comprises of references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

We also conducted searches of Embase (November 2007), LILACS, www.ClinicalTrials.gov (05 January 2010), and the WHO ICTRP (30 June 2017).

Date of most recent search of the Group's Haemoglobinopathies Trials Register: 16 February 2017.

Selection criteria

Randomised and quasi-randomised controlled trials that compared the administration of supplemental fluids adjunctive to analgesics by any route in people with any type of sickle cell disease during an acute painful episode, under medical supervision (inpatient, day care or community).

Data collection and analysis

No relevant trials have yet been identified.

Main results

Sixteen trials were identified by the searches, all of which were not eligible for inclusion in the review.

Authors' conclusions

Treating vaso-occlusive crises is complex and requires multiple interventions. Extra fluids, generally oral or intravenous, are routinely administered during acute painful episodes to people with sickle cell disease regardless of the individual's state of hydration. Reports of

their use during these acute painful episodes do not state the efficacy of any single route, type or quantity of fluid compared to another. However, there are no randomised controlled trials that have assessed the safety and efficacy of different routes, types or quantities of fluid. This systematic review identifies the need for a multicentre randomised controlled trial assessing the efficacy and possible adverse effects of different routes, types and quantities of fluid administered to people with sickle cell disease during acute painful episodes.

PLAIN LANGUAGE SUMMARY

Replacing fluids to treat acute episodes of pain in people with sickle cell disease

Review question

To assess the best route, quantity and type of fluid replacement for people with sickle cell disease with acute painful crises.

Background

Sickle cell disease is a common genetic disorder characterised by periodic episodes of pain which usually happen again and again throughout life. These episodes occur when sickled cells obstruct blood vessels. The degree of pain may range from a mild discomfort to a severe disabling pain where the person needs treatment in hospital. A drop in body fluid levels promotes and sustains the sickling process. Routine treatment includes the use of drugs to relieve pain and the maintenance of adequate fluid levels. Fluid levels will fall if insufficient fluids are taken in compared to the amount of fluid lost. The kidneys of people with sickle cell disease do not concentrate urine properly, which results in poor control of bodily fluids. Additional fluids are given to try and slow or stop the sickling process which should reduce the amount and duration of pain. Fluids may be given in many ways, but orally or intravenously are most common. Fluids should be given with care so as to prevent fluid overload which may in turn cause adverse events such as heart failure or fluid building up in the lungs. We looked for randomised controlled trials to show the best way to replace fluids, which type of fluids and how much fluid to replace to treat acute episodes of pain in people with sickle cell disease. This is an update of a previously published Cochrane Review.

Search date

The evidence is current to: 16 February 2017.

Trial characteristics

We did not find any randomized controlled trials (trials where the people taking part are put into different treatment groups completely at random) which we could include in the review.

Key results

We conclude that there is a need for large multi-centre trials to assess fluid replacement therapy for people with sickle cell disease with acute painful crises.

BACKGROUND

Description of the condition

Sickle cell disease (SCD) is comprised of a group of autosomal recessive haemoglobin disorders characterised by the production of abnormal haemoglobin, haemoglobin S (HbS). The common feature in SCD is the presence of the sickle gene either homozygous or heterozygous. Sickle cell anaemia (HbSS) occurs as a result of homozygous inheritance of the sickle gene and is the most common and severe form of the disease (Serjeant 1992). Other clinically significant diseases are compound heterozygous conditions, in which the sickle haemoglobin interacts with other haemoglobins, such as haemoglobin C (HbSC) or β-thalassaemia (HbSb+ and HbSb0) (Lane 2001a).

Acute painful or vaso-occlusive crisis is the most common manifestation of SCD (Steinberg 2006). These painful episodes are periodic, often recurrent, and may occur throughout life; among women of child-bearing age, vaso-occlusive crisis tends to occur more frequently during pregnancy (Adam 1996). The range of duration of painful crises remains unclear; pain often lasts for between four and six days but may persist for weeks (Steinberg 1999). The pain rate (number of episodes per year) has been used as a proxy to identify people with poor clinical outcome as it correlates well with early death in people with sickle cell anaemia between the second and third decade of life (Platt 1991). However, in people less than 20 years of age, no correlation exists between pain and mortality. People who experience three or more acute painful episodes per year requiring treatment with parenteral opioid analgesics in a medical facility for four or more hours are considered to have a poor clinical outcome (Charache 1995).

Description of the intervention

The treatment of acute painful crises is at present predominantly symptomatic, comprising of: pharmacological agents (non-opioid and opioid analgesics with or without adjuvants); non-pharmacologic approaches (heat or ice packs, relaxation, acupuncture, self-hypnosis); as well as other measures such as packed red cell transfusion, oxygen therapy, the treatment of associated infections and fluid replacement therapy (Ballas 2005; Ballas 2007; De Ceulaer 1982; Gaston 1986; Lane 2001a). Fluid replacement therapy is of paramount importance because dehydration from insensible water loss, reduced fluid intake and polyuria causes a reduction in plasma volume with an increase in blood viscosity, which promotes and sustains the sickling process (Adekile 1999). Hyposthenuria, the inability to concentrate urine, is the most common renal abnormality in people with SCD (Allon 1990; Kontessis 1992). This functional impairment in the concentrating mechanism arises due to hypoxia in the renal tubules and as a consequence of subclinical intravascular sickling in the hypertonic renal medulla (Keitel 1956). Hyposthenuria is most marked in HbSS (Statius van Eps 1967). As a result of hyposthenuria, people with SCD produce a higher than usual obligatory urine output and are more susceptible than normal individuals to dehydration (Saborio 1999). During episodes of illness, people with SCD often decrease their intake of fluids and may become dehydrated. While people with SCD in painful crisis may not be clinically dehydrated, their red blood cells are known to be dehydrated (Brugnara 1995).

How the intervention might work

Sickling of red blood cells is dependent on the intracellular concentration of deoxyhaemoglobin S which in turn is a function of the osmolality of the plasma. The aim of hydrating people in painful crisis is to slow or stop the sickling process by increasing the plasma volume, thereby decreasing blood viscosity and indirectly reducing red cellular dehydration as well as the intracellular concentration of Haemoglobin S. It has been suggested that routinely giving extra oral fluids in mild vaso-occlusive crisis shortens the episode and relieves pain (Steinberg 1999). Supplemental fluids may be given either orally or intravenously, nasogastrically, subcutaneously or rectally. By inducing severe dilutional hyponatremia (abnormally low levels of blood sodium) in people with SCD using a vasopressin analogue and 5% dextrose in water (5DW) or half normal saline as fluid therapy as well as dietary salt restriction, it is possible to reduce the mean red cell haemoglobin S concentration (Rosa 1980). This, however, may be associated with severe adverse effects and is not a consistent finding (Charache 1981; Charache 1983). The use of 5DW or half normal saline as fluid therapy instead of normal saline has not been demonstrated to significantly affect the intracellular concentration of Haemoglobin S, or to prevent or abort painful crises (Charache 1983). In children and adolescents between one and one-and-a-half times the estimated daily fluid maintenance requirements are recommended (Lane 2001b). Increased fluids may be needed if the individual is dehydrated or insensible losses are increased as in persistent fever, or both. The recommendations for adults is that fluid replacement is administered at an hourly rate of 250 mL for eight hours, and then reduced to 125 mL hourly if there are no signs or past history of congestive heart failure or renal failure (SCIC 2005). For those receiving opioids for pain, fluids should be given with care; opiates decrease cardiac output and fluid overload could precipitate heart failure. In people with acute chest syndrome, fluids are usually given at daily maintenance levels, as over-hydration could cause regions of pneumonitis to develop (SCIC 2005). The clinical effectiveness of fluid replacement therapy for treating painful sickle crisis during pregnancy is, however, not known (Martí-Carvajal 2009).

Why it is important to do this review

Treating a vaso-occlusive crisis is complex and requires multiple interventions. The routine administration of extra fluids, regardless of the individual's state of hydration, is currently advocated as a potentially beneficial adjunctive treatment in this condition. However, a systematic review of available evidence on the benefits and actual reported harms of fluid supplementation and the routes of supplementation is needed to clarify the uncertainties surrounding this intervention.

This is an update of previously published versions of this review (Okomo 2007; Okomo 2012; Okomo 2015).

OBJECTIVES

To determine the optimal route and quantity of fluid replacement for people with SCD with acute painful crises. A post hoc objective is to determine, where possible, the most appropriate type of fluid replacement for any route of administration.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials. We had planned to include trials in which quasi-randomised methods, such as alternation were used, if there was sufficient evidence that the treatment and control groups were similar at baseline.

Types of participants

People with SCD (SS, SC, Sb+ and Sb0) proven by electrophoresis and sickle solubility test, with family studies or DNA tests as appropriate, of all ages and both sexes in any setting (both developed and developing countries).

Types of interventions

We reviewed all studies that compared the administration of supplemental fluids adjunctive to analgesics by any route in people with any type of sickle cell disease during an acute painful episode, under medical supervision (inpatient, day care or community). We had planned to also consider secondary comparisons between different fluid types and quantity of fluid administered if a suitable number of adequately sized trials had been identified, including between the different types of sickle cell disease.

Types of outcome measures

Primary outcomes

1. Duration of pain crisis

Secondary outcomes

1. Length of hospital stay (for hospitalised patients)
2. Pain severity
   a. score
   b. analgesia use
3. Reported adverse events such as:
   a. fluid overload (pedal oedema, pulmonary oedema)
   b. iatrogenic infections (thrombophlebitis)
   c. other
4. Development of major sickle complication, e.g. acute chest syndrome (ACS), acute splenic sequestration (ASS), cerebrovascular accident (CVA)
5. Death

Search methods for identification of studies

Electronic searches

Relevant trials were searched for in the Group's Haemoglobinopathies Trials Register using the terms: (sickle cell OR (haemoglobinopathies AND general)) AND pain AND hydration. There were no restrictions regarding language or publication status.

The Haemoglobinopathies Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library) and weekly searches of MEDLINE. Unpublished work is identified by searching the abstract books of five major conferences: the European Haematology Association conference; the American Society of Hematology conference; the British Society for Haematology Annual Scientific Meeting; the Caribbean Public Health Agency Annual Scientific Meeting (formerly the Caribbean Health Research Council Meeting); and the National Sickle Cell Disease Program Annual Meeting. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We also conducted searches of Embase, LILACS, the WHO ICTRP and the website www.ClinicalTrials.gov. Please refer to the 'Appendices' section of the review for further details (Appendix 1; Appendix 2; Appendix 3).

Date of the last search of the Group's Haemoglobinopathies Trials Register: 16 February 2017.

Data collection and analysis

Selection of studies

The two authors independently screened the 16 trials found by the searches of all the databases and reference lists to identify papers with potential relevance to the review. Only one potentially relevant article was found, the full text of which was obtained and translated into English. We were not blinded to trial authors, institutions, journal of publication or trial results.

Data extraction and management

When trials are included in the review, data extraction will be undertaken by each author. Data will be extracted with a data extraction form developed by the authors. Disagreements will be resolved by consensus between the authors.

We planned to compare outcomes measured at 1, 4, 8, 12 and 24 hours after commencement of treatment, and daily thereafter (where in-patient facilities exist, until discharge from hospital).

Assessment of risk of bias in included studies

When trials are included in the review, each author will assess every trial using a simple form and will follow the domain-based evaluation as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We aimed to assess the following domains as either a low, unclear, or high risk of bias:

1. randomisation;
2. concealment of allocation;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting.

Measures of treatment effect

As no trials have yet been included in the review, we are unable to carry out any analysis. However, we had intended to analyse binary data using an odds ratio (OR) with 95% confidence intervals (95% CI). We planned to analyse continuous data using weighted mean differences (WMDs) if outcomes were measured in a standard way across trials, or standardised mean differences (SMDs) if outcomes were conceptually the same but measured in different ways, along with 95% CIs.

Dealing with missing data

Missing data will be requested from the original investigators.

Assessment of heterogeneity

We planned to quantify the impact of statistical and clinical heterogeneity in the meta-analysis using a measure of the degree of inconsistency in the trials' results (Higgins 2003). This measure (I^2) describes the percentage of total variation across studies that are due to heterogeneity rather than chance (Higgins 2003). The values of I^2 lie between 0% and 100%, and a simplified categorisation of heterogeneity that we planned to use is of low (I^2 value of 25%), moderate (I^2 value of 50%), and high (I^2 value of 75%) (Higgins 2003).

Assessment of reporting biases

We were to examine publication bias using a funnel plot, assessed visually and quantitatively, and use meta-regression to look for associations between key measures of trial quality and treatment size.

Data synthesis

Where heterogeneity was found to be statistically significant, we intended to use the random-effects model of statistical analysis. Where it was found not to be statistically significant, we would have used a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

If we had found heterogeneity, we planned to investigate the possible causes further. We had intended to examine for methodological and statistical heterogeneity if they were encountered. Furthermore, had there been sufficient numbers of adequately-sized trials, we would have assessed clinical heterogeneity by subgroup analysis, stratified according to sickle status: 'severe genotypes' (SS and Sb0) and 'mild genotypes' (SC and Sb+); severity of disease (number of episodes per year); age (child and adult) and setting (developed versus developing countries).

Sensitivity analysis

We planned to perform a sensitivity analysis based on the methodological quality of the trials, including and excluding quasi-randomised trials.

RESULTS

Description of studies

No trials have been identified which are eligible for inclusion in the review.

The trials listed as 'Excluded studies' were not eligible for inclusion for all or some of the following reasons: the randomisation was unclear; the studies were not RCTs or quasi-RCTs; the trial participants or interventions (or both) were not relevant to the review; the authors could not be contacted for further clarification (Alvim 2005; Beiter Jr 2001, Charache 1981, Charache 1983, de Araujo 1994, Gonzalez 1988; Gonzalez 1991, Guy 1971, Guy 1973, Hardwick Jr 1999, Hatch 1965, Kalinyak 2005, Nalbandian 1971, Orringer 2001, Oski 1965, Rhodes 1974).

Risk of bias in included studies

No trials eligible for inclusion in this review have been identified.

Effects of interventions

No trials eligible for inclusion in this review have been identified.

DISCUSSION

It is surprising that despite the widespread prevalence of sickle cell disease and the well described nature of the acute painful episodes that are its most common manifestation, there are no randomised controlled trials to provide evidence for the routine use of extra fluids of any type and by any route during acute episodes of pain in people with sickle cell disease. The result of one non-randomised study had suggested that oral hydration alone is inadequate to maintain the hydration status and that vigorous intravenous fluid therapy provides the quickest and most effective method of restoring a satisfactory state of hydration during acute episodes of pain (Hatch 1965). The report of another non-randomised controlled trial suggested that treatment of sickle cell crisis with rapid infusion of hypotonic saline can lower serum osmolality, decreases pain and is well tolerated (Guy 1971). Intravenous urea in sugar solutions have also been shown to abort sickle cell crises in the absence of narcotics and analgesics (Nalbandian 1971). However, this also required the co-administration of Ringer's lactate to prevent dehydration consequent upon the profound diuresis caused by the urea solution. The methodological limitations of these studies made it inappropriate to draw valid conclusions from them. The authors embarked upon a randomised controlled study but no information on this was found in any of the database searches. In the absence of randomised controlled trials that assessed the effects of different types of supplemental fluids given through any route in sickle cell painful crisis, this systematic review found no evidence to either support or refute these observations.

AUTHORS' CONCLUSIONS

Implications for practice

No conclusions can be drawn at the present time about the effectiveness of fluid replacement therapy of any type for acute painful crises in people with sickle cell disease nor about the optimal mode of delivery.

Implications for research

The absence of randomised controlled trials of fluid replacement therapy in sickle cell disease as shown by this extensive literature search is not justified. Research is needed in this area, and this should take into account both demographic and clinical variables. Well-designed, adequately-powered trials should incorporate people of different age groups, social background and ethnic classifications. The trial design should also take into account the types of fluids, routes of administration and appropriate volumes. Multicentre collaboration may be needed. Outcomes to be assessed in these trials should be such as would address the needs and concerns of patients, care-givers and health providers. Similar outcome measures should also be used in different patient groups and across trial sites to facilitate comparability of results and future synthesis of data in meta-analysis.

An appropriate review will be possible, if data are reported in the publications describing trials in the future.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Alvim 2005	1. Randomisation unclear 2. Interventions not relevant 3. Outcomes not relevant
Beiter Jr 2001	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Charache 1981	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Charache 1983	1. Study not RCT or quasi-RCT 2. Interventions not relevant
de Araujo 1994	1. Group allocation not clear (contacted authors several times for clarification, but to date have received no reply)
Gonzalez 1988	1. Interventions not relevant
Gonzalez 1991	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Guy 1971	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Guy 1973	1. Study not RCT or quasi-RCT
Hardwick Jr 1999	1. Interventions not relevant
Hatch 1965	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Kalinyak 2005	1. Participants not relevant 2. Interventions not relevant
Nalbandian 1971	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Orringer 2001	1. Interventions not relevant
Oski 1965	1. Study not RCT or quasi-RCT 2. Interventions not relevant
Rhodes 1974	1. Interventions not relevant

RCT: randomised controlled trial

APPENDICES

Appendix 1. EMBASE Search Strategy (November 2007)

Search terms
1. RANDOM$
2. FACTORIAL$
3. CROSSOVER$ OR CROSS ADJ OVER$
4. PLACEBO$
5. DOUBL$ ADJ BLIND$
6. SINGL$ ADJ BLIND$
7. ASSIGN$
8. ALLOCAT$
9. VOLUNTEER$
10. (CROSSOVER ADJ PROCEDURE).DE.
11. (DOUBLE ADJ BLIND ADJ PROCEDURE).DE.
12. (RANDOMIZED ADJ CONTROLLED ADJ TRIAL).DE.
13. (SINGLE ADJ BLIND ADJ PROCEDURE).DE.
14. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13
15. SICKLE ADJ CELL
16. SICKLE-CELL-ANEMIA#.DE. OR SICKLE-CELL#.DE.
17. 15 OR 16
18. HYDRATION
19. HYDRATION#.W..DE.
20. FLUID
21. FLUID ADJ REPLACEMENT
22. FLUID-THERAPY#.DE. 23. 18 OR 19 OR 20 OR 21 OR 22
24. 14 AND 17 AND 23

Appendix 2. LILACS Search Strategy (05 January 2010)

Search terms
1. ((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD) AND NOT (Ct ANIMALS AND NOT (Ct HUMAN AND Ct ANIMALS)) OR (Pt CLINICAL TRIAL OR Ex E05.318.760.535$) OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind $ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh PLACEBOS OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR (Mh RESEARCH DESIGN) AND NOT (Ct ANIMALS AND NOT (Ct HUMAN AND Ct ANIMALS)) OR (Ct COMPARATIVE STUDY OR Ex E05.337$ OR Mh FOLLOW-UP STUDIES OR Mh PROSPECTIVE STUDIES OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct ANIMALS AND NOT (Ct HUMAN AND Ct ANIMALS))) AND NOT Mh ANIMALS
2. AND (sickle) or "SICKLE" or "SICKLECELL"
3. AND ((fluid) or "FLUID THERAPY") or ((hydration) or (liquido) or "HYDRATION")

Appendix 3. Clinicaltrials.gov Search Strategy (05 January 2010)

Search terms
Sickle cell AND hydration

(Continued)
And also
Sickle cell AND fluid

Appendix 4. WHO International Clinial Trials Registry Platform search strategy (30 June 2017)

Search terms
Sickle cell And acute pain AND fluid

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	No new studies are expected in this area, therefore, we do not plan to update this review.

HISTORY

Protocol first published: Issue 3, 2005
Review first published: Issue 2, 2007

Date	Event	Description
3 July 2017	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Haemoglobinopathies Trials Register and the WHO ICTRP did not identify any potentially eligible trials.
3 July 2017	New citation required but conclusions have not changed	Minor changes have been made throughout the review, including the re-formatting of the plain language summary in line with more recent guidelines.
4 March 2015	New search has been performed	A search of the Cochrane Cystic Fibrosis and Genetic Disorders Group's haemoglobinopathies Trials Register did not identify any potentially relevant trials for inclusion in the review.
4 March 2015	New citation required but conclusions have not changed	The study by de Araujo has been moved to excluded studies following unsuccessful attempts to contact the authors for further clarification (de Araujo 1994).
27 April 2012	New citation required but conclusions have not changed	Minor changes to the text have been made throughout the review.
9 February 2012	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials eligible for inclusion in this review.
5 January 2010	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials eligible for inclusion in this review.

Date	Event	Description
		Searches of LILACs and www.ClinicalTrials.gov did not identify any trials eligible for inclusion in the review. The Background section has been updated.
18 April 2008	New search has been performed	A search of the Group's Haemoglobinopathies Trials Register did not identify any trials eligible for inclusion in this review. Comments by the CFGD Group's Medical Statistician have been addressed.
18 April 2008	Amended	Converted to new review format. The original 'Synopsis' has been replaced with a new 'Plain language summary' in line with guidance from The Cochrane Collaboration.
21 February 2007	New citation required and conclusions have changed	Review first published

CONTRIBUTIONS OF AUTHORS

Uduak Okomo (UO) conceived the review and drafted the protocol and review.

Martin Meremikwu (MM) contributed to protocol and review development.

DECLARATIONS OF INTEREST

Both authors: none known.

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INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [etiology] [*therapy]; Anemia, Sickle Cell [complications] [*therapy]; *Fluid Therapy; Pain Management [*methods]

MeSH check words

Humans