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Interventions for treating painful sickle cell crisis during pregnancy (Review)

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[Intervention Review]

Interventions for treating painful sickle cell crisis during pregnancy

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ABSTRACT

Background

Sickle cell disease is a group of genetic haemoglobin disorders. All over the world, about 300,000 children with these disorders are born each year. Acute sickle cell pain episodes are the most common cause of hospitalisation. Pregnancy in women with sickle cell disease is associated with an increased incidence of maternal and fetal morbidity and mortality. The painful crisis is a severe complication of this illness, and it requires several interventions: packed red cell transfusion, fluid replacement therapy, analgesic drugs, oxygen therapy and steroids; but the approach is not standardised.

Objectives

To assess the effectiveness and safety of different regimens of packed red cell transfusion, oxygen therapy, fluid replacement therapy, analgesic drugs, and steroids for the treatment of painful sickle cell crisis during pregnancy.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (December 2007), the Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register (October 2007), *LILACS* database (1982 to December 2007) and the following web sites: ClinicalTrials.gov (http://www.clinicaltrials.gov) (December 5, 2007); Current Controlled Trials (http://controlled-trials.com/) (December 5, 2007), and Sistema de Información Esencial en Terapéutica y Salud (http://www.icf.uab.es/informacion/Papyrus/sietes.asp) (December 1, 2007). We also handsearched the European Haematology Association conference (June 2007), the American Society of Hematology conference (December 2007) and reference lists of all retrieved articles.

Selection criteria

We intended to include randomised clinical trials.

Data collection and analysis

We intended to summarise data by standard Cochrane Collaboration methodologies.

Main results

We could not find any randomised clinical trials on interventions (packed red cell transfusion, oxygen therapy, fluid replacement therapy, analgesic drugs, and steroids) for the treatment of painful sickle cell crisis during pregnancy.

Authors' conclusions

This review found no randomised clinical trials on the safety and efficacy of interventions for treating painful sickle cell crisis during pregnancy. The effects of interventions need to be tested in randomised clinical trials.

PLAIN LANGUAGE SUMMARY

Interventions for treating painful sickle cell crisis during pregnancy

Evidence to establish the beneficial and harmful effects of interventions for treating painful sickle crisis during pregnancy is lacking.

Sickle cell disease covers a group of inherited (genetic) haemoglobin disorders that cause a defect in red blood cells. The disease has been declared by WHO as a major world health problem.

The changes in the red blood cells can lead to damaged and blocked blood vessels. The most frequent complication of sickle cell disease is a painful vaso-occlusive crisis. Treatment may involve the non-surgical intervention with packed red cell transfusion, fluid replacement therapy, analgesic drugs (nonsteroidal anti-inflammatory agents or opiates), oxygen therapy and steroids (prednisone, dexamethasone, or methylprednisolone). Pregnant women with sickle cell disease have an increased incidence of sickle cell crises. Their unborn infants are also at high risk of illness and death. The effectiveness and safety of the different treatments is, therefore, particularly important. For example, sickle cell disease can lead to severe placental damage, yet the opiate morphine constricts the blood vessels in the placenta and so may harmful to the fetus.

The review authors searched the medical literature for randomised controlled trials in which non-surgical approaches were compared for their efficacy and safety. They could not find any randomised clinical trials on non-surgical interventions for the treatment of painful sickle cell crisis during pregnancy. Pregnant women were excluded from clinical trials studying opiate or non-opiate analgesics for treating painful sickle cell crisis.

BACKGROUND

Sickle cell disease (SCD) is a group of genetic haemoglobin disorders - abnormal structure of the haemoglobin - (Bunn 1997; Pauling 1949; Serjeant 2001) which have their origins in sub-Saharan Africa and the Indian sub-continent (Stuart 2004; Weatherall 2006). The term SCD includes sickle cell anaemia (Hb SS); haemoglobin S combined with haemoglobin C (Hb SC); haemoglobin S associated with ß Thalassemia (Sß0 Thal and Sß + Thal) and other double heterozygous conditions which cause clinical disease (Sauntharajah 2004; Serjeant 2001; Weatherall 2006). Haemoglobin S combined with normal haemoglobin (A), known as sickle trait (AS), is asymptomatic and therefore not part of this review. Population mobility has spread haemoglobin disorders through Europe, Asia, and the Americas. It means that millions of people have SCD worldwide. In Africa, the number of newborns affected by SCD is estimated at 200,000 per year (Diallo 2002); all over the world, about 300,000 children with SCD are born each year (Serjeant 1997). SCD is a major health problem (WHO 2006).

Recently, the pathophysiology of SCD has been reviewed (Hebbel 2004; Steinberg 2006; Stuart 2004; Weatherall 2006). Although SCD is primarily a defect of red blood cells (a haematological defect), changes in the red blood cells result in chronic vasculopathy (damage to blood vessels) (Hebbel 2004). It is mediated by a dysfunction of the nitric oxide (NO) biochemistry (Kato 2007; Mack 2006; Wood 2008).

The most frequent complication of SCD is vaso-occlusive or painful crises; this is a process of vascular obstruction in very small and, sometimes, large vessels that is initiated by sickle erythrocytes (Steinberg 2006). The remarkable symptom is severe or moderate bone pain, which indicates a haematological emergency. Acute sickle cell pain episodes are the most common cause of hospitalisation of patients with SCD (Ballas 2005). Up to 58% of patients with SCD have been described with this complication (Babela 2005; Odum 2002).

In 1941, Kobak et al were pioneers in describing the complications associated with pregnancy and SCD (Kobak 1941). Pregnancy in women with SCD is a high-risk situation (Rajab 2006; Sun 2001). It is associated with increased incidence of maternal and fetal morbidity and mortality (Adam 1996; Leborgne-Samuel 2004; Serjeant 2004; Villers 2008); however, in Hb SC females, pregnancy outcome is generally benign compared with SS disease (Serjeant 2005). Recently, the mechanisms of low birthweight in neonates of mothers with SS disease was reviewed (Thame 2007). Vaso-oclusive sickle cell crisis tends to occur more frequently during pregnancy (Adam 1996) and is the most common maternal complication in pregnancy associated with sickle haemoglobinopathies (Martin 1986). Up to 55.8% will have at least one painful episode during pregnancy (Powars 1986). The management of sickle cell crisis during pregnancy should be based on multidisciplinary management involving an obstetrician, a haematologist, an anaesthetist, and a haemoglobinopathy specialist nurse (Oteng-Ntim 2006).

The painful crisis in people with SCD could require several interventions: packed red cell transfusion, fluid replacement therapy, analgesic (Non steroidal anti-Inflammatory drugs -NSAID - and opioid or narcotic) drugs, oxygen therapy and steroids. However, their clinical effectiveness is unknown.

Morphine (opioid analgesic drug) is a vasoconstrictor of the placental vasculature (Kopecky 2000), and SS disease is associated with severe placental damage (Thame 2007); therefore, this combination could be deleterious for the fetus. There is no evidence for supporting morphine use for painful crises in SCD during pregnancy; however, this drug appeared at the top of a list of therapies for this medical condition (Chamberlain 1991). Furthermore, opiates administration, both orally and parenterally by intravenous, intramuscular, or subcutaneous routes, has been recommended (ACOG 2007; Kondylis 1998). However, pregnant women are excluded from clinical trials studying opiate or non-opiate analgesics for treating painful sickle cell crisis (Finkel 2007; Quinn 2007; Shord 2007; van Beers 2007). Ongoing clinical trials performed in women with painful sickle cell crisis exclude pregnant women (Macias 2007; NIHCC 2007).

Because of the above-mentioned arguments, it may be appropriate to ask two questions. First, is it ethical to prescribe a drug to pregnant women when they have been excluded from trials of this drug? Secondly, why do physicians prescribe drugs during pregnancy for this medical emergency when pregnancy is an exclusion criterion for clinical trials addressing developed in sickle cell scope?

Therefore, the primary aim of this review will be to examine the evidence for the effectiveness of the interventions, including the safety of their use, for painful sickle cell crisis during pregnancy.

OBJECTIVES

To assess the effectiveness and safety of different regimens of packed red cell transfusion, oxygen therapy, fluid replacement therapy, analgesic drugs, and steroids for the treatment of painful sickle cell crisis during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised clinical trials that compare interventions with any other treatment for sickle cell crisis in pregnant women, irrespective of their publication status (we considered trials published in abstract form or letters), language or country. We only considered quasi-randomised controlled trials to evaluate the adverse events.

Types of participants

Pregnant women with all types of sickle cell disease irrespective of age, or setting.

We excluded pregnant women with sickle trait.

Types of interventions

Randomised trials in which non-surgical approaches have been compared. Non-surgical treatment includes packed red cell transfusion, oxygen therapy, fluid replacement therapy, analgesia (nonsteroidal anti-inflammatory agents or opiates agents), and steroids (prednisone, dexamethasone, or methylprednisolone). The comparisons include each other, or with placebo, or standard care.

Types of outcome measures

Primary outcomes

We chose outcome measures pertinent to the woman's experience of acute sickle pain (Dunlop 2006):

1. patient observer-rated pain intensity, pain relief, or both;
2. duration of pain (hours);
3. low birth weight;
4. preterm delivery;
5. perinatal death;
6. maternal death.

Secondary outcomes

1. Number of days of analgesic use;
2. number of days off work;
3. normal daily activities;
4. numbers and type of analgesics used (e.g. opiates);
5. days in hospital and other measures of health resources used (e.g. intensive care);
6. obstetric management (e.g. induction of labour);
7. Apgar score.

Adverse events

We used the following definition of adverse events: "any untoward medical occurrence not necessarily having a causal relationship with the treatment, but having resulted in the discontinuation of treatment" (ICH-GCP 1997).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (December 2007).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. monthly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness search of a further 36 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the following, using the terms using the terms sickle cell AND pregnancy:

1. The Cochrane Cystic Fibrosis and Genetic Disorders Group's Trials Register (October 2007);
2. *LILACS* database (1982 to December 5 2007);
3. ClinicalTrials.gov (http://www.clinicaltrials.gov) (December 5, 2007);
4. Current Controlled Trials (http://controlled-trials.com/) (December 5, 2007);
5. Sistema de Información Esencial en Terapéutica y Salud (http://www.icf.uab.es/informacion/Papyrus/sietes.asp) (December 1, 2007).

Searching other resources

We searched the abstract books of two major conferences:

1. The European Haematology Association (June 2007);
2. The American Society of Hematology (December 2007).

We checked the reference lists of all the trials identified by the above methods.

We did not apply any language restrictions.

Data collection and analysis

We planned to screen the results of our search strategy for potentially relevant trials, and independently assess them for inclusion or exclusion using a pre-designed eligibility form based on the inclusion criteria. We planned to resolve disagreements through discussion until a consensus was reached. We did not find any potentially relevant randomised trials. If we identify trials that meet our inclusion criteria in the future, we will adhere to the prespecified protocol described in Appendix 1.

RESULTS

Description of studies

We identified seven potentially relevant references through the initial bibliographical searches. After manually checking the titles and abstracts, we regarded none of the papers as eligible for further evaluation, as they did not report on interventions for treating painful sickle cell crisis during pregnancy.

Risk of bias in included studies

No studies were included.

Effects of interventions

The searches did not identify any randomised trials eligible for inclusion in this systematic review. We could not identify any ongoing trials either. There were no quasi-randomised studies which we could use to assess harmful effects of interventions for treating painful sickle crisis during pregnancy.

DISCUSSION

We have been unable to identify any clinical trials addressing the efficacy and safety of treatment approaches for treating painful sickle crisis during pregnancy; an emergency in this population. This is surprising in light of the high number of pregnant

women worldwide who suffer from the most common and severe complication of SCD (sickle cell disease), a public health problem all over the world (WHO 2006).

AUTHORS' CONCLUSIONS

Implications for practice

We found no randomised clinical trials of non-surgical treatments including packed red cell transfusion, oxygen therapy, fluid replacement therapy, analgesia (non-steroidal anti-inflammatory agents or opiates agents), and steroids (prednisone, dexamethasone, or methylprednisolone) for treating painful sickle cell crisis during pregnancy for inclusion in this review. Therefore, it is not possible to determine whether any of those interventions is beneficially effective or harmful for treating pregnant women with painful sickle cell crisis.

Implications for research

This systematic review has identified the need for well-designed, adequately powered randomised clinical trials to assess the benefits and harms of non-surgical treatment as a way of treating the painful crisis in pregnant women with sickle cell disease. The trials regarding this issue should be reported according to the CONSORT statement (www.consort-statement.org) for improving the quality of reporting of efficacy and get better reports of harms in clinical research.

ACKNOWLEDGEMENTS

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As part of the pre-publication editorial process, this review has been commented on by four peers (an editor and three referees who are external to the editorial team) and the Group's Statistical Adviser.

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APPENDICES

Appendix 1. Methods to be used

Assessment of methodological quality

The author will use a standard data extraction form (Zavala 2006). We will independently extract the data and will systematically contact the authors of trials in order to obtain missing data where possible.

We will examine the adequacy of the methods used to generate the allocation sequence; the concealment of allocation; and the level of blinding (clinician, participant, or outcome assessor). For each trial the authors will classify the risk of bias as high, moderate, or low. Overall, we will consider trials to be at low risk of bias if allocation concealment and blinding of participants are adequate.

We will also evaluate the risk of attrition bias, as estimated by the percentage of participants lost to follow up. We will exclude studies with total attrition more than 30%, or where the difference between groups exceeds 10%, or both, from the meta-analysis, but include them in the review.

We intend to use the following definitions.

Generation of the allocation sequence

Adequate, if the allocation sequence was generated by a computer or random-number table. We will consider drawing of lots, tossing of a coin, shuffling of cards, or throwing of dice adequate if a person who was not otherwise involved in the recruitment of participants performed the procedure. Unclear, if the trial was described as randomised, but the method used for the allocation sequence generation was not described. Inadequate, if dates, names, or admittance numbers were used for the allocation of participants. These studies are known as quasi-randomised and we will exclude them from the efficacy analysis.

Allocation concealment

- Adequate, if the allocation of participants involved a central independent unit, on-site locked computer, numbered drug bottles, or containers of identical appearance prepared by an independent pharmacist or investigator, or if sealed, opaque envelopes were used.
- Unclear, if the trial was described as randomised, but the method used to conceal the allocation was not described.
- Inadequate, if the allocation sequence was known to the investigators who assigned participants or if the study was quasi-randomised.

Blinding (or masking)

Adequate, if the participants of the trial were blinded to the intervention. Unclear, if there is no information on blinding.Not performed, if the participants were not blinded to the intervention.

Follow up

- Adequate, if the numbers and reasons for dropouts and withdrawals in each group were described or if it was specified that there were no dropouts or withdrawals.
- Unclear, if the trial gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.
- Inadequate, if the number or reasons for dropouts and withdrawals were not described.

We plan to extract the relative risk for each outcome. For continuous outcomes, we plan to record either mean change from baseline for each group or mean post-treatment or intervention values and their standard deviation or standard error for each group. We also plan to calculate a pooled estimate of treatment effect by calculating the mean difference. If statistical information is missing (such as standard deviations), we will try to extract them from other relevant information in the paper, such as P-values and confidence intervals. We will also contact the first author of the paper for missing data. We will seek data on the number of participants by allocated treatment group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up. If we are not able to do so, for each study we will record whether the results pertain to an intention-to-treat or to an available case analysis.

We will examine data for skewness using the means and standard deviations as described in the Cochrane Handbook of Systematic Reviews for Interventions (Higgins 2005). If data are skewed, we will present log-transformed data.

We will quantify the impact of statistical heterogeneity using I^2, which describes the percentage of total variation across studies that is due to heterogeneity rather than sampling error (Higgins 2003). If the identified studies are comparable enough, we will summarise their findings using a fixed-effects model. In the case of significant heterogeneity, we will devote further research to identifying possible causes of heterogeneity by exploring the impact of the participants' and study's characteristics.

We anticipate clinical heterogeneity in the effect of the intervention for the following participant characteristics: age, severity of painful crisis, type of disease, type of interventions and gestational age. We will explore these sources of heterogeneity in the assessment of each

outcome by subgroup analyses comparing, for example, mild and severe disease; disease type (i.e. SS type versus SC type); country and within country; teenage pregnant women with non-teenage pregnant women; type of intervention and regimens.

We plan to conduct a sensitivity analysis by comparing the results of all studies to those of high methodological quality. We will also attempt to assess whether the review is subject to publication bias by using a funnel plot.

FEEDBACK

Quirolo, 6 May 2009

Summary

These studies are not mentioned in this review, leading me to believe that it is incomplete:

- Koshy M, Burd L, Wallace D, Moawad A, Baron J. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. N Engl J Med. 1988;319:1447-1452.

- Howard RJ, Tuck SM, Pearson TC. Pregnancy in sickle cell disease in the UK: results of a multicentre survey of the effect of prophylactic blood transfusion on maternal and fetal outcome. Br J Obstet Gynaecol. 1995;102:947-951.

(Feedback received from Keith Quirolo)

Reply

The Koshy 1988 trial is a trial of **prophylactic** blood transfusions for pregnant women with sickle cell disease. The focus of our review is **treating** painful sickle cell crisis; therefore, this trial does not meet our inclusion criteria. The Howard 1995 report is also about prophylactic blood transfusions but is not a trial. It is a survey and therefore is not eligible for inclusion in this review either.

Contributors

Arturo Martí-Carvajal.

WHAT'S NEW

Date	Event	Description
16 May 2012	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 1, 2009

Date	Event	Description
11 August 2009	Amended	Declarations of interest updated.
11 August 2009	Feedback has been incorporated	Feedback from Keith Quirolo added and reply from authors added.
9 January 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr Arturo Marti-Carvajal wrote the first draft of the review with input from Dr Guiomar Peña-Martí, Dr Gabriella Comunián, and Dr Arturo Martí-Peña.

DECLARATIONS OF INTEREST

In 2004 Arturo Martí-Carvajal was employed by Eli Lilly to run a four-hour workshop on 'How to critically appraise clinical trials on osteoporosis and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

In 2007 Arturo Martí-Carvajal was employed by Merck to run a four-hour workshop on 'How to critically appraise clinical trials and how to teach this'. This activity was not related to his work with The Cochrane Collaboration or any Cochrane review.

Guiomar E Peña-Martí, Gabriella Comunián-Carrasco, Arturo J Martí-Peña: None known.

SOURCES OF SUPPORT

Internal sources

- Universidad de Carabobo, Venezuela.

External sources

- Iberoamerican Cochrane Centre, Spain.

INDEX TERMS

Medical Subject Headings (MeSH)

*Pain Management; Anemia, Sickle Cell [*therapy]; Pregnancy Complications, Hematologic [*therapy]

MeSH check words

Female; Humans; Pregnancy