Interventions for the prevention and treatment of epidural-related maternal fever: protocol for a systematic review

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Contributions of Protocol Authors
Matthew Wilson conceived the review. Anna Cartledge, Daniel Hind and MW designed the review.

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BACKGROUND

The phenomenon of epidural related maternal fever is observed in roughly 15-25% of labouring women who receive epidural analgesia. Specifically, it is observed only in women in labour, not nonpregnant women receiving epidural analgesia, or even pregnant women undergoing elective caesarean delivery[1,2]. A slow rise in maternal temperature has been observed when labouring women elect to receive epidural analgesia, versus other non epidural methods of analgesia[3,4]. Various mechanisms to explain this observation have been proposed, including thermoregulatory factors, inhibition of fever by systemic opioid use in women not receiving epidural analgesia, and inflammatory processes[1].There is trial evidence to support the role of sterile inflammation in the development of epidural related fever, with notable serum IL-6 elevation[2]. The exact mechanism remains unclear but is likely to be a local-anaesthetic induced phenomenon[1,2].

The consequences of epidural-related fever for the mother are mainly transient. Physiological changes such as increased heart rate and oxygen consumption are rarely harmful in otherwise healthy women[1]. More significantly, identification of maternal fever often leads to changes to obstetric management, particularly increased rates of caesarean delivery[5,6].Lieberman et al. identified a 2-fold increase in rates of operative vaginal or caesarean deliveries amongst women with an intrapartum fever, compared to afebrile woman, after adjusting for birthweight, length of labour and choice of analgesia[5].

Despite these effects on the mother, the burden of intrapartum fever is predominantly felt by the neonate. Intrapartum maternal fever is associated with direct consequences in the postpartum period for the neonate including, lower 1 and 5 minute apgar scores, endotracheal or mask ventilation, and a need for supplementary oxygen[1]. Wassen et al. found that epidural related maternal fever is independently associated with neonatal sepsis[7], and Impey at al. found maternal fever is independently associated with neonatal encephalopathy, when adjusting for other intrapartum risk factors[8]. What is most concerning however, is the association between intrapartum maternal fever and subsequent development of cerebral palsy[1]. Intrapartum fever due to infective causes is significantly associated with an increased risk of unexplained cerebral palsy, as well as reduced 5 minute apgar scores[9]. The mechanism of how maternal fever can lead to neonatal brain injury is not fully understood but appears to be due to inflammatory processes, rather than infective[1,8]. This evidence suggests that the widespread use of epidural analgesia and related maternal fever can mechanistically be linked to the development of cerebral palsy in the neonate.

Recent systematic reviews in the area have established the association between epidural analgesia and development of intrapartum fever[10,11] and also established that intrapartum

fever of any cause is associated with neonatal brain injury, independent of gestational age at delivery[11]. However, this same systematic review by Morton et al. failed to quantify an association between epidural related maternal fever and neonatal brain injury due to a lack of evidence evaluating this link[11]. There is also currently a lack of consistent and good quality evidence regarding therapeutic interventions that have the potential to either prevent or treat the development of epidural related maternal fever[1]. Various randomised control trials have assessed the effectiveness of potential interventions such as reduced dose epidural[12,13], prophylactic paracetamol[14] or steroids[15], and antibiotics[16] and a previous systematic review has evaluated whether intravenous remifentanil as an alternative for epidural analgesia is effective at reducing the risk of intrapartum maternal fever, but the evidence was inconclusive[17]. However there has been no review comparing all available interventions in order to determine which, if any, are most effective at reducing the incidence of epidural related maternal fever. Therefore, we will perform a systematic review of the literature to evaluate the available evidence for interventions for the prevention or treatment of epidural related intrapartum fever.

OBJECTIVES

The aim of this systematic review is to evaluate the randomised control trial evidence for the effectiveness of preventive and therapeutic interventions for epidural-related maternal fever.
Preventative strategies include the use of alternative analgesia, thereby avoiding the need for epidural analgesia, or various regimens of reduced dose epidurals. Prophylactic paracetamol or steroids will also be evaluated if administered with an epidural. Therapeutic strategies are those administered on identification of a clinical fever in a labouring woman, after use of epidural analgesia. These include paracetamol, steroids and antibiotics.

Preventive strategies

- Population: women in spontaneous or induced active labour
- Intervention: not placing epidurals (alternative anaesthetic techniques); reduced dose epidural
- Comparator: standard epidural analgesia
- Outcome: maternal fever in labour

Therapeutic strategies

- Population: women in spontaneous or induced active labour who use epidural analgesia
- Intervention: therapeutic interventions to treat fever (e.g. regular maternal paracetamol, maternal steroids (systemic/epidural), antibiotics)
- Comparator: usual care; the absence of experimental interventions; placebo
- Outcome: maternal fever in labour

METHODS

Eligibility Criteria

Study design
We will include all types of randomised controlled trials. We will exclude observational studies, cross-sectional studies, case series and case reports.

Preventive strategies
Population:
We will include studies examining women in spontaneous or induced active labour. Studies will be excluded if their focus is primarily febrile women.

Interventions:
We will include studies that examine methods of preventing the development of epidural related fever, such as:

- Alternative method of analgesia
- Reduced dose epidural analgesia
- Regular paracetamol (acetaminophen)
- Steroids, if administered with the epidural analgesia

Comparator:
No restrictions will be imposed on the inclusion of studies by comparators. Due to the wide range of potential interventions, the comparator used will depend on the intervention under study. Studies evaluating different routes of administration of a therapeutic intervention, for example oral vs intravenous, will be included, as will studies comparing different doses.

Outcomes:
We will not select studies according to whether they report particular outcomes. The primary outcome measure for this review will be intrapartum maternal fever. Secondary outcomes will include rates of neonatal sepsis evaluation, rates of neonatal admission to level 2 care and inflammatory markers, as reported, including - but not limited to - cord blood IL-6 levels, and C-Reactive Protein.

Therapeutic strategies
Population:
We will include studies examining women in spontaneous or induced active labour who request epidural analgesia. Studies will be excluded if their focus is febrile women, however defined.

Interventions:
We will include studies that examine methods of treating epidural related fever, such as:

- Steroids, if administered on identification of maternal fever
- Paractamol, if administered on identification of maternal fever
- Antibiotics

Comparator:
No restrictions will be imposed on the inclusion of studies by comparators. Due to the wide range of potential interventions, the comparator used will depend on the intervention under study. Studies evaluating different routes of administration of a therapeutic intervention, for example oral vs intravenous, will be included, as will studies comparing different doses.

Outcomes:
There are no restrictions on eligibility by outcome. The primary outcome measure for this review will be intrapartum maternal fever. Secondary outcomes will include rates of neonatal sepsis evaluation, rates of neonatal admission to level 2 care and inflammatory markers, as reported, including - but not limited to - cord blood IL-6 levels, and C-Reactive Protein.

Review criteria
We will place no restrictions by publication status, setting, language, or date.

Search strategy
Literature search strategies will be developed using a combination of thesaurus terms and free text words.
We will search the following databases:

- MEDLINE (via OVID, from inception to search date)
- EMBASE (via OVID, from inception to search date)
- CINAHL (via EBSCO, from inception to search date)
- Web of Science (from inception to search date)
- Cochrane Central Register of Controlled Trials

This will be supplemented by searching the grey literature. This will involve hand searching conference proceedings of the Society of Obstetric Anaesthesia and Perinatology (SOAP), and organisations such as Society for Maternal Foetal Medicine, the Royal College of Obstetrics and Gynaecology and the Obstetric Anaesthetists Association (OAA) for any relevant guideline publications. Finally, we will hand search the reference lists and perform citation searching in Google Scholar of included studies to ensure literature saturation. We will rerun the search just before final analyses to ensure any recently published studies are identified and retrieved for inclusion.

No study type, language or date limits will be applied to the search. The Medline search strategy will be developed using the pearl growing technique, and finalised after consultation with an information specialist. A draft Medline search strategy is detailed in Appendix 1. After finalisation of the search strategy in Medline, the MeSH subject headings will be adapted to the thesaurus terms of the other databases.

DATA COLLECTION AND ANALYSIS
Data management
Literature search results will be exported to Rayyan and depuplicated. This internet based software will enable collaboration between review authors during study selection.

In the case of identification of duplicate publications, the individual study will be the unit of analysis for the systematic review, but citations will be given for all papers. This many to one relationship will be illustrated in the prisma flow diagram.

Study selection
Study selection will be done using Rayyan in two stages. Two review authors will independently screen the titles and abstracts of the studies retrieved by the search against the predefined inclusion criteria. Full texts of all relevant studies will be independently assessed by two review authors and each author will decide whether the study meets the

inclusion criteria. We will then compare the lists of included studies and resolve any disagreement through discussion. If a decision on whether to include a study cannot be reached, a third review author will be consulted. We will record reasons for exclusion based on review of the full texts and a PRISMA flow diagram will be created to display the screening process.

The reference lists of the included studies will be hand searched for any references not identified by the database search.

Data extraction

Two review authors will independently extract data from the included studies, following a predetermined data extraction sheet. The data extraction form will be piloted on a sample of studies identified for inclusion through scoping searches to ensure all relevant data can be extracted sufficiently. If multiple publications report on the same study, and both include relevant data, the articles will be examined for inconsistencies and data will be extracted into the same extraction sheet. We will highlight in the form which data is extracted from each publication to allow appropriate referencing in the text. In the case of studies with multiple treatment arms evaluating doses of an intervention, compared to a control, the treatment arms will be combined for binary outcome data extraction. We will select a single treatment arm for extraction of continuous outcome data. Once data extraction is complete any discrepancies between review authors will be resolved through discussion.

We will contact study authors to attempt to obtain any missing data.

The following data will be extracted from each study:

Trial characteristics

- Design
- Setting/location
- Sample size
- Power calculations
- Treatment allocation
- Randomisation
- Blinding
- Stopping rules
- Funding source

Population characteristics

- Age
- Parity (whether nulliparous, multiparous, mixed)
- Labour spontaneous or induced.
- Maternal weight
- Gestation
- Baseline temperature
- Baseline cervical dilation

Interventions and comparators

- Brief definition or name
- Pharmaceutical manufacturer(s)

- Dose
- Route
- Frequency of bolus including PCEA, intermittent mandatory bolus techniques
- Who administered the intervention: anaesthetic, obstetrician, midwife
- Any modifications

Primary outcome (for both preventive and therapeutic strategies):
- Incidence of intrapartum maternal fever

Secondary outcomes
- Incidence of neonatal sepsis evaluation
- Incidence of neonatal admission to level 2 care
- Indices of neonatal wellbeing (however defined; including, but not limited to APGAR scores)
- Inflammatory markers, as reported, including - but not limited to:
  - cord blood IL-6 levels
  - C-Reactive Protein.

Assessment of risk of bias in included studies

Two independent reviewers will assess the risk of bias for each included study using the Cochrane Risk of Bias 2 (RoB 2) tool.[18] The risk of bias will be assessed within the following domains:
- Randomization process
- Deviations from intended interventions
- Missing outcome data
- Measurement of the outcome
- Selection of the reported result

For each domain we will grade the risk of bias as ‘low’, ‘high’ or ‘some concerns’. This will be presented in a ‘risk of bias’ table where each judgment will be followed by a free text box detailing the evidence that lead to the grade. Any disagreement between reviewers will be resolved by discussion with a third reviewer.

The results of the risk of bias assessment will be included in the GRADE summary of findings tables as part of the evaluation of the quality of the available evidence. The findings will also be incorporated into the narrative synthesis, and if appropriate we will conduct sensitivity analyses excluding trials with a high risk of bias.

Data synthesis

We will report risk ratios and 95% confidence intervals for dichotomous outcomes, and mean differences with standard deviations for continuous outcomes. If a sufficient number of trials report on the same outcome we will perform meta-analysis using a random effects model in RevMan 5 (Non-Cochrane mode). Due to the likelihood of a high heterogeneity between studies, for dichotomous outcomes we will use the DerSimonian and Laird inverse variance method for meta-analysis[19]. If we are unable to perform a meta-analysis, a narrative summary will be undertaken.

A systematic narrative synthesis will be undertaken to summarise and explain the characteristics and findings of included studies[20]. This will be presented in the text and in tables. We will report on all studies, regardless of the results of the risk of bias assessment.

Assessment of heterogeneity

We will assess for heterogeneity by calculation of the I2 statistic. The Cochrane Handbook[19] provides a rough guide for interpretation of the I2 statistic:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We do not plan to impose a threshold heterogeneity requirement for meta-analysis. However, if heterogeneity is >50% we will report the results of the meta-analysis with appropriate warnings about the evidence for statistical heterogeneity.

Subgroup analysis

Based on our current understanding of the literature there are three broad categories of intervention. These types of intervention are:

- Alternative methods of analgesia and reduced dose epidural
- Pharmacological prophylaxis, such as paracetamol or steroids administered at the same time as the epidural
- Pharmacological therapies, such as paracetamol, steroids or antibiotics administered on identification of maternal fever

Adhoc decisions regarding subgroup analysis will be made based on the population and intervention characteristics of the included studies.

Assessment of reporting bias

If ≥10 trials report on the same outcome we will produce funnel plots to identify small study effects and assess the risk of population bias[21]. Using the ORBIT classification system we will assess the risk of outcome reporting bias in each included study and score each as ‘high’, ‘low’ or ‘high’ risk[22]. We will produce an outcome matrix to identify any missing outcomes and attempt to obtain any unpublished data by searching trial registries and databases, and contacting study authors if required.

‘Summary of findings’ tables

The quality of evidence for all outcomes will be assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[23]. This will be used to produce a ‘summary of findings’ table that summaries the relative effect and absolute risk of each intervention on each outcome.

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APPENDIX

1. Example search strategy for Medline via OVID interface
   No study design, date or language limits will be applied to the search.

1	exp fever/ or exp body temperature/ or exp inflammation/ or fever.mp or febrile.mp or heat.mp or pyrexia.mp or hyperthermia.mp or inflammation.mp or high temperature.mp
2	exp pregnancy/ or exp pregnancy complications/ or exp labor, obstetric/ or exp labor complications/ or exp delivery, obstetric/ or pregnan*.mp or intrpartum.mp or maternal.mp or maternity.mp or labour.mp or labor.mp
3	exp injections, epidural/ or exp anesthesia, epidural/ or exp analgesia, epidural/ or epidural.mp or combined spinal epidural.mp or cse.mp or neuraxial block*.mp
4	1 and 2 and 3
5	exp acetaminophen/ or paracetamol.mp or acetaminophen.mp or exp steroids/ or steroid*.mp or exp ant-bacterial agents/ or antibiotic*.mp or dexmedetomidine.mp or exp antipyretics/ or anti?pyretic*.mp or intervention*.mp or treatment*.mp or prevent*.mp or therap*.mp
6	epidural adj3 (intermittent or irregular or reduced dose or infrequent or alternate).mp
7	5 or 6
8	4 and 7