Combined spinal and epidural anaesthesia and maternal intrapartum temperature during vaginal delivery: a randomized clinical trial

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Editor’s key points

- Maternal intrapartum fever has been observed during epidural anesthesia; however, data are lacking for combined spinal–epidural (CSE) anesthesia.
- This study revealed that the use of CSE might be associated with a significant increase in maternal temperature.
- The increase in maternal temperature did not appear to provoke any deleterious effects on the mother or child.
- Differential diagnosis with chorioamnionitis has to be considered.

Background. We determined the association between combined spinal–epidural (CSE) anaesthesia and an increase in maternal intrapartum temperature and intrapartum fever.

Methods. A randomized, open clinical trial was performed with 70 pregnant women, 35 receiving CSE and 35 receiving only non-pharmacological methods of pain relief during delivery. Association between CSE and changes in the patient’s temperature, the risk of maternal fever, and other maternal and perinatal outcomes was determined at a 5% significance level. Number needed to harm (NNH) was calculated for maternal fever.

Results. Patients receiving CSE anaesthesia during vaginal delivery experienced a significant increase in intrapartum temperature and five (14%) developed fever, whereas no cases occurred in the group receiving only non-pharmacological methods of pain relief during delivery. Association between CSE and changes in the patient’s temperature, the risk of maternal fever, and other maternal and perinatal outcomes was determined at a 5% significance level. Number needed to harm (NNH) was calculated for maternal fever.

Conclusions. The use of CSE is associated with a significant increase in maternal temperature and in the incidence of intrapartum maternal fever. However, the increase in maternal temperature does not appear to provoke any deleterious effects on the mother or child.

Keywords: combined anaesthesia; epidural analgesia; fever; labour pain; obstetric labour; obstetrical analgesia

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Methods

A controlled, prospective, open clinical trial was conducted to compare a group of women receiving CSE anaesthesia for pain relief during labour and a group that received only non-pharmacological methods. The study population consisted of 70 women admitted to the antepartum unit of the Instituto de Medicina Integral Prof. Fernando Figueira between February and May 2010. The study protocol was previously approved by the Institutional Review Board under approval #1107 and registered with clinicaltrials.gov under #NCT00992524.

Women were included in the study after evaluation by the obstetrician to ensure that the patient complied with all the inclusion and exclusion criteria and after the patient had agreed to participate and signed an informed consent form. Participants consisted of pregnant women carrying a single, full-term fetus with cephalic presentation and cervical dilatation of 3–6 cm. Women with fever before or at the time of randomization, those in use of antibiotics, those with high-risk pregnancies (placenta previa, placental abruption, severe preeclampsia/eclampsia, premature delivery, HIV-positive patients), and women with an indication for an immediate Caesarean section were excluded from the study.

Sample size was calculated based on the following parameters: for an α=0.05, Zα=1.96, a power of 80%, Zβ=0.84, and considering an incidence of fever of 26.2% in the epidural group and 3.1% in the control group, a sample size of 60 patients would be required. In order to compensate for any exclusions that might occur after randomization, this size was increased to 70 patients, 35 in each group.16

The variables studied were an increase in maternal intrapartum temperature, maternal fever, maternal and neonatal antibiotic therapy, maternal and neonatal infection, duration of the first phase of labour, duration of the expulsion period, need for Caesarean section, need for instrumental delivery, Apgar scores, and umbilical cord blood pH.

A table of random numbers generated using the Random Allocation software program, version 1.0 (2004), was used for the randomization procedure. Sealed, opaque envelopes were then prepared containing the allocation group to which each participant was to be assigned. After the envelopes were opened and the groups were revealed, but before commencing the pain relief method allocated to the patient, the vital signs (temperature, arterial pressure, heart rate, and ventilatory frequency) of each patient were evaluated. Fetal auscultation was also performed using Doppler sonar to record fetal heartbeat before, during, and after a contraction.

All the women in both groups received continuous support throughout labour, consisting of assistance provided by a ‘doula’ or a trained layperson and the use of exercise balls, massage, and music therapy.17 18 The women were permitted and even encouraged to move around freely. None remained being confined to their bed in the labour room. Combined anaesthesia was initiated only when requested by the parturient. Puncture of the subarachnoid and epidural spaces was performed using the double-puncture technique. First, the subarachnoid space was punctured with a 27 G Whitacre spinal needle (Becton Dickinson) after which a solution containing 2.5 mg of 0.5% heavy bupivacaine associated with 5 μg of sufentanil was injected. Immediately afterwards, the epidural space was punctured using an 18 G Tuohy needle and a catheter was inserted into the same interspinous space used for subarachnoid puncture. Only 30 min after subarachnoid puncture, administration of 5 ml of a solution containing 0.05% bupivacaine and sufentanil 0.2 μg ml⁻¹ was initiated through the epidural catheter. This solution was administered intermittently every 30 min until delivery of the infant.19 All the women in both groups were monitored hourly and their temperature, arterial pressure, heart rate, and breathing rate were recorded, independent of uterine contraction. Uterine dynamics and fetal heart rate were monitored following the World Health Organization requirements for low-risk pregnancies: intermittent auscultation every 30 min during labour and every 5 min or following each contraction during the expulsion period.20 21 Cervical dilatation was evaluated every 2 h.

An increase in maternal temperature was defined as any increase in temperature above the baseline levels measured at randomization. Maternal fever was defined as an increase in temperature to values ≥38°C in women in labour, measured in the axilla using a Med Term thermometer, model 0205 RPC.7 15 Maternal and neonatal infection was defined in accordance with the criteria established by the Centers for Disease Control—CDC (1999) (US Joint Commission on Maternal Welfare).22 23 The duration of the first phase of labour was measured in minutes from admission to the study up to the time of pushing with full dilatation. The duration of the second phase was measured in minutes from the beginning of pushing with full dilatation until delivery. In this institution, one single episode of fever does not justify performing supplementary tests to investigate for infection. Investigation is only made in patients with fever associated with a high-risk delivery (presence of meconium, prematurity, acute fetal distress). In the case of a single episode of fever with no risk factors, the conduct of choice is to follow-up the newborn infant.

In the case of an indication for Caesarean section during labour, women in the combined analgesia group initially received a 15 ml dose of 2% lidocaine associated with 0.8 mg of morphine administered through the epidural catheter and, if the level of anaesthesia proved inadequate for surgery, supplementary 2 ml doses of 2% lidocaine were administered until the adequate level of anaesthesia was established (fourth thoracic vertebra).24 The patients in the non-pharmacological methods group were submitted to spinal anaesthesia with 12 mg of heavy bupivacaine associated with 0.08 mg of morphine.

Statistical analysis

Data analysis was performed using the Epi-Info software program, version 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA, USA). This analysis was carried
out on an intention-to-treat basis, that is, the patients were analysed as belonging to the group to which they had originally been allocated at randomization irrespective of whether or not a change in management had occurred during labour.\(^\text{15}\)

To test the association between CSE and maternal fever, Caesarean section, instrumental delivery, and non-reassuring fetal heart rate patterns, the \(\chi^2\) test of association with Yates' correction were used together with Fisher's exact test whenever indicated (if one of the expected values was \(<5\)). Risk ratios and their 95% confidence intervals (95% CIs) were calculated as a measure of the relative risk of various outcomes according to the use of combined analgesia. The number needed to harm (NNH, i.e. the number necessary to treat in order to produce harm) and its 95% CI were calculated for maternal fever in the combined analgesia group.

For analysis of the temperature curve during labour, the longitudinal model was used.\(^\text{26}\) This was possible because temperature was a longitudinal variable with multiple measurements for each woman. Since this is also a variable for which distribution is not normal, the median was used as a measure of central tendency and the Wilcoxon test was applied. Significance was defined as 5%.

### Results

Eighty-eight pregnant women were selected for participation in the study; however, only 72 fulfilled all the inclusion and none of the exclusion criteria and were invited to join the study. Two women refused to participate, which resulted in a total of 70 women, who were then submitted to the randomization procedure, 35 being allocated to the CSE group and 35 to the group allocated to receive only non-pharmacological methods of pain relief (Fig. 1). No loss-to-follow-up occurred after randomization. In one patient randomized to the pharmacological group, pain was not intense enough to justify the use of this technique, the patient remaining calm throughout labour and reporting only very mild pain right up to the time of delivery. On the other hand, one patient in the non-pharmacological group reported unbearable pain and requested to be given combined anaesthesia, after which she reported no further pain until delivery.

Analysis of the control variables, age, parity, gestational age, maternal temperature, and cervical dilatation recorded at the time of randomization, confirmed the homogeneity of the two groups (Table 1).

Median maternal temperature at the time of randomization was the same in both groups (36.2°C). Nevertheless, after the first hour of labour, an increase in maternal intrapartum temperature was recorded in the patients who received combined anaesthesia, the median temperature measured each hour being significantly higher in the group using the pharmacological method \((P<0.0001)\). This elevation in temperature occurred early, initiating between the first and second hour after randomization, and the difference remained throughout delivery until no further statistically significant difference was found between the two groups from the sixth hour onwards \((P=0.8)\) (Fig. 2).

Of the 35 women in the CSE group who participated in the study, five (14%) developed intrapartum fever, while no case of fever was found in the women receiving only non-pharmacological pain relief methods \((P=0.027)\) (Table 2). Nonetheless, no woman with fever received antibiotics or was submitted to investigation for infection and all progressed well without complications. No cases of chorioamnionitis or any other form of maternal infection were found. The calculated NNH for maternal fever in relation to combined analgesia was 7.0 (95% CI: 3.8–51.9).

Of the 70 women who participated in the study, 11 (15.9%) were submitted to Caesarean section and there

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**Fig 1** Flow chart of the women admitted to the study.
was no statistically significant difference between the two groups with respect to this variable. In relation to the duration of the expulsion period, the need for oxytocin, and instrumental delivery, no statistically significant differences were found between the two groups (Table 2). On the other hand, the first stage of labour was significantly shorter (median 180 min) in the group submitted to CSE (Table 2).

In relation to neonatal results, median 5 min Apgar score was the same in both groups; no statistically significant difference was found in the incidence of non-reassuring fetal heart rate, and no newborn infant had umbilical cord blood pH < 7.2 mm Hg. None of the infants born to the mothers who had intrapartum fever went on to develop neonatal sepsis or required antibiotic therapy or were investigated for neonatal infection (Table 3).
The rationale behind this increase is based both on a theoretical imbalance between heat production and elimination and on a disturbance in central thermoregulation. 1 – 3 27

On the other hand, the hyperthermia seen in pregnant women receiving CSE anaesthesia is different from that found in women submitted to epidural anaesthesia, since the increase in temperature in this study appeared between the first and second hours after analgesia, continued throughout the first hours of labour and disappeared after the sixth hour. Other investigators have published conflicting findings, reporting that ‘epidural fever’ is more common in prolonged labour, only 7% of women being affected in the first 6 h compared with over 36% when labour persists for more than 18 h. 28

We were unable to explain this possible difference in hyperthermia with these two techniques; however, it should be emphasized that the present study was not designed to compare CSE with epidural anaesthesia; therefore, further studies conducted to compare these two techniques should include both temperature levels and intrapartum maternal fever as outcomes in order to verify whether this difference really occurs and the reasons for its occurrence.

The association of intrapartum fever with epidural anaesthesia has been demonstrated in several studies. 4 7 8 29 – 31 Nevertheless, before the present study, no clinical trials had been conducted to clarify the association between maternal fever and CSE. 8 32 Conversely, the results of the present study suggest that combined anaesthesia (CSE) for pain relief during labour is also associated with intrapartum maternal fever, although this fever is not indicative of any increased risk of maternal or neonatal infection.

It is known that maternal fever associated with analgesia during labour is not a consequence of infection, and this was corroborated in the present study. The major concern, however, is that in the majority of studies, even when a higher rate of maternal and perinatal morbidity resulting from infection was not found, the presence of intrapartum maternal fever results in major investigations, since both the mothers and the newborn infants are submitted more often to exams to screen for infection and to antibiotic therapy. 29

Even taking the risk described in the literature into consideration, no additional investigation was performed in the present study to exclude the possibility of systemic infection in the mothers or in their newborn infants, since no risk factors were present in the women evaluated. None of the infants of the mothers who suffered intrapartum fever was submitted to any supplementary tests or to antibiotic treatment. This probably resulted from the fact that the obstetricians and neonatologists involved in the study were aware that the patients had been submitted to analgesia during labour, knew of the association described in the literature between analgesia and maternal fever, and detected no other factors that could have been associated with this elevation in temperature.

This knowledge permitted women who developed fever after combined analgesia but who had no other signs indicative of maternal or neonatal infection (such as tachycardia, the presence of meconium in amniotic fluid, or prematurity) to be followed up clinically, with supplementary tests and antibiotic therapy only being indicated in cases of unfavourable progression. The same form of management was applied to the newborn infants. This form of conduct has been recommended by various authors, who propose a review of the obstetrical and neonatal criteria governing supplementary testing and antibiotic therapy in cases of intrapartum fever associated with anaesthesia. 29 33 Likewise, studies have shown that, despite the association between epidural anaesthesia and an increased risk of developing maternal fever, there are no repercussions on fetal well-being. 34

Findings that deserve particular mention concern the Caesarean section rate, the need for instrumental delivery (use of forceps), duration of the first and second stages of

<table>
<thead>
<tr>
<th>Neonatal results</th>
<th>Groups</th>
<th>Combined analgesia (n = 35)</th>
<th>Non-pharmacological methods (n = 35)</th>
<th>RR</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5th min Apgar (median/25th–75th percentile)</td>
<td>10 (9–10)</td>
<td>9 (9–10)</td>
<td>—</td>
<td>—</td>
<td>0.5*</td>
<td></td>
</tr>
<tr>
<td>Non-reassuring fetal heart rate (n/%)</td>
<td>2 (5.7)</td>
<td>3 (8.6)</td>
<td>0.66</td>
<td>0.11–3.74</td>
<td>0.5**</td>
<td></td>
</tr>
<tr>
<td>Umbilical cord pH (median/25th–75th percentile)</td>
<td>7.38 (7.34–7.42)</td>
<td>7.36 (7.34–7.38)</td>
<td>—</td>
<td>—</td>
<td>0.27*</td>
<td></td>
</tr>
</tbody>
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labour, and the need for oxytocin. The Caesarean rate in the present study was similar in both groups (11% vs 18%) and is within the limits considered acceptable in the literature.\(^3\) In fact, the majority of more recent studies on analgesia in labour show no increase in Caesarean rates, which is corroborated in the Cochrane systematic reviews.\(^9\)\(^–\)\(^11\)

On the other hand, unlike studies reported in the literature that describe an increase in the duration of the second stage of labour but no significant effects on the first stage,\(^9\)\(^10\)\(^16\) a reduction in the duration of the first stage of labour was found in the present study, with no significant effect on the duration of the expulsion period or on the use of oxytocin. It should also be remembered that most of the studies on analgesia during labour compare epidural anaesthesia with other pharmacological methods such as meperidine, whereas in the present study, the control group received no pharmacological methods, which may justify any differences in the present findings.

With respect to instrumental delivery, in conflict with reports in the literature, the use of forceps at delivery was not found to be higher in the group receiving analgesia in the present study. This may reflect the absence of a prolonged expulsion period or the reality of a university teaching hospital that adopts the recommendations of the American College of Obstetricians and Gynecologists (ACOG) with respect to the duration of the expulsion period in patients receiving analgesia, instrumental delivery only being performed when specific indications are present.\(^37\)

It is worth emphasizing that calculation of the sample size in the present study was based on the incidence of fever in mothers submitted or not to epidural anaesthesia for analgesia during labour. Therefore, a pertinent criticism is that this sample size may have been insufficient to determine the relative risk related to the incidence of Caesarean sections, instrumental deliveries, the use of oxytocin, and neonatal acidosis, since, in accordance with the incidence of each one in particular, a different sample size may have been necessary.

In conclusion, the present study shows that combined analgesia is associated with an increase in intrapartum maternal fever (one case of fever for every seven patients submitted to analgesia), albeit without any apparent repercussions for the mother or infant. Further, well-controlled studies should be conducted to investigate the causes and consequences of intrapartum fever, including studying its prevention in order to identify means of improving the care given to patients receiving analgesia for pain relief during labour.

**Conflict of interest**

None declared.

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