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CONTROVERSIES CONTINUED

The rise in maternal temperature associated with regional analgesia in labour is harmful and should be treated

Proposers: S. Banerjee, P. J. Steer

Academic Departments of Obstetrics & Gynaecology & Neonatology, Faculty of Medicine, Imperial College London, UK

Epidural analgesia and maternal pyrexia

Fusi et al. in 1989 first reported the association of raised maternal temperature with the use of epidural analgesia in labour when compared to women receiving opioid analgesia.[1] Since then a number of observational and randomised studies have confirmed this association.[2–10] About 6–23% of women in labour with epidural analgesia will develop clinical pyrexia >38 °C. The degree of rise has been estimated to be 1 °C for every seven hours of exposure to epidural analgesia.[1] Thus, the clinical observation of pyrexia in labour becomes more likely after five hours of exposure to epidural analgesia. The effect is also more likely to be observed in nulliparous women because they have longer labours. Although the rate of fever with epidural analgesia varies in different studies, the association has been consistent, suggesting a causal link. The variation in reported rates is probably explained by variations in the parity of the population studied (and hence in the mean duration of labour), in baseline rates of fever in women without epidural analgesia due to differences in the susceptibility of various populations to infection, and variations in the ambient temperature. The hotter the labour and delivery room, the greater the effect is likely to be. Whatever the background rate of pyrexia in a given population, it is evident from the studies that among nulliparous women, an additional 10–15% will become febrile if they are using epidural analgesia for pain relief.[11]

Could this all be infection?

Although the association between epidural analgesia and maternal pyrexia has been clearly established, the underlying cause has been debated. Most researchers believe that the underlying cause is not infection but altered maternal thermoregulation in labour. Heat loss by the mechanisms of convection and radiation is increased in the lower part of the body following the vasodilatation produced by epidural analgesia. This along with some reduction of skeletal muscle activity due to adequate pain relief should tend to decrease a parturient's temperature. However, the reduction in hyperventilation secondary to pain relief, reduction in sweating produced by the sympathetic blockade and reactive vasoconstriction in the upper part of the body all tend to diminish heat loss.[12–14] There is also evidence that dissociation between the block of cold and warm sensation during regional analgesia results in an early block of the warm sensations allowing cold stimuli to persist.[15] This tends to bias the thermal information reaching the temperature control centre, which may respond by stimulating heat producing mechanisms, resulting in pyrexia. There may also be an increase in sweating threshold.[16] The ambient temperature of labour rooms is traditionally kept high to reduce neonatal hypothermia, which may also play a significant role. In effect the administration of an epidural block seems to create an imbalance between the heat producing and heat dissipating mechanisms in labour leading to pyrexia, particularly in the presence of a high ambient temperature.

Some investigators have postulated an infectious aetiology for maternal pyrexia with epidurals based on

S. Banerjee, **P. J. Steer**, Academic Departments of Obstetrics & Gynaecology & Neonatology, Faculty of Medicine, Imperial College London, Chelsea and Westminster Hospital, 369 Fulham Road, London, SW10 9NH, UK.

Correspondence to: Dr S. Banerjee, 4 Bourne Court, New Wanstead, London, E11 2TG, UK. Tel.: +02089230582;
E-mail: sujoybanerjee@doctors.org.uk

the longer labours and therefore possible longer duration of ruptured membranes associated with it.[17] This is unlikely as women who do not receive epidural analgesia fail to show a rise in temperature regardless of the duration of labour.[1,2] Lieberman et al. report that the rate of fever among women without epidural analgesia remains low regardless of the length of labour.[7] Impey et al. in their prospective study of nearly 5000 low-risk women found an independent association of maternal fever with epidurals but no association with prolonged rupture of membranes, regarded as a precursor of perinatal infection.[18] Yancey et al. studied the effect of introducing an on-demand epidural service on the rates of maternal pyrexia and neonatal infection in the Tripler Army Medical Center following a Department of Defense mandate.[19] A dramatic increase in epidural uptake from 1 to 83% was accompanied by an equally impressive rise in the incidence of maternal temperature >38 °C from 0.6 to 11% (Relative risk 18.3; 95% CI 5.8, 57.8). There was, however, no significant rise in the documented incidence of neonatal infection despite increased evaluation for neonatal sepsis. Obstetric and neonatal practices were unlikely to have changed over such a short period. Other studies have similarly confirmed a rise in neonatal sepsis evaluation without a rise in confirmed neonatal infection.[4,7] Recent work in our own department studied 52 women with prolonged rupture of the membranes having epidural analgesia in labour, and although 25% developed an oral temperature above 37.5 °C, no significant infections were detected despite intensive microbiological investigation of mother and baby.

More recently Goetzl et al. proposed a non-infective inflammatory theory to explain epidural-related fever in labour.[20] In a secondary analysis of a study set up to investigate a different issue, they demonstrated higher levels of IL6 in maternal and fetal cord blood samples in the febrile than in the afebrile epidural group. There was no demonstrable increase in maternal or neonatal infection. However, such elevations in cytokines were not demonstrated in our own study, and cytokine levels need to be examined in further studies before we can draw any conclusions.

How does a raised maternal temperature affect the fetus?

The most important determinant of fetal and immediate neonatal temperature is the maternal temperature. The fetus generates heat from its metabolism and the main way it loses this heat is by transfer to the maternal circulation across the placenta (less than 20% is lost by direct convection through the amniotic fluid). The second law of thermodynamics dictates that the fetal temperature has to be higher than the intrauterine temperature, so that heat can be lost down a temperature gradient to the mother (the only exception to this rule is when the mother heats up very rapidly, when the fetus can be temporarily cooler than the mother due to thermal inertia). Therefore, when maternal temperature increases, the temperature of the fetus also rises. It has been shown in humans that oral temperature measurement underestimates the intrauterine temperature by an average of 0.6 °C.[21] The fetal core temperature in turn is higher than the maternal intrauterine temperature by at least 0.5 °C and the difference may reach as much as 1 °C in some cases.[22] Thus if the maternal oral temperature reaches 38.5 °C, the fetal core temperature is likely to rise to a level close to 40 °C. In the study by Macaulay et al. 5% of the fetuses were likely to have reached a core temperature in excess of 40 °C.[8] In a classic study on pregnant baboons, hyperthermia in the absence of infection was associated with the development of fetal hypoxia, hypotension and metabolic acidosis.[23]

The obstetric implications of maternal pyrexia

The diagnosis of chorioamnionitis is often difficult to make with certainty in women receiving epidural analgesia in labour. A rise in maternal temperature is known to increase the fetal heart rate proportionately.[1] Effective epidural analgesia makes the assessment of uterine tenderness difficult. Supportive laboratory parameters for diagnosing infection such as white cell count and C-reactive protein are often unreliable in labour and definitive methods such as culture results are not available at the time of making a clinical decision. Therefore in the presence of maternal fever and fetal tachycardia, the clinician is likely to err on the side of diagnosing chorioamnionitis and treat the woman with intrapartum antibiotics. This impression is confirmed in the study by Mayer et al. which showed that women receiving epidural analgesia were more likely to be pyrexial and receive intrapartum antibiotics without any microbiological or pathological evidence of an increased incidence of chorioamnionitis.[5]

The jury is still out on whether epidural analgesia overall is associated with an increase in instrumental vaginal delivery and caesarean section. Most studies have examined the overall effect of epidural analgesia on these outcomes, which are likely to be different in the febrile epidural group. Lieberman et al. examined the association of elevated maternal temperature with caesarean and instrumental vaginal delivery in 1233 low-risk nulliparous women in term spontaneous labour.[24] They found that women with temperatures in excess of 99.5 °F were three times more likely to have caesarean

section and also three times more likely to have instrumental delivery. Of these women, 90% had received epidural analgesia and the association remained after controlling for confounding factors in a multivariate analysis. It is possible that a clinical diagnosis of chorioamnionitis based on an elevated maternal temperature and persistent fetal tachycardia may lead to increased intervention in this group.

Maternal pyrexia and neonatal outcome

Intrapartum maternal fever has now been reported in many observational studies to be associated with adverse neonatal outcomes. Badawi et al. in the Western Australian case-controlled study reported a nearly four-fold increase in neonatal encephalopathy when mothers developed a fever >37.5 °C.[25] In their prospective cohort study of 4915 low-risk women at term, Impey et al. confirmed this finding and reported a five-fold increase in neonatal encephalopathy when mothers developed pyrexia >37.5 °C.[18] Maternal fever was associated with epidural use but not with pre-labour prolonged rupture of membranes. Perlman, in a retrospective analysis of 25 000 term births, observed an increased need for resuscitation including chest compression and intubation in term babies born to mothers with a fever exceeding 38 °C in labour.[26] Lieberman et al. observed similar effects including global hypotonia, need for resuscitation and, more significantly, a 3.4-fold increase in neonatal seizures in babies born to mothers with intrapartum fever.[27,28] There was no concomitant rise in maternal or neonatal infection.

Neonatal encephalopathy and seizures are the strongest clinical indicators in the neonatal period of neurodevelopmental problems in later childhood. In this context the study by Grether and Nelson assumes great significance.[29] This was a retrospective population-based study of children with birth weight >2500 g and unexplained spastic cerebral palsy. The risk of unexplained cerebral palsy among infants was nine-fold higher when maternal intrapartum temperature exceeded 38 °C. They attributed the cause of maternal fever to infection. However, in this study, the observation of pyrexia >38 °C alone was sufficient for a woman to be classified as having chorioamnionitis, without requiring additional evidence of infection. It is possible therefore that the outcome reflected the direct effect of pyrexia, independent of infection.

As mentioned before, several studies have reported increased neonatal sepsis evaluation by laboratory investigation in babies born to pyrexial mothers who received epidural analgesia in labour, without an actual rise in confirmed neonatal sepsis. Other hospitals may not use invasive laboratory tests to evaluate these newborns but most will prefer to observe them in hospital for an extended period if there is a history of maternal pyrexia. Besides the stress and the anxiety this generates among parents, such unnecessary in-patient stays will have a significant impact on hospital and manpower resources.

What degree of temperature elevation could potentially be harmful? What is the underlying pathophysiology?

The important question that arises from these discussions is whether the modest rise in body temperature associated with epidural analgesia is enough to pose problems for the fetus and the newborn. Animal studies have demonstrated that an increase in brain temperature of even 1 °C increases the degree of brain damage from a hypoxic ischaemic insult.[30,31] Among adults admitted with stroke, higher body temperature at admission has been associated with an increase in stroke severity, infarct size and mortality.[32] Experimental research on adult rats has shown that although exposure to lipopolysaccharide at the time of hypoxia-ischaemia worsened brain injury, this effect was not seen when the lipopolysaccharide-induced hyperthermia was prevented.[33] These findings suggest that maternal intrapartum fever could be injurious to the fetus by increasing the risk of neurologic injury independent of infection. Cerebrospinal fluid concentrations of excitatory amino acids such as glutamate and glycine are higher in hyperthermic patients in the first 12 h after stroke, consistent with the hypothesis that some of the adverse effects are mediated by excitatory neurotransmitters.[34] Conversely, hypothermia has been shown to be neuroprotective in animal studies if used appropriately.[35,36] Oxygen free radicals are produced during resuscitation from a hypoxic-ischaemic insult and in animals, cooling the brain reduces the production of free radicals.[37] The most consistent and dose-related benefits of hypothermia in preventing neuronal loss have been shown when it is instituted at the time of the hypoxic ischaemic insult (primary phase of injury).[38] In clinical practice this is impossible to implement as most of these events occur before birth. The effects of brief hypothermia in the latent or resuscitation phase on neuronal loss have been modest, at best inconsistent and with a narrow window for implementation.[38–41] Prolonged hypothermia into the secondary phase has potential but the optimum degree of hypothermia and the duration remain to be determined. Most believe that the best results are probably obtained in this phase if therapeutic hypothermia is instituted within 6 h of birth.[42] The difficulties of appropriate case selection, logistics of transferring a sick baby and implementation of hypothermia in a tertiary unit, within this therapeutic window, may be important factors in success. Thus pri-

mary prevention of maternal hyperthermia assumes greater importance.

Is there a threshold effect?

It is not clearly known whether the adverse effect of elevated temperature is only seen in the presence of concomitant hypoxia and ischaemia. The critical temperature and duration of exposure also remain to be determined. Most animal studies have used the hypoxic ischaemic model and therefore fail to answer the question when there is no concomitant hypoxic ischaemic insult. However, every labour and birth is potentially hypoxic and adverse intrapartum events are mostly unpredictable. Therefore, if maternal pyrexia is indeed a cause for concern then measures to prevent hyperthermia will have to be implemented in all labours with epidural anaesthesia. Despite improvements in neonatal intensive care over the last two decades, we have not seen a proportionate fall in cerebral palsy rates in term babies. Most children with cerebral palsy do not show evidence of problems in the neonatal period and a search for the missing link should explore all possibilities.

Further research

Given the background above, there is an urgent need for studies to develop practical techniques for continuous accurate maternal temperature monitoring in labour, and effective methods for preventing a rise in temperature. Once these have been developed, we will need trials of temperature control versus conventional care to investigate the effect of epidural-induced maternal pyrexia in labour on short and long-term neonatal outcomes. If any of the potential adverse effects of maternal hyperthermia as outlined above are confirmed, then we will need to implement universal strategies of early detection and prevention of maternal hyperthermia.

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Opposer: L. Irestedtz

Department of Anesthesiology and Intensive Care, Karolinska Hospital, Stockholm, Sweden

Recently, two systematic reviews dealing with effects of epidural analgesia on labour, maternal and neonatal outcomes were published in the same supplement of American Journal of Obstetrics and Gynecology.[1,2] Unintended effects of labour analgesia have for decades been the subject of controversy, as illustrated by these two articles which had a fairly contradictory interpretation of available scientific data. Typically enough, these reviews represent anesthesiological versus obstetrical/perinatological points of view. One of the most recent, yet unresolved, controversies deals with increased likelihood of maternal intrapartum fever associated with epidural analgesia first described more than ten years ago.[3,4]

Intrapartum fever, defined as a temperature of at least $38.0\,^{\circ}C$, develops more frequently in women with epidural analgesia than in those receiving other forms of pain relief such as systemic opioids. While the incidence on average rises from 1–4% to 10–15%[5,6] it seems also mainly associated with nulliparity and long labours.[6,7]

The controversy surrounding cause and consequence of temperature rise associated with epidural labour analgesia can be divided into four elements.

1. Why and how is increased maternal temperature associated with epidural pain relief?
2. Could the association be purely non-causal?
3. Could it affect maternal and neonatal medical treatment?
4. Could it be harmful?

Why and how is increased maternal temperature associated with epidural pain relief?

Plausible reasons whereby epidural analgesia may increase maternal temperature include decreased hyperventilation, paralysis of sweat glands in the lower body and compensatory vasoconstriction in the upper body, all leading to decreased heat loss.[6] Shivering before delivery

Lars Irestedt, Associate Professor, Department of Anesthesiology and Intensive Care, Karolinska Hospital, SE-171 76 Stockholm, Sweden. Tel.: +46-8-517 72341; E-mail: lars.irestedt@ks.se