



Epidural Fever: Hiding in the Shadows

Puneet Khanna¹ , Shikha Jain² , Karishma Thariani³ , Shashikant Sharma¹ , Akhil Kant Singh¹

¹Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, New Delhi, India

²Department of Anaesthesiology, Pain Medicine and Critical Care, All India Institute of Medical Sciences, Bhopal, India

³Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, New Delhi, India

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Abstract

Recent research has focused on inflammation and oxidative stress that is seen in women developing intrapartum fever. The interleukin-6 (IL-6) levels have been found to be elevated in women who receive epidural analgesia and become febrile. This suggests that the epidural itself induces an inflammatory response and it is not a physiologic process of labour. Similar findings with additional proinflammatory mediators and reactive oxygen species seem to support this theory. Epidural analgesia also affects the body's thermoregulatory mechanisms. It causes an increase in shivering and appears to be associated with a decrease in heat dissipation via sweating and hyperventilation, most likely because of blockade of the sympathetic stimulation. Considering these factors, it is probable that epidurals do contribute to the development of the associated fever. There remains the possibility that subclinical chorioamnionitis might be the underlying cause of a subset of maternal intrapartum fevers. In summary, histologic chorioamnionitis and epidural analgesia appear to be the independent contributors to intrapartum fever.

Keywords: Analgesia, epidural, fever, inflammation, pregnancy

Introduction

Epidural analgesia is the most popular method used for pain relief during labour. Fusi et al. (1) first reported the occurrence of maternal fever associated with epidural analgesia. This is contrary to the conventional belief that below the level of epidural blockade, there is peripheral vasodilation that leads to slight decrease in core temperature. Multiple publications have now linked intra partum fever, temperature $\geq 38^{\circ}\text{C}$ and epidural analgesia with a cumulative risk ranging between 11% and 33%. The consequences of intrapartum fever may include increased incidence of neonatal sepsis, low one-minute Apgar scores, increased use of antibiotics, and prolonged hospital stay. However, its association with neonatal encephalopathy is of greater clinical concern, with an estimated incidence of 1.9%, which increases subsequently to 12.5% with concomitant acidosis.

The precise mechanism for the development of maternal fever with epidural analgesia is unclear. However, the possible mechanisms may include non-infectious systemic inflammation due to increased interleukin-6 (IL-6) levels and altered thermoregulation caused by the epidurals. There is reduced heat dissipation via decreased sweating and reduced hyperventilation because of better pain relief that leads to increased body temperature. Though there are reports of increased incidence of maternal fever with epidurals, there remains the possibility that a subclinical chorioamnionitis condition might be the underlying cause of a subset of maternal intrapartum fevers. Women may be more likely to request an epidural if they are experiencing symptoms of subclinical chorioamnionitis, such as uterine tenderness. The anaesthesiologist must consider the possibility of epidural analgesia-associated fever in view of this evidence.

Multiple prospective studies have demonstrated that the patients who had self-selected epidural analgesia during labour, had a higher incidence of fever as compared to those who selected other methods of pain relief. Fusi et al. (1) conducted a study which included 40 women either receiving epidural analgesia or pethidine. They found that the average vaginal temperature of the women receiving epidural showed an increase in temperature by 1°C over a period of 7 hours, as compared to the non-epidural group with unchanged temperature. None of the patients had any causative factors of fever. One of the possible mechanisms of increased temperature in this study could be that because the investigators measured the vaginal temperature, the vasodilation caused by the neuraxial anaesthesia,

which must have induced the sympathetic blockade, could have caused a rise in the vaginal temperature.

In the study by Camann et al. (2), 53 labouring women were allowed to self-select either epidural analgesia or intravenous nalbuphine. Women who selected epidural were randomized to receive either epidural bupivacaine alone or epidural bupivacaine and fentanyl. To possibly account for the effect of epidural analgesia on temperature measurements, they recorded the rise in the tympanic membrane temperature (rather than the vaginal or rectal temperatures) in both the epidural groups as compared to the nalbuphine group. The rise in the temperature was 0.07°C per hour on an average, with no difference between groups.

In retrospective analyses, it was similarly found that women who selected labour epidural showed a rise in temperature (Table 1). Herbst et al. (3) conducted a retrospective analysis, in which 61.1% (44 out of 72) of the women who opted for labour epidural developed epidural fever. However, in another observational study, Frölich et al. (4) recorded the hourly oral temperature of 81 labouring women from admission to delivery. To evaluate the possible role of epidural related fever, they compared the slope of temperature before and after starting the labour epidural analgesia. They found a linear trend of temperature with time. The temperature increase was found to be associated with higher body mass index values and longer interval from the rupture of the membranes to delivery. They concluded that the epidural labour analgesia had no effect on the maternal temperature. However, they excluded women with chorioamnionitis (temperature >38°C) from the analysis.

Multiple randomized controlled trials (RCT) also illustrate the association of epidurals with intrapartum fever. Sharma et al. (5) randomized 459 women to receive either epidural or intravenous meperidine. Out of 226 women randomized to receive epidural, 214 received labour epidural analgesia. Of 233 women randomized to receive intravenous meperidine, 207 received meperidine and the others refused. Out of 226 women allocated to the epidural group, 75 (33%) women developed clinical fever, with temperature >38°C, against only 7% developing fever in the meperidine group (16 out of 233

women), with $p < 0.0001$. Lucas et al. (6) randomized 738 labouring women to either receive labour epidural analgesia or intravenous meperidine to compare their peripartum and perinatal effects in the patients having pregnancy-induced hypertension. The authors reported a significantly higher incidence of fever in the epidural group (22% vs 8%). The authors also reported a higher incidence of chorioamnionitis in the epidural group, although it is not clear whether the diagnosis was confirmed histologically. Consequently, whether the rise in temperature in the epidural group was because of the epidural, or chorioamnionitis could not be inferred.

Impey et al. (7) carried out a prospective cohort study, which included 4915 women in labour. Of these, 336 (6.8%) participants had fever. Univariate analysis showed that the development of a maternal fever was associated with nulliparity, induced labour, use of epidural analgesia, a longer labour, oxytocin usage, higher birthweight, and greater gestation.

Clinical and Research Consequences

Intrapartum fever is a condition seen in a small percentage of pregnant women during labour. It is more common in primiparas under long labour and use of epidural anaesthesia, and has a variable incidence depending on how it is defined, and the population being studied. Fusi et al. (1) demonstrated that the women who received epidural analgesia during labour had a rise in the vaginal temperature at a rate of 1°C every 7 hour vs women who received intramuscular opioids and in whom the vaginal temperature remained constant. According to the estimates, the elevation of the intrapartum temperature begins within 4-6 hours after the epidural placement and rises at a rate of 0.08°C to 0.14°C per hour.

Intrapartum fever has been associated with short-term complications in newborns, such as lower 1 min Apgar scores, increased use of bag and mask resuscitation and increased oxygen treatment in the nursery, higher frequency of hypotonia, increased admissions to the intensive care nurseries, and increased instances of mechanical ventilation. Of concern is its association with neonatal encephalopathy, which is estimated to be 1.9% and increases to 12.5% with concomitant acidosis (8).

There have been multiple proposed mechanisms for epidural analgesia contributing to intrapartum fever, which are as follows: (i) high ambient temperature in the delivery rooms, (ii) a decrease in heat dissipating hyperventilation with effective pain relief, (iii) an increase in metabolic expenditure in labour, (iv) altered thermoregulation, which may involve an elevated sweating threshold below the level of the blockade (2) or an increase in the likelihood of heat producing shivering, (v) Local anaesthetic drugs causing the release of cytokines acting directly on the central nervous system (9, 10), (vi) non-infec-

Main Points:

- Fever is a common finding associated with epidural analgesia during labour.
- Attributed to various causes ranging from infection to inflammation.
- Can have a deleterious effect on the neonate
- Pinpointing the cause can prevent extra costs, unnecessary medications and tests and excessive hospital stay.

Table 1. Incidence of intrapartum fever with epidural analgesia

Author	Design	Fever definition, site (° Celsius)	Epidural group n/N (%)	Non- epidural group n/N (%)	UOR/OR/RR (95% CI)
Camann et al. (2)	Prospective	unavailable	Higher temperature in the epidural group	Higher temperature in the epidural group	Not available
Herbst et al. (3)	Retrospective observational	>38, oral	44/683 (6.4)	28/2426 (1.1)	UOR, 5.90 (3.64–9.55); AOR, 4.3 (2.4–7.8)
Sharma et al. (5)	RCT	>38	75/226 (33.0)	16/223 (7.0)	UOR, 6.74 (3.78–12.01)
Lucas et al. (6)	RCT	>38	76/372 (20.4)	26/366 (7.1)	UOR, 3.36 (2.09–5.38); AOR, 2.9 (1.5–5.6)
Impey et al. (7)	Prospective cohort	>37.5, oral	Study involving 4915 low risk women. Higher incidence of fever in women receiving epidural (univariate analysis)	Study involving 4,915 low risk women. Higher incidence of fever in the women receiving epidural (univariate analysis)	Not available
Riley et al. (11)	Prospective Observational	38, oral	34/150 (22.7)	3/50 (6.0)	UOR, 4.59 (1.34–15.68); AOR, 4.9 (1.1–22.4)
Vinson et al. (25)	Observational	>37.5, tympanic	11/41 (26.8)	3/36 (8.3)	UOR, 4.03 (1.03–15.86)
Ploeckinger et al. (26)	Retrospective observational	>38, axillary	17/1056 (1.6)	11/6261 (0.2)	UOR, 9.30 (4.43–19.90)
Macaulay et al. (27)	Prospective observational	>37.5, uterine	15/33 (45.0)	2/24 (8)	UOR, 9.17 (1.85–45.47)
Halpern et al. (28)	RCT	>38	19/124 (15.0)	10/118 (8)	UOR, 1.95 (0.87–4.40)
Ramin et al. (29)	RCT	>38	98/432 (22.7)	21/437 (4.8)	UOR, 5.81 (3.55–9.51)
Sharma et al. (30)	RCT	>38	58/243 (23.9)	16/259 (6.2)	UOR 4.76 (2.65–8.55)
de Orange et al. (31)	RCT	>38	5/35 (14.0)	0/35 (0.0)	UOR, 12.80 (0.68–241.04)
Philip et al. (32)	RCT	>38, tympanic	54/358(15.1)	14/357(4.0)	AOR, 4 (2.0–7.7)
Yancey et al. (33)	Retrospective, before-after study	≥37.5, ≥38 tympanic	41/498 (8.2), 3/498 (0.6)	150/572 (26.2); 63/572 (11.0)	RR, 20.2 (7–86) (≥38)
Akerman and Hall (34)	Audit prospective/retrospective	≥38	Higher incidence of fever in the epidural group	Higher incidence of fever in the epidural group	Not available
Reilly and Oppenheimer (35)	Retrospective	>38 or 2 >37.5, Oral	156/10,999 (1.42)	5/5484 (0.09)	AOR, 5.5 (4.0–7.0); RR, 16 (4.9–51)
Bensal et al. (36)	Retrospective	>38	No difference in fever	No difference in fever	UOR, 1.25 (0.99–1.57)

UOR: unadjusted odds ratio; OR: odds ratio; RR: relative risk; AOR: adjusted odds ratio

tious systemic inflammatory mechanism (11), and (vii) infectious aetiology-intrapartum infection (11).

The incidence of clinical fever in labouring women varies widely from 1% to 46%, depending on the differences in the

study population, while chorioamnionitis is estimated to be present in 3–5% of all births (US estimates) (12). The incidence of chorioamnionitis varies but the highest estimates are exceeded by the incidence of epidural fever. Sharma et al. (13) demonstrated the failure of prophylactic antibiotics

to prevent epidural fever. Additionally, the *in vivo studies* of local anaesthetics demonstrate significant antimicrobial action against the common pathogens (14, 15). Therefore, the absence of efficacy of the prophylactic antibiotics in preventing maternal fever coupled with a consistent lack of positive microbiology obtained from the observational studies suggests that the aetiology of the epidural fever is not primarily infectious in nature.

In their study, Sharma et al. (16) demonstrated the association of epidural related fever with neutrophilic placental inflammation. These findings further support a report by Riley et al. (10), which demonstrated an association between the intrapartum fever and non-infectious placental chorioamnionitis.

So, the key question remains, if not infection, then what is the underlying cause of intrapartum fever related to epidural? (Table 2) Theoretically, the epidural analgesia triggers an inflammatory response either in the placenta or epidural space leading to a clinical fever. It is well established that labour incites an inflammatory reaction. Spontaneous labour is associated with increased production of pro-inflammatory cytokines and immunomodulators (17). Neal et al. (18) demonstrated circulating levels of inflammatory biomarkers, such as IL-6 and IL-10 to be higher, and their rate of change over time since admission to be faster in the patients in active labour, as compared to the patients not in active labour. Also, epidural fever has not been described in patients who are not in labour, such as those who have caesarean sections. Riley et al. (11) found a relation between a higher baseline levels of IL-6 and IL-8 (at admission) and development of fever. Thus, the evidence points to epidural fever having an inflammatory causation.

This supposition is further buttressed by the following. Recently, it has been suggested that epidural itself causes an inflammatory response, resulting in the release of proinflammatory cytokines, such as IL-6, and reactive oxygen species. A study conducted in orthopaedic patients who underwent surgeries

under epidural anaesthesia did not support this hypothesis as the magnitude of systemic cytokines released was not enough to explain the magnitude of systemic inflammatory response seen in the epidural related maternal fever (19). However, this observation has to be tempered with the findings obtained by epiduroscopy, which demonstrated a denser vasculature than normal (20). Therefore, local inflammation remains a probable cause for epidural fever.

According to another theory, the epidural related fever can be explained based on the direct action of the local anaesthetic drugs, which can exert their action through immunomodulation and cell injury. Local anaesthetics are known to cause inhibition of the neutrophil mobility, phagocytosis, chemotaxis, and apoptosis. These injured cells release alarmins, which set off a cascade leading to the production of cytokines.

Goetzl et al. (21) successfully prevented epidural fever with maternal systemic steroids. They randomized women during epidural placement to the placebo group (n=100), group with intravenous 25 mg methylprednisolone administered every 8 hours (n=50), and group with 100 mg methylprednisolone administered every 4 hours (n=49). Fever occurred in 22 (21.8%) women in the placebo group, 17 (34%) in the low dose steroid and 1 (2%) in the high dose steroid groups. The high dose steroids decreased the incidence of epidural fever by 90% ($p<0.001$). However, high dose steroids have been reported to have increased incidence of neonatal bacteraemia and we observed four (9.3%) in the high dose group, one (2.1%) in the low dose group, and none in the placebo group. Though this complication renders the high dose steroid therapy practically ineffective in the setting of labour; however, it supports the inflammatory nature of the epidural related fever.

To overcome the limitations of systemic steroids, Wang et al. (22) administered continuous dexamethasone infusion through the epidural catheter and observed a reduction in the maternal temperature increments, with lower plasma IL-6 levels. These data are suggestive of the non-infectious

Table 2. Criticisms of studies on epidural related fever

1. Selection bias- women who have longer labours or subclinical chorioamnionitis are likely to request more for epidurals.
2. Crossover after randomization and dropouts- women with more complicated and longer labours tend to leave the non-epidural group due to ineffective analgesia and switch over to the epidural group. So epidural group gets biased with more complicated labours.
3. Antipyretic effects of systemic opioids
4. Differences in the obstetric management with effective epidural analgesia-
Increased use of oxytocin.
More cervical examinations
5. Flaws in the temperature measurements- Women without labour epidurals are more likely to hyperventilate, subsequently leading to decrease in oral temperature. Measuring vaginal temperature below the level of blockade cause an increase in the temperature due to sympathectomy via epidural.

aetiology of the epidural fever, which is suppressed by the immunosuppressive, anti-inflammatory qualities of the steroids.

Research is ongoing into the nature of the inflammatory reaction that leads to epidural related maternal fever. Sterile inflammation, which is inflammation in the absence of a pathogen, seems to be the most likely cause. It is known to be initiated by alarmins, which are endogenous molecules released because of the tissue damage, broadly classified as damage associated molecular patterns (DAMPs). DAMPs are usually internally sequestered in those cells that remain unrecognized by the immune cells, but under conditions of stress or tissue injury, are released or actively secreted (23). These alarmins activate inflammasomes, which are the intracellular protein complexes that aid in the maturation of cytokines, such as IL-1 β and IL-18, and subsequent induction of other pyrogenic cytokines (24).

In conclusion, our review suggests that the intrapartum fever is linked to epidural fever. Table 1 lists the studies present in the literature which demonstrate the relation between intrapartum fever and presence of epidural catheter (2, 3, 5-7, 11, 25-36). It further supports the non-infectious aetiology of the epidural related fever; hence, potential interventions could be taken to prevent the maternal inflammation in response to epidural analgesia without compromising the maternal and foetal health, and avoid the usage of unnecessary antibiotics.

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