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Brief Academy

Comment on "A randomized trial of the effects of antibiotic prophylaxis on epidural-related fever in labor"☆

Comentario sobre "Estudio aleatorio sobre el efecto de la profilaxis antibiótica en la fiebre epidural durante el trabajo de parto"

*Eduardo Kattan, Hector J. Lacassie**

Anesthesiology Division, Faculty of Medicine, Pontificia Universidad Católica de Chile, Chile

Introduction

This work presents a critical analysis of the article by Sharma et al.[1]

Neuraxial analgesia is the method of choice for pain management during labor.[2] Some recent reports have suggested a link between epidural analgesia (EA) and the development of maternal fever.[3] Possible etiologies include: increased metabolic expenditure, decreased heat loss due to lack of hyperventilation as a result of pain relief, thermoregulatory changes induced by epidural analgesia, direct effects of local anesthetics on the central nervous system, paralysis of the sudoriferous glands which reduce heat loss, non-infectious inflammatory processes and intrapartum infection, among others.[1]

The consequences of maternal fever during labor include an increase in neonatal evaluations for sepsis, use of maternal and neonatal antibiotics and prolonged hospital stays.[4] Microorganisms that are usually isolated in an infectious process such as chorioamnionitis include aerobic and anaerobic agents.[5]

Objective of the study

To evaluate the relationship between EA used in labor, the presence of intrapartum fever and the possible role of an infectious component.

Study design

A prospective randomized, unicentric and double-blind clinical study was designed. Previous to authorization from the Ethics Committee, 400 late-term pregnant women were recruited who were classified as ASA I-II with the fetus in cephalic presentation, in the first stage of spontaneous labor and who requested EA. Exclusion criteria are not described.

Patients were randomly distributed into two groups. One group received 2 g of cefoxitin intravenously, the other saline solution, repeating the dosage every 6 h. The epidural injection was then administered. 0.25% of bupivacaine was administered in successive 3 ml doses and a continuous EA was maintained to obtain a T10 sensitivity level.

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* *Corresponding author at:* Dpto. Anestesiología, Hospital Clínico UC, Marcoleta 367, 3er piso, Santiago, Chile.
E-mail address: lacassie@med.puc.cl (H.J. Lacassie).

Obstetrical management included the artificial rupture of membranes, oxytocic acceleration and pelvic examination every 2 h. Temperature was measured with a tympanic thermometer. If the patients presented with fever, ampicillin and gentamicin were administered in doses to treat chorioamnionitis until the fever was absent for 24 h. In the neonates of mothers with fever or when sepsis was suspected (at the discretion of the neonatologist), a sepsis examination was conducted and antibiotics were administered for 48 h.

The placentas were evaluated by a pathologist blinded to the randomized study. The presence of neutrophilic infiltration and chorioamnionitis were evaluated along with the severity and presence of funisitis (inflammation and neutrophilic infiltration of the umbilical cord).

The primary outcome was maternal fever (>38 °C tympanic temperature). The secondary outcomes were characteristics of labor, placental histopathology and neonatal results. Standardized statistical testing was conducted and the randomization sequence was kept hidden. The study was conducted with no intention to treat and was financed by departmental funding.

Results

The groups were similar in their initial variables, though there was a significantly higher representation of the Afro-American ethnicity in the placebo group. All 400 patients completed the study, but only 305 placentas (75.5%) were analyzed pathologically. There was no difference in the incidence of fever among the groups (38% and 40% (p = not significant (ns))). The number of pelvic examinations (a risk factor for chorioamnionitis) was similar, and 15% required a cesarean section. The duration times were similar for the first and second stages of labor, time from analgesia until delivery, rupture of membranes, and the number of patients with labor >10 h (p = ns).

In the histopathology, the use of cefoxitin did not have an effect on the incidence of neutrophilic infiltration (45% vs 48%, p = ns). Upon subdividing the patients in fever vs. no fever groups, the first group presented with increased placental neutrophilic infiltration (46% vs. 23%, $p < 0.001$Q), chorioamnionitis and funisitis.

In neonates there was no difference in weight, temperature, Apgar score, umbilical arterial gases, nor admissions to the intensive care unit (ICU). The analysis of the subgroup of patients with fever vs those without fever, the former presented with significantly more neonates with an Apgar score ≤ 7 after 1 min (14% versus 8%, $p = 0.013$), a difference which was lost after 5 min. There was no difference in umbilical cord blood gases nor in admission to the ICU.

Reviewers' commentary

This study presents a low risk of bias since it was prospective, unicentric and randomized with a hidden randomization sequence for patients and physicians, including blind outcome assessment. It should be highlighted that exclusion criteria are not mentioned and an explanation is provided for why 98 placentas were not available, which could have changed the results since 25% of samples were not included.

Approximately 40% of the pregnant women who requested EA presented with fever, a figure that did not vary with the use of antibiotics. The histopathological and neonatal results were not affected either. In other words, the fever is unlikely to be caused by infection. However, by subdividing the groups according to the presence of infection, the fever group had a higher level of neutrophilic infiltration, an increase in histological chorioamnionitis and a higher incidence of Apgar under 7 in the first minute, which is to be expected in patients with infection. This analysis of the subgroup does not answer the original question of the study, but is rather a clinical finding that must be reported.

There are some limitations. Firstly, with the choice of antibiotic, cefoxitin is a second-generation cephalosporin with anti-Gram-positive, Gram-negative and anaerobic bacteriostatic activity and is not active against *Chlamydia trachomatis*,[6] which could explain the lack of response to treatment. Secondly, it is worth noting the high rate of maternal fever (up to 40%), even when compared to previous results of the same group.[3] This could be explained on the one hand by the tympanic method of measurement which could increase the rate of false positives, or on the other hand by non-strict diagnostic criteria. Whichever it may be, these rates are higher than usual in our practice, which raises the possibility of the incidences reported being due to the Hawthorne effect (a psychological factor involved in human research in which subjects of the study modify their behavior or modify the variable that is measured because they know they are part of a study, rather than being secondary to the manipulation of the studied variable),[7] however, it could really be of the reported magnitude. Given this, it would have been interesting to use other study methods to conclude more robust results. For example, the microbacterial culture of placenta samples or the determination of serum inflammatory markers such as interleukins[8] could be used to evaluate changes in connection with the administration of prophylactic antibiotics.

It seems necessary to explore other physiopathological alternatives that explain the cause of fever and then propose the appropriate treatment options, such as the potential protective effect of magnesium sulfate for fever during labor,[8] or the use of epidural dexamethasone associated with analgesia in labor.[9] However, further studies of high methodological quality are needed before recommending their routine use.

In conclusion, in first-time pregnant women in late-term spontaneous labor, fever associated with EA presents an inflammatory component (proven by the presence of placental inflammation), which was not reduced with the administration of prophylactic antibiotics, which makes the infectious etiology unlikely.

Conflict of interest

The authors declare no conflict of interest.

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