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Effects of epidural and systemic maternal analgesia in term infants: the NoPiL study

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1. ABSTRACT

The aim of the No Pain in Labour (NoPiL) study was evaluate the stress and clinical outcome of infants vaginally born without maternal analgesia and after maternal epidural or systemic analgesia. We studied 120 healthy term infants, 41 in the no analgesia group, 38 in the epidural analgesia group, and 41 in the systemic analgesia group. Cortisol, ß-endorphin, oxidative stress markers [ie: total hydroperoxide (TH) and advanced oxidation protein products (AOPP)], interleukin-1β (IL-1β), and interleukin-8 (IL-8) cytokines were measured in arterial cord blood samples. Infants in the 3 groups had similar Apgar score, cord blood pH and occurrence of hypoglycaemia, hyperbilirubinemia, and respiratory depression. Cortisol and endorphin plasma levels did not differ in the groups, nor did TH and AOPP values. IL-1β and IL-8 cytokine were higher in infants born after maternal epidural analgesia than in other groups. Short-term outcome and stress were similar in infants vaginally born without maternal analgesia and after epidural and systemic analgesia. The possible implications of the highest interleukin levels in the epidural analgesia group deserve further study.

2. INTRODUCTION

Obstetric analgesia is a widely diffused procedure although there is a paucity of data regarding the potential side-effect on term infants due to maternal drugs administration during delivery (1). In this regard, newborns' outcomes have been extensively investigated through several methods, such as the Apgar score, blood gas analysis, and tests evaluating neonatal behaviour (2). Results on potential side-effect on newborns whose mothers were subjected to obstetric analgesia are to date controversial and matter of debate.

Labor pain can cause a generalized neuro-endocrine stress response that has widespread physiological effects on the parturient, on fetus and finally on newborn (2-4). Of note, it is also known that labor and delivery mode may affect newborn oxidative balance (5) and cytokines plasma levels (6,7). These facts could be of relevance since free radicals are known to be involved in the pathophisiological cascade of events leading to damage neonatal organs, especially the brain (8). Furthermore cytokine profiles at birth might influence the neonatal immune response occurring in the transition from an almost

sterile to a normal environment (6,7) and the development of allergic disorders (9).

On the other hand, side-effects of maternal pain such as hyperventilation, secretion of stress related hormones (i.e. catecholamines, cortisol), and increased oxygen consumption can be prevented and/or limited by local (epidural anesthesia) or systemic analgesia. Data on different analgesia methods relationship with neonatal outcomes such as Apgar scores, umbilical cord gas analyses, respiratory depression requiring naloxone use following epidural (10-12) or systemic maternal treatment support the notion on their safety (13-15). Thus, systemic analgesia is currently used in clinical practice when epidural analgesia is contraindicated (16,17) or refused by the parturient.

To date, data on potential side-effects on short term outcome in term infants due to vaginal delivery and maternal analgesia, are still lacking. Therefore, the No Pain in Labour (NoPiL) study group investigated by a prospective multicenter study whether there were any differences among clinical outcomes of infants vaginally delivered with or without maternal analgesia (epidural or systemic). Infants' stress was evaluated by a panel of biochemical markers, such as cortisol, ß-endorphin, oxidative stress markers, interleukin-1β (IL-1β), and interleukin-8 (IL-8) cytokines in arterial cord blood samples.

3. MATERIALS AND METHODS

3.1. Approval

The NoPiL-study was approved by the local ethic committees and the parents of infants admitted into the study gave informed and signed consent.

3.2. Patients

The subject of the present study were 120 term infants of whom 41 were enrolled in the no analgesia group, 38 in the local analgesia group, and 41 in the systemic analgesia group. Maternal age (32.9 $\pm$ 5.7 vs. 32.9 $\pm$ 4.3 vs. 33.6 $\pm$ 4.9 years) and parity (1.0 $\pm$ 1.0 vs. 0.6 $\pm$ 1.0 vs. 0.8 $\pm$ 0.8) were similar in the 3 groups.

From May 2008 to April 2009 healthy singleton infants (18) with gestational age $\geq$37 weeks and birth-weight appropriate for gestational age, born after uncomplicated pregnancy by vaginal delivery without analgesia or after maternal epidural or systemic analgesia. were enrolled. Exclusion criteria were the lack of parental consent, the need of operative vaginal delivery, and incomplete data recording.

Women received local or systemic analgesia, regardless of parity and whether labor was spontaneous or induced, only after their specific request and after obtaining their written informed consent at 32 weeks of gestation. All women were in active labor (cervical dilation of 3–6 cm) with regular contractions every 3–4 min lasting for 1 min.

Epidural analgesia was performed with the following procedures: under asepsis the skin was infiltrated with 2 mL 2% lidocaine (Lidocaina® Angelini, Rome, Italy); the epidural space was identified at L2-L3 interspace using a midline approach and loss of resistance technique, with a 18G Tuohy needle. An epidural catheter (Perifix®, B Braun, Rome, Italy) was advanced cephalad 3-4 cm into the epidural space. After negative aspiration, analgesic boluses such as 15-20 mL of 0.0625% bupivacaine (Bupivacaina®, Angelini, Rome, Italy) or 10 ml of 0.125% bupivacaine, in relationship to the labor condition, plus fentanyl (Fentanest®, Pfizer, Milan, Italy) 50 μg until a maximum total dose of 100 μg. Boluses were administered to maintain a visual analogue pain scale (VAPS) $\leq$4, until the beginning of the delivery phase.

Systemic analgesia was obtained with intravenous continuous infusion of remifentanil (Ultiva®, GlaxoSmithKline, Verona, Italy) as previously reported (19). Briefly, remifentanil solution (25 μg·ml– 1) was given at the dose of 0.0125-0.15 μg·Kg–1·min–1 based on vital maternal and fetal signs (systemic arterial pressure, heart rate, respiratory rate, oxygen saturation, cardiotocography) and to maintain a visual analog pain scale (VAPS) $\leq$4.

Maternal age and parity, gestational age, birth weight, sex, type of delivery, umbilical cord artery pH, Apgar score at 1 and 5 minutes, respiratory depression necessitating naloxone use, and possible complications, such as jaundice or hypoglycemia occurring before discharge from the nursery were recorded for each newborn. Jaundice was recorded when the neonatologist on charge judged it necessary to measure bilirubin; hypoglycemia was recorded when glycemia was <45 mg/dL (20).

Blood samples of 5 mL were obtained at birth from the cord artery of all enrolled infants to study neonatal pH and perform the following assays.

3.3. Cortisol and endorphin assays

Plasma cortisol was measured by solid-phase chemiluminescent immunoassay (ADVIA Centaur® XP Immunoassay System, Bayer Health Care Diagnostics, Milan, Italy) with a lower limit of sensitivity of 1μg/dL. ß-endorphin was assayed in neonatal plasma by an enzyme immuno-assay (ß-Endorphin, EIA Kit, Burlingame, CA, USA) with a lower limit of sensitivity at 0.23 ng/ml.

3.4. Oxidative stress assay

Total hydroperoxide (TH) concentration is a measure of overall oxidative stress, given that it is the intermediate oxidative product of lipids, peptides, and amino acids. Its production was measured using a spectrophotometric method (d-ROMs Kit®, Diacron srl, Grosseto, Italy) as described by Buonocore *and coll.* (21). This method makes it possible to estimate the TH. The results were expressed in conventional units, (Carr units: the value of 1 Carr unit is equal to a concentration of 0.08 mg/dL of hydrogen peroxide).

Simultaneous determination of the advanced oxidation protein products (AOPP) provides information regarding another aspect of protein involvement in free

Table 1. Clinical characteristics and main complications in infants born without maternal analgesia, those born after maternal epidural analgesia and after maternal systemic analgesia

	No Analgesia **(n=41)**	**Epidural Analgesia (n=38)**	**Systemic Analgesia (n=41)**
Gestational age (weeks)	40 (38-41)	40 (37-41)	39 (37-41)
Birth weight (grams)	3449±412	3424±386	3310±542
Male	18 (44)	23 (60)	22 (54)
Apgar Score :			
1st minute	9 (8-10)	9 (8-10)	9 (8-10)
5th minute	10 (9-10)	10 (9-10)	9 (8-10)
Cord blood pH	7.30±0.09	7.31±0.05	7.30±0.07
Respiratory depression	0	0	0
Jaundice	8 (20)	11 (29)	13 (32)
Hypoglycemia	4 (10)	2 (5)	3 (7)

Median (range) or mean (± SD) values

Table 2. Cortisol, ß-endorphin, TH, AOPP, IL-1β, and IL-8 levels in infants born without maternal analgesia, those born after maternal epidural analgesia and after maternal systemic analgesia

	No Analgesia (n=41)	**Epidural Analgesia (n=38)**	**Systemic Analgesia (n=41)**
Cortisol (ng/ml)	649±256	646±249	698±304
ß-endorphin (pg/ml)	0.89±0.25	0.92±0.57	0.92±0.36
TH (Carr unit)	164±55	173±90	186±61
AOPP (μmol/L)	16.6±18.1	19.4±22.0	19.7±17.4
IL-1β (pg/ml)	0.5+1.6	1.5+0.7*	0.6+2.4
IL-8 (pg/ml)	4.5±4.5	20.8±20.7**	4.2±0.10

Mean (± SD) values.*p<0.0001 vs. local analgesia and p=0.029 vs. systemic analgesia; **p<0.0001 vs. no analgesia and systemic analgesia.

radical reactions, namely oxidized proteins that have lost their oxidant properties (22). We measured AOPP by the method of Witko-Sarsat *and coll.* (22) using a spectrophotometric method. AOPP concentrations were expressed as μmol/L chloramine-T equivalents.

3.5. Cytokine assays

To measure IL-8 we used a commercial immunoassay kit (IL-8 Human Elisa Kit, Invitrogen Corporation, Camarillo, CA, USA) following the prescribed procedures. The minimum detectable dose for IL-8 is <0.1 pg/ml. To measure IL-1β we used another commercial immunoassay kit (IL-1β Human Elisa Kit, Invitrogen Corporation, Camarillo, CA, USA) which follows the same protocol as IL-8. The minimum detectable dose for IL-1β is 0.1 pg/ml. All samples were analyzed in duplicate by personnel unaware of the patients' assigned group.

We decided to measure these cytokines because: 1) IL-1β is an important mediator in the early inflammatory response by recruiting and activating inflammatory cells and causes the release of other cytokines (including itself); 2) IL-8 is probably the most important chemotactic factor (23) in the human immune system.

3.6. Data analysis and statistical comparisons

In planning our study, we calculated that a sample size of at least 37 infants for each group (infants born without maternal analgesia, infants born after maternal local analgesia, infants born after maternal systemic analgesia) was required to detect a statistically significant change of 20% in cortisol plasma value with 80% power at 0.05 level.

The clinical characteristics of the two groups were described by median (and ranges) or mean (± SDs) values, while laboratory results were reported as mean values (±SDs). Statistical analysis was performed using Student's "t" test for parametric continuous variables (since studied variables showed a normal distribution) and Fisher's exact test for categorical variables. A $p<0.05$ was considered statistically significant. Data analysis was performed by D.C..

4. RESULTS

Neonatal characteristics are given in Table 1. Infants in the 3 groups had similar gestational age, birth weight and sex distribution, as well as Apgar score and cord blood pH. Moreover, the occurrence of respiratory depression, hypoglycemia and hyperbilirubinemia did not vary between the groups.

Cortisol and ß-endorphin plasma levels did not differ between the groups, nor did TH and AOPP values. On the other hand, IL-1β and IL-8 cytokine blood concentrations were similar in infants born without maternal analgesia or after maternal systemic analgesia, but lower than in infants born after maternal epidural analgesia (Table 2). In addition, IL-1β was not detectable in 61% (25/41) of infants born without maternal analgesia, in 27% (11/41) of infants born after epidural analgesia, and in 66% (25/38) of infants born after maternal systemic analgesia; IL-8 was not detectable in 8% (3/41) of infants born without maternal analgesia, in 12% (5/41) of infants born after epidural analgesia, and in 13% (5/38) of infants born after maternal systemic analgesia.

5. DISCUSSION

In our study we evaluated the effects of local and systemic maternal analgesia on term infants' stress at birth and outcome at nursery discharge. We did not find any

clinical differences between infants born without or after maternal labor analgesia. In addition, we observed that the oxidative stress was similar in the studied groups, while IL-1β and IL-8 concentrations were higher in infants in the epidural analgesia group than in other groups.

Our data confirm that the outcome of infants born after epidural maternal analgesia is similar to that of infants born with no maternal pain relief, particularly in relationship to the post-delivery adaptation (24). In fact a recent meta-analysis detailed that these infants have the same risk (relative risk 1.56, C.l. 955 0.54-4.52) of having an Apgar score less than 7 at 5 minutes of life (25). In addition we observed that the most common neonatal complication occurring in healthy infants in the nursery, namely jaundice and hypoglycemia, have the same rate in infants born without maternal analgesia or after local maternal analgesia.

We also found that the neonatal outcome and the complication rate of infants born after systemic analgesia are similar to those of infants born with no maternal pain relief or after epidural maternal analgesia. This depended certainly on the favorable pharmacological characteristics of remifentanil which is considered an ideal drug in obstetrics because it has the most rapid onset of peak effect, shortest half-life, and greatest clearance of the commonly used opioids (26). Its concentration decreases by 50% within 3 to 5 minutes of stopping drug administration, regardless of the duration of the infusion (26). The drug rapidly crosses the placenta and is quickly metabolized by fetal esterases (27). Therefore, as expected, our data are in agreement with previous studies which did not report lower Apgar scores, unacceptable umbilical cord pH, or neonatal respiratory depression necessitating naloxone use after maternal remifentanil treatment (14,15,19,27,28).

It is interesting that our study is the first to show the occurrence of neonatal hyperbilirubinemia, and hypoglycaemia in term infants born after maternal labor analgesia, which were evaluated because they are practical markers of infant extra-uterine well-adaptation. Therefore, we cannot compare these findings with others studies and they deserve further confirmation.

In agreement with previous studies (29,30) we found that the cortisol blood level was similar in infants born without maternal analgesia and after epidural analgesia studied groups, as well as the ß-endorphin blood level. This latter result disagrees with findings of Vogl *and coll.* who found that infants born after epidural analgesia have a higher ß-endorphin level than those born with no maternal pain relief (30). This discrepancy might be due to different inclusion criteria and study design, since Vogl's study included only nulliparous women at nearly the same length of gestation, and/or epidural analgesia is not detailed by the authors (30). It is noteworthy that there are no other data in the literature on cortisol and ß-endorphin levels in infants born following systemic maternal analgesia.

The issue of fetal/neonatal oxidative stress has not been thoroughly investigated and is still subject to debate. Although a number of studies have compared the oxidative stress of infants born by vaginal delivery or cesarean section with contradictory and inconclusive results (31-33), we could not find any study comparing the oxidative stress of infants born by vaginal delivery with or without maternal analgesia. However, our study demonstrated that maternal analgesia does not affect the oxidative stress of infants born by vaginal delivery. To explain this finding we considered that oxidative stress takes place as a consequence of inadequate inactivation of accumulating oxygen free radicals by the antioxidant defense system (34). The effects of this imbalance are difficult to predict especially in the second half of pregnancy. The antioxidant capacity of rat embryo was reported to gradually increase with gestational age (35) and this increase might be the basis for better fetal coping with oxidative stress in the second half of pregnancy. In addition, term labor was found to induce an up-regulation of fetal antioxidant reserve that was thought to protect against the increased production of reactive oxygen species which occurs during labor secondary to the repeated ischemic reperfusion periods associated with uterine contractions and against the relative hyperoxia that is experienced by the newborn infant at birth (36). Thus, it is likely that maternal analgesia did not affect the oxidative stress of our patients because it cannot influence the aforesaid events.

We found that infants born after maternal epidural analgesia show higher levels of IL-1β and IL-8 than infants born without maternal analgesia or after systemic analgesia. The role of labor as an important trigger of neonatal pro-inflammatory cytokine production has been previously demonstrated (6), but the effect of different modes of maternal analgesia on their production has never been investigated. Previous studies demonstrated that IL-1β is higher in infants born by vaginal delivery than in infants born by cesarean section (6,37) while IL-8 is similar (37). In addition, Bessler *and coll.* demonstrated that the capacity of peripheral blood mononuclear cells to produce IL-1β is higher in newborns of mothers treated with epidural analgesia than in newborns of untreated mothers or those treated with systemic analgesia (38). To explain our results, we considered that some factors--including an increased risk of neurologic injury from needle- or catheter-induced mechanical trauma, local anesthetic toxicity, and neural ischemia secondary to local anesthetic additives (39) might help to induce maternal pro-inflammatory events which in turn also increase IL-1β and IL-8 production in infants born after epidural analgesia. Moreover, this hypothesis could explain the still unknown mechanism by which epidural labor analgesia induces an increase in maternal and neonatal temperature (40), since cytokine level increase is associated with fever development (41). However, to date the physiological role of pro-inflammatory cytokines in the neonatal period has not been clarified and the possible long-term effect of their changes, particularly on the development of allergic disorders, remains to be elucidated.

6. CONCLUSIONS

In summary, we studied the clinical outcome and stress of infants vaginally born without maternal analgesia or after maternal epidural or systemic analgesia. We found

that the short-term outcome and the occurrence of the main neonatal complications did not differ between the groups. Moreover, the stress of the newborns, measured in terms of concentration of cortisol, ß-endorphin, and oxidation markers in arterial cord blood samples, were similar among the three groups. We also found that IL-1β and IL-8 levels were higher in infants born after maternal epidural analgesia than in the other two groups but the possible implications of this finding deserve further study.

7. ACKNOWLEDGMENT

The authors declare that they have no conflicts of interest.

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