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ORIGINAL ARTICLE

Epidural analgesia during labour and stress markers in the newborn

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ABSTRACT

Labour and modes of delivery can influence the plasma levels of stress hormones and cytokines involved in pathophysiologic cascade, potentially damaging brain development of the newborn. This prospective observational, single-centre, case-control, non-profit study aimed to detect potential differences in foetal well-being such as stress neuroendocrine responses. Quantitative determinations of the stress markers interleukin (IL)-1β, IL-8, and β-endorphin were compared between the control group and the epidural analgesia group. We found higher IL1-β levels but lower IL-8 and β-endorphin levels in the epidural analgesia group than in the control group. No significant inter-group differences were observed for any parameters. Our findings demonstrate that epidural analgesia for pain relief during labour does not result in significant differences in blood stress response markers.

IMPACT STATEMENT

- **What is already known on this subject?** We already know that plasma levels of stress hormones and cytokines are influenced by labour and delivery modes. This has a deep impact on the newborn in terms of brain damage, immune system deficits, and altered hypothalamic-pituitary axis responses. We also know that epidural analgesia is a widespread practice that offers pain relief to the woman in labour, but there are few studies on the potentially negative effects of epidural labour analgesia on the unborn child.
- **What do the results of this study add?** This study found no significative differences in blood stress response markers between the epidural analgesia group and the control group. Under this study circumstances we found out that epidural analgesia does not significantly influence the newborn's well-being during labour and delivery.
- **What are the implications of these findings for clinical practice and/or further research?** These findings must be confirmed by further studies to verify whether epidural analgesia is safe for the newborn's development.

KEYWORDS

Epidural; analgesia; labour; stress response; blood marker; development; newborn

Introduction

Labour pain causes a stress reaction characterised by a general neuroendocrine response that has many consequences on the labouring woman and the newborn (Neumark et al. 1985; Littleford 2004). Labour and delivery mode can influence plasma levels of stress hormones (Lurie et al. 2007) and cytokines (Buonocore et al. 1995; Ly et al. 2006). These factors are involved in a cascade of pathophysiologic events that can damage the development of several organs – the brain, in particular – in the newborn (Buonocore et al. 2003). Furthermore, cytokine levels at birth may also affect the newborn's immune response and cause the development of allergies (Sugiyama et al. 2007). The exposure to high stress levels during labour, at birth, or during early childhood, may alter the hypothalamic-pituitary axis response, affecting the newborn's future development (Rothenberg et al. 1996).

Studies on rats demonstrated that alterations of plasma steroid concentrations in the first weeks of life significantly influence neurogenesis and neuronal death (Bohn and Lauder 1980).

Labour analgesia is a widespread practice consisting of the administration of pain relievers to the labouring woman. The epidural route of administration of labour analgesia, which has greater proven efficacy than inhaled analgesia, is becoming increasingly more common and enables the systemic intravenous administration of opioids and non-pharmacological analgesics (Jones et al. 2012). However, few studies to date have examined the potentially negative effects of epidural labour analgesia on the unborn child (Westgren et al. 1986; Mattingly et al. 2003; Vogl et al. 2006; Dani et al. 2010; Wang et al. 2018).

The main endpoint of this study is to detect potential differences in foetal well-being in terms of neuroendocrine

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In Italy, observational studies do not require any registration but the ethical committee one.

responses to stress between children who are born from natural birth with versus without labour epidural analgesia.

Methods

Study design

In this prospective observational, single-centre, case-control, nom-profit study, patients were enrolled between October 2015 and March 2016 at the Obstetrics & Gynaecology Department of the University Hospital 'G. Rodolico' in Catania, Italy. The study began after obtaining approval from the hospital ethical committee 'Catania 1', registration code 123/2015/PO (September 21 2015). All women provided written informed consent prior to enrolling.

Women who gave birth without labour analgesia were identified as potentially recruitable patients after their admission to the Department of Obstetrics & Gynaecology. Those who decided in favour of labour analgesia were enrolled during the preanesthetic evaluation.

After every birth, our delivery room staff routinely obtains a cord blood sample for blood gas analysis (BGA) and Coombs test. For the enrolled patients, we took an additional 2.5 mL of cord blood to determine cytokine levels. The blood samples were collected in test tubes with added ethylenediaminetetraacetic acid, centrifuged, and stored at −20 °C.

After all the samples were collected, we performed the quantitative determinations of the stress markers: interleukin (IL)-1β, IL-8, and β-endorphin. We used a Human IL-1β kit and a Human IL-8 kit (DIACLONE SAS, Basançon, France) and enzyme-linked immunosorbent assays to determine the IL-1β and IL-8 values, respectively. We employed a free extraction kit (Peninsula Laboratories, San Carlos, CA, USA) with the enzyme immunoassay method in accordance with the V protocol provided by the kit manufacturer to determinate the β-endorphin values. We employed the plaster readers PANTEC s.r.l.

Participants

The study enrolled 44 nulliparous Caucasian woman aged 18–40 years at term (37th–41st week of pregnancy) with a single foetus and uncomplicated pregnancy course undergoing a vaginal delivery.

We excluded patients who were multiparous, had an induced labour, or had diseases such as hypertension, gestational diabetes, or preeclampsia. We also excluded patients who had dystocial or surgical deliveries, caesarean sections, or a foetus with a prenatal diagnosis. Women who refused to give consent to participate in the study were also excluded.

Eligible patients who gave consent to receive epidural analgesia were allocated to the epidural analgesia group, while eligible women who did not choose epidural analgesia were assigned to the control group.

Statistical analysis

We used the following input parameters to calculate the needed size of our sample: $\alpha = 0.05$; power $(1-\beta) = 0.80$; and a medium effect size = 0.89. The analysis provided a required experimental population of 42 participants.

Qualitative data are expressed as absolute frequency and percentage. Normally distributed quantitative data are shown as man and standard deviation. Non-normally distributed quantitative data are shown as median and interquartile range (IQR).

The evaluation of the titre of sodium hydroxide solution was performed using the Kolmogorov-Smirnov test. Student's *t*-test was used to examine paired data, while the Mann–Whitney *U*-test was used to examine normally and non-normally distributed data. The Chi-squared test with Yates' correction or Fisher's exact test was used to compare qualitative data (Table 1).

Table 1. Characteristics of the patients enrolled.

Variable	Labour analgesia group	Control group
Mother's age (years old)	30	28
PGA (weeks)	39	39
APGAR 1°	9/10	9/10
Weight (g)	3300	3300
Sex (F)	71%	66%

Table 2. Levels of IL-1β, IL-8, β-endorphins in the two groups of patients.

	IL-1β		IL-8		β-endorphins	
	LA	NLA	LA	NLA	LA	NLA
Mean (pg/ml)	24.99	14.48	16.80	24.45	0.09	0.11
Standard Deviation	25.89	10.07	16.46	20.40	0.07	0.16

LA: labour analgesia group; NLA: control group.

Results

During the recruitment period, 44 patients were enrolled (23 in the control group, 21 in the epidural analgesia group). The two groups were homogeneous in terms of mother's age, post-gestational age, APGAR scores, and foetal weight and sex distribution (Table 2).

The statistical analysis demonstrated higher mean IL-1β levels but lower IL-8 and β-endorphin levels in the epidural analgesia group. However, no significant inter-group differences were noted (Table 3).

Discussion

The two groups were homogeneous according to the considered parameters. However, other factors were not considered in the study, including neuroendocrine response (Alehagen et al. 2005) of the mother related to her mental status during labour, women's BMI, and newborn weight by post-gestational age were heterogenous. Moreover, decisions made by other professionals during labour and delivery (e.g. administration of oxytocin in the final stage or use of obstetrics manoeuvres) could have influenced the final results.

The clinical outcome, defined as adaptation to extrauterine life, was similar in the two groups: only one newborn required neonatal care unit admission.

The measured markers were of great clinical importance. Indeed, IL-1β, a marker of the early inflammatory response;

Table 3. Statistical analysis.

IL-1β epidural analgesia group		
Mean value	24.99524	5.650298
95% confidence interval	13.20892–36.78155	
Standard deviation	25.892918	
Minimum	0.000	
Maximum	81.100	
Range	81.100	
Interquartile range	27.525	
Asymmetry	1.165	0.501
Kurtosis	0.145	0.972
IL-1β control group		
Mean value	14.48161	2.100012
95% confidence interval	10.12645–18.83677	
Standard deviation	10.071304	
Minimum	0.137	
Maximum	38.900	
Range	38.763	
Interquartile range	13.370	
Asymmetry	0.947	0.481
Kurtosis	0.194	0.935
IL-8 epidural analgesia group		
Mean value	16.800	3.5923
95% confidence interval	9.307–24.293	
Standard deviation	16.4620	
Minimum	0.000	
Maximum	35.200	
Range	35.200	
Interquartile range	32.000	
Asymmetry	−0.084	0.501
Kurtosis	−2.183	0.972
IL-8 control group		
Mean value	24.452	4.2539
95% confidence interval	15.630–33.274	
Standard deviation	20.4008	
Minimum	0.000	
Maximum	71.000	
Range	71.000	
Interquartile range	33.0	
Asymmetry	0.176	0.481
Kurtosis	−0.437	0.935

IL-8, the fundamental chemotactic factor; and β-endorphin, an endogenous neurotransmitter, are all involved in the newborn's stress response and development (Bohn and Lauder 1980).

Our results demonstrated similar blood levels of β-endorphin in the two groups as reported by the NoPil study (Dani et al. 2010). In contrast, Vogl et al. (2006) reported higher β-endorphin levels in the epidural analgesia group.

The NoPil study, in contrast to our results, found higher IL-1β and IL-8 levels in the epidural group. A possible explanation to this difference could be the different inclusion criteria of the NoPil study, which recruited multiparous women, had a different study plan, and used different techniques to analyse the samples.

Despite its small sample size, this study is an important addition to the knowledge on the topic, as there is a lack of scientific literature in this field. The markers taken under consideration – IL-1β and IL 8, pro-inflammatory cytokines, and β-endorphin, an endogenous neurotransmitter – are markers of stress in the newborn and could be involved in its development. Accordingly, an evaluation of the different humoral response by delivery mode becomes important to the newborn's well-being and future development. However, further investigations are needed. Our findings demonstrate that epidural analgesia for pain relief during labour does not demonstrate significant differences in blood stress response markers compared to the control group.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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