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Labor epidural analgesia onset time and subsequent analgesic requirements: a prospective observational single-center cohort study

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ABSTRACT

Background: We investigated the correlation between lumbar epidural analgesia onset time and pain intensity at 60 and 120 min after initiation.

Methods: We conducted a prospective observational study of nulliparous women receiving lumbar epidural analgesia (initial bolus 15 mL bupivacaine 0.1% with fentanyl 3.33 µg/mL), followed by patient-controlled epidural analgesia (PCEA). The measured variable was lumbar epidural analgesia onset time (time to pain numerical rating score ≤3). Secondary outcomes were pain score at 60 and 120 min and at full dilatation; and analgesic requirements through the labor.

Results: One-hundred-and-five women were eligible for analysis. There was a significant correlation between lumbar epidural analgesia onset time and pain intensity at 60 min (Spearman's $R^2=0.286$, $P=0.003$), but not at 120 min ($R^2=0.030$, $P=0.76$). Women who requested more PCEA boluses during the first 120 min had a longer lumbar epidural analgesia onset time ($R^2=0.321$, $P=0.001$) and reported higher pain scores at 60 min ($R^2=0.588$, $P<0.001$) and at 120 min ($R^2=0.539$, $P<0.001$). Women who reported higher pain scores at 60 min had more pain at 120 min ($R^2=0.47$, $P<0.001$) and higher analgesic consumption during labor ($R^2=0.403$, $P<0.001$). Women who were at a greater cervical dilatation at 60 and 120 min had higher pain scores at the same time point ($R^2=0.259$, $P=0.008$ and $R^2=0.243$, $P=0.013$ respectively).

Conclusion: There was a correlation between the onset time of lumbar epidural analgesia during labor and the pain score 60 min later but this had disappeared by 120 min.

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Keywords: Labor epidural analgesia; Epidural analgesia onset time; Pain in labor

Introduction

Lumbar epidural analgesia (LEA) for labor and delivery alleviates pain, improves co-operation with care providers and improves the labor experience.^{1–4} Moreover, LEA can moderate extreme changes in cardiac output and blood pressure and improve uterine blood flow.²

The mean LEA onset time to satisfactory analgesia after an initial bolus is approximately 15 min.^{3,4} Typically analgesia is achieved within 30 min from injection but this time may vary widely.^{6–9} Various factors affect the analgesic onset time, such as local anesthetic drug pharmacodynamic and pharmacokinetic properties,⁵

the concentration, the infused volume^{6,7} and the temperature of the anesthetic solution.⁷

After initiation, LEA is typically maintained using patient-controlled epidural analgesia (PCEA).^{8–11} Some women will experience inadequate pain relief and require additional physician-administered boluses. Factors associated with breakthrough pain include a first labor, greater fetal weight and initiation of LEA at a low cervical dilatation.⁹ The predictability of the effect of LEA during various stages of labor and delivery is clinically important.¹⁰ Insufficient analgesia may necessitate a conversion to general anesthesia if emergency cesarean delivery is needed.¹¹

In this prospective observational study, our primary aim was to investigate the correlation between LEA onset time and subsequent pain intensity during labor at 60 and 120 min, in a nulliparous population. Secondary study aims were to measure the relationship between

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the self-reported pain level at 60 and 120 min after the initial bolus and pain during the second stage. We hypothesized that a longer LEA onset time predicts higher pain intensity during the labor and delivery at specific time points, as well as higher analgesic consumption.

Methods

We performed a prospective observational non-interventional cohort study at the Lis Maternity Hospital, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. Our center has 11702 annual deliveries (4983 (43%) nulliparas, 56% using LEA and 20% having a cesarean delivery). We followed the STROBE statement for performance of the study and preparation of the manuscript. The study received ethical approval (0619-15-TLV) from the Institutional Review Board of Tel Aviv Medical Center, Tel Aviv, Israel (Chairperson Prof. Marcel Topilsky) on January 4, 2016 and written informed consent was obtained.

We approached a convenience cohort of nulliparous women who presented to the labor and delivery unit in early active labor, for potential study enrollment. The informed consent procedure was performed prior to the request for LEA. Inclusion criteria were nulliparous women of American Society of Anesthesiologists (ASA) class II, with a singleton term pregnancy at 37–42 weeks, a vertex presentation with a re-assuring fetal monitor tracing and cervical dilatation <6 cm, and who reported a numerical pain rating scale (NPRS) score >2 (NPRS 0–10) during contractions prior to LEA performance. Exclusion criteria were opioid analgesia used within 24 h of LEA initiation, pain requiring LEA during the recruitment process and an inability to report pain score during LEA initiation. Women who had consented to enrollment but had difficult epidural catheter insertion (more than three attempts), accidental dural puncture or analgesia failure (defined as no pain score reduction 30 min after initiation) were excluded from the study.

Upon request for analgesia each woman was asked to rank her pain during a contraction according to the NPRS. Prior to needle insertion, the skin was anesthetized using 5 mL lidocaine 2% and women were asked to report their pain score during the injection.¹² The LEA was achieved using a standardized technique with a 18-gauge Tuohy needle, loss-of-resistance to air¹³ (Portex® Epidural Minipack, Smiths Medical, Minneapolis, Minnesota, USA), and introduction of a closed-end multipoint 20-gauge epidural catheter at the L3-L4 or L4-L5 intervertebral space. All time intervals related to LEA drug administration and pain assessments refer to t_0 , the start of injection of the initial 5 mL bolus of bupivacaine 0.1% with fentanyl 3.33 µg/mL. This was followed two minutes later by a

further 10 mL bolus if intrathecal placement was not suspected.^{9,14} A patient-controlled epidural analgesia (PCEA) device was connected and bupivacaine 0.083% with fentanyl 1.67 µg/mL infused at 6 mL/h, with a self-administered 5 mL demand bolus at a lockout time of 10 min.

Pain intensity was assessed at the end of each contraction by asking: “Please rank the pain of this last contraction from 0 to 10”. The LEA onset time was predefined as the time interval from t_0 until a NPRS of ≤ 3 was reported.^{7–9} The number of PCEA bolus requests per hour during the first stage of labor was recorded. The bupivacaine consumption rate per hour was calculated from the total bupivacaine dose used during the first stage (including drug delivered via the PCEA basal infusion, all PCEA boluses and rescue doses delivered by the anesthesiologist), divided by the duration of the first stage of labor since LEA initiation. This outcome was not recorded for women who had a cesarean delivery.

To address potential selection bias, we approached all nulliparous women who met our inclusion criteria to recruit a convenience sample, according to the availability of an investigator. The study recruitment explanation was conducted in a consistent way after study recruiters (AN, BA) had undergone a training period. The LEA was not performed by a single anesthesiologist, however, a standard protocol was used. The investigators (AN, BA) who measured the pain scores did not perform the LEA. Only nulliparous women were recruited in order to maximize the potential duration of LEA required during the labor. Missing data were not imputed. Pain intensity was measured at three time points: 60 and 120 min after LEA initiation and during the second stage of labor (as described on a questionnaire distributed the day following the delivery). The number of PCEA bolus requests and boluses actually delivered were recorded hourly. The following data were obtained from the hospital database: the parturient’s age, gestational age, pregestational weight, current weight, height, body mass index, the neonatal estimated and actual weight, neonatal gender, cervical dilatation at LEA initiation then one and two hours later, gestational diabetes, companion presence during LEA procedure, labor induction, rupture of membranes at LEA initiation and cesarean or instrumental delivery.

The primary study outcomes were the LEA onset time and the pain intensity at 60 and 120 min after LEA. The secondary outcomes were the number of PCEA bolus requests and average bupivacaine consumption rate per hour during the first stage of labor; pain intensity during the second stage of labor; and self-reported patient satisfaction with their LEA experience (measured on the first postpartum day using a NPRS).

Statistical analysis

Our sample size calculation that 104 women should be recruited (allowing for 5% dropout rate) was based on the expectation that 50% of the women would have NPRS ≤ 3 by 15 min after LEA initiation; and that there would be a 20% difference in the number of women at 60 min who reported NPRS ≤ 3 based on whether the NPRS ≤ 3 was reached less than or greater than 15 min (power 0.8, significance level 0.05).¹⁵

Data were entered into Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA) and analyzed using IBM SPSS version 21.0.0 for Windows (IBM Corp. Armonk, NY, USA). Continuous parametric data are presented with their mean (standard deviation (SD)). Non-normally distributed data, after assessment for normality using a Q-Q plot, are presented by median (interquartile range (IQR)). Categorical data are presented as count (%). Demographic data and baseline clinical characteristics were tabulated and are presented as mean (SD) median (IQR) or number (%) as appropriate. Spearman's Rank correlation was calculated to assess the correlation between continuous variables such as cervical dilatation, LEA onset time and the outcome variables of pain intensity, number of PCEA bolus requests, bupivacaine consumption per hour and self-reported patient satisfaction. The R-square and significance level are shown. All statistical tests were two-sided and a *P*-value of ≤ 0.05 was considered statistically significant.

Results

Among 2447 nulliparous women who presented to our labor and delivery during the study period (January 2016–July 2016) 130 eligible women were approached and 119 recruited. No data were collected in real time for 13 of the 119 women and one woman did not have analgesia 30 min after LEA initiation. Thus, 105 women were included in the final analysis (Fig. 1). The maternal and obstetric characteristics are presented in Table 1.

The pain score 60 min after LEA initiation had a median of 1 (IQR 0–2). It had a weak but significant negative correlation with LEA onset time ($R^2=0.286$, $P=0.003$, Fig. 2a). At 120 min the score was 1 (IQR 0–3) and it was no longer correlated to LEA onset time ($R^2=0.030$, $P=0.76$). There was a positive correlation between analgesia onset time and the number of PCEA bolus requests during the first 120 min of LEA, but no correlation with either pain during the second stage of labor or satisfaction. A positive trend was seen between the LEA onset time and cervical dilatation one hour after LEA initiation and this was significant after two hours (see Table 2).

Pain intensity 60 min after LEA initiation correlated with that at 120 min (Fig. 2b) and both significantly

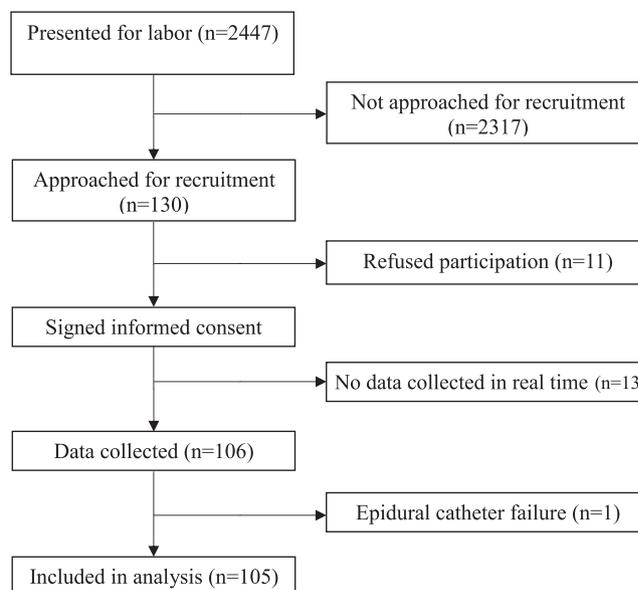


Fig. 1 Study cohort trial recruitment profile

Table 1 Characteristics of the nulliparous cohort

Age (y)	30.9 ± 4.1
Gestational age (weeks)	39.9 ± 1.2
Pre-gestational weight (kg)	60.1 ± 9.2
Current weight (kg)	73.7 ± 10.7
Height (cm)	164.6 ± 6.3
Body mass index (kg/m ²)	22.2 ± 3.2
Gestational diabetes	8 (7.6%)
Estimated fetal weight (kg)	3.30 ± 0.36
Neonatal weight (kg)	3.27 ± 0.40
Neonatal gender – male	64 (61%)
Labor induction	25 (23.8%)
Cesarean delivery	10 (9.5%)
Instrumental delivery	25 (23.8%)
Non-instrumental vaginal delivery	70 (66.7%)
Rupture of membranes at LEA initiation	52 (49.5%)
Cervical dilatation at LEA initiation	3.7 ± 1.2
Companion presence during LEA procedure	36 (34.3%)
Time to analgesia (min)	14 (10–19)
Motor block (Bromage score <4) during the first 120 min after LEA initiation	7 (6.7%)

LEA: labor epidural analgesia. Time to analgesia is presented by median (interquartile range). Other quantitative parameters presented by median ± standard deviation.

correlated with bupivacaine consumption rate (Fig. 2c and d). Cervical dilatation at 60 min and 120 min correlated to corresponding pain scores at those time points. The total bupivacaine dose and the rate of bupivacaine consumption were calculated for women who had achieved full cervical dilatation. These data were available for 80 (77%) women because some had a cesarean delivery prior to full dilatation and some had loss of data due to an inadvertent PCEA device reset after delivery. In this cohort mean bupivacaine consumption rate was 10.9 ± 4.4 mg/h.

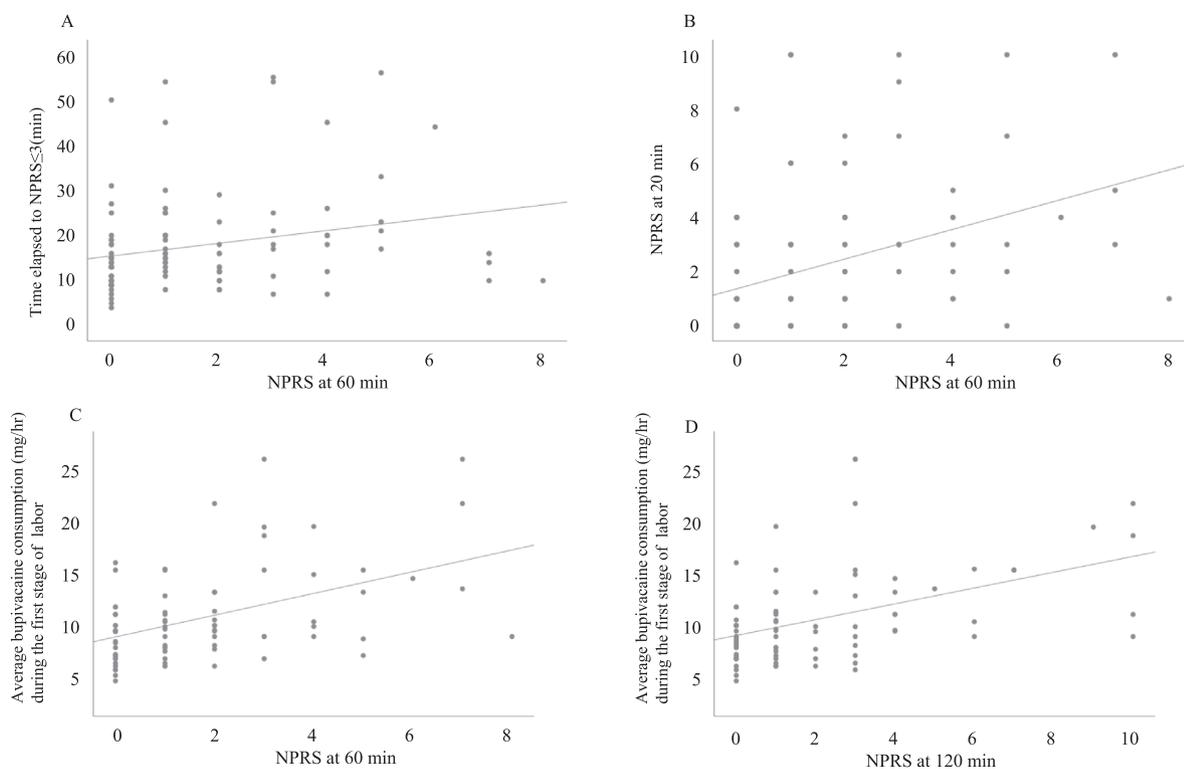


Fig. 2 Graphical representation of correlations between selected outcomes; (a) pain at 60 min and time elapsed to achieve a verbal numerical rating score of 3 ($R^2=0.283$, $P=0.003$); (b) pain at 60 min and pain at 120 min ($R^2=0.47$, $P<0.001$); (c) pain at 60 min and bupivacaine consumption rate during the first stage of the labor ($R^2=0.403$, $P<0.001$); (d) pain at 120 min and bupivacaine consumption during the first stage of the labor ($R^2=0.433$, $P<0.001$)

Table 2 Relationship between pain intensity and time to analgesia onset at 60 and 120 min after labor epidural analgesia initiation

	All study recruits n=105	Time to onset of LEA (NPRS ≤ 3) ^c		Pain intensity 60 min after onset of LEA (NPRS) ^c		Pain intensity 120 min after onset of LEA (NPRS) ^c	
		R^2	P -value	R^2	P -value	R^2	P -value
Pain intensity at contraction prior to onset of LEA (NPRS) ^a	9 (8–10)	0.107	0.28	0.142	0.15	0.087	0.39
Pain intensity during local anesthetic injection prior to LEA (NPRS) ^a	4 (2–6)	–0.09	0.37	–0.025	0.80	0.166	0.10
No. PCEA attempts 60 min after onset of LEA ^a	0 (0–1)	0.361*	<0.0001	0.361*	<0.001	0.224*	0.023
No. PCEA attempts 120 min after onset of LEA ^a	1 (0–3)	0.321*	0.001	0.588*	<0.001	0.539*	<0.001
Cervical dilatation at 60 min ^a	4.9 \pm 2.2	0.178	0.07	0.259*	0.008	0.126	0.204
Cervical dilatation at 120 min ^a	6.0 \pm 2.6	0.219*	0.026	0.329*	0.001	0.243*	0.013
Total bupivacaine dose from LEA initiation to complete dilatation (mg) ^{b,d}	55.2 \pm 35.0	0.089	0.435	0.045	0.692	–0.004	0.974
Pain intensity at pushing in second stage (NPRS) ^a	6 (1–9)	–0.028	0.80	0.062	0.56	0.190	0.07
Maternal satisfaction with LEA (NPRS) ^a	10 (9–10)	0.01	0.92	–0.036	0.73	–0.196*	0.05

LEA: labor epidural analgesia; NPRS: numerical pain rating score (0–10); PCEA: patient-controlled epidural analgesia.

^aMedian (interquartile range).

^bMean (standard deviation).

^cSpearman's rank correlation.

^dData calculated for n=80 (see text).

*Statistically significant.

Discussion

This prospective observational study among nulliparous women investigated the relationship between LEA onset time and subsequent pain intensity at 60 and 120 min after LEA onset. We found a negative correlation between a longer time to satisfactory analgesia and pain levels one hour, but not two hours, after LEA initiation. We noted a higher number of PCEA bolus requests and greater bupivacaine consumption two hours after LEA initiation among those women with longer LEA onset times. Women started to use the PCEA after 30 min from LEA initiation, possibly explaining the analgesic difference at 60 min but not at 120 min. This idea is supported by more severe pain among women who had a longer analgesic onset, although this appeared to be alleviated by two hours after initiation as a result of additional PCEA. This assumption is further supported by the similar average rate of bupivacaine consumption during the first stage of labor, pain intensity during the second stage of labor and satisfaction with LEA, regardless of the time to onset.

Although several studies attempted to minimize the LEA onset time, the relationship between it and subsequent analgesic efficacy has, to our knowledge, not been investigated as a primary objective. Sviggum et al.⁷ reported that the time to a pain score ≤ 3 could be shortened by heating the epidural solution to body temperature and the reported mean time to NRS ≤ 3 was 16 min in their control group, which is similar to that of our cohort. However, the authors reported no significant difference between the groups in pain or local anesthetic consumption after the first 30 min of LEA. Mehta et al.¹⁶ also investigated the effect of pre-heated opioid-free bupivacaine 0.5% on LEA onset time. Subsequent analgesia was maintained by intermittent boluses. They found that pre-heating shortened the onset time but not the time to the first maintenance bolus. Capiello et al.¹⁷ reported that, although the dural puncture epidural technique expedited the LEA onset time, there was no effect on subsequent analgesic requirements during the first three hours of labor. Thus, although the time to LEA onset may be shortened, manipulation of the LEA onset time does not predict the subsequent quality of analgesia.

The only obstetric factor in our study that was associated with pain intensity was a higher cervical dilatation at the time of evaluation: this has been demonstrated in several studies.^{18,19} Orbach-Zinger et al.¹² reported a correlation between the pain experienced during local anesthetic injection for spinal anesthesia for cesarean delivery and the intensity of postoperative pain. As an exploratory analysis, we examined the association between pain caused by local anesthetic injection before epidural insertion and subsequent labor pain at 60 and 120 min; there was no apparent relationship. One potential reason for this difference

is that spinal anesthesia for elective cesarean delivery is performed when a pregnant woman is not in pain, whereas LEA is usually performed when pain is already occurring due to contractions and the signal for greater pain intensity may be lost. Labor pain may affect the nociception, transduction and interpretation of other painful stimuli.

In this study we found a positive correlation between pain at 60 and 120 min after LEA initiation. Higher scores at these time points were associated with more PCEA bolus requests per hour and more rapid analgesic solution consumption. We speculate that the intensity of pain 60 min after LEA initiation may be a predictor of subsequent pain during labor. However, we did not assess pain beyond two hours from LEA initiation and further research is warranted. Nevertheless, it may be useful to pay attention to women with higher levels of pain at 60 min as this might assist in determining pro-active management of labor pain.¹⁶

There are some limitations of this study. First, pain was assessed only until 120 min after LEA initiation. Additional assessments might have impacted on data quality and there was increasing variability in the length of labor as fewer participants reached these stages. Each woman could choose how much additional analgesia she required and so additional analgesia requests may be a marker of more severe pain or a desire for better quality analgesia. We did not interrogate the women regarding the reasons for the demand boluses they administered, although we assume that the PCEA boluses were to manage unacceptable pain. Furthermore, it is not possible to know what the pain scores at 60 and 120 min would have been if the woman had not administered any PCEA boluses. Using our institutional PCEA protocol, the majority of women in this study were free of pain or experienced mild pain (median score 1) at one hour and two hours after LEA initiation.

In conclusion, there was a correlation between the onset time of LEA in labor and pain at 60 min, but this was no longer the case at 120 min. We found a relationship between pain intensity at 60 min and later local analgesic consumption and suggest that an assessment of labor pain at 60 min might help anticipate more intense subsequent labor pain, perhaps related to faster labor.

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