

# Effects of Labor Epidural Analgesia on Short Term Neonatal Morbidity

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Khalil Mohd Salameh   
Vellamgot Anvar Paraparambil  
Abedin Sarfrazul  
Habboub Lina Hussain  
Salim Sajid Thyvilayil  
Alhoyed Samer Mahmoud

Department of Pediatrics and  
Neonatology, Al Wakra Hospital, Hamad  
Medical Corporation, Al Wakra, Qatar

**Background:** Epidural Analgesia (EA) is the most effective and most commonly used method for pain relief during labor. Some researchers have observed an association between EA and increased neonatal morbidity. But this observation was not consistent in many other studies.

**Objectives:** The primary objective of the study was to examine whether exposure to epidural analgesia increased the risk of NICU admission. The secondary objectives included the risks of clinical chorioamnionitis, instrumental delivery, neonatal depression, respiratory distress, birth trauma, and neonatal seizure during the first 24 hours of life.

**Methods:** This was a retrospective cohort study involving 2360 low-risk nulliparous women who delivered at AWH, Qatar, during the two years between January 2016 December and 2017. Short-term neonatal outcomes of the mothers who received EA in active labor were compared with a similar population who did not receive EA. As secondary objectives, labor parameters like maternal temperature elevation, duration of the second stage of labor, and instrumental delivery were compared.

**Results:** Significantly higher numbers of neonates were admitted to the NICU from the EA group ( $P < 0.001$ , OR 1.89, 95% CI 1.45 to 2.46). They were more likely to have respiratory distress ( $P = 0.01$ , OR 1.49, 95% CI 1.07 to 2.07), birth injuries ( $P = 0.02$ , OR = 1.71, 95% CI 1.06 to 2.74), admission temperature  $> 37.5^{\circ}\text{C}$  ( $P = 0.04$ , OR 3.40, 95% CI 1.00 to 11.49), need for oxygen on the first day ( $P = 0.04$ , OR 1.44, 95% CI 1.01 to 2.07) and receive antibiotics ( $P < 0.001$ , OR 2.06, 95% CI 1.47 to 2.79). There was no difference in the Apgar score at 1 minute ( $P = 0.12$ ), need of resuscitation at birth ( $P = 0.05$ ), neonatal white cell count ( $P = 0.34$ ), platelet count ( $P = 0.38$ ) and C reactive protein ( $P = 0.84$ ). Mothers who received EA had a lengthier second stage ( $P < 0.001$ ), temperature elevation  $> 37.5^{\circ}\text{C}$  ( $P < 0.001$ , OR 7.40, 95% CI 3.93 to 13.69) and instrumental delivery ( $P < 0.001$ , OR 2.13, 95% CI 1.69 to 2.68).

**Conclusion:** EA increases NICU admission, antibiotic exposure, neonatal birth injuries, need for positive pressure ventilation at birth, and respiratory distress in the first 24 hours of life. Mothers on epidural analgesia have prolonged second stage of labor, a higher rate of instrumental delivery, meconium-stained amniotic fluid, fetal distress, and temperature elevation.

**Keywords:** epidural analgesia, neonatal morbidity, NICU admission

## Definitions

Short term neonatal morbidity-sick conditions of neonates during the early neonatal period. For the current study, any morbidity during the first 24 hours of age like the need for NICU admission, respiratory distress, birth trauma, etc.

Chorioamnionitis (intraamniotic infection): Infection of the placenta and the amniotic membranes.

Apgar score: the standard code used for coding the condition at birth and the need for resuscitation in neonates.

Correspondence: Khalil Mohd Salameh  
Department of Pediatrics and  
Neonatology, Al Wakra Hospital, Hamad  
Medical Corporation, Al Wakra, Qatar  
Tel +974 40114258  
Email Ksalameh@hamad.qa

Nulliparous women: women with no previous history of delivery.

Significant congenital anomaly: any birth defect which needs NICU admission

## Introduction

Morbidity during the immediate neonatal period is distressing to the babies, parents, and healthcare workers. Birth asphyxia, birth injuries, infections, and respiratory distress are among the leading morbidities during the immediate neonatal period. Affected babies often need admission to NICU. Although essential for meticulous care of sick neonates, the NICU stay separates the baby from the mother, causes parental anxiety, breastfeeding failure, and puts the baby at risk for medical errors and healthcare-associated infections. This is in addition to the cost factors. Maternal factors like prolonged labor, instrumental delivery, and intrapartum fever may contribute to these morbidities.<sup>1-3</sup>

Good pain relief is one of the most critical factors related to patient satisfaction<sup>4,5</sup> and EA is the most effective and most widely accepted method of pain relief during labor. Internationally, the rate of epidural use varies between 20–70% of all deliveries.<sup>2,6-8</sup> Administration of local anesthetic along with the opioid analgesic to the lumbar epidural space is very effective in attaining labor analgesia.<sup>9</sup> EA and CSE are the two most widely accepted techniques. Systemic hypotension and pruritus are the two most common side effects of EA. Both techniques have similar effects on the neonatal outcome.<sup>6,4</sup>

Previous studies have shown a higher rate of the prolonged second stage of labor and instrumental delivery with EA.<sup>6</sup> Instrumental delivery and prolonged labor increase neonatal morbidity.<sup>1</sup> Additionally, EA is associated with a significantly higher incidence of maternal intrapartum fever.<sup>2,10,11</sup> Maternal fever during labor increases the risk of neonatal morbidity.<sup>3,12</sup> Some studies have shown that neonates born to mothers with epidural associated fever have a higher likelihood of being investigated and treated for neonatal sepsis.<sup>2,13</sup> However, many other studies failed to show any significant effects of epidural analgesia on neonatal outcomes.<sup>6,14</sup>

Most of the previous studies focused on maternal outcomes along with a few aspects of neonatal outcome.<sup>2,3,6,13</sup> Our search did not identify similar published studies from the Middle East. During the year 2017, 58 % of nulliparous mothers received EA in our institution. As these numbers are high, even rare adverse effects are likely to be significant.

Since many of these adverse effects are likely to be dependent on individual obstetric and neonatal management practices, it was justifiable to study the neonatal effects of EA, if any, in our setting. The result could be potentially used while educating mothers seeking labor analgesia.

## Objectives

### Primary Objective

to study retrospectively whether exposure to EA increased the risk of NICU admission for babies born at AWH between 1st January 2016 and 17th December 2017.

### Secondary objectives

1. To study whether EA exposure increased the risk of – instrumental delivery, neonatal depression, respiratory distress, and neonatal seizure during the first day.
2. To study the rate of epidural associated fever in low-risk nulliparous women and its relation to sepsis workup and antibiotic use in neonates.

## Materials and Methods

This was a retrospective cohort study involving all the low-risk nulliparous women who delivered at Al Wakra Hospital, Qatar, during the 2 years from January 2016 to December and 2017.

The Medical Research Centre and the Institutional Review Board (IRB), Hamad Medical Corporation approved the study. Since it was retrospective and all subjects were coded and de-identified, the need for consent was waived off by the IRB.

The study group consisted of low-risk nulliparous women who received EA in active labor. A similar population of mothers who did not receive EA served as control. The short-term outcomes of their neonates were compared between the groups.

Nulliparous mothers are more likely to have prolonged labor, and the effects of EA are likely to be more pronounced. This also provided a more homogenous population.

## The Method of Analgesia

In the EA group, all the mothers received EA in active labor after the cervical dilatation was 4 cm or more. Combined spinal-epidural (CSE) was the technique used. The epidural catheter was inserted into the L3-L4 lumbar intervertebral space in the sitting position. Spinal Bupivacaine (0.5%) was delivered by Whitacre G27 spinal needle, followed by epidural infusion of fentanyl and levobupivacaine.

## Inclusion Criteria

Singleton delivery, nulliparous mother, gestational age at birth 37 and 41+6 weeks, birth weight between 2.5 and 4 Kg, mother in active labor at least for an hour and cephalic presentation

## Exclusion Criteria

Multiple pregnancy, gestation <37 weeks or more than 41 +6 weeks, elective LSCS, emergency LSCS within one hour of onset of labor, precipitate labor, pre-existing obstetric risk factors which may affect the neonatal outcome (hypertension, GBS bacteriuria, spontaneous premature rupture of membranes >18 hours, fever at the onset of labor, STD), mother received general anesthesia or morphine during labor, birth weight <2.5kg ≥4kg, major congenital anomalies or inborn errors of metabolism, neonates with culture-proven early-onset sepsis, NICU admission for reasons like jaundice and social reason, admission after 24 hours of life, mother's age <18 years and >40 years, fetal presentations other than cephalic and incompletely documented parameters

The short-term outcomes of neonates in the two groups (EA and non-EA) were compared.

## Study Population and Study Setting

The study was conducted at NICU – AWH. Neonatal and maternal files were examined for all deliveries between January 2016 and December 2017 (24 months).

## Data Collection & Confidentiality

Complete delivery statistics for the study period was obtained from the Medical records Department, AWH. Term, nulliparous, singleton live births were selected from this. Elective LSCS, low birth weight and large for gestational age babies were then excluded. The further exclusion was performed by detailed verification of the electronic medical record (Cerner Millennium) of each patient. All links to the identity were destroyed at the end of data collection and verification.

Maternal data included age, parity, gestational age, need for labor induction, duration of the second stage of labor, mode of delivery, instrumental delivery, pathological CTG (baseline fetal heart rate <100, reduced or increased variability/sinusoidal pattern, repetitive late or prolonged decelerations), meconium-stained amniotic fluid, peak intrapartum temperature, suspected chorioamnionitis, placental histopathology and culture and whether received EA or not.

Newborn data included, birth weight, sex, Apgar score at 1 and 5 minutes, need for positive pressure ventilation, need of NICU admission, reason for NICU admission, seizure during the first 24 hours, highest level of respiratory support and its duration, whether received antibiotics during the first 24 hours, duration of antibiotic therapy, length of NICU stay, lab/radiological parameters, C reactive protein during the first 24 hours, leukocyte count and platelet count.

The data was in the safe custody of the Principal Investigator. The electronic data was stored in the office computer of the NICU and protected by a password. After entering the data, the papers with coded identity were stored locked in the personal locker of PI, located inside the NICU duty room.

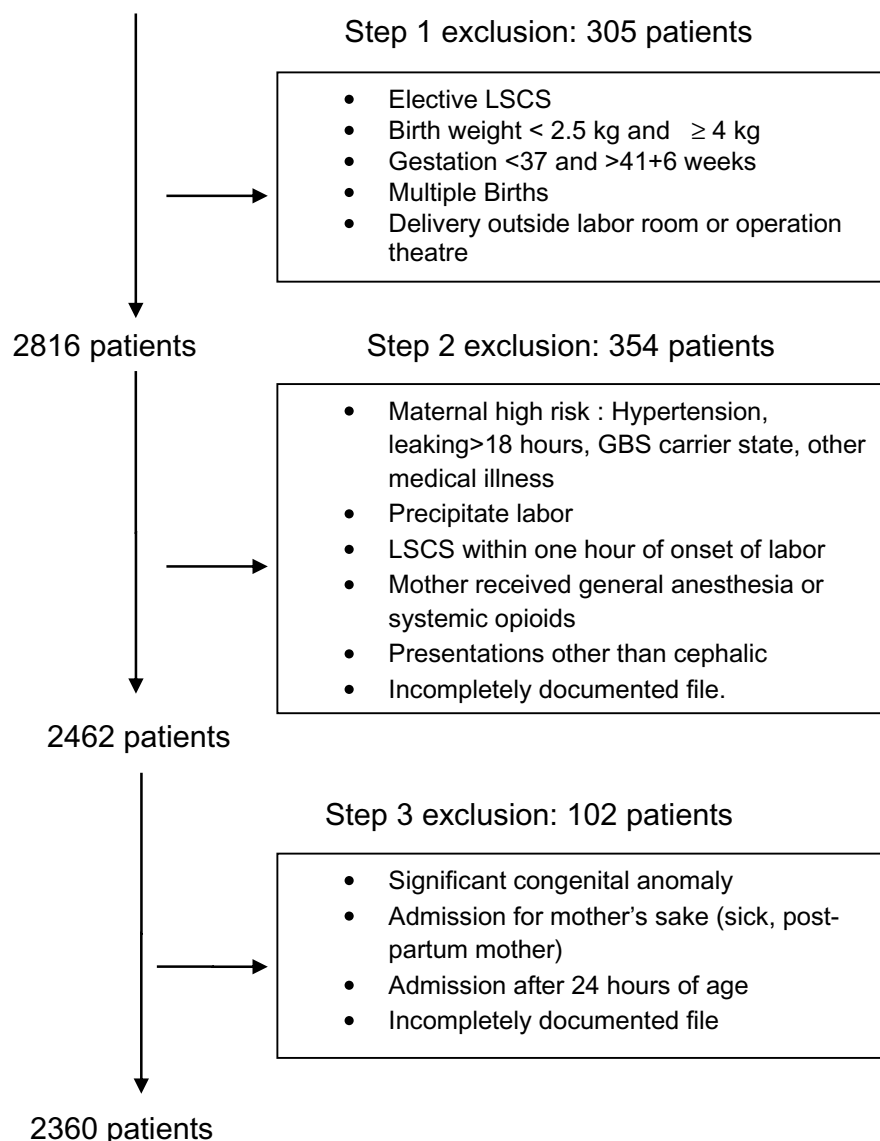
## Data Analysis

Anonymous data were collected and entered into a standard electronic database chart designed according to the study design and objectives. Descriptive statistics were used to summarize all clinical data of mother & baby and outcome variables as needed for NICU admission, the reason for admission, treatment needed, etc. The results were reported with mean and standard deviation (SD) or frequencies and percentages as per the type of data. Associations between two or more qualitative variables were assessed using the chi-square ( $\chi^2$ ) test or Fisher Exact test as appropriate. Quantitative variables mean between two and more than two independent groups were analyzed using the unpaired *t*-test and one-way analysis of variance (ANOVA). The logistic regression test was applied to calculate the Odds Ratio of outcome in the epidural exposed and non-exposed group. All *P* values presented were two-tailed, and *P* values <0.05 were considered as statistically significant. All Statistical analyses were done using statistical packages SPSS 22.0 (SPSS Inc. Chicago, IL) software.

## Results

Between Jan 2016 and Dec 2017, AWH recorded 10,802 live births. Among these, 3121 were nulliparous mothers (Figure 1). Step 1 exclusion was performed by reviewing the labor room registry and medical records data. This step excluded 305 patients including preterm, post-term, low birth weight, large for gestational age, multiple gestations, elective Caesarian section, and delivery outside the labor room or operation theatre. Second step exclusion was performed by reviewing the individual maternal files.

## 3121 live births (nulliparous mothers)



**Figure 1** Flow chart: exclusion process.

This step excluded further 354 subjects who had risk factors (leaking >18 hours, hypertension, positive GBS carrier state or other significant medical illnesses), precipitate labor, LSCS within one hour of onset of labor, presentation other than cephalic, incompletely documented files or who received general anesthesia or opioid analgesia. The third step excluded 102 subjects by reviewing the baby file. This step excluded significant congenital malformations, incomplete documentation, admission after 24 hours of age or admission for the mother's sake (sick, postpartum mother).

The final cohort consisted of 2360 patients. Among them, 1490 subjects received EA and 870 received no analgesia.

Baseline maternal and neonatal characteristics included mother's age, gestational age, induced labor, gestational diabetes, sex, and birth weight. These were compared between the EA and non-EA groups (Table 1). Except for gestational age and birth weight, there were no statistically significant differences between the baseline parameters. The statistical significance observed for gestational age (mean difference 0.19 weeks) and birth weight (mean difference 0.089 kg) was not clinically significant.

**Table 1** Baseline Maternal and Neonatal Characteristics

	Epidural =1490	Non-Epidural =870	Mean Difference (95% CI)	Odds Ratio (95% CI)	P-Value
Mother's age-Years (SD)	26.42 (4.20)	26.51 (4.60)	-0.093 (-0.46 to 0.27)		0.62
Gestational age-Weeks (SD)	39.36 (1.30)	39.17 (1.05)	0.61 (0.94 to 0.29)		<0.001
Induced labor No. (%)	239 (16)	117 (13.4)		1.23 (0.96 to 1.56)	0.09
Gestational diabetes No. (%)	327 (21.90)	202 (23.2)		0.93 (0.76 to 1.13)	0.47
Male No. (%)	744 (49.90)	418 (48)		0.92 (0.78 to 1.09)	0.37
Female No. (%)	746 (50.10)	452 (52)			
Birth weight-Kg (SD)	3.276 (0.34)	3.186 (0.346)	0.089 (0.06 to 0.11)		<0.001

**Abbreviations:** SD, standard deviation; No(%), number(percentage).

The duration of the second stage of labor was significantly higher in the EA group ( $P<0.001$ ) with a mean difference of 49.36 minutes (95% CI 40.45 to 58.28). Mothers in the EA group also had higher peak intrapartum temperature ( $P<0.001$ , Mean difference 0.12°C, 95% CI 0.09 to 0.14). EA group had a higher chance of having intrapartum temperature  $>37.5^{\circ}\text{C}$  ( $P<0.001$ , OR 7.40, 95% CI 3.93 to 13.69). Fetal distress ( $P<0.001$ , OR 1.60, 95% CI 1.30 to 1.98), meconium staining of amniotic fluid ( $P=0.01$ , OR 1.31, 95%CI 1.05 to 1.62) and need for instrumental delivery ( $P<0.001$ , OR 2.13, 95% CI 1.69 to 2.68) were significantly higher in the EA group. There was no difference in the rate of LSCS ( $P=0.72$ ) (Table 2).

In Table 3, we have compared cord arterial pH, Apgar score at 1 and 5 minutes, birth injury and need of resuscitation at Birth. The birth injury was more frequent in the EA group ( $P=0.02$ , OR 1.71, 95% CI 1.06–2.74). There was no difference in Apgar score, cord pH and need for resuscitation at birth. Table 4 shows a comparison of the clinical

parameters of neonates. Our primary outcome measure, NICU admission, was significantly higher in the EA group – ( $P<0.001$ , OR 1.89, 95% CI 1.45 to 2.46). Among other parameters, neonatal admissions due to suspected maternal chorioamnionitis were significantly higher in the EA group ( $P<0.001$ , OR 4.30, 95% CI 2.44 to 7.58). A substantially higher number of neonates in the EA group received antibiotics on day 1 ( $P<0.001$ , OR 2.06, 95% CI 1.47 to 2.79).

Among babies admitted to NICU, lab parameters were not significantly different between the two groups (Table 5).

## Discussion

Our final cohort consisted of 2360 subjects. Among them, 1490 (63%) received Epidural Analgesia. The overall use rate of EA in our institution is 33%. The higher rate observed in the study population was attributable to the exclusion of non-nulliparous mothers and elective Caesarian deliveries. In recent years its use has increased worldwide, being used between 20–70% of all deliveries.<sup>2,6–8</sup>

**Table 2** Maternal Outcomes in EA

	Epidural=1490	Non-Epidural=870	Mean Difference (95% CI)	Odds Ratio (95% CI)	P Value
Duration of second stage of labor-in Minutes (SD)	94.5 (75.3) (recorded in 565 cases)	45.1 (47.5) (recorded in 342 cases)	49.36 (40.45 to 58.28)		<0.001
Peak maternal temp during labor (SD)	37.04 (0.38) recorded in 1456	36.92 (0.27) recorded in 863	0.12 (0.09 to 0.14)		<0.001
Peak maternal temp during labor $>37.5^{\circ}\text{C}$ No. (%)	127 (8.7)	11 (1.3)		7.40 (3.93 to 13.69)	<0.001
Meconium stained amniotic fluid No.(%)	282 (18.9)	131 (15.1)		1.31 (1.05 to 1.62)	0.01
Fetal distress No. (%)	374 (25.1)	150 (17.2)		1.60 (1.30 to 1.98)	<0.001
LSCS No.(%)	340 (22.8)	193 (22.2)		1.03 (0.84 to 1.26)	0.72
Instrumental delivery No. (%)	360 (24.2)	113 (13)		2.13 (1.69 to 2.68)	<0.001

**Abbreviations:** SD, standard deviation; No(%), number(percentage).

**Table 3** Perinatal Outcome

	Epidural=1490	Non-Epidural =870	Mean Difference (95% CI)	Odds Ratio (95% CI)	P Value
Cord arterial pH-pH (SD)	7.235 (0.089) Done in 521	7.239 (0.096) Done in 224	-0.003 (-0.018 to 0.01)		0.61
Cord arterial pH <7.1 No. (%)	36 (6.9) Done in 521	17 (7.6) Done in 224		0.90 (0.49 to 1.64)	0.75
1-minute Apgar (SD)	8.851 0.77	8.906 (0.63)	-0.054 (-0.115 to 0.006)		0.07
1-minute Apgar <7. No. (%)	32 (2.1)	11 (1.3)		1.71 (0.85 to 3.41)	0.12
5-minute Apgar (SD)	9.97 0.23	9.97 0.39	0.00 (-0.026 to 0.025)		0.97
Birth injury No. (%)	69 (4.6)	24 (2.8)		1.71 (1.06 to 2.74)	0.02
Positive pressure ventilation at birth No. (%)	69 (4.6)	26 (3)		1.57 (0.99 to 2.49)	0.05

**Abbreviations:** SD, standard deviation; No(%), number(percentage).

**Table 4** Effect of Epidural Analgesia on Neonatal Clinical Parameters

	Epidural=1490	Non-Epidural =870	Mean Difference (95% CI)	Odds Ratio (95% CI)	P Value
NICU admission No. (%)	245 (16.4)	82 (9.4)		1.89 (1.45 to 2.46)	<0.001
NICU admission when maternal temperature 37° C or less	181 (13.6) Total -1329	73 (8.6) Total -852		1.68 (1.26-2.24)	<0.001
NICU stay duration-days (SD)	3.11 (2.08) Done in 245/245	2.91 (3.17) Done in 82/82	0.19 (-0.40 to 0.80)		0.51
Admissions due to suspected maternal chorioamnionitis No.(%)	98 (6.6)	14 (1.6)		4.30 (2.44 to 7.58)	<0.001
Temperature upon NICU admission- °C (SD)	37.05 (0.42) Done in 245/245	36.89 (0.45) Done in 82/82	0.159 (0.05 to 0.26)		<0.01
Temperature upon NICU admission >37.5°C No. (%)	28 (11.4) Recorded in 245/245	3 (3.7) Recorded in 82/82		3.40 (1.00 to 11.49)	0.04
Respiratory distress No. (%)	134 (9)	54 (6.2)		1.49 (1.07 to 2.07)	0.01
Admission for post resuscitation care No. (%)	34 (2.3)	13 (1.5)		1.53 (0.80 to 2.93)	0.22
Need for any respiratory support No. (%)	109 (7.3)	45 (5.2)		1.44 (1.01 to 2.07)	0.04
Mechanical ventilation No. (%)	6 (0.4)	6 (0.1)		0.58 (0.18-1.81)	0.37
Antibiotic started on day 1 No. (%)	137 (11.6)	53 (6.1)		2.06 (1.47 to 2.79)	<0.001
Antibiotic duration-5 days or more No.(%)	21 (1.4)	1 (0.1)		12.42 (1.66-92.55)	0.01
Transient tachypnea No. (%)	71 (4.8)	39 (4.5)		1.06 (0.71 to 1.59)	0.75

**Abbreviations:** SD, standard deviation; No(%), number(percentage).

Baseline maternal and neonatal characteristics (mother's age, gestational age, nationality, induced labor, gestational diabetes, sex, and birth weight) did not differ between the groups. The statistically significant

differences observed in gestational age and birth weight were not clinically significant. This observation was noted in previous studies also.<sup>7,15</sup> Gestational diabetes is associated with significant neonatal morbidity.<sup>16,65,66</sup>



**Table 5** Effect of Epidural Analgesia on Neonatal Lab Parameters (Done in the Patients Who Needed NICU Admission)

	<b>Epidural=1490 (Admitted=245)</b>	<b>Non-Epidural =870 (Admitted=82)</b>	<b>Mean Difference (95% CI)</b>	<b>Odds Ratio (95% CI)</b>	<b>P Value</b>
C Reactive protein- max (SD)	16.04 (21.98) Done in 123/245	18.4 (31.96) Done in 35/82	-2.35 (-11.63 to 6.91)		0.61
C Reactive protein max >10 No. (%)	50 (40.7) Done in 123/245	13 (37.1) Done on 35/82		1.15 (0.53 to 2.51)	0.84
Leukocyte count $\times 10^6$ (SD)	18.24 (5.04) Done in 201/245	18.99 (6.42) Done in 68/82	-0.75 (-2.25 to 0.74)		0.32
Platelet count $\times 10^6$ (SD)	247.66 (62.46) Done in 200/245	255.46 (68.53) Done in 69/82	-7.8 (-25.4 to 9.8)		0.38

**Abbreviations:** SD, standard deviation; No(%), number(percentage).

There was no significant difference between the groups in terms of the number of gestational diabetic mothers.

Neonates in the epidural group were more likely to get admitted to NICU. They were more likely to have respiratory distress, birth injuries, admission temperature  $>37.5^\circ\text{C}$ , need for positive pressure ventilation at birth, and receive antibiotics.

Mothers in the epidural group had a significantly higher intrapartum temperature, clinical chorioamnionitis, lengthier second stage, more fetal distress, and instrumental delivery.

A significantly higher number of neonates were admitted to NICU from the EA group ( $P<0.001$ , OR 1.89, 95% CI 1.45 to 2.46). Several studies that examined the association of EA with NICU admission found conflicting results. A 10 Years Retrospective study in Austria by Kraft et al<sup>18</sup> observed an increased rate of NICU admission in the EA group. A similar result was seen in studies by Rouse et al,<sup>19</sup> Herrera-Gómez et al<sup>8</sup> and Wisborg et al.<sup>20</sup>

Conversely, a recent Cochrane meta-analysis by Anim-Somuah et al<sup>14</sup> concluded that EA is not associated with a higher rate of NICU admission. Previous studies by Wang et al<sup>62</sup> and Soncini et al<sup>21</sup> also did not find an association between EA and NICU admission. The difference in observation could be partially due to the difference in the NICU admission criteria of different institutions. Many institutions have observation rooms attached to the delivery rooms, facilitating short-term observation. Our facility allows observation in the delivery room for up to 2 hours. As intravenous medications are not administered in the postnatal ward, all babies requiring intravenous therapy were admitted to NICU.

The chief reasons for NICU admission included suspected neonatal sepsis, post-resuscitation observation, observation of significant birth injuries, transient tachypnea, and meconium aspiration.

Admissions due to suspected maternal chorioamnionitis were significantly higher in the epidural group ( $P<0.001$ , OR 4.30, 95% CI 2.44 to 7.58). Abramovici et al<sup>69</sup> found a strong correlation between EA and clinical chorioamnionitis in the mother (OR 8.3, 95% CI 2.63–26.40).

Neonates born in the EA group are more likely to receive antibiotics on the first day of life ( $P<0.001$ , OR 2.06, 95% CI 1.47 to 2.79). They were also more likely to receive antibiotics for more than five days ( $P=0.01$ , OR 12.42, 95% CI 1.68–92.5). None of the babies had a positive blood culture. We did not find any published studies which compared the antibiotic duration. EA is associated with significant intrapartum temperature elevation.<sup>2,10,11</sup> Intrapartum maternal fever increases the likelihood of neonatal admission for sepsis evaluation. Many of the previous researches demonstrated the association between EA and antibiotic use in neonates. A large population-based study by White et al<sup>13</sup> found that neonates born to women who received an epidural had 1.26 times increased odds of antibiotic treatment. Lieberman et al,<sup>28</sup> Goetzl et al,<sup>63</sup> Heesen et al,<sup>29</sup> and Wisborg et al<sup>20</sup> found similar association. In the long term, antibiotic exposure is associated with necrotizing enterocolitis and altered gut microbiome<sup>22–25</sup>. Altered neonatal gut microbiome may increase the risks of chronic diseases like atopy.<sup>26,27</sup>

Kaul et al<sup>30</sup> did not find any association between EA and antibiotic use in neonates. Capogna<sup>31</sup> suggested that,

while the number of neonates receiving sepsis evaluations varies between institutions, epidural exposure did not increase the incidence of neonatal sepsis.

Interestingly, the increased risk for NICU admission persisted even when the mothers without temperature elevation ( $<37.5^{\circ}\text{C}$ ) were analyzed separately ( $P<0.001$ , OR 1.68, 95% CI 1.26–2.24). Goetzl et al<sup>63</sup> studied the rate of neonatal sepsis evaluation among mothers who received epidural analgesia and remained afebrile. They found that neonatal sepsis evaluation rate was higher in the epidural group even when the mothers were afebrile (OR 3.1, 95% CI 2–4.7).

More newborns in the EA group had admission temperature  $>37.5^{\circ}\text{C}$  ( $P=0.04$ , OR 3.40, 95% CI 1.00 to 11.49). Fetal temperature increases proportionate to the maternal temperature.<sup>68</sup> Kaul et al,<sup>30</sup> Wasson et al,<sup>71</sup> and Agakidis et al<sup>72</sup> also observed neonatal temperature elevation in association with EA.

Neonatal Birth injuries were more frequent in the EA group. ( $P=0.024$ , OR 1.71, 95% CI 1.06 to 2.74). Armani et al<sup>32</sup> observed a significantly higher incidence of cephalhematoma in the EA group. In our study, mothers who received EA had more instrumental deliveries ( $P<0.001$ , OR 2.13, 95% CI 1.69 to 2.68). Neonatal birth trauma is strongly correlated to be an operative vaginal delivery.<sup>36</sup> Birth trauma was documented in 3.9 % of the whole sample. Cephalhematoma was the most frequent injury noted (40% of all birth injuries). Others included clavicle fracture, mild subgaleal bleeding, brachial plexus injury, significant scalp laceration, cut injuries, facial paralysis, and deep forceps mark with significant bruising.

In admitted babies, we looked for the predominant symptom during the first 24 hours. Respiratory distress was the most frequent symptom (54%). 22 % of babies were asymptomatic (admitted for post-resuscitation observation or suspected neonatal sepsis due to maternal chorioamnionitis). Remaining babies had hypoactivity, poor sucking or vomiting.

We found that babies from the EA group were significantly more likely to have respiratory distress during the first 24 hours ( $P=0.01$ , OR 1.49, 95% CI 1.07 to 2.07). Although the need for oxygen was slightly more in the epidural group ( $P=0.04$ , OR 1.44, 95% CI 1.01 to 2.07), there was no difference in the need for mechanical ventilation. ( $P=0.25$ ).

Kumar et al<sup>33</sup> conducted a case-control study of NICU admitted babies. They found that Epidural analgesia increased the incidence of respiratory distress in the immediate newborn period.

Two babies from EA and one baby from non-EA group developed seizure during the first 24 hours. Greenwell<sup>34</sup> observed increased encephalopathy and neonatal seizures with EA. This was correlated to the maternal temperature elevation. Wisborg et al<sup>20</sup> also observed a higher incidence of neonatal convulsions with epidural analgesia. A study by Tornell et al<sup>2</sup> found an association between EA and neonatal encephalopathy. Wang et al<sup>67</sup> examined the neonatal adaptive score at 2 hours and 24 hours. No difference was observed between EA and non-EA group.

Among admitted babies, symptoms like poor sucking ( $P=0.26$ ) hypoactivity ( $P=0.79$ ) and vomiting ( $P=1$ ) were not different between the groups. The mean length of stay was also comparable ( $P=0.51$ ).

Mothers who received EA had a lengthier second stage ( $P<0.001$ ). The recent Cochranemeta-analysis by Anim-Somuah et al<sup>14</sup> had confirmed this observation. Many previous studies had similar findings.<sup>35–37</sup> Zhang et al<sup>38</sup> and Mousa et al<sup>39</sup> did not find any association between EA and prolonged second stage. In our study, Instrumental vaginal deliveries were more frequent in the EA group ( $P<0.001$ , OR 2.13, 95% CI 1.69 to 2.68). The vast majority of previous studies had observed this association between EA and increased instrumental delivery.<sup>6,7,14,15,36,40</sup> However, the post hoc subgroup analysis of a recent Cochrane review<sup>14</sup> showed that this effect is not seen in recent studies (after 2005), suggesting that modern approaches to epidural analgesia in labor did not increase this outcome.

Pathological CTG (baseline fetal heart rate  $<100$ , reduced or increased variability/sinusoidal pattern, repetitive late or prolonged decelerations) findings were more frequent in the epidural group ( $P<0.001$ , OR 1.65, 95% CI 1.30 to 1.98).

Neuraxial analgesia during labor has been associated with fetal heart rate (FHR) abnormalities with an incidence ranging from 4% to 21%.<sup>41–47</sup> One of the suggested mechanisms of fetal bradycardia is that the rapid onset of analgesia can lead to an imbalance of plasma adrenaline and noradrenaline, which may result in uterine hypertonus. Other proposed mechanisms include hypotension and aortocaval compression. A study by Leighton et al<sup>17</sup> did not find any association between EA and fetal heart rate changes.

Maternal temperature  $>37.5^{\circ}\text{C}$  was significantly more frequent in the EA group ( $P<0.001$ , OR 7.40, 95% CI 3.93 to 13.69). Most of the previous studies observed this relationship.<sup>2,11,14,48</sup> The maternal temperature of more than  $37.5^{\circ}\text{C}$  is strongly associated with neonatal



encephalopathy.<sup>12</sup> The proposed mechanisms of epidural induced fever include inflammatory response, oxidative stress, alteration in sympathetic stimulation, and subclinical chorioamnionitis. Patients with suspected chorioamnionitis were significantly higher in the epidural group ( $P<0.001$  OR 4.30, 95% CI 2.44 to 7.58). This is attributable to the higher rate of elevated maternal temperature in the EA group. Confirmatory tests for chorioamnionitis (placental culture or histopathology) were done only in 51% clinical chorioamnionitis. There was no difference in the number of confirmed chorioamnionitis between the epidural and nonepidural groups ( $P=0.62$ ). This may be explained by the fact that epidural analgesia and maternal fever are associated with a higher rate of histologic chorioamnionitis.<sup>70</sup>

Meconium staining of the amniotic fluid may be a sign of fetal hypoxia. We compared the rate of meconium-stained fluid between the two groups. We found a statistically significant association between EA and meconium-stained amniotic fluid ( $P=0.01$ , OR 1.31, 95% CI 1.05 to 1.62) Kism et al<sup>49</sup> found a higher rate of meconium-stained fluid in association with EA. But the majority of previous studies did not find any association between EA and meconium-stained amniotic fluid.<sup>17,50,51</sup>

The rate of LSCS was similar in EA and non-EA groups. ( $P=0.72$ , OR 1.03, 95% CI 0.84 to 1.26). Although some of the previous studies have reported a higher rate of LSCS with EA,<sup>52</sup> the vast majority of studies showed that EA is not associated with an increase in the LSCS rate.<sup>14,49,53–55</sup>

Low cord arterial pH is a significant risk factor for neonatal mortality, hypoxic-ischemic encephalopathy, intraventricular hemorrhage, and periventricular leucomalacia.<sup>55</sup> We did not find any association between EA and cord arterial pH  $<7.1$  ( $P=0.75$ , OR 0.90, 95% CI 0.49 to 1.64). Majority of previous studies had similar observation.<sup>7,17,18,56–58</sup> Hintz et al<sup>59</sup> and Tawhid Soderholm et al<sup>15</sup> found a decrease in cord arterial pH  $<7.1$  in association with EA. One study<sup>19</sup> observed better cord pH in patients with EA.

We did not find any association between EA and Apgar score  $<7$  at 1 minute ( $P=0.12$ , OR 1.71 95% CI 0.85 to 3.41). At 5 minutes, only 3 patients had an Apgar score  $<7$ . Apgar score at 5 minutes  $<7$  is significantly associated with neurological disability, which may persist years postnatally.<sup>60</sup> Almost all the previous studies on neonatal effects of EA examined Apgar score at birth. Our findings on Apgar score correlate well with the majority of the previous studies. These include the recent Cochrane analysis by Anim-

Somuah<sup>14</sup> and many other studies.<sup>6,7,17,54,61</sup> None of them found any correlation between EA and 5 minute Apgar score. A recent study by Wang et al<sup>62</sup> also found no association between EA and Apgar score at one or 5 minutes. The correlation of low 1 minute Apgar with epidural analgesia observed by Hincz Petal<sup>59</sup> and Herrera-Gómez et al<sup>8</sup> might be attributable to the difference in the opioid used.

We examined the need for any positive pressure ventilation at birth. There was no difference between the groups ( $P=0.05$ , OR 1.57, 95% CI 0.99 to 2.49) Herrera-Gomez et al<sup>8</sup> and Greenwell et al<sup>34</sup> observed the increased need for any assisted ventilation in the EA group. Antonio et al<sup>7</sup> and Naito et al<sup>58</sup> looked for the need for advanced resuscitation and did not find any difference between the groups.

There is strong evidence that EA is associated with maternal fever.<sup>2,6,14,48</sup> Hence there is a theoretical possibility that the inflammatory response aroused by EA may extend to the fetus and hence may affect the White cell, platelets or C reactive protein. We compared the lab parameters of the neonates. There was no difference in the mean white cell count ( $P=0.32$ ), mean platelet count ( $P=0.38$ ) and C reactive protein  $>10$  mg/dL ( $P=0.845$ ). Our search did not identify any published study which looked for the association between EA and these parameters.

## Conclusion

Our study suggests that labor EA adversely affects the short-term neonatal outcome. It increases the NICU admission rate, antibiotic exposure, neonatal birth injuries, respiratory distress, and need for oxygen in the first 24 hours of life. But no effects were observed on the Apgar score, need for resuscitation, mechanical ventilation rate, and neonatal lab parameters. Mothers on epidural analgesia had a prolonged second stage of labor, a higher percentage of instrumental delivery, meconium-stained amniotic fluid and fever. The need for Caesarian delivery remains unaffected. Healthcare staff needs to provide information on this topic to all pregnant women who request for EA. The main limitation of this study is the retrospective design. Well-designed prospective studies addressing the safety of EDA are needed.

## Abbreviations

EA, Epidural Analgesia; NICU, Neonatal Intensive Care Unit; AWH, Al Wakra Hospital; CSE, Combined Spinal Epidural analgesia.; LSCS, Lower segment Caesarian Section; STD, Sexually transmitted diseases; GBS,

Group B Streptococcus; OR, Odds Ratio; CI, Confidence Interval; SD, Standard Deviation.

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## Disclosure

The authors report no conflicts of interest in this work.

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