Local and Regional Anesthesia

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ORIGINAL RESEARCH

The Maternal and Neonatal Glycemic Stress Response in Normal Vaginal Delivery: A Comparative Study Between Epidural and Parenteral Opioids Analgesia

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Background: It has been recognized that the type of anesthetic and analgesic technique and the relative pain degree may have an influence on hyperglycemic-stress response to surgery. This comparative study aimed to assess glucose levels in both mothers and infants during normal vaginal delivery. This study aimed to investigate this stress response between mothers who received parenteral analgesia versus epidural analgesia (EA) as an objective reflection for pain response.

Methods: One hundred and seventeen patients participated in this prospective comparative study. They were categorized into two groups: parenteral analgesia group (who received subcutaneous morphine) and EA group. The primary outcome was to measure the difference in blood glucose level before delivery (at 3 cm cervical dilation), at full dilation, and at the third stage of labor and compare these values between both groups. The secondary outcome was to assess the factors affecting the glycemic stress response in mothers and neonates.

Results: The change in maternal glucose level at full dilation and after delivery were significantly lower in the EA group. Neonatal glucose levels were not significantly different between the two groups. The change in maternal glucose level was influenced by the number of gravity and miscarriages. Neonatal glucose levels were associated with the gestational age of delivery, birth weight, and maternal glucose level at full cervical dilation.

Conclusion: EA appears superior to parenteral opioids analgesia, providing better pain management and subsequent lower stress response levels for mothers during vaginal delivery. These findings highlight the importance of the choice of analgesia during labor to optimize maternal well-being. Optimizing maternal factors (such as glycemic response) and neonatal factors (such as prematurity and birth weight) may influence the stress response of the neonates.

Keywords: epidural, morphine, normal vaginal delivery, glucose

Introduction

Pain is an integral aspect of the body's response to various stimuli, and numerous definitions have been proposed by the scientific community to better understand this complex phenomenon. The International Association for the Study of Pain has put forth a widely accepted definition: "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".[1] For the majority of women, labor is associated with significant pain and distress. This pain is both visceral and somatic, with distinct neural pathways and physiological responses during each stage of labor. The physiological effects of labor pain are widespread and include, but are not limited to: respiratory alkalosis and hyperventilation; elevated blood pressure and increased cardiac output; delayed

Received: 5 October 2024
Accepted: 23 December 2024
Published: 31 December 2024

gastric emptying; uterine hypoperfusion and impaired contractility; and metabolic acidosis.[2] It is also important to note that inadequate management of labor pain can have both short- and long-term effects, including confusion, mental health impairment, deterioration of marital relationships, anxiety and fear of future pregnancies, and chronic postpartum pain.[3–5] Interestingly, maternal satisfaction with obstetric care is less focused on pain management and more centered around involvement in intrapartum decision-making and a maternal sense of empowerment.[6,7]

Pain is directly related to the glycemic stress response. Preservation of glycemic homeostasis and avoidance of stress-induced hyperglycemia in surgical patients by modification of the factors affecting stress such as painful stimuli are the cornerstone for the current surgical practice. Acute hyperglycemia, a typical feature of the metabolic response of the body to surgery, has been related to a compromise to immune function and contributes to poor clinical outcome.[8,9] The degree of this response was shown to be proportionally related to the severity, length and pain of the surgical injury.[10]

Specifically, parenteral opioids can be used during the first stage of labor, with evidence suggesting they remain effective for about 2 hours after administration. However, they can lead to various maternal and fetal adverse effects. These effects include, but are not limited to: nausea and vomiting; dizziness; sedation; respiratory depression and oxygen desaturation; reduced fetal heart rate variability; and neonatal respiratory depression.[11,12] On the other hand, the use of regional analgesia has become increasingly popular among obstetricians and peripartum women, with the use of epidural analgesia (EA) in the United States tripling between 1981 and 2001.[13]

In this prospective observational study, we compared the effects of parenteral subcutaneous morphine analgesia and EA as methods for labor pain management. Our analysis will focus on assessing and comparing maternal and fetal responses to each type of analgesia within the study cohort.

Methods

Patients and Data

This study was approved by the institutional review board of Jordan University of Science and Technology (JUST), and written, informed consent was obtained from all subjects. This study was conducted at King Abdullah University Hospital, a tertiary care center that is affiliated with the JUST. We prospectively identified and investigated those pregnant women who were scheduled for normal vaginal delivery (NVD) between June 2022 and December 2022. The following data were recorded: demographics (eg age), obstetrical history (gestational age at delivery, gravidity, parity, diabetes, number of gestations, steroid injections, and the utilized medications in pregnancy), and the presence of third trimester-urinary tract infection. In addition, the type of analgesia (either EA or parenteral opioids) was determined. Moreover, the preoperative and postoperative blood glucose levels were measured for both the mother and newborn. Finally, neonatal data recorded were fetal gender (male, female), birthweight, Apgar scores (at 1 and 5 minutes), and admission to the neonatal unit were assessed.

Eligibility Criteria

Women eligible for inclusion in this study were those who delivered through NVD and who had received either effective EA or parenteral opioids. They were eligible for enrollment if they were at least 18 years of age, receiving either EA or parenteral opioids, American Society of Anesthesiologists physical status 1 or 2, with a single or twin gestation in the cephalic presentation at 37–42 weeks of gestation. The exclusion criteria comprised a history of nongestational diabetes mellitus, chronic advanced renal disease, and preeclamptic disorders. Moreover, women with a chronic pain syndrome, chronic use of pain medication, antidepressants, or treatment with parenteral opioid analgesia within 4 hours of NVD were excluded. Furthermore, women induced for stillbirths and fetal congenital abnormalities, all cases of NVD who were converted to cesarean sections, instrumental vaginal delivery, and home deliveries were excluded. In addition, any women with absolute contraindications for either the EA or the parenteral opioids were also excluded. We also excluded births when mode of delivery, child identity, or data for analgesia during labour were not recorded.

Outcomes, Patients' Groups, and Randomization

The participants were randomized based on their choices and preferences. Pregnant women were categorized into two groups: women who received EA and women who received parenteral analgesia. The primary outcome was to measure the difference in blood glucose level before delivery (at 3 cm cervical dilation), at full dilation, and at the third stage of labor and compare these values between EA and parenteral analgesia. Secondary outcomes were to investigate the factors (maternal and medical) affecting these blood glucose levels in mothers and neonates, and to assess the neonatal blood glucose levels based on these factors.

Anesthetic Setting

One consultant anesthesiologist and senior residents performed and supervised the conduction of analgesia in both patterns, EA and parenteral analgesia. At the labor room, two intravenous cannulas were inserted, and monitoring of blood pressure, electrocardiogram, and oxygen saturation were conducted.

Regarding the EA, under aseptic technique and after local anesthetic infiltration, epidural catheters were placed at the L2- L3, L3-L4, or L4-L5 interspace when women have a cervical dilatation of at least 4 cm. EA was initiated with epidural bupivacaine 0.1–0.125% and 50–100 μg of fentanyl, followed by a patient-controlled epidural analgesic with bupivacaine 0.0625% and fentanyl 2 μg /mL. The infusion for the patient-controlled pump included was set between 8 and 10 mL/h, demand bolus of 5 mL, and lockout interval of 5–10 min. The infusion was continued until perineal suturing was finished.

Regarding the parenteral opioids, at the cervical dilation of 4 cm, the women received subcutaneous 10 mg morphine. For all women in this study, this was the only dose of morphine administered for the participated women.

For both groups, on request for pain treatment, the staff can administer 500 mg acetaminophen orally with or without codeine (30 mg) every 4 hours.

For both groups, no serious side effects were reported.

Obstetrical Settings

The NVD operations were performed by a single consultant obstetrician. Foley's catheter was inserted. The women were placed on an external fetal monitor. During labor routine electronic fetal monitoring was performed via a scalp electrode. Furthermore, patients were monitored every hour for the first 12 hours and then every 4 hours for 12 hours by the nursing staff for sedation level, respiratory rate, pruritus and nausea/vomiting. Metoclopramide 10 mg intravenously for nausea every 4 hours and nalbuphine 5 mg intravenously for pruritus every 6 hours could be administered if needed. After delivery of the baby, all women received intravenous 10 IU oxytocin bolus and 20 IU oxytocin infusion over 1 hour. Both groups were given 2–3 liters of crystalloids fluid. No complications including meconium-stained amniotic fluid, cardiotocograph abnormalities or pathological durations of the labor were reported during the delivery process in any of the study participants. The newborn was examined immediately by pediatricians for Apgar score and for the baseline perinatal examination.

Glucose Measurement

For women in both groups (received EA or parenteral subcutaneous morphine), the blood glucose concentration was obtained baseline before delivery at 3 cm of cervical dilation. Another reading was obtained at full cervical dilation. Moreover, the third readings were obtained just after delivery and before placental delivery. A neonatal venous sample was obtained when the neonate was examined and was stable Blood glucose concentration was measured using a lancet device (Joycoo BG-102; Joycoo, Amman, Jordan).

Statistical Analysis

The collected data was inserted into a spreadsheet and analyzed statistically using the IBM SPSS statistical package for Windows v.26 (Armonk, New York, USA). The factors that were examined relating to glucose level were described using the frequency distribution of categorical variables and the mean ± standard error (SE) for continuous variables. The data

were examined using Pearson's chi-square ($\chi 2$) tests to examine associations between categorical variables and Student's t-tests were used for continuous variables. A value of $p < 0.05$ indicated a statistically significant difference. Multiple linear regression analysis was utilized to examine the effect of many factors on the glucose response. The sample size was calculated using power of analysis formula with the assumption of alpha level of 0.05, power of analysis at 90%, estimated glucose level for both groups of 100 and 90 mg/dl.

Results

Demographic and Clinical Characteristics

A total of 117 patients were included in the analysis cohort. The mean age was 29.20 ± 0.50 years while the mean gestational age at delivery was 38.22 ± 0.20 weeks. The study cohort consisted mainly of singleton pregnancies (n = 114, 97.4%). Gestational parameters possessed an average gravidity of 3.01 ± 0.10, parity of 1.95 ± 0.10, and miscarriages of 0.36 ± 0.07. Obstetrical complications as in GDM (n = 10, 8.50%) and GBS infection (n = 7, 6.00%) were observed. Prenatal steroidal therapy was administered to 29.10% of the cohort (n = 34). Apgar scores were 7.95 ± 0.07, 8.95 ± 0.05, and 9.12 ± 0.05 at 1, 5, and 10 minutes respectively. The cohort's birth weight was 3140.30 ± 41.30 grams. NICU admission was needed in 31.6% of the neonates (n = 37). Participants were randomly and evenly distributed in terms of analgesia type, with 50.40% (n = 59) receiving parenteral subcutaneous morphine and 49.60% (n = 58) receiving EA. Neonatal mean glucose levels were 83.95 ± 2.20 mg/dL. Maternal glucose levels before delivery (at 3 cm dilation) were 103.58 ± 2.80 mg/dL reaching 106.89 ± 2.30 mg/dL at full cervical dilation. Maternal glucose levels decreased to 98.97 ± 1.90 mg/dL at the third stage of labor. Table 1 summarizes the demographic and clinical characteristics of the study cohort.

Demographic and Clinical Characteristics Differences Across Analgesia Subgroups

Data revealed that mothers who received parenteral subcutaneous morphine analgesia were significantly older than those who received an EA (30.90 ± 0.70 years vs 27.50 ± 0.60 years, P = 0.001). Participants who received parenteral subcutaneous morphine had significantly (P = 0.001) higher gravidity (3.88 ± 0.2) compared to those who received an EA (2.12 ± 0.1). Similarly, parity was significantly (P = 0.001) higher in the parenteral subcutaneous morphine group (2.47 ± 0.2) compared to the EA group (1.41 ± 0.1). Additionally, the incidence of miscarriages was higher in participants who received parenteral subcutaneous morphine (0.56 ± 0.1) compared to those who received EA (0.16 ± 0.05), with a significant difference (P = 0.004). There was no statistical difference between the two groups concerning GDM, antenatal steroid injections, and GBS infections. Neonatal parameters also did not show significant differences between the two groups. However, NICU admission rates approached significance, with 23.7% of newborns from the parenteral subcutaneous morphine group admitted compared to 39.7% from the EA group, yielding a P-value of 0.049. Regarding maternal glucose levels, significant differences were found before delivery (at 3 cm dilation) with parenteral subcutaneous morphine analgesia showing a glucose level of 97.83 ± 2.3 mg/dL compared to 109.64 ± 5.2 mg/dL with an EA (P = 0.037). At full cervical dilation, the glucose level with parenteral subcutaneous morphine was 116.36 ± 3.5 mg/dL versus 96.91 ± 2.3 mg/dL with an EA (P = 0.0001). No significant differences were observed in maternal glucose levels post-delivery. The changes in maternal glucose levels from before delivery to full dilation and post-delivery showed significant differences. At full dilation, the glucose level change was 18.53 ± 3.30 mg/dL with parenteral subcutaneous morphine analgesia versus −12.73 ± 5.00 mg/dL with the EA (P = 0.0001). Post-delivery, the change was 3.00 ± 2.80 mg/dL with parenteral subcutaneous morphine versus −12.64 ± 5.60 mg/dL with the EA (P = 0.012). Table 2 summarizes the demographic and clinical characteristics differences across the analgesia subgroups.

Factors Affecting the Levels of Maternal Glucose Before Delivery

Our analysis of the association between maternal glucose levels before delivery and various variables revealed several significant relationships. Specifically, the regression coefficient (B) for maternal glucose levels in relation to maternal age was −1.10 ± 0.40 (P = 0.029). Significant differences were also seen between the presence and absence of GDM. The mean maternal glucose level was significantly (P = 0.033) lower in participants with GDM (84.00 ± 9.00 mg/dL)

Table 1 General Demographical and Clinical Characteristics of the Study Cohort

Variables	*n* (%) or mean ± SEM
Mother age (years)	29.20 ± 0.50
Gestation age at delivery (weeks)	38.22 ± 0.20
Number of gestations	
Singleton	114 (97.40)
Twins	3 (2.60)
Gestational parameters	
Gravity	3.01 ± 0.10
Parity	1.95 ± 0.10
Miscarriages	0.36 ± 0.07
GDM	
Yes	10 (8.50)
No	107 (91.50)
Receiving antenatal steroid injection	
Yes	34 (29.1)
No	83 (70.9)
Development of GBS infection	
Yes	7 (6.00)
No	110 (94.00)
Neonatal parameters:	
Birth weight (grams)	3140.30 ± 41.30
Apgar score at 1 minute	7.95 ± 0.07
Apgar score at 5 minutes	8.95 ± 0.05
Apgar score at 10 minutes	9.12 ± 0.05
NICU admission for newborn	
Yes	37 (31.60)
No	80 (68.40)
Type of pain analgesia	
Parenteral subcutaneous morphine	59 (50.40)
Epidural block	58 (49.60)
Levels of glucose (stress response)	
Neonatal glucose level (mg/dL)	83.95 ± 2.2
Maternal glucose level before delivery (at 3 cm dilation) (mg/dL)	103.58 ± 2.8
Maternal glucose level at full cervical dilation (mg/dL)	106.89 ± 2.3
Maternal glucose level after delivery (third stage) (mg/dL)	98.97 ± 1.9
Difference of maternal glucose level between (before delivery) and (at full dilation) (mg/dL)	3.30 ± 3.3
Difference of maternal glucose level between (before delivery) and (after delivery) (mg/dL)	−4.62 ± 3.1

Abbreviations: SEM, standard error of the mean; GDM, gestational diabetes mellitus; GBS, Group B Streptococcus; NICU, neonatal intensive care unit.

compared to those without GDM (105.45 ± 2.90 mg/dL). Additionally, the type of analgesia administered was associated with significant differences where higher mean glucose levels were recorded in the EA group in comparison with the parenteral subcutaneous morphine group (109.64 ± 5.20 mg/dL vs 97.83 ± 2.30 mg/dL, $P = 0.037$). In contrast, the gestational age at delivery, number of gestations, gestational parameters, steroidal therapy, GBS development, and neonatal parameters revealed insignificance. Table 3 summarizes the association between these variables and the levels of maternal glucose before delivery.

Factors Affecting the Change in Maternal Glucose Levels at Full Dilation

The regression coefficient (B) for the change of maternal glucose level at full dilation in relation to the maternal age was 1.44 ± 0.50 ($P = 0.013$). Gestational parameters also significantly affected the change in maternal glucose levels at full dilation. The regression coefficient (B) for gravidity was 5.59 ± 1.50 ($P = 0.001$), parity 6.48 ± 2.20 ($P = 0.005$), and

Table 2 Demographical and Clinical Differences Between Epidural Block and Morphine Analgesia Subgroups

Variables	n (%) or mean ± SEM		*P*-value
	Parenteral Subcutaneous Morphine Analgesia (*n* = 59)	Epidural Block (*n* = 58)	
Mother age (years)	30.9 ± 0.70	27.5 ± 0.60	0.001
Gestation age at delivery (weeks)	38.31 ± 0.20	38.14 ± 0.20	NS
Number of gestations			
Singleton	58 (98.30)	56 (96.60)	NS
Twins	1 (1.70)	2 (3.40)	
Gestational parameters			
Gravity	3.88 ± 0.20	2.12 ± 0.10	0.001
Parity	2.47 ± 0.20	1.41 ± 0.10	0.001
Miscarriages	0.56 ± 0.10	0.16 ± 0.05	0.004
GDM			
Yes	5 (8.50)	5 (8.60)	NS
No	54 (91.50)	53 (91.40)	
Receiving antenatal steroid injection			
Yes	14 (23.70)	20 (34.50)	NS
No	45 (76.30)	38 (65.50)	
Development of GBS infection			
Yes	2 (3.40)	5 (8.60)	NS
No	57 (96.60)	53 (91.40)	
Neonatal parameters:			
Birth weight (gram)	3178.14 ± 57.20	3101.07 ± 59.60	NS
Apgar score at 1 minute	7.85 ± 0.10	8.06 ± 0.07	NS
Apgar score at 5 minutes	8.95 ± 0.07	8.94 ± 0.07	NS
Apgar score at 10 minutes	9.17 ± 0.08	9.07 ± 0.07	NS
NICU admission for newborn			
Yes	14 (23.70)	23 (39.70)	0.049
No	45 (76.30)	35 (43.80)	
Levels of glucose (stress response)			
Neonatal glucose level (mg/dl)	87.37 ± 3.10	80.28 ± 3.20	NS
Maternal glucose level before delivery (at 3 cm dilation) (mg/dL)	97.83 ± 2.30	109.64 ± 5.20	0.037
Maternal glucose level at full cervical dilation (mg/dL)	116.36 ± 3.50	96.91 ± 2.30	0.0001
Maternal glucose level after delivery (third stage) (mg/dL)	100.83 ± 2.80	97.00 ± 2.50	NS
Change of maternal glucose level at full dilation (mg/dL)	18.53 ± 3.30	−12.73 ± 5.00	0.0001
Change of maternal glucose level at (after delivery) (mg/dL)	3.00 ± 2.80	−12.64 ± 5.60	0.012

Abbreviations: SEM, standard error of the mean; GDM, gestational diabetes mellitus; GBS, Group B Streptococcus; NICU, neonatal intensive care unit.

miscarriages 10.20 ± 4.20 (P = 0.018). The mean change in maternal glucose levels at full dilation approached a significant (P = *0*.049) difference between patients with and without GDM. For those with GDM, the mean change was 22.80 ± 7.70 mg/dL, compared to 1.45 ± 3.30 mg/dL for those without GDM. Additionally, the regression coefficient (B) for the change in maternal glucose levels at full dilation with respect to the Apgar score at 1 minute was −11.24 ± 4.60 (P = 0.016)., while other neonatal parameters yielded insignificant results. Furthermore, the type of analgesia administered also influenced the change in maternal glucose levels at full dilation. The mean for the change of maternal glucose at full dilation in relation to parenteral subcutaneous morphine was 18.53 ± 3.30 mg/dL, compared to −12.73 ± 5.00 mg/dL with an epidural block (P = 0.0001). While the variables mentioned earlier showed significant results, other clinicopathological variables did not. Table 3 summarizes the association between these variables and the change in maternal glucose levels at full dilation.

Table 3 Factors Affecting the Levels of Maternal Glucose Level Before Delivery, Change of Maternal Glucose Level at Full Dilation and After Delivery

Variables	Mean ± SEM* or B Regression Coefficient ± SEM **					
	Maternal Glucose Level Before Delivery (mg/dL)	*P*-value	Change of Maternal Glucose Level at Full Dilation (mg/dL)	*P*-value	Change of Maternal Glucose Level at (after delivery) (mg/dL)	*P*-value
Mother age (years)**	−1.10 ± 0.40	0.029	1.44 ± 0.50	0.013	0.91 ± 0.5 0	NS
Gestation age at delivery (weeks)**	−0.62 ± 1.50	NS	−0.395 ± 1.80	NS	−1.38 ± 0.07	NS
Number of gestations*						
Singleton	104.64 ± 2.80	NS	2.66 ± 2.30	NS	−5.34 ± 3.00	NS
Twins	64.40 ± 20.70		27.33 ± 20.10		22.66 ± 19.10	
Gestational parameters**						
Gravity	−2.66 ± 1.40	NS	5.59 ± 1.50	0.001	3.82 ± 1.50	0.014
Parity	−3.50 ± 2.00	NS	6.48 ± 2.20	0.005	3.83 ± 2.20	NS
Miscarriages	−0.39 ± 3.60	NS	10.20 ± 4.20	0.018	8.39 ± 4.00	0.041
GDM*						
Yes	84.00 ± 9.00	0.033	22.80 ± 7.70	0.049	19.00 ± 10.60	0.019
No	105.45 ± 2.90		1.45 ± 3.30		−6.87 ± 3.20	
Receiving antenatal steroid injection*						
Yes	105.33 ± 6.50	NS	−1.27 ± 6.10	NS	−6.03 ± 7.10	NS
No	102.87 ± 3.00		5.14 ± 3.70		−4.04 ± 3.30	
Development of GBS infection*						
Yes	113.00 ± 12.40	NS	−2.00 ± 12.30	NS	−12.14 ± 12.50	NS
No	102.97 ± 2.90		3.65 ± 3.40		−4.12 ± 3.20	
Neonatal parameters**						
Birth weight (gram)	0.005 ± 0.006	NS	0.002 ± 0.007	NS	−0.005 ± 0.007	NS
Apgar score at 1 minute	6.50 ± 4.00	NS	−11.24 ± 4.60	0.016	−11.23 ± 4.30	0.011
Apgar score at 5 minutes	8.03 ± 5.60	NS	−9.67 ± 6.50	NS	−12.97 ± 5.10	0.038
Apgar score at 10 minutes	−1.26 ± 5.10	NS	2.51 ± 5.90	NS	−3.94 ± 4.10	NS
Type of pain analgesia*						
Parenteral subcutaneous morphine	97.83 ± 2.30	0.037	18.53 ± 3.30	0.0001	3.00 ± 2.80	0.012
Epidural block	109.64 ± 5.20		−12.73 ± 5.00		−12.64 ± 5.60	

Note: *Mean ± SEM **B Regression Coefficient ± SEM.
Abbreviations: SEM, standard error of the mean; GDM, gestational diabetes mellitus; GBS, Group B Streptococcus.

Factors Affecting the Change in Maternal Glucose Levels After Delivery

Significant effects on the change in maternal glucose levels after delivery were observed with gravidity, miscarriages, presence of GDM, Apgar scores at 1 and 5 minutes, and type of analgesia. The regression coefficients (B) for gravidity and miscarriage were 3.82 ± 1.50 (P = 0.014) and 8.39 ± 4.00 (P = 0.041), respectively. The mean change in maternal glucose after delivery in relation to presence (19.00 ± 10.60 mg/dL) and absence (−6.87 ± 3.20 mg/dL) GDM were also significant (P = 0.019). First and second Apgar scores were associated with significant decreases in the change of maternal glucose levels after delivery whereas the third score was not. The regression coefficients (B) were −11.23 ± 4.30 (P = 0.011) at 1 minute and −12.97 ± 5.10 (P = 0.038) at 5 minutes. The type of analgesia also had significant effect on the change of maternal glucose after delivery with a mean change of 3.00 ± 2.80 mg/dL for parenteral subcutaneous morphine and −12.64 ± 5.60 mg/dL for EA (P = 0.012). Insignificant results were seen with other clinicopathological variables. Table 3 summarizes the association between these variables and the change in maternal glucose levels after delivery.

Factors Affecting Neonatal Glucose Levels

Analysis of factors influencing neonatal glucose levels revealed significant associations with gestational age at delivery, birth weight, and maternal glucose levels at full dilation. The results are summarized in Table 4. The regression coefficient (B) for neonatal glucose levels in relation to gestational age at delivery was 2.81 ± 1.20 (P = 0.023). For birth weight, the regression coefficient (B) was 0.01 ± 0.0005 (P = 0.046). Similarly, maternal glucose levels at full

https://doi.org/10.2147/LRA.S499370

dilation had a regression coefficient (B) of 0.176 ± 0.008 (P = 0.049). Other maternal and neonatal parameters lacked significance in relation to neonatal glucose levels.

Discussion

To the best of our knowledge, this is the first study to compare the glucose stress response between EA and opioids in cases of pain management in NVD along with their newborns. This study revealed that EA achieved better stress glucose levels changes which reflects better pain management. Moreover, EA was the preferred choice in younger women with lower gravity and parity. Furthermore, gestational diabetes mellitus was associated with more fluctuation in glucose stress levels. In addition, the older age, the higher gravity and number of miscarriages were associated with higher levels of fluctuation of glucose stress response. Interestingly, the higher the levels of glucose stress response were associated with lower Apgar scores. Regarding the neonatal glucose stress response, the higher the gestational age, the heavier the birth weight, and the higher the maternal glucose stress response were associated with higher neonatal glucose stress response.

There are two important components to the surgical stress response: a neurohormonal response and an immunological response. Elevated stress levels, commonly observed during procedures that cause tissue trauma, can lead to unfavorable outcomes, including increased morbidity and worsened postoperative recovery. Therefore, it is crucial to mitigate stress through effective management during surgeries. Surgical trauma activates the sympathetic-adrenal-medullary axis, which stimulates the sympathetic nervous system, resulting in increased heart rate and blood pressure. Additionally, pancreatic function is affected; glucagon levels rise while insulin levels decrease, promoting glycogenolysis and gluconeogenesis, and temporarily spiking glucose levels.[14] Overwhelming clinical data have elucidated that perioperative hyperglycemia negatively affects prognosis and increases the risk of pneumonia, wound infections, and cardiovascular events.[15] It was found that different anesthetics and anesthetic techniques can influence the degree of glycemic stress response. In a study by Bani Hani et al, general anesthesia (GA) was associated with a greater glycemic stress response compared to spinal anesthesia (SA) during cesarean sections.[16] In a study by J. Van Loocke et al, the rise in glucose levels with opioid-free anesthesia was more modest during elective laparoscopic bariatric surgery compared to opioid anesthesia.[17] Additionally, studies on the relationship between opioids and hyperglycemia revealed that both synthetic and endogenous opioids increase blood glucose levels.[18] In general, perioperative hyperglycemia is influenced by the patient's metabolic state, degree of tissue injury, insulin resistance, and intraoperative management. However, the type of anesthesia plays an important role as a modulator of the glycemic response by affecting neuroendocrine pathways and can even alter insulin release in the absence of surgical stress.[19]

A study by Kehlet demonstrated that EA decreases the hyperglycemic response during surgery, most likely through its inhibitory action on the hypothalamic-pituitary-adrenal axis.[20] Houghton et al assessed the glucose tolerance tests during pelvic procedures and they showed that EA improved tissue glucose uptake.[21] Another mechanism suggested Shaw et al that EA attenuated the hyperglycemic response during surgery by inhibiting hepatic glucose release rather than improving tissue glucose utilization.[22]

Pain management can significantly impact the birthing experience. Multiple methods of pain relief have been suggested and studied in the literature, with some mothers opting out of any pharmacological intervention. Nonpharmacological approaches with or without pharmacological methods vary in efficacy and evidence.[11,23,24] On the other hand, clinical and basic data on pharmacological methods are widely available and well-supported. Systemic and regional analgesia methods are commonly used in labor. Systemic options include parenteral opioids, parenteral nonopioids (analgesics, antihistamines, sedatives), and inhaled medications (like nitrous oxide and flurane). While all these methods can improve pain scores, parenteral opioids generally provide better pain control compared to other systemic options.[11,12] Regional analgesia involves neuroaxial techniques where a local anesthetic, with or without an opioid, is injected into the epidural or spinal space near the nerves that transmit pain. This is typically done via a catheter, achieving a central nerve blockade.[25] A review unveiled low-quality evidence of better pain control with EA compared to nonepidural analgesia.[25,26] The advantages of regional analgesia include a shorter time to pain relief (approximately 15 minutes with an epidural block), profound pain relief, prolonged duration of action, and the ability to be administered upon request at any stage of labor.[11,12] Additionally, maintenance of analgesia can be achieved for longer periods if needed through either intermittent or continuous injections, with a preference for intermittent injections due to their lower

Table 4 Factors Affecting Neonatal Glucose Level

Variables	Mean ± SEM or B Regression Coefficient ± SEM	
	Neonatal Glucose Level (pg/mL)	*P*-value
Mother age (years)**	−0.283 ± 0.30	NS
Gestation age at delivery (weeks)**	2.81 ± 1.20	0.023
Number of gestations*		
Singleton	84.43 ± 2.20	NS
Twins	65.95 ± 1.50	
Gestational parameters**		
Gravity	−0.33 ± 1.10	NS
Parity	−0.43 ± 1.60	NS
Miscarriages	−0.43 ± 2.90	NS
GDM*		
Yes	74.85 ± 4.40	NS
No	84.82 ± 2.30	
Receiving antenatal steroid injection*		
Yes	83.38 ± 4.30	
No	84.15 ± 2.60	NS
Development of GBS infection*		
Yes	97.56 ± 11.70	NS
No	83.05 ± 2.20	
Neonatal parameters**		
Birth weight (gram)	0.01 ± 0.0005	0.046
Apgar score at 1 minute	−3.59 ± 3.10	NS
Apgar score at 5 minutes	−4.94 ± 4.30	NS
Apgar score at 10 minutes	−4.34 ± 3.90	NS
Type of pain analgesia*		
Parenteral subcutaneous morphine	87.37 ± 3.10	NS
Epidural block	80.28 ± 3.20	
NICU admission for newborn*		
Yes	79.05 ± 4.20	NS
No	86.20 ± 2.50	
Levels of glucose (stress response)**		
Maternal glucose level before delivery (at 3 cm dilation) (mg/dL)	0.003 ± 0.07	NS
Maternal glucose level at full cervical dilation (mg/dL)	0.176 ± 0.008	0.049
Maternal glucose level after delivery (third stage) (mg/dL)	0.024 ± 0.10	NS
Change of maternal glucose level at full dilation (mg/dL)	0.084 ± 0.06	NS
Change of maternal glucose level at (after delivery) (mg/dL)	0.006 ± 0.06	NS

Note: *Mean ± SEM **B Regression Coefficient ± SEM.
Abbreviations: SEM, standard error of the mean; GDM, gestational diabetes mellitus; GBS, Group B Streptococcus; NICU, neonatal intensive care unit.

local anesthetic consumption and better pain control in obstetric analgesia.[27,28] Adverse effects of EA include maternal fever, risk of respiratory depression, maternal hypotension, post-dural puncture headaches, and variable prolongation of the second stage of labor. Contrary to prior belief, modern techniques of EA are not associated with an increased need for assisted vaginal deliveries or cesarean sections.[11,12,25]

A Cochrane review comparing EA to opioid analgesia found that the EA group experienced lower pain intensity and higher satisfaction rates. There were no significant differences between the two methods regarding cesarean section rates, long-term maternal back pain, postnatal depression, or neonatal outcomes. Both methods were associated with side effects; hypotension, fever, motor blockade, and urinary retention were more common with EA, while respiratory

depression, nausea, and vomiting were reported more frequently in the opioid group than the regional anesthesia.[29] Low-quality evidence indicated a higher association between EA and the need for assisted deliveries; however, modern epidural techniques have shown no such association.[11,25]

A systematic review revealed that there was no difference in the 5-min APGAR score, and fetal heart rate abnormality between the epidural and opioids groups except that 1-min poor APGAR score and the need for neonatal naloxone were higher in the opioids group.[30] Another review found that EA in NVD may result in lower 1-min APGAR score but not at 5-min.[31] According to Cochrane review there was no evidence of significant difference in the 5-min APGAR score of neonates born of mothers with epidural and those treated with opiates.[32] EA has been associated with better Apgar scores at 1- minute, no difference at 5-min and a reduced need for administration of neonatal naloxone.[33,34]

This study is not without limitations; the age discrepancy may have introduced confounding factors, such as differences in pain tolerance and comorbidities. Although there was no significant difference in sample size between the two groups, a larger sample may enhance the generalizability of the results. Furthermore, pain scoring was included in this study. Future research should consider conducting similar studies across multiple sites to increase participant diversity and improve generalizability.

Conclusions

This study revealed that EA may be associated with better pain response and subsequently more controllable hyperglycemic stress response. Women with previous history of recurrent miscarriages may have the benefit of EA. Neonates would have better stress outcome through the optimization of perinatal factors. Labor pain may be the most painful experience for any women to encounter. The experience is different for each woman and the different methods chosen to relieve pain depend upon the techniques available locally and the personal choice of the individual. The women should have the right to deliver with minimal pain and to offer the choice of the preferred analgesic methods depending on the clinical situation.

Availability of Data and Materials

Data are available upon request from the corresponding author.

Ethical Approval

The Just Institutional Review Board (IRB) and research committee approved the study's ethical conduct. Under the approval number (58/137/2021). The study is carried out in compliance with the ethical guidelines in place at our institute, taking the Helsinki Declaration as an ethical guideline for research involving human subjects. Written informed consents were obtained from all the participants.

Funding

This research received no funding.

Disclosure

The authors declare no conflict of interest.

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