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ORIGINAL RESEARCH

Salivary Substance P Levels During Cesarean Section Under Spinal versus General Anesthesia: A Prospective Study

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Background: Substance P is a key neuropeptide involved in the transmission of nociceptive (pain) signals. The choice of anesthesia for childbirth, particularly for cesarean section (CS), is a critical decision that directly impacts the mother's physiological response to the procedure. This study aims to compare the levels of salivary SP in pregnant women undergoing CS under spinal versus general anesthesia.

Methods: Eighty-three patients participated in this prospective comparative study. They were categorized into two groups: general and spinal anesthesia groups. The primary outcome was to measure the mean difference in salivary substance P level at three different time points of CS, and to compare these values between both groups. The secondary outcome was to assess the factors affecting the substance P levels in the mothers.

Results: The study included 44 (53%) who received spinal anesthesia and 39 (47%) who received general anesthesia. Median substance P levels were significantly higher in the spinal anesthesia group (761 pg/mL [IQR 532–1335]) compared with the general anesthesia group (409 pg/mL [IQR 118–1094]; U = 1188.0, p = 0.0026). On multiple regression analysis, type of anesthesia was the independent variable influenced the levels of salivary substance P.

Conclusion: This study demonstrates that participants receiving spinal anesthesia have significantly higher salivary substance P levels compared to those undergoing general anesthesia for CS. Further research is needed to understand the mechanisms underlying this observation and to determine its clinical implications for maternal and neonatal outcomes.

Keywords: cesarean section, ELISA, general anesthesia, spinal anesthesia, substance P

Introduction

The experience of childbirth is a profound physiological event characterized by intense pain, which is mediated by a complex interplay of neural, hormonal, and chemical factors.[1] The pain of labor is classically described in two stages: visceral pain from uterine contractions and cervical dilation, and somatic pain from the stretching of the perineum and pelvic structures.[2] Understanding the biochemical mediators of this pain is crucial for optimizing analgesic strategies and improving maternal and fetal outcomes.

Substance P (SP), an undecapeptide belonging to the tachykinin family, is a key neuropeptide involved in the transmission of nociceptive (pain) signals.[3] SP is released from the central terminals of primary afferent C-fibers in the dorsal horn of the spinal cord upon noxious stimulation, such as the intense contractions and tissue distension experienced during labor.[2,4] Its function is to amplify or excite cellular processes, acting as a potent neurotransmitter and neuromodulator in the central and peripheral nervous systems.[5] The concentration of SP in the plasma and cerebrospinal

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fluid is often used as a biological marker of nociception and stress.[6] Dysregulation of SP has been implicated in various conditions, including chronic pain, anxiety, and even pregnancy-related pathologies like preeclampsia.[7,8]

The biological actions of SP are mediated primarily through the neurokinin-1 (NK1) receptor, a G protein-coupled receptor that is widely expressed in the central and peripheral nervous systems, as well as in immune and non-neuronal cells.[9] Upon binding of SP to the NK1 receptor, downstream intracellular signalling cascades are activated, including phospholipase C, protein kinase C, and mitogen-activated protein kinase pathways, resulting in membrane depolarisation, enhanced nociceptive transmission, and promotion of neurogenic inflammation.[10]

The choice of anesthesia for cesarean section, is a critical decision that directly impacts the mother's physiological response to the procedure. Neuraxial anesthesia, such as spinal anesthesia, is the preferred method for CS due to its rapid onset, excellent analgesia, and reduced risk of complications compared to general anesthesia.[11,12] However, the physiological effects of different anesthetic techniques on the neurochemical stress response, specifically SP levels, are not fully elucidated.

Pain associated with CS represents a distinct clinical and physiological entity compared to labour pain. CS involves surgical incision through the anterior abdominal wall and uterus, eliciting both somatic and visceral nociceptive signals that activate peripheral and central pain pathways.[13] The acute postoperative pain following CS is driven by tissue trauma, inflammatory mediator release, and sensitization of peripheral nociceptors at the wound site.[14] Inadequately managed CS pain can lead to prolonged recovery, impaired maternal-neonatal bonding, increased risk of chronic postsurgical pain, and postpartum depression. Unlike vaginal delivery, in which pain is primarily generated by uterine contractions and perineal distension, CS pain arises from direct surgical manipulation of somatic and visceral structures under controlled anaesthetic conditions. Understanding the nociceptive mediators involved in CS pain is therefore essential for optimising perioperative analgesia and improving maternal outcomes.

Regional anesthesia, by blocking the transmission of nociceptive input at the spinal cord level, is hypothesized to attenuate the release of pain mediators.[15] Conversely, the systemic administration of general anesthetics may have different, sometimes less direct, effects on central and peripheral neuropeptide release. Studies examining the effects of general anesthetics on SP release in animal models have shown that agents like propofol and isoflurane may not significantly alter SP release or the internalization of its receptor (NK1r) in the spinal dorsal horn, suggesting a complex mechanism of action distinct from the direct blockade provided by local anesthetics.[16,17] Other research has investigated the impact of different anesthetic methods on neuropeptide levels, such as Brain Natriuretic Peptide (BNP), and found that the choice of anesthesia (general versus spinal) can differentially affect the perioperative stress response in parturient women.[18] Given the established role of SP as a central mediator of pain and stress, a comparison of SP levels between the two groups is warranted. Such a comparison would provide insight into the relative degree of neurochemical stress and nociceptive activation associated with each anesthetic technique during cesarean section. The primary objective of this study was to compare the levels of salivary SP in pregnant women undergoing CS under spinal versus general anesthesia. Secondary objectives included exploring the influence of maternal and perinatal factors on SP levels, thereby contributing to a more comprehensive understanding of the neurochemical response to different anesthetic modalities in the peripartum period.

Methods and Materials

Patients and Data Collection

This prospective cohort study was conducted at King Abdullah University Hospital (KAUH), Irbid, Jordan, between January 2024 and January 2025, and included women undergoing CS. Participants were categorized according to the type of anesthesia administered: spinal anesthesia and general anesthesia. The primary comparison was between spinal and general anesthesia groups. Clinical and demographic data, including maternal age, body-mass index (BMI), gestational age at delivery, neonatal birth weight, presence of gestational diabetes mellitus (GDM), preeclampsia, and neonatal intensive-care-unit (NICU) admission, were extracted from medical records. Participants with incomplete clinical data or missing saliva samples were excluded from the final analysis according to the predefined study protocol.

Women eligible for inclusion in this study were those who delivered through CS and who had received either spinal or general anesthesia. They were eligible for enrollment if they were at least 18 years of age, American Society of Anesthesiologists physical 2, with a single or twin gestation at 37–42 weeks of gestation. The exclusion criteria comprised a history of nongestational diabetes mellitus, and chronic advanced renal disease. Moreover, women with a chronic pain syndrome, chronic use of pain medication, and antidepressants were excluded. Furthermore, all cases of spinal anesthesia converted to general anesthesia were excluded. Any women with absolute contraindications for either the spinal or general anesthesia were also excluded; two such cases were excluded, and both received epidural anesthesia.

Outcomes and Patients' Groups,

Participants were allocated to either spinal or general anesthesia according to clinical indications and patient preference. Pregnant women were categorized into two groups: women who received spinal anesthesia and women who received general anesthesia. The primary outcome was to measure the difference in the mean salivary SP levels at the induction of anesthesia, at the CS incision, and at skin closure. Secondary outcomes were to investigate the factors (maternal and medical) affecting these salivary SP levels in mothers.

Anesthetic Setting

Consultant anesthesiologists and senior residents carried out and supervised the conduction of anesthesia. At the theater, two intravenous cannulas were inserted prior to the procedure for hemodynamic management, one for fluid resuscitation and the other for medication administration, and continuous monitoring of blood pressure, oxygen saturation, respiratory rate, and electrocardiogram were conducted.

Spinal Anesthesia

At the level of L3-L4 or L4-L5 of the vertebral column, the SA was conducted under aseptic technique using 25- or 27-gauge spinal needles with 2.3 mL of 0.5% heavy bupivacaine and 0.4 mL of 0.005% fentanyl (25 μg; 50 μg/mL). Adequate hydration with crystalloid solution (Ringer's lactate at 10–20 mL/kg/h) was performed before the procedure along with100% O2 through a nasal cannula to maintain adequate intravascular volume.

General Anesthesia

Rapid-sequence induction was done with the insertion of endotracheal tube sized 6.5–7.5 mm according to patient throat size; the induction was performed by using propofol (2.5 mg/kg) and rocuronium (0.5 mg/kg). Anesthesia was maintained using isoflurane (0.5–0.75%) in 50% oxygen and 50% air. After delivery of the baby and cutting the umbilical cord, fentanyl was given, and the analgesic regimen mainly consisted of 150 mg diclofenac sodium and/or 10 mg subcutaneous morphine; inhaled anesthetic agents were discontinued, and anesthesia was maintained with a propofol infusion. At the end of surgery, neostigmine (2.5 mg) and atropine (1 mg) were given intravenously.

Obstetrical Settings and Samples Collection

The CS operations were performed by a single consultant obstetrician. Foley's catheter was inserted. Lower-segment transverse uterine incision was carried out. 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, depending on intraoperative fluid loss and hemodynamic status. The newborn was examined immediately by pediatricians for Apgar score and for the baseline perinatal examination.

Unstimulated saliva samples were collected from each participant during CS; 5 minutes before induction of anesthesia, at the CS incision, and at skin closure; using sterile collection tubes sterile pipette. Samples were immediately placed on ice, transported to the diagnostic laboratory and centrifuged at 3000 × g for 15 minutes to remove debris. The clarified supernatant was aliquoted and stored at −80 °C until analysis. Samples were coded with serial numbers by a registered nurse, and group allocation was blinded to both the main investigator and the ELISA technician. For analysis, the mean value of the three time-point samples per patient was used to represent SP levels in the results.

Substance P Quantification

SP levels were quantified using the Abcam Substance P ELISA Kit (ab288318, Cambridge, UK) following the manufacturer's protocol. The sandwich ELISA utilized Substance P-specific antibodies pre-coated on 96-well plates. Standards and diluted samples were incubated with a biotin-conjugated detection antibody and streptavidin–HRP, followed by TMB substrate development and absorbance measurement at 450 nm. The standard curve range was 39–2500 pg/mL with a sensitivity of <15 pg/mL. Samples were diluted 1:10, or 1:1 for low concentrations. All samples were run in duplicate, and concentrations were calculated using a four-parameter logistic (4-PL) regression. Quality controls and blanks were included on each plate to ensure assay reliability. The selection of sampling time points was based on the expected fluctuation of Substance P levels during different intraoperative pain-threshold stages, and intraoperative measurements were used to assess the effect of anesthesia techniques.

Statistical Analysis

Data were entered into a spreadsheet and analyzed using IBM SPSS Statistics for Windows, Version 26.0. Categorical variables were summarized as frequency and percentage, while continuous variables were reported as median and interquartile range (IQR) due to non-normal distribution.

Normality of continuous variables was assessed using the Shapiro–Wilk test. Because Substance P levels were not normally distributed, non-parametric statistical tests were applied. Comparisons between the spinal anesthesia and general anesthesia groups for continuous variables were performed using the Mann–Whitney *U*-test, while categorical variables were compared using Fisher's exact test.

To evaluate factors associated with Substance P levels, multiple linear regression analysis was performed. Because Substance P concentrations were markedly right-skewed, a logarithmic transformation was applied prior to regression analysis to approximate normality and stabilize variance. The log-transformed Substance P values were entered as the dependent variable in the regression model. Predictor variables included anesthesia type, maternal age, body mass index (BMI), gestational age at delivery, birth weight, and the presence of gestational diabetes mellitus (GDM). The sample size was estimated using the power of analysis equation. Assuming a power of 90%, an alpha level of 0.05, and anticipated mean substance P levels of 400 pg/mL and 470 pg/mL for the two groups, The yielded required sample size was 31.

Results

Patient Demographics

A total of 83 women were included in the analysis, comprising 44 (53%) who received spinal anesthesia and 39 (47%) who received general anesthesia. Baseline maternal and perinatal characteristics were comparable between the two groups. There were no significant differences in maternal age, body mass index (BMI), gestational age at delivery, or fetal birth weight (all $p > 0.05$). Similarly, the prevalence of gestational diabetes mellitus (GDM), preeclampsia, antenatal corticosteroid use, and neonatal intensive care unit (NICU) admissions did not differ significantly between groups. Operative time was relatively homogeneous across patients, with a mean of 44.1 minutes. These findings confirm that the spinal and general anesthesia cohorts were well matched for clinical and demographic variables, ensuring the validity of comparisons in SP concentrations (Table 1).

Comparison of Substance P Levels

Normality testing using the Shapiro–Wilk test demonstrated that SP concentrations were not normally distributed ($p < 0.001$). Therefore, non-parametric analysis was applied. Median SP levels were significantly higher in the spinal anesthesia group (761 pg/mL [IQR 532–1335]) compared with the general anesthesia group (409 pg/mL [IQR 118–1094]; $U = 1188.0$, $p = 0.0026$) (Table 2). The data distribution was markedly right-skewed, further supporting the use of non-parametric testing. A boxplot (Figure 1) visually depicts this difference, showing a clear upward shift in SP concentrations among participants who received spinal anesthesia.

Table 1 Baseline Maternal and Clinical Characteristics by Anesthesia Type

Characteristic	Spinal (n = 44)	General (n = 39)	p-value
Maternal age (years)	30.8 [27.4–33.6]	31.2 [28.5–34.9]	0.64
BMI (kg/m^2)	27.3 [24.9–30.5]	27.9 [25.6–31.2]	0.58
Gestational age (weeks)	38.5 [37.2–39.3]	38.3 [37.0–39.1]	0.71
Fetal birth weight (kg)	3.25 [2.95–3.50]	3.18 [2.88–3.45]	0.66
Gestational diabetes mellitus (GDM)	6 (13.6%)	5 (12.8%)	0.91
Preeclampsia	4 (9.1%)	3 (7.7%)	0.83
Steroid use	5 (11.4%)	4 (10.3%)	0.88
NICU admission	7 (15.9%)	6 (15.4%)	0.95

Table 2 Baseline Characteristics and Substance P Levels for Each Group

Group (Anesthesia)	N	Median	IQR (Q1–Q3)	Min	Max
Spinal	44	761.07	532.32–1334.69	114.14	2766.48
General	39	408.73	117.58–1093.67	6.78	3780.93

Secondary Analyses

To evaluate the influence of maternal and perinatal variables on SP concentrations, a multiple linear regression model was constructed using log-transformed SP values as the dependent variable. Predictors included anesthesia type, maternal age, BMI, gestational age, neonatal birth weight, and GDM status. After adjustment, general anesthesia remained independently associated with lower SP levels ($\beta = -0.868$, $p = 0.0008$). None of the other predictors, including age, BMI, gestational weeks, birth weight, or GDM, were significant (all $p > 0.25$) (Table 3). The model accounted for approximately 10% of the variance in SP concentrations (adjusted $R^2 = 0.10$), indicating a modest association between anesthesia type and neuropeptide level differences in this cohort. Regression coefficients represent unstandardized beta coefficients (B) with 95% confidence intervals.

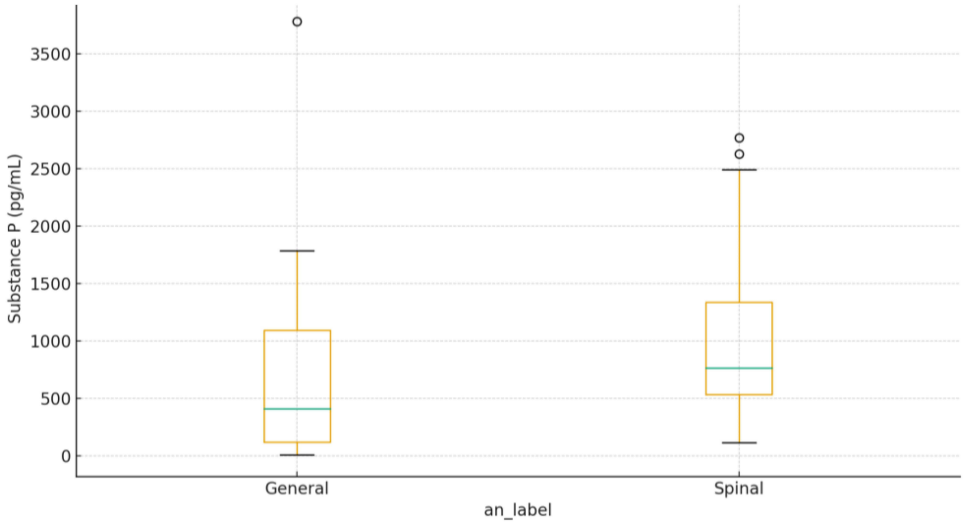

Figure 1 Boxplot of Substance P levels by anesthesia type.

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Table 3 Multivariable Linear Regression Analysis for Predictors of Log-Transformed Substance P Levels

Predictor	Coefficient (β)	95% CI	p-value
Anesthesia (General vs Spinal)	−0.868	−1.36 to −0.38	0.0008
Maternal age	−0.004	−0.020 to 0.012	0.63
BMI	−0.014	−0.110 to 0.082	0.77
Gestational weeks	0.028	−0.470 to 0.526	0.91
Birth weight (kg)	0.089	−0.410 to 0.588	0.70
GDM	−0.593	−1.600 to 0.414	0.25

Notes: P-values were calculated using Spearman's rank correlation for continuous variables and the Mann–Whitney *U*-test for comparisons between two independent groups.

Table 4 Univariate Associations Between Maternal Variables and Substance P Levels

Factor	Statistics	P-value
Mode of anesthesia (Spinal vs General)	U = 1188	0.0026
Maternal comorbidities	16.93	0.459
Previous menstrual irregularities	233	0.484
Single vs multiple gestation	2.97	0.227
Mode of admission	164	0.304
GDM	227	0.558
Preeclampsia	74	0.217
Placenta previa spectra	941	0.412

Factors Affecting Substance P Levels

Among all examined maternal and obstetric factors, the mode of anesthesia was the only variable that showed a statistically significant association with salivary SP levels ($p = 0.0026$), indicating a notable difference between patients who received spinal versus general anesthesia (Table 4).

Distribution of Substance P Levels

The overall distribution of SP concentrations across all participants demonstrated substantial variability, with values ranging from 6.78 pg/mL to 3780.93 pg/mL and a pronounced right-skewed pattern (Figure 2). This pattern suggests considerable inter-individual variation in neuropeptide release during cesarean section, likely reflecting differing nociceptive and stress responses.

Discussion

This study found that salivary SP levels were significantly higher in women receiving spinal anesthesia compared to those under general anesthesia during CS. While this result contrasts with the expectation that neuraxial blockade would reduce the release of pain- and stress-related neuropeptides such as SP,[19] it may reflect a more complex interaction between anesthetic technique and the maternal neuroendocrine stress response during labor and delivery.

The primary explanation for our results may lie in the phenomenon of neurogenic inflammation and the differential effects of local versus general anesthetics on this process. While spinal anesthesia provides profound sensory and motor

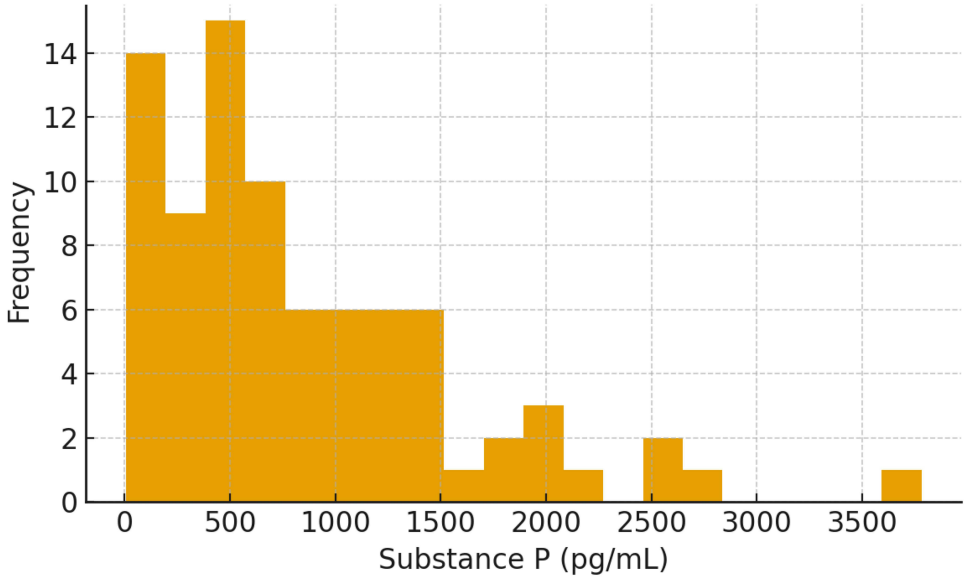

Figure 2 Histogram showing the overall distribution of Substance P levels (pg/mL).

blockade, the administration of a local anesthetic into the subarachnoid space can itself trigger a localized inflammatory response.[20,21] This response may involve the activation of glial cells and the release of various pro-inflammatory mediators, including SP, from the central terminals of primary afferent neurons that are not completely blocked, or from other cell types within the spinal cord.[22] It is also possible that the rapid onset of a dense spinal block leads to a paradoxical upregulation of SP in response to the abrupt cessation of afferent input, a phenomenon that has been observed with other neurotransmitter systems.[5]

This finding stands in contrast to the well-established notion that regional anesthesia is superior to general anesthesia in blunting the overall surgical stress response, particularly regarding classical stress hormones. For instance, studies comparing cortisol levels consistently report that spinal anesthesia leads to significantly lower serum cortisol levels than general anesthesia in both elective surgical patients and those undergoing cesarean section.[23,24] Our observation of elevated SP in the spinal group suggests that SP may not strictly follow the pattern of the hypothalamic-pituitary-adrenal (HPA) axis hormones but rather may reflects a localized neurogenic response to the neuraxial block itself. This distinction underscores SP's dual role as both a systemic stress marker and a mediator of local neurogenic inflammation.[25,26]

In contrast, general anesthetics exert their effects systemically, producing a state of unconsciousness and amnesia that is accompanied by a more global suppression of central nervous system activity.[27] Several studies have demonstrated the anti-inflammatory properties of various general anesthetic agents, such as propofol and volatile anesthetics, which have been shown to attenuate the release of inflammatory cytokines and other mediators.[21,28,29] Specifically, some general anesthetics have been found to inhibit the release of SP from nerve terminals, which would be consistent with the lower SP levels observed in our general anesthesia group.[30] For instance, pentobarbital has been shown to protect against neurogenic inflammation by inhibiting SP release from peripheral nerves in rats.[31]

Furthermore, the relationship between anesthetic technique and systemic inflammation is complex. While some studies on cesarean delivery show general anesthesia significantly increases pro-inflammatory cytokines like TNF-α and IL-6 compared to spinal anesthesia,[32] others in non-obstetric surgery have found no significant difference in the pattern of change for IL-6 and C-reactive protein (CRP) between the two anesthetic groups.[33,34] The lower SP levels in our general anesthesia group, alongside the variable cytokine response reported in the literature, reinforces the idea that general anesthetics may exert a unique, suppressive effect on the neuropeptidergic system that is distinct from their influence on the broader inflammatory cascade.

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The higher SP levels in the spinal anesthesia group could also be related to the hemodynamic consequences of neuraxial blockade. Spinal anesthesia-induced sympathectomy often leads to vasodilation and hypotension. The body perceives this hemodynamic instability as a physiological stressor, triggering compensatory neuroendocrine responses. SP is a potent vasodilator and plays a crucial role in cardiovascular regulation, including the baroreceptor reflex.[19] Research indicates that SP is released in the Nucleus Tractus Solitarius (NTS) in response to baroreceptor activation, such as during hypotensive episodes, as part of the body's effort to maintain hemodynamic homeostasis. Therefore, the systemic hypotension and autonomic changes experienced during SA could directly stimulate SP release as a component of this compensatory mechanism or as a byproduct of baroreflex activation.[35] Although not measured in our study, the release of other stress hormones, such as cortisol and catecholamines, may also be differentially affected by the two anesthetic techniques and could interact with the SP system.[36]

Furthermore, the psychological experience of the patient must be considered. Participants undergoing spinal anesthesia remain awake and aware of their surroundings, which, despite the absence of pain, can be a source of significant anxiety and stress.[5] Psychological stress is a potent stimulus for SP release, and it is plausible that the conscious experience of surgery, even without pain, contributes to the elevated SP levels in the spinal anesthesia group.[5,37] In contrast, general anesthesia eliminates consciousness and the psychological component of the surgical stress response.

Our findings are in contrast to some studies that have suggested a reduction in stress markers with regional anesthesia.[38] However, the literature is not entirely consistent, and other studies have reported an increase in certain inflammatory markers after regional techniques.[39]

A particularly relevant study by Janicki et al, which directly compared plasma SP concentrations in patients undergoing surgery under GA versus SA, reported that the administration of GA was accompanied by a decrease in plasma SP levels.[40] This finding, which predates our study by several decades, aligns perfectly with the lower SP levels we observed in our general anesthesia group. However, Janicki et al's study did not report on the SP levels in the SA group relative to the GA group, making a direct comparison of the differential effect on SP challenging. Furthermore, the study was conducted in orthopedic surgery patients, highlighting the need to consider the unique physiological context of pregnancy and childbirth. For example, pregnancy is associated with altered sensitivity to both local and general anesthetics, and the hormonal of the peripartum period can influence the expression and activity of neuropeptides and their receptors.[41]

While spinal anesthesia remains the preferred technique for most cesarean deliveries due to its excellent safety profile and maternal-fetal benefits, our findings raise important questions about its impact on the neurochemical stress response.[42] The elevated levels of SP in the spinal anesthesia group could have several potential clinical implications. SP is not only a marker of nociception but also a potent pro-inflammatory mediator that can increase vascular permeability, promote vasodilation, and modulate immune cell function.[25,26] Chronically elevated SP levels have been implicated in the pathophysiology of persistent postsurgical pain and other chronic pain conditions.[43,44] Although a single measurement of SP during childbirth cannot predict the long-term risk of chronic pain, it does suggest that the neurochemical environment created by spinal anesthesia may be more pro-inflammatory than previously thought.

This study has several limitations that should be acknowledged. First, the sample size is relatively small, which may limit the generalizability of our findings. Second, we measured SP in saliva, which, while a convenient and non-invasive method, may not perfectly reflect the concentrations of SP in the central nervous system or at the site of tissue injury. While some studies have reported a significant positive correlation between plasma and cerebrospinal fluid SP levels, the relationship between salivary and plasma SP remains less consistent. One pharmacological study demonstrated that salivary SP correlated with plasma levels following cholinergic stimulation[45] yet direct comparisons in pain populations are limited this. Third, we did not collect data on other stress hormones or inflammatory markers, which would have provided a more complete picture of the neuroendocrine response to anesthesia. Fourth, the allocation to spinal or general anesthesia was based on clinical indications and patient preferences rather than randomization, which may introduce confounding by indication and selection bias. Fifth, the incidence of postoperative nausea and vomiting was not assessed. Finally, this was an observational study, and while we controlled several potential confounding variables, the possibility of residual confounding cannot be excluded.

Future research should aim to replicate our findings in a larger, more diverse cohort of participants. It would also be valuable to measure SP and other stress markers in both plasma and cerebrospinal fluid to gain a more comprehensive

understanding of the systemic and central effects of different anesthetic techniques. Additionally, studies that correlate SP levels with clinical outcomes, such as the incidence of persistent postsurgical pain, postpartum depression, and other peripartum complications, are needed to determine the clinical significance of our findings.

Conclusion

In conclusion, this study found that participants receiving spinal anesthesia had significantly higher salivary SP levels compared with those undergoing general anesthesia for CS. This observation suggests that the neuroendocrine response to different anesthetic modalities during cesarean delivery may vary and may not always align with the commonly assumed attenuation of stress responses with regional anesthesia. Further research is needed to understand the mechanisms underlying this observation and to determine its clinical implications for maternal and neonatal outcomes.

Data Sharing Statement

The datasets used and/or analysed during the current study are presented in tables and text.

Ethical Approvals

This work was approved by the institutional review board (IRB) committee at King Abdullah University Hospital (KAUH). IRB No.: 10/141/2021, date: 01/07/2021, and IRB No: 18/172/2024, date: 29/07/2024. All patients provided written informed consent before enrolment into the study. The study was conducted in accordance with the Declaration of Helsinki, good clinical practices and relevant regulatory guidelines.

Consent for Publication

Written informed consent was obtained from all patients.

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Disclosure

The authors declared no conflict of interest.

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