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The Perioperative Neonatal and Maternal Glycemic Response and APGAR Score During Elective Cesarean Section: Factors and Anesthetic Management

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ABSTRACT

Background: The type of anesthesia and intensity of pain experienced during surgery are linked to the body's stress response, as reflected in preoperative and postoperative glucose levels. **Objective:** This comparative study aims to assess the hyperglycemic stress response to cesarean sections performed under different types of anesthesia. **Methods:** This prospective study included 302 participants, divided into two groups: a general anesthesia group and a spinal anesthesia group. Our primary objective was to investigate the effects of general versus spinal anesthesia on pregnant women undergoing cesarean section. Secondarily, we aimed to assess the impact of other factors on the maternal and neonatal stress response during surgery. **Results:** Both groups exhibited a significant proportional increase in mean blood glucose levels after surgery. However, this increase was more pronounced in the general anesthesia group than in the spinal anesthesia group. Therefore, spinal anesthesia had a greater effect in attenuating the hyperglycemic response to surgery during cesarean section compared to general anesthesia. Maternal blood glucose levels were significantly associated with steroid injection, type of anesthesia, and gestational age. In contrast, neonatal blood glucose was significantly associated with gestational age, APGAR score, maternal steroid injection, type of anesthesia, maternal age, and both preoperative and postoperative maternal blood glucose levels. **Conclusion:** Spinal anesthesia was superior to general anesthesia in attenuating both maternal and neonatal hyperglycemic responses during the cesarean section. This highlights the significant impact of anesthesia type on maternal and neonatal well-being.

Keywords: Neonates, General anesthesia, Spinal anesthesia, APGAR score.

1. BACKGROUND

Cesarean section (CS) rates are rising globally, with a recent World Health Organization (1,,2). (WHO) study estimating that one-third of pregnancies will be delivered by CS by 2030 (1). When performed for medically indicated cases, CS is associated with reduced maternal and neonatal mortality. Moreover, recent clinical data highlight significant differences in outcomes based on the anesthetic technique used (2). Interestingly, the shift from general anesthesia (GA) to neuraxial anesthesia has reduced anesthesia-related maternal mortality by half (3).

There has been a great deal of interest in the potential beneficial effects of preservation of glucose homeostasis and early avoidance of stress-induced hyperglycemia in surgical patients by modification of the stress response. Acute hyperglycemia, a typical feature of the metabolic response of the body to surgery, has been showing a significantly compromise to immune function and contributes to poor clinical outcome (4-7). The degree of this response was shown to be proportionally related to the severity and length of the surgical injury (8), and the magnitude of insulin resistance increased during surgery according to the degree of surgical injury (9).

It has long been recognized that the type of anesthetic technique has an influence on hyperglycemic response to surgery (10). During surgery, stress-induced hyperglycemia is more pronounced with inhalation anesthesia.

In animals, earlier studies revealed that inhalational anesthetics such as enflurane and halothane impaired glucose tolerance in dogs and that was related to inhibition of insulin secretion and decreased tissue insulin sensitivity (4). In contrast, some studies have revealed reduction in blood glucose and norepinephrine levels when high-dose propofol infusion is used, thereby reducing the hyperglycemic stress response to surgery (11). Regarding anesthesia techniques, recent clinical data revealed a greater increase in blood glucose when CS were performed under GA compared to CS under spinal anesthesia (SA) (12).

2. OBJECTIVE

In this study, we aim to investigate the effect of GA and SA on pregnant women who are scheduled to undergo CS. Also, this study aims to understand the effect of other factors on the maternal stress response during CS.

3. MATERIAL AND METHODS

This study was conducted at King Abdullah University Hospital, a tertiary care center that is affiliated with the Jordan University of Science and Technology, and Princess Badi'ah Hospital that is affiliated to the Ministry of Health. After obtaining the institutional review approval, we prospectively identified, assessed and followed those pregnant women who were scheduled to undergo elective CS surgery between June 2019 and December 2019. The following information were obtained: demographics (e.g. 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 anesthesia was determined. Moreover, the preoperative and postoperative blood glucose levels were measured.

The included group comprises any women who was scheduled to undergo an elective CS with the American Society of Anesthesiologists (ASA) physical status of I–II, above the age of 18 years, and fasting time preoperatively between 8 and 12 hours. Women with diabetes mellitus, chronic advanced renal disease, preeclampsia, and psychiatric disorders were excluded. In addition, all cases who was converted to GA from SA were excluded. Moreover, any women with absolute contraindications for either the GA or SA were excluded. Women with gestational diabetes were included in the study to investigate and compare the effect of gestational diabetes. Based on their choices, pregnant women were categorized into two groups: the GA group and SA group. Written informed consent was obtained from all women.

Anesthetic setting

Consultant anesthesiologists and senior residents carried out and supervised the conduction of anesthesia. At the CS operating theater, two intravenous access sites were inserted. For all pregnant women in the study, standard monitoring of blood pressure, three-lead electrocardiogram, and pulse oximetry oxygen saturation were conducted and continuously monitored during the intraoperative and postoperative periods.

Spinal anesthesia

The SA was conducted under aseptic conditions, at the level of L3-L4 or L4-L5 of the spinal column. SA was performed with 2.3 ml of 0.5% heavy bupivacaine and 0.4 ml of 0.005% fentanyl using 25- or 27-gauge spinal needles; 100% O2 was administered through a simple face mask with a flow of 4 liters per minute.

General anesthesia

The GA started by breathing oxygen for 3 minutes via a face mask. After that, anesthesia was induced with 2–2.5 mg/kg propofol and 1.2 mg/kg rocuronium to facilitate tracheal intubation using a regular 6.5-7.5 mm ID endotracheal tube. After delivery of the baby and cutting the umbilical cord, 3 μg/kg fentanyl was given. Before delivery of the baby, anesthesia was maintained with 0.7% isoflurane in 50% oxygen and 50% nitrous oxide, and after delivery and cutting the umbilical cord, anesthesia was maintained with a propofol infusion at a rate of 150 μg/kg/min and the inhaled anesthetic agents were discontinued. ETCO2 was maintained between 30mmHg and 40mmHg throughout the surgery. At the end of surgery, anesthetic maintenance was discontinued, and reversal of the neuromuscular blockade consisting of 2.5 mg of neostigmine and 1 mg of atropine was given intravenously. The extubation of the trachea was performed when the patient was breathing spontaneously with a good tidal volume, fully awake, and could sustain head elevation for more than 5 seconds.

Obstetrical settings

The CS operations were performed by consultant obstetricians. Upon arrival at the operating theater, both groups received 750 mg of cefuroxime IV, 8 mg of dexamethasone IV, 50 mg of ranitidine IV, and 10 mg of metoclopramide IV before starting anesthesia. Foley's catheter was inserted. The women were placed on an external fetal monitor. After sterilization, Pfannenstiel incision was performed. After that, lower-segment transverse uterine incision was carried out. After the fetus is delivered, the umbilical cord is doubly clamped and cut.

After delivery of the baby, all women received 10 IU oxytocin IV bolus and 20 IU oxytocin infusion over 1 hour. Both groups were given 2000–3000 ml crystalloids IV; half of the amount was 0.9% normal saline, and the other half was Ringer's lactate solution.

Glucose measurement

For the women underwent GA, the blood glucose concentration was obtained 5 minutes before induction and 5 minutes after the surgery. For the SA group, the glucose concentration was obtained 5 minutes before the injection of the local anesthetic agent and 5 minutes after the surgery. Blood glucose concentration was measured using a blood glucose monitoring kit with a lancet device (Joycoo BG-102; Joycoo, Amman, Jordan). After disinfecting with alcohol, swap the tips of the fingers of the nondominant hand pricked with a lancet tip to measure the blood glucose concentration.

Statistical analysis

Data were entered into a spreadsheet. Statistical analyses were performed using IBM SPSS Statistics Software (v.21), 2012. Data were presented as frequency distributions for categorical variables and mean ± standard error of the mean for continuous variables. Data was tested at a significance level of 0.05%. Pearson χ2 test was used to investigate the significance of association between categorical variables, while student's t-test and ANOVA were applied to examine the significance level for continuous normally distributed variables. The normality of the distribution of data was tested using the Kolmogorov- Smirnov test. Kruskal- Walis and Mann-Whitney tests were applied for the abnormally distributed continuous variable. If a significant (P<0.05) relationship was found, then a posthoc residual analysis for categorical variables and a Fisher's least significant difference test for continuous variables were applied to determine the exact significance between groups for each variable. Multiple linear and multiple logistic regression analyses were utilized to study the multiple effect of different variables.

Variable	Number	Percent (%)
	Mean ± SE	
Mother age (years)	31.0 ± .3	
Gestational diabetes	14	4.6
Steroid Injection	111	36.8
Gravidity		
1	39	12.9
2	66	21.9
3	61	20.2
4	56	18.5
5	37	12.3
6	15	5.0
7	8	2.6
8	12	4.0
9	6	2.0
11	1	.3
13	1	.3
Parity		
0	51	16.9
1	80	26.5
2	62	20.5
3	55	18.2
4	33	10.9
5	11	3.6
6	5	1.7
7	4	1.3
8	1	.3
Number of Miscarriages		
1	69	67.0
2	21	20.4
3	8	7.8
4	3	2.9
6	1	1
8	1	1
GBS	16	5.3
Nationality		
Jordanian	289	95.7
Non- Jordanian	13	4.3
Number of fetus		
1	290	96.0
2	8	2.6
3	4	1.3
Type of anesthesia		
GA	171	56.6
SA	131	43.4
Gestational age (weeks)	37.4 ± .1	
Gestational age (days)	263.3 ± .7	
Birth weight (gram)	3008.5 ± 32.0	
Mother Sugar before delivery (mg/dL)	93.4 ± 1.1	
Mother sugar after delivery (mg/dL)	100.3 ± 1.2	

Table 1. General characteristics. Abbreviations: SE: standard error; GBS: group-B streptococcus; GA: gestational age; SA: spinal anesthesia

4. RESULTS

Patients' characteristics

The study included 302 patients who satisfied the inclusion and exclusion criteria of the study. The average age of mothers included in the study was 31 years (table 1), the majority of patients in our sample were Jordanian (95.7%). The number of patients with gestational diabetes was 14 with a percentage of 4.6%.

About 36.8% of patients in our sample had received a steroid injection before delivery. As regards to gravidity and parity, gravida 2 (21.9%) and para 1 (26.5%) were most commonly encountered. Also, most women (67%) has a history of single miscarriage. In addition, 5.3% of the women had Group B streptococcus positive colonization or had a genitourinary infection of another cause. Most patients had singleton pregnancy with a percentage of 96%.

GA was more commonly utilized in Cesarean sections (56.6%) compared with SA (43.4%). The average gestational age at time of delivery was 37.4 weeks and the average birthweight of neonates was 3008.5 grams. When it comes to maternal sugar, the average reading before delivery was 93.4 mg/dL compared to 100.3 mg/dL after delivery.

Differences GA and SA

It was found that the age of mothers is similar between both groups. However, the results revealed that mothers who had SA delivered at earlier gestational ages with a mean gestational age for the SA group of 36.7 weeks and for the GA group of 37.9 weeks (P = 0.000) (Table 2).

Regarding pre-operative maternal blood sugar, the readings were significantly higher in women who underwent GA in comparison with women who underwent SA (100.8 mg/dL vs. 83.6 ± 1.5, P = 0.000). Also, the post-operative readings were significantly higher in the GA group with a mean sugar level of 110.1 mg/dL and a mean sugar level in the SA group of 87.7 mg/dL (P = 0.000). Moreover, the perioperative difference in the sugar level (postoperative-preoperative) was significantly higher in the GA group.

There was no significant difference in the number of gestational diabetes patients between both groups. The gravidity and parity did not affect the type of the utilized anesthesia. Most patients who have GBS colonization or a history of GUI underwent SA (10.7%) compared to 1.2% who underwent GA (P = 0.000). The number of fetus did not affect the type of anesthesia used. Higher number of patients who had a steroid injection before delivery underwent SA (63.4%) compared to 16.4% in the GA group (P = 0.000).

Factors affecting neonatal blood sugar

The neonatal sugar was significantly associated with the gestational age, APGAR score, maternal steroid injection, type of anesthesia used, maternal age, and pre-operative and post-operative maternal blood sugar (Table 3).

Neonates born to mothers who received a steroid injection before delivery had neonatal blood sugar mean of 67.4 ± 1.9 mg/dL (P = 0.000). The mean neonatal blood sugar was higher in the GA group as compared to SA group (P = 0.000). As the mother age increases by 1 year the neonatal blood sugar falls 0.9 mg/dL with a SD of 0.2 (P = 0.000). As gestational age increases by 1 week, the neonatal blood sugar increases by 3.0 ± 0.7 mg/dL (P = 0.000). Moreover, a significantly (P = 0.001) positive correlation was found between gestational age when calculated by day, as gestational age increases by one day the neonatal blood sugar increases by 0.4 mg/dL with a SD of 0.1. Having higher APGAR score was translated as lower neonatal blood sugar (P = 0.000). Higher maternal blood sugar was reflected with increased neonatal blood sugar (P = 0.000).

Neonatal blood sugar levels were similar between babies born to diabetic and non-diabetic mothers. Maternal drug use of ASA, methyldopa or thyroxine did not affect the sugar level in babies. Having higher gravidity, parity, or number of previous miscarriages did not significantly affect the neonatal blood sugar. Mothers who tested positive for GBS or had a previous GUI did not significantly had babies with higher blood sugar readings. The number of babies, history of NICU admission and the neonatal birthweight as well were not determining factors of neonatal blood sugar level.

Variable	GA N (% within GA)	Spinal N (% within spinal)	p- Value
Mother age (years) (mean±SE)	30.5 ± .5	31.5 ± .5	NS
Gestational age (weeks) (mean±SE)	37.9 ± .1	36.7 ± .2	0.0
Gestational age (Days)	266 ± .9	260.0 ± 1.1	0.0
Birth weight (gram) (mean±SE)	3069 ± 40.4	2931.8 ± 50.7	0.033
Mother's sugar before delivery (mg/dL) (mean±SE)	100.8 ± 1.4	83.6 ± 1.5	0.0
Mother's sugar after delivery (mg/dL) (mean±SE)	110.1 ± 1.6	87.7 ± 1.3	0.0
Mother's perioperative difference in sugar level (mg/dL) (mean±SE)	9.1 ± 1.6	4.2 ± 1.3	0.02
Gestational diabetes	6 (3.5)	8 (6.1)	NS
Gravidity			
1	22 (12.9)	17 (13.0)	NS
2	37 (21.6)	29 (22.1)	
3	32 (18.7)	29 (22.1)	
4	32 (18.7)	24 (18.3)	
5	25 (14.6)	12 (9.2)	
6	6 (3.5)	9 (6.9)	
7	4 (2.3)	4 (3.1)	
8	9 (5.3)	3 (2.3)	
9	3 (1.8)	3 (2.3)	
11	0 (0.0)	1 (0.8)	
13	1 (0.6)	0 (0.0)	
GBS / GUI	2 (1.2)	14 (10.7)	0.0
Number of babies			
1	168 (98.2)	122 (93.1)	NS
2	2 (1.2)	6 (4.6)	
3	1 (0.6)	3 (2.3)	
Steroid Injection	28 (16.4)	83 (63.4)	0.0

Table 2. GA versus SA. Abbreviations: SE: standard error; GBS: group-B streptococcus; GA: gestational age; SA: spinal anesthesia

5. DISCUSSION

In this study, we compared the effects of spinal and general anesthesia on changes in blood glucose concentrations before and after CS in non-diabetic patients. Although mean blood glucose concentrations showed a significant proportional increase after surgery in both groups, this effect was much more significant with GA than with SA. Therefore, SA had a significant effect on hyperglycemic response attenuation to surgery during CS than GA.

Turina et al. (5) illustrated that short-term hyperglycemia is associated with increased mortality and risk of infection in critically ill patients related to a significant decrease in monocyte HLA-DR expression due to hyperglycemia and hyperinsulinemia.

The process of hyperglycemia management puts the patient in an increased risk of having a hypoglycemic response which will result in developing the risks associated with hypoglycemia, and thus avoidance of stress-induced hyperglycemia is preferable for treating dysglycemia (13). Other studies on isoflurane inhalational anesthetic demonstrated an increase in the plasma glucose concentration during anesthesia even without surgical stress related to impairment of glucose tolerance and stimulation of whole-body glucose production (4, 6, 14). Furthermore, the hyperglycemic stress response in patients undergoing major abdominal surgery under isoflurane GA could be related to an increase in endogenous glucose production accompanied by a decrease in glucose utilization (4, 15). Tanaka et al. (16) stated that there was a glucose intolerance and impairment of insulin secretion and glucose utilization during sevoflurane and isoflurane anesthesia in a dose-independent manner. According to the results of a study by Cok et al. (17), although isoflurane and propofol, both combined with remifentanil, provided a clinically comparable insulin and cortisol response to surgery in craniotomy operations, propofol attenuated the increase in plasma blood glucose. This suggested that propofol may be preferred over isoflurane when tight control of blood glucose is desired.

With regards to neuraxial anesthesia such as epidural or spinal block with local anesthetics, it leads to a blockage of both afferent input from the operative site to the central nervous system and the hypothalamic-pituitary axis and efferent autonomic neuronal pathways to the liver and adrenal medulla. Consequently, the adrenocortical and glycemic responses to surgery are greatly inhibited (7, 18). Another study by Kehlet (19) showed that epidural blockade attenuated the hyperglycemic response during surgery, most likely mediated through its inhibitory action on the hypothalamic-pituitary-adrenal axis. Some of the studies looking at glucose tolerance tests during pelvic procedures illustrated that epidural block improved tissue glucose uptake (20, 21). By contrast, other studies revealed that epidural block attenuated the hyperglycemic response during surgery by inhibiting hepatic glucose release rather than improving tissue glucose utilization (22, 23). In a study by Lattermann et al. (7) it was concluded that epidural blockade attenuated the hyperglycemic response to abdominal surgery through modification of glucose production without affecting glucose utilization. However, it is still unclear whether the inhibitory effect of the epidural block on the hyperglycemic response during surgery was a consequence of the improvement in tissue glucose uptake, a decrease in glucose production, or a combination of both. In any case, it has been well recognized that epidural blockade with a local anesthetic inhibits or even prevents the endocrine and metabolic responses to surgery including hyperglycemia (7). An earlier study by Engquist et al. (24) showed that epidural blockade, established before the start of surgery, prevented the increase in plasma glucose and cortisol levels in response to surgery in patients undergoing hysterectomy. A more recent study by Hadimioglu et al. (25) demonstrated that combined general and epidural anesthesia, when compared with GA alone, reduced inflammatory activation and insulin resistance responses to the stress of the renal transplantation procedure and that inhibition of stress responses had a beneficial effect on length of stay in hospital postoperatively. As a summary for the previously mentioned studies, epidural anesthesia attenuates the hyperglycemic response during surgery. Our study looked at SA, a different neuraxial technique, and confirmed the results of those earlier studies as SA resulted in effects comparable to epidural anesthesia with attenuation of the hyperglycemic response to surgery.

Factors	**Neonatal Sugar (Mean ± S.E)** **B value for interval variable**	**p- value**
Maternal DM	67.5 ± 6.4	NS
Steroid Injection	67.4 ± 1.9	0.000
Drugs		
methyldopa	68.5 ± 7.0	NS
ASA	66.2 ± 3.8	
Thyroxine	71.6 ± 7.2	
Gravidity		
1	85.0 ± 3.7	NS
2	81.9 ± 2.9	
3	76.0 ± 2.7	
4	79.0 ±2.9	
5	80.2 ± 4.1	
6	69.4 ± 6.5	
7	66.4 ± 10.9	
8	76.4 ± 5.2	
9	71.8 ± 8.8	
11	60.0 ± 0.0	
13	104.0 ± 0.0	
Parity		
0	86.4 ± 3.3	NS
1	80.1 ± 2.5	
2	74.9 ± 2.7	
3	79.3 ± 3.2	
4	71.8 ± 4.0	
5	81.4 ± 8.1	
6	80.2 ± 8.7	
7	81.5 ± 10.2	
8	50.0 ± 0.0	
Miscarriage		
1	81.5 ± 2.9	NS
2	71.1 ± 5.0	
3	69.6 ± 7.1	
4	83.0 ± 17.0	
6	60.0 ± 0.0	
8	104.0 ± 0.0	
GBS or GUI	68.1 ± 5.3	NS
Number of babies		
1	79.1 ± 1.4	NS
2	75.8 ± 6.8	
3	76.3 ± 10.3	
NICU admission	71.3 ± 4.4	NS
GA	90.3 ± 1.5	0.00
Spinal	64.3 ± 1.6	0.00
Mother age	- 0.9 ± 0.2	0.00
Gestational age (weeks)	3.0 ± 0.7	0.00
Gestational age (Days)	0.4 ± 0.1	0.001
Birthweight	0.0 ± 0.0	NS
APGAR score 1	- 6.3 ± 1.1	0.00
APGAR score 2	- 9.6 ± 1.7	0.00
Mother sugar before delivery	0.6 ± 0.1	0.00
Mother sugar after delivery	0.6 ± 0.1	0.00
Difference between pre and post operative maternal blood sugar	0.1 ± 0.1	NS

Table 3.

Hyperglycemia in patients with diabetes who undergo surgery is associated with an increased rate of surgical site infection (SSI), myocardial infarction, stroke, and death (26-40). Hyperglycemia also occurs in up to two thirds of surgical patients who are not known to have diabetes, and its effect has not been well characterized in surgical patients without diabetes (NDM) (41). Recent observational studies have demonstrated an increased risk of complications associated with hyperglycemia in NDM patients when compared with DM patients. Kwon et al (42) found that NDM patients who had perioperative hyperglycemia had nearly twice the risk of infections, re-operative interventions, and in-hospital deaths as DM patients and hyperglycemia. Frisch et al (43) found an increased risk of 30-day mortality associated with hyperglycemia for NDM patients when compared with those with diabetes.

These recent studies suggest that a disease known for complications related to hyperglycemia may have a lower risk of postsurgical complications in the setting of hyperglycemia than in people without diabetes. There are several possible mechanisms to explain this observation. The higher rate of complications among NDM patients may reflect a more extreme inflammatory and stress response that causes a NDM patient to have the same level of hyperglycemia as a DM patient. This increased stress level may be the reason for the increased rate of complications in NDM patients, with hyperglycemia serving as a marker rather than a cause of the problem. Second, the increased risk of complications in NDM patients may be the result of under-diagnosis of diabetes that is revealed in the surgical setting. Third, it may reflect under-treatment of perioperative hyperglycemia with insulin in NDM patients. It is also possible that the lower risk of adverse events among DM patients who have postoperative diabetes is indicative of insulin being poorly tolerated in patients who have not previously been exposed to it. Finally, the lower risk may reflect a form of adaptation associated with more chronic exposure to hyperglycemia.

Understanding the mechanism by which NDM patients have an increased risk of complications has important implications for quality improvement activities related to preoperative assessment of diabetes status and management of postoperative hyperglycemia. To evaluate this paradox and explore possible mechanisms, we undertook an observational study of the association between perioperative hyperglycemia, insulin use, and adverse events in a statewide surgical cohort.

As we mentioned previously, SA is the most common technique used to provide anesthesia for patients undergoing elective CS due to the lower risk of maternal and fetal complications associated with it compared to GA. The results of our study favor the use of SA in the obstetric population since SA facilitates glycemic control in the perioperative period. This might be of a great beneficial outcome in reducing the incidence of previously mentioned complications associated with hyperglycemia and other maternal and fetal complications. Therefore, these added benefits of SA over GA should be conveyed to patients during patient counseling about cesarean sections.

6. CONCLUSION

According to this study, there was a significant proportional increase in mean blood glucose concentrations from glucose-check timing with both GA and SA. The effect of GA on blood glucose concentrations was significantly greater than the effect of SA, which indicates that the hormonal stress response is much greater in GA than in SA.

- **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.
- **Declaration of patient consent**: Written informed consent was obtained from all participants. Data are available upon request from the corresponding author. The data collection sheets used are available in the appendix for use.
- **Author's contribution**: All authors gave a substantial contribution to the conception, design of the work, contribution of data, contribution to the acquisition, analysis, or interpretation of data for the work, and article preparing for drafting or revising it critically for important intellectual content. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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