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ORIGINAL RESEARCH OBSTETRIC ANESTHESIA

Changes in blood oxidative stress biomarker and cholinesterase activity after general vs spinal anesthesia for elective cesarean sections

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ABSTRACT

Background & Objective: There is an increased ratio of cesarean sections (CS) compared to normal deliveries the world over. Both general and regional anesthetic techniques are in practice for CS. Limited information is available on the determination of blood cholinesterase (ChE) activity in conjunction with oxidative stress biomarkers after the CS. The purpose of the present study was to determine and compare the plasma and erythrocyte ChE activity as well as malondialdehyde (MDA) level and total antioxidant status in pregnant women before anesthesia and after the use of general anesthesia (GA) or spinal anesthesia (SA) for elective CS.

Methodology: A pre-post study was conducted on 102 full-term pregnant women, who underwent elective CS in four hospitals at Duhok (Iraq) from January 2022 to July 2022. GA with propofol and SA with bupivacaine 0.5% were administered to 52 and 50 women, respectively. Maternal blood samples before anesthesia and after the completion of operation were assayed for the ChE activity in the plasma and erythrocytes, and plasma oxidative stress biomarkers malondialdehyde and total antioxidant status.

Results: Plasma ChE activity significantly decreased in the GA and SA groups after the cesarean-deliveries compared to the corresponding pre-anesthetic values. The plasma MDA level in both GA and SA groups, but not the total antioxidant status, was significantly reduced. Estimation of the odds ratio and the relative risk indicated that a risk factor is associated with the reduced plasma ChE activity in women after the CS when the general anesthetic propofol is used.

Conclusion: Both general anesthesia with propofol and spinal anesthesia with bupivacaine inhibited plasma cholinesterase activity and reduced oxidative stress biomarker malondialdehyde after the cesarean sections.

Abbreviations: CS - Cesarean section; ChE: Cholinesterase; EChE: Erythrocyte Cholinesterase; MDA: Malondialdehyde; OS: Oxidative Stress; PChE: Plasma ChE; TAS: Total Antioxidant Status.

Key words: Anesthesia, Spinal; Cesarean section; General anesthesia; Malondialdehyde; Oxidative stress

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1. INTRODUCTION

Elective cesarean section (CS) or cesarean delivery has gained high preference compared to the vaginal birth among women in many countries.[1−4] For this purpose, either general anesthetics are used with propofol or other injectable anesthetics, or the spinal or epidural

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anesthesia with local anesthetics such as bupivacaine and lidocaine.[3–6]

Many studies have attempted to examine the pharmaco-biochemical outcome, including blood cholinesterase (ChE) activity and oxidative stress (OS) biomarkers after different anesthetics.[7–12] Any change in these variables could be attributed to the surgical procedures applied and their durations, as well as to the type(s) of anesthesia and anesthetics-drug combinations used.[8,10,13,14] Most importantly, several reports showed that blood cholinesterase (ChE) activities of the plasma (PChE) and erythrocytes (EChE) and OS indices such as plasma malondialdehyde (MDA) level and total antioxidant status (TAS) or total antioxidant capacity (TAC) as well as other biochemical variables, can be affected by normal physiological changes that occur during pregnancy, especially in the period close to delivery.[15–17]

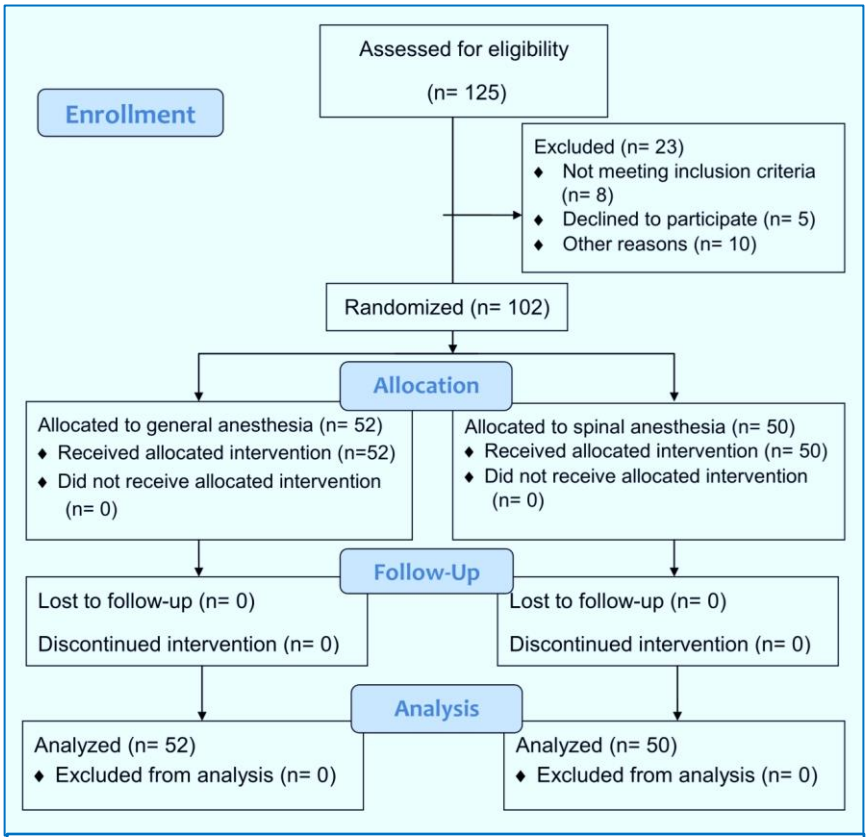

Figure 1: CONSORT flow diagram for allocation of the intervention groups

What complicates the matter is the fact that during CS, there is enhancement of OS markers which may be due to physical and emotional stress, as well as due to anesthetic drugs used.[18,19] On the other hand, in vitro and in vivo evidence suggests that the commonly used anesthetic propofol possesses antioxidant properties,[20–22] with cholinergic implications in its anesthetic action.[22,23] Local anesthetics such as lidocaine and bupivacaine were also reported to possess anti-ChE properties, especially on PChE activity.[24] However, limited information is available on blood ChE activity in conjunction with OS changes after the CS in the light of the expected profuse blood loss and changes in blood biochemical variables.[25–27] The purpose of the present study was to determine PChE and EChE activities as well as plasma MDA level and TAS in pregnant women before anesthesia and after the use of GA or SA for elective CS.

2. METHODOLOGY

Ethical approval was obtained from the Committee of Post Graduate Studies, College of Pharmacy, University of Duhok, KRG, Iraq (No. 470, October 6, 2021) and from the Research Ethics Committee, Duhok Directorate General of Health, Duhok, KRG, Iraq (No. 10112021-11-17, November 10, 2021). All women in the study were informed about the study purpose, nature of blood sampling procedures to be used and the expected outcome of the study; a written consent was obtained from each one.

2.1. Inclusion and exclusion criteria

Full term pregnant women were considered for the study when they underwent elective CS under general or spinal anesthesia in four different hospitals in Duhok, KRG, Iraq. Their ages ranged from 20 to 45 y. Emergency cases of CS or those of multiple pregnancy were excluded from the present study.

2.2. Study design and participants

In a pretest-posttest study design (https://explorable.com/pretest-posttest-designs), the study was conducted from January 2022 to July 2022. The included and excluded participants in the study are shown in the CONSORT flow diagram (Figure 1). Accordingly, 102 women were finally allocated into two intervention groups, based on the type of anesthetics used, which were the Group GA to receive GA with

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propofol (n = 52) or the Group SA to undergo SA with 0.5% bupivacaine (n = 50) for the elective CS.

Sample size estimation for clinical research set by Benchmarksixsigma.com was used, considering a confidence level of 95%, power of the test 80%, and 20% difference of PChE (before anesthesia vs. after operation) which is statistically the most significant measurement with a 5% margin of error (alpha).

2.3. Anesthesia protocols

A specialized surgical and anesthetic team from each hospital managed the GA, SA, and the CS in a similar manner during the course of the study.

2.3.1. General anesthesia

Participants received 1% propofol 2-2.5 mg/kg IV for the induction of GA in the standard dose for weight basis. The propofol brands used were from different manufacturers, including, Propofol-PF 1%, Polifarma, Istanbul, Turkiye, Somnopol, Aversi, Tbilisi, Georgia, and Propofol 1%, Fresenius, Fresenius Kabi, Graz, Austria. Non-depolarizing neuromuscular blockers were used for endotracheal intubation. They were atracurium (Atacure, Hikma Pharmaceuticals, Amman, Jordan) or rocuronium (Rocuronium Kabi, Fresenius Kabi, Graz, Austria). The maintenance of the general anesthesia was done by using isoflurane (Floran, Hikma Pharmaceuticals, Amman, Jordan).

2.3.2. Spinal anesthesia

Participants received intrathecal 0.5% bupivacaine 7.5 mg for spinal anesthesia. Bupivacaine used was from different manufacturing sources, which were: Bupivacaine, Aguettant Corporate, Lyon, France, Buvasin, Vem Ilac, Istanbul, Turkiye, or Marcaine, Aspen, Turkiye

2.4. Blood sampling

Approximately 5 mL of venous blood sample was collected in heparinized tubes from each patient, before anesthesia and immediately after the end of the CS, before the administration of any drug such as neostigmine and atropine in the Group GA. The period between the two blood samples was 30.3 ± 11.3 min for GA and 22.1 ± 8.7 min for SA. The blood samples were centrifuged at 1037 g for 15 min to separate the plasma and erythrocytes which were kept at –20 ºC pending ChE, MDA and TAS assays within 2−3 weeks.

2.4.1. Blood ChE activity

An electrometric method was used to determine PChE and EChE activities using 0.2 mL samples and 0.1 mL of 7.1% acetylcholine iodide as a substrate with a reaction time of 20 min.[28,29] The enzymatic activity was expressed as Δ pH/20 min.

2.4.2. Plasma MDA level

Plasma MDA level was determined by a spectrophotometric method at 535 nm,[30] with minor modification as described before.[31]

2.4.3. Plasma TAS

A spectrophotometric kit (Elabscience Biotechnology Inc., USA) was used to determine plasma TAS using a microplate reader (ELx800, Biotek, USA) at 660 nm.

3. Statistical analysis

All data were statistically analyzed using the statistical software program PAST4.09. Paired Student's t- test was used for comparison of mean values of pre-anesthesia and post-CS. Correlation was also determined among the variables. Odds ratio and risk ratio were estimated for cases of observed and expected low PChE activity at 20% reductions.[31] The level of statistical significance was at $P < 0.05$.

3. RESULTS

The demographic data as well as the surgical operation characteristics (duration of operation, and time to recovery from anesthesia) of 102 participants who underwent elective CS are given in Table 1. The mean age in years of both GA and SA groups was (29.1 ± 5.5). The duration of surgery for Group GA was significantly

Table 1: Comparative demographic and surgical characteristics of both groups

Variable	Group GA (n = 52)	Group SA (n = 50)	P-value
Age (y)	28.24 ± 5.55	29.98 ± 5.37	0.11147
Weight (kg)	74.55 ± 12.501	73.59 ± 12.90	0.848
Height (cm)	158.86 ± 5.78	160.37 ± 6.25	0.484
Gestation week	37.08 ± 1.14	37.73 ± 1.09	0.132
Parity	1.52 ± 1.53	2.06 ± 2.02	0.130
Gravidity (frequency)	2.56 ± 1.53	3.16 ± 2.07	0.097
Duration of operation (min)	30.29 ± 11.304	22.12 ± 8.65*	0.0001
Time to recovery from anesthesia (min)	37.46 ± 11.16	**	

** Significantly different from the propofol group, Unpaired Student's-t-test, p < 0.05.*
***The time to recovery ranged between 4−6 h.; Values expressed as mean ± SD.*

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Table 2: Comparison of plasma and erythrocyte cholinesterase (ChE) activities in both groups before GA and SA and after the operation

Variable	Group GA (n = 52)	% Change	Group SA (n = 50)	% Change	P – value (GA; SA)
Plasma ChE (Δ pH/20min)					
Before	0.75 ± 0.160	–17	0.71 ± 0.168	–11	$7.0169E^{-06}$; $5.5731E^{-08}$
After	0.62 ± 0.217*		0.63 ± 0.184*		
Erythrocyte ChE (Δ pH/20min)					
Before	1.48 ± 0.111	–2	1.43 ± 0.276	0	0.241; 0.670
After	1.45 ± 0.172		1.43 ± 0.283		

*Values are mean ± SD; *Significantly different from the corresponding pre-anesthetic value, P < 0.05.*

Table 3: Comparison of plasma malondialdehyde (MDA) and total antioxidant status (TAS) levels before anesthesia and after the surgery

Variable	Group GA (n=52)	% Change	Group SA (n= 50)	% Change	P-value (GA; SA)
MDA (µmol/L)					
Before	4.13 ± 0.958	–13	4.52 ± 1.052	–24	$8.2805E^{-05}$; $6.793E^{-12}$
After	3.58 ± 0.706*		3.43 ± 0.827*		
TAS (mmol Trolox Equivalent/L)					
Before	1.29 ± 0.378	+2	1.36 ± 0.265	–1.5	0.649; 0.758
After	1.31 ± 0.353		1.34 ± 0.302		

*Values are mean ± SD; *Significantly different from the corresponding pre-anesthetic value, P < 0.05.*

longer than that of the Group SA, and the recovery time from the GA was substantially shorter than that of the SA.

3.1. Blood ChE activity

PChE activities before anesthesia and after the surgery in Group GA and Group SA were measured. In both groups, the PChE activity was significantly ($P < 0.05$) reduced after the CS in comparison to pre-anesthesia values by 17% and 11%, respectively. However, there was no significant difference in EChE activity in both groups with respect to their pre-anesthesia values (Table 2).

3.2. Plasma oxidative stress biomarkers

In both groups the plasma MDA level was significantly ($P < 0.05$) reduced after the operation in comparison to the pre-anesthesia values. MDA level reduced by 13% and 24%, in Group GA and Group SA, respectively. However, there was no significant difference in the TAS

Table 4: The frequency of occurrence of reduced PChE activity (Δ pH/20min) at values ≤ 0.62 for GA and at ≤ 0.63 for SA

Sample time	Group GA		Group SA	
	PChE ≤ 0.62*	PChE > 0.62	PChE ≤ 0.63*	PChE > 0.63
After operation	25	27	26	24
Before anesthesia	12	40	19	31

**Significantly different bench mark point for PChE activity compared to the corresponding pre-anesthesia value as reported in Table 2.*

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Table 5: Odds ratio and risk ratio of significantly reduced PChE activity in both groups

Statistics	Group GA	Group SA
Odds ratio	3.09	1.77
95% confidence interval	1.3,7.2	0.8,3.9
p value	0.009	0.161
Risk ratio	2.08	1.37
95% confidence interval	1.2, 3.7	0.9, 2.1
p value	0.012	0.165

in both groups with respect to their pre-anesthesia values (Table 3).

3.3. Risks of reduced PChE after the CS

We constructed a table of odds ratio (Table 4) using the frequency of distribution of PChE activity values (Δ pH/20 min) ≤ 0.62 for the GA and ≤ 0.63 for SA in women who underwent CS. It was noticed that estimation of the odds ratio and the risk ratio indicated a risk factor of reduced PChE activity in women who underwent CS with the use the general anesthetic propofol (Table 5).

3.4. Correlation between PChE, EChE and MDA

There was no correlation between PChE vs. EChE (r = -0.086), PChE vs. MDA (r = 0.130) and EChE vs. MDA (r = -0.23) in women set undergoing elective CS and either GA or SA, taking into account the pre-anesthetic and after the operation ChE activities.

4. DISCUSSION

Current evidence strongly suggests an increasing preference of parturients for elective cesarean-delivery, apparently to avoid labor pains and the stress related to normal delivery, in many regions around the world,[1–3,32,33] including Iraq.[4,34] For elective CS, the most preferred GA is with propofol and SA with bupivacaine. The present study was conducted in four hospitals in Duhok, Iraq, to examine the effects of these two most commonly used anesthetics, on blood OS biomarker and ChE activity. The most prominent finding of the present study was a reduction in PChE activity post-operatively in both types of anesthesia. This enzyme is found in the liver, plasma and other tissues, and it is involved in the metabolism of some anesthetics and related muscle relaxants.[35,36] Reduced PChE activity is a biomarker of exposure to pesticides,[29,31,37] and it has been implicated in different cardiovascular and hemodynamic imbalances during anesthesia, especially at the level of the autonomic nervous system.[9,24,38]

The mean PChE activities (Δ pH/20min) before anesthesia were 0.75 and 0.71 in GS and SA, respectively. These values are generally below normal ranges reported by others,[28,29] using the same electrometric method we applied in the present study. This could be related to physiological hemodynamic changes expected during pregnancy.[35,39-42] Within this context, the results of the present study demonstrated that PChE is further reduced in both GA and SA groups after the CS, and therefore, caution should be practiced during application of anesthetics and neuromuscular blocking agents in surgical operations for the CS. Additionally, it is reasonable to suggest that monitoring blood ChE activity should be a routine integration of maternal health assessment before any CS.

The reduction in PChE activity after the CS in the GA group could be due to the direct effect of propofol. Propofol has been reported to interact with central cholinergic system, during GA, possibly by reducing acetylcholine release and cholinergic functions that are related to anesthesia-induced immobility, amnesia and loss of consciousness.[43] In support of this notion, physostigmine reverses propofol-induced unconsciousness in human volunteers,[44] and its pretreatment increases the dose of propofol needed to induce unconsciousness in patients.[45] On the other hand, the local anesthetic bupivacaine was reported to possess an inhibitory action over PChE activity.[46] This effect could explain the reduction in PChE activity in the SA group of the present study.

Alterations in serum ChE activity were not attributed to the bupivacaine spinal application alone in patients undergoing lower limb surgery, and they were rather attributed in part to surgery-related depression in cellular secretory function as well as to protein depletion due to blood loss.[24] It should be stressed here, that we cannot rule out the possible effects of adjuvants, maintenance anesthetics and other medications on PChE activity when used intra-operatively during the CS. Such a reduction of PChE activity after the anesthesia calls for careful hemodynamic support during CS.[7,9,24,35,39,42]

As reported earlier, EChE activity increases during pregnancy, and this was also true in the present pre-anesthetic activity of this enzyme when compared to normal values reported in non-pregnant women using the same electrometric method.[28,29] However, in contrast to PChE, there was no significant difference between the pre-anesthesia and post-CS values of EChE activity in the present study, suggesting a differential effect of both propofol and bupivacaine on PChE vs. EChE. This

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finding is also in accordance with a previous report about the selective inhibition of butyryl ChE (vs. true ChE) by bupivacaine.[47] However, in the study of Gramavy,[22] there was a significant reduction of EChE activity with propofol in non-pregnant women as well as in males. This discrepancy could be related to the fact that in the present study the women were in the last stage of pregnancy and were very close to the due date of delivery, which is known to be accompanied by various metabolic changes, including activities of PChE and EChE.[39,40,48]

Pregnant women who undergo CS are at high risk of suffering from OS due to the physical and emotional stress of surgery and the anesthesia.[19] In the present study, pre-anesthesia (GA) levels of plasma MDA significantly decreased after the CS, suggesting a reduction in the OS status of the women.

Several factors may have contributed to the present finding; most importantly, propofol, being an antioxidant, reduces the impact of OS, probably through inhibition of nuclear factor kappa B (NF-κB) signal transduction pathway in liver.[49] The plasma OS biomarker MDA, is a byproduct of lipid peroxidation of cell membranes, which also occurs during pregnancy.[50,51]

It has been reported that propofol results in inhibition of lipid peroxidation and enhancement of antioxidant capacity.[49,52] The antioxidant effect of propofol could be due to the phenolic structure of the drug which is similar to α-tocopherol, an antioxidant.[53] While there was no significant effect at the TAS level with propofol in the present study, the results suggest a specific effect of the anesthetic at the level of MDA mechanism in pregnant women who underwent CS. However, TAS is the result of overall contributions of several antioxidant mechanisms such as albumin, iron, bilirubin, uric acid;[54,55] and it is possible that all these variables were not affected considerably enough by the present CS/anesthetic paradigm.

Similar to the effect of propofol (reduction of the plasma MDA level) in the present study, SA with bupivacaine also significantly reduced MDA level, but not that of TAS after the CS. This finding is reported at present as the first of its kind, though its mechanism is not yet clear. However, it is conceivable to deduce that removing the burden of pregnancy by the CS might have contributed to the antioxidant properties of both propofol and bupivacaine. This effect, however, needs further follow up clinically.

There was no correlation between the PChE and EChE activity, as well as between PChE activity and MDA level, although the PChE activity and MDA values were affected by anesthetics in the present study. This was also true about EChE activity and MDA level. This finding correlates with that of Garmavy[22] who found also poor correlation (r = 0.323) between PChE and EChE activity in patients who received propofol. In contrast, a study in pregnant women with gestational diabetes reported a negative correlation between serum ChE activity and the MDA level and a strong correlation between this enzyme and total antioxidant activity in the serum;[56] apparently serum ChE acted as a scavenger of free radicals in the presence of OS.

5. LIMITATIONS

Extended follow up and interval blood sampling was needed; however, none of the participants were willing to pursue the study beyond the CS. The choices of anesthetics (general or local) were limited in the hospitals, probably because of their availability and the preferences of the surgeons. Otherwise, it would have been interesting to study other anesthetics that can be applied in the CS.

6. CONCLUSION

Propofol and bupivacaine were used for general anesthesia and spinal anesthesia respectively, for elective cesarean sections in Duhok, Iraq. Inhibition of plasma ChE activity and reduced oxidative stress biomarker MDA occurred differentially after the cesarean sections under GA and SA; with the possibility of health risk association with reduced plasma ChE in case of using propofol. Clinical follow-up studies on the variables used are warranted on women after the cesarean sections.

7. Data availability

The numerical data of this study is available with the first author.

8. Conflict of interests

The authors declare no conflicts of interest with respect to the authorship and/or publication of this article.

9. Acknowledgments

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10. Authors' contribution

RSK: Dealt with the participants, obtained blood samples and executed laboratory assays; conducted literature search, statistical analyses and shared in drafting the manuscript.

FKM: Conceptualized and supervised the study, shared in literature search, statistical analyses and drafting the manuscript. Both authors have read the manuscript and approve it for publication.

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