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Effects of High-concentratıon Oxygen Inhalation during Cesarean Section with Spinal Anesthesia on Lipid Peroxidation, Oxidant and Antioxidant Systems

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Authors' contributions

This work was carried out in collaboration between all authors. Authors EK and NK designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors NK and BK managed the literature searches, analyses of the study statistical data. Authors HA and FD managed experimental process and the analyses of laboratory parameters. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The benefit of supplemental oxygen during elective Cesarean section under regional anesthesia is controversial.
Methodology: In this study, parturients were randomized two groups, to breathe either room air (air group, inspired oxygen fraction 21%) or oxygen at a flow rate of 6 L.min-1 (oxygen group, inspired oxygen fraction 40%) by nasal cannula. At delivery, a segment of umbilical cord was isolated using double clamps before the infant's first breath and umblical vein blood samples were obtained. After then, 5th min of oxytocin infusion, a sample of maternal blood was obtained for analysis. The remainder of the sample was centrifuged at 4400 rpm for 4 min and the plasma was stored at -70℃ for subsequent batch analysis for 8- isoprostane, TOS, TAC. Oxidation Stress

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Index (OSI) was assessed as the percentage ratio of TOS level to TAC level.
Results: There were significant differences in maternal oxygenation but not neonatal oxygenation in supplemental oxygen group. The parameters indicating lipid peroxidation (8-isoprostane concentration) and oxidative stress (TOS, TAC, OSI) in maternal and umblical blood were higher in FiO_2 supplementation group but this increase was not significant.
Conclusions: Although supplemental oxygen increased maternal oxygenation, fetal oxygenation did not changed. Breathing supplemental oxygen did not increased the parameters indicating lipid peroxidation and oxidative stress in maternal and umbilical cord blood in healthy women having elective cesarean section under spinal anesthesia.
Consequently, breathing supplemental oxygen does not have a significant effect on neonatal well-being and is unnecessary in healthy women undergoing elective Cesarean section under spinal anaesthesia.

Keywords: Oxygen; lipid peroxidation; oxidative stress; anesthesia.

1. INTRODUCTION

During spinal anaesthesia, changes in respiratory function occur [1] and oxygen supplementation is commonly given to prevent maternal oxyhaemoglobin desaturation and to optimize fetal oxygenation [2]. There has been little research into the need for supplemental oxygen during elective cesarean section under spinal anaesthesia. The benefit of administering supplementary oxygen during elective cesarean section under regional anaesthesia is controversial [3].

It is known that maternal and fetal arterial oxygen partial pressures (PaO2) increase with increasing maternal inhaled oxygen concentration (FiO2). It is recognized that there is a graded maternal and fetal PaO2-response to increasing maternal FiO2 such that as maternal FiO_2 is increased, there is a concurrent and proportionate increase in both maternal and fetal blood oxygen pressures and content [4].

The studies during regional anaesthesia for elective cesarean section have shown that the use of high FiO2 can induce a concomitant increase in free radical activity, causing lipid peroxidation in the mother and fetus [2]. Lipid peroxidation causes tissue damage and compromises the defence of the fetus against further oxidative stress by depleting the antioxidants in the baby [5-8].

We conducted a prospective, randomized controlled study in which mothers were allocated randomly to breath room air or high inspired oxygen fraction during elective Cesarean section under spinal anaesthesia. The main outcomes we assessed were maternal arterial and umblical cord blood gases and maternal and neonatal plasma concentrations of 8-isoprostoglandin F2α (isoprostane), a marker of lipid peroxidation in patients having elective Cesarean section under spinal anaesthesia. We also sought to the effect of administration of high FiO_2 on maternal and neonatal oxidant and antioxidant systems.

2. METHODS

After approval of the Clinical Research Ethics Committe of the Akdeniz University and written informed consent from each patient, 50 ASA I parturients between 37-40 weeks of gestation scheduled for elective cesarean section under spinal anaesthesia were recruited. Patients with diabetes mellitus, chronic hypertension and pregnancy-associated hypertension, oligohydramniosis, intrauterine growth retardation, known fetal abnormality antenatal haemorrhage were excluded.

On arrival at the operating room, i.v. access was secured and standard monitoring, comprising non-invasive blood pressure, electrocardiogram and pulse oximetry, was attached. Patients were randomized two groups, to breathe either room air (air group, inspired oxygen fraction 21%) or oxygen at a flow rate of 6 $L.min^{-1}$ (oxygen group, inspired oxygen fraction 40%) by nasal cannula. Oxygen therapy was initiated after i.v. acces was secured and continued until the end of surgery patients in oxygen group. After an i.v. preload of 10 $mL.kg^{-1}$ of lactated Ringer's solution, spinal anaesthesia was performed with the patient in the right lateral position.Using a 25-27 gauge pencil-point needle at the L_{2-3} or L_{3-4} level, anaesthesia was established with 8-12 mg ml of hyperbaric bupivacaine 0.5%. The patient was then turned supine with left lateral tilt and prepared for surgery after checking that the level of the block (T_4) was adequate.

Hypotension was considered to be present if a systolic blood pressurel pressure <100 mmHg or a decrease in blood pressure >20% than pre-anaesthetic values occured and was treated with small i,v. increments of ephedrine together with rapid infusion of lactated Ringer's solution. Our contingency for patients in the air group who developed a pulse oximetry reading of <95% was to withdraw the patient from the study, and to administer the appropriate FiO2 to restore the oximetry reading to ≥ 95%. Such cases were excluded from the study. The times skin incision-to-delivery interval and uterine incision-to-delivery interval were recorded. At delivery, a segment of umblical cord was isolated using double clamps before the infant's first breath and umbilical vein blood samples were obtained. After then, 5th min of oxytocin infusion, a sample of maternal blood was obtained for analysis. For each blood sample, blood gas analysis was performed immediately using a Corning 278 pH / blood gas analyser. The remainder of the sample was centrifuged at 4400 rpm for the plasma was stored at -70℃ for subsequent batch analysis for 8- isoprostane, Total oxidant status (TOS), Total antioxidant capacity (TAC). Total plasma isoprostane was determined using specific enzym immunoassey (EIA) method. The TAC and TOS of the serum was measured using a novel automated colorimetric measurement method developed by Erel. Oksidation Stress Index (OSI) was assessed as the percentage ratio of TOS level to TAC level. All blood analyses were performed by an investigator who was blinded to the FiO2 and did not participate in patient care.

After delivery, neonate was assessed by a pediatrician who was not aware of the treatment, who recorded Apgar scores 1min and 5 min after birth.

2.1 Statistically Analysis

Power analysis showed that a sample size of 25 patients in each group would yield 95% power to detect a 5% change with a type I error of 0.05. Data were tested initially for equality of variances using Levene's test, and the normal probability plot was used subsequently to test for normality. On the basis of these findings, statistical comparison was performed using either Student-*t* test or Mann-Whitney *U*- test. The X^2 test was used to compare equality of proportions, and the association between PaO_2 and 8-isoprostane, TOS, TAC in maternal and umbilical blood was compared using Spearman rank correlation. Results are presented as mean and standart deviation. *P*<0.05 was considered significant.

3. RESULTS

The maternal and neonatal characteristics, skin incision-to-delivery interval, and uterine incision-to-delivery interval were similar in the two groups. The incidence of hypotension and the requirement of ephedrine were similar in the two groups (Table 1). No treatment for maternal desaturation was required.

3.1 Maternal Blood Analysis

With regard to the maternal blood gasses analysis, there were significant differences in maternal PaO_2, PCO_2 and SaO_2 values between two groups (Table 2)($p<0.05$).

The parameters indicating lipid peroxidation and oxidative stress (8-isoprostane concentration, TOS, TAC, OSI) in maternal blood were higher in FiO_2 supplementation group than air breathing group. Although the PaO_2 increased in direct proportion with increased FiO2, there were no significant differences in the maternal 8-isoprostane concentration, TOS, TAC, OSI data between two groups ($p>0.05$) (Table 3).

3.2 Umbilical Cord Analysis and Apgar Scores

In the assessment of umbilical cord blood gasses, there were no significant differences between two groups in SaO_2 and PaO_2 ($p<0.05$). However, there were significant differences in $PaCO_2$ and pH data between study groups ($p<0.05$) (Table 4). But the measurements of umbilical cord pH were considered to be normallly in both groups.

The parameters indicating lipid peroxidation and oxidative stress (8-isoprostane concentration, TOS, TAC, OSI) in umbilical cord were higher in FiO2 supplemention group than air breathing group but this differences were not significant ($p>0.05$) (Table 5).

Apgar scores were similar between two groups, with all scores >7 at 1st min and >9 at 5th min.

No significant correlation between the maternal PaO_2 and maternal 8-isoprostane,TOS, TAC data were found in two groups ($p>0.05$) (Figs. 1,2,3).

No significant correlation were found between the maternal and umbilical cord 8-isoprostane ($r=0.037$, $p=0.86$) (Fig. 4), maternal and umbilical

Table 1. Patient characteristic and intraoperative details. Values are mean±SD

	Group I (O2) (n=25)	Group II (air) (n=25)
Age (yr)	28.12±4.25	30.72±5.53
Weight (kg)	80.28±11.82	77.08±12.96
Height (cm)	161.80±4.44	161.88±6.30
Gestation (week)	38.36±0.56	38.20±0.50
Skin incision-to-delivery interval (min)	10.40±2.08	9.56±2.97
Uterine incision-to-delivery interval (min)	5.20±1.32	4.44±1.50
Birth weight (gr)	3233.32±286.20	3286.36±270.54
Ephedrine requirement (yes/no)	6/19	5/20

Table 2. Blood gasses data in the mothers. Values are mean±SD

	Group I (FiO2) (n=25)	Group II (air) (n=25)	*p*-value
pH	7.39±0.02	7.39±0.02	0.126
PaO_2 (mmHg)	157.64±39.55	117.62±14.7	**0.001***
$PaCO_2$ (mmHg)	29.69±3.03	27.84±2.00	**0.005***
SaO_2 (%)	99.04±0.63	98.30±0.63	**0.001***

* *p<0.05 (significant difference between groups)*

Table 3. The parameters indicating lipid peroxidation and oxidative stress (8-isoprostane concentration, TOS, TAC, OSI) in maternal blood. Values are mean±SD

	Group I (FiO2) (n=25)	Grup II (air) n=25	*p*-value
8-isoprostane (ng ml^{-1})	91.04±29.19	69.77±40.21	0.11
TAC (µmol Trolox eqv./l)$^{-1}$	1.78±0.26	1.63±0.19	0.10
TOS (µmol H2O2 eqv./l)$^{-2}$	7.31±1.80	7.08±3.28	0.13
OSI (TOS/TAC)	4.15±1.14	4,34±1,85	0.93

Table 4. Blood gasses data in the umbilical cord. Values are mean ±SD

	Group I(FiO2) (n=25)	Grup II (air) (n=25)	*p*-value
pH	7.31±0.04	7.33±0.03	**0.03***
PaO_2(mmHg)	27.21±10.23	24.77±5.62	0.38
$PaCO_2$(mmHg)	44.57±7.72	40.61±4.84	**0.02***
SaO_2 (%)	42.62±19.08	40.82±15.60	0.70

* *p<0.05 (significant difference between groups)*

Table 5. The parameters indicating lipid peroxidation and oxidative stress (8-isoprostane concentration, TOS, TAC, OSI) in umbilical cord. Values are mean±SD

	Group I (FiO2) (n=25)	Group II (air) n=25	*p*-value
8-isoprostane(ng ml^{-1})	69.08±34.47	60.49±31.35	0.33
TAC(µmol Trolox eqv./l)$^{-1}$	1.98±0.31	1.95±0.27	0.88
TOS(µmol H2O2 eqv./l)$^{-2}$	14.12±12.25	12.36±6.72	0.60
OSI (TOS/TAC)	6.57±4.48	6.25±3.24	0.67

cord TOS (r=0.30, p=0.13) (Fig. 5) data in two groups. The correlation between maternal and umbilical TAC data was found significant in two groups (r=0.48, p=0.015) (Fig. 6).

In addition, there was a significant correlation between umbilical cord TOS and TAC measurements (p=0.00, r=0.70).

4. DISCUSSION

Although spinal anaesthesia is the preferred anaesthetic technique for elective cesarean section [9-11], there has been little research into the need for supplemental oxygen intra-operatively during elective cesarean section under spinal anaesthesia [12-15].

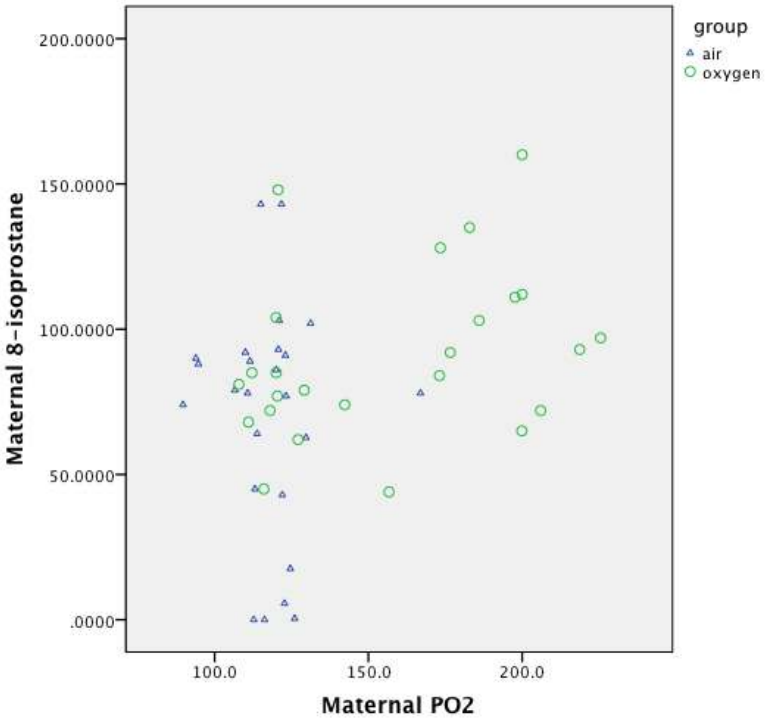

Fig. 1. Scatter plot of maternal 8- isoprotane level against PaO_2 with cases labelled according to FiO_2 supplemention group or air breathing group

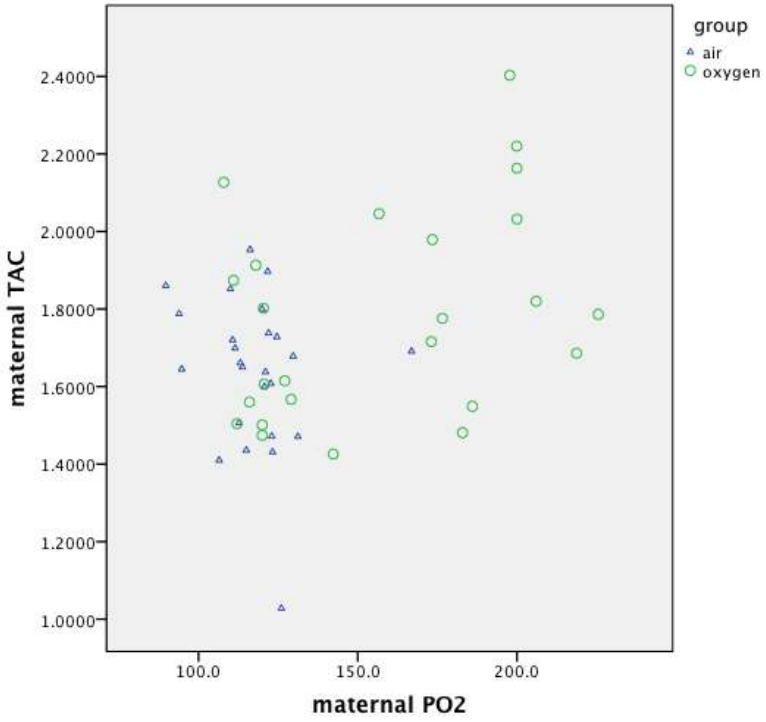

Fig. 2. Scatter plot of maternal TAC level against PaO2 with cases labelled according to FiO2 supplemention group or air breathing group

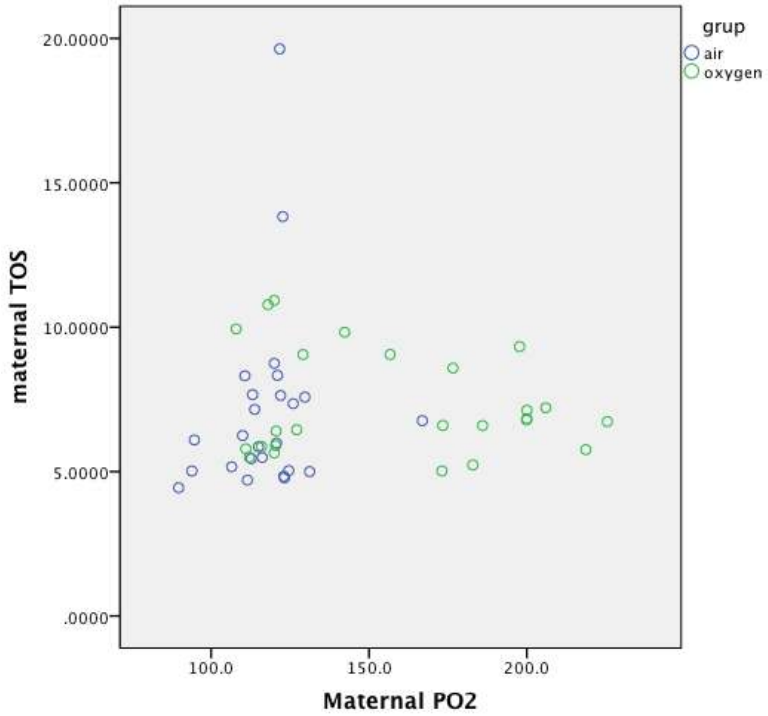

Fig. 3. Scatter plot of maternal TOS level against PaO_2 with cases labelled according to FiO_2 supplemention group or air breathing group

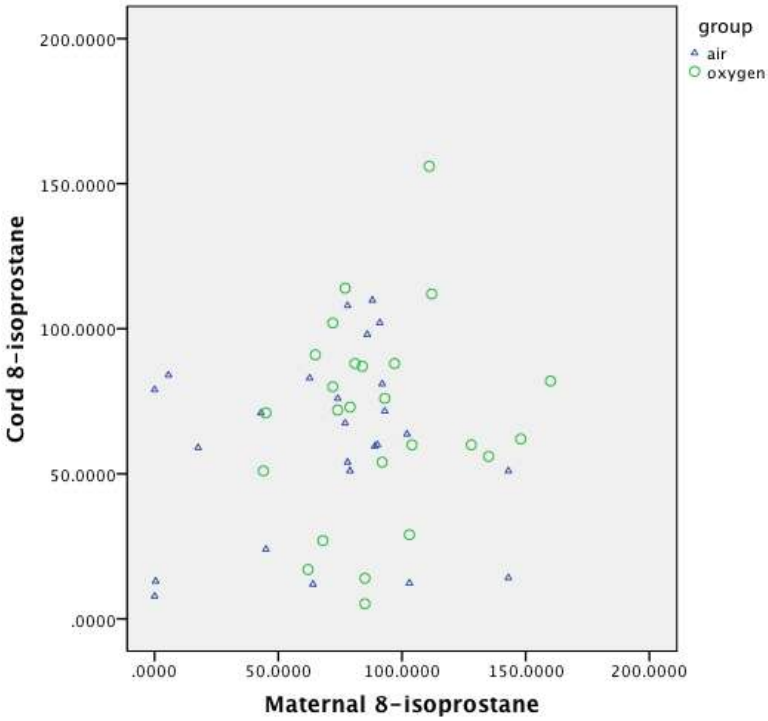

Fig. 4. Scatter plot of maternal 8- isoprotane against umbilical 8-isoprostane with cases labelled according to FiO_2 supplemention group or air breathing group

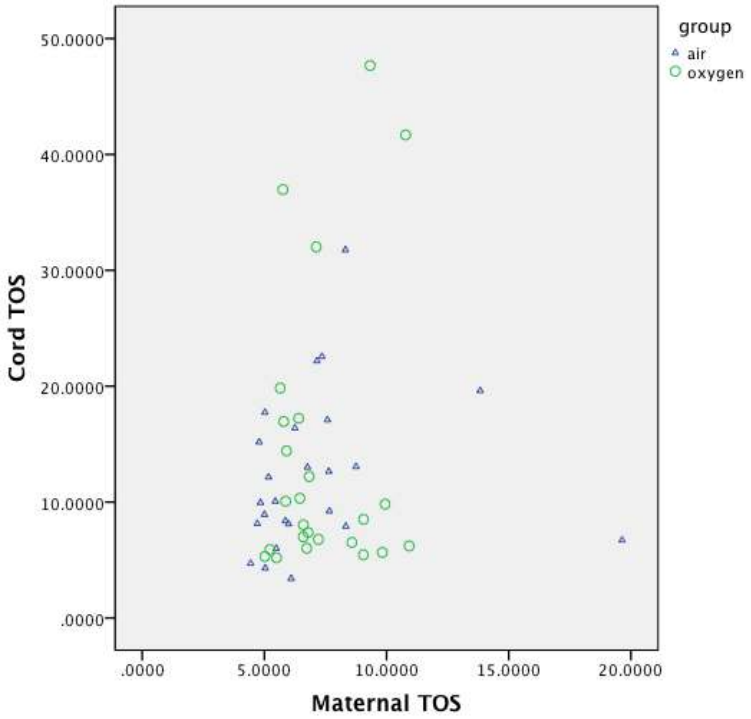

Fig. 5. Scatter plot of maternal TOS against umbilical TOS with cases labelled according to FiO2 supplemention group or air breathing group

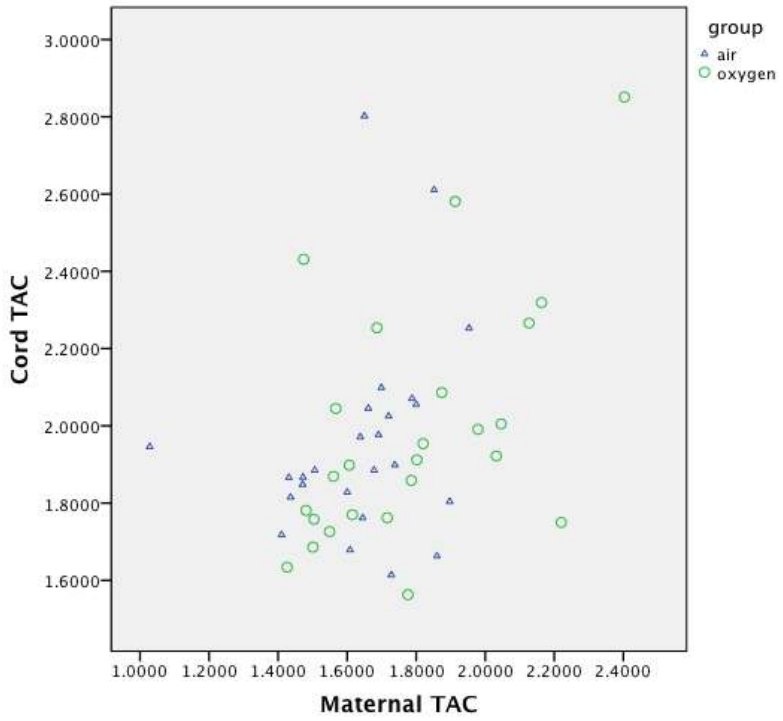

Fig. 6. Scatter plot of maternal TAC against umbilical TAC with cases labelled according to FiO2 supplemention or air breathing

Many women undergoing elective cesarean section under regional anaesthesia still routinely receive supplemental oxygen. The benefit of supplemental oxygen during elective cesarean section under regional anaesthesia is controversial [3]. Supplemental oxygen intuitively given carte blanche by many anaesthesiologists to mothers during cesarean section on the assumption that it might do some good, such as improving fetal oxygen reserve, but will not do any harm [3]. Although deterioration of respiratory function can be demonstrated when mothers are given regional anaesthesia, maternal or fetal hypoxia does not normally occur when the mothers breathe room air [1]. It has been shown that there is a linear relationship between maternal PaO_2 and UV PO2 and UA PaO2 [16] and, on the basis of this, it has been advocated that all women undergoing cesarean section under regional anaesthesia should receive supplemental oxygen [17]. This hyperoxygenation is thought to provide the fetus with a supplemental store of oxygen in order to withstand any unforesen intra-operative or postnatal oxygen deprivation [17,18]. Ramanathan and colleagues reported that UV PO_2 was improved when parturients receiving epidural anaesthesia breathed increased (47-100%) FiO_2 [16]. However, Kelly et al. [1] have suggested that, despite the intra-operative reduction in maternal respiratory function, administration of supplemental oxygen during cesarean section does not significantly alter fetal umblical vein partial pressure of oxygen. Khaw KS, et al. [2] reported that administering high FiO2 (%60) during elective cesarean section under spinal anaesthesia modestly increased fetal oxygenation but caused a concomitant increase in oxygen free radical activity in both mother and fetus. However, they found that breathing 60% oxygen during emergency cesarean section under regional anaesthesia increased fetal oxygenation with no associated increase in lipid peroxidation in mother or fetus [15]. In another study, Khaw KS, et al. [19] reported that when the uterine incision-to-delivery interval was prolonged, administration supplementary oxygen did not improve fetal pH or oxygen indices.

Direct detection of free radicals is extremely difficult because of their brief lifespan [20]. Isoprostanes are highly specific markers for in vivo oxidative stress and the best-characterized isoprostane is 8-isoprostoglandin F2 α (8-isoprostane) [21]. Lipid peroxide concentrations were much greater in UV than in UA blood, suggesting that the main site of free radical activity was the placenta, the interface where hyperoxia occurs. Concentrations of 8-isoprostane were greater in umbilical than in maternal blood, implying generation in the fetoplacental unit [22]. In the maternal blood, the increase in lipid peroxidas results from the not effect of lipid peroxidation and free radical scavenging throughout the body, whereas the increase in the umblical vein reflects the origin more specifically at the placenta. A positive correlation between maternal PaO_2 and umbilical lipid peroxide concentration suggests a direct relationship between the oxygen partial pressure and the extent of free radical activity in the fetoplacental unit [6].

Umblical cord blood gas analysis after delivery reflects the fetal condition immediately before delivery, with UA blood gas measurements representing the fetal condition and UV measurements representing the maternal condition and uteroplacental gas exchange [23]. We observed no significant difference between the oxygen supplementation group and control group about umblical cord gas analysis. Our results demonstrated that the administration of supplemental oxygen for elective cesarean section under spinal anaesthesia associated with increased maternal oxygenation but the parameters indicating lipid peroxidation (8-isoprostane concentration) and oxidative stress (TOS, TAC, OSI) in maternal blood did not increase significantly. Although increased maternal oxygenation, neonatal oxygenation and the parameters indicating lipid peroxidation (8-isoprostane concentration) and oxidative stress (TOS, TAC, OSI) in umbilical cord. did not increase significantly.

Cogliano MS, et al. [24] reported that supplementary oxygen is unnecessary in healthy women having elective cesarean section under spinal anaesthesia Thorpe et al. [25] demonstrated giving mothers O2 just before birth may have been detrimental to the fetus; babies of mothers who were given O2 for greater than 10 min during second stage of labour showed a deterioration of cord blood gas values at birth. With babies at risk, e.g. with fetal distress or maternal haemorrhage, administration of O2 to the mother is doubtless of value.

Our study was confined to healthy, elective cases with uncomplicated pregnancies. Based on our results, breathing supplemental oxygen during elective cesarean delivery of healthy

parturients under spinal anesthesia does not have a significant effect on neonatal well-being, lipid peroxidation in maternal and fetal blood.

In the supplemental oxygen group, although maternal oxygen increased, fetal oxygen in umblical cord did not increase. In addition, the parameters indicating lipid peroxidation and oxidative stress in maternal and umblical cord blood did not increase in supplemental group having elective cesarean section under spinal anaesthesia.

Our data do not support routine administration of supplemental oxygen during elective cesarean section under spinal anaesthesia. However, further investigation is required to clarify the advantages and disadvantages of high FiO2 in fetal distress and emergency cesarean section.

5. CONCLUSION

In conclusion, breathing supplemental oxygen does not have a significant effect on neonatal well-being and is unnecessary in healthy women undergoing elective cesarean section under spinal anaesthesia.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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