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SCIENTIFIC ARTICLE

Supplemental Oxygen in Elective Cesarean Section under Spinal Anesthesia: Handle the Sword with Care

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Abstract

Background and objectives: We aimed to investigate the effect of 21% and 40% oxygen supplementation on maternal and neonatal oxidative stress in elective cesarean section (CS) under spinal anesthesia.

Methods: Eighty term parturients undergoing elective CS under spinal anesthesia were enrolled in the study. We allocated patients randomly to breathe 21% (air group) or 40% (oxygen group) oxygen from the time of skin incision until the end of the operation. We collected maternal pre- and post-operative and umbilical artery (UA) blood samples. Total antioxidant capacity (TAC), total oxidant status (TOS) and the oxidative stress index (OSI) were measured.

Results: Age, weight, height, parity, gestation week, spinal-skin incision time, skin incision-delivery time, delivery time, operation time, 1st and 5th minutes Apgar scores, and birth weight were similar between the groups ($p > 0.05$ for all comparisons). There were no differences in preoperative TAC, TOS, or OSI levels between the groups ($p > 0.05$ for all comparisons). Postoperative maternal TAC, TOS and OSI levels significantly increased in the oxygen group ($p = 0.047$, < 0.001 and 0.038 , respectively); umbilical artery TAC levels significantly increased in the oxygen group ($p = 0.003$); and umbilical artery TOS and OSI levels significantly increased in the air group ($p = 0.02$ and < 0.001 , respectively).

Conclusions: The difference in impact on maternal and fetal oxidative stress of supplemental 40% compared to 21% oxygen mandates further large-scale studies that investigate the role of oxygen supplementation during elective CS under spinal anesthesia.

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Introduction

Spinal anesthesia is one of the preferred anesthetic techniques for elective cesarean section (CS).¹ Anesthesiologists commonly give oxygen supplementation intra-operatively during CS under regional anesthesia on the basis of supposed maternal and fetal benefits including compensation for the respiratory effects of a high regional block and provision of an oxygen reserve for unforeseen situations.^{2,3}

However, the results of previous research on supplementary oxygen during CS under spinal anesthesia display great differences in various inspired oxygen fractions (FiO_2) and between emergent and elective cases. Some studies report improvement in the umbilical blood gases with high oxygen fractions,^{4,5} while other studies failed to detect similar improvement in umbilical vein oxygenation and umbilical blood gases with 35% and 40% FiO_2 .^{3,6} A high FiO_2 such as 60% was found to be related to maternal hyperoxia and the concomitant increase in oxygen-free radical activity in both mother and fetus in elective CS under spinal anesthesia.⁴ We aimed to investigate whether 21% (air group) and 40% (oxygen group) oxygen supplementation influenced maternal and neonatal oxidative stress during elective CS with spinal anesthesia by measuring total antioxidant capacity (TAC), total oxidant status (TOS) and the oxidative stress index (OSI) with this randomized, double-blinded study.

Materials and Methods

Patient selection

The Institutional Ethical Committee approved this study, which was performed in accordance with the ethical principles for human investigations as outlined by the Second Declaration of Helsinki. We recruited eighty ASA physical status I-II term parturients undergoing elective CS under spinal anesthesia once written informed consent was obtained. The indications for CS were breech presentation, cephalopelvic disproportion, or previous CS. We did not enroll subjects with any metabolic, endocrine, hepatic, cardiac or renal diseases; malignancies; preeclampsia; hypertension; or recent use (within 48h) of any drug with anti-oxidant properties such as nebivolol, carvedilol, vitamins E and C, or acetylcysteine.

We randomly allocated patients to breathe 21% (air group) or 40% (oxygen group) oxygen from the time of skin incision to the end of the operation by drawing from shuffled, opaque, sealed envelopes. The administration of supplemental oxygen or air by facemask was double-blinded. A purpose-built delivery system, similar to that of Cogliano et al.,⁶ was set up prior to entering the operating room by an operating department practitioner. The delivery system consisted of oxygen and medical air supplies combined at a common gas outlet connected to the facemask. An electronic switching device enabled either oxygen or air to be delivered from the common gas outlet without the attending anesthetist or patient knowing which gas was being delivered. Air or

oxygen was supplied from a flow meter to a masked high-flow Venturi-type face mask (Intersurgical, Wokingham, UK) to provide the assigned FiO_2 .

We secured intravenous (i.v.) access in the operating room and standard monitoring included non-invasive arterial pressure, electrocardiography, and pulse oximetry. After an i.v. preload of 15 mL.kg⁻¹ of lactated Ringer's solution, we performed spinal anesthesia and turned the patient to supine with a right lateral tilt and prepared for surgery once the level of the block was deemed adequate.

We recorded the durations from spinal anesthesia to skin incision, skin incision to delivery, and the duration of the operation time. A pediatrician who was unaware of group allocation assessed the Apgar scores.

Blood sampling

We collected maternal pre- and post-operative blood samples in the operating room. Upon delivery, we isolated a segment of umbilical cord using double clamps, and umbilical artery (UA) blood samples were obtained, as lipids in the umbilical arterial serum have been reported to be more susceptible to peroxidation than lipids in the umbilical venous serum.⁷ Postoperative blood samples were collected at the onset of skin closure. Samples were separated by centrifugation at 1,200 rpm within 45 minutes (min) of vein puncture and were stored at -20°C until testing.

Measurement of total oxidant status

The total oxidant status of serum was measured using an automated measurement method.⁸ Oxidants oxidize ferrous ion-o-dianisidine complex into ferric ions. Ferric ions react with xylenol orange in an acidic medium to produce a colored complex. Color intensity, which can be measured by spectrophotometry, is linked to the total amount of oxidant molecules. We calibrated the assay with hydrogen peroxide, and the results were expressed in terms of micromolar hydrogen peroxide equivalent per liter ($\mu\text{mol H}_2\text{O}_2$ equiv.L⁻¹). The assay has excellent precision values lower than 2%.

Measurement of the total antioxidant capacity

The total antioxidant status of serum was determined using an automated measurement method.⁹ Free radical reactions were initiated with the production of a hydroxyl radical via the Fenton reaction, and the rate of reaction was monitored by following the absorbance of colored dianisidyl radicals. This method used an automated analyzer (Aeroset®, Abbott, MA, USA) to measure the antioxidative effect of the sample against potent free radical reactions initiated by a synthesized hydroxyl radical. Both intra- and inter-assay coefficients of variation were less than 3%. Data are expressed in terms of mmol Trolox equiv.L⁻¹.

Oxidative stress index (OSI)

The ratio of TOS to TAC produces OSI, an indicator of the degree of oxidative stress.^{8,9} For calculations, we changed the resulting unit of TAC to mmol.L⁻¹, and the OSI level was

calculated according to the following formula: OSI (arbitrary units) = TOS ($\mu\text{mol H}_2\text{O}_2 \text{ equiv.L}^{-1}$)/TAC (mmol Trolox equiv.L⁻¹).

Statistical analysis and sample size

We performed statistical analysis using SPSS for Windows, version 11.5 (SPSS, Chicago, IL). We analyzed the distribution of continuous variables with a one-sample Kolmogorov-Smirnov test, and all data were distributed normally. We used Student's *t* test to evaluate comparisons between groups with respect to demographic, clinical and biochemical values. We expressed the results as the mean and SD or median and range where appropriate. We considered a two-tailed P-value of 0.05 statistically significant.

We calculated the sample size according to the results of the first sixteen patients in the study, in which we observed a difference of 0.2% in postoperative OSI levels with a standard deviation of 0.27% between the groups. From these differences and assuming a two-tailed α value of 0.05 (sensitivity 95%) and a β value of 0.20 (study power: 80%), we determined that at least 40 patients were required for each group.

Results

All of the patients completed the study. Age, weight, height, parity, gestation week, spinal-skin incision time, skin incision-delivery time, delivery time, operation time, 1st min and 5th min Apgar scores, and birth weight were all similar between the groups (Table 1). There were no differences in preoperative TAC, TOS and OSI levels between the groups (Table 1).

Table 1 Demographic, clinical and operative characteristics and baseline laboratory findings of study population.^a

| | 21% oxygen n = 40 | 40% oxygen n = 40 |
|-----------------------------|----------------------|----------------------|
| Age | 24 (18-38) | 24 (18-39) |
| Weight (kg) | 70.1 (6.8) | 71.5 (6.9) |
| Height (cm) | 160.6 (7.5) | 161.4 (7.2) |
| Parity | 2 (1-4) | 2 (1-4) |
| Gestation week | 38.17 (0.9) | 38.32 (0.85) |
| Spinal-skin incision | 580.5 (70) | 579.4 (70) |
| Skin incision-delivery time | 389.5 (45) | 403.5 (39) |
| Operation time | 59.4 (7.4) | 58.4 (7.5) |
| Apgar score (1 min) | 8 (8-10) | 8 (8-10) |
| Apgar score (5 min) | 10 (8-10) | 10 (8-10) |
| Birth weight | 3041 (243) | 3048 (277) |
| TAC | 0.98 (0.15) | 0.92 (0.16) |
| TOS | 3.07 (0.97) | 3.15 (1.03) |
| OSI | 0.24 (0.04) | 0.25 (0.06) |

OSI, oxidative stress index; TAC, total antioxidant capacity; TOS, total oxidant status.

Values are mean (SD) or median (range).

^ap > 0.05 for all comparisons.

Table 2 Postoperative maternal TAC, TOS, OSI levels.

| | 21% oxygen n = 40 | 40% oxygen n = 40 | p |
|------------------|----------------------|----------------------|---------|
| TAC ^a | 1.14 (0.29) | 1.30 (0.38) | 0.047 |
| TOS ^a | 12.4 (3.7) | 15.6 (3.9) | < 0.001 |
| OSI ^a | 1.09 (0.28) | 1.25 (0.34) | 0.038 |

OSI, oxidative stress index; TAC, total antioxidant capacity; TOS, total oxidant status.

Values are mean (SD).

^ap > 0.05 for all comparisons.

Table 3 Umbilical artery LOOH, TOS, OSI, SH, TAC levels.

| | Umbilical artery 21% oxygen n = 40 | Umbilical artery 40% oxygen n = 40 | p |
|------|--|--|---------|
| TAC* | 0.85 (0.13) | 0.95 (0.16) | 0.003 |
| TOS* | 19.77 (4.16) | 17.99 (2.27) | 0.020 |
| OSI* | 2.35 (0.56) | 1.92 (0.38) | < 0.001 |

OSI, oxidative stress index; TAC, total antioxidant capacity; TOS, total oxidant status.

Values are mean (SD).

^ap > 0.05 for all comparisons.

Postoperative maternal TAC, TOS, and OSI concentrations are summarized in Table 2. Postoperative maternal TAC, TOS and OSI levels showed a statistically significant increase in the oxygen group compared to those of the air group (p = 0.047, < 0.001 and 0.038, respectively).

Umbilical artery TAC, TOS, and OSI concentrations are summarized in Table 3. Umbilical artery TAC levels showed a statistically significant increase in the oxygen group compared to those in the air group (p = 0.003), and TOS and OSI levels showed a statistically significant increase in the air group compared to those in the oxygen group (p = 0.02, < 0.001, respectively).

Discussion

We hypothesized that 21% and 40% FiO₂ oxygen supplementation via face mask would influence oxidative stress in mothers and newborns during elective CS. Our results demonstrated that: (i) postoperative maternal TAC, TOS and OSI levels were significantly increased in the oxygen group compared to those in the air group; and (ii) postoperative umbilical artery TOS and OSI levels were significantly increased and TAC levels significantly decreased in the air group compared to those in the oxygen group.

We reported a significant relationship between the maternal and umbilical vein PaCO₂ during general anesthesia for CS and faster times to first respiration and higher Apgar scores with maternal hyperoxia,¹⁰ despite the major methodological limitation of including hypoxic patients in the study. Contrarily, a concordant increase in maternal and umbilical arterial oxygen tensions was unrelated to an improvement in Apgar scores and umbilical artery pH¹¹ during regional anesthesia for CS, and use of 35-40% supplemental oxygen via face mask or nasal cannula did not show any increase in

fetal oxygenation during elective CS.^{3,5,6} Similarly, 35% oxygen administration during CS did not significantly modify the fetal umbilical vein pH (UVpH) or the partial pressure of oxygen (UVPO₂), although a restrictive ventilatory defect was associated with spinal blockade.³ By contrast, umbilical arterial or UVpH partial pressure of oxygen and partial pressure of carbon dioxide did not change with either 40% or 21% oxygen via face mask or oxygen at 2 L.min⁻¹ by nasal cannula.⁶ Nevertheless, studies demonstrated that breathing high FiO₂ (60%) is necessary to achieve a significant increase in fetal oxygenation,^{4,5} as administration of 60% oxygen increased the oxygen content of the umbilical vein blood compared to the regular breathing of air. However, the administration of oxygen with no increase in the UV oxygen content in patients with a prolonged uterine incision-to-delivery interval during elective CS under spinal anesthesia and functional shunting of the placental circulation was proposed as the possible mechanism.⁵

Aside from the impact on maternal and fetal oxygenation, 60% oxygen led to an increase in lipid peroxidation markers such as 8-isoprostane, malondialdehyde and hydroperoxide in both mother and fetus and modestly increased UVPO₂ in elective CS under spinal anesthesia. Therefore, authors suggested maternal hyperoxia as the mechanism responsible for the generation of free radicals.⁴ However, breathing 60% oxygen was reported to improve fetal oxygenation with no concomitant increase in lipid peroxidation in the mother or fetus with nearly identical methodology in emergent CS under regional anesthesia.¹² This finding contradicts an animal study that demonstrated fetal hypoxic stress induced by lipid peroxidation to increase upon reperfusion with the breathing of 60% oxygen.¹³ The authors proposed that possible pathophysiological mechanisms for the conflicting results with regard to lipid peroxidation among previous studies include variable oxygen exposure durations and variable basal free radical activity, magnitude of hypoxic stress and ischemia-reperfusion, and coexistence of certain clinical and surgical features influencing lipid peroxidation unrelated to breathing supplementary oxygen in CS patients.^{4,12,13}

The present study is the first to compare the effects of supplemental 40% oxygen with those of air via face mask on maternal and fetal oxidative stress in elective CS under spinal anesthesia. As a novel approach, we used TOS and TAC to more accurately measure oxidative and antioxidative status, respectively.⁹ Our study's findings highlight the two edges of the sword: 40% oxygen induced an increase in maternal TOS and OSI, an increase in TAC, and induced a decrease in umbilical artery TOS and OSI levels. As a novel finding, 40% oxygen may have induced maternal oxidative stress as was reported for 60% oxygen⁴, and maternal hyperoxia might be the main mechanism for this increase. The unique finding of increased oxidative stress in the air group compared to the oxygen group might be explained by hypoxic stress similar to prolonged labor and oligohydramnios¹⁴ and supports previous reports revealing the beneficial effect of maternal oxygenation on fetal oxygenation.^{4,5,12}

Several limitations of this study should be considered. One of the potential limitations is the absence of long-term clinical follow-up. Although we observed no difference in the neonatal outcome using comparable Apgar scores between the groups, Apgar scores can only signify gross changes. Another major limitation is the absence of assessing maternal and fetal oxygenation. While this assessment was avoided to minimize the invasiveness of our study, it has been the subject of several previous studies.^{4,5,12}

In conclusion, umbilical artery TOS and OSI levels showed a significant increase and TAC levels a significant decrease; and postoperative maternal TAC, TOS and OSI levels showed a significant increase with 40% oxygen compared to 21% oxygen supplementation via face mask during elective CS under spinal anesthesia. The potentially novel finding of 40% oxygen-induced maternal oxidative stress, as was found with 60% oxygen, highlights the need for further large-scale studies to assess the impact of various oxygen supplementation levels on fetal and maternal oxygenation and oxidative stress to determine the optimal oxygen supplementation levels (21, 30, 35, 40, 60...) for patients undergoing CS to improve maternal and fetal well-being. Evaluation of the possible clinical consequences of the present study's findings would require future randomized trials. Our data project either an increase or decrease in maternal oxygenation to be preferable in the case of either maternal disorders or fetal distress; however, further studies with specific clinical scenarios are needed to confirm/refute the findings of our study.

Conflicts of interest

The authors declare no conflicts of interest.

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