

**Title:**

**The effects of perioperative oxygen concentration on oxidative stress in adult surgical patients: a systematic review**

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## **Abstract:**

The fraction of inspired oxygen (FIO<sub>2</sub>) administered during general anaesthesia varies widely despite international recommendations to administer FIO<sub>2</sub>=0.8 to all anaesthetised patients to reduce surgical site infections (SSIs). Anaesthetists remain concerned that high FIO<sub>2</sub> administration intraoperatively may increase harm, through increased oxidative damage and inflammation, resulting in more complications and worse outcomes. In previous systematic reviews associations between FIO<sub>2</sub> and SSIs have been inconsistent, but none have previously examined whether lower FIO<sub>2</sub> administration reduces perioperative oxidative stress.

## Methods

EMBASE, MEDLINE, and Cochrane databases were searched from inception to 9<sup>th</sup> March 2020 for randomised controlled trials (RCTs) comparing higher with lower perioperative FIO<sub>2</sub> and quantifying oxidative stress in adults undergoing non-cardiac surgery. Candidate studies were independently screened by two reviewers and references hand-searched. Methodological quality was assessed using the Cochrane Collaboration Risk of Bias tool.

## Results

From 19,438 initial results, seven trials (n=422) were included. Four studies reported markers of oxidative stress during caesarean section (n=328) and three reported oxidative stress during elective colon surgery (n=94). Risk of bias was low (4 studies) to moderate (3 studies). Pooled results suggested high FIO<sub>2</sub> was associated with greater malondialdehyde, protein-carbonyl concentrations and reduced xanthine oxidase concentrations, together with reduced antioxidant markers such as superoxide dismutase and total sulfhydryl levels although total antioxidant status was unchanged.

## Conclusion

Higher FIO<sub>2</sub> may be associated with elevated oxidative stress during surgery. However, limited studies have specifically reported biomarkers of oxidation. Given the current clinical controversy concerning perioperative oxygen therapy, further research is urgently needed in this area.

## Introduction

In 2016, the World Health Organization (WHO) recommended administering a fractional inspired oxygen concentration (FIO<sub>2</sub>) of 0.8 to all intubated patients undergoing surgery to reduce surgical site infections (SSIs).<sup>1 2</sup> This was based on a meta-analysis of 15 trials performed by the WHO guideline development group (GDG),<sup>3</sup> and remains controversial amongst anaesthetists.<sup>4-6</sup> Notably, the findings of the largest trial available at the time (the PROXI study, n=1378,<sup>7</sup>) were deemed 'biologically implausible' by the GDG for reasons that remain obscure.<sup>2</sup> Post-hoc analyses from PROXI suggested higher intraoperative FIO<sub>2</sub> could be associated with higher long-term mortality in patients with cardiac disease and/or cancer.<sup>8</sup> <sup>9</sup> A better understanding of the mechanisms underlying such outcome differences is essential to resolve this debate.

Systemic detrimental effects of oxygen are often thought to be mediated through 'oxidative stress' - an imbalance between the production of highly reactive by-products of metabolism (reactive oxygen species, ROS) and endogenous antioxidant defence mechanisms, also affecting local and systemic redox status.<sup>10-12</sup> ROS are largely formed during mitochondrial oxidative phosphorylation, or within neutrophil/macrophages and non-phagocytic cells.<sup>13-15</sup> ROS can irreversibly damage lipids, proteins and DNA; triggering cell death through apoptosis or necrosis.<sup>13 14</sup> Oxidative stress can be beneficial (e.g. in phagocytosis) but can also lead to tissue damage and organ failure.<sup>16 17</sup>

Direct detection of ROS remains challenging due to their short half-life. Markers of oxidation and antioxidant status are therefore used as indirect measures of ROS activity. Common markers of oxidation include lipid peroxides (e.g. malondialdehyde (MDA), F<sub>2</sub>-isoprostanes and organic hydroperoxides (OHP)), which indicate levels of cellular lipid oxidation.<sup>18 19</sup>

Similarly, protein carbonyl moieties (PCO) reflect levels of cellular protein oxidation.<sup>20</sup> Xanthine oxidase (XO), a ROS generating enzyme, has also been used to assess ischaemic/reperfusion injury perioperatively; with tissue damage thought to be mediated by ADP catabolism, acidosis, subsequent XO production and neutrophil mediation.<sup>21–23</sup>

Well-studied antioxidant enzymes include superoxide dismutase (SOD), glutathione peroxidase and catalase. Thiols (protein or non-protein compounds with free sulfhydryl groups) are also major targets of ROS-induced oxidation and common markers of extracellular (e.g. plasma) redox status, whilst the reduced to oxidized glutathione (GSG/GSSG) ratio is a common intracellular marker.<sup>24</sup> Total antioxidant status (TAS) is a popular colorimetric assay used to compare overall levels of ‘antioxidant reserve capacity’ across different clinical samples.<sup>25 26</sup>

Oxidative stress, fundamental to the inflammatory surgical stress response,<sup>16 27 28</sup> is associated with more post-operative complications and worse post-operative outcomes.<sup>28–31</sup> However, whether administering lower FIO<sub>2</sub>s intraoperatively reduces the magnitude of perioperative oxidative stress has not previously been determined.

## **Methods**

This review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),<sup>32</sup> and was prospectively registered online at International Prospective Register of Systematic Reviews (PROSPERO, ID: CRD42017078995).

### Selection criteria

Randomised controlled trials (RCTs), published in English, in adult (aged 18 years or more) patients undergoing any non-cardiac procedure in an operating theatre under general anaesthesia and not requiring one lung ventilation, neurosurgery or hyperbaric oxygen therapy were eligible. All included studies reported biochemical levels of oxidative stress (as agreed by all authors) in response to administration of either a high or low intraoperative FIO<sub>2</sub> (>0.6 vs <0.4, or ≥ 20% difference between interventional groups).

### Search Strategy

EMBASE, MEDLINE, and Cochrane databases were searched from inception until 9<sup>th</sup> March 2020 for keywords relating to ROS, oxidative stress, oxygen, hyperoxia, anaesthesia and surgery. Full search strategies are detailed in Appendix A. Two authors (AHO & AFC) independently identified potentially eligible studies by screening all titles and abstracts using Rayyan (systematic review web application,<sup>33</sup>). Any disagreements were resolved by discussion with all other authors. Full texts of potentially eligible studies were obtained and reviewed by two authors (AHO & AFC). Review by other authors was available if consensus could not be reached, but not necessary. Included articles' references were then hand-searched for completeness.

### Data Extraction & assessment of methodological quality

Data was extracted, placed in an analysis table and independently cross checked by two authors (AHO & AFC). One author (AHO) used the Cochrane Collaboration Tool to assess Risk of Bias (CCRB) to assess methodological quality. Studies were scored as high, low or unclear risk in each of the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, complete outcome

data, selective reporting and other biases. Due to the high level of heterogeneity in the small number of results, a meta-analysis was not performed.

## **Results**

The initial search located 19,438 results, of which 984 were duplicates. 124 were deemed potentially eligible following title and abstract review but 116 were excluded on reviewing the full texts, leaving 8 eligible studies (see figure 1). The most common reasons for exclusion were only reporting clinical outcomes and not specifically reporting on biochemical measures. One article was subsequently excluded from the analysis due to missing data despite attempts to contact the authors.<sup>34</sup> Data from 422 patients in 7 studies were included in the final analysis.

### Characteristics of included studies

From the available data, mean age was 38 (SD 13.9) years and weight 66.9 (SD 3.1) Kg. Of the 6 trials reporting participants' sex (n = 392 total), only 47 (12%) participants were male. All 7 RCTs included in the analysis reported different biomarkers of oxidative stress in surgical patients (see table 1).<sup>35-41</sup> Four studies (three of which were from the same group) reported oxidative stress in maternal and fetal blood samples collected during either elective or emergency caesarean section.<sup>37-39 41</sup> One trial reported markers of oxidative stress in serum and bronchoalveolar lavage samples collected from 40 patients undergoing a hemicolectomy procedure under general anaesthesia,<sup>40</sup> and the final two studies (both from the same group) studied both mucosal and arterial levels of MDA intraoperatively and postoperatively during colon surgery.<sup>35 36</sup>

### Risk of bias in included studies

Of the seven studies analysed, four were deemed to have low risk of bias across all domains,<sup>38-41</sup> and three articles were deemed to have a moderate risk of bias due to no reporting on blinding and patient group allocation concealment.<sup>35-37</sup> A risk bias summary grid depicting these results is shown in figure 2. Combined results are listed in tables 1 and 2.

### Markers of Oxidation

MDA was the most commonly reported biomarker of oxidative stress, reported in 5 of the 7 studies.<sup>35-37 40 41</sup> Two studies demonstrated significant increases in MDA with higher FIO<sub>2</sub> in maternal & umbilical serum,<sup>37</sup> and bronchial lavage.<sup>40</sup> Two other studies (from the same group) reported significantly lower mucosal and postoperative arterial MDA concentrations with an FIO<sub>2</sub> of 0.8,<sup>35 36</sup> and neither maternal nor umbilical MDA concentrations changed in the remaining study.<sup>41</sup>

Three separate studies (from the same group) reported maternal and umbilical isoprostane concentrations.<sup>37-39</sup> Although the earliest of these reported significant increases in the higher FIO<sub>2</sub> (=0.6) group,<sup>37</sup> no significant differences were demonstrated in the latter two studies.<sup>38</sup>

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High FIO<sub>2</sub> was also associated with higher fetal organic hydroperoxide (OHP) concentrations,<sup>37</sup> lower bronchial PCO concentrations<sup>40</sup> and lower mucosal XO concentrations<sup>36</sup> in three separate studies.

### Antioxidant and cellular redox status

No differences in oxidised and reduced glutathione were demonstrated, either intraoperatively (1 hour after induction) or 6 hours after surgery, in two separate studies (both FIO<sub>2</sub> 0.3 vs 0.8) from the same group.<sup>35 36</sup>

Only two RCTs reported on other markers of antioxidant status (see Table 2). Koksai *et al.* reported significant decreases in arterial and BAL SOD and PSH, and also BAL NPSH, with lower FIO<sub>2</sub> (0.4 vs 0.8) in 40 patients having colorectal surgery,<sup>40</sup> and Ahuja *et al.* reported no changes in TAS between control (FIO<sub>2</sub> 0.21) and intervention (FIO<sub>2</sub> 0.5) and in either maternal arterial, fetal arterial or fetal venous blood during elective and emergency Caesarean section.<sup>41</sup>

## **Discussion**

Evidence from this systematic review suggests that higher intraoperative FIO<sub>2</sub> could be associated with increased perioperative oxidative stress. Evidence from 138 patients across four studies demonstrated increased biomarkers of oxidative stress in serum and alveolar samples collected from patients receiving high FIO<sub>2</sub>.<sup>35-37 40</sup> However, the number and size of all of these studies was small and considerable uncertainty remains about which redox pathways might be most affected by intraoperative oxygen administration. We believe this to be the first systematic review reporting oxidative stress in response to different FIO<sub>2</sub>s during surgery, and our findings show few (exclusively small single-centre) trials have explored this during surgery to date. This is surprising given that in many other clinical settings adverse outcomes have been associated with both excess oxygen administration,<sup>42-50</sup> and also different markers of redox activity.<sup>51-60</sup>

Significant increases in MDA (used as a serum and tissue marker in 4 of the 7 included trials) were observed across neonatal cord blood, arterial, bronchial and colon mucosal samples given high FIO<sub>2</sub>. MDA and isoprostane represent final oxidation products of polyunsaturated fatty acids, suggesting FIO<sub>2</sub> might affect lipid membrane composition during surgery. Interestingly, serum MDA concentrations showed no change between different FIO<sub>2</sub> levels (0.4 and 0.8) in one study, but did increase within BAL and arterial samples, suggesting most oxidative stress may occur within the pulmonary vasculature.<sup>40</sup> ROS induced hyperoxia induced acute lung injury (HALI), a state of increased permeability of the alveolar/vascular interface and endothelial disruption (also mediated by interleukins, cytokines and chemokines) is well described,<sup>61</sup> and direct disruption of type 2 epithelial cells by oxidative and inflammatory mediators promotes cellular apoptotic and necrotic pathways.<sup>62</sup>

In contrast during elective C-section, isoprostane and MDA concentrations in both maternal and umbilical serum increased up to 2-fold with FIO<sub>2</sub> 0.6,<sup>37</sup> supporting other research showing that redox mediators can cross the placenta.<sup>63</sup> However, MDA concentrations did not change in a second study where mothers received FIO<sub>2</sub> of 0.21 or 0.5 during both elective and emergency operations,<sup>41</sup> possibly due to either the lower FIO<sub>2</sub> or shorter duration (<10 minutes vs >52 minutes) of oxygen exposure. Oxidative stress has been implicated in multiple obstetric complications including preterm labour, maternal vascular disease and miscarriage, with ROS formation causing lipid peroxidation, membrane disruption of placental tissue, and dysregulation of fetal growth and development.<sup>64-66</sup> It is worth noting that all participants in Khaw *et al.*'s trials received spinal (regional) anaesthesia alone, so these results may not be directly comparable to patients undergoing endotracheal intubation and general anaesthesia.

Only one trial reported xanthine oxidase (XO) expression, an enzyme family known to directly generate ROS,<sup>36</sup> suggesting that inspiring high FIO<sub>2</sub> may attenuate XO activity at a tissue level and reduce ROS production. Given that urate, a common product of XO activity, is also one of the main constituents of many assays used to measure total antioxidant capacity,<sup>67</sup> other measures of antioxidant activity might also be expected to respond similarly to hyperoxia. Lack of consistency as to how antioxidant status is reported makes direct comparison challenging - two studies only reported oxidised and reduced glutathione concentrations,<sup>35 36</sup> whilst two other trials reported alternative markers of activity including SOD, NPSH, PSH and TAS.<sup>40 41</sup> In one of these latter trials, SOD expression and both NPSH and PSH concentrations were significantly reduced with high FIO<sub>2</sub> administration,<sup>40</sup> suggesting that lower concentrations of oxygen may stimulate a greater antioxidant response or that excess oxygen might 'consume' cellular antioxidant capacity. In contrast, the other trial reported no significant differences in TAS,<sup>41</sup> suggesting oxidative stress was not associated with reciprocal anti-oxidation responses in these procedures performed under regional (as opposed to general) anaesthesia.

Our analysis is limited by the quantity and quality of research conducted in this area. Of the seven studies identified in the current systematic review, only four studies were deemed to have low risk of reporting bias in all domains (figure 3). Furthermore, a high proportion of participants were young females as four of the seven included studies (more than half of all of the included trials) only recruited participants having Caesarean section procedures. It is not known how perioperative redox changes might differ between obstetric and non-obstetric surgery, but redox markers are known to vary with age, sex, body habitus and pregnancy.<sup>68</sup> Another limitation that has hampered progress in this field is the lack of a

conceptual framework for what oxidative stress actually means *in vivo*. Many different readouts have been proposed and are currently being used as indicators of the involvement of ROS in clinical settings without a clear understanding what any of these analytes actually 'mark' or how these different 'readouts of cellular activity' may interact with each other.<sup>69</sup>

Taken together, our findings evidence a striking lack of high-quality research exploring the cellular consequences of perioperative oxygen administration in patients undergoing major surgery. Historically, perioperative oxygen research has focussed on the effects of hyperoxia on SSI rates as well as nausea and vomiting.<sup>70-72</sup> However, larger trials (such as PROXI) and meta-analyses demonstrate that the presumed association between hyper-oxygenation and reduction in SSI rates is uncertain,<sup>73</sup> and there remains strong evidence to suggest that ROS formation increases perioperative tissue inflammation.<sup>68</sup> Understanding whether oxygen causes shifts in the production of ROS and antioxidants has considerable clinical implications and more work is urgently needed to explore these mechanisms that underlie so many current practices in perioperative medicine.

### **Detail of author contributions**

Study conception and design: All authors

Data acquisition: AHO and AFC

Data interpretation: All authors

Manuscript drafting: AHO and AFC

Manuscript revision, editing and approval: All authors

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## **Declaration of interests**

DSM has received honoraria for speaking and consultancy work from Siemens Healthineers and Edwards Lifesciences, and is a director of Oxygen Control Systems Ltd. MPWG serves on the medical advisory board of Sphere Medical Ltd. and is a director of Oxygen Control Systems Ltd. He has received honoraria for speaking for and/or travel expenses from BOC Medical (Linde Group), Edwards Lifesciences and Cortex GmbH. MPWG leads the Xtreme Everest Oxygen Research Consortium and the Fit-4-Surgery research collaboration. Some of this work was undertaken at University Southampton NHS Foundation Trust–University of Southampton NIHR Biomedical Research Centre. MPWG serves as the UK NIHR CRN national specialty group lead for Anaesthesia Perioperative Medicine and Pain and is an elected council member of the Royal College of Anaesthetists and president of the Critical Care Medicine Section of the Royal Society of Medicine. All other authors have no pertinent conflicts of interests to declare.

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**Fig. 1 Consort diagram**

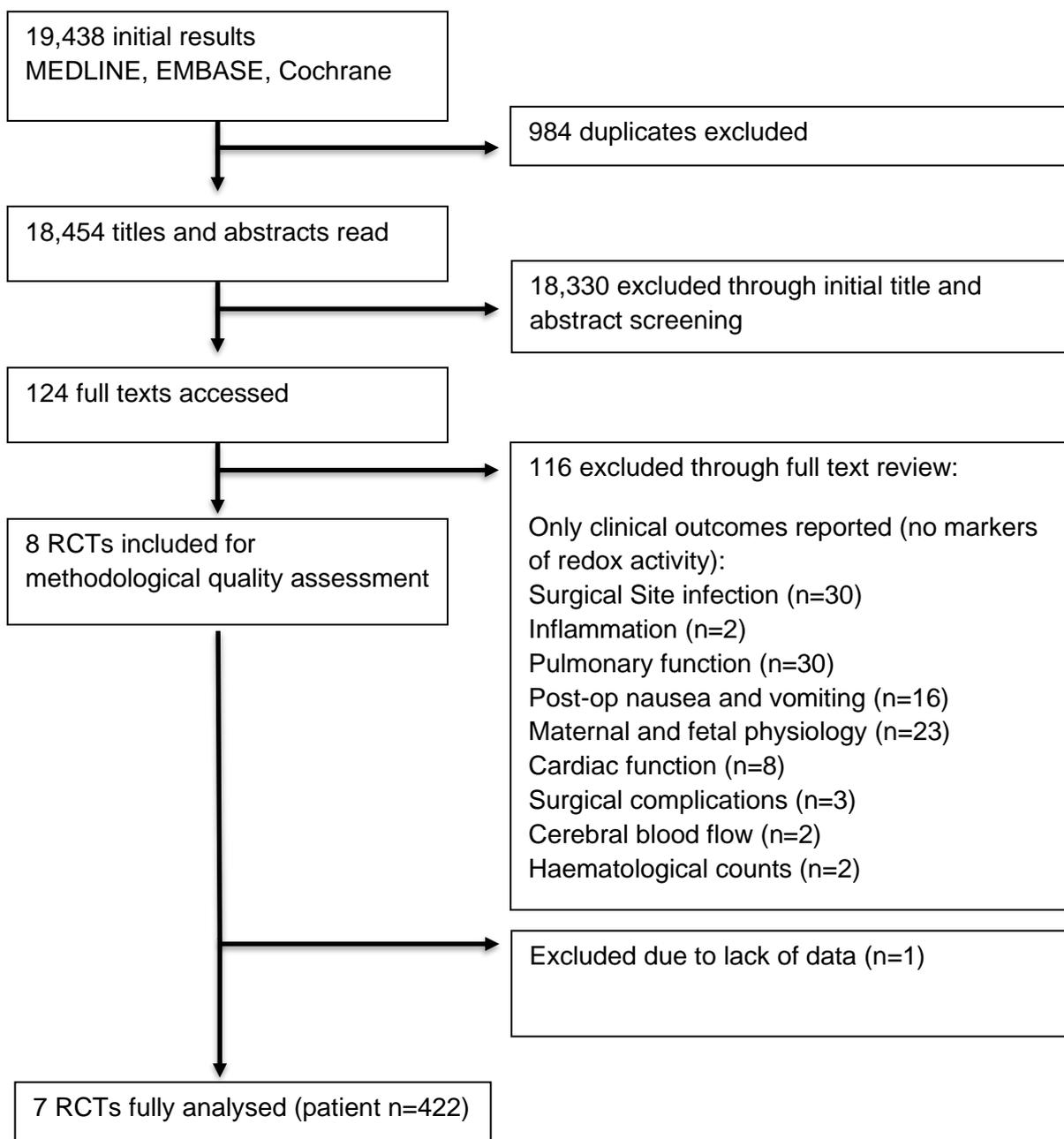


Fig 2. Bias grid

	Khaw et al. 2002	Garcia de la Asuncion et al. 2007	Khaw et al. 2008	Khaw et al. 2010	Garcia de la Asuncion et al. 2013	Koksal et al. 2016	Ahuja et al. 2018
Random sequence generation	+	?	+	+	+	+	+
Allocation concealment (selection bias)	+	?	+	+	?	+	+
Blinding of participants and personnel (performance bias)	+	?	+	+	?	+	+
Blinding of outcome assessment (detection bias)	?	?	+	+	?	+	+
Complete outcome data (attrition bias)	+	+	+	+	+	+	+
Selective reporting (reporting bias)	+	+	+	+	+	+	+
No other bias	+	?	+	+	+	+	+

## Tables

**Table 1.** Combined results of RCTs reporting on markers of oxidative stress in arterial blood, fetal blood, and bronchial lavage samples. \*p<0.05 \*\*p<0.01. EL C/S elective cesarean section; EM C/S: emergency cesarean section.

Author	Patient no.	Control vs. Intervention (FIO <sub>2</sub> )	Sample (units)	Isoprostane	Organic Hydroperoxides	Malondialdehyde, MDA	Protein carbonyl, PCO	Xanthine Oxidase, XO
Khaw et al. 2002	44	0.21 vs. 0.6	Maternal arterial (μmol L <sup>-1</sup> )	121.8 vs. 200.6**	0.14 vs 0.14	0.89 vs. 1.2**	-	-
			Umbilical venous (μmol L <sup>-1</sup> )	135.3 vs 403.0**	0.15 vs. 0.5*	0.47 vs. 0.78*	-	-
			Umbilical arterial (μmol L <sup>-1</sup> )	122.1 vs 215**	0.18 vs 0.39**	0.4 vs. 0.4**	-	-
Khaw et al. 2009	125	0.21 vs. 0.6	Maternal venous (pg ml <sup>-1</sup> )	225 vs. 240.7	-	-	-	-
			Umbilical venous (pg ml <sup>-1</sup> )	427 vs. 471	-	-	-	-
			Umbilical arterial (pg ml <sup>-1</sup> )	457 vs. 473	-	-	-	-
Khaw et al. 2010	39	0.3 vs. 0.5 vs. 1.0	Maternal arterial (pg ml <sup>-1</sup> )	154 vs. 156 vs. 158	-	-	-	-
			Umbilical venous (pg ml <sup>-1</sup> )	480 vs. 416 vs. 441	-	-	-	-
			Umbilical arterial (pg ml <sup>-1</sup> )	410 vs. 368 vs. 468	-	-	-	-
Koksal et al. 2016	40	0.4 vs. 0.8	Subject arterial (nmol mg <sup>-1</sup> )	-	-	8.1 vs. 8.1	5.8 vs. 7.5	-
			Subject bronchial lavage (nmol mg <sup>-1</sup> )	-	-	7.7 vs. 12.6**	10.1 vs. 4.5**	-
Ahuja et al. 2018	60 (EL C/S)	0.21 vs. 0.5	Maternal arterial (μM)	-	-	6.1 vs. 6.2	-	-
			Umbilical venous (μM)	-	-	5.3 vs. 4.8	-	-
			Umbilical arterial (μM)	-	-	5.4 vs. 4.3	-	-
		0.21 vs. 0.5	Maternal arterial (μM)	-	-	6.1 vs. 6.2	-	-

	60 (EM C/S)		Umbilical arterial ( $\mu\text{M}$ )	-	-	5.1 vs. 5.5	-	-
			Umbilical venous ( $\mu\text{M}$ )	-	-	5.4 vs. 4.8	-	-
<b>Garcia de la Asuncion et al. 2007</b>	30	0.3 vs 0.8	Subject arterial 1 hour after induction ( $\text{nmol ml}^{-1}$ )	-	-	0.6 vs. 0.5	-	-
			Subject arterial 6 hours post-op ( $\text{nmol ml}^{-1}$ )	-	-	0.65 vs. 0.4*	-	-
<b>Garcia de la Asuncion et al. 2013</b>	24	0.3 vs. 0.8	Subject mucosal ( $\text{nmol mg}^{-1} \text{protein}^{-1}$ )	-	-	2.0 vs. 1.0**	-	-
			Subject mucosal ( $\text{mU mg}^{-1} \text{protein}^{-1}$ )	-	-	-	-	595 vs. 310*
			Subject arterial ( $\text{nmol mg}^{-1} \text{ml}^{-1}$ )	-	-	1.5 vs. 0.4**	-	-

**Table 2.** Results of RCTs reporting on antioxidant levels in blood and bronchial lavage. \*p<0.05 \*\*p<0.01.

Author	Patient no.	Control vs. Intervention (FIO <sub>2</sub> )	Sample	Superoxide Dismutase, SOD (nmol mg <sup>-1</sup> )	Non-protein sulfhydryl, NPSH (nmol mg <sup>-1</sup> )	Protein sulfhydryl, PSH (nmol mg <sup>-1</sup> )	Reduced Glutathione, GSH (μmol ml <sup>-1</sup> )	Oxidised Glutathione, GSSG (nmol mg <sup>-1</sup> ml <sup>-1</sup> )	Total Antioxidant Status, TAS (mM)
Koksal et al. 2016	40	0.4 vs. 0.8	Subject Arterial	3.6 vs. 1.4**	2.56 vs. 2.7	3.2 vs. 2.6*	-	-	
			Subject Bronchial Lavage	13.7 vs. 13.4**	2.2 vs. 1.2**	11.8 vs. 6.7**	-	-	
Garcia de la Asuncion et al. 2007	30	0.3 vs 0.8	Subject arterial 1 hour after induction	-	-	-	0.68 vs 0.58	20 vs 30	
			Subject atrial 6 hours post-op	-	-	-	0.78 vs. 0.7	42 vs 30**	
Garcia de la Asuncion et al. 2013	24	0.3 vs. 0.8	Subject arterial	-	-	-	-	42 vs 30	
Ahuja et al. 2018	60 (EL C/S)	0.21 vs 0.5	Maternal arterial	-	-	-	-	-	1.1 vs. 1.1
			Umbilical arterial	-	-	-	-	-	1.2 vs. 1.3
			Umbilical venous	-	-	-	-	-	1.3 vs. 1.3
	60 (EM C/S)	0.21 vs 0.5	Umbilical arterial	-	-	-	-	-	1.1 vs. 1.1
			Umbilical venous	-	-	-	-	-	1.6 vs. 1.5