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Oxidative stress under general intravenous and inhalation anaesthesia

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Oxidative stress occurs when reactive oxygen species (ROS) production overwhelms cell protection by antioxidants. This review is focused on general anaesthesia-induced oxidative stress because it increases the rate of complications and delays recovery after surgery. It is important to know what effects of anaesthetics to expect in terms of oxidative stress, particularly in surgical procedures with high ROS production, because their either additive or antagonistic effect may be pivotal for the outcome of surgery. *In vitro* and animal studies on this topic are numerous but show large variability. There are not many human studies and what we know has been learned from different surgical procedures measuring different endpoints in blood samples taken mostly before and after surgery. In these studies most intravenous anaesthetics have antioxidative properties, while volatile anaesthetics temporarily increase oxidative stress in longer surgical procedures.

KEY WORDS: glutathione; malondialdehyde; reactive oxygen species; superoxide dismutase; TBARS

Abbreviations

CPB – cardiopulmonary bypass; F_2-IsoPs – F_2-isoprostanes; CAT – catalase; GPx – glutathione peroxidase; GSH – glutathione; GSHR – glutathione reductase; GST – glutathione transferase; HNE – 4-hydroxynonenal; $LOO^{\cdot}$ – lipidperoxyl radicals; MDA – malondialdehyde; 8-OHdG – 8-hydroxydeoxyguanosine; OSI – oxidative stress index; PUFA – polyunsaturated fatty acids; ROS – reactive oxygen species; SIRS – systematic inflammatory response syndrome; SOD – superoxide dismutase; TAC – total antioxidative capacity; TAS – total antioxidative status; TBARS – thiobarbituric acid reacting substances; TOS – total oxidative status

Oxidative stress is the imbalance of reactive oxygen species (ROS) production and antioxidative cell defence, which disrupts redox signalling and control and causes molecular damage (1). It is considered to be involved in the process of ageing, inflammations, cancers, degenerative diseases (2), and exposure to xenobiotics and drugs, such as anaesthetics (3). Anaesthetics-induced oxidative stress may affect lipids, proteins, and DNA. Among them, the most susceptible to oxidation are lipids (4). ROS interact with polyunsaturated fatty acids (PUFA) to form highly reactive lipoperoxides. Oxidative attack on lipids may result in the production of aldehydes such as 4-hydroxynonenal (HNE) and malondialdehyde (MDA) or prostaglandin-like compounds called F_2-isoprostanes (F_2-IsoPs) (5). Anaesthetics-related oxidative stress is most often measured as plasma MDA levels or thiobarbituric acid reacting substances (TBARS) (6).

Oxidative damage to proteins results in their functional impairment or loss and in increased susceptibility to proteases (7, 8). Biomarkers of oxidative stress of proteins are carbonyl groups introduced into amino acid side chains, but they are not measured frequently in studies on anaesthetics-induced oxidative stress.

DNA damage is established by upregulation of 8-hydroxydeoxyguanosine (8-OHdG) and migration of broken DNA measured either by single-cell gel electrophoresis (comet assay) or more specific comet assays such as formamidopyridine DNA *N*-glycolase (Fpg) or enzyme-modified and human 8-oxoguanine DNA glycosylase (hOGG1) comet assay. In human studies DNA damage is measured in peripheral blood lymphocytes. In animal studies measurements may involve other organs as well.

Oxidative stress can be prevented or decreased by natural cell antioxidant defence, which transforms highly reactive oxygen species to less reactive compounds. Among numerous antioxidants the most frequently measured are glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GSHR), and glutathione transferase (GST).

Other biomarkers of oxidative stress include total antioxidant status (TAS), total oxidative status (TOS), and

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oxidative stress index (OSI). OSI is the ratio between TOS and TAS and indicates the level of oxidative stress.

Surgery patients undergo procedures that can cause surgical trauma, inflammation, and ischaemia-reperfusion injury, all of which cause oxidative stress (9–11). To avoid further tissue injury caused by anaesthetics, it is very important to choose the ones that would minimise oxidative stress. This review seeks to summarise the effects of the most common intravenous and inhalation (volatile) anaesthetics in terms of oxidative stress and related genotoxic potential. We relied on preclinical (*in vitro* and animal) and available clinical data. Even though they are often inconclusive and even controversial, because the experiments greatly vary in cell cultures, animal species, concentrations, times of exposure, and different end-points, our goal was to find common grounds that could provide some informed advice to anaesthetists and surgeons.

INTRAVENOUS ANAESTHETICS

Propofol

Propofol (2,6-diisopropylphenol) is a widely used anaesthetic with many favourable properties. It reduces intracranial pressure and prevents inflammation and convulsions (12). Its pharmacokinetics in adults has been aptly described by Kanto and Gepts (13) and in children by Rigby-Jones and Sneyd (14). Children have higher clearance than adults and need higher induction and maintenance doses to achieve the same propofol blood concentration.

As propofol contains a phenolic OH-group, *in vitro* studies suggest that it has a high potential to prevent lipid peroxidation (15) by scavenging lipidperoxyl radicals ($LOO^{\cdot}$) and could replace α-tocopherol in that respect (16). It also seems to strengthen the GSH system in rat cells by inhibiting GPx and increasing GSHR and GST activity (17).

Genotoxicity studies seem to agree that propofol does not damage DNA. In primary rat astroglial cells it has been reported to protect DNA from lesions by scavenging peroxynitrite (18). In patients who underwent ear surgery propofol did not cause DNA damage in peripheral blood lymphocytes (19, 20). Similar was reported for 21 patients who underwent open-heart surgery and showed no increase in chromosomal aberrations of peripheral blood lymphocytes (21).

In rat studies *in vivo*, propofol has been reported to protect from kidney (22), heart (23), and liver ischaemia/reperfusion injury (24), decrease lipid peroxidation in the spinal cord after injury (25), attenuate postoperative signs of organ injury after liver transplantation (26, 27), protect from obstructive jaundice (28), hepatocyte necrosis, and infiltration of inflammatory cells, and restore liver architecture after halothane-induced intoxication (29).

In dogs anaesthetised with propofol, however, findings are less straightforward regarding total antioxidant capacity (TAC). One study reported unchanged TAC up to 48 h after gas evacuation for pneumoperitoneum (30), and another study a significant decrease in TAS with unchanged TOS at the end of anaesthesia for laparotomy and gastrotomy, which resulted with significant increase in OSI (TOS and TAS ratio) (31). A study on rats did not give consistent results regarding plasma TBARS, GSH/GSSG, SOD, CAT, and GSHR (32).

Findings in humans are generally favourable. One study (33) showed no significant plasma MDA changes in 29 liver donors anaesthetised with propofol before and after surgery. Another study (19) in 15 patients who underwent minor surgery and were receiving propofol anaesthesia for two hours showed increased plasma TAS and tocopherol concentrations, which confirmed its antioxidative properties. One clinical trial (34) comparing 50 patients under propofol anaesthesia and 50 patients on ketamine reported lower blood lipid peroxidation, GPx, and SOD activity in the first group. In 10 children with acyanotic heart disease, plasma MDA, GSH, lactate, and pyruvate concentrations remained unchanged after surgery (35). One study with 12 patients who underwent laparoscopic cholecystectomy (36) showed a significant drop in plasma MDA 1 min before desufflation and 20 min after desufflation when compared with concentrations before insufflation. In contrast, another study (37) reported higher plasma MDA concentrations in patients (N=17) undergoing partial hepatectomy after 60 min of propofol anaesthesia. These returned to preoperative values 24 h after surgery. A comparative study in patients with radical oesophagectomy showed significantly lower incidence of severe postoperative complications with propofol (7 of 92) than with sevoflurane anaesthesia (18 of 94) (P=0.03) (38).

Because of its antioxidative properties, propofol has, in fact, been proposed for application other than anaesthetic and sedative. In cultured neonatal rat cardiomyocytes it reduced doxorubicin-induced stress, and the authors of the study suggested that it could be used as adjuvant in doxorubicin therapy (39). It was also suggested for the treatment of glioblastoma, as it triggered apoptosis in human brain glioblastoma multiforme cells by decreasing Bcl-2 and increasing Bax and caspase activity (40). It also showed beneficial effects in critically ill patients with systemic inflammatory response and sepsis (41).

Thiopental

Thiopental or penthiobarbital (2-thio-5-ethyl-5-sec-pentylbarbituric acid) is a rapid-onset short-acting general anaesthetic. Even though it has largely been replaced by propofol, it is still used for rapid induction of anaesthesia in emergency cases. Research of its antioxidative and immunomodulating properties in human neutrophils showed a significant drop in O_2^{-}, H_2O_2, and OH levels in the

presence of clinically relevant thiopental plasma concentrations (30 μg/L) (42). Thiopental also showed anti-inflammatory properties by significantly reducing chemotaxis and phagocytosis (43).

Animal studies of thiopental effects on oxidative stress report uneven findings. In rats with spinal cord contusion injury it showed beneficial effects, because spinal cord MDA was significantly lower than in control rats not treated with thiopental (25). In another study (44), in contrast, rats showed higher MDA and lower GSH, GPx, and GSHR levels in brain, heart, and bronchial tissues. In dogs with surgical trauma thiopental significantly increased plasma TOS, while TAS remained unchanged, which resulted with increased OSI (31).

In humans, the study with patients who underwent laparoscopic cholecystectomy (36) showed no changes in plasma MDA throughout the whole procedure, which suggests antioxidative effects of thiopental.

Ketamine

Ketamine ($C_{13}H_{16}ClNO$) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist (45).

In vitro, ketamine was reported to produce toxic effects only at levels much higher than those corresponding to anaesthetic concentrations (46, 47). When they did correspond to plasma concentrations in anaesthesia (30 μg/mL), human neutrophil ROS (O_2^-, H_2O_2, and OH) production did not differ from controls (43).

In rats, ketamine showed protective effects against oxidative stress. In fact, ketamine anaesthesia resulted in significantly lower kidney and liver tissue MDA than propofol, thiopental, and fentanyl (28, 48). In another study (44), the authors attributed significantly higher MDA and lower GSHR and GPx levels to ketamine-triggered boost of adrenaline, which is known to induce oxidative stress (49). In mice, ketamine also turned out to mitigate (secondary) brain injury which occurs when ROS production overwhelms the antioxidant system (50). It lowered brain MDA content in these mice and increased GPx, SOD, and NRf2 activity. These effects were accompanied by a significant reduction of brain water content and improved brain function (grip test) score.

Reports of ketamine effects in humans are positive. In adult and paediatric patients with cardiopulmonary bypass (CPB) ketamine mitigated the systemic inflammatory response syndrome (SIRS) by reducing proinflammatory IL-6 and IL-8, and/or increasing anti-inflammatory IL-10 (51–53).

Etomidate

Etomidate (R-1-(1-ethylphenyl)imidazole-5-ethyl ester) is a short-acting intravenous anaesthetic, whose R (+) enantiomer has a much higher hypnotic activity than the S (-) enantiomer (54). It has been in clinical use since 1972 thanks to high therapeutic index and minimal effects on blood pressure and breathing. However, its use as anaesthetic has been limited since reports of serious adrenocortical suppression and myoclonus were published (55). It is no longer used to induce anaesthesia in critically ill patients, because adrenal suppression decreases cortisol release and thus weakens anti-inflammatory response. This means longer stays at intensive care units and higher mortality rate (56).

In vitro, etomidate does not affect TBARS production and the glutathione defence system (GPx, GSHR, GST) (17).

Similar was observed in animal studies. It does not seem to affect MDA levels or change SOD activity (57) in rat brain, while it significantly decreased MDA and increased GSH levels in the spinal cord after injury (58).

In human studies, its effect on plasma MDA was compared with that of thiopental and propofol. In patients who underwent laparoscopic cholecystectomy it fared worse than either (36), as it increased MDA levels before and after desufflation compared to other anaesthetics. In another study with 60 patients who underwent tibial fracture surgery (59) etomidate did not affect SOD activity, and patients receiving it had shorter hospitalisation time because of fewer postoperative complications such as numbness, lower limb pain, and coldness than patients on propofol.

INHALATIONAL (VOLATILE) ANAESTHETICS

Sevoflurane

Sevoflurane [fluoromethyl-2,2,2trifluoro-1-(trifluoromethyl) ethyl ether] has been used for general anaesthesia since the 1990s. It has a lower blood-gas partition coefficient than other volatile anaesthetics, which allows rapid induction of anaesthesia and quick reawakening. Because it does not cause irritation, acts as bronchodilator, and barely has any smell, it is the anaesthetic of choice in children (60), especially those with respiratory infections, airway hyper-reactivity, and seasonal allergies (61).

Genotoxicity studies point to none to low DNA damage. In one study (62), alkaline comet assay showed no sevoflurane genotoxicity in human peripheral lymphocytes, but in another (63) DNA damage was found in kidney homogenates of rats exposed for two hours over three consecutive days. Excessive exposure in this experiment may explain why the comet tail length and intensity increased gradually until the end of experiment (24 h). In peripheral lymphocytes of patients who underwent minimally invasive surgery that lasted two hours, the assay revealed no DNA damage (20), and no damage was reported in peripheral lymphocytes of children under sevoflurane anaesthesia for about one hour (64). In patients with lower abdominal surgery DNA damage was short-lived and tail

parameters started to return to normal on the third day, and repair was complete five days after anaesthesia (65).

In animal studies, findings of its effects on oxidative stress parameters vary, however. One study (66) reported higher GST and SOD activity and TBARS level in the liver of young and adult female rats after sevoflurane anaesthesia. In adult male rats it also increased MDA in the lungs, but decreased it in the kidney and brain (67). It also significantly reduced liver MDA levels in rats with ischaemia/reperfusion injury (57). Compared to isoflurane in another study (68), it produced significantly lower TBARS levels.

Several human studies suggest that sevoflurane does not increase oxidative stress, especially in minor surgeries (3), and where it does (as in major surgeries such as orthopaedic, cholecystectomy, hysterectomy, and alike) oxidative stress parameters return to normal 24–48 h after exposure has stopped. In patients who underwent laparoscopic surgery it did not increase plasma MDA and protein carbonyls (69) nor did it affect MDA, GSH, lactate, and pyruvate levels in peripheral blood of ten acyanotic children who underwent elective cardiac surgery (35) or GPx activity and TOS in 15–50-year-old patients who underwent laparoscopic cholecystectomy (70), while their TAS significantly increased. In a study of 12–36 months old children undergoing hypospadias repair surgery (71) sevoflurane increased SOD, GPx, and caspase-3 mRNA levels two hours after surgery, but these returned to normal three days later. The authors conclude that sevoflurane temporarily increases oxidative stress in children.

Desflurane

Desflurane (1,2,2,2-tetrafluoroethyl difluoromethyl ether) has the blood-gas partition coefficient lower than any other anaesthetic, which grants rapid recovery from general anaesthesia. It is contraindicated in children because of its pungent smell, which makes children hold their breath, cough, and salivate profusely (61).

Animal studies report controversial findings. One study comparing the effects of desflurane on oxidative stress in pig peripheral blood and bronchoalveolar lavage (BAL) fluid with those of sevoflurane and propofol (72) reported significantly higher MDA levels and lower GPx activity. Another, comparing it with sevoflurane, reported no brain accumulation of IL-6 and TNF-a or cognitive impairment in six days old mice (73).

Clinical studies also report inconclusive findings. In mothers with elective Caesarean section serum TOS and OSI were significantly lower after surgery than before it (74), but compared to sevoflurane, these parameters were significantly higher, especially in umbilical artery blood, which also had higher LOOH. In patients with laparoscopic cholecystectomy (70) it increased total oxidant capacity, but did not affect TAS and GPx activity. Similar were the findings reported for Turkish patients who underwent unspecified elective surgery (75): while serum GPx and erythrocyte SOD activity did not change, MDA levels soared, and α-tocopherol plummeted in the first hour after surgery, but both returned to baseline values 12 h later. This transitory increase in MDA and protein carbonyl content was also reported six hours after desflurane anaesthesia (given together either with fentanyl or N_2O), which started to returned to normal 24 h later (69).

As for its genotoxic potential, one study reports that desflurane does not cause DNA damage if used for minor surgeries for at least 90 minutes (76), while another study (77) revealed significantly higher 8-OHdg concentrations in plasma samples in addition higher comet tail length and intensity in BAL samples taken after anaesthesia, which points to oxidative stress as the mechanism of genotoxicity (77).

Isoflurane

Isoflurane (2-chloro-2-(difluoromethoxy)1,1,1-trifluoro-ethane) has been used as anaesthetic since the 1980s (3, 20) thanks to particularly (s)low metabolism and solubility, which results in very short induction and recovery time.

Isoflurane has antioxidative properties *in vitro* (3, 78), but *in vivo* it induces oxidative stress by increasing lipid peroxidation (68). In an animal experimental model simulating liver transplantation isoflurane induced significantly higher TBARS levels than sevoflurane.

Clinical studies evidence some oxidative stress. In one, isoflurane increased plasma MDA in patients undergoing donor hepatectomy, but it did not affect TOS, TAC, and SOD activity (33). Plasma SOD and GPx activities were also not affected in another study (79).

Genotoxicity/mutagenicity studies generally suggest no effects (77, 80), especially not after a minor surgery (19, 20). However, after a major lower abdominal surgery, one study (65) reported significantly increased comet assay parameters in peripheral blood lymphocytes two hours after the beginning of isoflurane anaesthesia. These parameters returned to normal three days later.

Nitrous oxide

Having the lowest potency among inhalational anaesthetics, nitrous oxide (N_2O) is often combined with more powerful ones (81) or used as anxiolytic. As it does not cause addiction but causes brief (several minutes long) bursts of euphoria, dissociation, and excitement, it is not prohibited by law, and people have also been using it for recreational purposes ever since 1775 (laughing gas parties) (82).

Even so, its use as anaesthetic has been in decline over postoperative nausea and vomiting, which are more pronounced if used for more than one hour (83). However, the European Society of Anaesthesiology believes that its benefits outweigh the adverse effects and find no real arguments to abandon it.

N_2O is not mutagenic in bacterial and mammalian cell systems (84). It is teratogenic to embryos of pregnant animals exposed to high doses of N_2O for 24 h during organogenesis but is not carcinogenic (76, 84). However, one study in nurses showed a positive correlation between the level of exposure to N_2O and oxidative DNA damage measured with the Fpg-modified comet assay (85). These nurses also had significantly higher lymphocyte ROS and plasma and urine TBARS levels and lower GPx activity than unexposed healthcare workers.

It is known that N_2O irreversibly inactivates methionine synthase (86), which leads to increased concentrations of homocysteine in plasma (87), which, in turn, inhibits the expression of antioxidant enzymes, including GPx. This effect can be counteracted by oral vitamin therapy (folate 2.5 mg, B_6 25 mg and B_{12} 500 mg) for one week before surgery (88). In addition, N_2O causes endothelial dysfunction in patients with cardiovascular disease undergoing non-cardiac surgery, which, in turn, increases the risk of postoperative cardiac events and mortality (87). One clinical study in patients anaesthetised with desflurane with or without N_2O (76) found no difference in lipid peroxidation, protein carbonyls, DNA damage, and ferric-reducing antioxidant power, which indicates that N_2O does not increase oxidative stress.

Volatile anaesthetic developmental neurotoxicity

One specific aspect of concern with anaesthetics – and particularly with sevoflurane, which is the most frequently used anaesthetic in paediatric surgery – is their neurotoxic potential. Considering that anaesthetics are lipophilic and readily pass the placental barrier, they may cause brain injury in foetuses and children. Judging by animal model studies (reviewed in ref. 89), exposure to sevoflurane during uterine quiescence can induce neuroinflammation, neuroapoptosis, and eventually memory impairment. Cognitive impairment was also reported in young mice repeatedly exposed to sevoflurane, which caused an increase in proinflammatory proteins IL-6 and TNF-α (73). IL-6 and Nrf2 were also increased in rats exposed to sevoflurane for five hours (90). Another review article (91) of preclinical intervention studies in neonatal mice suggests that volatile anaesthetics can lead to oxidative stress-related acute neurotoxicity and learning and memory deficits later in life. The risks of attention deficit, hyperactivity disorder, disabilities in language acquisition, and disabilities in abstract reasoning after prolonged anaesthesia have also been highlighted in a review article by Olsen and Brambrink (92). However, a randomised multicentre controlled trial following up 722 children for two and five years (93) after their one-hour general anaesthesia reported no significant neurocognitive or behavioural deficits.

CONCLUSIONS

Research of oxidative/antioxidative effects of anaesthetics has produced ambiguous findings so far, which stem from differences in exposure related to specific surgical procedures, length of anaesthesia, and timing of blood and tissue sampling. Even so, intravenous anaesthetics generally have antioxidant properties and short exposure to volatile anaesthetics does not seem to increase oxidative stress, while the effects of longer exposure are transient. Transient anaesthetics-induced oxidative stress may be the most relevant for the outcome of surgery with procedures that cause oxidative stress themselves. In such cases anaesthetics with antioxidative properties are drugs of choice.

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Oksidacijski stres uzrokovan općom intravenskom i inhalacijskom anestezijom

Ovo je pregledni rad o oksidacijskom stresu uzrokovanom općim anesteticima zbog toga što uzrokuje komplikacije nakon operacije i usporava oporavak. Oksidacijski stres nastaje kada je stvaranje reaktivnih kisikovih spojeva (ROS) veće od stanične zaštite antioksidansima. Poznavanje učinka anestetika na oksidacijski stres posebice je važno pri planiranju kirurških zahvata kod kojih je poznato da uzrokuju nastanak veće količine ROS-a. Naime, antagonistički ili aditivni učinak anestetika na oksidacijski stres može kod takvih kirurških zahvata biti ključan za ishod operacije. Brojna su istraživanja o toj temi, no protokoli pokusa na staničnim kulturama i pokusnim životinjama vrlo su različiti. U istraživanjima na ljudima anestetici su upotrebljavani tijekom vrlo raznorodnih kirurških zahvata, često uz primjenu više anestetika, mjereni su različiti parametri oksidacijskoga stresa, a uzorci (najčešće krvi) uzimani su obično prije zahvata i u različitim intervalima nakon njega. Zbog svega je toga ponekad teško razlučiti kakav je učinak nekog anestetika na oksidacijski stres. Općenito intravenozni anestetici imaju antioksidacijsko djelovanje, imaju ga i plinoviti anestetici – uglavnom nakon kratkotrajne anestezije, a dugotrajna anestezija uzrokuje privremeni porast oksidacijskoga stresa.

KLJUČNE RIJEČI: glutation; malondialdehid; reaktivni kisikovi spojevi; SOD; TBARS