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Effect of Low and High Dose Propofol Anesthesia on Oxidant/Antioxidant Balance

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Abstract: The normal balance between pro-oxidant and antioxidant substances is transiently altered in favor of the former as a result of surgical trauma. Interest has focused lately on the potential of anesthetics to protect against such oxidant mediated cell damage. The intravenous anesthetic, 2,6-diisopropylphenol, propofol, has been shown to have antioxidant properties. Most of the former studies, however, demonstrated that this antioxidant effect of propofol is more pronounced with the use of high dose. The aim of this study was to assess and compare the impact of low- versus high-dose propofol total intravenous anesthesia (TIVA) on the oxidative status through the determination of serum malondialdehyde (MDA), the oxidative stress biomarker; serum total antioxidant status (TAO), and the erythrocyte antioxidant enzymes:superoxide dismutase (E-SOD) and glutathione peroxidase (E-GPx).Material and Methods**:** This study was conducted on consented 60 patients (ASA I-II), scheduled for major elective abdominal surgical interventions (Time ≈ 2 hours). General Anesthesia was induced using IV sufentanil: (0.20-0.30 $\mu g \cdot Kg^{-1}$), IV vecuronium: (0.08-0.12 $mg \cdot Kg^{-1}$) and propofol IV. Patients were divided into two groups: Group I (HI): *(n=30):* received IV Propofol (2-2.5 $mg \cdot Kg^{-1}$) bolus and an induction dose followed by (200 $\mu g \cdot Kg^{-1} \cdot min^{-1}$) for maintenance with continuous total intravenous anesthesia technique (TIVA). Group II (LO): *(n=30):* received IV Propofol (1-2.5 $mg \cdot Kg^{-1}$) bolus as an induction dose followed by (100 $\mu g \cdot Kg^{-1} \cdot min^{-1}$) for maintenance with continuous total intravenous anesthesia technique (TIVA) using syringe pump. Venous blood samples were taken at pre-induction, 10, 60 minutes after induction, at the end of surgery and 24 hours after recovery for the determination of serum MDA and TAO, and E-SOD and E-GPx. Results**:** Alterations of serum MDA and TAO and E-SOD were only observed with low-dose propofol.MDA showed a significant drop at the end of surgery ($P<0.01$), whereas both serum TAO and E-SOD showed significant elevations 10 min after induction of anesthesia and 24 h after surgery ($P<0.01$). E-GPx, on the other hand, showed significant elevations with both high-dose (1 hour after induction of anesthesia and at the end of surgery, $P<0.01$), and low-dose propofol (only 1 hour after induction of anesthesia, $P<0.01$).Marked hemodynamic changes occurred with high dose propofol infusion. Conclusions**:** Our results revealed that low-dose propofol is superior to high-dose propofol in reducing oxidative stress and enhancing antioxidant defense mechanisms. These results might be attributed to the marked hemodynamic changes occurred with high dose propofol infusion. Further studies, with maintained hemodynamic stabilities, are required to explore the antioxidant potential of high-dose propofol.

Key words: Low and high dose propofol,oxidant/antioxidant balance,MDA,TAO,E-SODand E-GPx.

INTRODUCTION

The normal balance between pro-oxidant and antioxidant substances is transiently altered in favor of the former as a result of surgical trauma .Oxidative stress can be defined as an increased production of ROS and/or defects in antioxidant defenses Lases *et al*. (2000).

ROS are molecules or atoms formed by reduction of oxygen and can be either free radicals or non radicals. Free radicals are electrically charged molecules .The most commonly known ROS are superoxide ($O_2^{-\bullet}$), hydrogen peroxide (H_2O_2), and $OH^{\bullet}$ Halliwell *et al* (1992).

Aerobic life is characterized by steady formation of ROS, through both mechanisms enzymatic and non-enzymatic, since free radical reactions are employed in the living systems for useful purposes such as regulation of smooth muscle tone and the bactericidal function of phagocytes Bast *et al* (1991). However,

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ROS, especially free radicals, represent a so-called double-edged sword. When present in wrong amount or milieu, they can easily produce cellular damage by oxidation and inactivation of enzymes, polysaccharide depolymerization, DNA base modification and peroxidation of polyunsaturated lipids in the plasma membrane Cross *et al* (1987).

Malondialdehyde (MDA) is a reflection of lipid peroxidation, which ultimately leads to damage and degeneration of tissues Allaouchiche *et al* (2001). It is not the only oxidation byproduct, but it is a simple and sensitive assay of lipid peroxidation for application to laboratory and clinical studies.

Fortunately, the biological effects of these highly reactive compounds are controlled in vivo by a wide spectrum of antioxidative defense mechanisms : vitamins E and C, carotenoids, metabolites such as glutathione and uric acid, and antioxidant enzymes .Among these enzymes, copper/zinc superoxide dismutase (Cu/Zn SOD) catalyzes the conversion of $O_2^{\cdot-}$ to H_2O_2 and works concomitantly with hydroperoxide-removing enzymes such as catalase and a selenoprotein, glutathione peroxidase (GPx) Repine *et al* (1997).

Interest has focused lately on the potential of anesthetics to protect against oxidant mediated cell damage, which is more pronounced in certain surgical procedures where ischemia-reperfusion (I/R) injury occurs, as in cardiopulmonary bypass (CPB) and organ transplantation as well as in patients with compromised liver, kidney or heart Kato and Foex (2002). Propofol, a highly lipid soluble hypnotic agent, has proven antioxidant activity in both *in vitro* and *in vivo* studies; this is based on the fact that its chemical structure is similar to that of a natural antioxidant: i.e., vitamin E .It has been demonstrated that propofol acts as a scavenger of oxygen free radicals, decreasing lipid peroxidation and increasing the antioxidant capacity of erythrocytes and other tissues in organs such as liver, kidney, heart and lung,both experimentally and clinically Kuang *et al* (2008). However, previous literature demonstrated this antioxidant property of propofol,mostly when administered at a clinically achievable large concentration Xia *et al* (2004). This high dose is a threat to haemodynamic stability.

Aim of the Work:

to assess and compare the impact of low- versus high-dose propofol total intravenous anesthesia (TIVA) on the oxidative status through the determination of serum malondialdehyde (MDA), serum total antioxidant status (TAO), and the erythrocyte antioxidant enzymes: superoxide dismutase (E-SOD) and glutathione peroxidase (E-GPx).It is our aim to elicit propofol antioxidant property while avoiding haemodynamic threats. This may have future application in limiting organ dysfunction after periods of tissue ischemia which results in oxidative damage.

Statistical Analysis:

The tables and graphs (charts) were summarized as means ± standard deviations by Microsoft Word 2003. An IBM compatible Pentium 4 system was used. Statistics were presented as mean ± standard deviations, median number and percentage (frequency distributions). Comparisons were done using a two-way analysis of variance with repeated measures on one factor. All *p*-values are two-sided. A *p* value less than 0.05 *($p<0.05$)* was considered statistically significant and less than 0.01 was considered highly significant*($p<0.01$)* Dawson and Trapp (2001).

Patients and Methods:

After the approval of the Ethics Committee of Theodor Bilharz Research Institute and obtaining an informed written patient consent from sixty patients of either sex (ASA I or II) admitted at the Urology and General Surgery Departments, scheduled for major elective abdominal surgical interventions, expected to last more than two hours were included in this study. They aged between 25 and 55 years, weighing 55 - 85kg. Patients were excluded if pregnant, lactating or menstruating; children, adolescents and geriatrics, underweighted or obese, cigarette smokers, addicts and drug abusers, malignancy, ASA III or more, patients with fever or sepsis or with known cardiovascular, pulmonary, CNS, endocrinal, hepatic, renal, metabolic and/or hematological abnormalities, patients on medications, therapy or supplementation (e.g. multivitamins), undergoing fluid replacement more than basal requirements as well as laparoscopic procedures.

Standard monitoring (Athena 9050, S&W Medico Teknik AIS, Denmark) was applied to the patients and included: modular monitor for electrocardiogram, non-invasive blood pressure and pulse oximeter, peripheral nerve stimulator (TOF- Guard INMT Organon, Teknika NV- Belgium), PET CO2 estimation (Capnography), (Ohmeda-520 CO2 Monitor, Ohmeda BOC Health Care, Lousiville CO, USA). Baseline readings were recorded, HR, NIBP and SpO2 taken before induction, at intubation, every 5 minutes forwards and 24 hours postoperatively.

Under sterile condition, two 18-gauge Teflon venous cannulae were inserted in the ante-cubital fossa in either arms; one of them was restricted for venous sampling. Prior to induction, 500 ml of Lactated Ringer's solution was infused to compensate for overnight fluid losses. No sedative premedication was given.

Preoxygenation was started for at least 3 minutes before the induction of anesthesia. Sufentanil IV (0.2µg.Kg-1) (Sufenta-forte®, Janssen-Cilag) was administered to all patients.

Patients were divided into two groups according to the induction and maintenance doses of Propofol (Diprivan 1%, Astra-Zeneca Ltd, UK): Group I (HI) (high dose propofol) and Group II (LO) (low dose propofol):

Group I (HI): (n=30): received IV Propofol (2-2.5 mg.Kg-1) bolus as an induction dose followed by (200 µg.Kg-1.min-1) for maintenance with continuous total intravenous anesthesia technique (TIVA) using syringe pump (Pilot A2 IS, Fresenius Vial Le Grand Chemin Brezins, France) .

Group II (LO): (n=30): received IV Propofol (1-2.5 mg.Kg-1) bolus as an induction dose followed by (100 µg.Kg-1.min-1) for maintenance with continuous total intravenous anesthesia technique (TIVA) using syringe pump (Pilot A2 IS, Fresenius Vial Le Grand Chemin Brezins, France) .

IV vecuronium (Norcuron, N.V. Organon OSS, Holland), (0.08-0.12 mg.Kg-1) was administered to facilitate tracheal intubation. Controlled ventilation was maintained with IPPV delivering Minute Volume of 70-80 mL.Kg-1 to achieve normocapnea using digital anesthesia machine with electronic ventilator (Fabius GS, Dräger Medical Corporation- Germany). IV sufentanil (0.2 µg.Kg-1.hr-1), IV vecuronium (1 µg.Kg.1min-1) and air: O2 = 3:1 (FiO2 ≈ 40%) were delivered to all patients. Intraoperative IV fluids were infused to maintain haemodynamic stability. Ephedrine 5 mg increments and atropine 10ug. kg-1 were prepared for use if a patient developed hypotension (MAP < 60 mmHg) or bradycardia (HR < 40 beat/min) respectively, and those patients were bound to be excluded from the study. At the end of surgery, residual curarization was reversed with prostigmine (40 µg.Kg-1) and atropine sulphate(20 µg.Kg-1) followed by suction and extubation.

No patient had a serious hemodynamic changes required stoppage of the TIVA infusion concentration or required medical intervention. Thus no patient was excluded from our study.

Venous blood - Serum and Plasma - samples were taken at pre-induction,10,60minutes after induction,at end of surgery and 24 hours after recovery for the determination of erythrocyte Superoxide Dismutase (E-SOD) (*RANSOD SD-125, Randox® Laboratories Ltd*), erythrocyte Glutathione Peroxidase (E-GPx) (*RANSEL RS-505, Randox® Laboratories Ltd; and double strength Drabkin's, Cat. No. MS-181, Randox® Laboratories Ltd*), serum Malondialdehyde (MDA) (*OxisResearch™ BIOXYTECH® USA- LPO-586™ Colorimetric Assay for Lipid Peroxidation assay*) and serum Total Antioxidant status (TAO) (*RANDOX Total Antioxidant Status (TAS) NX-2332 Reagent, Randox® Laboratories Ltd).*

RESULTS AND DISCUSSION

Demographic data of the patients are comparable in both groups(table 1). Changes of arterial blood pressure (systolic and diastolic blood pressure), and heart rate compared to the preoperative values, in both studied groups were summarized in table 2 and 3, respectively. Finally, changes in oxidative stress and antioxidants biomarkers during operations are summarized in tables 4 and 5.

Significant alterations in systemic blood pressure were recorded with high-dose propofol, where a significant drop of the mean SBP and DBP ($P<0.01$) after 15 min of the anesthetic induction was observed as compared to the preoperative levels (Figure 1 and 2). The drop in both parameters was still significant ($P<0.05$) at the 30 min measurement, whereas at the 60 min measurement, only the DBP was still significantly decreased as compared to the preoperative value ($P<0.05$). Significant elevation of both, SBP and DBP, was recorded 15 min postoperatively ($P<0.01$). Low-dose propofol, on the other hand, showed a significant drop in SBP only 15 min after induction of anesthesia ($P<0.05$). Both SBP and DBP showed significant elevation at the end of anesthesia ($P<0.05$) and 15 min postoperatively ($P<0.01$) (Figures 1 and 2).

Alterations of serum MDA, the oxidative stress biomarker, TAO and E-SOD were only observed with low-dose propofol (table 4), where serum MDA showed a significant drop at the end of surgery ($P<0.01$) (Figure 3), whereas both serum TAO (Figure 4) and E-SOD (Figure 5) showed significant elevations 10 min after induction of anesthesia and 24 h after surgery ($P<0.01$). E-GPx, on the other hand, showed significant elevations with both high-dose (table 5) (1 hour after induction of anesthesia and at the end of surgery, $P<0.01$), and low-dose propofol (table 4) (only 1 hour after induction of anesthesia, $P<0.01$) (Figure 6).

The principal finding of this clinical study is the high antioxidant potential of low-dose versus high-dose propofol. Although this finding contradicts previous reports, our results should be interpreted in relation to the hemodynamic changes recorded with either dose regimen, since alterations of systemic blood pressure were more pronounced with the high-dose one. As we suggested that the link between the clinical and biochemical data observed in the current study is the vascular endothelium, a brief discussion about its vital role in vascular homeostasis is warranted.

Table 1: Demographic data, ASA classification of the patients and time of operations in the 2 groups.

	Group I (High-dose Propofol)	Group II (Low-dose Propofol)
Number	15	15
Age (years)	30.80 ± 5.53	30.53 ± 5.23
Weight (Kg)	72.47 ± 5.86	73.80 ± 5.89
Height (cm)	168.9 ± 5.85	171.0 ± 4.89
Sex (Male/Female) ratio	7/8	9/6
ASA I/II ratio	14/1	14/1
Duration of operation (minutes)	110.33 ± 13.6	109.0 ± 7.02

Values are expressed as means ± standard deviation (SD). No statistically significant differences were detected between the two groups.

Table 2: Effects of anesthesia on mean SBP and mean DBP (mmHg) in both studied groups.

Group	Pre-Induction	15-min Post-Induction	30-min Post-Induction	60-min Post-Induction	End of anesthesia	15-min Post-nduction
Group I-	132.8/81.91	104.7**/71.33**	115.5*/73.2*	118.5/75.33*	121.9/75.93	155.6**/98.4**
HI:	±	±	±	±	±	±
SBP/DBP	17.9/ 9.23	12.8/8.45	14.5/11.33	12.5/3.68	20.8/11.7	18.4/10.04
Group II-	130.5/85.1	116.3*/76.07	122.9/85.4	125.9/83.13	140.4*/88.25*	156.0**/99.6**
LO:	±	±	±	±	±	±
SBP/DBP	10.53/9.91	12.6/5.57	17.1/13.17	8.92/6.82	13.6/12.1	19.0/13.7

*Group I- HI: Group I- High-dose propofol, Group II- LO: Group II-Low-dose propofol. Values are expressed as means ± standard deviations. * Significance from preoperative values: * Significant at p< 0.05, ** Highly significant at p< 0.01.*

Table 3: Effects of anesthesia on mean HR (Beat/minute) in both studied groups.

Group	Pre-Induction	15-min Post-Induction	30-min Post-Induction	60-min Post-Induction	End of anesthesia	15-min Post-Induction
Group I- HI	82.4±11.62	78.6±10.76	69.2±7.66**	70.8±8.26*	72.4±14.11	81.0±10.97
Group II- LO	92.07±9.67	87.53±7.66	86.53±12.34	77.53±8.89*	78.33±11.65*	84.67±10.6

*Group I- HI: Group I- High-dose propofol, Group II- LO: Group II-Low-dose propofol. Values are expressed as means ± standard deviations. * Significance from preoperative values: * Significant at p< 0.05, ** Highly significant at p< 0.01.*

Table 4: Impact of low-dose propofol on oxidative status parameters.

Group	Preinduction	10 minutes Post	One hour after	At the end of	24 hours after
Serum MDA (µmol/l)	6.96 ± 3.49	4.93 ± 1.85	4.44 ± 1.65	3.50 ± 1.16**	5.17 ± 2.43Serum
TAO (mmol/l)	1.41 ± 0.29	1.78 ± 0.20**	1.66 ± 0.31	1.49 ± 0.33	1.78 ± 0.08**
E-SOD (U/ml)	270.8 ± 102.3	338.4 ± 119.1**	282.0 ± 116.3	265.4 ± 85.4	374.7 ± 146.3**E-
GPx (U/l)	6955 ± 1419	6645 ± 1460	7530 ± 1259**	7465 ± 1600	6363 ± 1119

*MDA: Malondialdehyde, TAO: Total anti-oxidant, E-SOD: Erythrocyte superoxide dismutase, E-GPx: Erythrocyte glutathione peroxidase. Values are expressed as means ± standard deviations. * Significance from preoperative values: ** Highly significant at p< 0.01.*

Table 5: Impact of high-dose propofol on oxidative status parameters.

Group	Preinduction (T0)	10 minutes Post-induction (T1)	One hour after induction (T2)	At the end of surgery (T3)	24 hours after recovery (T4)
Serum MDA (µmol/l)	3.77 ± 0.49	4.99 ± 2.07	4.69 ± 1.71	4.94 ± 2.24	3.83 ± 0.79
Serum TAO (mmol/l)	1.60 ± 0.29	1.64 ± 0.44	1.74 ± 0.31	1.79 ± 0.39	1.54 ± 0.28E-SOD
(U/ml)	176.5 ± 46.2	216.5 ± 64.5	206.3 ± 66.0	208.9 ± 67.4	196.5 ± 34.7
E-GPx (U/l)	8141 ± 710	8867 ± 1279	9276 ± 1135**	9122 ± 965**	8250 ± 595*MDA:*

Malondialdehyde, TAO: Total anti-oxidant, E-SOD: Erythrocyte superoxide dismutase, E-GPx: Erythrocyte glutathione peroxidase. Values are expressed as means ± standard deviations. Significance from preoperative values: ** Highly significant at p< 0.01.*

Being in direct contact with blood flow, the vascular endothelium acts as a mechanotransducer by sensing and transducing the changes in local mechanical forces into cellular signals. Endothelial function, shape, physiology, and pathophysiology are greatly regulated by the types (uni-directional laminar or disturbed flow conditions) and magnitudes (high or low) of the shear stress, imparted upon them Ross R. (1993). Wall shear stress is the drag force acting on the endothelial cells as a result of the blood flow Kamiya and Togawa (1980).

The intact endothelium is able to sense shear stress and to induce luminal diameter modifications to keep shear stress constant at a predetermined level. How do cells, and the endothelium in particular, sense a change in shear stress, and what are the signaling pathways for the cellular response? From a simplistic standpoint, changes in fluid shear stress could be sensed directly by cell membrane components such as membrane proteins, ion channels, or caveolae or by alterations of the cellular cytoskeleton; subsequent cellular signaling cascades through phosphorylation events or generation of reactive oxygen species (ROS) can lead to diverse effects such as the release of cytokines and other mediators, activation of transcription factors, altered gene and protein expression, and cell division or death Lieu *et al* (2000).

ROS generation may also be important in the physiological regulation of vascular tone in at least two ways, first via interactions with NO and second through the direct effects of H_2O_2. It is well established that endothelium-derived NO undergoes a very rapid reaction with $O_2^{-}\cdot$ that results in inactivation of NO Cai and Harrison (2000). A fundamental aspect of the regulation of vascular tone and blood flow by NO is its rapid sensitivity to alterations in local stimuli (such as increases in shear stress) and the dependence on appropriate local vasodilator actions to achieve integrated increases and/or redistribution of blood flow among specific vascular beds. The physiological local generation of $O_2^{-}\cdot$ is quite likely to be important in the spatial restriction of the actions of NO, together with other molecules such as hemoglobin .In this regard, it is of interest that increased vascular flow is a potent stimulus for the release of both $O_2^{-}\cdot$ and NO .Local SOD activity may also play an important role in regulating the $NO/O_2^{-}\cdot$ balance Li and Shah (2004).

The normal balance between pro-oxidant and antioxidant substances is transiently altered in favor of the former as a result of the surgical trauma and general anesthesia, and the consequent oxidant stress seems to contribute to the pathological injury of tissues observed in several experimental and clinical models of surgical trauma Lases *et al* (2000). Several studies also indicate that oxidative stress occurs in critical illnesses, specifically in sepsis, shock, organ dysfunction, acute respiratory distress syndrome (ARDS), and disseminated intravascular coagulation. Under such pathological conditions, erythrocytes become one of the critical targets for free radicals generated in cells and tissues. Moreover, these oxidative stresses are sometimes accompanied by deleterious shear mechanical stresses due to instability of osmotic pressure, body fluid imbalance, and circulatory disturbance Kameneva (1999).

Of the frequently applied anesthetics, propofol (2,6-diisopropylphenol) has been reported to exert greater antioxidant effects than other anesthetics Kuang *et al* (2008). Propofol is a lipophilic hypnotic drug with proven antioxidant activity in both *in vitro* and *in vivo* studies resulting in part from its chemical structure, which is similar to the natural antioxidant vitamin E Ansley *et al* (1998). Several studies have demonstrated that propofol acts as a scavenger of OFRs, decreasing lipid peroxidation in the liver, kidney, heart, and lung Pilar *et al* (2008).

Most of the studies have demonstrated an antioxidant effect of propofol which is more pronounced with the use of high dose. Ansley *et al(1999)* observed that high-dose propofol (2–2.5 mg/kg bolus followed by a continuous infusion of 200 $\mu g\cdot kg^{-1}\cdot min^{-1}$) enhanced red blood cell antioxidant capacity during CPB in humans. Red blood cell antioxidant capacity with low-dose propofol or isoflurane anesthesia was, on the contrary, similar. In another study, Runzer *et al* (2002) investigated the antioxidant effects of high and low dose propofol in various tissues in a rat model and compared them with that of halothane. Red cell malondialdehyde (MDA) and tissue thiobarbituric acid reactive substances were determined as markers of oxidative stress. Their findings demonstrated that large-dose propofol significantly enhances both tissue and RBC antioxidant capacity.

Xia *et al* (2004) compared experimentally, high vs low dose propofol and related the increased antioxidant capacity in the high-dose propofol group of 120 μg/(kg·min) to improved myocardial function (high cardiac index) 12 h postoperatively. However, the cardiac index in the low-dose propofol group of 60 μg/(kg·min) was similar in their study.

Our results, however, are at odds with the previous reports, as although we observed the antioxidant power of both low- and high dose propofol regimens, the highest antioxidant potential was recorded with the low-dose regimen. Our findings are reinforced by the interesting observation that MDA levels rise after cessation of low-dose propofol and decrease after cessation of the high-dose propofol (Figure 3). This suggests the highly scavenging effect in the former condition and the provocative oxidative effect in the later one. At first glance, these results could be bewildering; but we could explain our novel results in relation to the recorded changes in systolic and diastolic blood pressure using the two modes of anesthesia.

In the current study, the drop of blood pressure was more significant and much prolonged with high- versus low-dose propofol (Figure 1 and 2). The hypotensive effects of propofol was previously reported and was attributed the decrease in sympathetic nerve activity, direct reduction of both vascular smooth muscle tone and cardiac contractility Robinson BJ *et al* (1997). As changes in arterial blood pressure led to corresponding changes in vascular shear stress Stauss and Persson (2000), and stimulation of ROS production has been demonstrated in response to changes in shear stress McNally *et al* (2003), we speculated that hemodynamic changes induced by high-dose propofol might provoke an oxidative stress. However, the lack of significant rise of serum MDA level during operation (Figure 3) could be attributed to the high power of propofol as an antioxidant, i.e. the deleterious effect of high-dose propofol on hemodynamics which might elicit an oxidative stress is counteracted and balanced by the higher potential of the higher dose of propofol as an antioxidant. On the other hand, with low-dose propofol, where hemodynamic changes were mild, the antioxidant property of propofol was apparent as manifested by the significant drop of MDA (Figure 3) and the significant elevation of all measured anti-oxidant parameters during operation (Figures 4, 5, and 6). If our hypothesis is correct, high-dose propofol must elicit a highest antioxidant potential if its hypotensive effects is abolished. Such hemodynamic stability could be achieved with the use of many drugs, e.g. ephedrine is conventionally given by for bolus injection , whereas dopamine and dobutamine are usually administered by continuous infusion Nishikawa *et al* (1996).

Previous studies have also demonstrated that propofol can increase the antioxidant capacity of red blood cells of both swine and humans *in vivo* Ansley *et al* (1998). Murphy *et al* (1992) have also observed this effect under clinical conditions of cardiopulmonary bypass. In a rat model, Runzer *et al* (2002) examined the effects of propofol and halothane on tissue and red blood cell antioxidant capacity. They determined red cell malondialdehyde and tissue thiobarbituric acid reactive substances as markers of lipid peroxidation. The authors demonstrated that propofol increases the antioxidant capacity of RBCs. The antioxidant effect may be attributable to the ability of propofol to capture electrons from free radicals and become a relatively stable intermediate by virtue of its phenolic structure. Previous studies support the claim that propofol acts primarily as a free radical scavenger as opposed to a modulator of enzymatic antioxidant systems Mouithys *et al* (1998). The present work also showed that propofol enhanced erythrocyte antioxidant enzymatic activities. This effect was more on E-SOD with the low-dose regimen (Figure 5), whereas it was more on E-GPx with the high-dose one (Figure 6). Interestingly, with low-dose propofol, we observed an initial drop of E-GPx 10 min after induction of anesthesia, followed by the significant elevation after one hour. Similar observation was recorded by Allaouchiche *et al* (2001) who stated that propofol first inhibits GPx activity to augment the pool of antioxidant defenses that protect the tissue against possible oxidative stress and then enhances GPx activity when oxidative stress situations do not occur. Other Studies on antioxidant defensive cell enzyme systems by De La Cruz JP *et al* (1998a,b), also suggest that, at clinically relevant doses, apart from inhibiting lipid peroxidation, propofol may also act on enzyme systems (in particular on the glutathione system) which would lead to a decrease in the activity of glutathione peroxidase and an increase in the activities of glutathione reductase and glutathione transferase. This effect would yield an increase in cellular deposits of reduced glutathione, and hence in defensive cellular deposits of antioxidants, thereby protecting tissues from oxidative stress.

Conclusion: our results revealed that low-dose propofol is superior to high-dose propofol in reducing oxidative stress and enhancing antioxidant defense mechanisms. These results might be attributed to the marked hemodynamic changes occurred with high dose propofol infusion. Further studies, with maintained hemodynamic stabilities, are required to explore the antioxidant potential of high-dose propofol. Furthermore, pharmacokinetic studies are warranted to determine the propofol dose thought to be “protective” with minimal side effects and to explore the antioxidant enzyme kinetics during anaesthesia.

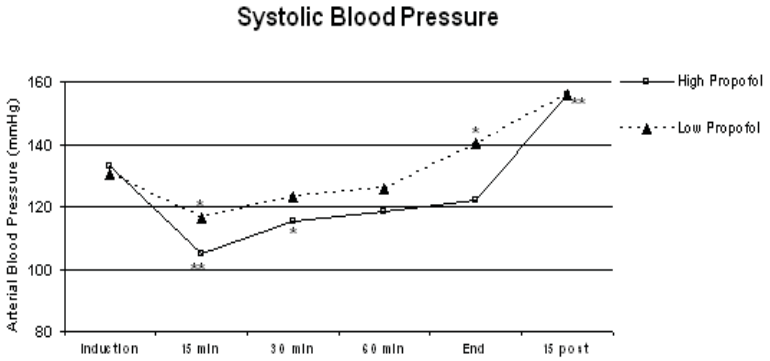

Fig. 1: Changes in systolic blood pressure in both studied groups (*: P<0.05, **: P<0.01).

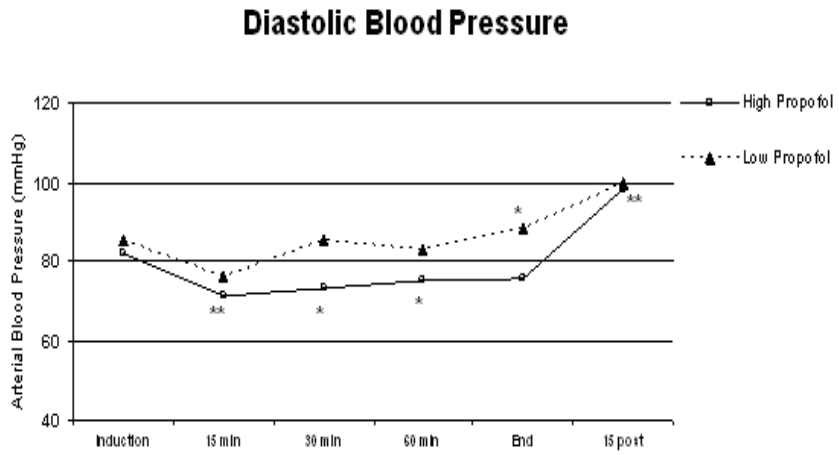

Fig. 2: Changes in diastolic blood pressure in both studied groups (*: P<0.05, **: P<0.01).

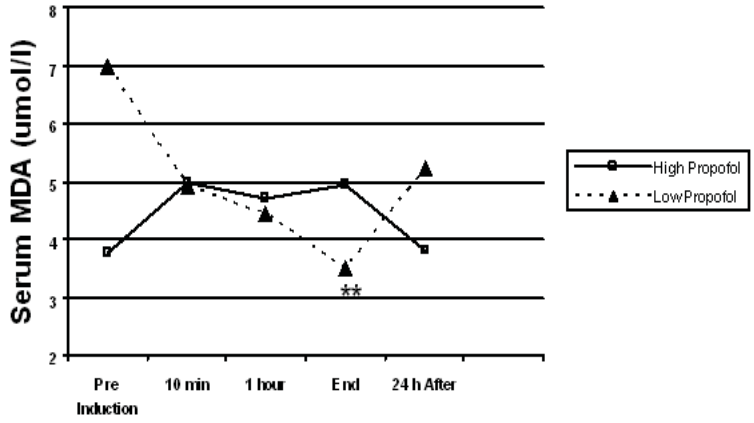

Fig. 3: Changes in serum malodialdehyde (MDA) in both studied groups (**: P<0.01).

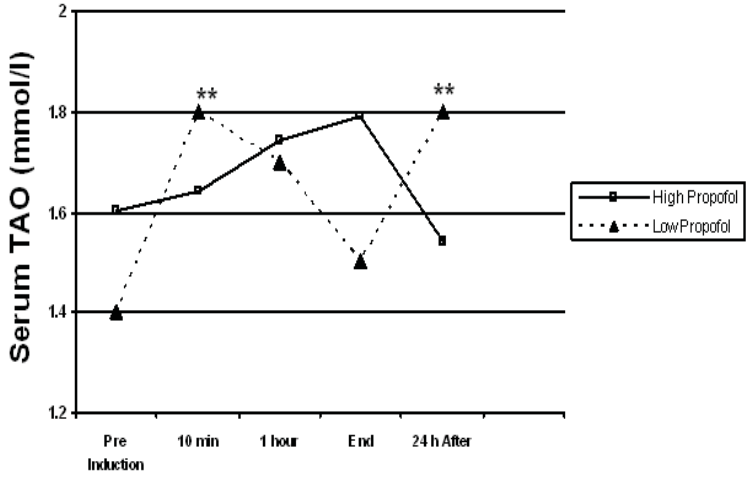

Fig. 4: Changes in serum total antioxidant (TAO) in both studied groups (**: P<0.01).

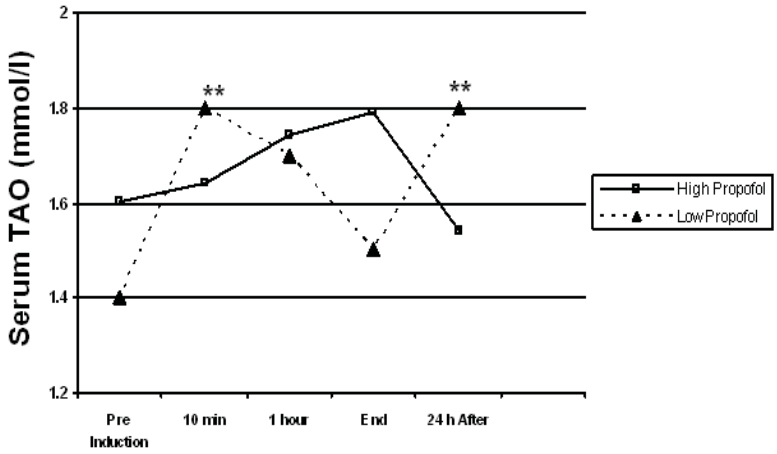

Fig. 5: Changes in erythrocyte superoxide dismutase (E-SOD) in both studied groups (**: P<0.01).

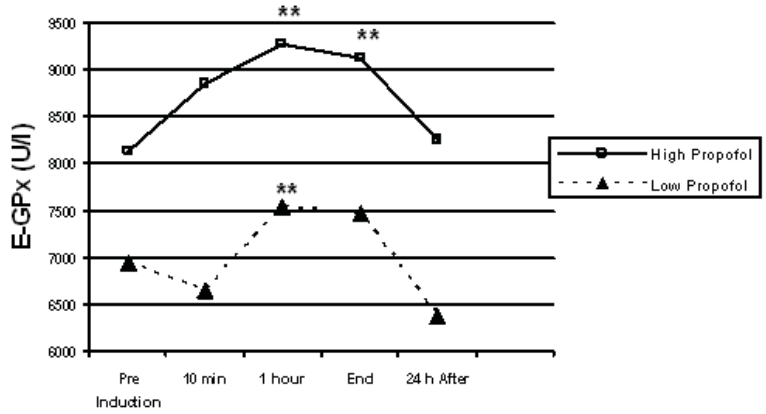

Fig. 6: Changes in erythrocyte glutathione peroxidase (E-GPx) in both studied groups (**: P<0.01).

REFERENCES

Allaouchiche, B. and R. Debon, 2001. Oxidative stress status during exposure to propofol, sevoflurane and desflurane. Anesth. Analg, 93: 981-985.

Ansley, D.M., J.U. Lee, V.D. Godin, 1998. Propofol enhances red cell antioxidant capacity in swine and humans. Can. J. Anaesth., 45: 233-239.

Ansley, D., J. Sun, W. Visser, J. Dolman, D. Godin, M.Garnettand A. Qayumi, 1999. High dose propofol enhances red cell antioxidant capacity during CPB in humans. Can. J. Anaesth., 46: 641-648.

Bast, A., G.R. Haenen and C.J.A. Doelmann, 1991. Oxidants and antioxidants: state of the art. Am. J. Med, 91: 2S-13S.

Cai, H. and D.G. Harrison, 2000. Endothelial dysfunction in cardiovascular diseases, the role of oxidant stress. Circ. Res., 87: 840-844.

Cross, C.E., 1987. Oxygen radicals and human disease. Ann. Intern. Med., 107: 526-545.

Dawson, B. and G.T. Trapp, 2001. Basic and Clinical Biostatistics, 3rd edition, Lange medical book, Appleton & Lange, Norwalk, Connecticut.

Halliwell, B., J.M. Gutteridge, 1992. Free radicals, antioxidants, and human disease: where are we now? J. Lab. Clin. Med., 119: 598-620.

Kameneva, M.V., A. Undar, J.F. Antaki *et.al*, 1999. Decrease in red blood cell deformability caused by hypothermia, hemodilution, and mechanical stress: factors related to cardiopulmonary bypass. Asaio. J., 45: 307-310.

Kamiya, A. and T. Togawa, 1980. Adaptive regulation of wall shear stress to flow change in the canine carotid artery. Am. J. Physiol., H14-H21.

Kato, R. and P. Foex, 2002. Myocardial protection by anesthetic agents against ischemia-reperfusion injury:an updater for anesthesiologist. Can. J. Anesth., 49: 777-791.

Kuang, C.C., J.L. Chen, H.L. Po, F.C. Chau, L.L. Yih, Z.S. Wei and J.C. Ya, 2008. Propofol attenuates the decrease of dynamic compliance and water content in the lung by decreasing oxidative radicals released from the reperfused liver. Anesth. Analg., 107: 1284-1289.

Lases, E.C., V.A. Duurkens, W.B. Gerritsen, *et.al*, 2000. Oxidative stress after lung resection: A pilot study. Chest, 117: 999-1003.

Li, J.M. and A.M. Shah, 2004. Endothelial cell superoxide generation: regulation and relevance for cardiovascular pathophysiology. Am. J. Physiol. Regul. Integr. Comp. Physiol., 287: R1014-R1030.

Lieu, D.K., P.A. Pappone and A.I. Barakat, 2000. G proteins mediate shear stress-sensitive ion channels in vascular endothelial cells. FASEB. J., 14: A459.

McNally, J.S., M.E. Davis, D.P. Giddens, *et.al*, 2003. Role of xanthine oxidoreductase and NAD(P)H oxidase in endothelial superoxide production in response to oscillatory shear stress. Am. J. Physiol. Heart. Circ. Physiol., 285: H2290-H2297.

Mouithys-Mickalad, A., P. Hans., G. Deby-Dupont, e*t.al*, 1998. Propofol reacts with peroxynitrite to form a phenoxyl radical: demonstration by electron spin resonance. Biochem. Biophys. Res. Commun., 249: 833-837.

Murphy, P.G., D.S. Myers, M.J. Davies, 1992. The antioxidant potential of propofol (2,6 diisopropylphenol). Br. J. Anaesth., 68: 613-618.

Nishikawa, K., M. Yabe, T. Mori, 1996. The effects of dobutamine and phenylephrine on atrioventricular conduction during combined use of halothane and thoracic epidural lidocaine. Anesth. Analg., 82: 551-557.

Pilar, S.C., M.R. José, L.N. Juan, S.L. Francisco, J.G. Francisco, C. Carlos, G.S. Rogelio and M. Clemente, 2008. The comparative abilities of propofol and sevoflurane to modulate inflammation and oxidative stress in the kidney after aortic cross-clamping. Anesth. Analg., 106: 371-378.

Repine, J.E., A. Bast ,I. Lankhorst, 1997. Oxidative stress in chronic obstructive pulmonary disease. Am. J. Respir. Crit. Care. Med., 154: 813-816.

Robinson, B.J., T.J. Ebert, T.J. O'Brien, M.D. Colinco and M. Muzi, 1997. Mechanisms whereby propofol mediates peripheral vasodilation in humans. Anesthesiology, 86: 64-72.

Ross, R., 1993. The pathogenesis of atherosclerosis: A perspective for the 1990s. Nature., 362: 801-809.

Runzer, T.D., D.M. Ansley, D.V Godin, 2002 Tissue antioxidant capacity during anesthesia: propofol enhances in vivo red cell and tissue antioxidant capacity in a rat model. Anesth. Analg., 94: 89-93.

Stauss, H.M. and P.B. Persson, 2000. Role of Nitric Oxide in Buffering Short-Term Blood Pressure Fluctuations. News. Physiol. Sci., 15: 229-233.

Xia, Z., D.V. Godin, and D.M. Ansley, 2004. Application of high-dose propofol during ischemia improves postischemic function of rat hearts: Effects on tissue antioxidant capacity. Can. J. Physiol. Pharmacol., 82: 919-926.