



[Home](#) > [Archives](#) > **Vol 7, No 3 (2015)**

Vol 7, No 3 (2015)

Full Issue

[View or download the full issue](#)

[PDF](#)

Table of Contents

Review Article

Chronodisruption and Obesity

Anna Meiliana, Nurrani Mustika Dewi, Andi Wijaya

[PDF](#)
117-28

Adipose Tissue, Inflammation (Meta-inflammation) and Obesity Management

Anna Meiliana, Nurrani Mustika Dewi, Andi Wijaya

[PDF](#)
129-46

Propofol Effect on Stress Response and Free Radicals in Patient during Surgery and Sedation Procedure

Theresia Monica Rahardjo

[PDF](#)
147-52

Research Article

Isolation of Mesenchymal Stem Cells from Adipose Tissue

Harsan Harsan, Silmi Mariya, Andi Asadul Islam, Eka Julianta Wahjoepramono, Irawan Yusuf

[PDF](#)
153-6

Free Radical Scavenging and Alpha/Beta-glucosidases Inhibitory Activities of Rambutan (Nephelium lappaceum L.) Peel Extract

Wahyu Widowati, Maesaroh Maesaroh, Nurul Fauziah, Pande Putu Erawijantari, Ferry Sandra

[PDF](#)
157-62

Dynamics of Interleukin-10 Levels in Chronic Rhinosinusitis with/without Allergy

Abdul Qadar Punagi, Sutji Pratiwi Rahardjo

[PDF](#)
163-6

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Elektronische
Zeitschriftenbibliothek

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All

[Search](#)

Browse

[» By Issue](#)
[» By Author](#)
[» By Title](#)

CURRENT ISSUE

ATOM 1.0
RSS 2.0
RSS 1.0

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ID 29	FR 1
IR 4	
IN 4	
US 4	
GB 2	
JP 1	
IQ 1	
BR 1	
DE 1	
CA 1	

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REVIEW ARTICLE

Propofol Effect on Stress Response and Free Radicals in Patient during Surgery and Sedation Procedure

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Abstract

BACKGROUND: Propofol is an intravenous anesthetic used worldwide as an anesthesia induction and maintenance agent. Propofol also used as sedation agent in Intensive Care Unit (ICU). Despite it's usual anesthesia properties, propofol has an unique pharmacologic characteristic, especially as antioxidant and stress response reduction. These advantages suggested propofol has positive effects when used as an anesthesia agent in surgery or sedation in ICU in conditions when high stress and free radical level are released.

CONTENT: Stress response and free radical can be elevated in various conditions including surgery or during care in ICU, especially critical ill patient. Cortisol is a major

stress hormone that influences metabolism, cardiovascular and central nervous system, either in acute or chronic phase. Oxidative stress was marked by free radical elevation called Radical Oxygen Species (ROS). Combination of both elements (cortisol and ROS) can worsen patient condition. Propofol with anti-stress and antioxidant properties could be used to reduce stress response and attenuate free radical level in order to improve patient condition.

SUMMARY: The anti-stress and antioxidant properties of Propofol are interesting, because these benefits can be added as adjunctive therapy when propofol was used as an anesthetic agent in surgery and a sedation in ICU.

KEYWORDS: propofol, stress response, antioxidant

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Introduction

Propofol is an intravenous anesthetic agent used worldwide as an induction and maintenance agent in general anesthesia (GA). Propofol is also used as a sedative agent in Intensive Care Unit (ICU) especially to non-cooperative or ventilated patients. Studies have reported propofol has advantages include stress response reduction, antioxidant, brain protection and immunology modulation.

Propofol can reduce stress response manifested as cortisol suppression. Propofol can act as an antioxidant

through neutralizing free radicals and reducing lipid peroxidation. Propofol can also protect a brain from ischemia through Cerebral Blood Flow (CBF), Cerebral Metabolic Rate (CMR) and Intracranial Pressure (ICP) reduction. Propofol directly activates γ -aminobutyric acid (GABA)_A receptor, suppress N-methyl-d-aspartate (NMDA) receptor and modulates calcium influx through slow calcium-ion channel. Propofol's activity as an immunology modulator achieved through inflammation dismissal. Other advantages are anxiolytic, anticonvulsion and antiemetic. This review will focus on how propofol can influence stress response and free radicals, including the pharmacology and

Pharmacology

mechanism of action. Propofol effects on stress response and free radicals become important because as an anesthetic agent, propofol can be used as an adjuvant therapeutic agent in high stress condition and free radicals.(1)

Propofol or 2,6-diisopropylphenol has an empiric form $C_{12}H_{18}O$ with molecular weight 178.27. Partition coefficient octanol/water of propofol is 6.761:1 at pH 6-8.5 with pKa 11. Propofol is hydrophobic so it formulated as a white oil emulsion in water contains 1% or 2% propofol, 10% bean oil, 1.2% egg phosphatide and 2.25% glycerol. Disodium edetate (EDTA) was added to block bacterial and fungi growth.(1,2)

Propofol is a sedative hypnotic anesthetic agent and can eliminate consciousness rapidly. The induction can be achieved with intravenous dose 2-2.5 mg/kgBW. Anesthesia could be maintained with continue infusion of propofol 6-12 mg/kgBW/hour or with an intermitten boluses 20-50 mg. There is no accumulation effect and propofol has a rapid recovery time, lipophylic and can get across blood brain barrier. After a single bolus with 2.5 mg/kg dose, propofol plasma concentration will decline rapidly in 10 minutes to less than 1 $\mu\text{g/mL}$ which is the mean propofol concentration in human when awake from anesthesia.(1,2) Propofol level in human blood can be calculated with high performance liquid chromatography (HPLC) as a gold-standard method.

Mechanism of Action

Study revealed, at clinical concentration, propofol will activate GABA_A receptor directly or block sodium channel resulting glutamate release suppression. Glutamate excessive accumulation inside extracellular space caused by central nervous system (CNS) ischemia is believed as early cascade of permanent neuron damage. Massive glutamate release following ischemia will over-stimulate glutamate ionotropic and metabotropic receptor and cause neuron damage.(1,2)

Propofol also suppress NMDA receptor and reduces calcium influx through calcium channel. Calcium influx into the cells will increase intracellular calcium and activate some enzymes like protease, lipase and endonuclease. These enzymes will degrade the cell components. NMDA receptor

antagonist shows neuroprotective characteristic to focal and global cerebral ischemia. Studies show variation results, in some studies propofol increase NMDA receptor effect to intracellular calcium but on the contrary propofol reduces glutamate neurotoxic effect through NMDA receptor. There is a possibility propofol neuroprotective efficacy only last for short time. Based on those results, propofol seems only block NMDA receptor partially.(1,2)

Clinical Effect

Effect to Cerebral Activity

Propofol causes dose dependent CNS depression, can get across blood brain barrier and suppress electroencephalography (EEG) activity caused by neuron activity reduction than direct effect to cerebral capillary. Propofol reduces CBF, CMR and Cerebral Perfusion Pressure (CPP), resulting ICP reduction. This effect has a positive implement to patient with raised ICP as in severe preeclampsia. Propofol also has brain protection effect through CBF and CMR reduction so oxygen consumption decreases and lower the ischemia risk. Propofol more effective than other agents in decreasing abnormal ion wave that happened during cerebral ischemia. No accumulation effect and rapid recovery time, that propofol has a positive benefit after surgery so neurologic examination could be done immediately, especially in severe preeclampsia which is impaired conscious level and neurologic disturbances often found.(1,2)

Effect to Cardiovascular System

Propofol causes systolic and diastolic depression, myocardial contractility, cardiac output and stroke volume suppression. Propofol can cause dose and time dependent hypotension with negative inotropic effect and vascular system resistance reduction. Even this effect seems positive in severe preeclampsia with high blood pressure but excessive hypotension and myocardial contractility suppression will give a contrary effect. Vital sign monitoring is a must during propofol procedure. Nevertheless, in single dose or continue maintenance infusion dose, there is no electrocardiography (ECG) rhythm changes. Tachycardia, not bradycardia, occurred at the last hours in animal experiment after 38 hours continue anesthetized.(1,2)

Drugs to increase blood pressure if hypotension occurs such as ephedrine and phenilephrine must be given

cautiously. Ephedrine, which has β -adrenergic effect, is preferable because has positive inotropic and chronotropic effect. Ephedrine also releases nitric oxide (NO) into uterus circulation so Uterus Blood Flow (UBF) can be maintained. Phenylephrine, a selective α 1-adrenergic receptor agonist, increase blood pressure through peripheral vasoconstriction so it used rarely because can interfere uterus circulation, especially in severe preeclampsia which is peripheral vasoconstriction occurred and phenylephrine can cause a high blood pressure spike.(1,2,3)

Effect to Respiratory System

Propofol causes center respiratory and laryngeal reflex suppression. The side effects to the respiratory system include decrease respiratory rate, bradipnea and even apnea. Bradipnea, both in human and animal, due to respiratory acidosis. Endotracheal intubation and mechanical ventilation can be done to prevent the complication if propofol used as anesthesia maintenance.(1,2)

Propofol Effect to Stress Response

Hypothalamic-pituitary-adrenal axis (HPA) is a major endocrine stress axis in human. Cortisol is a major stress hormone in this axis and influences metabolism, cardiovascular and CNS either acute or chronic phase. During acute stress, cells in paraventricular nucleus (PVN) at hypothalamus will release Corticotropin Releasing Hormone (CRH), it stimulates the pituitary gland to release Adrenocorticotrophic Hormone (ACTH) release into the blood stream. ACTH at the adrenal cortex will release the cortisol secretion into the blood. Generally all cells in human body have cortisol receptor so cortisol gives a wide range effect to all body systems including metabolism, cardiovascular and immune response.(4)

Cortisol regulates its release through negative feedback mechanism in CNS through specific receptor binding in all limbic system, including hippocampus (HC), amygdala (AG) and prefrontal cortex (PFC). Cortisol basal secretion in no stress condition follows circadian rhythm, starts as spike elevation at morning followed by gradual decrease along the day and has a lowest level in the evening. (4,5) Reduction in cortisol levels has been documented both in anaesthetized and intensive care patients receiving propofol and *in vitro* findings suggest a direct inhibitory action of propofol on adrenal steroidogenesis. However,

more recent studies argue that propofol inhibits cortisol release to stimulatory insults.(6)

Studies on propofol effect to stress response is very limited. One of the studies compares cortisol, adrenaline, noradrenaline, glucose and interleukin (IL)-6 level in female patients (aged 18-65 years old) with American Society of Anesthesiologists (ASA) I or II who were given propofol and sevoflurane induction and underwent total hysterectomy. Propofol induction used Total Intra Venous Anesthesia (TIVA) and sevoflurane used Volatile Inhalation Mask Anesthesia (VIMA). Propofol was given with early concentration 2.5 μ g/ml with remifentanyl 5.0 ng/ml addition. Maintenance anesthesia achieved with propofol and remifentanyl dose adjustment. Sevoflurane was given 6 vol%, N_2O 6 L/minute and O_2 2 L/minute for 5 minutes with maintenance dose 1.5 vol%. The result showed cortisol, adrenaline, noradrenaline, and glucose have a significant lower level at induction (T1), intubation (T2), incision (T3) and extubation (T4) with propofol compare to sevoflurane, but IL-6 level has no differences between the two groups.(7)

Other study compared between propofol and sevoflurane effect in animal gave the same result. Cortisol and noradrenaline level in propofol anesthesia were lower than sevoflurane anesthesia after premedication (t0), immediately after surgery procedure finished (t1) and four hours after anesthesia finished (t2).(6,7) Study compared propofol and isoflurane effect to cortisol, glucose and C-Reactive Protein (CRP) in women aged 16-50 years old with ASA I or II classification underwent gynecologic laparoscopic also showed cortisol and glucose level were lower significantly in propofol than isoflurane but CRP level has no differences between two groups. Cortisol, glucose and CRP examination were done after intravenous access established (P0), 60 minutes after incision (P1) and 60 minutes after surgery (P2).(8)

As a sedative agent, propofol is commonly administered for sedation in ICU patients to minimize the physiological responses to a variety of noxious stimuli including factors related to patient's condition, invasive procedures and to enhance patient tolerance to mechanical ventilation. Adequate sedation is known to reduce complications from stress response such as stimulation of the sympathetic nervous system, alteration of hormonal order and immunosuppression. Propofol has been associated with a reduction in blood cortisol levels, but responsiveness to a adrenocorticotrophic hormone challenges was not changed. Propofol gains its popularity because it has a rapid onset and offset compared with other commonly used ICU sedatives.(9)

Besides the relation to stress response, the ICU stay may lead to psychological problems as well. Many patients developing post-traumatic stress syndromes have reported memories of vivid nightmares, hallucinations and altered sense of reality after their discharge from the ICU. Sedation also has been proposed as a neuroprotective strategy in head-injured patients and in status epilepticus. Propofol can achieve many of these goals, taking into consideration that this drug does not have analgesic properties and that it might be administered in combination with other classes of drugs to maximize benefits and minimize side effects relating to single drug use.(9)

One study compared the sedative efficacy of propofol to midazolam at patients after Coronary Artery Bypass Graft (CABG) surgery and showed propofol has a shorter mean duration of sedative infusion in ICU, lower fentanyl as analgetic agent and shorter extubation time than patients sedated with midazolam.(10)

Propofol Effect to Oxidative Stress

Oxidative stress was marked by free radical elevation called Radical Oxygen Species (ROS). One of ROS effects is lipid peroxidation which produces malondialdehyde (MDA) as a major component and often revealed as Thiobarbituric Acid Reactive Substances (TBARS). High MDA level will follow massive lipid peroxidation caused by excessive ROS so MDA can be used as oxidation stress marker.(11-15)

Propofol is an lipophylic and phenolic antioxidant which can neutralize free radical, decrease lipid peroxidation, inhibit oxidative damage and increase glutathion level in tissue. Chemical structure of propofol has similarity with phenol based antioxidant like vitamin E. Studies showed propofol has antioxidant capacity similar with water soluble vitamin E analog (Trolox C). Propofol and vitamin E has equal ability in increasing cell function at isolated cell membrane and the effect has a correlation with lipid peroxidation. With other word, propofol can replace vitamin E as an antioxidant. Another studies showed that propofol has a protective effect to oxidative stress so can stabilize mitochondria membrane.(1,2,11-14)

Studies about the corelation between propofol with MDA in human, only calculate and compare MDA level in normal human, unpregnant woman, normal pregnancy and preeclampsia. Studies in specific condition, like preeclampsia, were very limited.(14-18)

Almost earlier studies about this issue were done in animal experiment. One of studies shows that anesthesia with propofol in animal provides a positive effect to oxidative status of erythrocyte through antioxidant enzyme activity attenuation like Sodium dismutase (SOD), Catalase (Cat) and Glutathione peroxidase (GPx). This study compared intravenous anesthesia with propofol and inhalation anesthesia with sevoflurane. The result showed that animal with propofol anesthesia has higher antioxidant enzymes level than animal with isoflurane anesthesia.(15) Other study described propofol will attenuate oxidative status through MDA level reduction during endotoxaemia. The study result showed an animal group with higher propofol concentration (30 mg/kg/hour) had a lower MDA level than groups with lower propofol concentration (15 mg/kg/hour). (17)

Studies in human showed similar results. One study compared the effects of propofol and halothane anesthesia on oxidative stress by determining MDA levels during knee arthroplasty. In this study, a statistically significant MDA decrease only occurred in propofol anesthesia.(18)

This *in vivo* results were further confirmed by two studies demonstrating propofol was more efficient than fentanyl in suppressing lipid peroxidation, F2-isoprostanes, complement C5a and neutrophil adhesion rate during coronary artery bypass grafting operations. The first study showed propofol attenuates myocardial lipid peroxidation during coronary artery bypass grafting surgery. This study examined twenty four patients undergoing CABG surgery for triple vessel disease divided into two groups. After induction of anesthesia with fentanyl 10 µg/kg and midazolam 0.1 mg/kg, patients in the fentanyl group received fentanyl infusion 10-30 µg/kg/hour and patients in the propofol group received propofol infusion 3-6 mg/kg/hour for anesthesia maintenance. The result showed TBARS level was less significantly in propofol group than fentanyl group.(19)

The second study included thirty adult patients referred for elective cardiac procedure with Cardio Pulmonary Bypass (CPB) and randomly allocated to a propofol group or a control group. Patients in the propofol group received propofol 0.1 mg/kg/minute intravenously for anesthesia maintenance, whereas those in the control group received fentanyl 10 µg/kg intravenously and inhaled enflurane 1%-1.5%. The result showed there were significantly higher levels of F2-isoprostanes, C5a, and more neutrophils adhering to endothelial cells in the control group than those in the propofol group, respectively.(20)

Immunomodulation Effect

Propofol has immunomodulation effect so it can eliminate systemic inflammation responsible to organs dysfunction. Propofol lipid component is made of soybean and contained many variations of triglyceride, phospholipid, glycerol, vitamin and mineral. Major lipid in soybean oil is linoleic acid, an unsaturated omega 6 long chain lipid acid and a few omega 3 long chain lipid acid. Long chain lipid is bioactive and influences synthesis and secretion of cytokine, free radical and other inflammation mediators. Lipid will integrate with cellular membrane and changes membrane structure and function in ion wave, second messenger and eicosanoid production.(1,2)

Anxiolytic, Analgesic and Anticonvulsion Effects

Propofol has anxiolytic effect without sedation. Propofol anxiolytic mechanism probably involves a positive modulation of GABA inhibition function through GABA_A receptor. This effect can be beneficial in anxious patients, as severe preeclampsia patient, who has a high anxiety level. (1,2)

Analgesic effect of propofol gives variation results in studies. Some of studies showed propofol can modulate pain through opioid system with onset 5 to 20 minutes. Other studies showed propofol has no analgesic effect and maybe can cause a hyperalgesic effect.(1,2)

Propofol anticonvulsion effect was found in two model studies using status epilepticus state in rabbit. In those studies, propofol with 12 mg/kg dose can suppress convulsion, and proved with EEG. In human, propofol known effective to prevent refractory status epilepticus to standard anticonvulsion. Anticonvulsion effect may be useful in convulsion prevention that occurred frequently in severe preeclampsia.(1,2)

Conclusion

Propofol has advantages as anti-stress response and antioxidant effect. Based on these benefits, propofol can be used as adjuvant therapy in conditions with a high stress response and oxidative stress such as surgery and during ICU stay.

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