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Propofol Infusion During Brachytherapy Affects Lipid Peroxidation Levels

Canan Kucuk MD*
Department of Anesthesiology and Reanimation, Ankara 29 Mayıs Hospital, Turkey

Original Research Article

***Corresponding author**
Canan Kucuk

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Abstract: The aim of this study was to investigate the effect of propofol on lipid peroxidation in patients operated for uterine cervix cancer and who planned to have external beam radiotherapy and brachytherapy. The cell membrane is protected against lipid peroxidation through endogeneous antioxidants such as lipid soluble α-tocopherol. The anesthetic agent propofol has a chemical structure which is similar to α-tocopherol, since it also contains a phenolic OH-group. The phenolic hydroxyl group is responsible for the antioxidant properties of propofol. 30 operated uterine cervix cancer patients were studied in two groups. Propofol induction (2 mg/kg) was performed in one group; propofol induction (2 mg/kg) and infusion (3 mg/kg/hr) during brachytherapy were performed in the other group. Blood samples were taken before (1st sampling) and after external radiotherapy (2nd sampling) and after brachytherapy (3rd sampling) for determination of lipid peroxidation (malondialdehyde, MDA) levels. Mean MDA levels were evaluated in both groups after external radiotherapy and brachytherapy. Changes in MDA levels with time were statistically significant in both of the groups (F=28.71 p=0.001). There was no significant difference between first and third time intervals in second group. This study shows that the levels of lipid peroxidation are elevated in operated uterine cervix cancer patients by external beam radiotherapy. In group I, a single dose of propofol induction had no protective effect toward increase in lipid peroxidation caused by brachytherapy. However, in propofol infusion receiving group (group II) propofol significantly decreased the levels of lipid peroxidation after brachytherapy.
Keywords: Propofol, Lipid peroxidation, Malondialdehyde, Radiotherapy, Brachytherapy.

INTRODUCTION

Propofol (Propofol®, Abbott, Germany) (2-6 diisopropylphenol) has been used extensively as a rapidly acting intravenous anesthetic agent with high therapeutic index for both induction and maintenance of general anesthesia [1]. It contains a phenolic OH-group which is similar to α-tocopherol and has been reported to act as an antioxidant. It has already been shown that propofol, used in clinically relevant concentrations, could inhibit lipid peroxidation in liver microsomes, mitochondria and brain synaptosomes [2-4]. Propofol inhibits lipid peroxidation in two ways; reacts with lipid peroxyl radicals to form the relatively stable propofol phenoxyl radical and scavenges peroxynitrite [2, 5]. Because of its good lipid solubility, it is able to penetrate into membranes; the concentrations of propofol which are able to inhibit the lipid peroxidation and to replace the α-tocopherol function in cell membranes are in the range which is clinically used in anesthesia. Therefore the antioxidant properties of propofol can be of clinical importance [6].

Low linear energy transfer radiation like χ- or γ-rays, damage the structure and function of mitochondria via oxidative insult to DNA, lipids, proteins, ionic homeostasis, thereby causing increased generation of superoxide anions [7]. Under normal conditions the intrinsic mitochondrial components like quinols, cytochrome c, vitamin E, manganese dependent superoxide dismutase and glutathione act as the cell's antioxidant defense system [8]. However irradiation adversely affects the inherent antioxidant system ultimately leading to bio-energetic catastrophe. For handling such a situation, supplementation of antioxidants in cellular milieu becomes inevitable to protect mitochondria from radiation damage [9-12].

An impairment of the antioxidant defence system has been implicated in many diseases including cancers and the activities of enzymic antioxidants have shown different patterns during neoplastic transformation [13]. Patients with uterine cervix cancer were found to have elevated levels of lipid peroxidation and radiation therapy is one of the most standard and effective modalities for the current treatment of cervical cancer [14-18]. Both uterine cancer itself and radiotherapy had an effect on lipid peroxidation. MDA is aldehydic by-product of lipid peroxidation that can be used as a marker.

The aim of this study was to investigate the effect of propofol on lipid peroxidation in patients operated for uterine cervix cancer who planned to have external radiotherapy and brachytherapy.

MATERIALS AND METHODS

30 operated Stage IA-IB (two or more lymph nodes positive, patients with negative lymph nodes who have microscopic positive or close margins of resection, deep stromal invasion, lymphatic/vascular permeation) uterine cervix cancer patients were studied. Exclusion criteria were; having another disease (diabetes mellitus, hypertension, coronary artery disease, congestive heart failure, and asthma), antioxidant supplementation and smoking. After obtaining institutional ethics committee approval and having received written informed consent, patients were randomly assigned into two groups according to protocol numbers odd or even. Radiotherapy treatment protocol was external beam radiotherapy and intracavitary radiotherapy. Radical pelvic irradiation with linear accelerator (Saturn 43, General Electrics, USA) was performed at adose of 1.8-2 Gy/fraction/day totally 50-50.4 Gy for five weeks. On the sixth week first ICRT and a week after first second ICRT were performed with Curitron HDR (Cis bio International, France) brachytherapy unit. The dose was given 500-750 cGy to 0.5 cm under vaginal mucosa at each session. Since the insertion of Fletcher ovoid was painful and the vagina was slightly distended by placing a spacer or washer between the ovoids and the vagina packed to push ovoids away from the rectum and to hold them in situ, these patients require anesthesia.

At the first ICRT after establishing standard monitoring procedures, propofol was given at a dose of 2 $mgkg^{-1}$ for induction to both groups during instrumentation for brachytherapy and then brachytherapy was given to them. Propofol infusion (3 $mgkg^{-1}hr^{-1}$) during brachytherapy was performed to the second group with patients' preference. Both groups received 2-3 $ltmin^{-1}$oxygen and saturation was monitorized during the session. Blood samples were taken before (1st sampling) and after external beam radiotherapy (2nd sampling) and at the end of the first ICRT session (3rd sampling).

Thiobarbituric acid (TBA) reactive substances (TBARS) level was determined according to the method of Buege and Aust[19]. TBA reacts with MDA and some other lipid peroxidation products to form a stable pink color with an absorption maximum at 535 nm. The simplicity and sensitivity of the TBA method, has made it the most widely used indicator of lipid peroxidation. Levels of lipid peroxidation measured as TBARS were expressed in µmol/l.

The values obtained were statistically analyzed using the Repeated Measures Analysis of Variance. A result of $p<0.05$ was considered significant.

RESULTS

The groups were similar in terms of demographics (Table-1) and procedures performed (Table-2). Mean MDA levels are shown in Table-3. Changes in MDA levels with time were statistically significant in both of the groups ($F=28.71$ $p=0.001$). In group I, mean MDA levels were found to be increased at the second and third samplings. But in group II, mean MDA levels were increased only at the second sampling. There was no significant difference between first and third samplings in second group (Figure-1).

Table-1: Demographic data and stage of cervix cancer

	Group I	Group II
Age (yr)*	56±7	54±10
Weight (kg)*	70±9	70±7
Height (cm)*	163±4	161±3
ASA	I	I
Stage (IA/IB)	6/9	7/8

*Values are expressed as mean±SD. No significant differences between groups

Table-2: Radiotherapy protocol (External beam and intracavitary radiotherapy)

RT(cGy)	1st week*	2nd week	3rd week	4th week	5th week**	6thweek***
EBRT	1000	1000	1000	1000	1000	
ICRT						500-750

*First sampling before the patient had the first EBRT (patient had no radiation)
**Second sampling at the end of the fifth EBRT (just after EBRT and patient had fifth week radiation)
***Third sampling just after ICRT

Table-3: Mean MDA levels (µmol/l)

	First Sampling	Second Sampling	Third Sampling
Group I	0,99±0.29	1.42±0.40	1.90±0.40
Group II	1.52±0.45	2.19±0.61	1.72±0.51

Values are expressed as mean ± SD

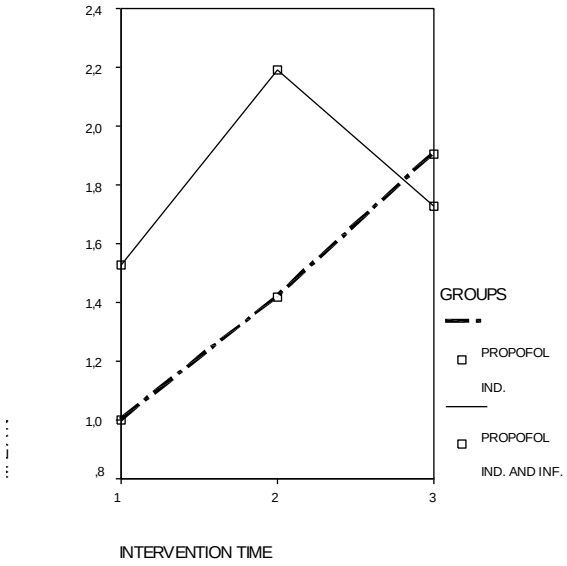

Fig-1: Mean MDA levels in Group I (Propofol ind) and Group II (Propofol ind. and inf) at the time of the sampling

DISCUSSION

This study shows that the levels of lipid peroxidation are elevated in operated uterine cervix cancer patients by external beam radiotherapy. Since the basal levels of lipid peroxidation in both groups were different, these two groups were not compared with each other. In group I, a single dose of propofol induction had no protective effect toward increase in lipid peroxidation caused by brachytherapy. However, in propofol infusion receiving group (Group II) propofol significantly decreased the levels of lipid peroxidation after brachytherapy (Figure-1). The protective action of propofol infusion is the most significant finding of this study.

Lipid peroxidation is a free radical initiated chain reaction resulting in sequential abstraction of hydrogen ions from polyunsaturated fatty acids, producing disruption of cell membranes and dysfunction of membrane bound ion pumps. Lipid peroxides, such as MDA, are markers of lipid peroxidation, indicating cell membrane and organelle damage [20].

Corcoran *et al*. [21] showed the effects of propofol on lipid peroxidation and inflammatory response in elective coronary artery bypass grafting. The samples in the control group showed a high serum MDA concentration 10 minutes after aortic cross-clamp release; MDA was not detected in any patient in propofol group at this time. This difference did not persist at 20 or 30 minutes after reperfusion. No significant difference between the two groups in systemic MDA concentrations measured up to 24 hours after cross-clamp release was observed. The reason of this; effect of propofol was not detectable after 10 minutes and half-life of MDA was quite short. In this study we took blood samples as soon as brachytherapy and so propofol infusion has ended.

Walichiewicz *et al*. [22] examined the effect of local ischemic preconditioning on postradiation lipid peroxidation in serum of total body irradiated rats. Modification of TBARS levels by local preconditioned ischemia was observed in the first 24 hour after animals were irradiated and showed a marked tendency to decrease during the next two days finally stabilizing at the same low level. On fifth day, TBARS levels started to increase and reached maximum on eighth day. 24 hour after irradiation, concentration of TBARS in rat serum was not significant.

An increased lipid peroxide level in proliferating cells leads to an increase in the serum lipid peroxide level in cancer patients [23]. Higher levels of lipid production were observed both in plasma and erythrocytes of cervical cancer patients compared to the control group. There was no significant change in lipid peroxidation and antioxidant status in the blood of cervical cancer patients directly after brachytherapy treatment [24].

Propofol has been shown to inhibit lipid peroxidation induced by oxidative stress in rat liver mitochondria, microsomes and brain synaptosomes [3]. Propofol increases basal endothelial nitric oxide release [25] and protects endothelial cells against highly toxic free radical peroxynitrite which is an important molecule in the cellular toxicity of ischemia/reperfusion [26]. Mikawa *et al*. [27] have shown that clinically relevant concentrations, propofol can also suppress neutrophil chemotaxis, phagocytosis and ROS production. Metabolite 1, 4-quinol exhibits an antioxidant activity similar to that of propofol. The

glucuroconjugated metabolites 1-QG and 4-QG still act as antioxidants and PG presents a limited antioxidant effect. Glucuronide metabolites are usually considered to be inactive and rapidly eliminated [28].

The concentration of propofol that caused an observable inhibitory effect on peroxynitrite chemiluminescence is in the same range as the anesthetic concentrations and it is therefore possible that propofol may act as an antioxidant during anesthesia [29].

Propofol chemically resembles the chain-breaking antioxidant α-tocopherol, because it also has a phenolic hydroxyl group [30]. The phenolic hydroxyl group is responsible for the antioxidant properties of propofol as found in various in vitro experiments [2, 4, 30]. Aars *et al*. [31] showed that introducing propofol into α-tocopherol depleted microsomes restores the GSH- dependent protection.

The evidence from recent studies is significantly strong to justify propofol has an antioxidant activity [32, 33]. We have shown for the first time in this study that propofol infusion has some protective effect to lipid peroxidation caused brachytherapy. Further clinical investigations are needed for the antioxidant effects of propofol toward radiotherapy.

REFERENCES

1. Bryson HM, Fulton BR, Faulds D. Propofol: An update of its use in anaesthesia and conscious sedation. *Drugs.* 1995; 50: 513-59.
2. Murphy PG, Bennett JR, Myers DS, Davies MJ, Jones JG. The effect of propofol anaesthesia on free radical-induced lipid peroxidation in rat liver microsomes. *Eur J Anaesth.* 1993; 10: 261-6.
3. Musacchio E, Rizzoli V, Bianchi M, Bindoli A, Galzigna L. Antioxidant action of propofol on liver microsomes, mitochondria and brain synaptosomes in the rat. *Pharmacol Toxicol.* 1991; 69: 75-7.
4. Eriksson O, Pollesello P, Saris NEL. Inhibition of lipid peroxidation in isolated rat liver mitochondria by the general anaesthetic propofol. *Biochem Pharmacol.* 1984; 44: 391-3.
5. Green TR, Bennett SR, Nelson VM. Specificity and properties of propofol as an antioxidant free radical scavenger. *Toxicol Appl Pharmacol.* 1994; 129: 163-9.
6. Kanto J, Gepts E. Pharmacokinetic implications for the clinical use of propofol. *Clin Pharmacol.* 1989; 5: 308-26.
7. Somosy Z. Radiation response of cell organelles. *Micron.* 2000; 31: 165-81.
8. Rafique R, Schapira AHV, Cooper JM. Sensitivity of respiratory chain activities to lipid peroxidation: effect of vitamin E deficiency. *Biochem J.* 2001; 357: 887-92.
9. Relevance of radioprotectors in radiotherapy: studies with tocopherol monoglucoside. *J Environ Pathol Toxicol Oncol.* 2004; 23(2): 153-60.
10. Protection against ionizing radiation by antioxidant nutrients and phytochemicals. *Toxicology.* 2003; 189(1-2): 1-20. Review.
11. Radioprotectants: current status and new directions. *Oncology.* 2002; 63 Suppl 2: 2-10. Review.
12. Nutritional approaches to radioprotection: vitamin E. *Mil Med.* 2002; 167(2 Suppl): 57-9.
13. Sun Y. Free radicals, antioxidant enzymes and carcinogenesis. *Free Radical Biol Med.* 1990; 8: 583-99.
14. Balasubramaniyan N, Subramanian S, Govindasamy S. Status of antioxidant systems in human carcinoma of uterine cervix. *Cancer Lett.* 1994; 87(2): 187-92.
15. Ahmed MI, Fayed ST, Hossein H, Tash FM. Lipid peroxidation and antioxidant status in human cervical carcinoma. *Dis Markers.* 1999; 15(4): 283-91.
16. Manju V, Kalaivani Sailaja J, Nalini N. Circulating lipid peroxidation and antioxidant status in cervical cancer patients: a case-control study. *Clin Biochem.* 2002; 35(8): 621-5.
17. Manoharan S, Kolanjiappan K, Kayalvizhi M, Sethupathy S. Lipid peroxidation and antioxidant status in cervical cancer patients. *J Biochem Mol Biol Biophys.* 2002; 6(3): 225-7.
18. Manoharan S, Kolanjiappan K, Kayalvizhi M. Enhanced lipid peroxidation and impaired enzymic antioxidant activities in the erythrocytes of patients with cervical carcinoma. *Cell Mol Biol Lett*. 2004; 9(4A): 699-707
19. Buege JA, Aust SD. Microsomal lipid peroxidation. *Methods Enzymol.* 1978; 52: 302-10.
20. Lazzarino G, Raatikainen P, Nuutinen M, Nissinen J, Tavazzi B, Di Pierro D, Giardina B, Peuhkurinen K. Myocardial release of malondialdehyde and purine compounds during coronary bypass surgery. Circulation. 1994 Jul 1;90(1):291-7.
21. Corcoran TB, Engel A, Sakamoto H, O'Callaghan-Enright S, O'Donnell A, Heffron JA, Shorten G. The effects of propofol on lipid peroxidation and inflammatory response in elective coronary artery bypass grafting. Journal of cardiothoracic and vascular anesthesia. 2004 Oct 1;18(5):592-604.
22. Walichiewicz P, Przybyszewski WM, Jochem J, Widel M, Koterbicka A. Inhibitory effect of local ischemic preconditioning on gamma-ray induced lipid peroxidation in rats: A preliminary study *Int J Tissue React.* 2002; 4: 143-150.
23. Masotti L, Casali E, Galeotti T. Lipid peroxidation in tumor cells. *Free Radical Biol Med.* 1988; 4: 377-386.
24. Mila-Kierzenkowska C, Kedziora-Kornatowska K, Wozniak A, Drewa T, Wozniak B, Drewa S, et al. The effect of brachytherapy on antioxidant status and lipid peroxidation in patients with cancer of the uterine cancer. *Cell Mol Biol Lett.* 2004; 9: 511-18.

25. Petros AJ, Bogle RG, Pearson JD. Propofol stimulates nitric oxide release from cultured porcine aortic endothelial cells. *Br J Pharm.* 1993; 109: 6-7.
26. Mathy-Hartert M, Mouithys-Mickalad A, Kohnen S, Deby-Dupont G, Lamy M, Hans P. Effects of propofol on endothelial cells subjected to a peroxynitrite donor (SIN-1). *Anaesthesia.* 2000; 55: 1066-71.
27. Mikawa K, Akamatsu H, Nishina K, Shiga M, Maekawa N, Obara H, et al. Propofol inhibits human neutrophil functions. *Anaesth Analg.* 1998; 87: 695-700.
28. Boisset S, Steghens JP, Favetta P, Terreux R, Guitton J. Relative antioxidant capacities of propofol and its main metabolites. *Mol Toxicol.* 2004; 78: 635-642.
29. Kahraman S, Demiryürek AT. Propofol is a peroxynitrite scavenger. *Anesth Analg.* 1997; 84: 1127-9.
30. Murphy PG, Myers DS, Davies MJ, Webster NR, Jones JG. The antioxidant potential of propofol (2,6-diisopropylphenol).*Br J Anaesth*. 1992; 68: 613-8.
31. Aarts L, Van der Hee R, Dekker I, de Jong J, Langemeijer H, Bast A. The widely used anesthetic agent proof can replace α-tocopherol as an antioxidant. *FEBS Letters.* 1995; 357: 83-85.
32. Erguin Y, Darendeli S, Imrek S, Kilinc M, Oksuz H. The comparison of the effects of anaesthetic doses of ketamine, propofol and etomidate on ischaemia/reperfusion injury in skeletal muscles. Fundam Clin Pharmacol. 2010; 24: 215–22.
33. Hatwalne MS. Free radical scavengers in anaesthesiology and critical care. Indian journal of anaesthesia. 2012 May;56(3):227.