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Full Length Research Paper

Anesthetics modulate oxidative stress during one-lung ventilation in lung cancer patients: Comparison of target-controlled propofol infusion and desflurane

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Lung injury following thoracic surgery is a relatively uncommon disease, but has a major complication with high mortality. Many factors, including; ischemia reperfusion injury and the use of one-lung ventilation (OLV) are involved in this process. This study was conducted to compare the results of target-controlled infusion (TCI) of propofol versus desflurane in the aspect of oxidative stress in lung cancer patients operated with OLV. Thirty patients with non-small cell lung cancer whom were operated with OLV were studied. In propofol group (n = 15), anesthesia was based on propofol and remifentanil, both simultaneously administered via target-control infusion and in desflurane group (n = 15), anesthesia was maintained with desflurane. Serum malondialdehyde (MDA) levels were measured during operation and postoperatively. In each group, cases showed a statistically significant increase in serum malondialdehyde levels during operation as compared to baseline levels (P < 0.05 for both). The mean baseline levels of MDA were not significantly different among groups, although mean serum MDA levels were statistically significantly decreased at 30 min OLV, at 5 min of reoxygenation and at postoperative 6 h measurements in propofol group as compared to desflurane group (P < 0.01 for all). TCI of propofol maintained hemodynamic stability similar with desflurane in lung cancer patients which underwent lobectomy with OLV. Findings of the present study suggested that the oxidative stress during OLV might be modified with anesthetic approach and that the favorable results with propofol in view of oxidative stress might lead to the preferred use of this drug as compared to desflurane for general anesthesia with OLV.

Key words: Oxidative stress, lung reexpansion, lung reperfusion, propofol, desflurane.

INTRODUCTION

Lung injury following thoracic surgery is a relatively uncommon disease, but has a major complication with high mortality. Acute inflammatory responses are encountered with all forms of lung surgery (Gothard, 2006). Many factors, including, cytokine imbalance, ischemia reperfusion injury and the use of one-lung ventilation (OLV) are involved in this process apart from the surgical insult itself (Grichnik and D'Amico, 2004). OLV is frequently applied to a clear operational field in thoracic surgery (Senturk, 2006). During OLV, the non-ventilated lung remains not only at electatic but also hypoperfused because of hypoxic vasoconstriction. When resuming, two-lung ventilation, re-expansion, along with oxygen re-entry through the airways, causes reactive pulmonary vascular dilatation, commencing reperfusion of the lung and thus, leads to excessive oxidative radical release (Cheng et al., 2005). Misthos et al. (2005) published further evidence to

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support the concept that oxidative stress contributes to lung damage after lung resection. In that study, the magnitude of oxidative stress that was measured by raised malondialdehyde (MDA) levels was found to be associated with use and duration of OLV. Clinical studies have also shown evidence of oxidative damage in patients undergoing pulmonary resection (Williams et al., 1998; Lases et al., 2000). Although, most patients are able to tolerate OLV, to apply OLV in patients with compromised antioxidant capacity, such as critical illness, sepsis and cancer is not extraordinary in clinical anesthesia (Dasgupta et al., 1997; Cowley et al., 1996; Huang et al., 2008). There is few data on the oxidative stress related with the anesthetics used for thoracic surgery. Propofol is a well-known intravenous anesthetic with antioxidant properties and desflurane since inhalation anesthetic has wide usage due to favorable effects on recovery time; accordingly, in this study, we aimed to compare the target-controlled infusion (TCI) of propofol and desflurane with respect to oxidative stress in lung cancer patients operated with OLV.

MATERIALS AND METHODS

Study population

This study was conducted in Ankara University Medical Faculty, among thirty adult non-small cell lung cancer (NSCLC) patients (American Society of Anesthesiologists physical status Class I to II, 39 to 65 years old) whom were scheduled for lobectomy involving a long period of intraoperative OLV (>60 min). Patients were included in the study after the local ethical committee approval and after giving written informed consent. All patients in this study were in Stages I to II operable lung cancer patients. In propofol group, 11 patients and in desflurane group, 12 patients were in Stage I.

All of them were ex-smokers (mean quit smoking age, 44.6) with mild Chronic obstructive pulmonary disease (COPD), suffering from NSCLC without any prior exposure to chemotherapy or radiotherapy. Patients with recent usage of antioxidants, such as vitamin preparations, and past with infectious/inflammatory/-rheumatologic disturbances, patients with chronic liver/kidney diseases were also excluded.

Study design

Patients were randomized to two groups according to the drug used for general anesthesia. In propofol group (n = 15), induction and maintenance of anesthesia was based on propofol (Propofol, AstraZeneca) and remifentanil (Ultiva, Glaxo Welcome), both simultaneously administered with an automatic TCI pump Orchestra Base Primea (Fresenius-Kabi) operated with a Acer TravelMate 202 TE computer. In desflurane group (n = 15), induction was made with thiopental sodium (7 mg/kg) and remifentanil (0.5 µg/kg) and 5 to 7% desflurane was used for maintenance. Vecuronium (0.1 mg/kg) was used as muscle relaxant in both groups. After induction of anaesthesia, an appropriate size of left bronchial catheter (Broncho-Cath, Mallinckrodt) was incubated and adjusted by using a fiberoptic bronchoscope before and after turning to the lateral decubitus position. Systolic blood pressure, diastolic blood pressure, heart rate, pulse oximetry, body temperature, urine output and peak airway pressure were monitored continuously. Ventilation was delivered mechanically. When OLV was started, the nondependent lung was collapsed and opened to air with suction if necessary, and the dependent lung was ventilated at a fraction of inspired oxygen (FiO_2) of 1, a tidal volume of 8 to 10 ml/kg, a respiratory rate of 12 to 16 breaths/min adjusted to maintain the arterial carbon dioxide between 35 and 45 mmHg, and an inspiration:expiration ratio of 1:2. The concentrations of inspiratory and expiratory gas mixture (FiO_2, end-tidal CO_2, fraction of inspired desflurane and end-tidal desflurane) were continuously monitored (Capnomac Datex). Demographic data, hemodynamic data, end-tidal CO_2, peripheral O_2 saturations, anaesthesia, surgery and OLV times were recorded.

Blood sampling and laboratory analysis

Blood samples were collected in every patient following a fixed blood sampling protocol. Peripheral venous blood of 5 cm^3 was collected at each time. The timing of blood sampling was as follows: (a) At the beginning of operation; (b) At 30th min after OLV onset, (c) 5 min after lung reoxygenation; (d) At 6th h postoperatively. Blood samples were collected in polystyrene tubes. The tubes were centrifuged at 500 g for 15 min. Sera were then removed and stored at -20°C until analysis. Serum MDA levels were measured by the double heating method (Stocks and Dormandy, 1971; Jain et al., 1998). The principle of the method was based on the spectrophotometric measurement during the reaction to thiobarbituric acid with MDA. Concentration of thiobarbituric acid reactive substances was calculated by the absorbance coefficient of MDA-thiobarbituric acid complex and was expressed in nmol/ml.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) software package (Version 15.0 for Windows, Chicago, IL. USA). Values were expressed as means ± standard deviation (SD). Distribution of values was evaluated with one-sample Kolmogorov-Smirnov test. Comparison of mean values between two groups was performed using Mann Whitney U test. Comparison of mean values at different time intervals was performed using repeated-measure analysis of variance and two-sided $P < 0.05$ was considered as statistically significance. An appropriate power analysis (with G Power 2.0) suggested that the study would have more than 95% power to detect a significant difference between groups in view of postoperative 6th h MDA levels (Posthoc power analysis based on postoperative 6th h MDA levels, alpha:0.05, n1: 15, n2:15; revealed power as 0:99).

RESULTS

The study group included 13 women (43.3%) and 17 men (56.7%) with age range of 39 to 65 years (mean 55.7 years). The side of the lesion was to the right in 21 cases (70%) and 9 (30%) to the left. Study protocol was successfully accomplished in all subjects.

There were no statistically significant differences between two groups in hemodynamic parameters, End-tidal carbon dioxide (ET CO_2), peripheral oxygen saturation and peak airway pressure. The mean OLV (159 ± 14 min in desflurane group, 155 ± 15 min in propofol group), anesthesia duration (232 ± 25 min in desflurane group, 221 ± 12 min in propofol group) and surgery times (224 ± 16 min in desflurane group, 211 ± 19

Table 1. Clinical and laboratory characteristics of the study population.

OLV time (min)	155 ± 15	159 ± 14
Surgery time (min)	211 ± 19	224 ± 16
Anaesthesia time (min)	221 ± 12	232 ± 25
Baseline MDA level (nmol/ml)	4.61 ± 1.2	4.53 ± 0.7
30th minute of OLV MDA level* (nmol/ml)	5.23 ± 0.77	6.09 ± 1.6
5th minute of reoxygenation MDA level* (nmol/ml)	9.67 ± 2.4	14.75 ± 2.8
Postoperative 6th hour MDA level* (nmol/ml)	7.21 ± 1.3	11.74 ± 2.5

*Difference between groups is statistically significant P < 0.01. min, Minutes; nmol/ml, nanomoles per mililiter.

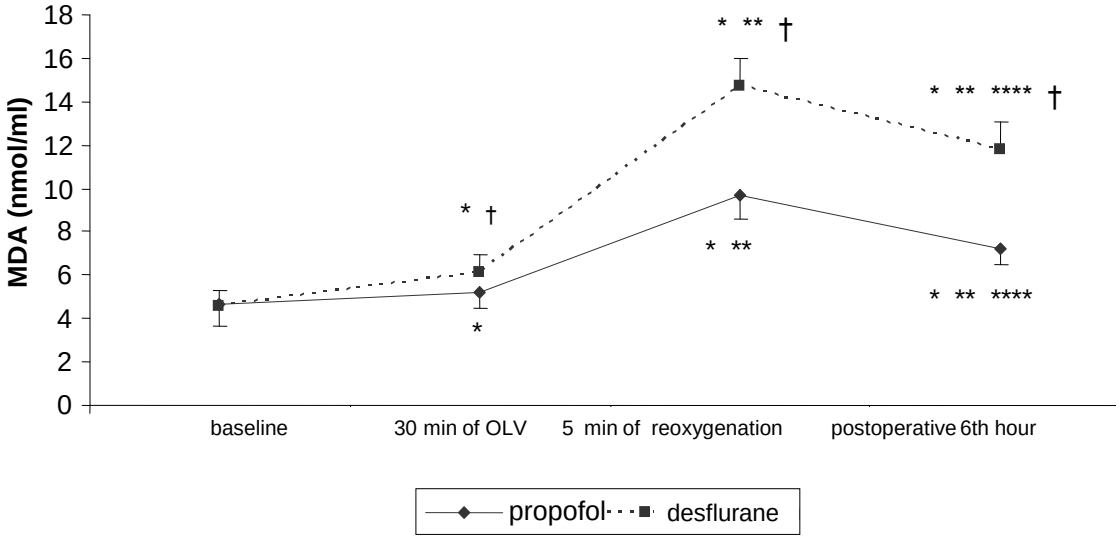

Figure 1. Serum MDA levels of propofol and desflurane group (nmol/ml). *, Difference from baseline values is statistically significant at P < 0.05. **, Difference from 30 min of OLV is statistically significant at P < 0.05. †Difference between groups is statistically significant at P < 0.01.

min in propofol group) were not significantly different between groups (Table 1). Baseline mean MDA levels of desflurane and propofol group were 4.53 ± 0.7 and 4.61 ± 1.2 nmol/ml, respectively, 30th min of OLV mean MDA levels of desflurane and propofol group were 6.09 ± 1.6 and 5.23 ± 0.77 nmol/ml, respectively. Mean MDA levels at 5th minute of reoxygenation in desflurane and propofol group were 14.75 ± 2.8 and 9.67±2.4 nmol/ml, respectively. Postoperative 6th hour mean MDA levels of desflurane and propofol group were 11.74 ± 2.5 and 7.21 ± 1.3 nmol/ml, respectively (Table 1). Both groups showed a statistically significant increase in serum MDA levels during operation as compared to baseline levels (P < 0.05). The mean baseline levels of MDA was not statistically significantly different between groups; however, mean serum MDA levels were statistically significantly decreased at 30th minute OLV, at 5th minute of reoxygenation and at postoperative 6th hour measurements in propofol group compared to desflurane group (P < 0.01 for all) (Figure 1).

DISCUSSION

Studies have revealed that lung reexpansion provoked severe oxidative stress and the degree of oxidative stress was associated with the duration of OLV (Cheng et al., 2005; Misthos et al., 2005). Protracted (>1 h) OLV showed to be a potential cause for cardiovascular complications through the generation of severe oxidative stress due to lung reexpansion, and it is well known that oxidative stress could easily trigger lung damage in the case of inadequate anti-oxidant capacity, such as those with cancer (Cheng et al., 2005; Misthos et al., 2006). Gupta et al. (2009) found that serum glutathione (GSH), and superoxide dismutase levels are significantly reduced in NSCLC patients as compared to healthy subjects. Tsao et al. (2007) also showed decreased GSH levels in plasma of NSCLC patients as compared to healthy subjects. On the other hand, there were several studies, showing elevated GSH levels in NSCLC tumor specimens which was thought to be one of the major

mechanisms of chemo resistance of NSCLC (Blair et al., 1997). Thus, it might be important to reduce the oxidative stress and improve antioxidant capacity for better clinical outcome in NSCLC.

Significant increase in serum MDA levels during operation compared to baseline levels was independent of the anesthetic method in our study. This study showed that TCI of propofol was related with relatively decreased oxidative stress as compared to desflurane with a statistically significance. There were no statistically significant differences between the two groups in hemodynamic parameters. These results are similar with that of Huang et al. (2008), who evaluated the effects of propofol infusion on oxidant/antioxidant balance during OLV to 2LV manipulation and compared them with those of isoflurane inhalation. They found that reactive oxygen species production was significantly decreased in the propofol infusion group. A higher total antioxidant status level was also maintained under propofol infusion, when compared with isoflurane. They also found in that study that a longer OLV time did not result in more ROS production after resuming 2LV. Huang et al. (2008) argued that the beneficial effects of propofol infusion might thus prevent pulmonary and cardiovascular complications arising from massive release of oxidative radicals from reexpansion of the collapsed lung. However the use of total intravenous anesthesia with propofol infusion may be limited because of their unstable hemodynamics in critically ill and aged patients. However, in this study, TCI of propofol maintain hemodynamic stability similar with desflurane. Propofol administered by TCI have shown to provide cardio-vascular stability and ensures smooth induction and fast recovery, in contrast with manually controlled infusion, which leads to potentially deleterious effects, such as massive changes in mean arterial pressures (Passot et al., 2005).

Propofol's antioxidant properties were defined in many studies (Runzer et al., 2002; Tsuchiya et al., 2001, 2002). Structure of propofol differs from other hypnotic sedatives, although it resembles the native antioxidant alpha-tocopherol (vitamin E), since it contains a phenolic hydroxyl group. The antioxidant property of propofol was presumed to this structural resemblance to alpha tocopherol and the hypothetic participation in ascorbate-driven recycling system of alpha tocopherol (Tsuchiya et al., 2002). Not only the structural resemblance to alpha tocopherol, propofol seemed to have further effects on lipid peroxidation, because 2,6-dimethylphenol which is structurally similar to alpha tocopherol much more than propofol (2,6-diisopropylphenol) has been proved to be less potent in inhibiting LP than propofol, conflicting with its structural similarity to reference antioxidants (Tsuchiya et al., 2010). In a recent study it was claimed that the phenolic structure of propofol with a 2-isopropyl group determines the antioxidant activity, and also the structure specific interaction with lipid membranes to modify the fluidity that appears to underlie the inhibitory effect on lipid peroxidation together with the radical scavenging action (Tsuchiya et al., 2010).

Allaouchiche et al. (2001) reported that animals exposed to propofol have decreased circulating and localized MDA levels and reduced glutathione peroxidase consumption as compared to desflurane both in serum and in lavage. They claimed that increased expression of proinflammatory cytokines in alveolar macrophages might be responsible for oxidative stress associated with desflurane (Allaouchiche et al., 2001).

Desflurane seemed to be associated with more oxidative stress, although desflurane offers excellent characteristics for fast-track anaesthesia in thoracic surgery (Song et al., 1998). Emergence after pulmonary surgery is faster with desflurane than as with sevoflurane or isoflurane allowing more rapid emergence and earlier recovery of cognitive and psychomotor functions. Desflurane also acts as a bronchodilator; which resulted in a reduction of peak inspiratory pressure and an increase in dynamic compliance at 1 minimum alveolar concentration (MAC), suggesting protective effects on mechanical forces applied to lung tissue (Dupont et al., 1999; Dikmen et al., 2003). Schilling et al. (2007) compared propofol and desflurane and showed in OLV that pro-inflammatory reactions during OLV were influenced by the type of general anaesthesia. The study demonstrated that OLV induced a pro-inflammatory reaction in the dependent ventilated lung. The immune response was attenuated by desflurane anaesthesia and the fraction of alveolar granulocytes, alveolar TNFα and soluble intercellular adhesion molecule (sICAM)-1 were significantly higher in the propofol group (Schilling et al., 2007). In a recent study, Schilling et al. (2011) also showed that volatile anesthetics desflurane and sevoflurane suppress the proinflammatory cytokine release (TNFα, Interleukin-8 and Interleukin-1 beta) in the ventilated lung after OLV, but not the systemic, inflame-matory responses. Propofol does not exert this alleviating effect on alveolar cytokines (Schilling et al., 2011). Propofol was shown to reduce oxidative stress in thoracic surgery, although recent studies showed altered lung immune function with propofol. The clinical effect of altered lung immune function during and after OLV remains to be studied.

Several limitations of the study should be considered, such as small sample size and using MDA as the sole indicator of oxidative stress. Assessing other oxidative stress markers like 4-hydroxynonenal which are more specific and antioxidant markers like reduced GSH would enrich our study; however, we do not have the oppor-tunity to perform these evaluations. Another potential limitation seems to be the absence of long term clinical follow up. Also, we used thiopental sodium in anesthesia induction in desflurane group, and thiopental might have influenced the results in desflurane group. Thus, studies comparing propofol and thiopental sodium revealed more

favorable results in view of oxidative stress with propofol (Basu et al., 2007).

In conclusion, TCI of propofol maintain hemodynamic stability similar with desflurane in lung cancer patients who underwent lobectomy with OLV. Oxidative stress during OLV might be modified with anesthetic method. The potential favorable results with propofol in view of oxidative stress might lead to the preferred use of this drug as compared to desflurane for general anesthesia with OLV. Further studies are needed to evaluate the results of different anesthetic agents and protocols on clinical outcome in cancer patients operated with OLV.

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