

The effects of propofol or sevoflurane on free radical production after tourniquet induced ischaemia-reperfusion injury during knee arthroplasty

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Abstract : *Background :* We studied the effects of anesthesia with propofol or sevoflurane on the production of free oxygen radicals during total knee arthroplasty performed with the use of an ischemic tourniquet by measuring the levels of malondialdehyde (MDA).

Methods : We studied two groups of patients (20 patients in each group) who underwent total knee arthroplasty. To maintain anesthesia we delivered 66 % nitrous oxide plus sevoflurane or propofol. Blood samples for the determination of the MDA levels were drawn before the application of the ischemic tourniquet and 5 and 30 minutes after its release.

Results : There were no differences between groups in regard to age, weight and duration of the tourniquet application.

MDA levels decreased significantly in the propofol group 30 minutes after the release of the tourniquet ($1.7 \mu\text{mol litre}^{-1}$ vs $1.57 \mu\text{mol litre}^{-1}$, Friedman's ANOVA, $P = 0.007$). In contrast, there was a small rise of the MDA levels in the sevoflurane group ($1.82 \mu\text{mol litre}^{-1}$ vs $1.96 \mu\text{mol litre}^{-1}$, Friedman's ANOVA, $P = 0.007$).

Conclusion : Propofol may have anti-oxidant properties in orthopaedic surgery requiring tourniquet application, but sevoflurane needs further study.

Key words : Sevoflurane ; propofol ; knee arthroplasty ; antioxidant activity ; malondialdehyde.

Tissue reperfusion after ischemia may cause further injury due to the release of free oxygen radicals and lipid peroxidation products such as MDA (9, 11). Tissue injury secondary to ischemia-reperfusion with high levels of blood and muscle MDA has been observed in orthopaedic surgery utilizing the application of an ischemic tourniquet (4, 13).

Propofol appears to inhibit lipid peroxidation secondary to oxidative stress in "in vitro" studies and to reduce lipid peroxidation within anaesthetic concentrations "in vivo" too (2, 10, 12-13, 15, 17).

Recent studies have shown that sevoflurane protects the ischemic myocardium and it offers greater protection than propofol in patients under-

going coronary artery by-pass grafting with or without the use of extracorporeal circulation (5-6, 14, 19-21). The effect of sevoflurane on tissue injury from peripheral ischemia-reperfusion has not been investigated. The goal of this paper is to study the effect of propofol and sevoflurane anesthesia on oxidative stress during total knee arthroplasty surgery performed with the application of an ischemic tourniquet.

MATERIALS AND METHODS

After obtaining institutional review board approval and informed consent we studied 40 patients, 14 men and 26 women, ASA I and II. The patients underwent scheduled total knee arthroplasty surgery performed with the application of ischemic tourniquet. Exclusion criteria were hepatic, renal or other metabolic disease or the preoperative administration of any antioxidative agent.

The patients were randomized using a sealed envelope into two groups. In the first group (Group I) induction to anesthesia was achieved with fentanyl $3 \mu\text{g kg}^{-1}$ and propofol $2-2,5 \text{ mg kg}^{-1}$, while in the second group with fentanyl $3 \mu\text{g kg}^{-1}$ and thiopentone 5 mg kg^{-1} . Endotracheal intubation was

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performed after the administration of cis-atracurium 0,15 mg kg⁻¹.

Anesthesia was maintained in the first group with the administration of propofol 6-10 mg kg⁻¹ hr⁻¹ (the maintenance dose was adjusted to clinical signs and anticipated demand) and in the second group with sevoflurane 1,5-2%.

Ventilation was maintained with 66% nitrous oxide in oxygen. Tourniquet pressure was twice the systolic arterial pressure.

Venous blood samples for the determination of the levels of lipid peroxidation products were performed before the application of the ischemic tourniquet and 5 and 30 minutes after tourniquet release.

Specimens were centrifuged for 10 minutes and the supernatant was stored in -70°C until analysis.

The lipid peroxides formed by peroxidation of the free radicals converted into MDA react with thiobarbituric acid to form a coloured complex. The degree of lipid peroxidation was determined as thiobarbituric acid reacting substances (TBARS) and the units are µmol litre⁻¹.

A comparison of continuous variables between groups was performed by an unpaired two-tailed Student's test. Wilcoxon matched pairs test was applied to discriminate differences between patients prior and following the application of tourniquet. Friedman's analysis of variance (ANOVA) for repeated measurements was used to assess post-treatment changes for non-parametric variables, as appropriate. Significance was defined as a p-value < 0.05.

RESULTS

There were no statistical significant differences between the two groups in age (70 ± 5.9 and 69.1 ± 5.2 years), weight (71.2 ± 8.2 and 72.3 ± 8.5 kg) and the duration of tourniquet application (79 ± 13.3 and 83 ± 15.4 min). No significant statistical differences were seen between the two groups regarding the MDA values before the application of the ischemic tourniquet (1.7 µmol litre⁻¹ in the propofol group and 1.82 µmol litre⁻¹ in sevoflurane group).

5 minutes after the tourniquet release in the propofol group the plasma concentration of the MDA increased slightly compared to the plasma concentration of the MDA before the application of the ischemic tourniquet (1.7 µmol litre⁻¹ vs 1.87 µmol litre⁻¹, P = 0.06), while no changes were

Table 1

Plasma concentrations before the application of the ischemic tourniquet and 5, 30 min after release of the tourniquet [MDA (µmol litre⁻¹)]

	Propofol	Sevoflurane
Before the application of the ischemic tourniquet	1.7 ± 0.76	1.82 ± 0.67
5 min after release	1.87 ± 0.76	1.8 ± 0.63
30 min after release	1.57 ± 0.67 *	1.96 ± 0.64 #

* P = 0.007, Friedman's ANOVA ; # P < 0.01, Friedman's ANOVA.

observed in the sevoflurane group at the same time (1.82 µmol litre⁻¹ vs 1.8 µmol litre⁻¹) (Table 1).

MDA levels decreased significantly in the propofol group 30 minutes after the release of the tourniquet (1.7 µmol litre⁻¹ vs 1.57 µmol litre⁻¹, Friedman's ANOVA, P = 0.007). In contrast, there was a small rise of the MDA levels in the sevoflurane group (1.82 µmol litre⁻¹ vs 1.96 µmol litre⁻¹, Friedman's ANOVA, P = 0.007) (Table 1).

DISCUSSION

Although skeletal muscle is fairly resistant to ischemic injury many studies have shown that free oxygen radicals cause skeletal muscle injury during reperfusion (3-4, 8).

Free oxygen radicals are produced during orthopedic surgery performed with the application of an ischemic tourniquet and many studies are found in the literature concerning the local, systematic metabolic and morphological effects of pneumatic tourniquet on skeletal muscles (2, 4). It seems that orthopedic surgery with tourniquet is a good human model for excessive production of oxidants and anesthetics with anti-oxidant properties or free radical scavenging activity could offer considerable protection and benefits in this setting.

It is known that propofol has in vitro anti-oxidant properties (1, 18). Two studies have shown that propofol does not offer oxidative stress protection when administered in the commonly used clinical concentrations (7, 10). In contrast, MURPHY *et al.* have shown that in concentrations required for anesthesia, propofol provides anti-oxidant protection (17).

Our study has shown that propofol (group I) caused a significant decrease of the free oxygen radicals 30 minutes after the release of the tourniquet. In contrast, in the sevoflurane group, at the same period, we observed a small rise of the MDA

levels, so it appears that propofol is a good choice of anaesthetic for orthopedic surgeries requiring ischemic tourniquet application. Similar results were shown in two other studies of patients undergoing total knee arthroplasty with the application of an ischemic tourniquet. More specifically, in the study by KAHRAMAN *et al.* one group was receiving propofol for anesthesia and the other isoflurane (13). Based on the obtained plasma and tissue MDA levels the authors conclude that propofol prevents lipid peroxidation secondary to ischemia-reperfusion and that it exerts a significant anti-oxidative effect during anesthesia. In patients receiving propofol anesthesia the authors observed a slight rise of the plasma MDA levels 15, 30 and 45 minutes after the release of the tourniquet compared to the levels before the reperfusion. In contrast, in the isoflurane group the authors observed a significant rise of the plasma MDA levels 15, 30 and 45 minutes after the release of the tourniquet. In the study by ALDEMIR *et al.* a decrease of the MDA levels was observed in the two groups (propofol vs halothane). The difference was statistical significant only in the propofol group. Baseline MDA levels were those obtained before the induction of anesthesia (2).

In our study, in the sevoflurane group there was a small rise of the MDA levels 30 minutes after the release of the ischemic tourniquet compared to the levels before the tourniquet application. In the study by KAHRAMAN *et al.* (propofol vs isoflurane), it has been demonstrated that MDA levels markedly increased in the isoflurane group, but in the study by ALDEMIR *et al.* (propofol vs halothane) reductions in MDA levels were observed in halothane group (2, 13). Many studies have shown the protective effect of sevoflurane and other halogenated anesthetics on the myocardium after ischemia and more specifically the limitation of myocardial dysfunction and necrosis in the reperfusion phase (16, 22). Compared to sevoflurane, propofol does not appear to be as protective for the myocardium (5-6, 14). At present sevoflurane is one of the most promising as preconditioning-inducing anesthetic agent for myocardial protection (14).

In our study propofol appears to be more protective against oxidative stress from peripheral ischemia-reperfusion. But there were two methodological limitations in our study. First, in the sevoflurane group, the induction to anesthesia was performed with the use of thiopentone which also has anti-oxidant properties. Second, no MDA samples were drawn before anesthesia induction and immediately before reperfusion. These samples would

have allowed us to study the effects of propofol and sevoflurane on tissue injury from peripheral ischemia-reperfusion in a more detailed manner.

In conclusion, propofol decreases oxidative stress during orthopedic surgery performed with the application of an ischemic tourniquet, due to its antioxidant properties. More studies are needed to clarify the effects of sevoflurane on oxidative stress in peripheral tissues.

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