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SCIENTIFIC ARTICLE

# Comparisons of the effects of the sevoflurane and propofol on acute ischemia reperfusion and DNA damages in rabbits

**Sema Oncul***, **Lale Karabiyik, Erdem Coskun, Ela Kadioglu, Ozlem Gulbahar**

*Gazi University Faculty of Medicine, Department of Anesthesiology and Intensive Care, Ankara, Turkey*

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**KEYWORDS**
Genotoxicity;
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Sevoflurane;
Ischemia reperfusion injury

**Abstract**
*Background and objectives:* The aim of this study was to compare the effects of sevoflurane and propofol anesthesia on oxidative DNA damage that occurs in low-extremity ischemia and is caused by tourniquet application.
*Methods:* Fourteen New Zealand rabbits were randomly allocated into two equal groups. Group S ($n = 7$) received sevoflurane (2.5–4 percent) inhalation and Group P ($n = 7$) received a propofol infusion (1–2 $mg \cdot kg^{-1} \cdot min^{-1}$), after which a pneumatic tourniquet was placed on the right lower extremity. Blood samples were collected prior to tourniquet placement (baseline), 120 min after ischemia, 15 min after ischemia and 120 minutes (min) after ischemia. Malondialdehyde (MDA) levels were analyzed to determine lipid peroxidation, and single cell gel electrophoresis (SCGE) was used to determine DNA damage.
*Results:* At 15 min after ischemia, the MDA levels in Group P ($8.15 \pm 2.61$ μM) were higher than baseline ($6.26 \pm 3.19$ μM, $p = 0.026$) and Group S ($4.98 \pm 0.77$ μM, $p = 0.01$). DNA damage was similar in both groups, although DNA damage was higher than baseline (tail moment $0.63 \pm 0.27$, tail intensity $3.76 \pm 1.26$) in Group P at the 15th minute of reperfusion (tail moment $1.05 \pm 0.45$, $p = 0.06$; tail intensity $5.33 \pm 1.56$, $p = 0.01$). The increase in tail moment and tail intensity returned to normal levels in both groups 2 hours after the termination of ischemia.
*Conclusion:* Given that oxidative stress and genotoxic effect disappear in the late stages of reperfusion, we conclude that neither sevoflurane nor propofol can be considered superior to the other in anesthesia practices for extremity surgeries involving the use of a tourniquet.


* Corresponding author.
*E-mail:* serdenish@yahoo.com (S. Oncul).

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**PALAVRAS-CHAVE**
Genotoxicidade;
Estresse oxidativo;
Propofol;
Sevoflurano;
Lesão de isquemia reperfusão

**Comparações dos efeitos de sevoflurano e propofol sobre isquemia-reperfusão aguda e danos ao DNA em coelhos**

**Resumo**
*Justificativa e objetivos:* O objetivo deste estudo foi comparar os efeitos da anestesia com sevoflurano e propofol sobre o dano oxidativo ao DNA que ocorre na isquemia de extremidade inferior e é causada pela aplicação de torniquete.
*Métodos:* Quatorze coelhos da raça Nova Zelândia foram alocados aleatoriamente em dois grupos iguais. Grupo S (n = 7) recebeu inalação de sevoflurano (2.5–4%) e Grupo P (n = 7) recebeu perfusão de propofol (1–2 $mg \cdot kg^{-1} \cdot min^{-1}$), logo após um torniquete pneumático foi colocado na extremidade inferior direita. Amostras de sangue foram coletadas antes da colocação do torniquete (fase basal), após 120 minutos de isquemia, 15 minutos após a isquemia e 120 minutos após a isquemia. Os níveis de malondialdeído (MDA) foram analisados para determinar a peroxidação de lipídios, e electroforese em gel de célula única (EGCU) foi usada para determinar o dano ao DNA.
*Resultados:* Aos 15 minutos após a isquemia, os níveis de MDA no Grupo P (8,15 ± 2,61 μM) foram superiores aos da fase basal (6,26 ± 3,19 μM, $p = 0,026$) e dp Grupo S (4,98 ± 0,77 μM, $p = 0,01$). O dano causado ao DNA foi semelhante nos dois grupos, embora tenha sido maior que na fase basal (momento da cauda 0,63 ± 0,27, intensidade da cauda 3,76 ± 1,26) no Grupo P no 15 minuto de reperfusão (momento da cauda 1,05 ± 0,45, $p = 0,06$; intensidade da cauda 5,33 ± 1,56, $p = 0,01$). O aumento no momento da cauda e intensidade da cauda voltou aos níveis normais nos dois grupos duas horas após o término da isquemia.
*Conclusão:* Como o estresse oxidativo e o efeito genotóxico desaparecem nos estágios finais da reperfusão, concluímos que não há superioridade tanto de sevoflurano quanto de propofol em práticas de anestesia para procedimentos cirúrgicos de extremidades que envolvem o uso de torniquete.


## Introduction

Proximal tourniquets are often used in limb surgeries to provide a bloodless operating field. When oxygen is reintroduced into ischemic tissue after tourniquet deflation, the existence of massive free oxygen radicals causes peroxidation of membrane lipids. This process triggers oxidation of the polyunsaturated fatty acids, destroying membrane structures and producing toxic metabolites such as malondialdehyde (MDA).[1,2] This process plays a significant role in the pathogenesis of reperfusion injuries. MDA is a low molecular weight aldehyde and an intermediate product a lipid peroxidation. It has often been used as a marker of free radical formation.

İschemia–reperfusion (I/R) induced oxygen radical formation causes oxidative DNA damage and plays a significant role in the pathogenesis of reperfusion injuries.[3,4] A limited amount of information exists on oxidative DNA damage in tourniquet-induced reperfusion injuries, although anesthetic drugs and surgery-related stress are known to cause cellular damage.[5]

Sevoflurane and propofol are volatile and intravenous agents that are in common use in the field anesthesia. Some clinical and experimental studies without I/R have shown that sevoflurane causes reversible DNA damage,[5,6] although different in vivo and in vitro studies have shown that propofol decreases DNA damage, or causes no DNA damage.[7–9]

Genotoxic assays are commonly used to monitor DNA damage. The SCGE (comet assay) has been widely used in both in vitro and in vivo studies, because it is a sensitive and simple methodology for measuring single-strand and double-strand breaks, alkali labile sites, oxidative lesions and DNA repair.[10,11]

This study compares the effects of sevoflurane and propofol on DNA damage in a tourniquet-induced lower extremity ischemia model. For the purpose of the study, the surgical stress factor was eliminated, MDA levels were measured to determine lipid peroxidation, and SCGE was used to determine DNA damage.

## Methods

Approval for the study was obtained from the Local Ethics Committee. The study was conducted at the Gazi University Experimental Research Laboratory in a manner similar to the acute I/R model described by Hardy et al.[12] Fourteen seven-month-old New Zealand rabbits were used with a mean weight of 3.5 kg. The standards found in the ''Guide for the Care and Use of Laboratory Animals'' were applied during the study.[13]

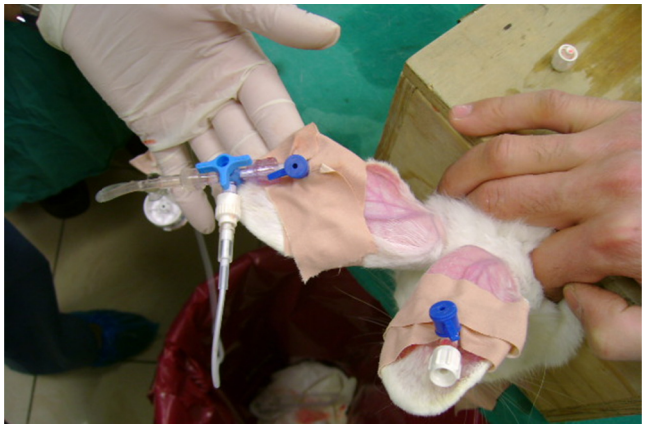

**Figure 1** Infusion of propofol, intravenous and intraarterial catheterization.

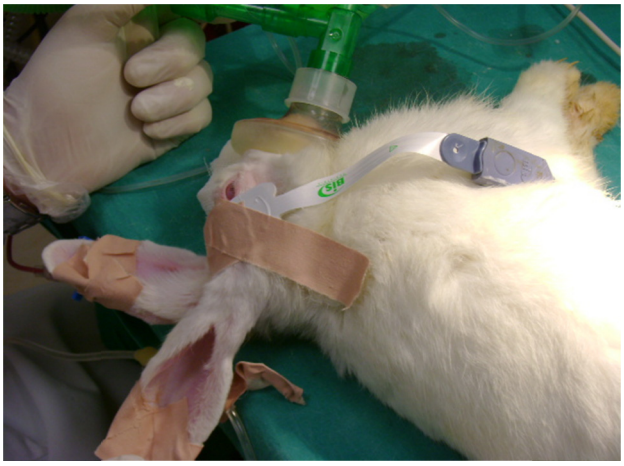

**Figure 2** Applying the mask of the gas mixture and BIS probe.

Arterial and venous lines were inserted through the ear in all test subjects during sampling and for isotonic saline infusion, respectively. Baseline blood samples were taken and the invasive arterial blood pressure was monitored (Fig. 1). Hemodynamic parameters of invasive blood pressure, heart rate, respiratory rate, peripheric oxygen saturation ($SpO_2$) (Nihon Cohden, Life Scope BSM-5135K, Japan) and Bispectral Index (BIS) Monitoring (Bispectral Index Monitor Model 2000, Aspect Medical Systems, Inc., Newton, MA, USA) were recorded at 15 min intervals during the procedure. After hair removal, pediatric probes were used for BIS monitoring (Aspect Medical Systems, Inc., Norwood, USA). During the study, the BIS was kept at 50 ± 10 percent and 5 $mL \cdot kg^{-1} \cdot h^{-1}$ isotonic saline was infused during the procedure.

The rabbits were randomly allocated to two groups of seven. Anesthesia was induced with the inhalation of 7–8 percent sevoflurane in Group S, and with the infusion of 1–2 $mg \cdot kg^{-1} \cdot min^{-1}$ propofol in Group P (Figs. 1 and 2). An adequate level of induction was determined by the disappearance of eye movements and cornea reflex in addition to maintaining BIS <60 percent. The anesthesia was maintained in Group S through the inhalation of 2.5–4 percent sevoflurane and through the infusion of 1–2 $mg \cdot kg^{-1} \cdot min^{-1}$ propofol in Group P. A gas mixture was administered by using a face mask at the flow rate of 4 $L \cdot min^{-1}$ (Dameca, Denmark). Spontaneous respiration was maintained to achieve an $O_2$ saturation of ≥95 percent. Both groups were completely expressed by rubber bandage from the right extremity, and a tourniquet was placed by applying 200 mmHg pressure (Pediatric cuff no 2, De Royal, Powell, TN, USA). Tourniquet was applied for 120 min.

Blood samples were collected as the baseline samples, 1 min before tourniquet deflation (BTD), and 15 and 120 min after tourniquet deflation (ATD 15 and ATD 120, respectively).

**Table 1** MDA levels (μM) [mean ± SD (min–max)].

| Time (min) | Group S ($n=7$) | Group P ($n=7$) | $p$-value |
|---|---|---|---|
| Baseline | 5.10 ± 1.94 (1.53–7.24) | 6.26 ± 3.19 (3.32–13.05) | 0.425 |
| BTD | 5.40 ± 1.36 (3.43–7.12) | 8.32 ± 3.86 (4.55–14.28) | 0.083 |
| ATD 15 | 4.98 ± 0.77[b] (4.22–6.12) | 8.15 ± 2.61[a] (5.45–13.39) | 0.01 |
| ATD 120 | 6.40 ± 3.00 (2.76–12.16) | 7.09 ± 2.91 (3.88–11.37) | 0.0672 |

BTD, before tourniquet deflation; ATD, after tourniquet deflation.
[a] $p = 0.026$, comparison with the baseline.
[b] $p = 0.01$, comparison with Group P.

## Malondialdehyde determination

One of the most common methods used to indicate the presence of free oxygen radicals is the determination of MDA as an index of lipid peroxidation. During the study, the decrease in the MDA levels assessed over the thiobarbituric acid (TBA) reactions was found to be an indirect indication of a decrease of free oxygen radicals. The plasma MDA level was measured by implementing the colorimetric method based on the TBA reaction with the MDA.[14]

## SCGE (comet assay) method

The comet assay followed the protocols described by Singh et al. and Tice et al. with some modifications.[15,16] The SCGE method examines the DNA damage and repair mechanisms under different experimental conditions. Normal lymphocytes have a round, bright-looking nucleus in the middle, which is less dense on the sides. It gains an irregularly edged appearance along with the beginning of the migration of DNA fragments outside the nucleus. Lymphocytes take the shape of a comet as the damage increases, hence the name 'comet assay'. Depending on the severity of the damage, the microscopic appearance of the cell extends from the center to the periphery. The tail intensity, in terms of fluorescence, *tail* length, and tail moment was evaluated by a computerized image analysis system.

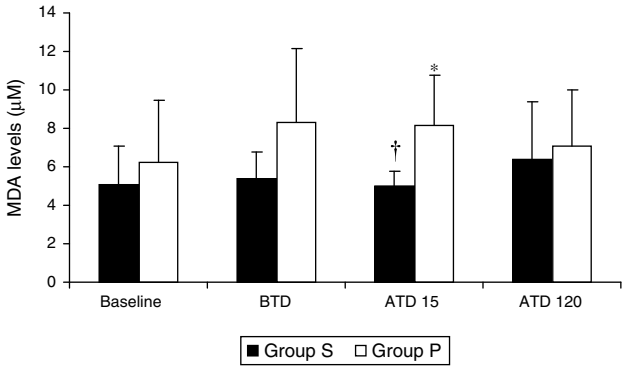


**Figure 3** MDA levels (mean ± SD) (*$p = 0.026$, comparison with the baseline; †$p = 0.01$, comparison with Group P. BTD, before tourniquet deflation; ATD, after tourniquet deflation).

### Statistical evaluation

Data analysis was performed by using Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0. Time-related changes within groups and in accordance with control were compared by Paired *t* test and Wilcoxon-X test, and comparisons between groups were performed by implementing the Student's *t* test and the Mann–Whitney *U* test. Data was expressed as mean ± SD and $p < 0.05$ was accepted as significant.

## Results

### MDA

MDA levels were not found to be statistically significant different compared with baseline samples in Group S. The increase in the MDA levels in Group P at ATD 15 was found to be higher than the baseline values (8.15 ± 2.61 μM; $p = 0.026$). At the same time, this value was significantly higher than in Group S (4.98 ± 0.77 μM) at ATD 15 ($p = 0.01$) (Table 1, Fig. 3).

### DNA damage assessment

There was no significant difference in the baseline, BTD, ATD 15 and ATD 120 levels between the groups (Table 2). The increase in the tail moment ($p = 0.031$) and the tail intensity ($p = 0.029$) in Group S at BTD were found to be statistically significant compared with baseline samples (Table 2). The increase in the tail moment ($p = 0.006$) and the tail intensity ($p = 0.01$) in Group P at ATD 15 were found to be higher than the baseline values (Table 2). There was no significant difference between Group S and Group P at all time periods.

## Discussion

Our findings indicate that neither sevoflurane nor propofol is superior to the other in terms of preventing the oxidative stress and genotoxicity that emerge in tourniquet-induced I/R injuries.

A proximal tourniquet is often used in limb surgery to provide a bloodless operating field. Tourniquet application causes metabolic changes that depend on the duration of tourniquet inflation and anesthetic technique.[17] The safe range of inflation time is accepted to be between 1 and 3 h. For this reason we opted for a tourniquet period of 2 h in the present study.

İschemia–reperfusion results in the generation of toxic reactive oxygen species (ROS) in the organs. İschemia reduces the activity of cellular defence enzymes against ROS, and reperfusion or the introduction of oxygen further disturbs the delicate balance of oxidants/antioxidants.[18] Measurement of MDA levels is the most sensitive marker to determine the degree of lipid peroxidation.[19,20] Sensitivity reaches its highest level between the fifth and twentieth minutes following tourniquet deflation.[2] In our study the increase in the MDA levels was found to be higher in the propofol group 15 min following tourniquet deflation than in the sevoflurane group. It was observed that the lipid peroxidation could be better suppressed in the sevoflurane group during the early reperfusion period as compared to the propofol group.

Budic et al. have demonstrated that total intravenous anesthesia with propofol and regional anesthesia techniques provide better antioxidant defence and reduce endothelial dysfunction than general inhalational anesthesia with sevoflurane during tourniquet application in pediatric extremity surgery.[19,20] Arnaoutoglou et al. have reported that propofol may have antioxidant properties in orthopedic surgery requiring tourniquet application, but the use of sevoflurane needs further study.[21] Some authors have demonstrated that plasma concentrations of propofol are able to inhibit lipid peroxidation in the range that is clinically used in anesthesia.[22] Braz et al., however, used clinical doses of propofol (plasma concentration: 2–4 $\mu g \cdot mL^{-1}$) in elective surgeries without I/R, and showed that propofol does not decrease lipid peroxidation.[7] These and several other authors believe that only higher concentrations of propofol could show free radical scavenging activity.[7,23] Similar to the study by Braz et al., we found that propofol did not decrease lipid peroxidation; contrary to other studies, however, we did not perform any surgery, and performed ischemia for 120 min. Although plasma propofol levels were not measured in our study, increased MDA levels were found at the 15th minute of reperfusion in the propofol group.

İschemia–reperfusion induced oxygen radical formation causes oxidative DNA strand breaks and plays a significant role in the pathogenesis of reperfusion injuries. The single cell gel electrophoresis (comet assay) is a simple, sensitive, and rapid method for estimating DNA damage.[10] Numerous studies have shown that I/R-induced DNA damage can be investigated in human peripheral leucocytes using the modified alkaline comet assay.[3,24] After ischemia, the genotoxic damage was detected in human peripheral leucocytes, and it leads especially to the release of substantial amounts of oxygen radicals and other reactive agents.[10] In our study, we used this method to analyze the DNA damage caused by anesthetic agents.

There has been little study on the oxidative DNA damage due to tourniquet-induced I/R. These study have examined the effects of tourniquet ischemia on the induction of DNA damage by comet assay in peripheral leucocytes.[3,24] Willy et al. have observed that DNA effects were most pronounced

**Table 2** Tail moment, tail length and tail moment, in 50 cells [mean ± SD (min–max)].

| Time (min) | Group S ($n = 7$) | | | Group P ($n = 7$) | | | $p$-value | | |
|---|---|---|---|---|---|---|---|---|---|
| | Tail moment | Tail length | Tail intensity | Tail moment | Tail length | Tail intensity | Tail moment | Tail length | Tail intensity |
| Baseline | 0.75 ± 0.27 (0.36–1.17) | 25.19 ± 1.88 (22.93–28.81) | 4.55 ± 1.37 (2.43–6.76) | 0.63 ± 0.27 (0.29–1.17) | 25.25 ± 3.55 (22.10–32.87) | 3.76 ± 1.26 (1.73–6.07) | 0.422 | 0.971 | 0.285 |
| BTD | 1.12 ± 0.38[a] (0.77–1.86) | 30.34 ± 9.79 (24.98–52.23) | 6.14 ± 1.48[a] (4.41–8.62) | 1.80 ± 1.72 (0.58–5.32) | 35.10 ± 18.05 (23.66–71.39) | 7.53 ± 4.23 (3.53–14.43) | 0.328 | 0.551 | 0.427 |
| ATD 15 | 1.51 ± 1.70 (0.51–5.34) | 34.46 ± 24.90 (23.61–90.89) | 7.47 ± 5.96 (3.52–20.76) | 1.05 ± 0.45[a] (0.50–1.90) | 27.69 ± 7.73 (21.77–44.36) | 5.33 ± 1.56[a] (3.33–8.42) | 0.506 | 0.505 | 0.377 |
| ATD 120 | 1.12 ± 0.68 (0.65–2.63) | 29.13 ± 9.51 (21.99–49.89) | 6.15 ± 3.35 (3.83–13.53) | 1.06 ± 0.56 (0.51–1.89) | 26.22 ± 5.28 (21.11–36.68) | 5.45 ± 2.09 (3.38–8.85) | 0.881 | 0.492 | 0.646 |

BTD, before tourniquet deflation; ATD, after tourniquet deflation.
There was no significant difference between the groups.
[a] $p < 0.05$, comparison with the baseline.

5–30 min after tourniquet release, and then declined over a 2 h period, but did not return to pre-ischemic baseline values; this suggests that I/R induces genotoxic effects in human leucocytes, presumably in response to oxidative stress during reperfusion.[3]

Some studies have demonstrated that genetic material can be damaged with the halogenated anesthetics, evaluated by single cell gel electrophoresis assay.[5,6,25] Karabiyik et al. used this method to evaluate DNA damage in patients who received sevoflurane and isoflurane anesthesia. The authors have concluded that both agents cause reversible DNA damage, but that there is no significant difference between them in this regard.[6] Propofol differs from volatile anesthetics because it does not show mutagenic effects in vitro or in vivo.[7,9] Braz et al. reported that propofol does not induce DNA damage in white blood cells (WBCs) by using an alkaline version of the single cell gel electrophoresis assay.[7] In addition, propofol did not induce sister chromatid exchanges (SCEs) in children's lymphocytes[8] and did not increase chromosomal aberrations in cardiac surgery patients.[9]

According to Alleva et al. it is difficult to assess in vivo whether anesthetics or surgical stress is the main cause of the cell damage. These authors evaluated genotoxicity in patients subjected to sevoflurane anesthesia and did not find significant alterations in DNA after 15 min anesthesia induction before surgery.[5] In a recent study, Braz et al. reported that patients who underwent minor surgery under general anesthesia with inhaled sevoflurane and isoflurane or with intravenous propofol did not induce DNA strand breaks or alkali-labile sites in human peripheral lymphocytes.[26] Similarly in our study, we eliminated the surgical stress factor and our results also contradicted those of other studies. In our study, tail moment and tail intensity levels (indicators of DNA damage) increased gradually in both groups when compared to the baseline levels. In the sevoflurane group, DNA damage increased at the 120th minute of ischemia; in contrast DNA damage was more prominent in the early period of reperfusion, and this increase was parallel to the increase in MDA levels. These findings may indicate the inability of propofol to suppress oxidative stress efficiently. In the sevoflurane group, increased DNA damage prior to reperfusion supports the genotoxic property of sevoflurane. The difference between the groups disappeared at the 120th minute of reperfusion.

## Conclusions

This experimental I/R study has shown that sevoflurane can control lipid peroxidation better than propofol. Propofol, may require higher doses (compared to the clinical dose) to prevent lipid peroxidation. Given the lack of difference between the two anesthetics in late stages of reperfusion, we believe that neither sevoflurane nor propofol can be considered superior in terms of preventing oxidative stress-related genotoxicity in extremity surgeries involving the use of a tourniquet. It is known that all anesthetics have harmful side-effects, and so what is important is to choose the appropriate agent with the least toxic side-effect. In this regard, it can be said that there is a need for more genotoxicity studies on oxidative stress.

## Limitations

The evaluation of DNA damage from the local tissue sample (muscle, etc.) and the measurement of plasma propofol levels would allow more informative studies. This might be considered as the limitations of our study.

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## Conflicts of interest

The authors declare no conflicts of interest.

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