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Effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets

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ABSTRACT

Introduction: The use of a tourniquet in lower extremity surgery can help surgeons optimize the surgical field. However, tourniquet inflation may create ischemic conditions in the extremity, and tourniquet deflation may pose a risk of ischemic reperfusion injury (IRI). Ischemic conditions can increase the production of reactive oxidative stress (ROS), which, if it occurs simultaneously with IRI, will produce malondialdehyde (MDA), a toxic metabolite. The prolonged use of tourniquets can cause damage to the local skin tissue at the tourniquet inflation and poses a risk of IRI to other organs. This study aims to observe the effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets.
Methods: This study is an observational study with a prospective cohort design to measure malondialdehyde levels in lower extremity surgery using tourniquets. When the data were normally distributed, a statistical test was performed using an independent sample t-test to compare the demographic data of the two groups. To compare the results of the observation after the induction, 15 and 120 minutes after the release of the tourniquets, a repeated measures ANOVA was performed when the data were normally distributed. Then, to examine the correlation between variables, Spearman's correlation test was applied when the data were not normally distributed.
Results: In this study, almost all the subjects in the isoflurane and dex-iso groups had no significantly different characteristics, and also showed no effect of tourniquet pressure on malondialdehyde levels.
Conclusion: Based on statistical analysis and discussion of the effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets, it can be concluded that there was no statistically significant effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets.

Keywords: Dexmedetomidine, Ischemic Reperfusion Injury, Malondialdehyde, Tourniquet.
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INTRODUCTION

The use of a tourniquet in lower extremity surgery can help surgeons optimize the surgical field. Tourniquet inflation may cause an ischemic condition in the extremity and direct damage to the skin and muscle tissue below the tourniquet inflation site. After the use of tourniquets for one hour, histopathological changes will result in the muscle cells. After two hours, more and more necrotic lesions will develop in the compressed muscles.[1] The deflation of the tourniquets will pose a risk of IRI at the local tourniquet inflation site, as well as in the systemic circulation and vital organs, such as the brain, heart, lungs, and kidneys. A return of blood flow after an ischemic period is essential to prevent irreversible cellular damage, but reperfusion can add to the secondary damage caused by ischemia.[2]

Ischemic conditions can increase the production of reactive oxidative stress (ROS) and will stimulate a proinflammatory state. Excessive ROS production without counterbalanced production of antioxidants will cause cellular damage through the oxidation of proteins, fats, and deoxyribonucleic acid (DNA).[2] When ROS occurs simultaneously with IRI, it will cause impaired functions through peroxidation of lipids in cell membranes and produce malondialdehyde (MDA), a toxic metabolite. As one of the products of fat peroxidase, MDA is an important marker for detecting the presence of IRI.[3] Studies in experimental animals reported liver, kidney, and lung damage in subjects who underwent tourniquet inflation for 3 hours.[4] In clinical studies, renal IRI due to the use of tourniquets was reported with an increase in myoglobin and lactoferrin serums, serving as sensitive indicators of damage to the function of the proximal kidney tubule.[5]

Several studies have been conducted on anesthetic drugs that can reduce oxidative stress and MDA. The combination of propofol and ketamine has been shown to significantly reduce MDA levels in patients undergoing tourniquet inflation.[6] Dexmedetomidine is a selective a_2-adrenergic receptor agonist. Besides having sympatholytic properties, dexmedetomidine also has anti-hypertensive, anti-anxiety, and sedative effects. Selective a_2-adrenergic receptor

agonists are effective agents for preventing hyperdynamic responses during the use of tourniquets in surgery because they prevent catecholamine release and show a preventive effect on IRI.[7] Kutanis et al. (2016) conducted an in vivo study on experimental animals rats, showing the antioxidant effect of dexmedetomidine to reduce the level of cell death in the brain and kidneys with IRI.[8]

No study has ever been conducted to measure MDA serum levels during the use of tourniquets in the scope of work of Dr. Soetomo Regional Public Hospital, Surabaya. This study aims to observe the effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets.

METHODS

This study is an observational study with a prospective cohort design to measure malondialdehyde levels in lower extremity surgery using tourniquets. The sample of this study was a population that met the inclusion and exclusion criteria, including patients aged 18-60 years with American Society of Anesthesiologists (ASA) I–II Physical Status Classification and lower extremity surgery patients using tourniquets (whether administered with dexmedetomidine or not) at Dr. Soetomo Regional Public Hospital from January to March 2023.

The preoperative vital signs (blood pressure and pulse rates) of the subjects who had signed an informed consent form were recorded. The samples were divided into the treatment group, anesthetized using a combination of isoflurane and dexmedetomidine, and the control group, anesthetized using isoflurane only. Based on previously known data, a total of 13 samples were obtained for each group. Malondialdehyde samples were collected three times (M_0, M_1, M_2) to measure MDA levels in serum. Prior to surgery, the subjects were scheduled for a preoperative visit to find out their comorbidities, explain to them the procedure of this study, and ask their willingness to sign an informed consent form. On the day of surgery, an M_0 venous blood sample (malondialdehyde sample taken before induction) was collected with an 18G infusion needle pre-installed in the pre-medication room. During the operation, several tourniquets were applied and inflated. After the procedure was complete, the tourniquets were deflated. An M_1 venous blood sample was collected with an 18G infusion needle 15 minutes after the deflation of the tourniquets. Then, an M_2 venous blood sample was collected with an 18G infusion needle 120 minutes after the tourniquets were released.

The collected data were then recorded and tabulated. Demographic data, including age, sex, and ASA PS, were presented in tabular form and compared between the two groups. In this study, the data were processed using SPSS v. 23.0 (SPSS Inc., Chicago, IL, USA). When the data were normally distributed, a statistical test was performed using an independent sample t-test to compare the demographic data of the two groups. When the data were not normally distributed, the Mann-Whitney test was applied. To compare the results of the observation after the induction, 15 and 120 minutes after the release of the tourniquets, a repeated measures ANOVA was performed when the data were normally distributed, and the Friedman's test was performed when the data were not normally distributed. Then, to examine the correlation between variables, Pearson's correlation test was applied when the data were normally distributed, and Spearman's correlation test was applied when the data were not normally distributed.

RESULTS

The demographic data, including age, sex, ASA PS, and BMI, were subjected to a homogeneity test to ensure that the demography of the two groups was homogeneous. Age and BMI data are presented on a ratio scale so that both were presented in the form of mean and standard deviation if normally distributed and in the form of median and range (minimum score–maximum score) if not normally distributed.

A homogeneity calculation indicated differences between the ASA PS, age, and BMI of the dex-iso and isoflurane groups, but they were not significant because the p-value was more than 0.05. It can be concluded that demographic data is homogeneous (Table 1).

The results of the descriptive calculation and the independent sample t-test on tourniquet inflation duration and tourniquet pressure between the dex-iso and isoflurane group showed that the data were not normally distributed; thus, the data is displayed in the form of a median and a range (minimum–maximum value). The calculation results indicated no significant difference between the tourniquet inflation duration of the dex-iso and isoflurane groups, with a P value of 0.832 (P > 0.05). The calculation results indicated no significant difference between the tourniquet pressure of the dex-iso and isoflurane groups, with a P value of 0.193 (P > 0.05) (Table 2).

Table 1. Description of Patient Demographic Data in the dex-iso group and isoflurane group.

Characteristic	Category	Frequency (%), Median (Range)		
		isoflurane	dex-iso	P value
Sex	Female	6 (60%)	4 (40%)	0.688
	Male	7 (43.8%)	9 (56.3%)	
ASA PS	1	3 (42.9 %)	4 (57.1%)	1.000
	2	10 (52.6%)	9 (47.4%)	
Age		40.00 (18–59)	34.00 (18–60)	0.938
BMI		23.0938 ± 2.92422	22.8631 ± 2.26538	0.824

Table 2. Description of the tourniquet inflation durations in the dex-iso group and isoflurane group.

Variabel	Mean ± SD, Median (Range)		
	Isoflurane	Dex-iso	P value
Tourniquet Inflation Duration	100.00 (90–140)	100.00 (90–150)	0.832
Tourniquet Pressure	230.00 (220–240)	230.00 (218–250)	0.193

The results of the descriptive calculations and the independent sample t-test on the fentanyl doses of the dex-iso and isoflurane groups indicated a significant difference in the fentanyl doses of the two groups, with a P value of < 0.05. The dose of fentanyl in the isoflurane group was higher than that in dex-iso group (Table 3).

The results of the descriptive calculation and the independent sample t-test on the M0 and M1 MDA of the dex-iso and isoflurane groups indicated no significant difference in the M0, M1, and M2 MDA of the two groups, with a P value of > 0.05 (Table 4).

The results of the ANOVA on the descriptive calculation and the independent sample t-test indicated differences in changes in the M0, M1, and M2 MDA levels of the isoflurane group. The results of the descriptive calculation revealed that M2 had the highest value, followed by M1, then M0. Due to differences in M0, M1, and M2 MDA levels, a paired difference t-test was conducted to observe which changes were different in pairs. The results of the paired difference t-test on M0, M1, and M2 MDA levels in the isoflurane group indicated significant differences between the M0 and M1, M0, and M2, and M1 and M2 MDA levels, with a P value below 0.05 (Tables 5 and 6).

The results of the ANOVA on the descriptive calculation and the independent sample t-test indicated differences in changes in the M0, M1, and M2 MDA levels of the dex-iso group. The results of the descriptive calculation revealed that M2 had the highest value, followed by M1, then M0. Due to differences in M0, M1, and M2 MDA levels, a paired difference t-test was conducted to observe which changes were different in pairs. The results of the paired difference t-test on M0, M1, and M2 MDA levels in the dex-iso group indicated significant differences between the M0 and M1, M0, and M2, and M1 and M2 MDA levels, with a P value below 0.05 (Tables 7 and 8).

The results of the independent sample t-test on changes in MDA levels of the dex-iso and isoflurane groups from M0 to M1, M0 to M2, and M1 to M2 revealed no significant difference (p>0.05) (Table 9). The Spearman's correlation test on the correlation between tourniquet inflation duration and M1 and M2 MDA levels resulted in positive correlation coefficients with P values of 0.011 and 0.000 (P < 0.05). A positive correlation value means that the longer the duration of tourniquet inflation, the higher the M1 and M2 MDA levels. A P value less than 0.05 implies a significant correlation between tourniquet inflation duration and M1 and M2 MDA levels (Table 10). The Spearman's correlation test on the correlation between tourniquet pressure and M1 and M2 MDA levels resulted in negative correlation coefficients of -0.465 dan -0.211, respectively, with P values of 0.465 dan 0.300 (P > 0.05) (Table 11). The Spearman's correlation

Table 3. Description of the fentanyl doses and independent sample t-test results on the fentanyl doses of the dex-iso group and isoflurane group.

Group	N	Mean ± SD	P value
Isoflurane	13	307.69 ± 46.08	0.000
Dex-iso	13	203.85 ± 45.468	

Table 4. Description of M0, M1, and M2 MDA levels and preoperative test results of the dex-iso group and isoflurane group.

Variable	Group	Mean	SD	P value
M0 MDA	Isoflurane	0.97708	0.122021	0.820
	Dex-iso	0.96654	0.111948	
M1 MDA	Isoflurane	1.28954	0.100537	0.503
	Dex-iso	1.26531	0.079779	
M2 MDA	Isoflurane	1.78146	0.366382	0.182
	Dex-iso	1.60438	0.286235	

Table 5. Description of changes in M0, M1, and M2 MDA levels in the isoflurane group.

Variable	Mean	Std. Deviation	P value
M0 MDA	0.97708	0.122021	0.000
M1 MDA	1.28954	0.100537	
M2 MDA	1.78146	0.366382	

Table 6. Paired difference t-test on changes in M0, M1, and M2 MDA levels in the isoflurane group.

Group pair		P value
M0	M1	0.000
	M2	0.000
M1	M2	0.000

Table 7. Description of changes in M0, M1, and M2 MDA levels in the dex-iso group.

Variable	Mean	Std. Deviation	P value
M0 MDA	0.96654	0.111948	0.000
M1 MDA	1.26531	0.079779	
M2 MDA	1.60438	0.286235	

Table 8. Paired difference t-test on changes in M0, M1, and M2 MDA levels in the dex-iso group.

Group pair		P value
M0	M1	0.000
	M2	0.000
M1	M2	0.001

test on the correlation between tourniquet inflation duration and changes in MDA levels from M0 to M1, M0 to M2, and M1 to M2 resulted in positive correlation coefficients of 0.890, 0.892, and 0.717, respectively with a P value of 0.000 (P < 0.05). A positive correlation value means that the longer the duration of tourniquet inflation, the higher the increase in MDA levels. A P value less than 0.05 implies a significant correlation between tourniquet inflation duration and changes in MDA levels (Table 12). The Spearman's correlation test on the correlation between tourniquet pressure and changes in MDA levels from M0 to M1, M0 to M2, and M1 to M2 resulted in negative correlation coefficients, indicating an insignificant correlation between the variables (Table 13).

Table 9. Description and independent sample t-test results on changes in M0-M1, M0-M2, and M1-M2 MDA levels of the dex-iso group and isoflurane group.

Variable	Group	N	Mean	Std. Deviation	P value
Change from M0 to M1	isoflurane	13	0.3125	0.1975	0.847
	dex-iso	13	0.2988	0.1592	
Change from M0 to M2	isoflurane	13	0.8044	0.4491	0.322
	dex-iso	13	0.6379	0.3876	
Change from M1 to M2	isoflurane	13	0.4919	0.3202	0.212
	dex-iso	13	0.3391	0.2869	

Table 10. Description and results of the Spearman's correlation test on the correlation between tourniquet inflation duration and M1 and M2 MDA levels.

Correlation	N	Median	Correlation coefficient	P value
Tourniquet Inflation Duration ←→M1 MDA	26	1.282 (1.141–1.457)	0.490*	0.011
Tourniquet Inflation Duration ←→M2 MDA	26	1.687 (1.168–2.536)	0.804**	0.000

Table 11. Description and results of the Spearman's correlation test on the correlation between tourniquet pressure and M1 and M2 MDA levels.

Correlation	N	Median (Min–Max)	Correlation coefficient	P value
Tourniquet Pressure ←→ M1 MDA	26	0.9495 (0.796–1.137)	-0.150	0.465
Tourniquet Pressure ←→ M2 MDA	26	1.282 (1.141–1.457)	-0.211	0.300

Table 12. Description and results of the Spearman's correlation test on the correlation between tourniquet inflation duration and changes in MDA levels from M0 to M1, M0 to M2, and M1 to M2.

Correlation	N	Median	Correlation coefficient	P value
Tourniquet Inflation Duration ←→Change from M0 to M1	26	0.32 (0.038–0.661)	0.890**	0.000
Tourniquet Inflation Duration ←→Change from M0 to M2	26	0.7465 (0.102–1.712)	0.892**	0.000
Tourniquet Inflation Duration ←→Change from M1 to M2	26	0.444 (-0.201–1.1)	0.717**	0.000

Table 13. Description and results of the Spearman's correlation test on the correlation between tourniquet pressure and changes in MDA levels from M0 to M1, M0 to M2, and M1 to M2.

Correlation	N	Median	Correlation coefficient	P value
Tourniquet Pressure ←→Change from M0 to M1	26	0.32 (0.038–0.661)	-0.036	0.861
Tourniquet Pressure ←→Change from M0 to M2	26	0.7465 (0.102–1.712)	-0.140	0.495
Tourniquet Pressure ←→Change from M1 to M2	26	0.444 (-0.201–1.1)	-0.185	0.366

DISCUSSION

In this study, almost all the subjects in the isoflurane and dex-iso groups had no significantly different characteristics. It indicates that the two groups have homogeneous or comparable sample members. There were no significant differences in the patients' demographic data, including sex, ASA PS, age, and BMI, in the two groups. Likewise, there was no significant difference between the tourniquet inflation period and tourniquet pressure in the dex-iso and isoflurane groups.

The total dose of fentanyl was calculated, and statistical analysis was performed. Statistically significant differences between the dex-iso and isoflurane groups were found. Pain during tourniquet use is triggered by several previously-suspected factors, one of which is the activation of C-nerve fibers, which, in physiological conditions, will be inhibited by A-delta fibers. The A-delta fibers will be blocked by the mechanical pressure caused by the tourniquets after 30 minutes of tourniquet inflation, while the C-nerve fibers will remain in function. Pain will cause an increase in hemodynamic response, such as blood pressure and pulse rate; thus, when hemodynamic fluctuations occur, a higher dose of fentanyl is required. Dexmedetomidine has an opiate-sparring effect, acting centrally and peripherally on the mu receptor, thereby reducing the need for opioids during surgery.

Ischemic conditions caused by the use of tourniquets and followed by reperfusion, will result in an increase in reactive oxygen species, which will result in cell damage. One of the main secondary products of lipid peroxidation is malondialdehyde. In this study, there was no statistically

significant difference between the levels of M0, M1, and M2 malondialdehyde in the dex-iso and isoflurane groups. It is in line with the results of several previous studies. Another study conducted on total knee arthroplasty patients in the treatment group anesthetized with dexmedetomidine and those in the control group measured their malondialdehyde (MDA) levels as a biomarker of oxidative stress and TNF-a and IL-6 as proinflammatory cytokines. There was no significant difference between malondialdehyde levels in the treatment and control groups 60 and 90 minutes after the release of the tourniquets. A significant difference was found in TNF-a and IL-6 levels 60 and 90 minutes after the release of the tourniquets.[9] Another study on patients who underwent surgery with the use of a one-sided lower extremity tourniquet showed similar results, that there was no significant difference between malondialdehyde levels and total antioxidant capacity (TAC) in the control and treatment groups.[10]

One possible explanation was dexmedetomidine's insignificant effect on the oxidative stress biomarkers. The product of lipid peroxidation, namely malondialdehyde, may not be involved in the protective effect of dexmedetomidine against IRI due to the use of tourniquets. It could also be due to the fact that the dexmedetomidine dose used in this study may not be sufficient to suppress oxidative stress. Although the theory of dose-dependent dexmedetomidine has been weakened in studies of intestinal damage in preclinical studies,[11] high doses of dexmedetomidine may contribute to adverse hemodynamic effects and are not suitable for clinical application.

Malondialdehyde levels will increase as the tourniquet usage time increases. The statistical tests implied that the treatment and control groups had the highest malondialdehyde levels 90 minutes after the release of the tourniquets (M2). Pneumatic tourniquets used in limb surgery will cause neutrophil activation and release of reactive oxygen products and vasoactive substances, such as those resulting from muscle ischemia, resulting in hypoxia, cell changes, anaerobic glycolysis, and reperfusion injury.[12,13] Release of free oxygen radicals causes lipid peroxidation and the formation of malondialdehyde, which is a strong indicator of free radical formation.[14] This is in line with studies in rats, which showed an increase in malondialdehyde levels with ischemic time in hepatic reperfusion injury.[15]

In another study, patients who experienced post-stroke showed increased levels of malondialdehyde in subjects who experienced reduced muscle mass and skeletal muscle strength.[16] It suggests that malondialdehyde may also be utilized as a biomarker in smooth muscle damage caused by post-surgical use of tourniquets. In this study, there was no significant difference between changes in MDA levels in the treatment and control groups, including differences between their initial MDA levels and their MDA levels 15 minutes after the release of the tourniquets; their initial MDA levels and their MDA levels 120 minutes after the release of the tourniquets; and their MDA levels 15 minutes and 120 minutes after the release of the tourniquets. It indicates no protective effect of dexmedetomidine against lipid peroxidation.

This study also showed no effect of tourniquet pressure on malondialdehyde levels. It might be due to the fact that in both groups, the tourniquet pressure given was high enough to create an ischemic condition in the tourniquet-mounted muscle. The pressure applied when it has passed arterial occlusion pressure will create ischemic conditions in the tourniquet-mounted distal tissue, and if used for more than 120 minutes, it will cause muscle damage and nerve damage due to tourniquet pressure.[17]

Several studies have observed the role of anesthetic substances in tissue damage due to reperfusion. Propofol is a widely-used anesthetic substance during anesthesia. In in vivo studies, propofol has been reported to protect the heart, kidney, and liver from reperfusion injury,[18–20] reducing lipid peroxidation in the spinal cord after trauma.[21] Studies on humans have had mixed results. A study showed no significant change in plasma malondialdehyde levels in 29 liver donor patients who were anesthetized with propofol.[22] Another study in patients undergoing laparoscopic cholecystectomy revealed a significant decrease in plasma malondialdehyde levels after deflation of carbon dioxide gas to aid development during laparoscopic action compared to before gas inflation.[23]

Isoflurane has an antioxidant profile in in-vitro studies[24,25] but, in vivo, can induce oxidative stress by increasing lipid peroxidation.[26] Several clinical studies have shown an increase in malondialdehyde in isoflurane use in hepatectomy donor patients but have no effect on TOS, TAC, and SOD activities.[22] Another study found an increase in blood lymphocytes on isoflurane use in patients with major abdominal surgery two hours after isoflurane use, but these parameters returned to normal a few days later.[27] Anesthetic technique can affect malondialdehyde levels. A study was conducted on 40 diabetic ulcer patients subjected to surgery, divided into two a group anesthetized with general anesthesia and a group anesthetized with regional anesthesia. The results showed that patients anesthetized with regional anesthesia had lower malondialdehyde levels than those anesthetized with general anesthesia.[28] Another study on patients anesthetized with dexmedetomidine as an adjuvant to peripheral nerve block sedation in the upper extremities showed reduced levels of malondialdehyde, creatinine phosphokinase, and uric acid in the reperfusion period compared to those in the control group.[23,29-32] It may be due to the use of upper extremity surgery, in which not much blood undergoes reperfusion.

This study has several limitations that the researchers are aware of. First, the loading interval between dexmedetomidine and tourniquet inflation time varied for each subject. This factor should be considered for data processing in subsequent studies. Second, serum malondialdehyde levels were measured using systemic circulating blood, which may be significantly different from the blood collected from the surgical site. The systemic serum collected might not reflect the anti-inflammatory effect of dexmedetomidine at the local surgical site. Third, higher doses of dexmedetomidine might be required to elicit anti-inflammatory effects, which could have adverse hemodynamic side effects and,

thus, not be clinically applicable. Fourth, malondialdehyde levels 120 minutes after the release of the tourniquets were not measured; thus, different results might be obtained between groups.

CONCLUSIONS

Based on statistical analysis and discussion of the effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets, it can be concluded that there was no statistically significant effect of dexmedetomidine administration on malondialdehyde levels in lower extremity surgery using tourniquets.

AUTHORS' CONTRIBUTION

All authors have contributed to the processes in this study, including conception and design, data analysis and interpretation, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, collection, and data assembly.

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This study received no sponsorship.

CONFLICT OF INTEREST

There is no conflict of interest for this manuscript.

ETHICAL CONSIDERATION

Ethical clearance for this study has been issued by the Health Research Ethics Commission of Dr. Soetomo Regional Public Hospital, Surabaya, based on a certificate of ethical clearance No. 0622/KEPK/III/2023.

REFERENCES

1. Coudert MM. The use of tourniquet in limb surgery. University of Zagreb. 2016;1:1–21.
2. Leurcharusmee P, Sawaddiruk P, Punjasawadwong Y, Chattipakorn N, Chattipakorn SC. The possible pathophysiological outcomes and mechanisms of tourniquet-induced ischemia-reperfusion injury during total knee arthroplasty. Oxidative Medicine and Cellular Longevity. 2018. doi: 10.1155/2018/8087598
3. Halladin NL, Ekeløf S, Alamili M, Bendtzen K, Lykkesfeldt J, Rosenberg J, Gögenur I. Lower limb ischaemia and reperfusion injury in healthy volunteers measured by oxidative and inflammatory biomarkers. Perfusion (United Kingdom). 2015;30(1):64–70. doi: 10.1177/0267659114530769
4. Bianco-Batlles MD, Sosunov A, Polin RA, Ten VS. Systemic inflammation following hind-limb ischemia-reperfusion affects brain in neonatal mice. Developmental Neuroscience. 2009;30(6):367–73. doi: 10.1159/000164686
5. Laisalmi-Kokki M, Pesonen E, Kokki H, Valta P, Pitkänen M, Teppo AM, Honkanen E, Lindgren L. Potentially detrimental effects of N-acetylcysteine on renal function in knee arthroplasty. Free Radical Research, 2009;43(7):691–6. doi: 10.1080/10715760902998206
6. Omer K, Nermin G, Ali A, Mehmet A, Unal D, Sezen KS, Hakan K. Tourniquet-induced ischaemia-reperfusion injury: the comparison of antioxidative effects of small-dose propofol and ketamine. Brazilian Journal of Anesthesiology (English Edition). 2017;67(3):246–50. doi: 10.1016/j.bjane.2015.09.005
7. Zalunardo MP, Serafino D, Szelloe P, Weisser F, Zollinger A, Seifert B, Pasch T. Preoperative clonidine blunts hyperadrenergic and hyperdynamic responses to prolonged tourniquet pressure during general anesthesia. Anesthesia and Analgesia. 2002;94(3):615–8. DOI: 10.1097/00000539-200203000-00025
8. Kutanis D, Erturk E, Besir A, Demirci Y, Kayir S, Akdogan A, Kural BV, Bahat Z, Canyilmaz E, Kara H. Dexmedetomidine acts as an oxidative damage prophylactic in rats exposed to ionizing radiation. Journal of Clinical Anesthesia. 2016;34:577–85. doi: 10.1016/j.jclinane.2016.06.031
9. Kim SH, Kim DH, Shin S, Kim SJ, Kim TL, Choi YS. Effects of dexmedetomidine on inflammatory mediators after tourniquet-induced ischemia-reperfusion injury: a randomized, double-blinded, controlled study. Minerva Anestesiologica. 2019;85(3):279–87. DOI: 10.23736/S0375-9393.18.13015-X
10. Bostankolu E, Ayoglu H, Yurtlu S, Okyay RD, Erdogan G, Deniz Y, Hanci V, Can M, Turan IO. Dexmedetomidine did not reduce the effects of tourniquet-induced ischemia-reperfusion injury during general anesthesia. The Kaohsiung Journal of Medical Sciences. 2013;29(2):75–81. doi: 10.1016/j.kjms.2012.08.013
11. Zhang XY, Liu ZM, Wen SH, Li YS, Li Y, Yao X, Huang WQ, Liu KX. Dexmedetomidine administration before, but not after, ischemia attenuates intestinal injury induced by intestinal ischemia-reperfusion in rats. Anesthesiology. 2012;116(5):1035–46. doi: 10.1097/ALN.0b013e3182503964
12. Dillon JP, Laing AJ, Chandler JRS, Wang JH, McGuinness A, Redmond HP. Pravastatin attenuates tourniquet-induced skeletal muscle ischemia reperfusion injury. Acta Orthopaedica. 2006;77(1):27–32. doi: 10.1080/17453670610045669
13. Weiskopf RB, Collard CD, Gelman S. Prevention of Ischemia – Reperfusion Injury. 2001;6:1133–8.
14. Girotti AW. Lipid hydroperoxide generation, turnover, and effector action in biological systems. Journal of Lipid Research. 1998;39(8):1529–42. doi: 10.1016/s0022-2275(20)32182-9
15. Fukai M, Hayashi T, Yokota R, Shimamura T, Suzuki T, Taniguchi M, Matsushita M, Furukawa H, Todo S. Lipid peroxidation during ischemia depends on ischemia time in warm ischemia and reperfusion of rat liver. Free Radical Biology and Medicine. 2005;38(10):1372–81. doi: 10.1016/j.freeradbiomed.2005.02.004
16. Mueangson O, Vongvaivanichakul P, Kamdee K, Jansakun C, Chulrik W, Pongpanitanont P, Sathirapanya P, Chunglok W. Malondialdehyde as a useful biomarker of low hand grip strength in community-dwelling stroke patients. International Journal of Environmental Research and Public Health. 2020;17(21):1–12. DOI: 10.3390/ijerph17217918
17. Masri BA, Eisen A, Duncan CP, McEwen JA. Tourniquet-induced nerve compression injuries are caused by high pressure levels and gradients–a review of the evidence to guide safe surgical, pre-hospital and blood flow restriction usage. BMC Biomedical Engineering. 2020;2(1):1–8. doi: 10.1186/s42490-020-00041-5
18. Bellanti F, Mirabella L, Mitarotonda D, Blonda M, Tamborra R, Cinnella G, Fersini A, Ambrosi A, Dambrosio M, Vendemiale G, Serviddio G. Propofol but not sevoflurane prevents mitochondrial dysfunction and oxidative stress by limiting HIF-1α activation in hepatic ischemia/reperfusion injury. Free Radical Biology and Medicine. 2016;96:323–33. doi: 10.1016/j.freeradbiomed.2016.05.002
19. Li S, Lei Z, Yang X, Zhao M, Hou Y, Wang D, Tang S, Li J, Yu J. Propofol protects myocardium from ischemia/reperfusion injury by inhibiting ferroptosis through the akt/p53 signaling pathway. Frontiers in Pharmacology. 2022;13(March):1–11. doi: 10.3389/fphar.2022.841410
20. Li Y, Zhong D, Lei L, Jia Y, Zhou H, Yang B. Propofol prevents renal ischemia-reperfusion injury via inhibiting the oxidative stress pathways. Cellular Physiology and Biochemistry. 2015;37(1):14–26. doi: 10.1159/000430329
21. Kaptanoglu E, Sen S, Beskonakli E, Surucu HS, Tuncel M, Kilinc K, Taskin Y. Antioxidant actions and early ultrastructural findings of thiopental and propofol in experimental spinal cord injury. Journal of Neurosurgical Anesthesiology. 2002;14(2):114–22. doi: 10.1097/00008506-200204000-00005
22. Ucar M, Ozgül U, Polat A, Toprak HI, Erdogan MA, Aydogan MS, Durmus M, Ersoy MO. Comparison of antioxidant effects of isoflurane and propofol in patients undergoing donor hepatectomy. Transplantation Proceedings. 2015;47(2):469–72. doi: 10.1016/j.transproceed.2014.11.043
23. Yagmurdur H, Cakan T, Bayrak A, Arslan M, Baltaci B, Inan N, Kilinc K. The effects of etomidate, thiopental, and propofol in induction on hypoperfusion-reperfusion phenomenon during laparoscopic cholecystectomy. Acta Anaesthesiologica Scandinavica. 2004;48(6):772–7. doi: 10.1111/j.0001-5172.2004.00417.x

24. Lee YM, Song BC, Yeum KJ. Impact of volatile anesthetics on oxidative stress and inflammation. BioMed Research International. 2015. doi: 10.1155/2015/242709
25. Schallner N, Ulbrich F, Engelstaedter H, Biermann J, Auwaerter V, Loop T, Goebel U. Isoflurane but not sevoflurane or desflurane aggravates injury to neurons in vitro and in vivo via p75NTR-NF-κB activation. Anesthesia and Analgesia. 2014;119(6):1429–41. doi: 10.1213/ANE.0000000000000488
26. Dal Molin SZF, Kruel CRP, De Fraga RS, Alboim C, De Oliveira JR, Alvares-Da-silva MR. Differential protective effects of anaesthesia with sevoflurane or isoflurane An animal experimental model simulating liver transplantation. European Journal of Anaesthesiology. 2014;31(12):695–700. doi: 10.1097/EJA.0000000000000127
27. Karabiyik, L., Şardaş, S., Polat, U., Kocabaş, N. A., & Karakaya, A. E. Comparison of genotoxicity of sevoflurane and isoflurane in human lymphocytes studied in vivo using the comet assay. Mutation Research - Genetic Toxicology and Environmental Mutagenesis, 2001: 492(1–2), 99–107. doi: 10.1016/s1383-5718(01)00159-0
28. Yazdi, A. P., Bameshki, A., Salehi, M., Kazemzadeh, G., Razavi, M. S., Rahmani, S., & Hashemy, S. I. The effect of spinal and general anesthesia on serum lipid peroxides and total antioxidant capacity in diabetic patients with lower limb amputation surgery. Archives of Bone and Joint Surgery, 2018: 6(4), 312–317. doi: 10.22038/abjs.2017.20994.1541
29. Yagmurdur, H., Ozcan, N., Dokumaci, F., Kilinc, K., Yilmaz, F., & Basar, H. Dexmedetomidine Reduces the Ischemia-Reperfusion Injury Markers During Upper Extremity Surgery With Tourniquet. Journal of Hand Surgery, 2008: 33(6), 941–947. doi: 10.1016/j.jhsa.2008.01.014
30. Pagehgiri HD, Puruhito I, Aditiawarman, Lestari P, Sembiring YE, Jiwangga D, Hakim AR, Aryananda RA. The role of transdermal carbon dioxide on changes in malondialdehyde levels as a marker of ischemia-reperfusion injury in patients with placenta accreta spectrum underwent temporary abdominal aortic cross-clamping as an adjunct procedure during cesarean hysterectomy. Bali Med J. [Internet]. 2022 Aug. 31 [cited 2023 May 3];11(2):1023-9. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/3646
31. Maharani M, Dewi PK, Prihatningtias R, Wildan A, Nugroho T, Limijadi EKS, Rahmi FL. Aqueous Humour Malondialdehyde Level as Oxidative Stress Marker In Types Of Glaucoma. Bali Med J. [Internet]. 2022 Mar. 14 [cited 2023 May 3];11(1):103-5. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/2599
32. Wijanarko B, Christrijogo Sumartono, Belindo Wirabuana, Hardiono, Bambang Pujo Semedi, Prananda Surya Airlangga. Effects of Tourniquet Inflation on Blood Pressure, Mean Arterial Pressure, and Pulse Rate during the Maintenance of Anesthesia Using a Combination of Dexmedetomidine and Isoflurane for Patients Undergoing Lower Extremity Surgery. Bali Med J. [Internet]. 2023 Mar. 27 [cited 2023 May 3];12(1):1033-40. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/4244