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The Effect of Dexmedetomidine and Propofol on Oxidative Stress and Antioxidizing System Studied on Liver Ischemia-reperfusion Model on Rats

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Abstract

Purpose: The presence or absence of protective or preventive role of dexmedetomidine and propofol against ischemia/reperfusion (I/R) injury at tissue level on liver I/R model was demonstrated.

Materials and methods: 24 rats were randomly divided into four groups. Following anesthesia laparotomy was done and hepatoduodenal ligament was explorated. Tissue samples were taken for both biochemical (MDA, SOD, GPx) and histological study.

Results: MDA level was hisghest in Group II and was significantly lower in Group III and Group IV. GPx level was lowest in Group II, the level of GPx was higher in Group III and Group IV with respect to Group II. SOD level was lowest in Group II and was highest in Group IV. SOD levels in Group II and Group III did not show statistical significance. In the histopathological study, in Group I the liver parenchyme and membrane integrity was protected; in Group II the hepatocyte cellular membrane integrity was distorted, microvesicule number increased and the liver sinusoids were shrunken; in Group III the hepatocyte membrane and nucleus was near normal and well protected; and in Group IV the cellular component structures were protected, hepatocyte cell membrane was protected in normal thickness.

Discussion: The results show that dexmedetomidine and propofol decrease the level of MDA in similarly; the effect of dexmedetomidine on GPx level was slightly lower than propofol and its effect on SOD level was lower than propofol. As a result, we believe that either propofol or dexmedetomidine can be effective in protecting hepatocytes from I/R injury especially in log term procedures but the former drug having dominance in this protective role.

Keywords: Liver ischemia-reperfusion (I/R); Propofol; Dexmedetomidine (dex); Antioxidising system; Lipid peroxidation

Introduction

One of the major problems about liver related surgery, cancer and transplantation is the vulnerability of liver to ischemia and reperfusion [1]. Postoperative bleeding after liver resection is the most important reason of mortality.

Ischemia reperfusion injury is one of the major problems faced by all tissues during inadequate oxygenation [2]. On ischemic period decreased production of energy in the cell, rapid break down of the stored ATP and the icrease in the anaerobic glycolysis trigger mitochondrial disfunction, free oxygen radicals produced by reperfusion gives the actual major damage.

One of today's most popular topics are avoiding or minimizing the structural and metabolic changes in the liver that occur during ischemia and reperfusion. The increase in the liver tumor and transplantation operations increases the importance of using radical scavangers to prevent the damage that occurs after ischemic reperfusion [1].

Many farmacological agents are used to clean free radicals and protect tissues from ischemic damage. One of these agents, its antioxidant activity proven in many studies is propofol. Its proven that each molecule of propofol can scavange two free radicals and prevent the lipid peroxidation inducted by oxidative stress [3,4]. The alfa 2 adrenoreceptor agonist dexmedetomidin used as an anxiolytic and sedative agent in intensive care units decreases the cathecolamine decharge inducted by ischemia and decreases the damage caused by reperfusion [5,6].

In this experimental study, whether the presence or absence of protective or preventive role of dexmedetomidine and propofol against ischemia/reperfusion (I/R) injury at tissue level on liver I/R model was demonstrated.

Materials and Methods

All experimental procedures and protocols were approved by the Animal Care and Use Committee of Hacettepe University School of Medicine.Male Sprague-Dawley albino rats weight ranging 300 ± 50 g were randomly divided into four groups (n=6 in each group. Drugs used in the present study were Propofol (Diprivan iv amp, Astra Zeneca) and Dexmedetomidine (Precedex flk, Abbott) administered intraperitoneally with a dose of 30 mg/kg for propofol and 25 mcg/kg for dexmedetomidine.

Surgical procedure

Anesthesia was induced with Ketamine to rats, (Ketalar flk, Eczacıbaşı) with a dose of 90 mg/kg. Under sterile cover, laporatomy was performed via midline incision. Hepatoduodenal ligament was

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exposed and the portal triad was clamped for 30 minutes via surgitape to totally prevent blood flow. Following 30 minutes of ischemia reperfusion continued for 45 minutes. Fluid loss was replaced with 10 mililiter of isotonic fluid in all rats. After the reperfusion period, tissue samples were taken from the rat liver and then the rats were sacrificed.

Groups

Study was performed on four groups. In the control group (Group 1, n=6), only simple laparotomy was performed and the hepatoduodenal ligament was exposed but not clamped. In I/R Group (Group2, n=6) following laparatomy, hepatoduodenal ligament was exposed and the portal triad was ligated via surgitape for 30 minutes and reperfused for 45 minutes. In Dex Group (Group 3, n=6) 15 minutes before ischemia 25 mcg/kg intraperitoneal dexmedetomidine was administered. Then laparotomy was performed and ischemia for 30 minutes and reperfusion for 45 minutes was performed. In Propofol Group (Group 4, n=6) 30 mg/kg propofol was administered intraperitoneally 15 minutes before ischemia. Ischemia was performed for 30 minutes and reperfused for 45 minutes. Samples were than taken for malonildialdehyde (MDA), glutathyon peroxidase (GPx), superoxide dismutase (SOD) and liver tissue samples for electron microscopic study.

Biochemical analysis

Tissue MDA levels were studied by the technique presented by Uchiyama and Mihara [7]. Tissue SOD activity was determined by the method defined by Sun et al. [8]. Tissue GPx activity was studied by the method defined by Paglia and Valentine [9]. Tissue protein determination was achieved by the method described by Lowry et al. [10].

Electron microscopic analysis

Liver tissue samples were taken after the I/R period and embedded in gluteraldehyde solution containing phosphate buffer. After the preperation of the specimen, the semi thin tissue was stained with toluidine blue and the sections taken by ultramicrotome were stained with Pb-citrate and uranylacetate. Electron microscopy was studied on Carl Zeiss EM 900 electron microscope.

Statistical Analysis

Biochemical parameters in the fourr groups were studied with Kruskal-Wallis test. To determine the group leading to difference was determined by Mann-Whitney U test and Bonferroni Correction. P<0.008 was accepted to be a significant difference.

Results

The results obtained from 24 rats, which were randomly divivded into four groups, were statistically compared for GPx, MDA and SOD levels obtained from liver tissue specimens. GPx (p=0.000), MDA (p=0.001) and SOD (p=0.005) levels showed statistical significance in each group (p<0.008, Kruskal-Wallis Test).

GPx values

The GPx levels obtained were 9.75 ± 1.39, 7.3 ± 0.36, 9.72 ± 0.58 and 13.6 ± 2.16 respectively in control Group, I/R Group, Dex group and Propofol Group. The difference between control and I/R groups were statistically significant (p=0.004). Control Group and Dex group results were similar (p=0.749). Control group and Propofol Group results showed no difference (p=0.010). I/R group and Dex group results were significantly different (p=0.004). I/R group and Propofol Group also showed statistically significant difference (p=0.004). There was alsa a statistical significance between Dex Group and Propofol Group results (p=0.004) (Table 1 and Figure 1).

MDA values

The mean MDA values obtained from the study groups were 15.37 ± 3.34 in the control group, 35.38 ± 3.77 in the I/R Group, 22.7 ± 4.66 in the Dex Group and 19.82 ± 4.89 in the propofol Group. The increase in the MDA levels were statistically significant between the control Group and the I/R Group (p=0.004). The control group and the Dex Group values were similar (p=0.037). The control Group and the Propofol group values were also similar (p=0.078). The difference between the Dex Group and the I/R Group values were statistically significant (p=0.004). The difference between the Propofol Group and I/R Group was also statistically significant (p=0.004). Dex Group and Propofol Group values were not statistically significant (p=0.262) (Table2 and Figure 2).

	GroupI (control)	GroupII (I/R)	Group III (Dex)	Group IV (propofol)
GPx	9.75 ± 1.39 [8.2-12]	7.33 ± 0.36 [6.8-7.7]	9.72 ± 0.58 [9-10.7]	13.6 ± 2.16 [11.1-16.9]
P		0.004*	0.749*	0.010*
			0.004**	0.004**
				0.004***

*:When compared with the control group.
**:When compared with the I/R group.
***:When compared with the Dex group.

Table 1: Mean GPx levels (mean ± standard deviation, range values).

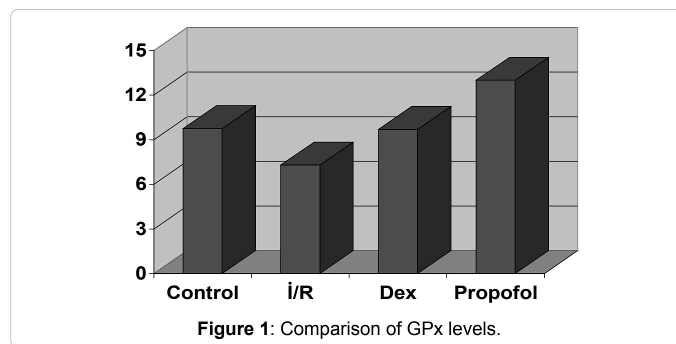

Figure 1: Comparison of GPx levels.

	Grup 1 (control)	Grup 2 (İ/R)	Grup 3 (Dex)	Grup 4 (propofol)
MDA	15.37 ± 3.34 [10.6-19.3]	35.38-3.77 [29.9-39.1]	22.7 ± 4.66 [15.3-28.1]	19.82 ± 4.89 [11.6-24.5]
p		0.004*	0.037*	0.078*
			0.004**	0.004**
				0.262***

Table 2: The mean MDA values of the Groups (mean ± SD, range values).

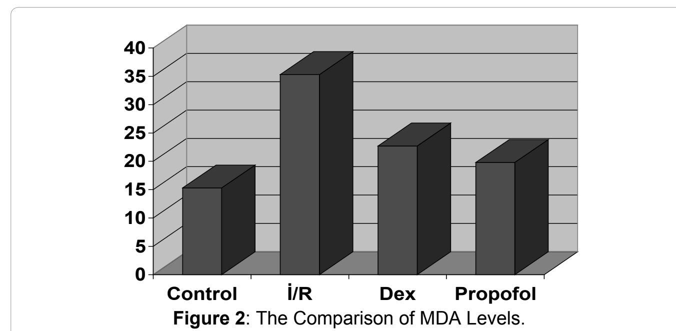

Figure 2: The Comparison of MDA Levels.

SOD values

The mean SOD values obtained from the groups were 2.53 ± 0.28, 1.39 ± 0.28, 1.86 ± 0.59 and 2.32 ± 0.45 in order of control, I/R, Dex and Propofol Group. The difference of the values obtained were statistically significant between the control group and I/R Group (p=0.004). The control group and the Dex group values were similar (p=0.078). The contol group values were similar to the values obtained from the Propofol group (p=0.20). I/R Group values were not statistically signifacant when compared with the Dex Group (p=0.229). The values obtained from the I/R Group were statistically significant from those obtained from the Propofol Group (p=0.004). The Dex Group and the Propofol group values were similar (p=0.078) (Table 3 and Figure 3).

Histological Findings

The histological changes observed in the Groups under electromicroscopic examination were as follows:

Group I (control group)

The cellular parenchyme and the nucleus of the hepatocytes were normal in structure. The distribution of the mitochondri, granulated and ungranulated endoplasmic reticulum were dominating. Cellular borders were stracturally normal. The liver sinusoids were dominating and the biliary ductuli were normally observed (Figures 4 and 5).

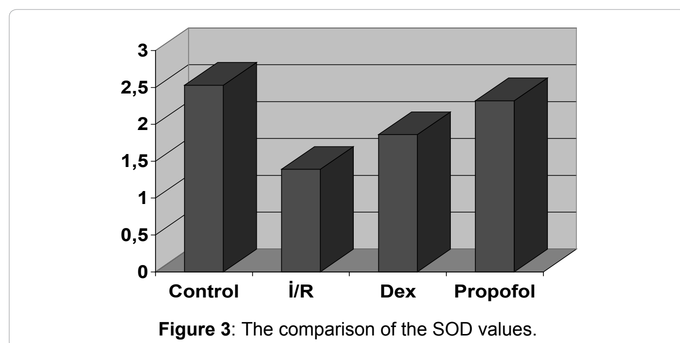

Figure 3: The comparison of the SOD values.

	Grup 1 (control)	Grup 2 (İ/R)	Grup 3 (Dex)	Grup 4 (propofol)
SOD	2.53 ± 0.28 [2.06-2.79]	1.39 ± 0.28 [1.02-1.72]	1.86 ± 0.59 [1.33-2.87]	2.32 ± 0.45 [1.76-3.11]
p				0.20*
		0.004*	0.078*	0.004**
			0.229**	0.078***

Table 3: The mean SOD values of the Groups (Mean ± SD, range values).

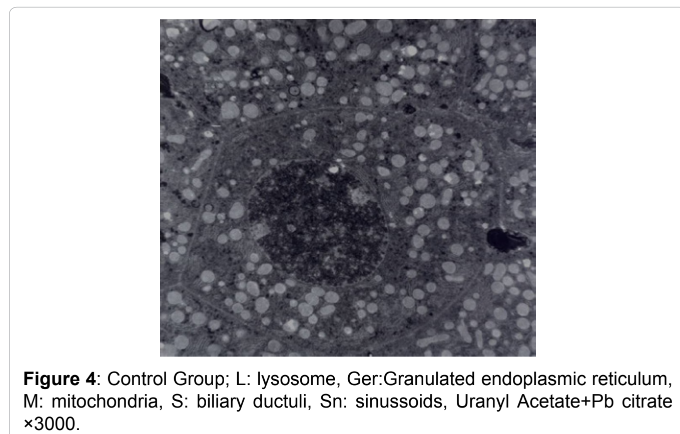

Figure 4: Control Group; L: lysosome, Ger:Granulated endoplasmic reticulum, M: mitochondria, S: biliary ductuli, Sn: sinussoids, Uranyl Acetate+Pb citrate ×3000.

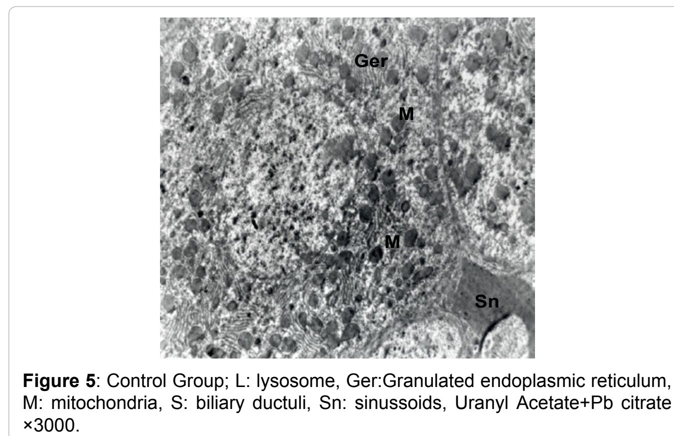

Figure 5: Control Group; L: lysosome, Ger:Granulated endoplasmic reticulum, M: mitochondria, S: biliary ductuli, Sn: sinussoids, Uranyl Acetate+Pb citrate ×3000.

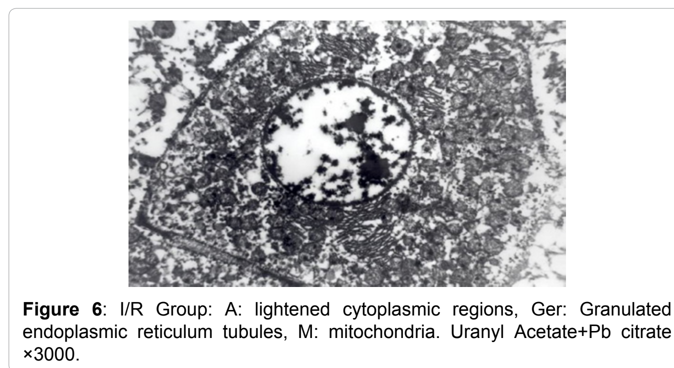

Figure 6: I/R Group: A: lightened cytoplasmic regions, Ger: Granulated endoplasmic reticulum tubules, M: mitochondria. Uranyl Acetate+Pb citrate ×3000.

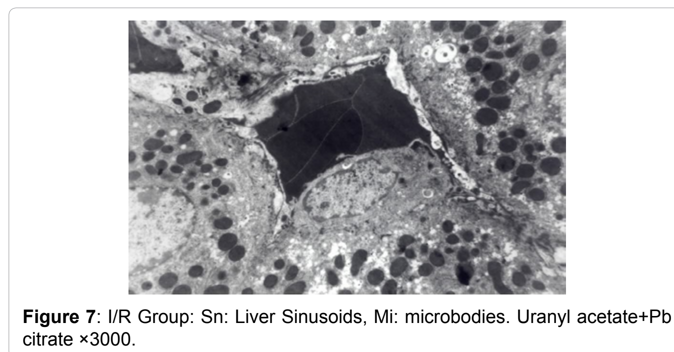

Figure 7: I/R Group: Sn: Liver Sinusoids, Mi: microbodies. Uranyl acetate+Pb citrate ×3000.

Group II (I/R group)

The mitochondrial structures were preserved but the mitochondrial matrix density was decreased. The granulated and ungranulated endoplasmic reticulum tubules were structurally normal. The microbodies showed a definite increase when compared to the control group. The glycogen area in the paranchymal hepatocytes were observed as enlarged spaces. The cellular integrity was segmentally destructed in the lateral borders. The liver sinusoids were clearly narrowed and the microvilli in the Space of Disse showed elongation (Figures 6 and 7).

Group III (Dex group)

The near normal ltrastructure were interestingly observed. The granulated and ungranulated endoplasmic reticulum tubules and the mitochondrial matrices were observed near normal. The microbodies were well developed, the cellular membrane and the nuclei were normal in structure. The presence of lipid droplets with a dense content was dominant (Figures 8 and 9).

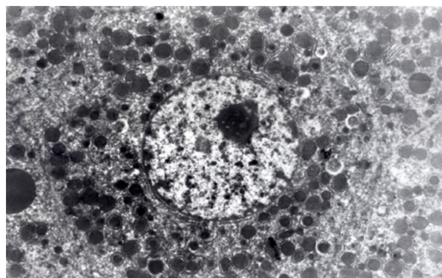

Figure 8: Dex Group: M: mitochondria, Mi: microbodies, Ger: granulated endoplasmic reticulum tubules. Uranyl acetate+Pb citrate ×3000.

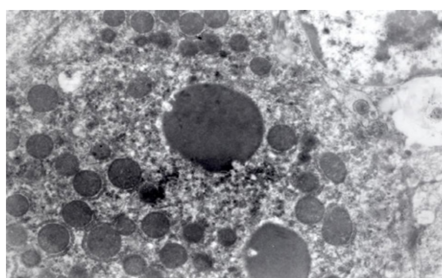

Figure 9: Dex Group: L: lipid. Uranyl acetate+Pb citrate ×3000.

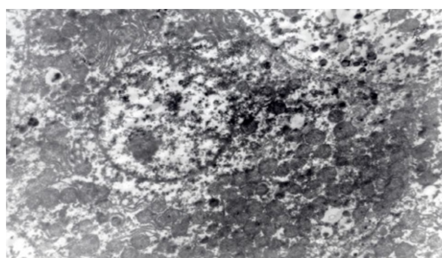

Figure 10: Propofol Group: Ger: grnulated endoplasmic reticulum tubules, M: mitochondria Uranyl acetate+Pb citrate ×3000.

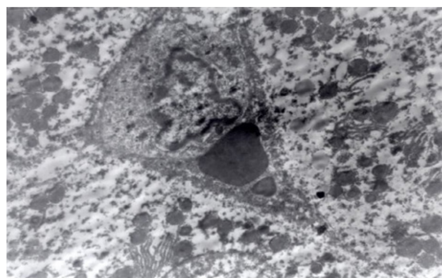

Figure 11: Propofol Group: L: lipid, Sn: sinussoid. Uranyl acetate+Pb Citrate.

Group IV (propofol group)

The normal tiny ultrastructure was observed. The endoplasmic reticuli tubules and the mitochondrial matrices were all structurally normal. Segmental lipid drolets with a dense content was dominating (Figures 10 and 11).

Discussion

I/R injury is one of the important problems that all the tissues are face to face in the presence of inadequate tissue oxygenation. The tissue damage that starts with the chemical reactions during the ischemia phase increases significantly with reoxygenation during the reperfusion phase [2]. Hepatocytes can stand against ischemia for 30-60 minutes. Following a 60 minutes of ischemia, free oxygen radicals starts to increase at the fifth minute and reaches to maximum level at the 15th minute [11]. Suzuki et al. reported that maximum injury occurs after 90 minutes of ischemia followed by a 60 minutes of reperfusion and thereby they have reported that the injury is proportional with the time of I/R injury duration [12].

The significance of using antioxidising agents such as ATP-$MgCl_2$, coenzyme Q10, superoxide dismutase (SOD), catalase, prostaglandins, verapamil, alpha tocoferol(vitamin E), pentoxyphiline and N-acetyl cysteine is increasing to prevent ischemia reperfusion injury produced during surgical procedures either on liver tissue or other organ systems [2]. Propofol is one of the intravenous agents searched for its antioxidising effect. Chemical structure of propofol (2,6-diisoproyl phenol) mimics butilised hydroxy toluen (BHT) and endogenous antioxidising agent alpha-tocopherol (vitamin E) which are phenol containing free oxygen radical scavengers and contains a phenolic hydroxy group [13]. All these molecules form complexes with either the cellular membranes or its structural components resulting in a less reactive molecules and each single propofol molecule can scavenger two free oxygen radicals [3,4]. Its also reported that propofol functions as both peroxynitrite scavenger which is produced by superoxide radicals binding to nitric oxide physiologically and inhibiting lipid peroxidation on cellular membranes [14,15]. Another function of propofol is increasing the function of gluthatione antioxidising system [16,17].

In a series of ischemia reperfusion systems, Propofol has been proven to prevent I/R related oxidative injury. Ko et al. has reported that propofol has a preventive effect on ventricles after a global ischemia of the heart [18]. And other similar models of I/R injury on neurons [19], leucocytes [4] and erythrocytes [20] prooved that propofol has a preventive effect against I/R injury. Aarts et al. has reported that propofol has a preventive role in cases such as coronary artery transplantation surgery, sepsis and burns, which of all lead into a decreased ontioxidising defense mechanism [13]. Also in some recent studies propofol has been reported to be a free radical scavenger due to its antioxidising property at anesthetic doses [21-23].

Free oxygen radicals lead to membrane lipid peroxidation and the end product of this reaction is malonyldialdehyde (MDA). Through the level of MDA level is directly proportional to the level of cellular damage. In this study MDA levels detected in I/R Group was higher than that detected in the Control Group and it was lower in Propofol Group than in I/R Group as expected. Mussacchio et al. has also demonstrated that Propofol decreases MDA formation by decreasing lipid peroxidation on hepatocyte microsomes and mitochondria, synaptosomes in the brain [24].

To determine the preventive efects of Propfol against I/R injury, besides determining the level of MDA, glutathione peroxidase (GPx) and superoxide dismutase (SOD) enzyme levels were also determined. In a study carried on the thrombocytes of the postoperative surgical patients, the antioxidising affect of propofol was significant on both decreasing the lipid peroxidation and increasing the activity of glutathione antioxidising system [16]. Cruz et al. have demonstrated the same effect of propofol on brain tissue [17]. In our study GPx levels were lower in I/R group in respect to control group but the level of GPx was higher in Propofol Group when compared to I/R Group. This finding is in parellel to literature which proves propofol to have a positive effect

on glutathione antioxidising system. SOD is another enzyme searched for its antioxidising effect. Green et al. reported that [25] propofol has no effect on SOD however in our study we found the increase in SOD level statistically significant in Propofol Group when compared to I/R Group. This results shows us that propofol has a positive effect on SOD levels thus to reduce the superoxide radicals to H_2O_2 spends more than normal SOD which leads to decrease in SOD levels. The end product H_2O_2 is than metabolysed by GPx and catalase. Therefore the decrease in antioxidising enzymes under I/R injury is natural.

It is reported that the level of catecholamines increase in the ischemia period studied on the I/R model of hapatocytes [26]. Kogure and Suzuki has occluded the hepatoduodenal ligamnet in changing time periods to produce I/R in their study and found norepinephrin levels in portal circulation to increase significantly where the ischemia time is 30 minutes or higher [27]. Lee et al. have demonstrated that when norepinephrine is injected externally it results in hepatic ischemia and necrosis [28]. Besides this direct effect, in series of I/R models on different tissue models, the free oxygen radicals produced by autooxidation end pruduct of the increased catecholamines may play a role in the tissue damage. Simonson et al. have produced I/R injury on rat brain and have observed the increase in H_2O_2 levels at the 5th minute of reperfusion and the reason for this increase was the oxidative deanimation of increased catecholamines by the monoamine oxidase (MAO) which increases in tissue by reperfusion [29]. Also in this study the level of oxidised glutathione was three times its normal value.

Dexmedetomidine was another agent searched in our study which has an alpha-2 adrenoceptor agonist effect and its effect on preventing I/R injury on several brain and heart I/R models were via decreasing the cathecolamine release during the ischemia period [5,6,30]. Hoffman et al. have produced cerebral ischemia on rat brain model and observed that the neurological and histopathological results on the dexmedetomidine group was better than the control group and this effect was returned by using alpha-2 adrenoceptor antagonists [31]. In a recent study carried out on renal I/R model on rats, histopathologic score obtained from the dexmedetomidine group was statistically significantly lower than I/R group and they reported that dexmedetomidine can decrease ischemia injury on kidneys and may increase tolerance to renal injury under I/R conditions [32]. Hall et al. studied on model where intracranial hypertension was created to rodents, they injected intracisternal dexmedetomidine and observed that the left ventricular function was well protected and they thought this result was due to prevention of increased catecholamine release by dexmedetomidine which results in decreased free oxygen radical formation in heart tissue. In this study also the MDA levels in the dexmedetomidine group was lower than that in the control group [33]. In a recent study where the effect of dexmedetomidine was searched to decrease I/R injury due to tourniquet application for upper limb surgery, the MDA values in the dexmedetomidine group was significantly lower in respect to control group during the reperfusion phase [34].

Our study demonstrated similar results to literature where the level of MDA was lower in the dexmedetomidine group when compared to I/R group.

Yet there is not enough number of clinical studies investigating the direct effect of dexmedetomidine on the antioxidising defense mechanism, in a recent study carried out by Hanci et al. on a model where I/R was created on rat testicles, the MDA levels obtained from the dexmedetomidine group was significantly lower than the I/R group values and the total antioxidising system activities were higher [35]. Simonson et al. also have reported similar results [29]. In our study the level SOD was similar in both the dexmedetomidine group and the I/R group but the GPx levels were significantly higher in the dexmedetomidine group in respect to the I/R group. This can be explained as dexmedetomidine decreases the level of catecholamines that tend to increase during the ischemic phase resulting in a reduced lipid peroxidation and SOD levels and preserving the GPx levels by decreasing its consumption.

In our study, when the effect of dexmedetomidine and propofol is compared, both agents decrease the level of MDA at a similar manner, propofol has a leading positive effect on GPx and dexmedetomidine has no effect on SOD. The histopathological tissue examination under electron microscopy showed a marked destruction on hepatocyte ultrastructure which was well preserved in either the dexmedetomidine group or the propofol group.

As a result, under long lasting I/R conditions, propofol having a stronger but both dexmedetomidine and propofol has a protective effect therefore especially in liver surgeries that can lead to long lasting I/R injury, we believe that the use of these two agents may provide advantage in preserving the normal tissue architecture and function.

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