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Short Communication

Prevention of glycerol-induced acute kidney injury by isoflurane inhalation in male rats

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ABSTRACT

Introduction: Acute kidney injury (AKI) is a severe complication of rhabdomyolysis (RM), where skeletal muscle injury leads to the release of cell contents into the bloodstream, ultimately obstructing renal tubules. This results in renal dysfunction due to increased oxidative stress, inflammation, and apoptosis. Glycerol (10 mL/kg) injection is one of the most common methods to induce experimental AKI; but 10 mL/kg dosage seems to be harmful to rats because we have observed some side effects. This study was designed to evaluate the effects of isoflurane pretreatment in the glycerol model of acute kidney injury, but at first we tried to find a better dosage of glycerol to induce AKI less harmful.

Methods: 28 male Wistar rats were used in our investigation. We first studied to find the most effective dosage of glycerol for AKI induction in three groups (5, 6.25, and 10 mL/kg), and accordingly 6.25 mL/kg was selected. Secondly, we investigated isoflurane (1.5%, 20 minutes) pretreatment effects on glycerol-induced AKI by estimating blood urea nitrogen (BUN), creatinine (Cr), Bax/Bcl-2 proteins ratio (Bcl-2-associated X/B-cell lymphoma 2), malondialdehyde (MDA), superoxide dismutase (SOD), and histological changes in renal tissues.

Results: The results showed that isoflurane pretreatment suppressed oxidative stress and apoptosis, and therefore was able to improve renal function.

Conclusion: Isoflurane pretreatment might be protective against rhabdomyolysis-induced AKI because of its anti-oxidant and anti-apoptotic activities.

Keywords:
Glycerol
Blood Urea Nitrogen
Creatinine
Isoflurane
Kidney

Introduction

An instantaneous reduction of renal function within hours to days leads to acute kidney injury (AKI) (Mercado et al., 2019). AKI is reported in up to 7% of hospital admissions and 30% of ICU admissions (Goyal et al., 2022). Almost 13.3 million patients suffer from AKI annually, and approximately 1.7 million people die from this illness (Zuk and Bonventre 2016). Yet there is no completely effective method to prevent or treat AKI (Wu et al., 2017).

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Skeletal muscle injury contributes to the release of cell contents, especially myoglobin, into the bloodstream, which induces rhabdomyolysis (RM) (Panizo et al., 2015; Taguchi et al., 2020). AKI is a severe complication of RM (Wu et al., 2017). One of the principal reasons of AKI pathogenesis is myoglobin precipitation in renal tubules (Michelsen et al., 2019; Mohsenin, 2017). Once renal tubules are blocked by myoglobin, nephrotoxicity occurs, which is observed in increased oxidative stress, inflammation, and apoptosis of the renal tissues (Panizo et al., 2015). Malondialdehyde (MDA) elevation and superoxide dismutase (SOD) reduction observed in the kidneys are the result of reactive oxygen species (ROS) attack (Liu et al., 2016). Two common factors reflecting the drop in glomerular filtration rate include the rise of blood urea nitrogen (BUN) and creatinine (Cr) (Gonsalez et al., 2019).

The most common experimental model to induce AKI by RM is glycerol intramuscular injection (Wu et al., 2017). Glycerol injection causes intracellular changes leading to proteases activation, resulting in muscle fiber destruction due to membrane injury and disruption of osmotic properties (Mahdy 2018; Mahdy et al., 2018). It has been shown that glycerol injection disrupts the balance between arachidonic acid metabolites, including prostacyclin (vasodilator) and thromboxane (vasoconstrictor), remarkably towards thromboxane, thus impairing renal circulation and inducing ischemic insult (Al Asmari et al., 2017). To treat RM, it is important to remove the main cause of muscle injury. Quick fluid replacement with crystalloid solution is the basis of RM-induced AKI pretreatment and treatment (Cabral et al., 2020). Fluid overload, such as isotonic saline and sodium bicarbonate, or hemodialysis and kidney replacement therapy, have been used as effective treatments for AKI for a long time. However, fluid overload can worsen compartment syndrome by volume enhancement and edema, specifically in children and the elderly (Taguchi et al., 2020).

Isoflurane is one of the most common anesthetics for initiating or maintaining anesthesia, with cytoprotective, anti-inflammatory, and cardioprotective properties (Englert et al., 2015). Liu et al, showed that isoflurane reduced inflammation and apoptosis by inhibiting pro-inflammatory cytokine production in oxygen-glucose deprivation-induced injury in H9c2 cardiomyocytes (Liu et al., 2016). Zhang et al, showed that isoflurane reduced the stimulation of Bax and decreased the suppression of Bcl-2 in lipopolysaccharide-induced injury in H9c2 cardiomyocytes. Furthermore, investigations showed that isoflurane had antioxidant activity on H9c2 cells (Zhang and Zhang 2018).

In this study, we investigated the effect of isoflurane pretreatment on AKI. Rats were kept in plexiglass cages, and after 24 hours of water deprivation, rats inhaled 1.5% isoflurane for 20 minutes (Hashiguchi et al., 2005; Rao et al., 2017). For AKI induction, rats were anesthetized with ketamine-xylazine, then received intramuscular injections of 50% (v/v) glycerol solution in saline (Press et al., 2017). Twenty-four hours after AKI induction (Abd-Ellatif et al., 2019), blood and kidney samples were collected to assess BUN, Cr, Bax, and Bcl-2 proteins, MDA, SOD, and histological changes.

Materials and methods

Animals

A group of 28 male Wistar rats were housed in plexiglass cages with free access to standard food and drinking water. They were kept under natural conditions with a temperature range of *22±3°C*, a 12:12 light–dark (LD) cycle, and a relative humidity of 30% to 40%. Firstly, 16 rats were investigated to determine the most effective dosage of glycerol to induce AKI: group I (Gly 5: glycerol 5 mL/kg, n=6), group II (Gly 6.25: glycerol 6.25 mL/kg, n=6), and group III (Gly 10: glycerol 10 mL/kg, n=6) (Press et al., 2017); and eventually, 6.25 mL/kg glycerol was selected as the effective dosage. Then, 12 rats were randomly divided into two groups: group IV (sham, n=6) and group V (isoflurane+glycerol, n=6).

Ethics

This study was conducted in compliance with the U.K. Animals (Scientific Procedures) Act, 1986, and all animal care and experimental procedures were accordingly conducted. Additionally, the study adhered to the ARRIVE Guidelines for reporting. Approval for this research was granted by the Research Ethics Committee of "Tehran University of Medical Sciences guidelines" (Approval ID: "IR.TUMS.MEDICINE.REC.1400.657").

Experimental protocols

Rats in the sham group were treated as follows: After 24 hours of water deprivation, rats were anesthetized us-

ing ketamine 100 (mg/kg) and xylazine 10 (mg/kg), then received several small intramuscular injections of saline (6.25 mL/kg) equally in both hind limb muscles within one minute.

Rats in the glycerol groups were treated as follows: After 24 hours of water deprivation, rats were anesthetized as mentioned above, then received several small intramuscular injections of 50% (v/v) glycerol solution in saline (6.25 mL/kg) equally in both hind limb muscles within one minute.

Rats in the isoflurane and glycerol group were treated as follows: After 24 hours of water deprivation, rats were transferred to plexiglass cages, inhaled 1.5% isoflurane for 20 minutes (Hashiguchi et al., 2005; Rao et al., 2017), and to wash out isoflurane, rats were exposed to normal air for 30 minutes. Rats were then anesthetized as mentioned before, then received several small intramuscular injections of 50% (v/v) glycerol solution in saline (Press et al., 2017) (6.25 mL/g) equally in both hind limb muscles within one minute.

Blood and kidney sample collection

24 hours after intramuscular injection of saline or glycerol (Press et al., 2017), all rats were anesthetized by ketamine-xylazine solution. Blood samples were collected through the inferior vena cava, immediately centrifuged with 3000 rpm within 10 minutes, and serum samples were collected for BUN and Cr assessment. Then kidney samples were dissected. The right kidneys were divided into three smaller pieces for the determination of oxidative stress by analyzing MDA, SOD, and Bax/Bcl-2 ratio. 10% neutral buffered formalin was freshly prepared to fix the left kidneys for histological examinations.

BUN and Cr assessment in blood

BUN and Cr concentrations were measured using spectrophotometry (HITACHI 704 Autoanalyzer) at 505 and 520 nanometers wavelengths, respectively.

Evaluation of oxidative stress by Bax/Bcl-2 ratio in kidney

The Bradford method was conducted to assess protein extracted from the tissue supernatant (Bradford 1976), Sodium dodecyl sulfate–polyacrylamide gel electrophoresis (SDS-PAGE) was provided with a 12% polyacrylamide gel and 60 µg protein loaded (n=6). Pre-stained protein markers were also loaded in each gel well to evaluate the final time of electrophoretic transfer. the electrophoretic gel was transferred to polyvinylidene fluoride membrane. After that, the blots were preserved in blocking buffer (5% nonfat dry milk in TBS-T (Tris-buffered saline containing 0.05% Tween-20)) for one hour at room temperature, and then incubated 18 hours at 4 °C with subsequent primary antibodies: Bax, Bcl-2, pAMPK, total AMPK, histone H3 and acetyle-H3K9 (1/1000, Cell Signaling Technology Co. USA) antibodies. Afterwards, the blots were subjected to a 15-minute incubation in Western blot stripping buffer restored at room temperature, to remove the antibodies, followed by one hour at room temperature for re-blocking. Subsequently, the β-actin antibody (1/1000, Cell Signaling Technology Co. USA) was incubated for three hours, and then TBS-T was used to wash it. Afterwards, the blots were incubated for 1.5 hours with the proper secondary antibodies. Antigens exposed to radiography film were visualized. To quantify the results, film densitometry was scanned. The integrated density of protein bands was measured by Image J analysis after background deletion, and β-actin was considered as the loading control (Niimura et al., 2006).

Evaluating the oxidative stress by MDA and SOD assessment in renal tissues

MDA level was assessed based on MDA reaction with TBA (Thiobarbituric acid). In this reaction, pink pigments are produced in which the maximum absorption is 532 nm, so the absorbance is read at this point, and MDA concentration is calculated by ε value of 153000 (Esterbauer and Cheeseman 1990).

SOD enzyme activity was estimated by a Nasdox ELISA kit in accordance with the instructions of the manufacturer. Lubricating buffer was added to kidney tissue. The homogenized solution was centrifuged, and the supernatant was collected. Finally, the light absorption of the samples was detected at 405 nm, and SOD activity was determined by the subsequent formula:

SOD activity (U/ mL or mg protein) =OD Test/OD Control×200

Histological evaluation

Kidney samples fixed in 10% formalin were dehydrated, embedded, and cut into 4 µm slices; then Hematoxy-

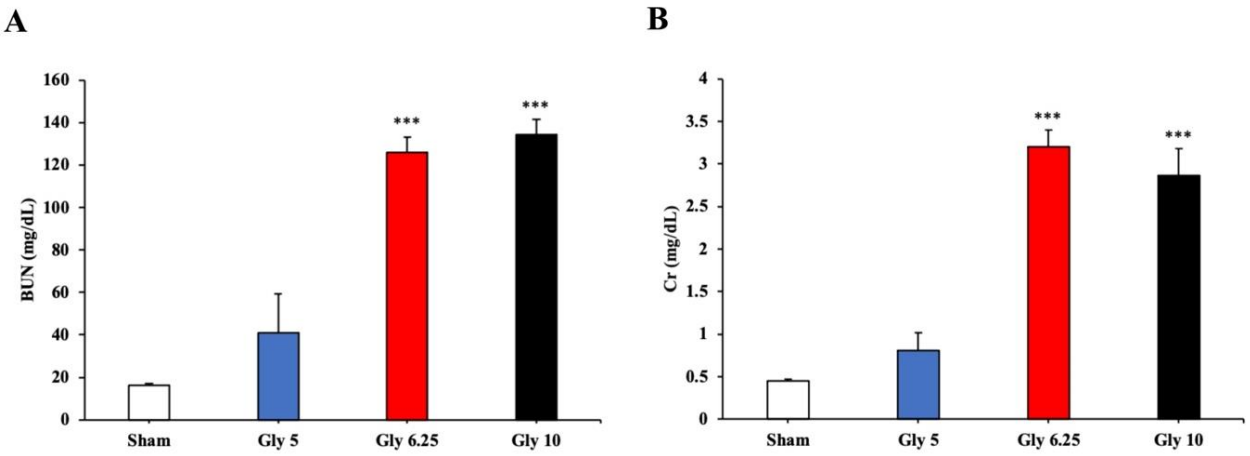

FIGURE 1. Evaluating renal activity after injecting different glycerol doses (5, 6.25, and 10 mL/kg). (A) BUN levels. (B) Cr levels. Each column represents the Mean±SEM (n=5 to 6). *** indicates a significant difference vs. sham with $P<0.001$.

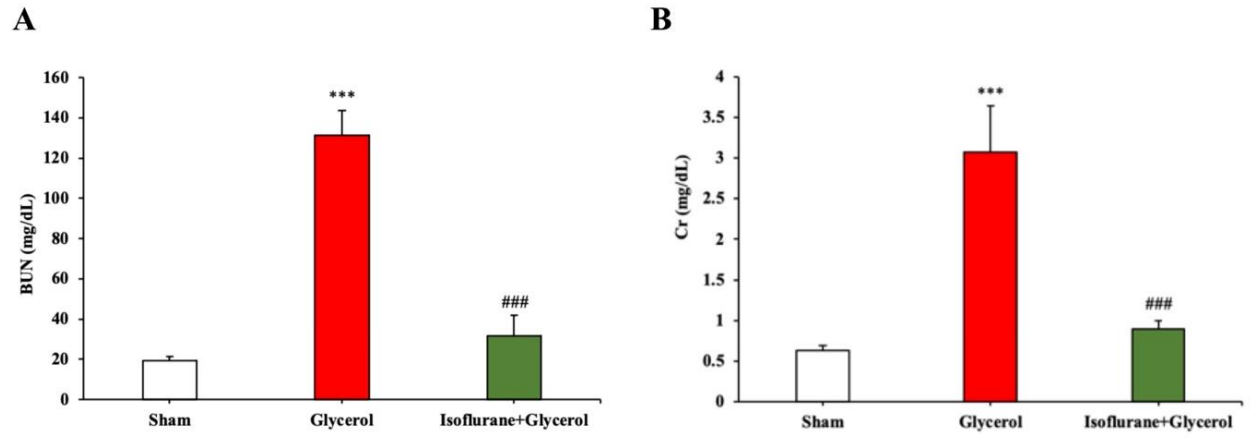

FIGURE 2. Evaluating renal activity after glycerol or isoflurane+glycerol treatment. (A) BUN levels. (B) Cr levels. Each column represents the Mean±SEM (n=6). ***indicates a significant difference vs. sham with $P<0.001$, ###indicates the significant difference vs. glycerol with $P<0.001$.

lin and Eosin staining (H&E) was adopted. Kidney slides were studied by light microscopy (*×400 magnification*). Histological evaluation and renal injury included an increase in the space of Bowman's capsule, a decrease in the diameter of epithelial cells, tubular dilatation, brush border elimination, and cast precipitation in the tubules.

Statistics

The *Mean±SEM (Standard error of the mean)* were utilized to report the data. For comparing quantitative data, a one-way analysis of Variance (ANOVA) was employed, followed by Tukey's post hoc test to identify groups with significant differences. A significance level of $P<0.05$ was deemed as indicating a meaningful difference.

Results

Isoflurane pretreatment decreased BUN and Cr levels in glycerol-induced AKI model rats

Since we have noticed nosebleeds by using a dose of 10 mL/kg glycerol, at first, we experimented with three different groups and compared the BUN and Cr levels to determine the optimal dosage of glycerol with less side effects to induce AKI. Figure 1A shows that BUN level of the glycerol 5 group was not significantly elevated compared to the sham group. However, the BUN level of the glycerol6.25 group was significantly elevated compared to the sham group ($P<0.001$). Additionally, the BUN level of the glycerol 10 group was also significantly increased compared to the sham group. Figure 1B shows that the Cr level was not significantly elevated in

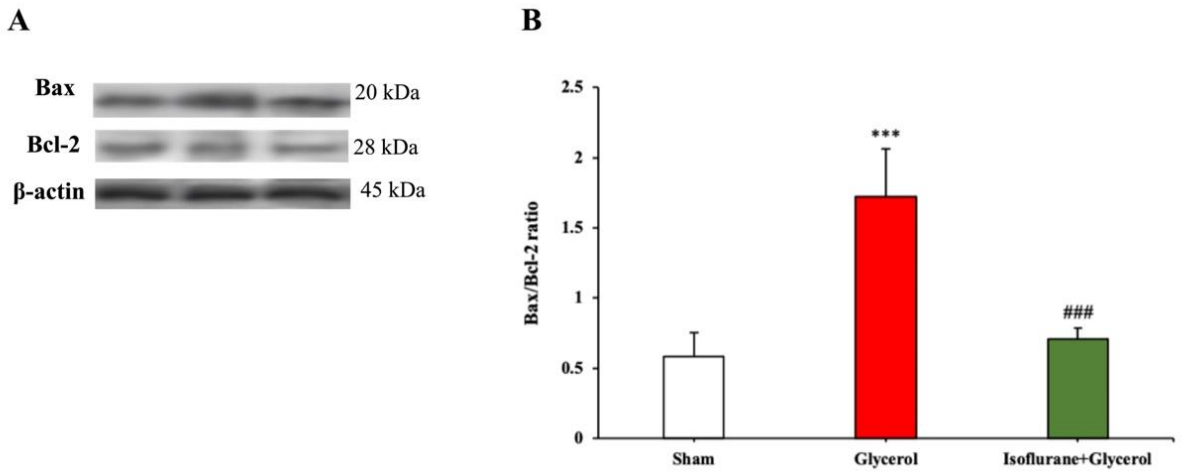

FIGURE 3. Evaluation of renal tissues oxidative stress after glycerol or isoflurane+glycerol treatment. (A) Western blot results showing Bax and Bcl-2 protein bands. (B) Evaluation of Bax/Bcl-2 ratio. Each column represents the Mean±SEM (n=6). *** indicates a significant difference vs. sham with $P<0.001$, ### indicates a significant difference vs. glycerol with $P<0.001$.

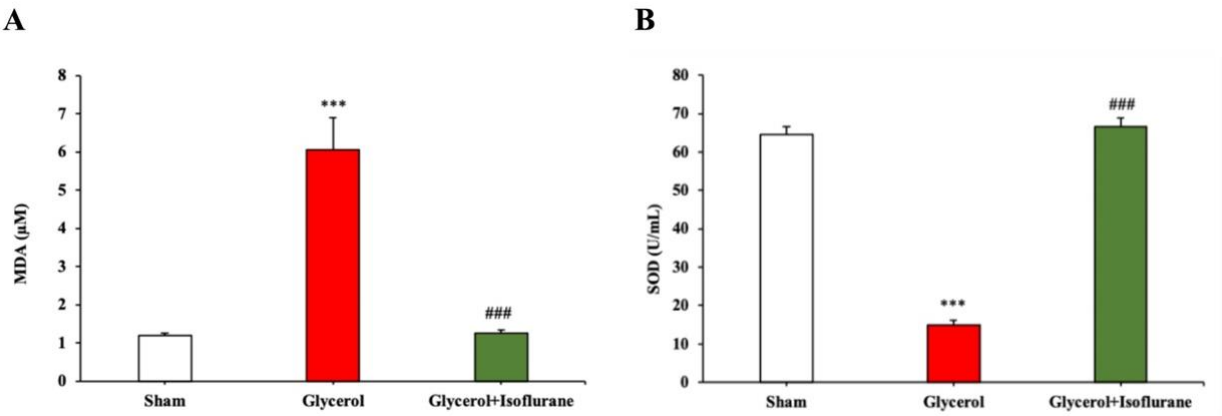

FIGURE 4. Evaluation of renal tissue oxidative stress after glycerol or isoflurane+glycerol treatment. (A) MDA levels. (B) SOD levels. Each column represents the Mean±SEM (n=6). *** indicates a significant difference vs. sham with $P<0.001$, ### indicates a significant difference vs. glycerol with $P<0.001$.

the glycerol 5 group compared to the sham group. However, the Cr level of the glycerol 6.25 group was significantly elevated compared to the sham group ($P<0.001$). similarly, the Cr level of the glycerol 10 group was significantly elevated compared to the sham group. Therefore, we chose the glycerol 6.25 group as the optimal glycerol-induced AKI model with fewer side effects in these rats.

Figure 2A shows that the BUN level of the isoflurane+glycerol group was significantly decreased compared to the glycerol group ($P<0.001$). Similarly, Figure 2B shows that the Cr level was significantly decreased in the isoflurane+glycerol group compared to the glycerol group ($P<0.001$).

Isoflurane pretreatment decreased the Bax/Bcl-2 ratio in glycerol-induced AKI model rats

Figure 3B shows that the renal Bax/Bcl-2 ratio in the glycerol group was significantly increased compared to the sham group ($P<0.001$). However, the Bax/Bcl-2 ratio in the isoflurane+glycerol group was significantly decreased compared with the glycerol group ($P<0.001$).

Isoflurane pretreatment decreased oxidative stress in glycerol-induced AKI model rats

Figure 4A shows that the renal MDA level in the glycerol group was significantly elevated compared to the sham group ($P<0.001$). Conversely, the renal MDA level in the isoflurane+glycerol group was significantly decreased compared to the glycerol group ($P<0.001$).

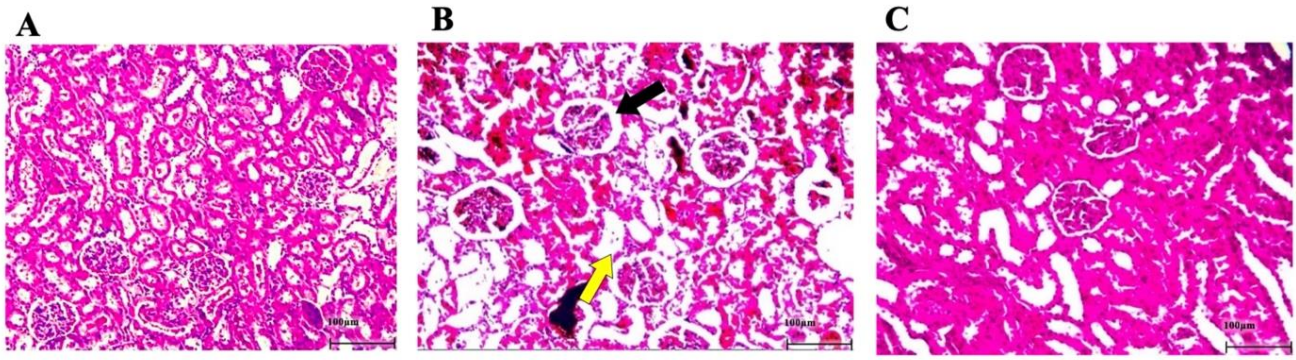

FIGURE 5. Histological evaluations of renal tissues by H&E staining (magnification, ×400; scale bar, 100 μm). (A) Sham group. (B) Glycerol group. Black arrow indicates an increase in the space of Bowman's capsule. Yellow arrow indicates tubular dilatation. (C) Glycerol+isoflurane group.

Additionally, Figure 4B shows that the renal SOD level in the glycerol group was significantly decreased compared to the sham group (P<0.001). However, the renal SOD level in the isoflurane+glycerol group was elevated compared to the glycerol group (P<0.001).

Isoflurane pretreatment decreased renal injury in glycerol-induced AKI model rats

The kidney sections of sham model rats (Figure 5A) demonstrated a normal structure of renal tissue with healthy epithelial cells in renal tubules and no notable pathological changes observed. Conversely, the kidney sections of the glycerol group (Figure 5B) showed an increase in the space of Bowman's capsule, a decrease in the diameter of epithelial cells, tubular dilatation, brush border elimination, and cast precipitation in the tubules compared to the sham group. However, the kidney sections of the isoflurane+glycerol group (Figure 5C) indicated a notable reduction in histological changes, including a decrease in the diameter of renal tubular cells and an increase in the space of Bowman's capsule compared to the glycerol group.

Discussion

Glycerol intramuscular injection induces skeletal muscle destruction, leading to the release of muscular enzymes and myoglobin precipitation in the bloodstream, ultimately resulting in tubular obstruction which is similar to clinical rhabdomyolysis-induced AKI (Sharawy et al., 2018). In this study, we first studied the effects of three different doses of glycerol (5, 6.25, and 10 mL/kg) to determine the most effective and least harmful model for AKI induction. BUN and Cr levels, two kidney functional indicators, increase when the kidneys fail to filtrate urea and creatinine adequately (Li et al., 2017). Injection of 6.25 mL/kg glycerol resulted in significant increases in BUN and Cr levels compared with the sham group, leading us to select 6.25 mL/kg as the optimal dosage. The results of our study demonstrated that isoflurane pretreatment administered 20 minutes before glycerol injection significantly attenuated the rise in AKI-induced BUN and Cr levels, similar to its effects in preventing AKI induced by ischemia/reperfusion (Liang et al., 2014; Qin et al., 2014).

Epithelial cell mitochondrial apoptosis mediated by Bax/Bak plays a key role in the pathogenesis of glycerol-induced AKI (Abd-Ellatif et al., 2019). The significant increase in renal Bax levels in the glycerol group indicates a shift of Bcl-2 family proteins toward apoptosis. Kim et al., showed that glycerol injection increases apoptotic cells by activating the Bcl-2 proapoptotic family (Kim et al., 2010). This study showed that isoflurane pretreatment alleviated glycerol-induced AKI by regulating apoptotic cell death (Liang et al., 2014). Isoflurane pretreatment probably inhibits renal cell death by upregulating antiapoptotic Bcl-2 expression (Kim et al., 2010).

MDA and SOD levels serve as markers of oxidative stress in the kidneys. Our investigation demonstrated that isoflurane pretreatment 20 minutes before glycerol injection resulted in a notable reduction in MDA levels and a significant increase in SOD enzyme activity in the kidneys compared to the glycerol group. This indicates that isoflurane may protect kidney tissues by preventing

lipid peroxidation.

As previously mentioned, glycerol intramuscular injection causes extensive muscular damage. Then heme molecules with pro-inflammatory effects on renal tubular cells are released from myoglobin. Exposure of endothelial and epithelial tubular cells to heme molecules results in the release of inflammatory mediators (Panizo et al., 2015). As macrophages and cytokines are increased, severe structural and functional disorders take place in kidneys, which if not resolved might contribute to renal death (Wen et al., 2011). Dilation of renal tubular lumens and a decrease in the thickness of epithelial cells, along with brush border elimination, may occur. Isoflurane pretreatment considerably prevented tubular damage, and it seems that isoflurane controls inflammation by down-regulating inflammatory cytokines (Liang et al., 2014).

In conclusion, this study demonstrates that 1.5% isoflurane pretreatment administered 20 minutes before glycerol injection confers protective effects against AKI in male rats by preventing apoptosis in the kidneys. This strategy reduces oxidative stress, balances the Bax/Bcl-2 ratio, decreases MDA levels, increases SOD activity, attenuates histological changes, and maintains renal function.

Acknowledgments

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Conflict of interest

There are no competing interests to declare.

Ethics approval

All animal caring and experimental procedures were carried out in accordance with the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran which is in accordance with international guidelines for animal experiments (Approval ID: IR.TUMS.MEDICINE.REC.1400.818).

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