Effect of Desloratadine on Oxidative and Inflammatory Ovarian Ischemia-Reperfusion Injury in Female Rats

Biochemical and Histopathological Evaluation

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OBJECTIVE: To examine the effect of desloratadine on ovarian ischemia-reperfusion (I/R) injury in rats by biochemical and histopathological methods.
STUDY DESIGN: I/R was induced in the right ovaries after distilled water was given to a group of female albino Wistar rats in this study. 15 mg/kg desloratadine was orally administered to another group and I/R was induced in their ovaries, whereas I/R was not induced in the sham operation group. After 2 hours of ischemia and 2 hours of reperfusion, malondialdehyde (MDA), total glutathione (tGSH), nuclear factor–κB (NF-κB), interleukin 1 beta (IL-1β), and tumor necrosis factor alpha (TNF-α) levels were measured in ovarian tissues extracted from the body of the animals sacrificed with a high dose of ketamine (120 mg/kg). Tissues were also evaluated histopathologically.
RESULTS: It has been revealed that desloratadine significantly inhibited the increase of I/R-associated MDA, NF-κB, IL-1β, and TNF-α levels in the ovarian tissues of animals and the decrease in tGSH levels. In addition, desloratadine decreased severe I/R-associated histopathological damage.
CONCLUSION: Our experimental results have shown that desloratadine is beneficial in terms of protecting ovarian tissue against I/R injury. (Anal Quant Cytopathol Histpathol 2020;42:61–68)

Keywords: desloratadine, ischemia, ischemia-reperfusion injury, ovarian, ovary, rat, reperfusion.

Ischemia is the decrease of absence of blood flow to the tissues for various reasons.[1] Unless reperfusion of ischemic tissue is achieved, irreversible damage develops in the cells and tissues.[2] Therefore, the first intervention to ischemic tissue is to ensure reperfusion. However, abundant molec-

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ular oxygen (O_2) supplied with the blood reacts with xanthine oxidase (XO), which accumulates in ischemic tissue and initiates the conversion of hypoxanthine to xanthine in reperfusion. It causes an increase in the production of reactive oxygen species (ROS) and a decrease in antioxidant defense mechanisms.[3] The elevation in ROS increases the production of nuclear factor–κB (NF-κB), a proinflammatory cytokine.[4] NF-κBs have been shown to induce the secretion of proinflammatory interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α), and other inflammation mediators.[5] As is known, in addition to oxidants, proinflammatory cytokines such as IL-1β, TNF-α, and NF-κB have also been reported to play a significant role in the pathogenesis of ischemia-reperfusion (I/R) injury.[6,7] Ovarian I/R injury occurs in the clinic after the detorsion procedure is performed in order to ensure reperfusion in torsioned ovaries. Ovarian torsion, which is the most common gynecological emergency, has a prevalence of 2.7%.[8] Delays in the diagnosis and treatment of ovarian torsion have been reported to result in severe ovarian damage and infertility.[9] In clinical practice the treatment strategy of torsioned ovaries is to preserve ovarian function with detorsion as soon as possible rather than ovariectomy. However, as stated above, reperfusion of torsion-induced ischemia by detorsion leads to exacerbation of oxidative and inflammatory events in the ovarian tissue. Therefore, studies on the pathogenesis of I/R injury and its treatment are still undertaken in the attempt to minimize torsion-detorsion damage. Desloratadine, which will be examined in this study for its protective effect against ovarian I/R injury, is a potent, non-sedating H1 histamine receptor antagonist indicated for symptomatic relief of urticaria and allergic rhinitis.[10] Roumestan et al have shown that desloratadine inhibits NF-κB production.[11] Moreover, Wu et al have argued that desloratadine inhibits both basal and histamine-induced NF-κB.[12] In subsequent studies, it has been reported that desloratadine antagonizes the increase of malondialdehyde (MDA), the production of lipid peroxidation, and the decrease of endogenous antioxidant glutathione (GSH) in the allergy model.[13] This information suggests that desloratadine can protect ovarian tissue from I/R injury. There is no study in the literature investigating the protective effect of desloratadine against ovarian I/R injury. In addition, there are no studies in the literature investigating the effects of desloratadine on proinflammatory cytokines such as IL-1β, TNF-α, and NF-κB, which play a role in the pathogenesis of I/R-related ovarian damage. Again, it has been observed that the protective effect of desloratadine against oxidative stress due to MDA increase and tGSH decrease in ovarian tissue during I/R has not been investigated. Therefore, the aim of this study is to investigate the effect of desloratadine on proinflammatory cytokines such as IL-1β, TNF-α, and NF-κB and oxidant/antioxidant parameters on ovarian I/R injury and to examine the histopathological effect on ovarian tissue.

Materials and Methods

Animals

Thirty female albino Wistar rats (6 months old) weighing between 265–278 g were used in this study. The animals were obtained from Ataturk University Medical Experimental Application and Research Center. The animals were kept (7 days) in the laboratory of the Department of Pharmacology at normal room temperature (22°C) and were fed with standard feed to adapt them to the study environment. During this time, the rats had 24-hour/day access to normal animal feed and tap water. The female rats that were to be used in the experiment were separated from male rats shortly after they were weaned. The protocols and procedures were approved by the local Animal Experimentation Ethics Committee (date June 27, 2019, meeting no. 7).

Chemicals and Experimental Design

The Ketamine used in the experiment was obtained from Pfizer Inc. (Turkey), and the desloratadine was obtained from Sanofi Ilac ve Sanayi Ticaret–Turkey. Female rats were divided into three groups: (1) OIR group (rats with induced ovarian I/R), (2) OIRD group (rats with induced ovarian I/R and treated with 15 mg/kg desloratadine, and (3) sham group.

Surgical Procedures

Desloratadine (5 mg/kg) was administered via oral gavage in the OIRD group before I/R was induced in rat ovaries. Different commercial forms and doses of desloratadine have been used in previous experimental studies.[14,15] OIR and sham group rats were treated with an equal volume of distilled water used as solvent. After ad-

ministration of desloratadine and distilled water, all rats were anesthetized with 60 mg/kg IP ketamine. During this period, the lower part of the abdomen was opened vertically at a length of 2–2.5 cm, and the ovaries were reached. Then, vascular clips were applied to the lower part of the right ovary (the region where the ovary was connected to the uterus) of the OIRD and OIR rats for 2 hours to induce ischemia. This procedure was followed by 2 hours of reperfusion.[16] The reason for choosing the right ovary in our study was that adnexial torsion is more common on the right side (66%) than on the left side in clinic.[17] The reason for our application of 2 hours of ischemia and 2 hours of reperfusion was that oxidant and proinflammatory parameters were significantly increased in the ovarian tissue during this period, and it has been observed that serious oxidative and inflammatory damage developed in the ovarian tissue.[18] The ovaries of the sham group were closed without ischemia. After reperfusion, all animals were sacrificed with a high dose of anesthesia. The right ovaries of the sacrificed rats were removed, and biochemical and histopathological examinations were performed in the ovarian tissue. The results obtained from the OIRD and sham groups were compared with those obtained from the OIR group.

Biochemical Operations

MDA Assessment. The method used by Ohkawa et al was taken as the basis for MDA assessment.[19] This method is based on the spectrophotometric assessment of the absorption of the pink complex created by thiobarbituric acid (TBA) and MDA at high temperature (95°C) at 532 nm wavelength. Homogenates were centrifuged for 20 minutes at 5,000 g, and these supernatants were used in the determination of the amount of MDA. 250 µL homogenates, 100 µL 8% sodium dodecyl sulfate (SDS), 750 µL 20% acetic acid, 750 µL 0.08% TBA, and 150 µL distilled water were vortexed into capped test tubes through a pipette. The mixture was incubated for 60 minutes at 100°C. 2.5 mL n-butanol was added to the mixture, and then spectrophotometric analysis was performed. The amounts of resultant red color were measured using 3 mL cuvettes at 532 nm. MDA amounts of the samples were determined by using the standard graphics formed with the MDA stock solution, which was previously prepared considering the dilution coefficients.

tGSH Assessment. The DTNB [5,5′-Dithiobis (2-nitrobenzoic acid)] in the assessment environment is a disulfide chromogen and is easily reduced by sulfhydryl group compounds. The resultant yellow color was spectrophotometrically assessed at 412 nm.[20] Homogenates were centrifuged for 10 minutes at 12,000 g, and the supernatants were used in the determination of the amount of MDA. 250 µL measuring buffer (200 mM Tris-HCl, pH=8.2 involving 0.2 mM EDTA), 500 µL supernatant, 100 µL 5,5′-Dithio-bis (2-nitrobenzoic acid) (DTNB), and 7,900 µL methanol were vortexed into capped test tubes through a pipette. The mixture was incubated for 30 minutes at 37°C, and then spectrophotometric analysis was conducted. The amounts of resultant yellow color were measured using 3 mL quartz cuvettes at 412 nm. GSH amounts of the samples were determined by using the standard graphics formed with the GSH stock solution, which was previously prepared considering the dilution coefficients.

NF-κB, TNF-α, and IL-1β Analysis. Tissue homogenate NF-κB and TNF-α concentrations were measured using rat-specific sandwich enzyme-linked immunosorbent assay. Rat NF-κB ELISA immunoassay kits (Cat. No. 201-11-0288, SunRed) and Rat TNF-α and Rat IL-1β ELISA kits (Cat No. YHB1098Ra, Shanghai LZ) were used. Analyses were performed according to the manufacturers' instructions. Briefly, monoclonal antibody specific for rat NF-κB, TNF-α, and IL-1β were coated onto the wells of the micro plates. The tissue homogenate, standards and biotinylated monoclonal antibody specific and streptavidin-HRP were pipetted into these wells and then incubated at 37°C for 60 minutes. After washing, chromogen reagent A and chromogen reagent B were added, which is acted upon by the bound enzyme to produce a color. It was incubated at 37°C for 10 minutes. Then stop solution was added. The intensity of this colored product is directly proportional to the concentration of rat NF-κB, TNF-α, and IL-1β present in the original specimen. At the end of the course, the well plates were read at 450 nm. The absorbance of the samples was calculated with formulas that used standard graphics.

Histopathological Examination

All of the tissue samples were first identified in a 10% formaldehyde solution for light microscope assessment. Following the identification process,

tissue samples were washed under tap water in cassettes for 24 hours. Samples were then treated with conventional grade of alcohol (70%, 80%, 90%, and 100%) to remove the water within tissues. Tissues were then passed through xylol and embedded in paraffin. Four-to-five micron sections were cut from the paraffin blocks, and hematoxylin-eosin staining was administered. Their photos were taken following the Olympus DP2-SAL firmware program (Olympus Inc., Tokyo, Japan) assessment. Histopathological assessment was carried out by the pathologist blind for the study groups.

Results

Biochemical Findings

MDA and tGSH Analysis Results. As can be seen in Figure 1, the amount of MDA in ovarian tissue of the ovarian I/R group was 16.6±1 µmol/g protein, while the amount of tGSH was 7.6±0.2 nmol/g protein. In the group treated with desloratadine, the amount of MDA is 7.6±0.2 µmol/g protein, while the amount of tGSH is 21±1.1 nmol/g protein. The MDA value of the sham group was 5.8±0.3 µmol/g protein; tGSH was recorded as 26.5±0.8 nmol/g protein. MDA production significantly increased in the kidney tissue of animals treated with I/R as compared to the sham group and the desloratadine-treated OIRD group ($p < 0.0001$). The difference in MDA levels between the desloratadine and sham groups was statistically insignificant ($p > 0.05$). In addition, the I/R procedure caused a decrease in tGSH in the kidney tissue. tGSH levels in the sham and desloratadine groups were significantly higher as compared to the I/R group ($p < 0.001$) (Figure 1).

NF-κB, IL-1β, and TNF-α Analysis Results. The measurements of NF-κB in ovarian tissue of the ovarian I/R group was 8.8±0.2, of the desloratadine-treated group was 2±1.8, and of the sham group was 1.6±1.1 ng/mL. The amounts of IL-1β were 11.6±0.7, 3.5±2, and 2.8±0.2 pg/mL. TNF-α levels were 9.2±0.2, 3.3±0.2, and 2.4±0.1 pg/mL, respectively. I/R significantly increased NF-κB, IL-1β, and TNF-α levels in ovarian tissue as compared to in the sham and desloratadine-treated groups ($p < 0.0001$). The difference in NF-κB, IL-1β, and TNF-α levels between the sham and desloratadine-treated groups was statistically insignificant ($p > 0.05$) (Figure 2).

Histopathological Findings

In Figure 3, no pathological findings were found in ovarian tissue of the sham group that underwent sham operation. In addition, ovarian tissue consisted of developing follicle structures and corpus luteum. However, diffuse congestion and hemorrhage were observed in ovarian tissue in the OIR group treated with I/R procedure. Sporadic fluid accumulation and inflammatory cell clusters/infiltrates were also observed in the subcapsular area, and necrotic changes were observed in the parenchyma, stroma, and follicle structures (Figure 4). In the OIRD group treated with desloratadine, congestion in ovarian tissue decreased as compared to in the OIR group. How-

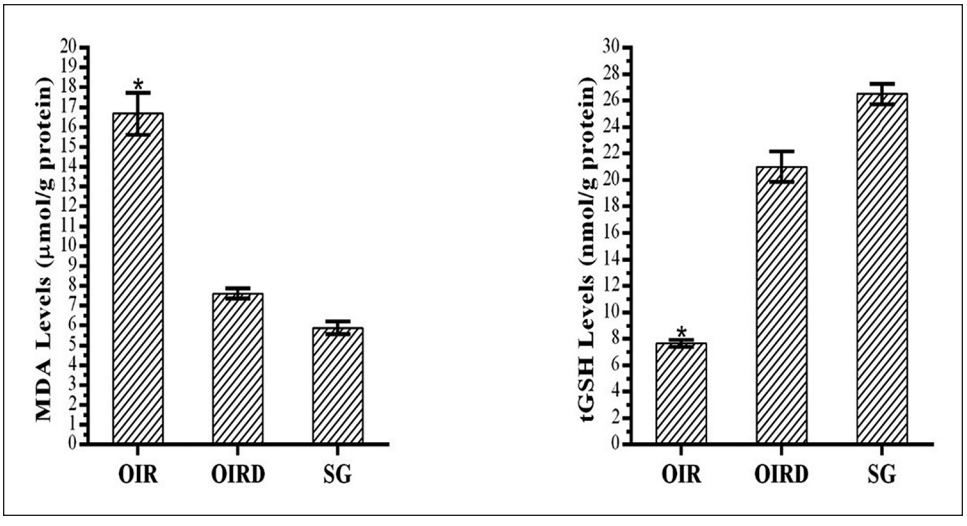


Figure 1
The levels of MDA and tGSH in the ovarian tissue of the study groups. *$p < 0.001$ according to OIRD and sham (SG) groups.

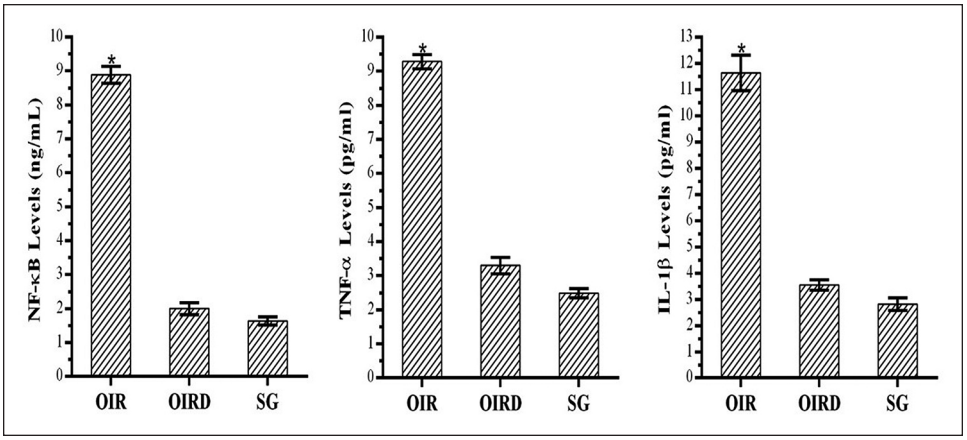


Figure 2
The levels of NF-κB, TNF-α, and IL-1β in the ovarian tissue of the study groups. *p<0.0001 according to OIRD and sham (SG) groups.

ever, severe hemorrhage observed in the OIR group was not seen in the desloratadine group. Furthermore, fluid accumulation in the subcapsular area and inflammatory cell infiltration were not observed in the desloratadine group. A reduction in necrotic changes in the parenchymal stroma, follicle structure, and corpus luteum was reported (Figure 5).

Discussion

The effect of desloratadine on ovarian I/R damage in animals was examined biochemically and histopathologically in this study. Understanding the biochemical mechanisms of a tissue and I/R injury are very important in terms of developing new treatment options to reduce tissue damage in clinical practice.[21] Biochemical studies have shown that ROS such as superoxide anion (O^-_2), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH) have a significant role in the pathogenesis of I/R injury.[22] ROS initiate lipid peroxidation (LPO), which causes cellular damage.[23] The best known of the various aldehydes resulting from LPO is MDA. MDA causes crosslinking and polymerization of membrane components. In addition, MDA causes serious cellular damage by inactivating membrane receptors, enzymes, and proteins.[23,24] The amount of MDA in ovarian tissue of animals treated with desloratadine was found to be significantly lower than that of the I/R and control groups. These findings indicate that desloratadine significantly suppresses I/R-related LPO reaction in ovarian tissue. A previous study has also reported that desloratadine inhibited MDA produc-

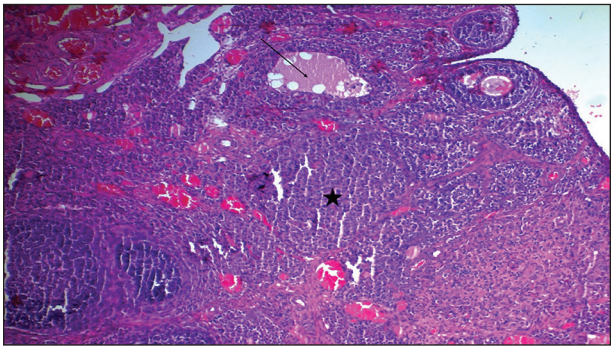


Figure 3 Cross section of normal corpus luteum (star) and normal developing follicular structures (arrows) in ovarian tissue of the sham group (H&E stain, ×100).

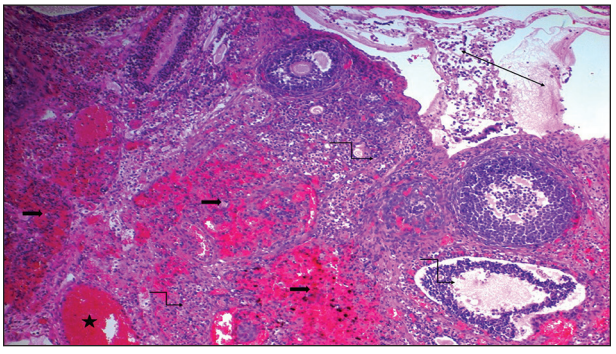


Figure 4 Ovarian tissue section showing diffuse congestion (star), hemorrhage (block arrows), subcapsular fluid accumulation and inflammatory cell infiltration (bidirectional arrow), and necrotic changes (zigzag arrows) in ovarian tissue of I/R-treated OIR animals (H&E stain, ×100).

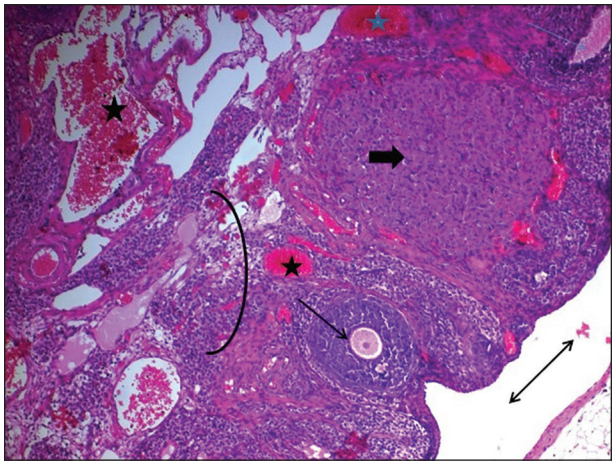


Figure 5 Ovarian tissue section showing mild congestion (star), subcapsular area with no fluid accumulation and inflammatory cell infiltrate (bidirectional arrow), and mild necrotic changes in parenchymal stroma (black arc) and in follicular structures (arrow) and corpus luteum (block arrow) in ovarian tissue of desloratadine-treated OIRD group (H&E stain, ×100).

tion.[13] Sadowska-Woda et al noted that desloratadine inhibited oxidative stress by inhibiting the production of MDA in vitro.[25] Living organisms develop numerous antioxidant mechanisms against the harmful effects of ROS. These mechanisms inhibit ROS production and eliminate the harmful effects of ROS. GSH is one of the most important and well-known antioxidant mechanisms in living tissues. GSH, which is a cellular tripeptide consisting of L-glutamate, L-cysteine, and glycine,[26] reacts with H_2O_2 and organic peroxides to chemically detoxify H_2O_2 and protects cells from ROS damage.[1] All this information indicates that there is an increase in ROS production in ovarian tissue treated with I/R. In many studies it has been shown that the tGSH level decreases in tissues with high oxidant levels.[18,27,28] In our study, desloratadine prevented the I/R-dependent reduction of tGSH in ovarian tissue. This has suggested that desloratadine inhibits ROS-associated tGSH depletion in ovarian tissue. Relevant data have also been found in the literature showing that desloratadine inhibits tGSH consumption due to oxidative stress.[13] Furthermore, data have shown that desloratadine suppresses ROS production.[29] Another study has shown that desloratadine exhibits antioxidant activity.[30] These findings indicate that our experimental results are consistent with the results of previous studies.

Proinflammatory cytokines such as IL-1β, TNF-α, and NF-κB are known to play a role in the pathogenesis of tissue I/R injury.[6,7] Gene transcription of a few proinflammatory cytokine signaling pathways is controlled by NF-κB.[31] In addition, secretion of IL-1β and TNF-α can be stimulated by NF-κB.[5] Therefore, NF-κB is known as a transcription factor for the expression of a series of proinflammatory cytokines that play a critical role in the regulation of inflammatory and immune responses.[32] Inhibition of NF-κB activation was shown to reduce TNF-α, IL-6, and IL-1β mRNA levels.[33] The levels of IL-1β, TNF-α, and NF-κB increased in the I/R-treated ovarian tissue as compared to that of the desloratadine and sham groups in our study. These results indicate that desloratadine exerts both antioxidant and anti-inflammatory effects in ovarian tissue. Roumestan et al also argue that desloratadine inhibits NF-κB production.[11] Inhibition of both basal and induced NF-κB by desloratadine[12] has noted that it is an NF-κB inhibitor. In their study, Chen et al stated that the strong antiallergic and anti-inflammatory properties of desloratadine are due to the blockage of the NF-κB pathway.[34] Severe histopathological symptoms such as diffuse congestion and hemorrhage, sporadic accumulation of fluid in the subcapsular area, inflammatory cell infiltration, and necrosis in parenchymal stroma and follicular structures were found in I/R-treated ovarian tissue, where oxidant and proinflammatory cytokines showed a significant increase. However, histopathological findings were much milder in the desloratadine group, where oxidant and cytokine levels were low. Congestion and hemorrhage are common histopathologic symptoms in ovarian I/R injury. Turkler et al showed that marked congestion and hemorrhage developed in I/R-treated ovarian tissue with increased oxidant and proinflammatory parameters.[16] Unlubilgin et al reported that in addition to congestion and hemorrhage, an I/R event caused inflammatory cell accumulation and necrosis in ovarian tissue.[18] In a study by Demiryilmaz et al, histopathological findings similar to the results of our study were found in I/R-associated oxidative ovarian injury.[35] Soyman et al also reported the development of some serious histopathological changes (follicular degeneration, perinuclear edema and degeneration in follicular granulosa cells and corpus luteum cells), with the exception of congestion and hemorrhage in I/R procedure in ovarian tissue.[36]

In conclusion, I/R procedure increased oxidative stress and the levels of proinflammatory markers in ovarian tissue in a rat model. Severe histopathological damage was found in the ovarian tissue where oxidant and proinflammatory markers were increased. Desloratadine was found to suppress the elevation in I/R-associated oxidant and proinflammatory cytokine levels in ovarian tissue and alleviate histopathological damage. This suggests that desloratadine may be beneficial in the treatment of ovarian I/R injury.

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