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The amelioration of testicular ischemia-reperfusion injury in rats by oxymatrine

Мелиорација оштећења исхемије и реперфузије тестиса код пацова оксиматрином

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SUMMARY

Introduction/Objective A crucial factor in testicular damage is the surplus of reactive oxygen species that arises from ischemia-reperfusion. Elevated levels of reactive oxygen species cause critical harm to cells. The present research focused on investigating the role of oxymatrine with antioxidative property in testicular ischemia-reperfusion injury induced by torsion and detorsion in a rat model.

Methods The study utilized a total of sixty rats, which were randomly assigned to one of three groups: a sham group with 20 rats, a testicular ischemia-reperfusion group with 20 rats, and a testicular ischemia-reperfusion group treated with oxymatrine, also consisting of 20 animals. Induction of testicular ischemia-reperfusion involved applying two hours of ischemia via 720-degree counterclockwise torsion to the left testis, with subsequent reperfusion initiated by detorsion. The activity of neutrophil nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, a catalyst for reactive oxygen species production, the concentration of a prevalent reactive oxygen species indicator malondialdehyde, and spermatogenesis were all detected in left testicular tissues collected at the 4 hours or 3 months post-detorsion.

Results Testicular ischemia-reperfusion notably elevated NADPH oxidase activity and malondialdehyde content, while it adversely affected spermatogenesis in the testes ($p < 0.001$). Conversely, the administration of oxymatrine significantly lowered both NADPH oxidase activity and malondialdehyde concentration, and it also improved spermatogenic function in the testes ($p < 0.001$).

Conclusion We found that oxymatrine attenuates injury from testicular ischemia-reperfusion, and this effect operates by limiting reactive oxygen species production through NADPH oxidase activity inhibition.

Keywords: oxymatrine; testicular torsion; ischemia-reperfusion

САЖЕТАК

Увод/Циљ Кључни фактор оштећења тестиса је вишак реактивних врста кисеоника који настају исхемијом-реперфузијом. Повишени нивои реактивних врста кисеоника наносе критичну штету ћелијама. Ово истраживање се фокусирало на истраживање улоге оксиматрина са антиоксидативним својством у исхемијско-реперфузијској повреди тестиса изазваној торзијом и деторзијом у моделу пацова.

Методе Студија је користила укупно 60 пацова, који су насумично додељени једној од три групе: лажна група са 20 пацова, група исхемије-реперфузије тестиса са 20 пацова и група исхемије-реперфузије тестиса третирана оксиматрином, која се такође састоји од 20 животиња. Индукција исхемије-реперфузије тестиса укључивала је примену два сата исхемије путем торзије 720 степени у смеру супротном од казаљке на сату на леви тестис, а накнадна реперфузија покренута деторзијом. Активност неутрофилне никотинамиде аденин динуклеотид фосфата (НАДПХ) оксидазе, катализатора за производњу реактивних врста кисеоника, концентрација преовлађујућег малондиалдехида показатеља реактивних врста кисеоника и сперматогенеза откривени су у ткивима левог тестиса прикупљеним у 4 сата или 3 месеца после деторзије.

Резултати Тестикуларна исхемија-реперфузија значајно је повећала активност НАДПХ оксидазе и садржај малондиалдехида, док је негативно утицала на сперматогенезу у тестисима ($p < 0,001$). Супротно томе, примена оксиматрина значајно је смањила и активност НАДПХ оксидазе и концентрацију малондиалдехида, а такође је побољшала сперматогену функцију у тестисима ($p < 0,001$).

Закључак Открили смо да оксиматрин ублажава повреде исхемије-реперфузије тестиса, а овај ефекат делује ограничавањем производње реактивних врста кисеоника инхибицијом активности НАДПХ оксидазе.

Кључне речи: оксиматрин; торзија тестиса; исхемија-реперфузија

INTRODUCTION

The occurrence of testicular torsion spans all ages, yet it predominantly affects male infants and teenagers in the 12–18 age range, making it a standard emergency seen in urological practice [1]. Testicular torsion occurs when the spermatic cord becomes twisted, leading to a

partial or total interruption of blood supply to the testicle. Early detection and quick surgical untwisting must be performed to reinstate testicular blood flow and forestall ischemic necrosis. Although the twisted testicle is surgically untwisted, subsequent atrophy and loss of function afflict 13.5% to 68% of such cases [2]. Ischemia-reperfusion injury remains the most recognized cause of testicular damage subsequent to testicular torsion and its surgical relief [3]. A crucial factor in testicular damage is the surplus of reactive oxygen species that arises from ischemia-reperfusion [3]. Elevated levels of reactive oxygen species (e.g., hydroxyl radical, superoxide anion, hydrogen peroxide) cause critical harm to cells by oxidizing membrane lipids, altering protein structures, and breaking DNA strands [3].

As of now, patients have no access to clinically utilized drugs that can reduce testicular ischemia-reperfusion injury. Oxymatrine is a type of quinolizidine alkaloid mainly isolated from Sophora flavescens, a plant utilized in traditional Chinese herbal practice [4, 5, 6]. $C_{15}H_{24}N_2O_2$ represents its molecular formula, while its weight is calculated as 264.36 g/mol [7, 8]. The antioxidative and anti-inflammatory properties of oxymatrine are among the numerous bioactivities that have been identified through multiple investigations [9, 10, 11]. Studies further report that oxymatrine mitigates damage from ischemia-reperfusion in several areas: the lung, brain, intestine, kidney, and liver [12–17]. Despite this, research has not addressed the therapeutic effect of oxymatrine on testicular ischemia-reperfusion injury. The present research focused on investigating the role of oxymatrine in testicular ischemia-reperfusion injury induced by torsion and detorsion in a rat model.

METHODS

Study subjects

The animals in this study consisted of sixty male Sprague-Dawley rats weighing between 250 and 300 grams, sourced from SLAC company, located in Shanghai, China. Their housing consisted of an air-conditioned room with tightly regulated conditions: a temperature of 21°C, varying by no more than 1°C, a relative humidity of 55%, varying within 5%, and a standard 12-hour light followed by 12-hour dark schedule. Throughout the experiment, the rats could consume standard food and water at will.

Medicinal compound and experimental substances

Sigma-Aldrich (St. Louis, MO, USA) was the provider of ketamine, oxymatrine, hematoxylin, and eosin. The Jiancheng Bioengineering Institute (Nanjing, China) supplied the kits for analyzing nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and malondialdehyde. The remaining reagents utilized during the investigation were premium grade and sourced from the market.

Research plan

A random distribution was performed for 60 Sprague-Dawley rats among three groups, namely sham, testicular ischemia-reperfusion, and oxymatrine-treated groups, with 20 animals in each group. The rats received ketamine (50 mg/kg) intraperitoneally for anesthesia and were then positioned on the operating table. Sterility was maintained throughout all experimental manipulations. The left testis was retrieved by a left ilioinguinal surgical approach. To simulate

the surgical procedure, an 11-0 atraumatic silk suture was positioned within the tunica albuginea of animals belonging to the sham group [18]. The procedure concluded with the replacement of the testis into the scrotum and the suturing of the skin. Ischemia in the testicular ischemia-reperfusion model was produced through a 720-degree counterclockwise twist applied to the left testis [18]. An 11-0 silk suture was used to attach the torsioned testis to the scrotum, thereby preserving the ischemic state. At the conclusion of the two-hour interval, restoring the testis to its natural alignment through untwisting enabled reperfusion. In the experimental group receiving oxymatrine, a two-hour period of testicular ischemia preceded reperfusion, at which time a 40 mg/kg dose of oxymatrine was injected intraperitoneally. The justification for the oxymatrine dose employed originated from various prior studies [15, 16, 17]. The rats received nalbuphine (2 mg/kg) subcutaneously for postoperative analgesia. Reperfusion was conducted for four hours, after which 10 rats in each group underwent left orchiectomy with the goal of assessing NADPH oxidase activity and malondialdehyde concentration. The remaining ten animals in each group were subjected to left orchiectomy after three months of reperfusion, allowing for the measurement of testicular spermatogenesis. Once the experimental procedures ended, all animals received a terminal intraperitoneal dose of pentobarbital sodium (200 mg/kg) to ensure a painless death.

Testicular tissue analysis for NADPH oxidase activity

After being homogenized in lysis buffer kept on ice, the samples were centrifuged at 4°C and 10,000 × g for a duration of 10 minutes. To measure NADPH oxidase activity, the supernatant was harvested with care. Assessment of NADPH oxidase activity relied on a kit purchased from a commercial source.

Determining malondialdehyde concentration in tissue from the testis

On ice, testicular tissue underwent homogenization in a buffer designed for lysis with malondialdehyde. The supernatant intended for the malondialdehyde assay was acquired by centrifuging the tissue homogenate at 5000 g for a duration of 15 minutes under 4°C conditions. Measurement of malondialdehyde levels in testicular tissue was performed via the thiobarbituric acid reactive substance assay, following the protocol supplied with a commercial kit.

Evaluation of sperm production within the testicles

Parameters such as seminiferous tubule epithelial layer number, Johnsen score, testicular weight, and seminiferous tubular diameter served as indicators for assessing testicular spermatogenesis [19]. After excision, the testis was placed on a scale for weight measurement. Histopathological examination was facilitated by fixing part of the testis in Bouin's fluid, dehydrating it with increasing ethanol concentrations, and embedding it in paraffin. The paraffin block was sectioned on a rotary microtome to produce slices of 5 μm in thickness. Hematoxylin-eosin staining was applied to the sections once the routine processes of deparaffinization and hydration were complete. Light microscopic evaluation of the testicular sections was performed by an assessor who was not informed of their origin. The evaluation procedure consisted of selecting twenty seminiferous tubules with circular or near-circular profiles from each histological section and measuring their epithelial layer number, Johnsen score, and diameter. To assess the seminiferous tubule epithelial layers, counts were performed starting at the basement membrane and proceeding inward to the lumen. Histology of the seminiferous tubules was scored in accordance with Johnsen's system, which grades findings based on germinal epithelial maturation [20]. Seminiferous tubules were graded according to

Johnsen's criteria, with scores spanning 1 to 10 [20]. A score of 1 is assigned when the seminiferous tubule is entirely devoid of cells. The highest score of 10 is awarded for complete spermatogenesis accompanied by plentiful spermatozoa, a germinal epithelium of standard thickness, and a patent tubular lumen. Using a microscope that had an ocular micrometer, researcher estimated the diameter of the seminiferous tubules.

Statistical analysis

The GraphPad Prism 4.0 (San Diego, CA, USA) served as the tool for statistical analysis. Using the Shapiro-Wilk test, we confirmed that the data exhibited a normal distribution. The variance homogeneity was verified by Bartlett's test. Data from the experiments were summarized using means and standard deviations. For intergroup comparisons, we employed one-way analysis of variance and subsequently conducted the Student-Newman-Keuls multiple comparison test. A p-value lower than 0.05 indicated that the differences were statistically significant.

Ethics: The Zhejiang Shuren University Ethical Committee provided ethical approval for all study protocols, which bears the reference number 202309021. The research methods involving animals were designed and executed following universally accepted ethical rules.

RESULTS

NADPH oxidase activity observed in testes

The activity of NADPH oxidase in testes was significantly higher in the ischemia-reperfusion group than in the sham group, a result depicted in Figure 1 ($p < 0.001$). Following testicular ischemia-reperfusion, the observed upregulation of NADPH oxidase activity was significantly

decreased by oxymatrine treatment ($p < 0.001$).

Testicular tissue levels of malondialdehyde

Figure 2 illustrated a significant elevation in testicular malondialdehyde levels in the ischemia-reperfusion group ($p < 0.001$) relative to the sham-operated controls. Relative to animals subjected to ischemia-reperfusion, those receiving oxymatrine showed significantly ($p < 0.001$) reduced malondialdehyde levels in testicular tissue.

Evidence of spermatogenic activity in testicular tissue

Testicular ischemia-reperfusion injury led to marked declines ($p < 0.001$) in several histological and morphometric parameters, including number of epithelial layers within the tubules, Johnsen scoring, weight of the testes, and diameter of the seminiferous tubules, relative to sham controls (Figures 3 and 4). Oxymatrine-treated animals exhibited significantly ($p < 0.001$) better outcomes for all four testicular parameters compared to those subjected to ischemia-reperfusion injury.

DISCUSSION

In the population of males under 25 years old, testicular torsion arises at a rate of 1 per 4000 [2]. For the conservation of testicular fertility, early detection and prompt surgical correction of torsion are essential. Testicular infarction occurs if torsion of the testis continues beyond six hours [3]. Timely surgery within a five-hour window of symptom appearance fails to avert

testicular atrophy in 27% of affected individuals [21]. The testes in our investigation remained viable after undergoing torsion for two hours and then being surgically restored. Severe impairment of spermatogenesis was observed in the testis three months post-detorsion, a consequence of the initial torsion-detorsion event. Key indicators of this damage, detailed in Figures 3 and 4, included a significantly reduced epithelial layer count in seminiferous tubules, a lower Johnsen score, diminished testicular weight, and narrower seminiferous tubular diameters.

From a pathophysiological perspective, torsion and detorsion of the testis is a quintessential ischemia-reperfusion phenomenon. Reactive oxygen species are produced in excess during ischemia and reperfusion of the testis [22]. The oxidation of proteins, DNA, and membrane lipids by surplus reactive oxygen species is a mechanism capable of initiating cellular damage [3]. The extreme reactivity and fleeting existence of reactive oxygen species make them exceedingly difficult to quantify in a direct manner [18]. Malondialdehyde, produced steadily at the end of lipid peroxidation initiated by reactive oxygen species, is largely considered a sensitive sign of their presence and activity [19]. We report here that testicular malondialdehyde levels rose significantly while spermatogenesis was significantly suppressed following ischemia-reperfusion (Figures 2–4). The evidence points to overproduction of reactive oxygen species as the underlying cause of testicular ischemia-reperfusion injury. The study demonstrated that oxymatrine supplementation lowered malondialdehyde concentration while boosting testicular spermatogenesis (Figures 2–4). According to our results, the antioxidant capacity of oxymatrine underlies its ability to mitigate testicular ischemia-reperfusion injury. Furthermore, the safety and therapeutic effectiveness of oxymatrine have been confirmed in clinical settings for treating chronic hepatitis B, plaque psoriasis, and liver fibrosis from chronic viral hepatitis [23–27]. Therefore, the findings provide a foundation for the potential therapeutic application of oxymatrine in cases of testicular ischemia-reperfusion

insult. Yet, the pathways responsible for the decrease in reactive oxygen species induced by oxymatrine are still poorly characterized.

Infiltrating neutrophils represent a primary cause of excessive reactive oxygen species production in tissues undergoing ischemia-reperfusion [28]. In neutrophils, NADPH oxidase is a key contributor to the formation of reactive oxygen species [28]. Ischemia promotes calcium influx into neutrophils, which in turn activates NADPH oxidase [29]. The reperfusion phase is characterized by the restoration of oxygen to previously ischemic tissue. Superoxide anion is generated from oxygen through catalysis by activated NADPH oxidase [29]. Superoxide anions undergo a self-reaction to generate hydrogen peroxide [30]. The interaction of superoxide anion and hydrogen peroxide yields hydroxyl radical [19]. Thus, reactive oxygen species accumulate in greater amounts following ischemia and subsequent reperfusion. Testicular ischemia-reperfusion in this study produced substantial rises in NADPH oxidase activity and malondialdehyde content, coupled with a pronounced decrease in spermatogenesis within the testes, as illustrated in Figures 1–4. The study implies that spermatogenic injury arises from reactive oxygen species overproduction, which itself results from upregulated NADPH oxidase activity in neutrophils following testicular ischemia-reperfusion. Moreover, our results revealed that oxymatrine significantly suppressed NADPH oxidase activity and reduced malondialdehyde content, while effectively restoring spermatogenesis in testicular tissue (Figures 1–4). The data imply that decreased reactive oxygen species production achieved by inhibiting NADPH oxidase activity in neutrophils underlies the protective role of oxymatrine in testicular spermatogenesis.

Khorsand et al. [3] evaluated whether naringin, which is a flavanone glycoside possessing well-documented antioxidant, anti-inflammatory, and anti-apoptotic effects, could prevent testicular ischemia/reperfusion damage induced by torsion/detorsion in mice [3]. Compared to controls,

the torsion/detorsion animals exhibited a significant reduction in sperm quality based on concentration, motility, and kinematics, a depletion of antioxidant reserves such as superoxide dismutase, total antioxidant capacity, and glutathione peroxidase, a drop in hormones like follicle-stimulating hormone, testosterone, and luteinizing hormone, a rise in malondialdehyde and apoptosis signals Bax, Bcl-2, and caspase-3, and a loss of fertility. Naringin produced a dose-dependent improvement in sperm indices, antioxidant defense, testicular structure, endocrine parameters, and fertility, particularly when given at 100 or 200 mg/kg. At 50 mg/kg, the treatment exhibited weak effectiveness. Naringin exerted its apoptosis-inhibiting effect via the enhancement of Bcl-2 and the simultaneous reduction of Bax and caspase-3. These findings suggest that testicular ischemia/reperfusion injury is significantly alleviated by naringin, with the 100 to 200 mg/kg doses being especially effective. The comparison reveals that, aside from malondialdehyde and testicular histology, the experimental design of Khorsand et al. [3] was distinct from ours with respect to the other assessed variables and the therapeutic strategies. The next phase of this research will integrate measurements of the other assessed factors, and evaluate the relative potency of oxymatrine *vs*. naringin for treating testicular ischemia-reperfusion damage, identifying the optimal therapeutic candidate.

Several limitations within our research must be thoroughly explored by future studies. Firstly, the impact of unilateral testicular torsion on the contralateral testicle was left unexamined. Secondly, our research only used one oxymatrine dose and lacked dose-response evaluation. Thirdly, our study only used a single animal species and lacked molecular confirmation of the proposed mechanism (e.g., NADPH oxidase isoforms, inflammatory cytokines, antioxidant enzymes, Bax, Bcl-2, and caspase-3).

CONCLUSION

This study presents the first indication that the protection offered by oxymatrine against ischemia/reperfusion-induced testicular injury involves the inhibition of neutrophil NADPH oxidase activity, resulting in reduced generation of reactive oxygen species. According to the results, oxymatrine may function as a viable therapeutic option in cases of testicular torsion-detorsion. The potential clinical usefulness of oxymatrine awaits confirmation from trials conducted in humans.

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Conflict of interest: None declared.

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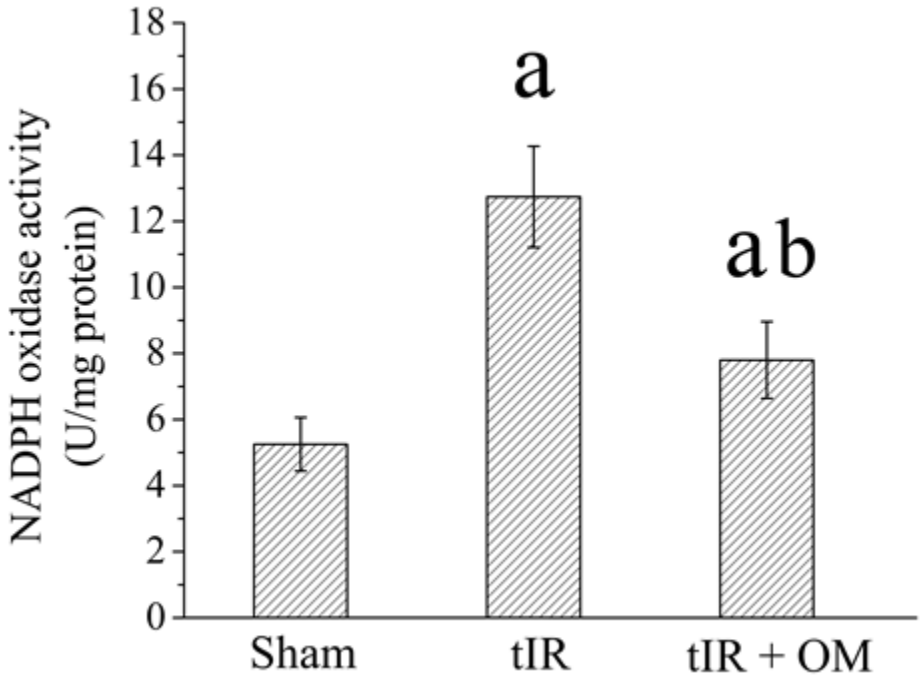

Figure 1. Testicular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity was analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment. Data (n = 10) from the experiments were summarized using means and standard deviations. a: with a p-value of less than 0.001 *vs*. the sham control; b: with a p-value of less than 0.001 *vs*. the tIR group

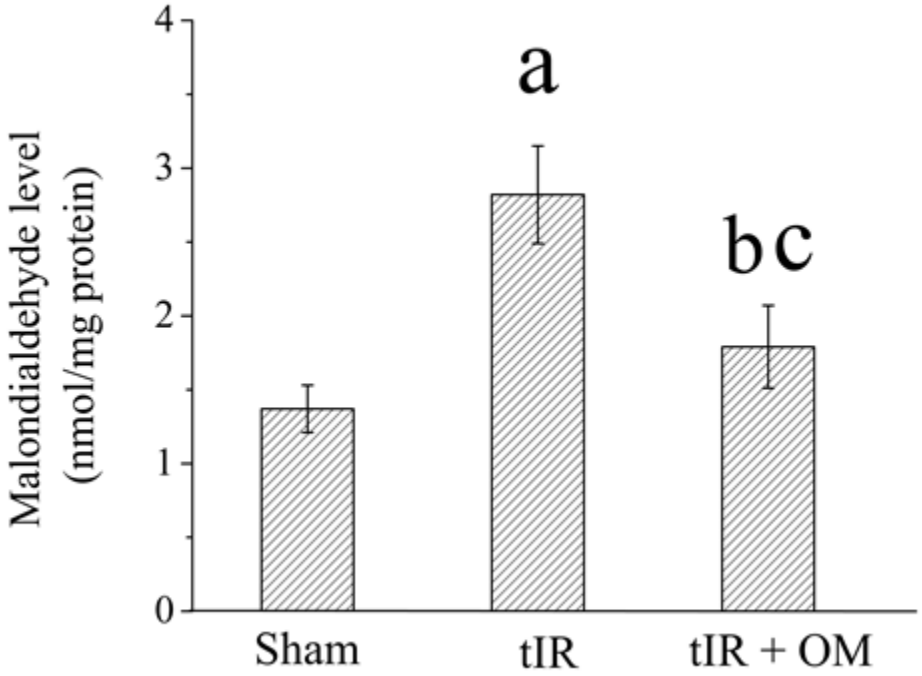

Figure 2. Testicular malondialdehyde level was analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment; data (n = 10) from the experiments were summarized using means and standard deviations; a: with a p-value of less than 0.001 *vs*. the sham control; b: with a p-value of less than 0.01 *vs*. the sham control; c: with a p-value of less than 0.001 *vs*. the tIR group

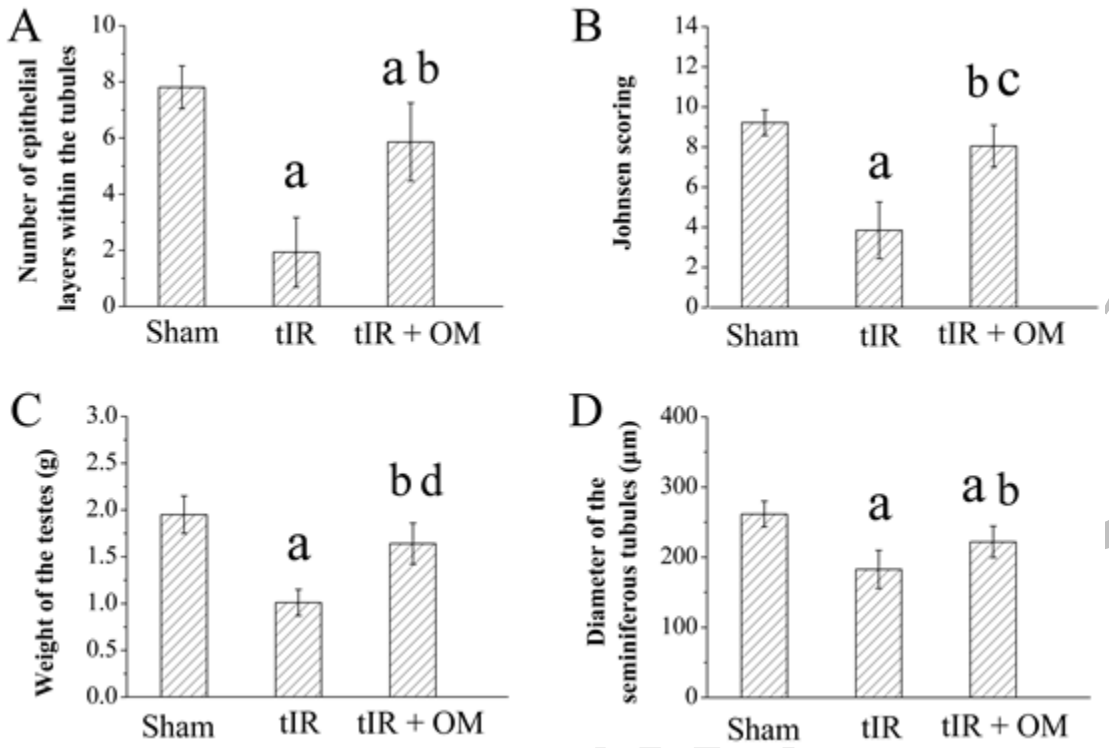

Figure 3. (A) – number of epithelial layers within the tubules; (B) – Johnsen scoring; (C) – weight of the testes; (D) – diameter of the seminiferous tubules were analyzed in the following conditions: sham operation, testicular ischemia-reperfusion (tIR), and oxymatrine (OM) treatment; data (n = 10) from the experiments were summarized using means and standard deviations; a: with a p-value of less than 0.001 *vs*. the sham control; b: with a p-value of less than 0.001 *vs*. the tIR group; c: with a p-value of less than 0.05 *vs*. the sham control; d: with a p-value of less than 0.01 *vs*. the sham control

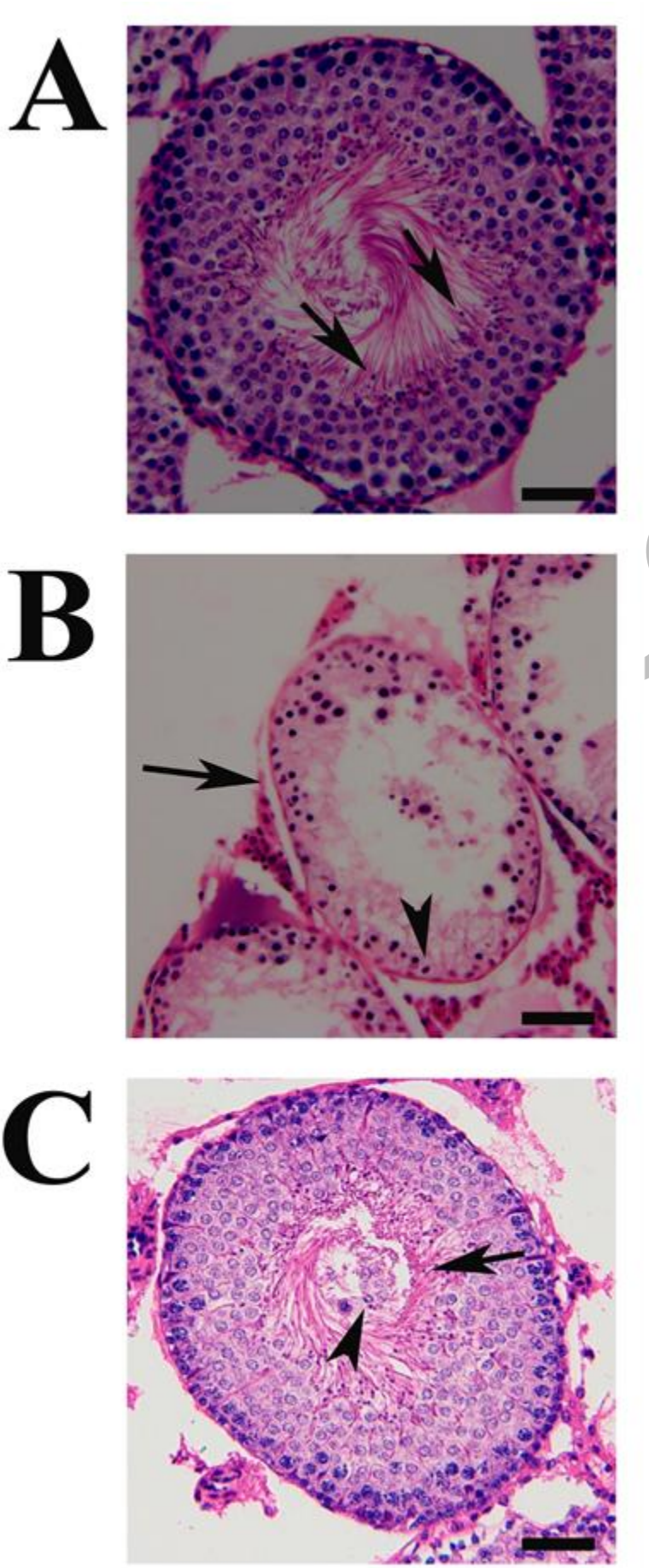

Figure 4. Testis tissue sections were illustrated for the three experimental conditions: sham operation, testicular ischemia-reperfusion, and oxymatrine treatment; at a magnification of × 200, testicular tissue sections underwent microscopic evaluation after being stained with hematoxylin-eosin; (A) – microscopic assessment of sham-operated testes indicated regular layering of the epithelium, full spermatogenic development ranging from early germ cells to spermatozoa (indicated by arrows), and standard tubular diameter; every seminiferous tubule contained a clearly open central lumen; (B) – the ischemia-reperfusion group presented with testicular structural anomalies: seminiferous tubules were atrophic (arrow), their epithelial layers were diminished (arrowhead), and germ cells showed maturation arrest (arrowhead); (C) – the gross morphology of the testes in the oxymatrine-treated group closely matched that of the sham group. Inside the tubules, researchers noted numerous mature sperm cells, which are pointed out with an arrow; an arrowhead indicates sloughed germinal cells within the tubular lumen, a condition that often led to blockage; 40 micrometers are the length represented by the scale bar

