IJVS 2017; 12(2); Serial No:27

IRANIAN JOURNAL OF VETERINARY SURGERY (IJVS)

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Original Article

Benidipine reduces ischemia/reperfusion injury following testicular torsion/detorsion in rats

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Abstract

Objective- This study aimed to determine the protective effects of benidipine on testicular injury after testis torsion/detorsion in rats.
Design-Experimental study
Animals-Fifteen male Sprague-Dawly rats weighing 200-220g
Procedure- Rats were randomly divided into 3 groups: sham (healthy group with sham operation, n=5), IRC group (control group in which I/R injury was performed by torsion the right testis 720 º clockwise for 2 hours and detorsion for 2 hours, n=5), and IRB group (IR + benidipine, I/R process was performed following orally benidipine administration + 4 mg/kg benidipine, n=5). Levels of glutathione peroxidase (GPx) and malondialdehyde (MDA) were determined in testicular tissues of rats. Testicular tissues were also examined histopathologically.
Results- The levels of MDA ($P<0.0001$) was significantly increased augmented in the testis of IRC group rat. Testicular GPx levels were significantly reduced ($p<0.0001$) after I/R. Administration of benidipine before torsion prevented the increase in lipid peroxidation and alleviated GPx levels. Benidipine also impeded ischemia/reperfusion cellular damage and histological alternations in testicular tissue.
Conclusion and clinical relevance- These results show that therapy with benidipine before torsion may induce protective effects against ischemia/reperfusion injury.
Key words- Benidipine, ischemic – reperfusion, testicular torsion, rat
Received: 4 September 2017; **Accepted:** 18 September 2017; **Online:**17 Febraury 2018

Introduction

Ischemia-reperfusion (I/R) injury is a detrimental clinical entity in the organism that takes place when blood circulation becomes normal after the occurrence of severe ischemia. In this kind of injury the blood circulation in the tissue is suspended and results in the damage to the tissues which are metabolically active. However, when the blood circulation becomes normal in the tissues, it causes paradoxical process of events, and eventually results in more cellular and tissue damage.[1]

These is increasing evidence that the oxidative stress (OS), which is related to the over-production of reactive oxygen specie (ROS), forms the fundamental pathological process of I/R injury.[1,2] In the clinical settings, testicular torsion (TT) is a typical I/R injury of the testicular tissue, which is a significant urologic exigency and the postponement in dealing with it, can result in infertility.[3] Although there is a lack of complete understanding regarding the major pathological mechanism of the testicular injury after

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DOI: 10.22034/ivsa.2017.97394.1128

TT, the I/R established during torsion and detorsion and OS generated by these events are regarded to be the main causes in the mecanisim. Even though there are many researches about the pathogenesis and therapy of the I/R damage in the related literature, its mechanism is not clearly understood. Many studies have shown the increased intracellular calcium ion concentration in ischemic tissues [4]. This kind of concentration results in the beginning of pathological incidents like apoptosis in the cells. These results show the beneficial effects of the antioxidative and anti-inflammatory drugs and those that prevent calcium canals before or after reperfusion in impeding the I/R damage and its complocations. [5,6,7] Benidipine, which is an L-type calcium channel blocking antihypertensive drug, was investigated in the present study against the I/R damage.[8,9] A number of studies have revealed that this drug decreases the antioxidatives and impedes the increase in the oxidative parameters in the heart tissue.[10] These results show that benidipine can be beneficial in the therapy for testicular I/R damage. There is a lack of information in the literature regarding the anti- oxidative effects of benidipine against I/R in the rat testicular tissues. Therefore, the present study aimed to determine the effectiveness of benidipine in the treatment of testicular I/R damage in rats.

Matherials and methods

Animals

This study used 15 adult male Sparaque-dawly rats which were 1 to 9 weeks old. The weight of the rats ranged from 200 to 220 g. Before the beginning of the experiment, the rats were accustomed to our laboratory for 1 week. The housing condition was standardized to provide 12-h light and dark cycle, temperature of 22 ±2˚C, and relative humidity of 60%. We followed the guidelines of the Ethics Committee of the International association for the study of pain in order to conduct the experiment.[11] All of the experiments were approved by the university Research Council. We divided the Rats were randomly divided into 3 groups: sham (healthy group with sham operation, n=5), IRC group (control group in which I/R injury was performed by torsion the right testis 720 º clockwise for 2 hours and detorsion for 2 hours, n=5), and IRB group (I/R + benidipine,I/R process was performed following orally 4 mg/kg benidipine administration, n=5).

Torsion /detorsion animal model

An intramascular injection of 80mg/kg Ketamine 5% (Alfasan, Woerden, Netherlands) and 10 mg/kg Xylazine 2% (Alfasan, Woerden, Netherlands) was used for anesthesia in each animal. Before the induction of anesthesia, 4 mg/kg benidipine (Deva, Istanbul, Turkey) was administered orally through a catheter to the rats in IRB group. Moreover, the same route was followed to administer distilled water in an equal amount as a solvent in rats in the sham an IRC groups. The skin of thescrotum of the rats was shaved and scrubbed by the means of betadine solution. All procedures were performed under sterile conditions. In order to expose the right testis, a right vertical paramedian incision was made on the scrotum. After the entry into the scrotum, tunica vaginalis was opened to deliver the right testis to the surgical field. The right testis was rotated 720º in a clockwise direction. In order to maintain it in the torsion position, it was fixed to the scrotum by 4-0 silk suture for 2 hours with the closure of scrotal incision.

After that, we de-rotated the spermatic cord and re-perfused the testis for 2 hours. We performed the right orchiectomy, at the end of the ischemia and reperfusion (4 hours). Anesthetic overdose was employed to euthanize the rats. Histopathological and biochemical analysis was conducted regarding the right testis.

Histopathological examination

The right testis of each animal was fixed in 10% neutral buffered formalin, dehydrated in graded ethanol series, cleared in xylol, embedded in paraffin wax and sectioned at about 5-6 µm. The sections were mounted on slides, stained with hematoxylin and eosine (H&E) and examined by light microscopy. Histopathological changes were evaluated on basis of the grading system described previously by Cosentino et al. [12], with some modification as shown in Table 1. Ischemia and reperfusion resulted in tissue damage with different degrees of severity observed in different four random areas of the rat testis with 10X magnification. Then, the final Cosentino's grade for each testis was determined and recorded by the mean of the all grades. Moreover, spermatogenesis in the tissue samples of the testes was evaluated according to the grading system described by Johnsen[13] as shown in Table 2. Ischemia and reperfusion resulted in spermatogenesis changes with

varying severity seen in different four random areas of each testis (in four random sections of seminiferous tubules) with 40X magnification. The final Johnsen's score for each testis was calculated and recorded by the mean of the all grades.

Biochemical assays

Assay of protein concentration

The method of Bradford was employed to assay the protein concentration in the testicular homogenate.[14]

Assay of lipid peroxidation

Malondialdehyde (MDA) was measured by the means of the thiobarbituric acid reactive substance (TBARS) method in order to determine the Lipid peroxidation in the testicular homogenate.[15]

Assay of glutathione peroxidase

The testis samples were homogenized in 1.15% KCL solution in order to measure the activity of cytosolic enzyme. According to Paglia and Valentine, Glutathione peroxidase (GPx) activity was measured by the use of Randox (United Kingdom).[16]

Statistical analysis

Analysis was performed using Graph Pad Prism, Version 5.05 (Graph Pad softeware, sndiego, USA). Analysis of parametric data were performed by One-Way ANOVA and repeated measure test Followed by Tukey Post-test (parametric methods); and Kruskal-Wallis multivariate analysis, followed by Dunns post-test (non-parametric methods). Results were expressed as mean±SD. P- Values less than 0.05 were considered statistically significant.

Results

Histopathological studies

Histological changes in the testicular tissue of rats in the experimental groups were evaluated by Cosentino's score and as shown in Figure 1. Histological examination of the all testes in group 1(sham operated rats) showed normal testicular architecture with orderly arranged normal germinal cells and tubules (these features corresponded to grade 1 in Cosentino's scoring system). While tissue samples in group 2(testicular I/R group); mean grade: 3.71; range: 3.5 4) demonstrated severe histological lesions in their testicular tissue including severe hemorrhage and coagulative necrosis of seminiferous tubules and the germinal cells. By contrast, in group 3 (testicular I/R + 4mg/kg benidipine group); mean grade: 1.43; range: 1.25 2) was observed mild histological lesions in their testicular tissue including non-cohesive germinal cells and closely packed seminiferous tubules with mild hemorrhage and necrosis. Upon comparison of the scores observed in the three experimental groups, statistically significant differences were identified between group 2 with groups 1 and 3 ($P<0.05$). However, there was no significant differences between groups 1 and 3 ($P>0.05$). In addition, spermatogenesis was evaluated histopathologically by Johnsen's score. Group 1 (sham operated) showed normal or slightly affected spermatogenesis (mean score: 9.25). By contrast, rats in group 2 (testicular I/R group); mean grade: 3.25) demonstrated severely damaged spermatogenesis. While in group 3 (testicular I/R + 4mg/kg benidipine group; mean grade: 6.625) was observed various scores from 4 to 9 (according to Table 2). In some tissue sections, numerous spermatocytes presented. But in more tubules numerous spermatids with a few spermatozoa were observed. Spermatogenesis evaluation demonstrated significant differences between three experimental groups ($P<0.05$).

Figure 1. Testis, rat, histopathological changes with ischemia and reperfusion. A: experimental group 1 (sham operated rats); all testes in this group showed normal testicular architecture (arrows). B: experimental group 2 (IR) demonstrated severe histological lesions in their testicular tissue including severe hemorrhage (arrows) and coagulative necrosis of seminiferous tubules. C: experimental group 3 (IR+Benidipine) exhibited mild histological lesions in their testicular tissue including closely packed seminiferous tubules with mild hemorrhage (arrows) and necrosis H&E, Scale bar= 190 µm.

Biochemical

Fig.2 shows the MDA and GPx and values for the different groups. The testes MDA levels in the IRC group were elevated by I/R injury ($p < 0.05$); however, benidipine treatment significantly decreased the I/R-induced elevation in the testes MDA level ($p < 0.05$). The I/R resulted in a significant decrease in testes GPx

level ($p < 0.05$) in comparison with the sham group, while the testes GPx level was increased ($p < 0.05$) in the benidipine-treated IR group, and was significantly different from that of the IRC group.

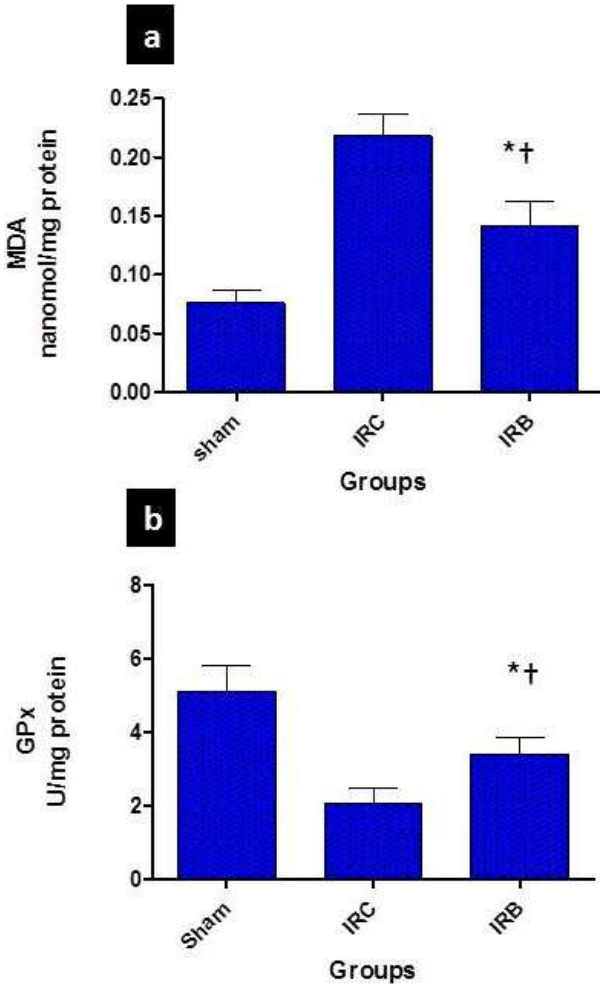

Figure 2. a) Malondialdehyde (MDA) and (b) glutathione peroxidase (GPx) levels in the testes tissue of sham-operated groups, ischemia-reperfusion (IRC)/ control groups and IR/benidipine -treated groups. Each group consists of five animals. * = $p < 0.05$, compared to sham operated group. † = $p < 0.05$, compared to IRC group. Group 1: sham-operated; Group 2: IR/control; Group 3: IR/benidipine treated.

Discussion

Testicular torsion causes biochemical and morphological changes mediated by I/R injury of the testicular tissue such as oxidative stress.[17] Various pathological mechanisms play a role in severe testicular damage as a result of torsion and detorsion, and lead to deleterious ischemia and reperfusion time-related injuries. Hypoxia is caused as a result of a decrease in blood flow during ischemia. Elevated levels of lipid peroxidation products such as lactic acid and hypoxanthine are engendered by Hypoxia. Moreover, Hypoxia leads to the development of thiobarbituric acid reactive products in ischemic tissue.[18] Large amounts of oxygen and/ or nitrogen-derived free radicals are formed as a result of increased blood flow after ischemia. In fact, this results in more damage to the ischemic tissue and is named reperfusion injury lesion which causes oxidative stress.[19] In the present study, I/R was examined as a cause of testis injury in terms of histopathological and biochemical results of oxidative stress in a rat model. The findings showed that I/R caused oxidative stress in testis. Moreover, based on the results, benidipine prevented this I/R related injury. MDA, which is regarded to be a reliable parameter of lipid peroxidation and oxidative stress based on the results of the previous studies, was increased in rat testis as a result of exposure to I/R.[20] It is clear that, the lesion was exacerbated by MDA since it polymerized and produced the cross links of membrane compound.[21] The evidence points to oxidative stress in testes exposed to I/R, in addition to increase in oxidative parameters, the development of oxdative stress is supported by the decrease in the condition of endogen anti-oxidative. Oxidative stress can be defined as the increase in oxidative status and/or reduction in antioxidative status in injured tissue.[22] Our finding regarding the significant reduction in GPx levels in testicular tissue of rats in IRC group is in line with the previous studies.[23,24] For instance, Parlaktas et al. reported that, MDA augmentation was directly proportionate to the severity of lesion while GPx decrease.[23] I/R injury is defined as complicated pathologic condition which commences with ischemia and leads to oxidative stress and inflammatory process. A number of other studies in the literature support the relation between oxidative stress and inflammation.[25] Moreover, since benidipine is a L-type calcium channel blocker, it may impede tissue from oxidative and inflammatory injury through calcium. It is known that, intracellular calcium is increased by I/R injury.[26] The increase in intracellular calcium activates the calcium related cytosolic protease.[27] Moreover, intracellular calcium changes the dehyrogenases into xanthine oxidase which plays a key role in the generation of reactive oxygen radicals.[28] Furthermore, pain and inflammation are caused by the augmentation in calcium levels and are relieved as a result of the decrease in calcium. TNF-a and IL-1b are produced in the primary phase of inflammation and have various

functions such as releasing the free radicals. [29,30] Some of the research studies have reported that benidipine inhibits proinflammatory cytokines such as TNF-a and IL-1b in various tissue.[31,32] At histopathological examination of testicular tissues, which was evaluated by Cosentino' s score, there were severe histapathological changes including disorganization, interstitial edema, degeneration of germ cells, hemorrhage and necrosis in IRC group, inaddition to increased levels of MDA, decreased levels of GPx. Whereas, these histapathological changes were significantly less obvious in testicular tissues with administration of benidipine. Moreover, this treatment resulted in less affected spermatogenesis that was assessed by Johnsen' s score, in compared with the IRC group. However, in limited monitoring time of this study, the spermatogenesis quality of treated group was not as well as the sham-operated control group. Because of this limitation, it seems that further studies are required to evaluate more precisely. In general, the present findings suggested that administration of benidipine in I/R injury can improve histopathological damages and spermatogenesis quality. Similar histopathological results were reported by Ozbal et al. regarding rat testis exposed to I/R.[33] Similarly, Taati et al. reported that, necrosis and apoptosis in testis tissue are caused as a result of I/R.[34] Moreover, the results of some studies have shown that, benidipine and other calcium canal blocker may have anti-inflammatory activity throughout the ROS, leukocyte infiltration, and inflammatory cytokines. [35]

The results of the biochemical and pathological examinations of the testicular tissues of rats supported that TT caused I/R in jury in the rat testis as evidenced by the alternations in oxidative parameters of testicular tissues. Moreover, the findings showed that treatment with benidipine activated the antioxidant mechanisms and weakened the I/R induced testicular damage. These results may highlight the potential therapeutic value of the therapy for post-ischemic testicular damage and may ameliorate the patients' fertility potential who had testicular torsion and detorsion incident in the clinical base. However, there is a need for further studies to reach accurate results.

Acknowledgments

The authors would like to thank Mr.Vatankhah, Drug Applied Research Center, Tabriz University of Medical Sciences, Pashmineh, Tabriz, Iran for his kindly helps.

Conflict of interest

None

Table 1. Histological scoring system of testicular damage in tissue samples of rats, as proposed by Cosentino et al with some modifications.

Score	Microscopic characteristics
1	Normal testicular architecture with an orderly arrangement of germinal cells and without hemorrhage and necrosis
2	Injury showed less orderly, non-cohesive germinal cells and closely packed seminiferous tubules with mild hemorrhage and necrosis
3	Injury exhibited disordered sloughed germinal cells, with reduced size of pyknotic nuclei and less distinct seminiferous tubule borders with moderate hemorrhage and necrosis
4	Injury exhibited seminiferous tubules that were closely packed with coagulative necrosis of the germinal cells with severe hemorrhage and necrosis

Table 2. Spermatogenesis grading system in the testicular tissue of rats, as proposed by Johnsen.

score	Microscopic characteristics
1	No germ cells and no Sertoli cells present
2	No germ cells, but only Sertoli cells present
3	Only spermatogonia present
4	Only a few spermatocytes present
5	No spermatozoa or spermatids, but numerous spermatocytes present
6	Only a few spermatids present
7	No spermatozoa, but numerous spermatids present
8	Only a few spermatozoa present in the section
9	Numerous spermatozoa present, but the germinal epithelium is disorganized
10	Complete spermatogenesis and normally organized tubules

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نشریه جراحی دامپزشکی ایران
سال ۲۰۱۷ ، جلد ۱۲ (شماره ۲)، شماره پیاپی ۲۷

چکیده

بنیدیپین آسیب ایسکمیک-رپرفیوژن پس از پیچش/ رفع پیچش بیضه در موش صحرایی را کاهش میدهد

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هدف- هدف از این مطالعه بررسی اثرات محافظتی بنیدیپین بر آسیب های بیضه پس از پیچش/ رفع پیچش بیضه در موش صحرایی بود.
طرح مطالعه- مطالعه تجربی
حیوانات- ۱۵سرنر رت نژاد اسپاراگو با وزن ۲۲۰-۲۰۰ گرم
روش کار- رت ها به طور تصادفی به ۳ گروه تقسیم شدند: گروه شم (گروه سالم با جراحی شم، n=۵)، گروه IRC (گروه کنترل که آسیب I / R با پیچش ۷۲۰ درجه در جهت عقربه های ساعت به مدت ۲ ساعت و رفع پیچش به مدت ۲ ساعت صورت گرفت، n = 5) و گروه IRB تزریق خوراکی ۴ میلی گرم بر کیلوگرم بنیدیپین +چرخش و رفع چرخش بیضه ، n = ۵) انجام شد. سطوح گلوتاتیون پراکسیداز (GPx) و مالون دی آلدئید (MDA) در بافت بیضه رتها تعیین شد. بافت بیضه همچنین از نظر هیستوپاتولوژیک مورد بررسی قرار گرفتند.

نتایج- سطح MDA در بیضه رت های گروهIRC به طور معنی داری افزایش یافت ($P < 0.0001$). سطوح GPx بیضه پس از I / R به طور معنی داری کاهش یافت ($P < 0.0001$). تجویز بنی دیپین قبل از پیچش بیضه باعث جلوگیری از افزایش پراکسیداسیون چربی و کاهش سطح GPX شد. بنی دیپین همچنین از آسیب سلولی و تغییرات بافتی در بافت بیضه جلوگیری کرد.
نتیجه گیری و کاربرد بالینی – این نتایج نشان می دهد که درمان با بنی دیپین قبل از چرخش بیضه می تواند اثرات محافظتی روی بیضه در برابر آسیب ایسکمی / رپرفیوژن ایجاد کند.
کلمات کلیدی - بنی دیپین, ایسکمیک-رپرفیوژن, پیچش بیضه, رت