UROLOGY - ORIGINAL PAPER

CrossMark

The effects of oxytocin on penile tissues in experimental priapism model in rats

Engin Kolukcu[1] · Sahin Kilic[2] · Bekir Suha Parlaktas[3] · Fikret Erdemir[3] · Velid Unsal[4] · Dogan Atılgan[3] ·
Nihat Uluocak[3]

Abstract

Purpose This study aimed to demonstrate the effects of oxytocin on penile tissues in ischemia–reperfusion injury developed after priapism.

Methods Forty Wistar Albino strain male rats were divided into four groups. The control group ($n = 10$) was not intervened. In Group 2, a rat model of priapism was constructed and maintained for 1 h. In Group 3, reperfusion was ensured for 30 min following priapism. Rats in Group 4 rats were given oxytocin 30 min before the induction of reperfusion following priapism. All rats were penectomized, and adequate amounts of blood sample were drawn. Inflammation, vasocongestion, desquamation, and edema in penile tissue were scored between 0 and 3 points (0: normal, 1: mild, 2: moderate, 3: severe) to evaluate the severity of tissue damage. The activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), and the levels of malondialdehyde (MDA), and nitric oxide (NO) in blood samples were determined spectrophotometrically.

Results In histopathological examination, statistically significant positive changes were detected in vasocongestion, inflammation, desquamation, and edema scores in Group 4 than in Group 2 and Group 3 ($p < 0.001$). Biochemical test results revealed that NO levels were significantly lower in Group 4 than in Group 3 ($p < 0.001$). Serum GSH-Px activities in Group 4 significantly increased when compared with the other groups 2 and 3 ($p = 0.002$, $p = 0.001$, respectively). There was no statistical difference among the groups regarding SOD activities and MDA levels ($p > 0.05$).

Conclusions Oxytocin protected against priapism-induced ischemia–reperfusion injury developed in cavernosal tissue as observed based on histopathological and biochemical evidence. Although this is an experimental study, oxytocin can be thought as an alternative drug in the treatment of priapism.

Keywords Ischemia–reperfusion injury · Oxytocin · Penile tissue · Priapism · Rat model

Introduction

Priapism is a term modified from the Greek God "Priapus" and defined as an involuntary, sustained, and prolonged (> 4 h) painful erection developed without sexual desire or stimulus [1, 2]. The mean incidence is approximately 1.5/100,000, and it can occur in all age groups [3]. Priapism has been divided into three main groups as ischemic (low-flow, veno-occlusive), non-ischemic (high-flow, arterial), and intermittent (stuttering) priapism.

Ischemic priapism is the most frequently seen type of priapism and requires emergency treatment. If it is not treated properly, erectile dysfunction may develop [2]. When tissue perfusion was instituted in ischemic priapism, permanent and unwanted changes occur in hypoxic tissues secondary to ischemia–reperfusion injury [4]. Ischemia–reperfusion injury leads to oxidative stress, increases the levels of MDA, the end-product of lipid peroxidation, and also increases the serum NO levels which enhances tissue perfusion by its vasodilatory action in ischemic conditions. Activities of antioxidant enzymes such as SOD and GSH-Px decrease

✉ Engin Kolukcu
drenginkolukcu@gmail.com

[1] Department of Urology, Tokat State Hospital, Tokat, Turkey

[2] Department of Urology, Fethiye State Hospital, Fethiye, Mugla, Turkey

[3] Department of Urology, Faculty of Medicine, Gaziosmanpasa University, Tokat, Turkey

[4] Mardin Artuklu University High School of Health and Central Research Laboratory, Mardin, Turkey

secondary to their utilization as protective agents against oxidative stress [5–7].

Ischemic priapism is a medical emergency. The traditional approach is the penile aspiration and the use of alpha-adrenergic agents. If medical therapy fails, several surgical approaches are indicated [8]. Different pharmacological agents have been investigated with the aim of reducing damage to penile cavernosal tissues in priapism that continues for short and long periods [9].

Oxytocin is known as a female hormone involved in the maintenance of parturition and lactation. In recent years, oxytocin receptors and functions have been studied in the male reproductive system [10]. Various studies demonstrated the anti-inflammatory, antioxidant, and immunomodulatory effects of oxytocin besides its classical functions [5].

In this study, we aimed to determine the effects of oxytocin against ischemia–reperfusion injury developed in cavernosal tissue following priapism. To our knowledge, this is the first experimental study in the modern medical literature that investigated the effect of oxytocin in a rat model of priapism.

Materials and methods

In our study, a total of 40 male, 10-week-old Wistar Albino strain rats with an average weight of 310 g were used. All procedures were performed in compliance with the provisions of the Strasbourg Universal Declaration on Animal Welfare of 1986 and approved by the Ethical Committee (2014 HADYEK 81). The rats were maintained at a temperature of 22 °C on a 12-h light/dark cycle. They were fed with standard pellets prepared for rodents and tap water ad libitum. Rats were randomized into four groups.

Group 1 Group 1 was assigned as the control group. The rats were penectomized, and 5 cc blood samples were drawn from their inferior venae cavae for biochemical sampling.

Group 2 Priapism was accomplished with the method described by Sanli et al. [11]. The tip of a 5-cc syringe was cut to accommodate the device to the base of the flaccid penis. Vacuum erection was performed with the tip of the 5-cc syringes under anesthesia. Then 2-mm-wide constriction bands pre-prepared from 16 Fr Foley catheters were tied around the roots of rat's penis to sustain the erection (Fig. 1). At the end of the first hour, rats were penectomized, and 5 cc blood samples were drawn from their inferior vena cava for biochemical sampling [12]. In Group 2, one rat was lost during 1-h-long priapism and excluded from the study.

Group 3 Priapism was induced under anesthesia as described above. It was terminated at the end of the first hour, and

Fig. 1 Priapism induced in rat model

penile reperfusion was allowed for 30 min [12]. Following that procedure, penectomy was performed to evaluate the severity of ischemia–reperfusion damage and blood samples were drawn from inferior vena cava of the rats.

Group 4 Priapism was induced under anesthesia and as mentioned above. It was terminated at the end of the first hour, followed by penile reperfusion applied for 30 min. Contrary to Group 3, rats were given 0.5 µg/kg oxytocin through intraperitoneal route half an hour before the reperfusion procedure (Postuintrin Fort Ampoule®; İbrahim Etem Ulagay Pharm Türk A.Ş.) [5]. At the end of the procedure, penectomy was performed to evaluate the effect of oxytocin on ischemia–reperfusion injury, and blood samples were drawn from inferior vena cava of the rats.

All surgical procedures were carried out under the appropriate depth of anesthesia. To this end, xylazine hydrochloride, an anesthetic agent with sedative and muscle relaxation effects (Rompun 2%, Bayer, Turkey), was administered at a dose of 10 mg/kg through intraperitoneal route. Also, ketamine hydrochloride with dissociative anesthetic effectiveness was given at a dose of 50–60 mg/kg via intraperitoneal route (Alfamine 10%, Ege Vet, Turkey).

At the end of the experiment, penises were placed in 10% formaldehyde solution for histopathological examination of penile tissues. SOD and GSH-Px activity, MDA, and NO levels were studied in all serum samples.

Biochemical evaluation

Measurement of plasma MDA levels

MDA reacts with thiobarbituric acid (TBA) at 90 °C to form a pink-colored chromogen. Based on the pink-colored

spectrophotometric measurement of the compound formed at 532 nm, quantitative analysis of MDA was performed [6].

Determination of plasma SOD activity

Serum SOD activity level was measured using the method introduced by Sun et al. and modified by Durak et al. Using this method, reduction of nitroblue tetrazolium (NBT) by superoxide produced by xanthine/xanthine oxidase system was used to determine the level of plasma SOD activity [13].

Determination of plasma GSH-Px activity

GSH-Px activity was evaluated based on the method described by Paglia et al. In the presence of hydrogen peroxide, GSH-Px catalyzes the oxidation of reduced glutathione (GSH) to oxidized glutathione (GSSG). GSSG created by GSH-Px is reduced into GSH with the aid of glutathione reductase and NADPH. During oxidation of NADPH to NADP, measurement of the decrease in the level of absorbance at 340 nm determines GSH-Px activity [14].

Measurement of plasma NO levels

NO has a half-life of only a few seconds because it is readily oxidized to nitrite (NO_2) and subsequently to nitrate (NO_3) which serve as index parameters of NO production. The method for the measurement of plasma nitrite and nitrate levels was based on the Griess reaction. Samples were initially deproteinized with Somogyi reagent. Total nitrite [nitrite + nitrate] was measured by spectrophotometry at 545 nm after conversion of nitrate to nitrite by copperized cadmium granules. A standard curve was established with a set of serial dilutions (108–103 mol/l) of sodium nitrite. Linear regression analysis was done by using the peak area from nitrite standards. The resulting equation was used to calculate the concentrations of the unknown sample. Results were expressed as micromole per liter plasma (mmol/l) [15, 16].

Histopathological evaluation

Histopathological evaluation was performed using a scoring system similar to that used by Sentürk et al. in their studies. Histopathological evaluation was performed under the light microscope (Nikon Eclipse E600, Japan) and at 40× magnification. The presence of vasocongestion, inflammation, desquamation, and edema was scored between 0 and 3 points as follows: 0: normal, 1: mild, 2: moderate, 3: severe (Fig. 2) [5].

Statistical evaluation

Descriptive analyses were performed to provide information about the general characteristics of the groups. The quantitative data were expressed as mean ± standard deviation and the qualitative data as n (%). Distribution of quantitative variables among the groups was analyzed using one-way analysis of variance while that of qualitative variables was investigated with the Chi-square test. Post hoc tests were conducted using the Games-Howell test for GSH-Px and Bonferroni test for NO biochemical parameters based on the assumption of homogeneity of variances. p Values less than 0.05 were considered as statistically significant. For calculations, available statistical software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY) was used.

Results

A significant difference was found among four groups as for inflammation, vasocongestion, desquamation, and edema ($p < 0.001$) (Table 1). When groups were evaluated individually, grades 0 and grade 1 inflammation were observed in 10% and 90% of the penile tissue samples in Group 1. In Group 2, grades 1 and 2 inflammation were seen in 44.4% and 55.6% of the samples. As for Group 3, 30% and 70% of the penile tissue samples had inflammation of grades 1 and 2, respectively. All penile tissue samples in Group 4 demonstrated grade 1 inflammation. Notably, the rates of grade 2 inflammation were higher in Group 3 than the other groups ($p < 0.001$).

In none of the groups, grade 0 vasocongestion was observed. In Group 1, all the tissue samples demonstrated grade 1 vasocongestion. Although grade 1 vasocongestion was not observed in Group 2, grades 2 and 3 were noted in 55.6% and 44.4% of the tissue samples, respectively. Group 3 was found to have grades 1, 2, and 3 vasocongestion in 30%, 60%, and 10% of the samples, respectively. As for Group 4, severe (grade 3) vasocongestion was not encountered, while vasocongestion of grades 1 and 2 was found in 60% and 40% of penile tissue samples. In Groups 2 and 3, vasocongestion of grade ≥ 2 was more frequently detected when compared with the other two groups ($p < 0.001$). Group 2 had higher rates of grade 3 vasocongestion compared with the other groups ($p = 0.011$).

Grade 0 desquamation was seen in all the penile tissue samples in Group 1. In Group 2, grade 0 desquamation was not observed in any tissue sample while rates of grade 1, 2, and 3 desquamation were 11.1%, 77.8%, and 11.1%, respectively. Grade 0 and 1 desquamation were observed in 20% and 80% of the samples in Group 3, whereas this rate was found to be 60% and 40% in Group 4, respectively. In Groups 2 and 3, desquamation of grade ≥ 1 was
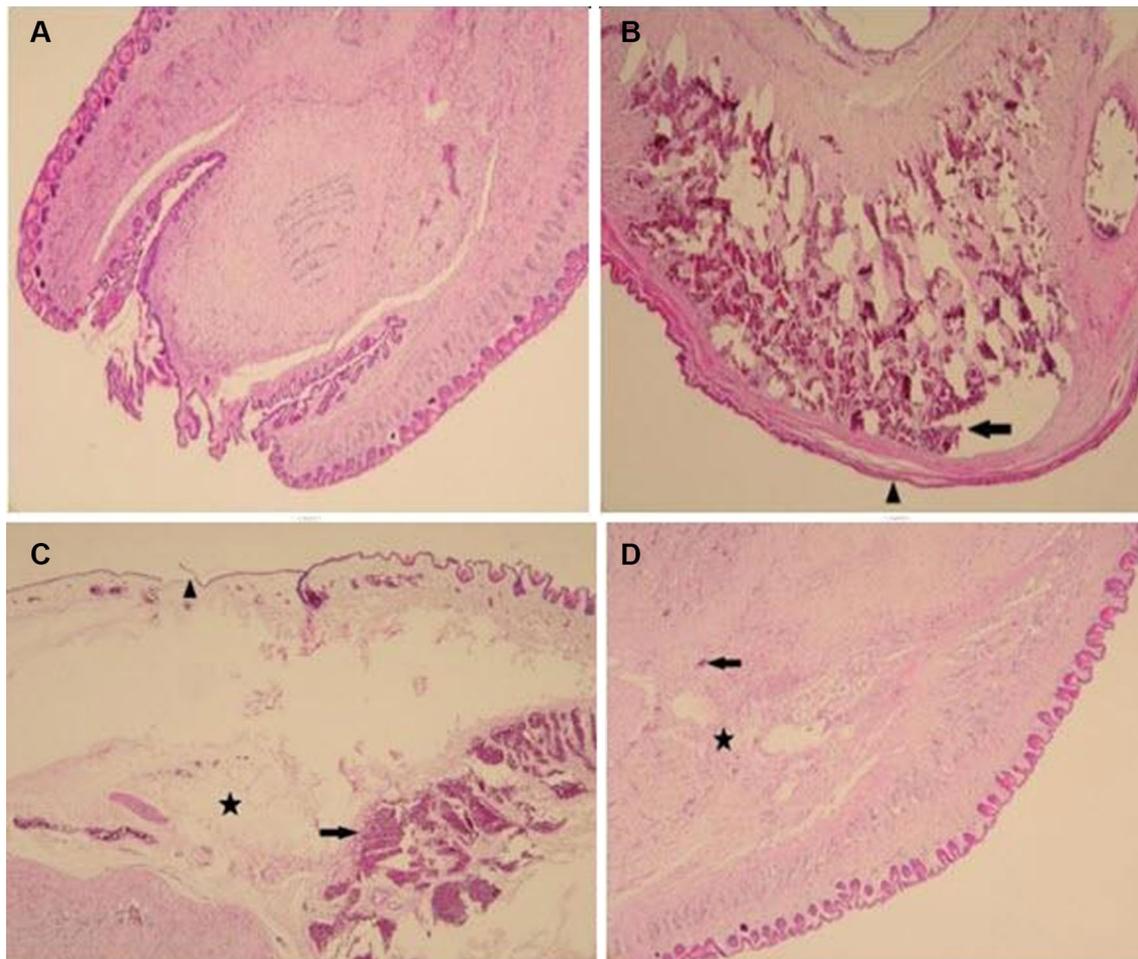
Fig. 2 Histopathological examination: normal penile tissue, vaso-congestion, desquamation and edema. **a** Penile tissue of the experimental animals in the control group (H&E, × 40). **b** Penectomized group after induction of priapism. Areas of marked vasocongestion (arrow) and desquamation (arrowhead) (H&E, × 40). **c** Group with induced priapism persisting for 1 h followed by reperfusion injury. Areas of marked vasocongestion (arrow), desquamation (arrowhead) and edema (asterisk) (H&E, × 40). **d** Group that received oxytocin administration before reperfusion injury. Areas of minimal vaso-congestion (arrow), mild edema (asterix), absence of desquamation (H&E, × 40)

more frequently detected when compared with the other two groups ($p < 0.001$). Group 2 had statistically significantly higher rates of grade ≥ 2 desquamation compared with the other groups ($p < 0.001$).

In Group 1, edema was observed to be grade 0 in 70% of the penile tissue samples while grade 1 edema was noted in 30% of the samples. In Group 2, grades 1 and 2 edema were seen in 66.7% and 33.3% of the penile tissue samples, respectively. In Group 3, grade 0 and 1 edema were not seen in any penile tissue sample; however, grade 2 and 3 edema were seen in 70% and 30% of the tissue samples, respectively. Grade 1 (30%) and grade 2 (70%) edema were detected in indicated percentages of the penile tissue samples in Group 4. In Group 3, higher rates of grade 3 edema was identified ($p = 0.024$).

In histopathological examination, statistically significant positive changes were detected in vasocongestion, inflammation, desquamation, and edema scores in Group 4 than in Group 2 and Group 3 ($p < 0.001$). Higher grade 2 inflammation and grade 3 edema rates were observed in Group 3 (p < 0.001, $p = 0.024$, respectively).

Mean serum values of antioxidant SOD enzyme in Groups 1, 2, 3, and 4 were 6.79 ± 1.09 U/ml, 6.86 ± 0.84 U/ml, 5.97 ± 1.79 U/ml, and 6.7 ± 2.62 U/ml, respectively. Measurements of stress-related lipid peroxidation product MDA in Groups 1, 2, 3, and 4 were 3.98 ± 1.35 μmol/l, 4.89 ± 0.54 μmol/l, 4.85 ± 0.45 μmol/l, and 4.7 ± 0.59 μmol/l, respectively. No difference was found among the four groups as for SOD activities and MDA levels ($p > 0.05$).

Table 1 Rates of vasocongestion, inflammation, desquamation, and edema observed in groups

Histopathological parameters	Group 1 ($n=10$)	Group 2 ($n=9$)	Group 3 ($n=10$)	Group 4 ($n=10$)	p Value[a]	p Value[b]
Grade 1 vasocongestion	10 (100.0)	–	3 (30.0)	6 (60.0)	<0.001*	<0.001*
Grade 2 vasocongestion	–	5 (55.6)	6 (60.0)	4 (40.0)	0.025*	
Grade 3 vasocongestion	–	4 (44.4)	1 (10.0)	–	0.011*	
Grade 0 inflammation	1 (10.0)	–	–	–	0.395	<0.001*
Grade 1 inflammation	9 (90.0)	4 (44.4)	3 (30.0)	10 (100.0)	0.001*	
Grade 2 inflammation	–	5 (55.6)	7 (70.0)	–	<0.001*	
Grade 0 desquamation	10 (100.0)	–	2 (20.0)	6 (60.0)	<0.001*	<0.001*
Grade 1 desquamation	–	1 (11.1)	8 (80.0)	4 (40.0)	<0.001*	
Grade 2 desquamation	–	7 (77.8)	–	–	<0.001*	
Grade 3 desquamation	–	1 (11.1)	–	–	0.331	
Grade 0 edema	7 (70.0)	–	–	–	<0.001*	<0.001*
Grade 1 edema	3 (30.0)	6 (66.7)	–	3 (30.0)	0.019*	
Grade 2 edema	–	3 (33.3)	7 (70.0)	7 (70.0)	0.003*	
Grade 3 edema	–	–	3 (30.0)	–	0.024*	

*Statistically significant ($p<0.05$)

[a]Multiple proportions test for equality of proportions (Post hoc Chi-square tests by grades)

[b]Chi-square test

Mean serum values of the antioxidant GSH-Px enzyme in Groups 1, 2, 3, and 4 were calculated as 325.35 ± 205.2 µmol/l, 149.96 ± 98.47 µmol/l, 134.96 ± 94.51 µmol/l, and 479.59 ± 197.58 µmol/l, respectively.

Mean serum NO values in Groups 1, 2, 3, and 4 were 48.09 ± 16.19 mmol/l, 60.67 ± 11.68 mmol/l, 81.99 ± 10.75 mmol/l, and 51.59 ± 16.35 mmol/l, respectively.

Biochemical test results revealed that NO levels were significantly lower in Group 4 than in Group 3 ($p<0.001$). Serum GSH-Px activities in Group 4 significantly increased when compared with the other groups 2 and 3 ($p=0.002$, $p=0.001$). Additionally, serum NO levels were elevated and GSH-Px levels were reduced in Group 3 compared with the control group ($p<0.001$ and $p=0.032$, respectively) (Table 2).

Discussion

Ischemic priapism constitutes nearly 95% of all priapism cases [17]. As a compartment syndrome, ischemic priapism manifests itself with a painful and rigidly erect penis secondary to decreased cavernous arterial inflow and venous congestion. Blood gas analysis reveals mostly the presence of a hypoxic, hypercapnic, and acidic state [2]. In ischemic priapism, ultrastructural changes in cavernosal smooth muscle show the development of interstitial edema 12 h later. Sinusoidal endothelial cell injury, the disintegration of basal membrane, and adhesion of platelets are observed up to 24 h after the onset of ischemic priapism. At the end of 48 h following the development of ischemic priapism, demonstration of thrombi in sinusoids, and fibroblast-like cells indicate an onset of smooth muscle necrosis [18]. In priapism, hypoxia induces the release of many mediators in cavernosal tissues like transforming growth factor and subsequently leads to fibrosis. Fibrosis developed in intact smooth muscle plays a direct role in the emergence of erectile dysfunction frequently observed in patients with priapism [19].

Ischemic priapism is related to oxidative stress [4]. Under normal conditions, reactive oxygen molecules are synthesized in tissues and eliminated by the action of antioxidants. These molecules also assume specific physiologic tasks. However, their serum levels increase in conditions where antioxidant mechanisms become inadequate. From a pathophysiological perspective, anaerobic mechanism due to inadequate oxygen supply becomes functional and induces accumulation of lactic acid and toxic metabolites in tissues under ischemic conditions. Intracellular oxidative phosphorylation process slows down because of the development of acidosis with a resultant decrease in the levels of high-energy molecules such as adenosine 5′-triphosphate and phosphocreatine. In this case, the cell lacks the energy source which it will use for its own homeostasis. This serious decline in the level of energy inhibits $Na^+ K^+$ ATPase pump and increases intracellular Na^+ and Ca^{2+} ion concentrations. These increased levels of Ca^{2+} ions exert a toxic effect on the cell. The decrease in energy levels induces increased synthesis of proinflammatory cytokines, leukocyte adhesion molecules and decreases the levels of antioxidant molecules. During the ischemic

Table 2 Mean ($\pm$ SD) comparison values of SOD, MDA, GSH-Px, and NO in 4 groups with ANOVA test

Biochemical parameters	Groups	N	Mean $\pm$ SD	p Values	Post hoc p values
SOD (U/ml)	1	10	6.79 ± 1.09	0.656	–
	2	9	6.86 ± 0.84		
	3	10	5.97 ± 1.79		
	4	10	6.70 ± 2.62		
MDA (μmol/l)	1	10	3.98 ± 1.35	0.607	–
	2	9	4.89 ± 0.54		
	3	10	4.85 ± 0.45		
	4	10	4.70 ± 0.59		
GSH-Px (μmol/l)	1	10	325.35 ± 205.20	< 0.001*	1–2[a]: 0.123
	2	9	149.96 ± 98.47		1–3[a]: 0.032*
	3	10	134.96 ± 94.51		1–4[a]: 0.346
	4	10	479.59 ± 197.58		2–3[a]: 0.986
					2–4[a]: 0.002*
					3–4[a]: 0.001*
NO (mmol/l)	1	10	48.09 ± 16.19	< 0.001*	1–2[b]: 0.356
	2	9	60.67 ± 11.68		1–3[b]: < 0.001*
	3	10	81.99 ± 10.75		1–4[b]: 1.000
	4	10	51.59 ± 16.35		2–3[b]: 0.013*
					2–4[b]: 1.000
					3–4[b]: < 0.001*

SOD superoxide dismutase, *MDA* malondialdehyde, *GSH-px* glutathione peroxidase, *NO* nitric oxide, *SD* Standard deviation

*Statistically significant ($p < 0.05$)

[a]Games-Howell post hoc test

[b]Bonferroni post hoc test

period, toxic-free oxygen radicals are produced in the tissue. Free oxygen radicals initiate lipid peroxidation and exert toxic effects on cells, lipid membranes, and protein structures leading to a disruption of cellular integrity and cellular dysfunction [20–22]. Reinstitution of blood circulation results in reperfusion and the free oxygen radicals released especially by polymorphonuclear leucocytes localized in tissues speed up the destruction at the tissue level. This event is termed as reperfusion-related tissue injury. Though a small amount of free radicals are produced during ischemia, much higher amounts of free radicals are produced in the reperfusion phase following reoxygenation and increase the severity of destructive changes [23]. In experimental studies conducted with rats, various scoring parameters were reported for evaluating ischemia and ischemia–reperfusion injury at tissue level depending on the histological structure of the related tissue [5]. In our study, statistically significant negative changes were detected in vasocongestion, inflammation, desquamation, and edema scores in ischemia and ischemia–reperfusion groups when compared with control group. However, the ischemia group (Group 2) scored higher vasocongestion and desquamation rates than that of the ischemia–reperfusion group (Group 3). We think that after reperfusion a vascular circulation is established and subsequently vasocongestion and desquamation might regress.

It has been demonstrated that priapism induces ischemia and oxidative stress which affects the mechanism of cellular injury as is seen in all ischemic pathologies [24]. Lipids are sensitive to the effects of reactive oxygen species such as MDA, one of the end products of lipid peroxidation [6]. Oxidative damage increases tissue levels of MDA. It is commonly used as a biomarker that determines oxidative stress in research. A study by Evliyaoglu et al. evaluating corporal MDA levels after priapism reported an increase in MDA concentration in all the priapic groups compared with the control group [25]. Similar results have been obtained in many studies in ischemia–reperfusion models [26, 27]. Our study showed that the levels of serum MDA were increased in Groups 2 and 3 compared to the control group; albeit, multiple comparisons indicated no significance ($p = 0.607$). The superoxide radical ($O_2^{\cdot-}$) is formed by the addition of an electron to the oxygen (O_2) molecule. The resulting superoxide radicals are reduced to hydrogen peroxide (H_2O_2) via SOD, an antioxidant enzyme. H_2O_2 is reduced to water (H_2O) and O_2 by another antioxidant enzyme GSH-Px [28]. NO is synthesized in smooth muscle, endothelial cells, and many other cells as a result of oxidation of guanidino nitrogen of the amino acid L-arginine mediated by nitric oxide synthase. NO is known as an endothelium-derived relaxing factor. It has critical roles in various physiologic or pathologic processes. Vascular endothelial tissue utilizes NO to

relax smooth muscles [29]. A multiple number of studies have shown that parameters demonstrating oxidative damage in ischemic pathologies increase while those associated with antioxidant mechanism decrease in number. In a study by Çiftçi et al., the authors induced priapism for 1 h followed by reperfusion in rat models and detected a significant increase in serum NO and decrease in serum SOD and GSH-Px levels in priapism groups relative to the control group [7]. Similarly, serum NO levels were elevated and GSH-Px levels were reduced in Group 3 compared with the control group ($p < 0.001$ and $p = 0.032$, respectively). However, there was no difference among the four groups as for SOD activities and MDA levels ($p > 0.05$). We believe it is due to the short (30 min) reperfusion time. Different results could have been obtained with a longer reperfusion time.

The fundamental approach to the alleviation of oxidative damage suggests the use of molecules with antioxidant or immunomodulatory properties. Accordingly, various success rates have been reported in the use of several agents such as lycopene [7], pentoxifylline [9], dipyridamole [12], allopurinol [25], n-acetylcysteine [26], melatonin [27], curcumin [30], oxytocin [5, 31], alfa-lipoic acid [32], and resveratrol [33] in the prevention of oxidative stress-induced injury manifesting secondary to many factors including diabetes mellitus, infections, and ischemia.

Oxytocin is structurally a peptide of nine amino acids. It is released from the pituitary gland. The expression of oxytocin receptors has been shown not only in the uterine myometrium and mammary glands but also in the male reproductive tract, thymus, pancreas, adipocytes, adrenal gland, kidney, brain, heart, and cardiovascular system. Oxytocin plays a role in successful milk ejection, uterine smooth muscle contraction, cardiovascular regulation, pain, body temperature, analgesic effects, memory, feeding, mental behavior, osmoregulation, and sexual behavior [10, 34, 35]. In addition to its properties mentioned earlier, oxytocin prevents the development of fibrosis, inflammation, and may demonstrate antioxidative effects as reported in many studies. For example, in their experimental study, Erbaş et al. induced renal injury using cisplatin and demonstrated that oxytocin administration decreased CRP and TGF-alpha levels [36]. Similarly, oxytocin used in the treatment of hepatic damage triggered by renal ischemia–reperfusion injury decreased oxidative stress parameters as was demonstrated in a study by Hekimoglu et al. in the year 2013 [37]. İşeri et al. revealed that oxytocin exerted antioxidant effects against sepsis-induced oxidative injury through inhibition of neutrophilic infiltration [31]. Another study by Erkanlı et al. revealed that the number of apoptotic cells developed due to skeletal muscle ischemia was decreased with oxytocin treatment [38]. In our study, statistically significant positive changes were detected in vasocongestion, inflammation, desquamation, and edema scores in Group 4 ($p < 0.01$).

Biochemical test results revealed that NO levels were significantly lower in Group 4 than in Group 3 ($p < 0.001$). Serum GSH-Px activities in Group 4 significantly increased when compared with the groups 2 and 3 ($p = 0.002$, $p = 0.001$, respectively).

Conclusion

In conclusion, we can say that priapism that is seen relatively more frequently in the urology practice induces oxidative damage, adverse effects at tissue level, and thus takes its place in the etiology of sexual dysfunction. Although our trial is an experimental animal study, we can indicate that oxytocin may be used in the clinical practice for the management of priapism because this treatment modality decreases oxidative damage. However, our study results should be supported by especially prospective, more randomized, and controlled studies to be performed in the future. Although our study adds a new function to oxytocin in priapism, further studies are needed to elaborate the mechanism.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest.

References

1. Papadopoulos I, Kelami A (1988) Priapus and priapism. From mythology to medicine. Urology 32:385–386. https://doi.org/10.1016/0090-4295(88)90252-X
2. Pryor J, Akkus E, Alter G et al (2004) Priapism. J Sex Med 1:116–120. https://doi.org/10.1111/j.1743-6109.2004.10117.x
3. Eland IA, van der Lei J, Stricker BH, Sturkenboom MJ (2001) Incidence of priapism in the general population. Urology 57:970–972. https://doi.org/10.1016/S0090-4295(01)00941-4
4. Munnariz R, Park K, Huang YH et al (2003) Reperfusion of ischemic corporal tissue: physiologic and biochemical changes in an animal model of ischemic priapism. Urology 62:760–764. https://doi.org/10.1016/S0090-4295(03)00484-9
5. Erkanli Senturk G, Erkanli K, Aydin U et al (2013) The protective effect of oxytocin on ischemia/reperfusion injury in rat urinary bladder. Peptides 40:82–88. https://doi.org/10.1016/j.peptides.2012.12.006
6. Esterbauer H, Cheeseman KH (1990) Determination of aldehydic lipid peroxidation products: malonaldehyde and 4-hydroxynonenal. Methods Enzymol 186:407–421. https://doi.org/10.1016/0076-6879(90)86134-H
7. Ciftci O, Oguz F, Beytur A, Polat F, Altıntas R, Oguzturk H (2014) Lycopene prevents experimental priapism against oxidative and nitrosative damage. Eur Rev Med Pharmacol Sci 18:3320–3325
8. Huang YC, Harraz AM, Shindel AW, Lue TF (2009) Evaluation and management of priapism: 2009 update. Nat Rev Urol 6:262–271. https://doi.org/10.1038/nrurol.2009.50
9. Erdemir F, Firat F, Markoc F et al (2014) The effect of pentoxifylline on penile cavernosal tissues in ischemic priapism-induced rat

model. Int Urol Nephrol 46:1961–1967. https://doi.org/10.1007/s11255-014-0769-z

10. Thackare H, Nicholson HD, Whittington K (2006) Oxytocin-its role in male reproduction and new potential therapeutic uses. Hum Reprod Update 12:437–448. https://doi.org/10.1093/humupd/dmk002

11. Sanli O, Armagan A, Kandirali E et al (2004) TGF-β 1 neutralizing antibodies decrease the fibrotic effects of ischemic priapism. Int J Impot Res 16:492–497. https://doi.org/10.1038/sj.ijir.3901261

12. Karaguzel E, Bayraktar C, Kutlu O et al (2016) The possible protective effects of dipyridamole on ischemic reperfusion injury of priapism. Int Braz J Urol 42:146–153. https://doi.org/10.1590/S1677-5538.IBJU.2015.0072

13. Sun Y, Oberley LW, Li Y (1988) A simple method for clinical assay of superoxide dismutase. Clin Chem 34:497–500

14. Paglia DE, Valentine WN (1967) Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J Lab Clin Med 70:158–169

15. Mueller AR, Platz KP, Langrehr JM et al (1994) The effects of administration of nitric oxide inhibitors during small bowel preservation and reperfusion. Transplatation 58:1309–1316

16. Hassanipour M, Amini-Khoei H, Shafaroodi H et al (2016) Atorvastatin attenuates the antinociceptive tolerance of morphine via nitric oxide dependent pathway in male mice. Brain Res Bull 125:173–180. https://doi.org/10.1016/j.brainresbull.2016.07.002

17. Levey HR, Segal RL, Bivalacqua TJ (2014) Management of priapism: an update for clinicians. Ther Adv Urol 6:230–244. https://doi.org/10.1177/1756287214542096

18. Spycher MA, Hauri D (1986) The ultastructure of the erectile tissue in priapism. J Urol 135:142–147

19. Broderick GA, Kadioglu A, Bivalacqua TJ, Ghanem H, Nehra A, Shamloul R (2010) Priapism: pathogenesis, epidemiology, and management. J Sex Med 7:476–500. https://doi.org/10.1111/j.1743-6109.2009.01625.x

20. Jennings RB, Reimer KA (1991) The cell biology of acute myocardial ischemia. Annu Rev Med 42:225–246. https://doi.org/10.1146/annurev.me.42.020191.001301

21. Green CJ, Gower JD, Healing G, Cotterill LA, Fuller BJ, Simpkin S (1989) The importance of iron, calcium and free radicals in reperfusion injury: an overview of studies in ischaemic rabbit kidneys. Free Radic Res 7:255–264. https://doi.org/10.3109/10715768909087950

22. Nieuwenhuijs VB, De Bruijn MT, Padbury RT, Barritt GJ (2006) Hepatic ischemia-reperfusion injury: roles of Ca^{2+} and other intracellular mediators of impaired bile flow and hepatocyte damage. Dig Dis Sci 51:1087–1102. https://doi.org/10.1007/s10620-006-8014-y

23. Chatauret N, Badet L, Barrou B, Hauet T (2014) Ischemia-reperfusion: from cell biology to acute kidney injury. Prog Urol 24:4–12. https://doi.org/10.1016/S1166-7087(14)70057-0

24. Kucukdurmaz F, Kucukgergin C, Akman T, Salabas E, Armagan A, Seckin S et al (2016) Duration of priapism is associated with increased corporal oxidative stress and antioxidant enzymes in a rat model. Andrologia 48:374–379. https://doi.org/10.1111/and.12455

25. Evliyaoglu Y, Kayrin L, Kaya B (1997) Effect of allopurinol on lipid peroxidation induced in corporal tissue by veno-oclusive priapism in a rat model. Br J Urol 8:476–479. https://doi.org/10.1046/j.1464-410X.1997.00371.x

26. Sehirli AO, Sener G, Satiroglu H, Ayanoğlu-Dülger G (2003) Protective effect of N-acetylcysteine on renal ischemia/reperfusion injury in the rat. J Nephrol 16:75–80

27. Uluocak N, Atılgan D, Erdemir F et al (2010) An animal model of ischemic priapism and the effects of melatonin on antioxidant enzymes and oxidative injury parameters in rat penis. Int Urol Nephrol 42:889–895. https://doi.org/10.1007/s11255-010-9706-y

28. Unsal V, Belge Kurutaş E (2017) Experimental hepatic carcinogenesis: oxidative stress and natural antioxidants. Open Access Maced J Med Sci 12:686–691. https://doi.org/10.3889/oamjms.2017.101

29. Bauer V, Sotníková R (2010) Nitric oxide – the endothelium-derived relaxing factor and its role in endothelial functions. Gen Physiol Biophys 29:319–340. https://doi.org/10.4149/gpb_2010_04_319

30. Abdel Aziz MT, Motawi T, Rezq A et al (2012) Effects of a water-soluble curcumin protein conjugate vs. pure curcumin in a diabetic model of erectile dysfunction. J Sex Med 9:1815–1833. https://doi.org/10.1111/j.1743-6109.2012.02741.x

31. Işeri SO, Sener G, Saglam B, Gedik N, Ercan F, Yegen BC (2005) Oxytocin protects against sepsis-induced multiple organ damage: role of neutrophils. J Surg Res 126:73–81. https://doi.org/10.1016/j.jss.2005.01.021

32. Sehirli O, Sener E, Cetinel S, Yüksel M, Gedik N, Sener G (2008) Alpha-lipoic acid protects against renal ischaemia-reperfusion injury in rats. Clin Exp Pharmacol Physiol Suppl 35:249–255. https://doi.org/10.1111/j.1440-1681.2007.04810.x

33. Toklu H, Alican I, Ercan F, Sener G (2006) The beneficial effect of resveratrol on rat bladder contractility and oxidant damage following ischemia/reperfusion. Pharmacology 78:44–50. https://doi.org/10.1159/000095176

34. Gimpl G, Fahrenholz F (2001) The oxytocin receptor system: structure, function, and regulation. Physiol Rev 81:629–683. https://doi.org/10.1152/physrev.2001.81.2.629

35. Kiss A, Mikkelsen JD (2005) Oxytocin anatomy and functional assignments: a minireview. Endocr Regul 39:97–105

36. Erbas O, Anil Korkmaz HA, Oltulu F et al (2014) Oxytocin alleviates cisplatin-induced renal damage in rats. Iran J Basic Med Sci 17:747–752

37. Tas Hekimoğlu A, Toprak G, Akkoç H, Evliyaoglu O, Ozekinci S, Kelle I (2013) Oxytocin ameliorates remote liver injury induced by renal ischemia-reperfusion in rats. Korean J Physiol Pharmacol 17:169–173. https://doi.org/10.4196/kjpp.2013.17.2.169

38. Erkanli K, Erkanli Şentürk G, Aydın U et al (2013) Oxytocin protects rat skeletal muscle against ischemia/reperfusion injury. Ann Vasc Surg 27:662–670. https://doi.org/10.1016/j.avsg.2012.10.012