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The effect of pentoxifylline on penile cavernosal tissues in ischemic priapism-induced rat model

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Abstract
Introduction Priapism is defined as persisting (>4 h), painful and abnormal tumescence that can occur without sexual stimulation. Three subtypes priapisms are seen—the non-ischemic priapism, intermittent and the ischemic priapism. In ischemic priapism, there is an abnormality in the veno-occlusive mechanism, resulting in venous stasis and accumulation of deoxygenated blood within the penile cavernosal tissue. Cavernosal tissue necrosis develops after extended period of ischemia and is eventually replaced by fibrotic tissue. It may results in erectile dysfunction if not treated promptly. Although, standard treatment of the ischemic priapism is penile aspiration and intracavernosal alpha-adrenergic agents, new oral agents have been investigated to reduce the cavernosal damage. In this study, the effect of different doses of pentoxifylline on cavernosal tissues was evaluated.
Materials and methods Thirty-six male Wistar albino rats, age 5.5–6 months and weighing 250–300 g, were used in this study. The rats were randomly divided into five groups. In Group 1 ($n = 7$), the control group, only penectomy was performed. In Group 2 ($n = 8$), after 1 h of ischemic priapism, penectomy was performed. Group 3 ($n = 7$) received daily a 10 mg oral pentoxifylline for 4 weeks after 1 h of ischemic priapism, group 4 ($n = 7$) received a daily 30 mg oral pentoxifylline for 4 weeks after 1 h of ischemic priapism, and group 5 ($n = 7$) received a daily 100 mg oral pentoxifylline for 4 weeks after 1 h of ischemic priapism. At the completion of a 4-week period, penile tissues were obtained. Before penile tissues were obtained, intracavernosal pressures measured with electrical field stimulation and smooth muscle collagen ratio were evaluated pathologically.
Results Electrical field stimulation-induced intracavernosal relaxation decreased in group 2 compared with group 1 ($p < 0.05$). Electrical field stimulation-induced relaxation enhanced in the group 3, 4 and 5 compared to group 2 ($p < 0.05$). In group 2, the collagen density was significantly higher than group 1. Administration of pentoxifylline reduced the collagen density caused by ischemic priapism in groups 3, 4 and 5 compared with group 2.
Conclusion The results of the present study showed that ischemic priapism caused damage in the penile tissues of rats, and treatment with pentoxifylline reduced the harmful effects of ischemic priapism.

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Keywords Penis · Priapism · Ischemia · Treatment · Pentoxifylline

Introduction

The term "priapism"' is derived from the name of Priapus, a minor deity of fertility, luck, gardens, and fields in Greek mythology [1]. Priapism is defined as prolonged and persistent penile erection lasting greater than 4 h, unassociated with sexual stimulation. Priapism is divided into three subgroups as non-ischemic priapism (high flow, arterial), ischemic priapism (low flow, veno occlusive), and stuttering (intermittent, recurrent ischemic) priapism. Ischemic priapism is the more common form of priapism and is usually idiopathic [2]. It is associated with venous outflow obstruction and venous stasis. These conditions results in significant cavernosal tissue hypoxia, acidosis, and ischemia. In penile cavernosal tissues, prolonged smooth muscle exposure to ischemia may result in varying extents of fibrosis with endothelial and trabecular destruction of the erectile tissue and subsequently in erectile dysfunction (ED) [3]. Ischemic priapism with a duration of <24 h has a 50 % chance of retaining some degree of erectile function, while beyond 24 h, the risk of penile deformity and complete erectile function is >90 % [4]. In the treatment of ischemic priapism, several surgical approaches, intracavernosal applications, and oral drugs have been used [5]. Despite these treatments, ED can be seen in patients with priapism. Although studies have confirmed the efficacy of penile aspiration and intracavernosal alpha-adrenergic agonists in reducing the damaging effect of priapism, different agents have been investigated to reduce the short- and long-term penile cavernosal damage. As phosphodiesterases regulate the intracellular levels of cyclic adenosine monophosphate and cyclic guanosine monophosphate, their inhibition can affect several processes, such as apoptosis, muscle contraction, cellular differentiation, migration, proliferation, and blood flow [6, 7]. Pentoxifylline, a nonselective phosphodiesterase inhibitor derived from xanthine, is a vasodilator. The efficacy of pentoxifylline in treatment is essentially due to its potential to increase blood flow and tissue oxygenation [8]. As related to this feature, pentoxifylline is used for claudication in patients with peripheral vascular disease, and experimentally for ischemic injury. In addition, it is known as an anti-fibrogenic drug [8–10].

The aim of this study was to evaluate the effect of pentoxifylline on cavernosal tissues in ischemic priapism-induced rat model.

Materials and methods

After obtaining approval from the local ethics committee (2011-HADYEK-014), a total of thirty-six male Wistar albino rats, 5.5–6 months old and weighing 250–300 g, were used in this study. The rats were handled in the laboratory according to institutional guidelines as well as the *Guide for Care and Use of Laboratory Animals* of the National Research Council. They were kept in a temperature-controlled room (20–23 °C), on a 12 h light/dark cycle with food (commercial rat chow), and fresh water available ad libitum. All surgical procedures were performed under xylazine/ketamine (50 mg/kg, ip) anesthesia in sterile conditions. All rats were killed after the experimental procedures. Priapism was accomplished as previously described in the literature [11]. The tip of a 5-cc syringe was cut to accommodate the device to the base of the flaccid penis, so a vacuum erection device was created. Before application of vacuum to the penis, a constriction band, which was cut from 16 Fr foley catheters in 2-mm slices, was loaded around the tip of the vacuum erection device. Then, the tip of the syringe was placed to the base of the penis and withdrawn gently to induce erection in the rat penis. After induction of erection in sufficiently, the constriction band was placed to the base of the penis by slipping off the syringe. The animals were divided into five groups. In the control group (Group 1, $n = 7$), only penectomy was performed. In the group 2 ($n = 8$) after 1 h of ischemic priapism, the band was removed from the base of the penis and the penectomy was performed. Group 3 ($n = 7$) received a 10 mg oral pentoxifylline for 4 weeks after 1 h of ischemic priapism, group 4 ($n = 7$) received a 30 mg oral pentoxifylline for 4 weeks after 1 h of ischemic priapism, and group 5 ($n = 7$) received a 100 mg oral

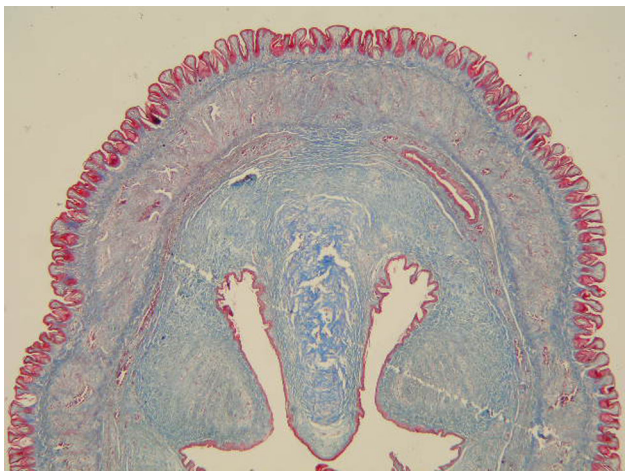


Fig. 1 The smooth muscle/collagen (*blue*) ratio of corpus cavernosum of rat was evaluated on the Masson's trichrome (MTC) staining (×100)

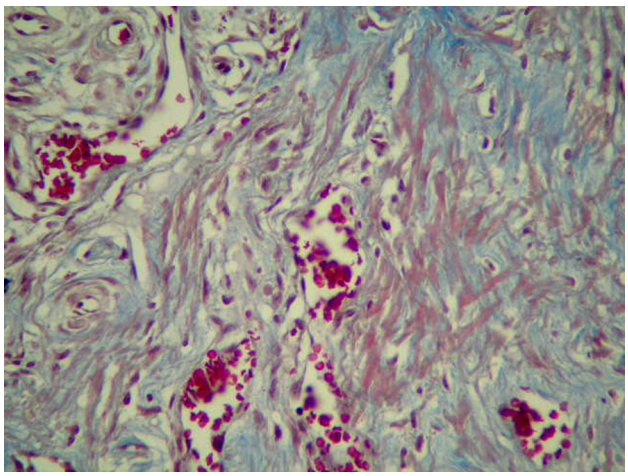


Fig. 2 The photomicrograph of penile corpus cavernosum in a group 1 showing (+) collagen (MTC, ×400)

pentoxifylline for 4 weeks after 1 h of ischemic priapism. At the completion of a 4-week period, penile tissues were obtained. Smooth muscle collagen ratios were evaluated pathologically in cavernosal tissues. The penectomy specimens were fixed in 10 % buffered formalin solution and processed routinely for paraffin embedding. Five-micron sections were cut and stained with Masson's trichrome stain to assess the amount of collagen (Fig. 1). In every slide, four high-power fields were randomly selected and the percentage of collagen density was semiquantitatively determined as the ratio of blue-stained collagen-positive area in the examining field. The Masson's trichrome-stained sections were graded on a scale (+) to (++++) according to the percentage of collagen in the penile corpus cavernosum in each group as follows: +, if 30 % or less collagen (Fig. 2); ++, if more than 30–50 % collagen; +++, if more than 50–70 % collagen; and ++++, if more than 70 % collagen.

At the completion of a 4-week period (Just before penile tissues were obtained), the intracavernosal pressures (ICP) were measured using a 25-gauge needle inserted into the left crus of the penis connected to polyethylene tubing filled with heparin. The ICP were measured using a data acquisition system (BIOPAC MP 45 SYSTEM, USA). The ICP, obtained by electronic averaging, were continuously recorded and displayed and stored using a Dell personal computer. For cavernosal nerve stimulation, the bladder and prostate were exposed through a midline abdominal incision. The cavernosal nerve was identified posterolaterally to the prostate on one side, and a stainless steel bipolar-stimulating electrode was placed on the nerve. The cavernosal nerve was stimulated with square wave pulses at a frequency of 16 Hz, voltage of 2.5 and 5 V, and pulse width of 5 ms for a duration of 30 s using a STN 0211 Nerve Stimulator.

Descriptive analyses were performed to provide information on general characteristics of the study population. Kolmogorov–Smirnov test was used to evaluate whether the distribution of continuous variables were normal. Therefore, two independent sample t test was used to compare the continuous variables between study and control groups. The continuous variables were presented as the mean ± SD. A p value <0.05 was considered significant. Analyses were performed using commercial software (IBM SPSS Statistics 19, SPSS inc., an IBM Co., Somers, NY).

Results

Electrical field stimulation (EFS)-induced intracavernosal relaxation decreased in group 2 compared with group 1 ($p < 0.05$). In 2.5 V EFS, the rate of change was 50.21 % for intracavernosal pressure ($p = 0.026$). This difference was 63.88 % for intracavernosal pressure in 5 V EFS. EFS-induced relaxation enhanced in the group 3, 4, and 5 compared with group 2 (Tables 1, 2 and 3). Intracavernosal pressures were detected as 3.46 ± 1.73, 6.17 ± 2.76, 6.24 ± 3.02, and 7.19 ± 4.65 mmHg, in group 2, group 3, group 4, and group 5, respectively, in 2.5 V EFS. These values were detected as 5.84 ± 3.75, 14.91 ± 14.15, 25.45 ± 38.23, and 9.66 ± 5.03 mmHg, respectively, in group 2, group 3, group 4, and group 5, respectively, in 5 V EFS. However, these differences were statistically significant only at 2.5 V. In group 2, collagen density increased compared with group 1. In group 1, there were no +++ and ++++ collagen densities. However, in group 2, ++ (Fig. 3), +++ (Fig. 4), and ++++ collagen densities rates were detected as 12.5, 50, and 37.5 %. Daily oral gavage feeding of pentoxifylline prevented collagen deposition in the corpus cavernosum in groups 3, 4, and 5 compared with group 2 (Tables 4, 5). In group 3, 4, and 5, ++++ (Fig. 5) collagen rates were 14.2 %. However, +++ collagen rates were detected as 28.5, 57.1, and 71.4 % in group 3, 4, and 5 (Table 4).

Discussion

Priapism has an incidence of 0.3–1.5 per 100,000 and can occur in all age groups from newborn to elderly. Typically, there is a bimodal peak of incidence, between 5 and 10 years in children and 20–50 years in adults [12, 13]. In addition, with the use of intracavernosal vasoactive injections, the incidence of priapism increases [14]. Ischemic priapism accounts for 95 % of priapism. Priapism is a urologic emergency that results from an imbalance of the vasoconstrictive and vasorelaxatory mechanisms, leading to the formation of a closed compartment syndrome in the

Table 1 Intracavernosal pressures in group 1 and group 2

	Group 1 ($n = 7$) (mmHg)	Group 2 ($n = 8$) (mmHg)	Changing ratio %	p
2.5 V	6.95 ± 3.46	3.46 ± 1.73	50.21	0.026
5 V	16.17 ± 10.02	5.84 ± 3.75	63.88	0.018

Table 2 The comparisons of intracavernosal pressures between group 1 and treatment groups

	Group 1 ($n = 7$) (mmHg)	Group 3 ($n = 7$) (mmHg)	Rate of change (%)	p	Group 4 ($n = 7$) (mmHg)	Rate of change (%)	p	Group 5 ($n = 7$) (mmHg)	Rate of change (%)	p
2.5 V	6.95 ± 3.46	6.17 ± 2.76	11.22	0.648	6.24 ± 3.02	10.21	0.690	7.19 ± 4.65	3.45	0.916
5 V	16.17 ± 10.02	14.91 ± 14.15	7.79	0.851	25.45 ± 38.23	57.39	0.546	9.66 ± 5.03	40.25	0.151

Table 3 The comparisons of intracavernosal pressures between group 2 and treatment groups

	Group 2 ($n = 8$) (mmHg)	Group 3 ($n = 7$) (mmHg)	Rate of change (%)	p	Group 4 ($n = 7$) (mmHg)	Rate of change (%)	p	Group 5 ($n = 7$) (mmHg)	Rate of change (%)	p
2.5 V	3.46 ± 1.73	6.17 ± 2.76	78.32	0.038	6.24 ± 3.02	80.34	0.045	7.19 ± 4.65	107.80	0.055
5 V	5.84 ± 3.75	14.91 ± 14.15	155.30	0.103	25.45 ± 38.23	335.78	0.171	9.66 ± 5.03	65.41	0.116

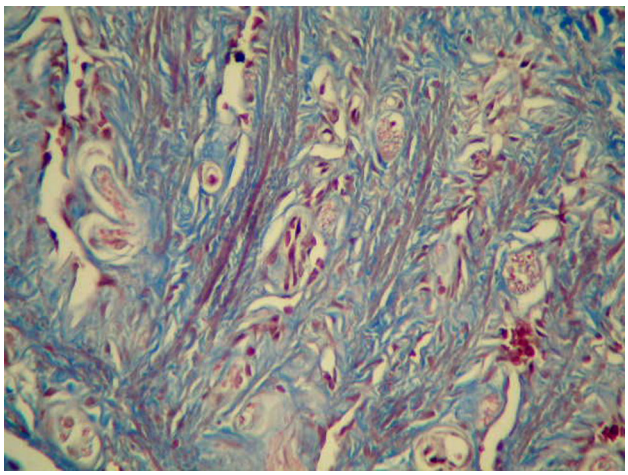


Fig. 3 Collagen content was scored as (++) in a group 2 (MTC, ×400)

penis, and this situation is biochemically characterized by hypoxia, hypercapnia, and acidosis. The combination of venous outflow obstruction, high pressure, and poor-to-absent inflow leads to trabecular interstitial edema and ultrastructural changes in smooth muscle cells. Destruction of the endothelial cells and formation of blood clots within the corpus cavernosum lead to widespread transformation of the smooth muscle cells to fibroblast-like cells. This pathologic change eventually results in ED [15–17]. Similarly, in present study, an ischemic condition was produced in the rat corpus cavernosum. It was observed that after an hour of ischemic priapism, tissue collagen density increased significantly in priapism-induced group when compared with the levels in control group.

Table 4 Collagen densities of penile cavernosal tissues in groups

Groups	+, n	++, n	+++, n	++++, n
Group 1 ($n = 7$)	85.7 % (6)	14.2 % (1)	0	0
Group 2 ($n = 8$)	0	12.5 % (1)	50 % (4)	37.5 % (3)
Group 3 ($n = 7$)	0	57.1 % (4)	28.5 % (2)	14.2 % (1)
Group 4 ($n = 7$)	0	28.5 % (2)	57.1 % (4)	14.2 % (1)
Group 5 ($n = 7$)	0	14.2 % (1)	71.4 % (5)	14.2 % (1)

It is well known that ischemic priapism persisting for longer that 4 h requires emergency intervention to avoid the potential consequences of irreversible cavernosal fibrosis and permanent ED. Incidence of ED is directly related to the duration of priapism and aggressiveness of treatment. Although successful detumescence can be achieved after medical intervention or shunt surgery, still there is a high incidence of ED in over half of these men and in 90 % if the priapism episode lasts more than 24 h [5, 17, 18]. In this context, on their long-term follow-up (mean 66 months), El-Bahnasawy et al. [18] reported only a 43 % rate of preserved erectile function after a long-lasting priapism (median range of duration 48 h).

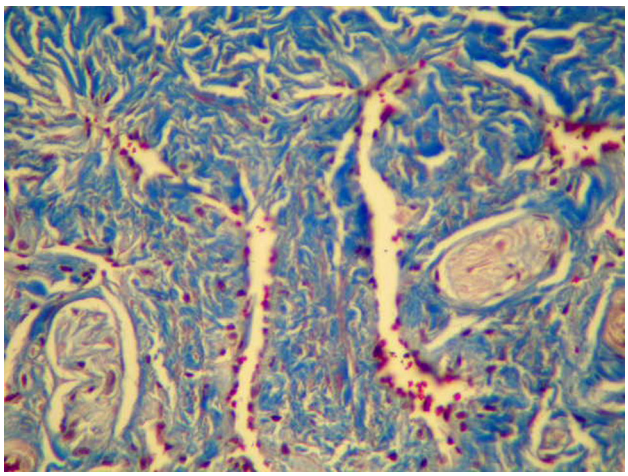


Fig. 4 The muscle content was decreased, and collagen content was increased. The score was (+++) in a group 2 (MTC, ×400)

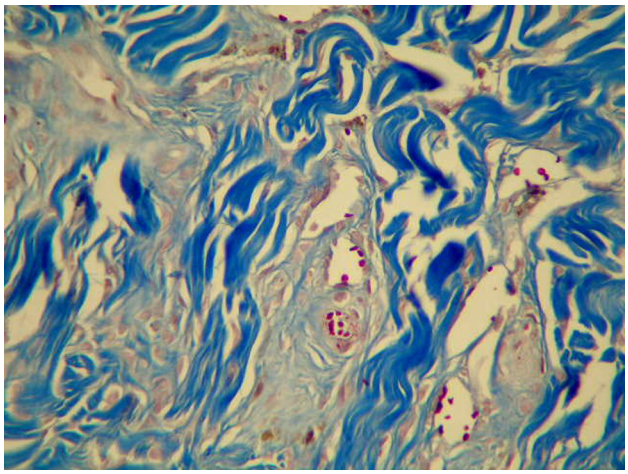


Fig. 5 Collagen content was scored as (++++) in a group 3 (MTC, ×400)

The treatment objective for ischemic priapism is to evacuate hypoxic blood, to decompress the corpora cavernosa, and to achieve increasing the outflow of cavernosal blood. For patients with ischemic priapism of relatively moderate duration (<4 h), penile aspiration and irrigation with saline remain standard first-line management strategies. This relieves pain and prevents or minimizes ischemia, necrosis, fibrosis, and ED. This procedure is followed by intracavernous injection of vasoconstrictive agents and finally progressing to surgical procedures designed to shunt blood from the corpora cavernosa to the corpus spongiosum or to the vena saphena. Pharmacological intervention comprises intracavernous injection of metaraminol or alpha-adrenergic agonists such as phenylephrine, norepinephrine, epinephrine, and oral or intravenous administration of sympathomimetic agents such as dopamine or terbutaline [19–21].

Table 5 Tissue collagen ratios

	Collagen				
	+	++	+++	++++	Total
Groups					
Group 1					
n	6	1	0	0	7
%	85.7	14.3	0	0	100.0
Group 2					
n	0	1	4	3	8
%	0	12.5	50.0	37.5	100.0
Group 3					
n	0	4	2	1	7
%	0	57.1	28.6	14.3	100.0
Group 4					
n	0	2	4	1	7
%	0	28.6	57.1	14.3	100.0
Group 5					
n	0	1	5	1	7
%	0	14.3	71.4	14.3	100.0
Total					
n	6	9	15	6	36
%	16.7	25.0	41.7	16.7	100.0

Because of all the values less than 5 in every square, *p* value was not calculated

Phosphodiesterase inhibitors are benefit to endothelial function, ischemia-reperfusion protection mechanisms. In addition to ED, their impact on several cardiovascular diseases, including pulmonary hypertension, heart failure, high-altitude pulmonary edema, Raynaud's phenomenon, coronary artery disease, diabetes mellitus, and atherosclerosis, has been shown [22–24]. As a nonselective phosphodiesterase inhibitor, pentoxifylline interferes with multiple cytokine pathways (TNF-α and TGF-β), which are involved in development of penile fibrosis and smooth muscle cell apoptosis. Pentoxifylline decreases blood viscosity, improves erythrocyte flexibility, and increases microcirculatory flow and tissue oxygen concentration. This agent is used for the treatment of intermittent claudication, neuropathy, and stroke [25–28]. Pentoxifylline have also been studied as an anti-fibrotic agent in various fibrotic conditions, such as liver fibrosis, peritoneal fibrosis, and renal fibrosis [29–31]. In addition, it is gaining acceptance as a conservative treatment for Peyronie's disease, in which it inhibits TGF-β-mediated collagen deposition and fibrosis in the tunica albuginea [32]. It is possible that pentoxifylline has salutary effects on smooth muscle cell preservation and fibrosis prevention due to inhibitory actions on TGF-β and phosphodiesterase. In this context, it has been shown that pentoxifylline was able to reduce collagen formation in

penile fibroblasts cultured in the presence of TGF-β [33]. In addition, a similar observation was made in TGF-β-pretreated vascular smooth muscle cells. In an experimental study, authors reported the beneficial effects of daily pentoxifylline treatment on recovery of erectile function in rats that underwent cavernosal nerve injury, thereby simulating postprostatectomy ED [34]. In urinary system, pentoxifylline have been used in different pathologic disorders such as nephrotoxicity, hemorrhagic cystitis, male infertility, testicular torsion, ischemic glans penis, and ureteral obstruction [35–40]. However, to our knowledge in the English literature, there is a only one experimental study, which evaluates the effect of pentoxifylline on penile cavernosal tissues in a rat model of ischemic priapism [41]. Placebo and pentoxifylline were given to rats prior to priapism being induced by a vacuum constrictive device. In this study, the protective effect of pentoxifylline was not shown on corporeal tissue in a rat model of ischemic priapism in terms of attenuation of lipid peroxidation. However, in that study, authors had been used only single-dose pentoxifylline to evaluate of the effect of pentoxifylline. In present study, the pentoxifylline reduced the negative effects of priapism after 4 weeks periods. Interestingly, in present study, the ++++ positive collagen ratios were lower in group 3, group 4, and group 5 in comparison to group 2. Except this finding, according to these results, we can say that the effect of different dosages of pentoxifylline on penile cavernosal tissues is similar. Similarly, in a case report, authors revealed that a daily anti-fibrotic regimen comprising the phosphodiesterase inhibitors pentoxifylline and sildenafil, and the NO precursor, L-arginine prevented the palpable corporeal fibrosis in two patients with priapism [42].

According to these results, we can say that pentoxifylline may prevent the negative effects of priapism in penile cavernosal tissues. However, more randomized, controlled, and well-designed studies with larger population are needed to confirm of these results.

Conflict of interest No conflict of interest was declared by the authors.

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