The effects of silibinin on corporal oxidative stress and antioxidant enzymes in ischemic priapism

Silibininin iskemik priapizmde korporal oksidatif stres ve antioksidan enzimler üzerine etkileri

Silibinin for ischemic priapism

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Öz

Amaç: İskemik priapizm, progresif hipoksi, hiperkapni ve asidozla seyreden ve sonrasında gelişen korporal fibrozisin erektil disfonksiyona yol açabildiği androlojik bir acildir. Silibinin çeşitli hayvan deneylerinde farklı organlar üzerinde antiapoptotik, antilipidemik ve antioksidan etkileri gösterilmiş bir flavonoid derivesidir. Yapılan çalışmalarda silibininin organ koruyucu etkisinin sıklıkla antioksidan etkilerine bağlandığı belirlenmiştir. Buna karşın,literatürde silibininin uzamış priapizm olgularında korporal doku üzerindeki etkilerine ilişkin yayın bulunmamaktadır. Çalışmanın amacı, iskemik priapizm hayvan modelinde silibininin farklı priapizm süreleri sonrasında korporal dokudaki oksidatif stres ve antioksidan enzim düzeyleri üzerine etkisinin incelenmesidir. Gereç ve Yöntem: Otuz adet Wistar-Albino erkek rat 5 eşit gruba bölündü. Bunlar kontrol, 12-saat priapizm+izotonik(Pİ), 12 saat-priapizm+silibinin (PS), 24 saat Pİ ve 24 saat PS grupları olarak belirlendi. Priapizm vakum ereksiyon sonrası penis köküne yerleştirilen konstriktör bant ile sağlandı. 12 ve 24 saatlik priapizm sonrası bantlar çıkarıldı ve ratlar oral gavajla 7 gün boyunca izotonik ya da silibinin ile beslendi. Bir hafta sonunda sıçanlar uyutularak penektomi yapıldı ve dokuda malondialdehit (MDA), superoksit dismutaz (SOD), glutatyon peroksidaz (GPx) and nitrik oksit (NO) düzeyleri değerlendirildi. Bulgular: Korporal MDA düzeyleri priapizm süresi uzadıkça anlamlı arttı. Silibinin tedavisi priapizm gruplarında MDA düşüşü sağladı. Korporal GPx ve SOD değerleri priapizm gruplarında kontrol grubuna oranla belirgin yüksekti. Ancak antioksidan enzim değerlerindeki değişim priapizm süresi ile korelasyon göstermedi. Silibinin ile beslenen ratlarda SOD ve GPx değerleri izotonik gruplarına göre anlamlı azaldı. Nitrik oksit değerleri gruplar arasında anlamlı değişiklik göstermedi. Tartışma: Çalışma sonunda priapizmin korporal dokuda zaman bağımlı olarak oksidatif stresi artırdığı ve silibinin tedavisinin oksidatif stres üzerinde azaltıcı etkisi olduğu gösterildi. Silibinin maddesi priapizm tedavisinde umut vaat eden bir madde olabilir.

Anahtar Kelimeler

Silibinin; Priapizm; Oksidatif Stres; Antioksidan Enzimler

Abstract

Aim: Ischemic priapism is characterised by progressive hypoxia,hypercapnia, and acidosis with subsequent corporal fibrosis which may lead to erectile dysfunction.In various studies, silibinin has been shown to have antiapoptotic,antilipidemic, and antioxidant activities in many organs. However,data is lacking about the effects of silibinin on penile tissues of prolonged priapism cases. The aim of the study was to investigate the possible protective effects of silibinin on oxidative stress and antioxidant enzyme levels in an animal model. Material and Method: Thirty male Wistar-Albino rats were divided into five groups as control,12-hours (h) of priapism+isotonic (PI),12-h priapism+silibinin (PS),24-h PI, and 24-h PS groups,respectively. Priapism was induced by vacuum device and a constrictor rubber band was placed at the base of the erect penis. The rats were fed by isotonic and silibinin with oral gavage for 7 days after corresponding duration of priapic episodes.Then,the rats were anesthesized and penectomies were performed to investigate levels of malondialdehyde (MDA),superoxide dismutase (SOD),glutathione peroxidase (GPx), and nitric oxide (NO). Results: Corporal MDA levels significantly increased as the duration of priapism prolonged.Administration of silibinin insignificantly decreased MDA levels in experimental groups.Corporal GPx and SOD levels were significantly higher in experimental groups than controls.However,increases in antioxidant enzymes were not significant between 12 and 24 hour vehicle groups.Administration of silibinin significantly reduced SOD and GPx levels in 12 and 24 hour priapism groups,respectively. Discussion: This study demonstrated that experimental priapism results in increased oxidative injury in corporal tissues and that treatment with silibinin alleviated those effects.Therefore,it can be extrapolated that silibinin may be used as an antioxidant agent in the treatment of ischemic priapism in future urology practice.

Keywords

Silibinin; Priapism; Oxidative Stres; Antioxidant Enzymes

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Introduction

The term priapism describes an emergent condition with full or partial erection that lasts more than 4 h beyond sexual stimulation and orgasm, or that is unrelated to sexual stimulation [1]. Priapism may be classified into three subtypes as ischaemic (low flow), stuttering (intermittent), and non-ischaemic (high flow) priapism [2,3]. Ischemic priapism(IP) is the most common form, associated with venous outflow obstruction and absence of arterial inflow. Subsequent time-dependent changes including progressive hypoxia, hypercarbia,and acidosis develop and ultimately ischemia and fibrosis in cavernosal smooth muscles may lead to erectile dysfunction [4,5].Since IP is a compartment syndrome, its management re-establishes corporal blood flow, which is associated with reperfusion of ischaemic tissues. Increased corporal oxidative stress may lead to irreversible cellular damage by alterations in cell membranes and the release of reactive oxygen species (ROS) into the systemic circulation [5]. Oxidative damage results in an increase in tissue levels of malondialdehyde (MDA) [6]. Antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) have protective effects against ROS. Previous studies have demonstrated that the levels of ROS increase with the duration of priapism and antioxidant enzymes were found to be elevated in priapic tissue [5,7]. Recently, Kucukdurmaz et al. reported that the oxidative stress and antioxidant enzyme activities increased as the priapic episodes prolonged [8]. Previously, various antioxidant agents have been reported to establish their protective effects in priapism models. Silibinin is the primary active constituent of a crude extract (silymarin) from milk thistle plant (Silybum marianum) seeds [9]. Many studies have reported that it had antioxidant, antiapoptotic, and therefore, cytoprotective effects in various organs. Silibinin exerts its antioxidative effects by direct scavenging of free radicals, preventing free radical formation by inhibiting specific ROS-producing enzymes and decreasing inflammatory responses by inhibiting NF-κB pathways [9]. The antioxidant properties of silibinin are considered to be responsible for its protective actions. Another effect of silibinin is to inhibit the synthesis of nitric oxide synthase (NOS), which is a pro-oxidative enzyme [10-12].

The aim of this study was to investigate the effects of silibinin on corporal oxidative stress, antioxidant enzymes, and nitric oxide levels in an animal model of ischemic priapism.

Material and Method

Animals

The protocol of the experimental study was approved by the local ethics committee. Thirty adult male Wistar-Albino rats (6–10 weeks old) weighing between 250 and 300 g were used for this study. All animals are subject to the ethical treatment in accordance with Guide for the Care and Use of Laboratory Animals. They were placed in plastic cages, three rats per cage, in a constant temperaturecontrolled room on a 12/12-h light/dark cycle. The rats were allowed to eat standard rodent chow and water ad libitum. The rats were divided into five groups of six each. Anesthesia for all procedures was provided by intraperitoneal injection of ketamine (50 mg/kg) and xylazine (10 mg/kg). Low-flow priapism was created using a vacuum constriction device with a constriction rubber band on the penis [13]. The cap of a 50- mL disposable syringe, holed at the tip, was connected to a syringe using a Foley catheter. After shaving and retracting the prepuce, the hollow tip of the cap was placed firmly over the flaccid penis. Suction was created by gently withdrawing the piston, and after tumescence, a constriction band (cutting 2 mm thickness of a 10 Fr Foley catheter) was placed around the base of the penis using forceps. During the artificially induced priapism, the animals were left undisturbed in their cages. Group 1 served as the control. After 12 h (groups 2,4) and 24 h (groups 3,5) of priapism, the constriction bands were removed and reperfusion was allowed for all rats. Then, rats in groups 2 and 4 were fed with vehicle (0.9% NaCl) and rats in groups 3 and 5 were fed with silibinin 100 mg/kg by oral gavage for 7 days, respectively. At the end of the 7th day, the rats were reanesthesized and penectomies were performed.Sacrificed animals' penile tissues were collected to evaluate the corporal changes in the levels of MDA, NO, and the activities of the SOD and GPx enzymes. Sacrification of animals was performed by cervical dislocation under anesthesia.

Preparation of Corporal Tissue Homogenates

The corporal tissues of the rats were quickly removed, washed, and rinsed with cold 0.9% NaCl, then blotted dry and immediately frozen in liquid nitrogen, to be kept at -80°C until they were analysed. Corporal tissue homogenates (10% w/v) were prepared with ice-cold solution containing 50 mmol/l of Tris–HCl (pH 7.4); 1% Triton X; 150 mmol/l of NaCl; and leupeptin, aprotinin and soya bean trypsin inhibitor (1 lg ml_1 each) at 0–4°C using a polytron homogeniser. In brief, corporal tissue homogenates were centrifuged at 600 9 g for 10 min at 4°C to remove crude fractions. Afterwards, supernatants were centrifuged at 10 000 9 g for 20 min to obtain the post-mitochondrial fraction. Measurement of tissue MDA levels was determined by the Buege & Aust method [14]. MDA reacts with thiobarbituric acid to give a red compound absorbing at 532 nm. The stock reagent (15% w/v trichloroacetic acid, 0.375% w/v thiobarbituric acid, 0.25 mol/l hydrochloric acid, and 0.01% butylated hydroxytoluene) was thoroughly mixed with the sample and heated for 15 min in a boiling water bath. After cooling, the precipitate was removed by centrifugation at 1000 9 g for 10 min and the absorbance of the supernatant was determined at 532 nm against a blank containing all the reagents. The breakdown product of 1,1,3,3-tetraethoxypropane was used as the standard. MDA levels were calculated using 1.56 x 10-5 mol-1 cm-1 as the molar extinction coefficient. MDA levels were expressed as nmol mg-1 protein for corporal tissue. Measurement of antioxidant enzyme activity SOD activity was determined as described by Fridovich [15]. The principle of the method is based on the inhibition of nitro blue tetrazolium chloride (NBT) reduction by the xanthinexanthine oxidase system, a superoxide generator. Xanthine (Sigma-Aldrich) and xanthine oxidase (Sigma-Aldrich) generate superoxide radicals, which react with NBT (SigmaAldrich) to form a red formazan dye. SOD activity was then determined according to the degree of inhibition of this reaction. One unit of SOD was defined as the quantity of enzyme (mg) causing 50% inhibition in the NBT reduction rate. SOD activity was expressed as units of SOD per mg protein. The glutathione peroxidase (GPx) activity assay was based

on the oxidation of nicotine adenosine dinucleotide phosphate (NADPH; Sigma-Aldrich) to NADP + , which is accompanied by a decrease in absorbance at 340 nm. The rate of this decrease is directly proportional to the GPx activity in the sample [16]. Therefore, GPx activity was measured by the enzymatic reaction that was initiated by adding H 2 O2 to a reaction mixture containing reduced glutathione, NADPH, and glutathione reductase (Sigma-Aldrich). The change in the absorbance at 340 nm was monitored using a Shimatzu UV-1601 spectrophotometer (Shimadzu Corp.). Protein levels were estimated as described by Lowry et al. [17] and activity was expressed in units of GPx per mg protein. The determination of concentration levels of nitrite, which is the stable end product of nitric oxide (NO) radicals, was used as a measure of NO production. Nitrite concentration was determined using a classic colorimetric Griess reaction. Briefly, equal volumes of samples and Griess reagent (Sigma-Aldrich) were mixed at room temperature. After 5 min, the absorbance was measured at 540 nm using a spectrophotometer (UV 1601; Shimadzu Scientific Instruments, Inc., Columbia, MD, USA). The concentration of nitrite was determined using a standard curve prepared with sodium nitrite [16].

Statistical Analysis

The distribution of continuous variables was evaluated according to the Kolmogorov– Smirnov normality test. If the distribution was normal, a parametric one-way ANOVA test was used for statistical analysis; if the distribution was not normal, a nonparametric Kruskal–Wallis test was used. Post hoc analysis was performed by Tukey's, Tamhane's, or Dunnett tests. The continuous variables were presented as the mean and standard deviation. A p-value of<0.05 was considered significant. Analyses were performed by using SPSS statistical software (PASW v15 SPSS Inc., Chicago, IL, USA).

Results

Corporal tissue MDA levels for groups 1,2,3,4, and 5 were 5.79±4.82, 11.38±3.45, 8.86±3.11, 21.79±3.72, and 16.24±3.20, respectively. Post-hoc analysis revealed that MDA levelssignificantly increased as the duration of priapism prolonged (p=0.001). In addition, MDA levels were found to be significantly increased with respect to duration of priapism in the groups treated with silibinin. Although administration of silibinin decreased MDA levels when compared to vehicle groups, this decline was not significant for the 12 and 24 hour priapism groups. SOD and GPx activities were also found to be increased with respect to the duration of priapism (p=0.001). Besides, corporal levels of those enzymes were found to be significantly different between groups 2 and 3 (p=0.001) and also between groups 4 and 5 (p=0.001), which means that silibinin may help to decrease antioxidant enzyme activities in priapic tissues. There were no significant changes among groups in terms of NO levels. Corporal tissue oxidative stress parameters and antioxidant enzymes are presented in Table 1. Corporal MDA levels are shown in Figure1.

Discussion

Ischaemic priapism (IP), which has been accepted as a compartment syndrome and thought to be caused by an imbalance between the vasoconstrictor and vasorelaxant mechanisms, represents more than 90% of priapism cases [5]. In IP, time-dependent changes such as progressive hypoxia, hypercapnia, and acidosis may result in corporal fibrosis with subsequent severe ED [18-19].

Ultrastructural changes in corporal microenvironment occur after 12 h in IP, focal necrosis after 24 h, and eventually necrosis and transformation of fibroblast-like cells after 48 h. If priapism is left untreated or treated late (>24 h), necrosis in cavernous smooth muscle, irreversible corporal fibrosis, and permanent erectile dysfunction will occur [19]. The most significant determining factor in the prevention of tissue damage after ischemic priapism is the duration of ischemia, which is directly correlated with reperfusion injury. Previous studies revealed that oxidative stress increased as the duration of priapic episodes prolonged [7,8]. In another study, male rabbits were exposed to a low-oxygen-tension breathing gas to achieve hypoxia within the corpora cavernosa and to decrease systemic oxygen saturation to 60%, and priapism was induced by clamping the base of the penis after pelvic nerve stimulation [5]. After varying durations of ischemia, it was determined that corporal partial oxygen pressure progressively decreased as the duration of priapism increased. Our data also supported the finding that MDA levels significantly increased with respect to time. Anti-

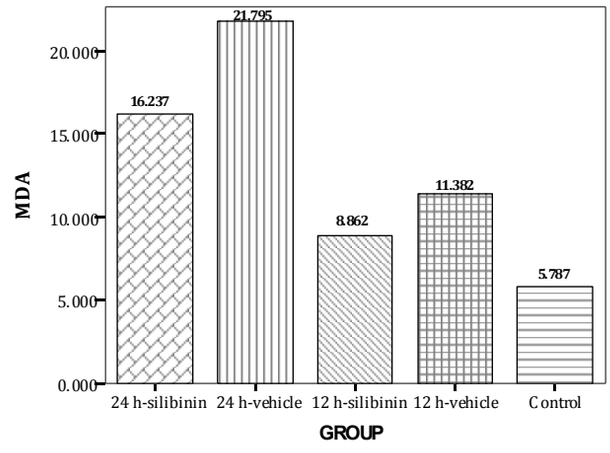


Figure 1. MDA levels among study groups
Significant differences between control and vehicle groups, p<0.001
Significant differences between 12 h and 24 h vehicle and treatment groups, respectively p<0.001

Table 1. Oxidative stress parameters and antioxidant enzyme activities among groups

	Control	12 h vehicle	12 h silibinin	24 h vehicle	24 h silibinin	p
MDA	5.79±4.82	11.38±3.45	8.86±3.11	21.79±3.72	16.24±3.20	0.001 [a,b,e,f]
SOD	0.17±0.10	0.33±0.05	0.20±0.02	0.53±0.15	0.27±0.06	0,001[a,c]
GPx	0.13±0.02	0.20±0.01	0.15±0.01	0.21±0.02	0.16±0.03	0,001[a,c,d]
NO	0.26±0.07	0.16±0.06	0.32±0.23	0.17±0.08	0.27±0.18	0.239

Data were presented as mean±SD,
a,significant difference between control-12 h vehicle and control-24 h vehicle groups
b,significant difference between control and 24 h silibinin groups
c, significant difference between 12 h vehicle and 12 h silibinin groups
d,significant difference between 24 h vehicle and 24 h silibinin groups
e, significant difference between 12 h silibinin and 24 silibinin groups
f, significant difference between 12 h vehicle and 24 h vehicle groups

oxidant enzymes such as SOD and GPx increase in response to increased oxidative stress in many I/R models. They are known to be the major enzymes that counteract the effects of ROS in reproductive organs. However, data about the level of antioxidant enzymes in priapic tissues are limited. An experimental model revealed that the levels of SOD and CAT were found to be higher in priapic tissue when compared to a control group [20]. Kucukdurmaz et al. [8] stated that antioxidant enzyme activities also increased in parallel to oxidative stress as the priapism prolonged. Similar to those reports, our study revealed that antioxidant enzyme activities increased with respect to the duration of priapism.

Silibinin is a pharmacologically active constitute of Silybum marianum. Silibinin possesses marked antioxidative, anticancer, and anti-inflammatory properties [9,21]. It is widely used in treatment due to its safety and lack of adverse effects [9]. Cytoprotective effects of silibinin are generally attributed to its antioxidant properties [9]. Silibinin exerts its antioxidant activities in various ways. These include direct free radical scavenging, inhibition of free radical producing enzymes, and decreasing inflammatory responses by inhibiting NF-κB pathways [22]. Silibinin seems to be a promising protective agent for repairing free-radical induced damage in a variety of pathological conditions [10]. Many studies reported the protective effects of silibinin in various organ systems. It has been shown that silibinin has hepatoprotective activity by its antioxidant and antiinflammatory properties [11,23]. Kalemci et al. reported that silibinin attenuated methotrexate-induced pulmonary injury by relieving oxidative stress(24). Another experimental study revealed that silibinin ameliorated arsenic-induced nephrotoxicity by decreasing oxidative stress and inflammation in kidney tissue [10]. Silibinin was also shown to protect cardiac cells from phenylephrine toxicity via antioxidant mechanisms involving mainly the inhibition of intracellular cell signals [25]. The effects of silibinin on nitric oxide are controversial; however, it is mostly stated that silibinin downregulates nitric oxide synthase and iNOS levels [10-12]. Kan et al. [26] reported that administration of silibinin inhibits tumor promotional triggers and tumorigenesis against experimentally induced skin carcinogenesis and downregulates oxidative stress and inflammation by decreasing mediators such as nitric oxide, iNOS, and interleukin-6.

It was previously mentioned that silibinin exerts its organ protective effects mainly by antioxidant mechanisms. Therefore, this study has been performed to investigate not only the changes in oxidative stress parameters and the antioxidant enzyme activities according to varying durations of priapism but also the effects of silibinin on those parameters in priapic tissues. For this purpose, rats were treated either by vehicle (0.9% NaCl) or silibinin for 7 days after 12 and 24 hours of priapic episodes. When silibinin and vehicle groups were compared, it was found out that silibinin insignificantly decreased MDA levels in both the 12 and 24 hour priapism groups. The decrease in oxidative stress with the administration of silibinin was consistent with the previously mentioned literature. In addition, when silibinin and vehicle groups were compared in terms of antioxidant activity, it was observedthat the levels of antioxidant enzymes were significantly lower in rats treated with silibinin. There were no significant differences among the groups in terms of corporal nitric oxide levels. To our knowledge, this is the first study thatinvestigates the effects of silibinin on corporal oxidative stress and antioxidant enzymes in animal model ischemic priapism. Our results showed that silibinin had beneficial effects to relieve oxidative stress in prolonged priapic episodes. Further research including histopathological investigations in corporal tissues should be conducted to investigate organ-protective effects of silibinin.

Conclusion

This study demonstrated that oxidative injury in cavernosal tissues of rats increased with the duration of priapism, and treatment with silibinin decreased oxidative stress and antioxidant enzyme activities when compared to the vehicle group. From the results of this experimental study, it can be concluded that silibinin may be used as a new antioxidant agent in the treatment of ischemic priapism.

Competing interests

The authors declare that they have no competing interests.

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