

Effects of Chronic Vardenafil Treatment Persist after End of Treatment in Rats with Acute Arteriogenic Erectile Dysfunction

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ABSTRACT

Introduction. In our previous study, chronic vardenafil treatment improved erectile function soon after the end of the treatment in rats with acute arteriogenic erectile dysfunction (ED).

Aim. The aim of this study is to evaluate whether the effects of chronic vardenafil treatment persist after the end of treatment using rats with acute arteriogenic ED.

Methods. Rats were randomly divided into three groups: (i) control; (ii) ligation; and (iii) vardenafil + no treatment. Rats in the ligation and vardenafil + no treatment groups underwent ligation of the bilateral internal iliac arteries to induce acute arteriogenic ED and were subsequently treated with vehicle or vardenafil (4.0 mg/kg/day), respectively, for 3 weeks. Subsequently, all rats were kept for a further 2 weeks with no treatment. Rats in the control group underwent sham surgery.

Main Outcome Measures. Erectile function was assessed by changes in intracavernous pressure (ICP). Smooth muscle (SM)/collagen ratios in corpus cavernosum were analyzed by Masson trichrome staining. Transforming growth factor- β_1 (TGF- β_1) mRNA and protein levels in corpus cavernosum (CC) were, respectively, evaluated by real-time polymerase chain reaction (PCR) analysis and Western blotting analysis.

Results. ICP/mean arterial pressure (MAP) in the ligation group remained significantly lower than that in control group ($P < 0.01$). Despite no treatment for 2 weeks, ICP/MAP in the var + no treatment group remained significantly higher than that in ligation group ($P < 0.05$). SM/collagen ratio in the ligation group remained significantly lower when compared with the control group ($P < 0.01$). The ratio in the var + no treatment group remained significantly higher when compared with the ligation group at 2 weeks after the end of treatment ($P < 0.05$). TGF- β_1 mRNA and protein levels did not differ among the groups.

Conclusions. The effects of chronic vardenafil treatment on erectile function and penile structure persist, even after the end of treatment, in acute arteriogenic ED rats. **Hotta Y, Ohno R, Kataoka T, Mikumo M, Takahata Y, Ohno M, Maeda Y, and Kimura K. Effects of chronic vardenafil treatment persist after end of treatment in rats with acute arteriogenic erectile dysfunction. J Sex Med 2012;9:1782–1788.**

Key Words. Arteriogenic; Erectile Dysfunction; Chronic PDE5 Inhibitor Therapy; Vardenafil; Structure; Improvement of Erectile Function

Introduction

Arteriogenic erectile dysfunction (ED) is caused by insufficiency of arterial inflow to sinusoidal spaces as a result of traumatic or atherosclerotic arterial occlusive disease of the pudendal, cavernous, or helicine arteries [1–3]. As therapy for arteriogenic ED, phosphodiesterase

type 5 (PDE5) inhibitors are initially taken on demand [4]. In cases where medication is ineffective, revascularization may be performed. Revascularization is an effective, but invasive, treatment and is rarely indicated for treatment of arteriogenic ED, as the majority of men with ED of this cause have small vessel atherosclerotic disease not amenable to bypass.

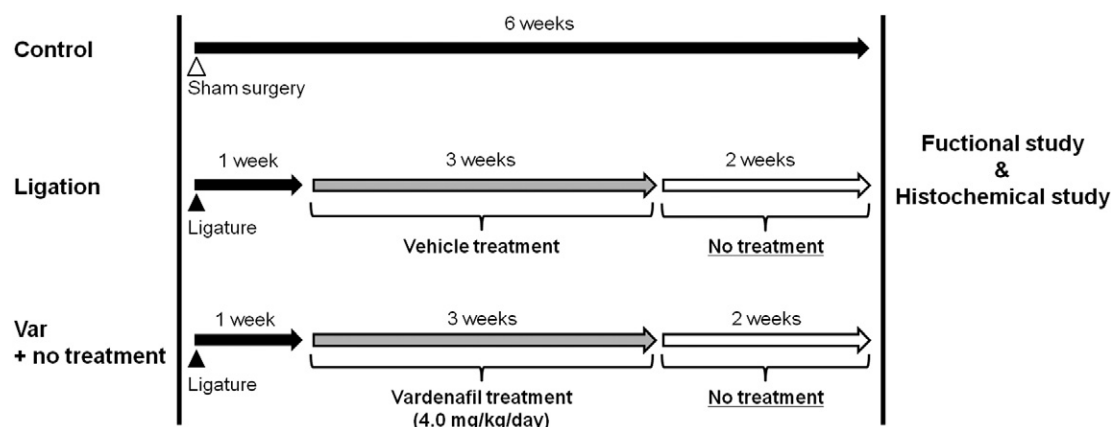


Figure 1 Experimental protocols. Control group: animals underwent sham surgery. Ligation group: animals underwent ligature and were kept for 2 weeks with no treatment after the end of vehicle treatment. Var + no treatment group: animals were kept for 2 weeks with no treatment after the end of vardenafil treatment. Var = vardenafil.

It was recently shown that sildenafil treatment nightly for 1 year improved the erectile function domain of the International Index of Erectile Function and peak systolic velocity of the penile cavernous arteries in men with mild-to-moderate arteriogenic ED in an open-label and randomized trial [5]. In addition, daily sildenafil treatment for ED in men was reported to improve penile blood flow and penile endothelial function without causing any relevant systemic effects [6].

Our previous study found that in rats with acute arteriogenic ED model induced by ligation of bilateral internal iliac arteries, daily vardenafil treatment for 3 weeks significantly improved erectile function when compared with vehicle treatment soon after the end of the treatment. This improvement appeared to be caused by maintenance of penile CC via downregulation of TGF- β_1 [7].

However, it is unknown whether the effects of chronic vardenafil treatment persist after the end of treatment. In this study, we used a model of acute arteriogenic ED caused by ligation of bilateral internal iliac arteries to investigate whether the effects of chronic vardenafil treatment persist after the end of treatment.

Materials and Methods

Animals

This experiment was performed using 8-week-old male Wistar-ST rats (SLC Inc., Shizuoka, Japan). Animals were housed in an environmentally (temperature and humidity) controlled room with a 12-hour light/dark cycle and free access to laboratory chow and water. All experiments were carried

out in accordance with the Guiding Principles for the Care and Use of Laboratory Animals of The Science and International Affairs Bureau of the Japanese Ministry of Education, Culture, Sports, Science and Technology, and with the approval of the Ethics Committee of Nagoya City University.

Experimental Protocols

Experimental protocols are shown in Figure 1. First, rats were randomly divided into three groups: (i) control; (ii) ligation; and (iii) var + no treatment. Sham-operated rats were used as a control group. Rats in the ligation and var + no treatment groups underwent ligation of bilateral internal iliac arteries to induce acute arteriogenic ED and were then treated with vehicle or vardenafil (4.0 mg/kg/day), respectively, for 3 weeks beginning at 1 week after surgery. Treatments were administered orally once daily. At the end of treatment, rats in both the ligation and var + no treatment groups were kept for two further weeks with no treatment. Vardenafil hydrochloride salt was dissolved in water containing 23% glycerol and 38% polyethylene glycol at a final concentration of 4.0 mg/mL. After the observation period, functional and histological studies were performed for each group.

Ligation Surgery

Under pentobarbital sodium anesthesia, a 3- to 4-cm midline longitudinal lower abdominal incision was made. The internal iliac arteries were identified and ligated under a dissecting microscope. After bilateral ligation, the incision was sutured.

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