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EFFECTS OF DAILY VARDENAFIL TREATMENT ON VOIDING DYSFUNCTION CAUSED BY LIGATION OF BILATERAL INTERNAL ILIAC ARTERIES IN RATS

Hypothesis / aims of study
Recently it has been reported that the treatment of phosphodiestherase-5 (PDE-5) inhibitors are effective for lower urinary tract symptoms. However it is unknown whether the treatment of PDE-5 inhibitor is effective for voiding dysfunction caused by ischemia. In this study we investigated the effect of chronic administration of vardenafil, which is one of the PDE-5 inhibitors, on ischemic bladder model rats.

Study design, materials and methods
Eight-week-old female Spargue-Dawley rats were divided into three groups: (1) Control group, (2) Ligation group, or (3) vardenafil (4.0 mg / kg / day) treated group. Rats of Control group were underwent sham operation and those of Ligation group were ligated bilateral internal iliac arteries. Vardenafil was given to ligated rats as oral administration once daily, for 3 weeks from 1 week after operation. At 4 weeks after surgery, cystometrogram was performed in all rats. After measurements, bladder was harvested to calculate bladder-to-body weight ratio and use to investigate the expression of neuronal nitric oxide synthase (nNOS) by RT-PCR and immunohistochemistry.

Results
Voiding intervals were significantly longer in Ligation group than in Control group ($P < 0.05$). The intervals were significantly shorter in Vardenafil group than in Ligation group ($P < 0.05$) and were almost equal to that in Control group. Among all groups, there were no differences in maximum voiding pressure (Table).

Table. Voiding intervals and maximum voiding pressure in each group.

Group	Voiding intervals (sec)	Maximum voiding pressure (cmH_2O)
Control	156.6 ± 23.0	58.6 ± 7.1
Ligation	314.7 ± 61.8*	63.7 ± 8.7
Ligation + Vardenafil	130.6 ± 25.5**	95.6 ± 17.1

*P < 0.05 v.s. Control group
**P < 0.05 v.s. Ligation group

There were no significant differences in bladder-to body weight ratio among all groups.
nNOS mRNA levels were significantly increased in Ligation group compared with in Control group ($P < 0.01$). The expression levels were significantly decreased in Vardenafil group compared with in Ligation group ($P < 0.01$) and almost equal to in Control group.
According to immunohistochemistry, there were no changes in expression among three groups. However, nNOS expression was obviously up-regulated in smooth muscle layer of Ligation group compared with Control group. Such up-regulation was not observed in Vardenafil group (Figure).

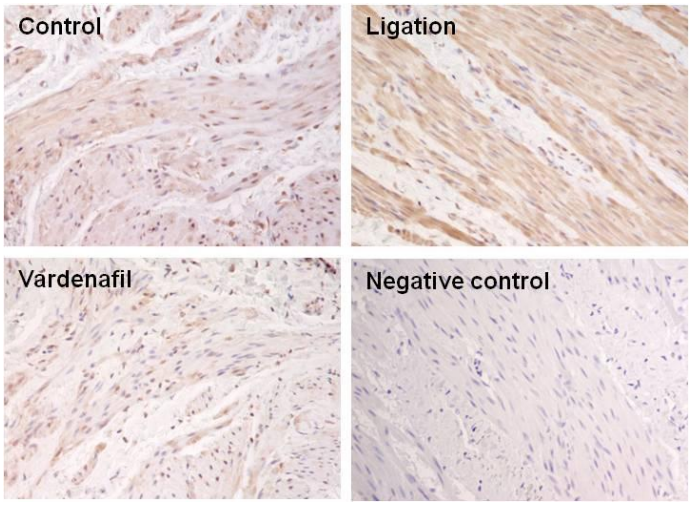

Figure. nNOS expression in bladder smooth muscle in each group.

Interpretation of results

Nitric Oxide was known to play an important role during urine collection. Thus, in this study the extension of voiding interval might be caused by nNOS over-expression. nNOS over-expression might be resulted from compensatory reaction of ischemia.
In addition daily vardenafil treatment normalized voiding interval. This might be resulted from prevention of the nNOS over-expression. Daily vardenafil treatment might provide negative feedback in nNOS expression to prevent the excessive production of NO, because NO-cGMP pathway is expected to be activated by inhibition of PDE-5 and increase of cGMP concentration.

Concluding message

Daily vardenafil treatment is effective for voiding dysfunction after ligation of bilateral iliac arteries, and may be developed to become clinically useful treatments for voiding dysfunction after pelvic ischemic condition such as trauma.

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Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
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