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SILDENAFIL COMPARED WITH VARDENAFIL IN EXPERIMENTAL MODEL OF BLADDER OUTLET OBSTRUCTION IN RATS. WHAT IS MORE POTENT FOR THE TREATMENT OF VOIDING DYSFUNCTION?

Hypothesis / aims of study:
Lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) are common conditions in middle-age or older men. LUTS range from mild to severe, depending on their occurrence, and can strongly worsen the quality of life (QoL). The symptoms are frequency, urgency, nocturia, intermittency, straining, incomplete emptying and weak stream [1].
Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection suficient to permit satisfactory sexual intercourse. ED may result from psychological, neurologic, hormonal, arterial, cavernosal impairment or from a combination of these factors [2].
ED is a highly prevalent comorbidity in men with LUTS. Although the underlying mechanisms for the relationship between LUTS and ED in BPH men are not fully elucidated, common links such as the nitric oxide–cyclic guanosine monophosphate (NO/cGMP) pathway, RhoA/Rho-kinase signaling, pelvic atherosclerosis, and autonomic adrenergic hyperactivity can be potential targets for phosphodiesterase type 5 inhibitors (PDE5-Is) [1].
Despite the large number of clinical studies involving PDE5-Is and LUTS, there is no comparative experimental study evaluating their action in an animal model of bladder outlet obstruction (BOO). Additionally, it is previously knowledge that PDE5-Is have similar efficacy to treat ED. But, are there difference between PDE5-Is to treat BPH? Based on this, the principal aim of this study was to compare the effects of Sildenafil and Vardenafil in Cystometric parameters of male mice with BOO induced by NO chronic deficiency with N^{ω}-nitro-L-arginine methil ester hidrocrolide (L-NAME).

Study design, materials and methods:
Twenty-four male mice (*Mus musculus*) were used, weighing between 40-50g, distributed as follows:

- Control Group: Six mice fed with standard diet and drinking water for 30 days.
- L-NAME Group: Six mice fed with standard diet and L-NAME diluted in drinking water (60mg/kg) for 30 days.
- Sildenafil + L-NAME Group: Six mice fed with standard diet and L-NAME diluted in drinking water (60mg/kg) for 30 days with daily administration of oral Sildenafil (40mg/Kg/day).
- Vardenafil + L-NAME Group: Six mice fed with standard diet and L-NAME diluted in drinking water (60mg/kg) for 30 days with daily administration of oral Vardenafil (10mg/kg/day).

All animals underwent cystometry at the end of the treatment. For cystometry, the animals were anesthetized with urethane (1.2 mg / kg) and submitted to laparotomy to expose the bladder dome, which was punctioned with a 19G butterfly connected to a pump for saline infusion and to a pressure transducer.
The following parameters were evaluated: Non-voiding contraction (NVC), threshold pressure (TP), Basal Pressure (BP), micturition frequency (MF) and Threshold Volume (TV).
For statistical analysis, the Kolgomorov-Smirnov (KS) test was used to evaluate the normality of the data distribution in each group. Between groups, analysis of variance (ANOVA) with Tukey's test were used. The level of statistical significance was 5% ($p < 0.05$) and GraphPad Prism ® version 5.00 for Windows ® (GraphPad Software, San Diego, California, USA, 2007) software was used for data analysis.
L-NAME is a nitric oxide synthase (NOS) inhibitor which is a tool used to cause systemic NO depletion.

Results:
Compared with Control, L-NAME caused significant increase in number of NVC, MF, TP, and BP. Administration of sildenafil concomitantly to L-NAME resulted in significant reduction of number of NVC, MF, TP, and BP. Administration of vardenafil concomitantly to L-NAME also resulted in significant reduction of number of NVC, MF, TP, and BP (Table 1). Comparing the Groups Sildenafil + L-NAME with Vardenafil + L-NAME, no significant difference between groups was observed in any variable.

Table1. Cystometric variables (mean±SD) observed in groups. Administration of L-NAME cause detrusor overactivity (increase in NVC and MF) and bladder outlet obstruction (increase in TP and BP). Administration of sildenafil as well vardenafil improve detrusor overactivity and relieve bladder outlet obstruction without significant difference between groups.
The p value refers to analysis of variance (ANOVA). † significant difference between groups. ‡ significant difference in relation to L-NAME.

	Control	L-NAME	Sildenafil + L-NAME	Vardenafil + L-NAME	p
NVC	3,16±1,60	7,16±3,64	2,16±1,60‡	2,66±2,06‡	p<0,05 †
TP	28,04±2,77	42,63±10,35	22,56±5,37‡	30,39±7,89‡	p<0,001†
BP	21,01±5,01	31,45±3,68	21,64±4,63‡	21,70±5,86‡	p<0,05†
MF	1,32±0,15	1,75±0,13	1,23±0,26‡	1,24±0,30‡	p<0,05†
TV	0,48±0,28	0,39±0,14	0,49±0,36	0,37±0,14	p=0,78

Interpretation of results:

The principal hypotheses it that chronic administration of L-NAME, resulting in chronic deficiency of NO, compromised smooth detrusor relaxation (increased number of NVC and FM) and urethral relaxation (increased TP and BP). This experimental model was already used in literature to cause detrusor overactivity (DO) and BOO. [3]
In previous studies, Sildenafil and Vardenafil showed relaxing effect on smooth muscle of the bladder, prostate and urethra. They also demonstrated improvement in urodynamic parameters in different models of bladder outlet obstruction. To our knowledge, this is the first study where the efficiency of Sildenafil and Vardenafil were compared in an experimental model of mice with BOO. Concomitant administration of Sildenafil or Vardenafil with L-NAME caused relaxation of smooth detrusor relaxation (decrease number of NVC and MF) and urethral relaxation (decrease TP and BP) due decreased degradation of cGMP. Comparing Groups Sildenafil + L-NAME with Vardenafil + L-NAME the improvement was similar.

Concluding message:
Sildenafil and Vardenafil had similar efficiency to treat voiding dysfunction in mice with bladder outlet obstruction induced by chronic nitric oxide deficiency.

References

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Disclosures

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