Effects of Isosorbide Dinitrate on the Urinary Flow Rate in Patients With Benign Prostatic Hyperplasia

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Purpose: To compare the immediate effects of a systemic nitric oxide (NO) donor with placebo on the uroflowmetric parameters in patients with benign prostatic hyperplasia (BPH).

Materials and Methods: Eighty patients with the mean age of 61.5 years (range, 49 to 74 years) who suffered from BPH were enrolled in the study. We examined peak flow rate, average flow rate, and residual urine in all the patients. Then, patients were randomized to receive either 20 mg sublingual isosorbide dinitrate (ISDN) (n = 40) or placebo (n = 40) 20 minutes prior to the second uroflowmetry, which was performed one day after the first test.

Results: The mean peak flow rate increased from 7.6 ± 0.41 mL/s to 10.2 ± 0.54 mL/s ($P = .013$) in the ISDN group, while it increased +0.40 mL/s in the placebo group ($P > .05$). Mean residual urine volume decreased significantly from 51 ± 3.1 mL to 29 ± 2.9 mL and from 56 ± 4.1 to 51 ± 2.6 in the ISDN ($P = .02$) and the placebo groups ($P > .05$), respectively. At baseline, the mean arterial pressure was 95 ± 2.1 mmHg and under the influence of the NO-donor, it decreased to 83 ± 1.9 mmHg, which was significant ($P < .001$). No significant changes of micturition parameters were found in the placebo group.

Conclusion: Organic nitrates influence micturition parameters in patients with BPH. This new approach could offer a potential pharmacological option to treat obstructive lower urinary tract symptoms.

Keywords: benign prostatic hyperplasia, isosorbide dinitrate, flowmetry

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a significant health-care problem affecting millions of men worldwide. Apart from the bothersome lower urinary tract symptoms (LUTS), BPH can lead to the detrusor overactivity, urinary retention, recurrent urinary tract infections, bladder stone formation, and even renal insufficiency.

Medical therapy is usually administered for bothersome LUTS due to BPH. Alpha-blockers and 5α- reductase inhibitors are the only agents recommended by different guidelines.[1,2] New pharmaceutical agents with acceptable cost and safety profile would be very welcome.[3]

During the past few years, nitric oxide (NO) has been found to be a fundamental biologic messenger mediating neurotransmission, smooth muscle relaxation, and vasodilation in various organs.[4-6] In the male genital tract, the bladder neck, the prostate, the vas deferens, the seminal vesicle, and the corpus

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cavernosum were found to have high levels of calcium dependent nitric oxide synthase (NOS) activity.[7] Nitric oxide plays an important role in the autonomic innervation of all parts of the prostate tissue.[4,8]

There is some evidence that drugs acting on NO/cyclic guanosine monophosphate (cGMP) pathway might have a potential role in treating subvesical obstruction caused by BPH.[9-12] The hypothesis relies on the relaxing effect of NO on the prostate smooth muscle cells that potentially decreases subvesical obstruction and improves both voiding and bothersome LUTS. Phosphodiesterase-5 inhibitors, which increase cGMP levels in the lower urinary tract, have already been shown to have a beneficial influence on LUTS.[9]

Functional in vivo studies assessing the direct effect of NO on the human lower urinary tract are rare. However, after oral administration in healthy humans, an NO-donor had a functionally relevant effect on the resting tone and contractile properties of the human external urethral sphincter in vivo.[10] In a functional study on humans with spinal cord injury, subvesical obstruction caused by detrusor-sphincter dyssynergia was successfully reduced by oral administration of an NO-donor.[11] Recently, using pressure-flow studies, a significant reduction was reported in the bladder outlet resistance in healthy men within 20 minutes of sublingual administration of an NO-donor.[12]

Some studies have investigated NO-donors in men with BPH, but the results are conflicting. The aim of our study was to evaluate the immediate effect of a sublingual administration of isosorbide dinitrate (ISDN), as an NO-donor, on the infravesical resistance in patients with BPH.

MATERIALS AND METHODS

This study was carried out on patients with LUTS suggestive of BPH who referred to urology clinic of Razi Hospital in Rasht between January 2007 and December 2007. Eighty men with the mean age of 61.5 years (range, 49 to 74 years), who met the inclusion criteria, were enrolled in this study. The inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Age < 75
Peak urinary flow ≤ 15mL/s
Total voided volume ≥ 150 mL
Prostate specific Antigen ≤ 4 ng/mL
International prostate symptom score (IPSS) ≥ 8
Prostate volume ≥ 20 cm^3
Exclusion criteria
Age >75 years or < 49 years
Evidence and suspicion of prostate cancer
Acute prostatitis
Residual urine volume > 150 mL
Serum creatinine level > 1.5 mg/dL
Neurogenic bladder dysfunction
Inability to spontaneous voiding
History of prostate surgery or other transurethral procedures
Urinary tract infection
Contraindications of nitrates
Unstable cardiovascular disease
Maintenance nitroglycerin administration

The study protocol was explained to all of the patients and written informed consents were obtained. The study was approved by the hospital's ethics committee. We measured peak flow rate (Q-max), average flow rate (Q-ave), and voided volume using the Urodyn rotating Flowmeter (Dantec, Copenhagen, Denmark) and residual urine volume by transabdominal ultrasonography

After baseline evaluation, each patient was assigned in chronological order to one of the randomization numbers using a computer generated randomization list to receive either 20 mg sublingual isosorbide dinitrate (Tolidarou Pharmaceutical co.) (group 1, n = 40) or identical sublingual placebo tablet (group 2, n = 40), 20 minutes prior to the second uroflowmetry, which was performed with a one-day interval from the baseline test. Both patients and researchers were blind to the drug/placebo groups. Residual urine volume was measured again. Blood pressure was monitored at baseline and 1 hour after drug or placebo administration.

The urofowmetry strips were manually read in a blinded fashion by an independent investigator. To be considered valid, a flow reading required a total voided volume of at least 150 mL with the peak rate maintained for at least 2 seconds. Baseline values were compared to the values after intervention by the paired *t* test. *P* values less than .05 were considered statistically significant.

RESULTS

The mean peak flow rate increased significantly from 7.6 ± 0.41 mL/s (range, 6.1 to 9.3 mL/s) to 10.2 ± 0.54 mL/s (range, 8.2 to 13.1 mL/s; $P = .013$) in the ISDN group, while the mean peak flow rate change in the placebo group was about +0.40 mL/s and statistically insignificant ($P > .05$). Mean residual urine volume decreased significantly from 51 ± 3.1 mL to 29 ± 2.9 mL and from 56 ± 4.1 to 51 ± 2.6 in the ISDN ($P = .02$) and the placebo groups ($P > .05$), respectively (Table 2).

At baseline, the mean arterial pressure of the patients was 95 ± 2.1 mmHg (range, 86 to 115 mmHg) and under the influence of the NO-donor, it decreased to 83 ± 1.9 mmHg (range, 74 to 92 mmHg), which was significant ($P < .001$). The drop in blood pressure was symptomatic in 7 patients as they reported dizziness after the intake of ISDN in contrast to the placebo group, in which there was not any drop in the blood pressure. These symptoms, however, were mild and short lasting, and no subject was affected in a way that prevented him from completing the study. Five of the subjects reported a headache after ISDN administration.

DISCUSSION

Nitric oxide produces smooth muscle relaxation by activating the soluble guanylate cyclase and hereby increasing the tissue levels of cGMP, which in turn interacts with various intracellular components that regulate activities of the contractile proteins.[13,14] Nitric oxide donors activate the soluble guanylate cyclase and increase the tissue levels of cGMP.[15] Exogenously applied NO in solution or NO-donors have been shown to cause relaxation in pre-contracted prostate tissue from rabbits, dogs, and humans.[8,16-18]

Several advantages of NO-donors make the clinical evaluation of their effect on the infravesical resistance worthwhile. First, many NO-donors are well-known drugs with good tolerability and long-established safety records .[19] Second, different formulations are available. This is especially notable for fast-acting formulations with an onset of action within seconds to minutes. They can be used alone or in combination with classical medical LUTS therapies, but the possibility of increased adverse events, eg, hypotension, has to be taken into consideratin.

Possibly, fast-acting NO-donors could also be used to treat acute urinary retention in an emergency setting. Since there is evidence that alterations in the NO-cGMP pathway are involved in the development of BPH and that NO has an antiproliferative effect on human prostate smooth muscle cells,[20] long-term use of NO-donors may also prevent or slow down BPH progression. Furthermore, the NO-cGMP pathway is suspected to be involved in the regulation of the threshold for afferent firing in the bladder.[21] Nitric oxide could, therefore, have a beneficial effect on LUTS beyond the decrease of the infravesical resistance.

Table 2. Mean variations in parameters during study period in two groups

Parameters	Baseline		After ISDN		*P*
	Placebo Group	ISDN Group	Placebo Group	ISDN Group	
International Prostate Symptom Score (IPSS)	15.4 ± 2.1	15.8 ± 2.4			>0.05*
Prostate Volume (cm^3)	28 ± 2.6	29 ± 2.1			>0.05*
Peak urinary flow rate (Qmax)(mL/s)	7.2 ± 0.61	7.6 ± 0.41	7.6 ± 0.44	10.2 ± 0.54	>0.05* 0.013† >0.05‡
Residual Urine volume (cc)	56 ± 4.1	51 ± 3.1	51 ± 2.6	29 ± 2.9	>0.05* 0.02† >0.05‡
Mean arterial Pressure (mmHg)	99 ± 1.6	95 ± 2.1	96 ± 2.2	83 ± 1.9	>0.05* 0.001† >0.05‡

*Baseline ISDN group versus Placebo group
†ISDN group before and after intervention
‡Placebo group before and after intervention
§ISDN indicates isosorbide dinitrate

In this study, we administered only single dose of ISDN to assess immediate effects on urinary flow rate, but in a non-randomized non-placebo-controlled study by Klotz and colleagues, patients with BPH with obstructive symptoms that were treated with oral ISDN with the dosage of 60 to 120 mg per day for 3 months exhibited improvement in the mean peak flow rates.[22]

Reitz and associates recently showed the relaxing effect of sublingual ISDN on the external urethral sphincter in spinal cord–injured patients as well as in healthy men within minutes after drug administration.[10,11] The most serious adverse effects of ISDN were pounding headache, flashing, vertigo, palpitation, and nausea or vomiting.[23]

In this study, we demonstrated a slight, but statistically significant increase of the peak urinary flow rate within 20 minutes after administration of an NO-donor in men with BPH. Whether this influence affected the outflow region of the lower urinary tract as a functional unit or individual segments (eg, the bladder neck, the prostate, or the urethra) to a variable extent cannot be determined with this study. We also chose to administer a relatively high dose of ISDN in this study to make sure that sufficient levels of the NO-donor were present systemically during the second uroflowmetry. In some studies, however, the administration of 10 mg instead of 20 mg ISDN is reasonable, since other studies have shown significant adverse effects with this dose.[10,11]

Our study had some limitations. First we did not measure NO levels in the target region, namely the prostatic urethra and the bladder neck. Second, learning curve might have affected the results of the second uroflowmetry. Repeated uroflowmetry several hours after ISDN administration would have been a convincing evidence for the specificity and short-term efficacy of ISDN treatment when returning to pretreatment values.

It should be emphasized that this is a preliminary study about a novel option in medical treatment of BPH and any conclusion regarding the usefulness of this therapy can only be drawn from larger studies with long-term follow-up.

CONCLUSION

A clinical improvement was found in micturition parameters in patients with BPH after medication with nitrates. However, further controlled studies with larger sample are necessary to prove whether nitrates could eventually enrich the BPH treatment.

CONFLICT OF INTEREST

None declared.

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