International Journal of Impotence Research (2004) 16, 8–12
 0955-9930/04 $25.00
www.nature.com/ijir

Sildenafil citrate *vs* intracavernous alprostadil for patients with arteriogenic erectile dysfunction: a randomised placebo controlled study

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We compared the effectiveness of sildenafil citrate and alprostadil in improving arterial penile inflow (peak systolic velocity (PSV)) and penile rigidity in 55 patients with erectile dysfunction caused by atherosclerosis. A total of 35 patients with pure vasculogenic impotency were randomly assigned to alprostadil (Av group; *n*=11), sildenafil (Sv group; *n*=12), or placebo (P group; *n*=12), and 20 patients with nonvasculogenic impotency were randomly assigned to alprostadil (A group; *n*=10) or Sildenafil (S group; *n*=10): Av and A used alprostadil injection (capable of giving a full erection) once a week for 1 month, Sv and S took daily oral sildenafil (25 mg) for 1 month, and P took daily oral placebo for one month. The PSV was measured with Duplex sonography and penile rigidity was assessed using the IIEF-15 questionnaire, both of which were administered before and after treatment. Although both treatments improved penile rigidity, they increased PSV only in the Av and Sv groups. Our results suggest that alprostadil and oral therapy should be the starting therapy in men with vasculogenic impotency, whereas alprostadil should be avoided as the first-line approach in men with nonvasculogenic impotency.
International Journal of Impotence Research (2004) **16,** 8–12. doi:10.1038/sj.ijir.3901123

Keywords: erectile dysfunction; treatment; duplex sonography; arteriogenic; sildenafil; alprostadil

Introduction

Peak systolic velocity (PSV) in cavernous arteries as assessed by penile duplex sonography (DS), is a safe, cost-effective and accurate predictor of arterial insufficiency as confirmed by angiographic studies.[1,2] Marshall reported that cavernous arteries, reassessed by DS after more than 3 years in the same patients without any therapy, underwent no substantial change in PSV. DS can be therefore considered a reliable tool to measure PSV in penile arteries.[3] Arterial anatomical variations might modify the penile hemodynamic response and cavernous PSV in the medium and distal segments after intracavernous (IC) injection, affecting the results of DS in impotent patients.[4] In addition, different segments of arterial penile tree show a high variability of the measured PSV values, thus leading to an incorrect diagnosis in 21.8% of cases. A statistically different value between the proximal and the distal segments of the cavernous arterial tree was found.[5]

Therefore, PSV measurements seem to be performed in the proximal site of the cavernous arteries in order to avoid misleading factors and to obtain the best controlled data.[6] Some falsely abnormal DS results might be due to the suppression of the vasoactive response because of anxiety and increased sympathetic stimulation.[7] However, in a wide impotent population, it has been found that arteriopathic impotent patients might be better identified by adding the flaccid PSV and acceleration measurements to the dynamic PSV, with a predictive power of 92.8%.[8] By means of a correctly performed DS, a cavernous dynamic PSV of 30 cm/s is generally accepted as the cutoff value to identify a vascular penile disease.[9-14]

Impairment of arterial penile inflow due to atherosclerosis is a frequent cause of erectile dysfunction. In an unselected population, an asymptomatic peripheral arterial disease was recently found in 24% of cases.[15] Being pathological processes in vasculogenic erectile dysfunction similar to those involved in atherosclerosis, an underestimated widespread occurrence of penile vascular disease might be reasonably suspected.[16]

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Received 20 February 2003; revised 10 June 2003; accepted 5 July 2003

The cavernosal lumen reduction due to atherosclerosis is associated with oxygen tension decrease that alters smooth muscle metabolism.[17] The damage in the vascular wall affects the accumulation of cyclic nucleotides cAMP and cGMP that lead to the relaxation of trabecular smooth muscle by activation of K^+ channels. Activation of Na^+/K^+ ATPase by nitric oxide (NO) seems to be another essential mechanism in the endothelium-dependent arterial wall relaxation.[18] Hypercholesterolemia may cause impairment of endothelium-dependent relaxation.[19] The defect in NO/cGMP/cAMP pathway appears to be reversible both in early hypercholesterolemia[20] and in advanced atherosclerosis of peripheral arterial occlusive disease.[21] Prostaglandin E1 (PGE1) has a direct effect on the vascular and cavernosal smooth muscles, inhibiting platelet aggregation and low-density lipoprotein access into the vascular wall, and reducing presynaptic noradrenaline release.

Experimental evidence revealed a relaxant effect of PGE1 in both healthy men and arteriogenically impotent men.[22] In peripheral arterial occlusive diseases,[23] an increased arterial circulation was observed by DS after PGE1 administration. After long-term treatment, in chronic erectile failure, PSV in cavernous arteries improved by some 34–35% after a mean period of 31–36 months of IC injections.[3,24] In 81–83% of patients' normal vascular values were found by DS after treatment compared to a normal cavernosal PSV found in 57–68% of patients before treatment.[25] Functional erections without injection were found in up to 54% of the patients, and no correlation was found between the total number of self-injections and PSV improvement.[3]

However, in the above-mentioned studies, a clear relation between hemodynamic response and different etiologies has not been established. Sildenafil, a specific inhibitor of PDE5 in trabecular tissue, increases cGMP for some hours, sustaining smooth muscle relaxation. Nocturnal erections increase due to a chronic assumption of oral sildenafil at bedtime has been previously described.[26] Recently, a positive effect on coronary flow reserve in men with severe coronary artery disease was found.[27]

Objective

In the present study, we observed the ability of sildenafil citrate and alprostadil to improve arterial penile inflow after a short treatment. We compared both drugs in arteriogenic and nonarteriogenic erectile dysfunction. Finally, for its good specificity and sensibility, the erectile function domain of IIEF-15 (1,2,3,4,5, 15 questions) was chosen to determine the treatment efficacy.[28]

Materials and methods

The Institutional Review Board approved this study, and all patients granted their written informed consent. Patients were recruited from an uro-andrological ambulatorial setting from March to June 2001 and were eligible if: (1) they had erectile dysfunction that was verified with the IIEF questionnaire and (2) the erectile dysfunction had persisted for no longer than 3 months. Patients were excluded if they had any organic cause of erectile dysfunction apart from vasculopathy (eg, endocrine disease, penile fibrosis, major neuropsychogenic disorders and systemic disease).

Of the 97 patients who attended our clinic during the study period, 56 were eligible. These patients underwent basal and dynamic DS to identify those with arteriogenic impotence. An average cavernosal peak systolic velocity less than 30 cm/s was considered pure vasculogenic impotence. On the basis of the initial DS results, we determined that 36 of the 56 patients had pure vasculogenic impotency. These 36 patients were randomly assigned to one of the following three groups: alprostadil (Av) (n=12), sildenafil (Sv) (n=12), or placebo (P) (n=12). The remaining 20 patients had nonvasculogenic impotency; they were used as controls and were randomly assigned to one of the following two groups: alprostadil (Group A) (n=10) or sildenafil (Group S) (n=10). All 56 patients were randomly assigned to the different treatment groups (first to Group A and then to S, Av, Sv, and P) on the basis of a five casual number sequence that had been previously written and group linked.

Study groups

- Patients of Group Av (alprostadil injection) received one to three consecutive IC injections of PGE1 once a week. When needed, the dose was increased from 5 to 20 μg to obtain a full erection lasting 10 min. One clinician assessed penile rigidity in all patients using hand palpation. One patient who did not respond to PGE1 was excluded. The remaining 11 patients In-Group Av underwent PGE1 injection treatment using the maximum efficacious dosage, once a week for 1 month.
- Group Sv (oral Sildenafil) was instructed to take 25 mg of the drug at bedtime every night for 1 month.
- Group P (placebo) received an oral placebo medication, which they were instructed to take at bedtime every night for 1 month.
- Groups A and S received the same treatment as Av and Sv groups, respectively.

All patients were required to attempt sexual intercourse at least once but no more than three times a week during the 4 weeks of treatment. Any IC home self-treatment was not permitted (Figure 1).

The main outcome measures were PSV as assessed by DS examination (with alprostadil 10 μg) and erection rigidity as assessed by the IIEF-15 questionnaire. Both instruments were employed before treatment and 7 days after the last treatment. The follow-up time of 7 days was arbitrarily chosen so ensure that the medication had been completely eliminated from each patient and would not skew the PSV measurements. A normal PSV is $\geq$30 cm/s.

Duplex sonography

During the DS examination, a 7.5 MHz B mode linear array transducer with a pulsed Doppler investigation and a color flow mapping capability (Esaote AU4) was employed by one investigator who was unaware of the group assignments. The angle of insonation was always approximately 45° for accurate angle corrected velocity calculation. The PSV was recorded on the proximal site of the cavernosal arteries. The entire penile arterial circulation was evaluated to exclude the presence of collateral vessels.

Statistical analysis

The age of five groups was compared with a two-tail Student's *t*-test. The pre- and post-treatment PSV data were compared using an unpaired two-tail Student's *t*-test with Welch correction. Only the erectile function domain of the IIEF-15 questionnaire was evaluated (six questions), with a score range from 6 to 30 points. The remaining domains were excluded (nine questions) because they were considered to be misleading for the study purpose. The pre- and post-treatment questionnaire data were compared using an unpaired two-tail Student's *t*-test, which is standard for IIEF data. All statistical analyses were performed with Graphpad InStat, (Graph Pad Software). $P<0.05$ was considered to be statistically significant. The data are presented as mean $\pm$ s.d.

Results

The age of the patients was not significantly different among the five groups. Table 1 shows the average PSV in all groups before and after treatment. Overall, sildenafil and alprostadil increased cavernosal PSV in the vasculogenic impotent men (Av and Sv) but not in the

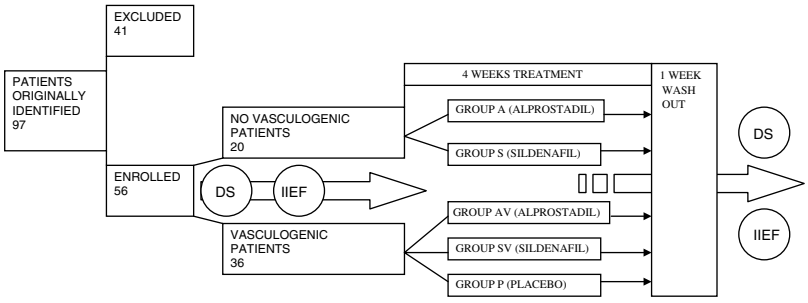

Figure 1 Study design comparing NO vasculogenic and vasculogenic patients.

Table 1 Average PSV (cm/s) before and after treatment as stratified by various subgroups

Group	*Patients*	*Age*	*Average PSV*		
			Before treatment	*After treatment*	*P value*[a]
A (no vasculop.) PGE1 1–3 times/week (vasculop.)	10	54.6±11.4	42.7±11.1	42.8±11.3	>0.05.
S (no vasculop.) (oral sildenafil) 25 mg at bedtime/night × 1 month	10	55.6±4.6	54.3±12.9	54.9±12.2	>0.05
Av (vasculop.) PGE1 1–3 times/week (vasculop.)	11	56.1±7.5	20.4±5.2	28.3±9.2	<0.05
Sv (vasculop.) (oral sildenafil) 25 mg at bedtime/night × 1 month	12	59.6±6.4	20.5±3.8	25.5±7.2	<0.05
P (vasculop.) (placebo) at bedtime/night for 1 month	12	57.8±6.4	19.6±3.0	21.6±6.3	>0.05

[a]Data were reported as mean±s.d.
In vasculogenic impotent men, PSV significantly increased ($P<0.05$); in some of them, this increase exceeded the normal value of 30 cm/s. The other subgroups, including placebo, remained unchanged.

Table 2 Comparison of IIEF scores in various subgroups

Group	*IIEF*		
	Before treatment	*After treatment*	*Significance before vs after*
A (no vasculop.) PGE1 1–3 times/week (vasculop.)	15.1±4.6	21.9±2.8	$P<0.001$
S (no vasculop.) (oral sildenafil) 25 mg at bedtime/night × 1 month	12.5±3.9	18.2±2.7	$P<0.05$
Av (vasculop.) PGE1 1–3 times/week (vasculop.)	14.5±4.9	19.7±5.6	$P<0.05$
Sv (vasculop.) (oral sildenafil) 25 mg at bedtime/ night × 1 month	13.3±7.1	20.6±8.6	$P<0.05$
P (vasculop.) (placebo) at bedtime/night for 1 month	10.5±8.1	12.0±10.5	$P>0.05$

Data were reported as mean ± s.d. All subgroups except placebo obtained good performances (total score ≥18) as tested by IIEF erectile function domain (questions 1,2,3,4,5 and 15). (Each IIEF domain was scored from 0 to 5: 0=did not attempt intercourse, 1=never/occasionally, 2=less than half the time, 3=sometimes/half the time, 4=more than half the time, 5=almost always.) The total score was calculated by totaling and taking mean of the response to all six domains of IIEF-15.

nonvasculogenic men (A and S). Table 2 shows the IIEF scores in all groups before and after treatment. Sildenafil and alprostadil significantly increased penile rigidity in all the patients.

Discussion

The purpose of this study was to compare the effectiveness of sildenafil citrate and IC alprostadil in improving arterial penile inflow and penile rigidity in patients with vasculogenic and nonvasculogenic impotency. We found that alprostadil and sildenafil significantly and similarly increased impaired penile circulation only in the patients with vasculogenic impotency. This could be due to a better vascular wall metabolism that allows an increased loading penile flow. The percent increase in PSV was 30% for the Av group and 39% in the Sv group, which is similar to results from previous studies. On the other hand, the same treatments did not modify the healthy penile vascular tree in the men with nonvasculogenic impotency. Both treatments, however, did improve erection rigidity in all the patients.

As shown by erectile domain IIEF testing, groups A, Av, S and Sv reported a significant improvement in erections during treatment, with a similar clinical significance of different therapeutic approaches.

The men with vasculogenic impotency could be expected to have a higher number of sinusoidal and arteriolar penile branches with reduced efficiency. In animal experiments, a unilateral chronic obstruction of arterial penile vessels lead to a contralateral compensatory enlargement of cavernosal arteries and the development of a rich network of collaterals with an increasing arterial flow.[27] In limb arterial occlusive disease, PGE1 administration improved blood flow by improving the ability of smooth muscle to relax.[28]

To our knowledge, there are not enough data to examine the possibility of having angiogenesis in the arterial penile tree. However, the improved blood flow seems to have been achieved by increasing the cavernosal lumen and by reopening sinusoidal and arteriolar branches, which had thickened because of the ongoing atherosclerosis.

On the other hand, arterial blood flow in the nonvasculogenic men did not improve. We believe that the flow threshold was already at its maximum and could not be improved.

Improvement in the erectile response depends on the exogenous stimulus towards cAMP and cGMP. In atherosclerosis, a decrease in the oxygen tension alters smooth muscle metabolism, leading to reduced cyclic nucleotide synthesis. It has been reported that an increase in experimental pO_2 leads to increased PGE1 synthesis and cAMP concentration up to 120 times in smooth muscle.[14] After sildenafil treatment, coronaries reserve also increases.[23]

In short, in atherosclerotic penile arteries, an increased compliance could be expected in consequence of a maximized blood flow with an improved metabolism of vascular wall. If endogenous cAMP and cGMP are increased, a permanent hemodynamic result should be expected in atherosclerotic men also.

The clinical significance of these data could be summarized in the following manner: different therapeutic approaches should be tried for vasculogenic *vs* nonvasculogenic impotent males. In vasculogenic impotent patients, a rise in PSV could be expected. Patients should receive IC injection as well as intensive oral treatment. Oral treatment could be discontinuously applied later on to maintain the hemodynamic results. Conversely, in nonvasculogenic impotent men, intensive oral treatment should be avoided because it is ineffective on the hemodynamic inflow. In these patients, an oral treatment could be suggested on demand only.

This study is the first to suggest that a different first-line treatment should be used in men with vasculogenic and nonvasculogenic impotency. Each time vascular disease is strongly suspected in an outpatient, a penile dynamic DS should be performed. Cavernosal disease could be treated with a

1-month course of IC injection at the hospital (clinically efficacious PGE1, once a week) or oral intensive therapy at home (sildenafil 25 mg, once a day), which would help recover sinusoidal and arteriolar vessels not totally compromised and avoid penile prosthesis implantation in the future. In these patients, early oral sildenafil administration might at least prevent both systemic arterial flow and penile circulation from decreasing. Unfortunately, in our study, most patients refused to stop treatment to allow us to examine follow-up results without any drug effects.

In our study, DS was used to measure PSV in cavernous arteries. Studies have shown that PSV in cavernous arteries as assessed by penile DS is a safe, cost-effective and accurate predictor of arterial insufficiency. Angiographic studies have confirmed a strong relationship between DS and vascular damage.[25,26]

Conclusion

Our data suggest that penile arterial blood flow, which is damaged in vasculogenic impotent men, could be improved by a short course of intensive drug treatment. This finding, however, does not apply to nonvasculogenic impotent men, where a hemodynamic therapeutic effect seems to be excluded. When an arteriogenic penile disease is strongly suspected, a DS should be suggested. If confirmed, cavernosal arteriopathy should be promptly and massively treated to reopen penile vessels not yet totally damaged. Further studies should test the therapeutic ability of higher oral dosages or long half-life drugs on arterial flow.

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