

A Double-blind Placebo-controlled Evaluation of the Effect of Topical Sildenafil on Erectile Dysfunction

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ABSTRACT

Several adverse effects have been reported with use of oral sildenafil in the treatment of erectile dysfunction (ED). In this study, a formulation of sildenafil topical gel was compared with sildenafil tablet in a randomized, double-blind, prospective, placebo-controlled clinical trial. A total of 94 patients, with clinically diagnosed ED were recruited. The patients were evaluated by treatment group, nature of ED, and age. The cases received a topical gel containing 1% sildenafil and placebo tablet, and the control group received 100 mg sildenafil tablet and a gel base (without drug) as placebo. The tablets were taken one hour before sexual activity and approximately 0.5 g of the topical gel was applied on the glans of the penis and was massaged for 5 minutes before sexual activity. In the case group, five patients (12.5%) had complete erection, five patients (12.5%) had moderate erection, and 30 patients (75%) had no erection. In the control group, these results were 28 (70%), 6 (15%) and 6 (15%) respectively. The

onset of erection in the case group (in patients with complete erection) was 7.4 ± 3.6 minutes, but was 37.8 ± 14.9 minutes in the control group. Four cases of mild headache were observed in the case group. This was pain treated four minutes before receiving any drugs for headache. Two cases of severe headache were observed in the control group. In the control group, one patient developed disturbance in visual function and one patient developed severe dyspepsia. The findings suggest that sildenafil delivery using a transdermal formulation can be enhanced by several synthetic or natural percutaneous absorption enhancers, and appears to be a promising approach for the treatment ED.

INTRODUCTION

Erectile dysfunction (ED) is a common problem with a prevalence of approximately 50% in men aged 40 to 70 years.¹ Sildenafil citrate, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), is an effective oral treatment of ED.² The physiologic mechanism of erection involves release of nitric oxide in the corpora during sexual stimulation. This release activates the enzyme guanylate cyclase and results in

increased levels of cGMP. This increased cGMP relaxes the smooth muscle in the corpus cavernosum and allows greater inflow of blood, thus increasing the intracavernosal pressure compressing the peripheral venules and leading to an erection. The main action of sildenafil is the enhancement of the effect of nitric oxide by inhibiting the cGMP-specific PDE5 degradation.³

The main adverse effects reported in clinical trials were headache, dyspepsia, visual disturbance (changes in perception of color hue or brightness), flushing, and rhinitis. These were mild in severity and the number of discontinuations because of adverse effects was small (< 1%).

In a prospective study, the adverse reactions most commonly observed were flushing (30.8%), headache (25.4%), nasal congestion (18.7%), and heartburn (10.5%).³ All events were short lived and mild in nature, with 31.6% of patients experiencing one or more adverse events. There was a significant association between higher doses and the occurrence of side effects.

In a recent study, no pattern of errors was evident in any visual function test following sildenafil administration.⁵ Sildenafil has been associated with a mild decrease in systemic arterial pressure as well as a synergistic and often major decrease in systemic arterial pressure in the presence of organic nitrates.⁶⁻⁸ Priapism (painful or uncomfortable erection persisting for several hours after ejaculation) was reported in one case.⁹ In another study, the number of deaths associated with sildenafil citrate and injections of alprostadil, both of which are used exclusively in the treatment of ED, were compared based on the number of deaths per filled prescription for these agents reported to the FDA.¹⁰ The results showed that the number of deaths per prescriptions filled

for sildenafil was significantly greater than that for injections of alprostadil.

Repeated doses of oral sildenafil are required to sustain plasma levels because of its short duration of action ($t_{1/2} = 1$ h) with high liver metabolism.¹¹ Thus, topical delivery through local tissue area may be an alternative to oral administration to reduce the incidence of adverse effects, increase the time to onset of response, and sustain effects for longer periods. Furthermore, transdermal delivery of sildenafil can offer several advantages over conventional dosage forms and the multiple dosing can be eliminated.¹² However, transdermal permeation of compounds in the local skin, in general, is slow due to low permeability resulting from physicochemical properties of the compound, low partition ability, and the tissue barrier from the stratum corneum, which creates a low diffusion coefficient.¹³ Liaw showed that after transdermal administration of 15.8 $\mu\text{g/mL}$ of sildenafil to nude mouse skin, it was detected in the bloodstream as early as 15 minutes.¹² The transport amount of sildenafil could be quantitated and, at pH of 8 to 11, had the highest permeation rate in nude mouse skin.

In the present study, sildenafil topical gel was compared with sildenafil tablet in a double-blind, placebo-control clinical trial.

MATERIALS AND METHODS

The following chemicals were used: Methylparaben and propylparaben, polyethylene glycol (PEG) 200, PEG 300, PEG 400, isopropyl alcohol, glycerin, ethanol, KH_2PO_4 , NaOH (supplied by Merck), HPMC K100M (supplied by Colorcon). The sildenafil powder was provided by Razak Company, Tehran, Iran. The sildenafil tablets were purchased from Rouz Daru Company, Tehran, Iran.

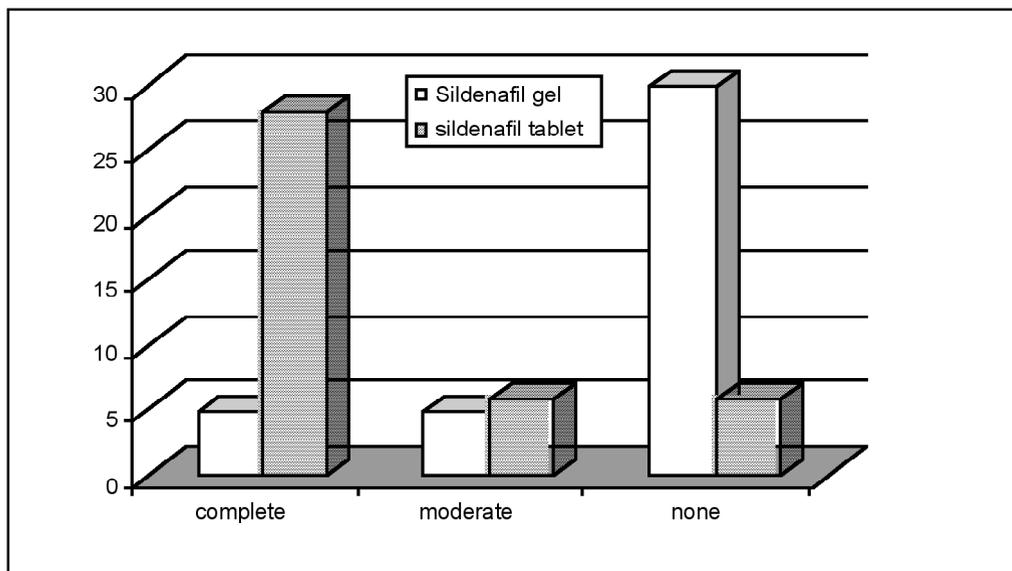


Figure 1. Comparison of the effect of sildenafil on ED in oral and transdermal administration.

Preparation of the Formulations

Several agents (PEG 200, 300, 400; ethanol, propylene glycol, glycerin) were used as cosolvent for sildenafil in water and a buffer (pH 7.4). The solubility of sildenafil in several systems was determined spectrophotometrically at 223 nm. The linearity interval established was 10-30 $\mu\text{g/mL}$ ($r^2 = 0.9997$).¹⁴

HPMC K100M was dispersed in preserved buffer (methylparaben 0.18% and propylparaben 0.02%) and ethanol for overnight. The sildenafil powder (1%)¹⁵ was dissolved in solvent system before the addition of polymer and stirred with a double bladed mixer (Ika-werk, Germany) 500 rpm for 30 minutes and then added to polymer dispersion and stirred till gel forming. The formulations were kept in 4°C, 25°C, and 40°C for physical stability evaluation during a two-week period. The drug release from gel base and percutaneous absorption was determined in vitro. Final formulations for clinical trial were controlled microbiologically based on USP XXIV.¹⁶

Clinical Trial

The study design was a randomized

(block-random sampling), double blind, prospective, placebo-controlled trial. Under the assumption of an overall mean difference of 0.5 units and a standard deviation of 0.5 units, 78 patients were required to achieve a power of 95% to reject a null hypothesis of equality, applying a two-sided test at the 5% significance level.

All patients with ED ($n = 94$) who presented to one urologist from July 2003 to May 2004 were considered for inclusion in the study. Men with anatomical defects of the penis, other sexual disorders, spinal cord injury, major psychiatric disorder, poorly controlled diabetes, stroke, a heart attack within six months, treatment with organic nitrate, active peptic ulcer disease, migraine, vision disorders, and allergic rhinitis, were excluded. A total of 14 patients were excluded from the trial based on these criteria. Thus, 80 patients with clinically diagnosed ED were included in the analysis.

In recognition of the multifactorial nature of ED, men with a broad variety of baseline etiologies were enrolled in the trial, including those with ED of

Table 1. Patient Characteristics

	Case	Control
Age		
Mean (year)	47.2	50.8
Range	26-63	37-65
Duration of ED (month)		
Mean	17.5	18.1
Range	7-34	7-36
Nature of ED		
Organic	17	16
Psychogenic	23	24
Mixed

organic, psychogenic, and mixed causes. Patients were divided categories by age (ie, < 50 and ≥ 50) and by ED etiology.

The case group received a topical gel containing 1% sildenafil and placebo tablet, and the control group received 100 mg sildenafil tablet and gel base (without drug) as placebo. The tablets were taken one hour before sexual activity and approximately 0.5 g of the topical gel was applied to the glans of penis and was massaged for five minutes before sexual activity.

The overall clinical response was assessed by erection (complete, moderate, and none) and the onset of erection. Headache, dyspepsia, rhinitis, diarrhea, heartburn, visual dysfunction, and priapism were studied as adverse drug reactions. The patients were followed for up to two weeks.

Statistical Analysis

Student *t* test, and Chi-square test were used to determine significant differences between groups, and a *P* value of < 0.05 was considered statistically significant.

RESULTS

A total of 24 solvent systems were investigated and the percent of solubility was determined. These results showed the best solubility in media buffer compared with distilled water. Of these solvents,

ethanol showed the best results. Several formulations of the topical gel formulations were investigated (data not shown). Carbopol did not show suitable results in selected systems and this finding could not be explained by the low ratio of water in selected systems. Several kinds of HPMC were tested as gelling agent and, of these, HPMC K100M showed the best results.

After evaluation of the physical stability of formulations, the most stable gels were chosen for clinical trial. The release profile of one selected formulation was studied in vitro. These results showed that ethanol had the most effect on the release profile of sildenafil.

Patient characteristics are shown in Table 1. Fourteen patients were excluded from the efficacy analyses: nine patients were given another drugs that stimulated erection and five patients suffered from other disorders during study.

In the case group, five patients (12.5%) had complete erection, five patients (12.5%) had moderate erection, and 30 (75%) had no erection (Figure 1). In the control group, these results were 28 (70%), six (15%), and six (15%), respectively.

The onset of erection was 7.4 ± 3.6 minutes in the case group (in patients with complete erection), and was 37.8 ± 14.9 minutes in the control group.

Four patients experienced mild headache in the case group. This pain was treated four minutes before receiving any drugs. In the control group, two patients developed severe headache, one experienced disturbance in visual function, and one patient experienced severe dyspepsia.

DISCUSSION

Despite the proven efficacy of oral therapy for ED, some patients are unable to take these medications because of drug interactions, side effects, or a lack of

response. Topical agents represent another minimally invasive option for the treatment of ED.¹⁷

Therefore, in this study, we evaluated drug release and kinetic of release of a topical gel formulation of sildenafil. More than 90% of the drug was released at 1.5 hours following application. This formulation showed percutaneous absorption as well (data not shown).

The results of our study demonstrate that oral sildenafil is more effective than transdermal administration of the drug ($P < 0.01$). However, the onset of erection was faster with transdermal administration ($P < 0.001$).

Our study identified a higher incidence of side effects with sildenafil tablet than with the transdermal gel. While mild headache was more common in the transdermal group than in the oral tablet group (10% vs 5%), severe dyspepsia and visual disorders were observed only in the oral tablet group. No cases of flushing, nasal congestion, heartburn, or priapism were observed in this study.

Dyspepsia was related to the route of administration, and the low blood concentration resulting from transdermal administration cannot produce this side effect. In addition to the inhibitory effect of sildenafil on PDE5—the target enzyme for therapeutic efficacy in patients with ED—the drug exerts a minor inhibitory effect on PDE6. Because PDE6 plays an important role in retinal phototransduction, its partial inhibition may account for the infrequent occurrence of visual effects observed in flexible-dose, controlled clinical trials of sildenafil in men with ED.⁵ It seems that the low blood concentration of sildenafil found in transdermal formulations can not induce this effect, but more studies are needed to confirm this potential advantage.

Other studies identified a higher incidence of side effects with sildenafil

tablet. For example, only 5% of patients in this study reported headache compared with 25.4% of sildenafil-treated patients in a study by Baylor et al³ and 16.0% in a study by Morales et al⁴. Visual disorders was reported in 5.8% and 3.0% of patients in the Baylor and Morales studies—an incidence that is similar to that found in our study. No cases of heartburn were observed in our study, however, it seems that our exclusion criteria may explain this subject. Flushing and nasal congestion were not observed in our study.

This investigation is the first controlled-randomized trial on sildenafil in Iran. Thus, further studies are needed for evaluation of sildenafil tablet side effects in our country.

CONCLUSION

In conclusion, sildenafil delivery using a transdermal formulation can be enhanced by several synthetic or natural percutaneous absorption enhancers, and appears to be a promising approach for the treatment ED.

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