

SS-Penogram: a New Diagnostic Test for Erectile Dysfunction

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The clinical reports on Sildenafil sulfate (Viagra) are mainly based on individual observations. However, there is a paucity of objective studies in the literature. In order to objectively examine the effect of Sildenafil, a SS (Sexual Stimulation)-Penogram that is a non-invasive, simple and physiologic method was developed using a radioisotope (RI). One hundred and four SS-penograms were performed on patients who had a documented erectile dysfunction (ED) lasting for more than 6 months. After an intravenous injection of ^{99m}Tc-RBC (15 mCi), the first penogram was taken immediately after sexual stimulation, which was done by 30 minutes of erotic videotape viewing. Forty minutes after administering 25 to 100 mg of Sildenafil, a second penogram was taken. The characteristics of each penogram were analyzed according to a previously reported method. The results were graded as follows; Type I (normal function; 5 min or more of peak erectile response with an induction period of 1 to 6 min), Type II-A (impossible function type; i.e., showing less than 2 times the basal radioactivity level), Type II-B (the unstable type; showing less than 5 min of peak erectile response), and Type II-C (the delayed type; which showed a delay of more than 15 min after the start of sexual stimulation). The patients were grouped according to their response after Sildenafil administration, and the effect of Sildenafil was assessed by comparing the radioactivity from between 7 to 22 minutes and the changes in the characteristics of the penogram. The mean age of the patients was 44.9 ± 10.2 (23-68) years. In the first penogram, Type I was found in 12 patients, and Type II-A in 14, Type II-B in 73, Type II-C in 1 and a mixed (II-B+C) type was found in 4 patients. A second penogram after Sildenafil administra-

tion, showed Type I in 46 patients, and Type II-A in 10, Type II-B in 46 and a mixed type was found in 2 patients. The responses after Sildenafil were categorized as follows: 1) An excellent response group (consisting of 56 patients-53.9%); Those who showed greater than 50% increase in the RI area after Sildenafil treatment. 2) A good response group consisting of (23 patients-22.1%); i.e., those who showed a less than 50% but greater than a 20% increase in the RI area after Sildenafil administration. 3) A borderline group (consisting of 15 patients-14.4%); showing less than a 20% change in the RI area after Sildenafil treatment. 4) non-response group (consisting of 10 patients-9.6%).

The therapeutic efficacy of Sildenafil, as determined by the SS-penograms, revealed that there was an augmentation in the erectile capabilities in 76% of men (79/104) but a non-response was observed in 9.6% (10/104). The efficacy of Sildenafil on the SS-penogram did not correlate with the patient's age ($p=0.198$). It is believed that the SS-penogram can be used to accurately evaluate the natural erectile status in sexual and pharmacological stimulation, and provides the most objective erectile response in any therapeutic trial. Consequently, the primary challenge for any erectile dysfunction remedy is to be able to demonstrate its efficacy. A further evaluation is warranted in the non-response group, which was not based on any severe organic dysfunction.

Key Words: Impotence, penogram, sildenafil

INTRODUCTION

Erectile dysfunction (ED) is divided into psychological and organic groups. In order to diagnose each type of ED, penile nocturnal tumescence monitoring, a pharmacological erection study and penile duplex ultrasonography are widely used. Penile nocturnal tumescence monitoring has been utilized as the primary diagnostic modality for diagnosing ED.¹⁻⁴ However, it has been found

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that a nocturnal erection has a different neuro-physiological circuit, and interpreting normal erectile function is difficult. A nocturnal erection is not a natural physiological erotic process. Therefore, a normal finding in nocturnal penile tumescence monitoring is not indicative of a normal erectile process in a patient.^{5,9} A pharmacological erection study and penile duplex ultrasonography both utilize pharmacologic drugs that are injected into the corpus cavernosum, which is far from being a natural erectile process, and as a result, there is a risk of priapism and corporal fibrosis.

To overcome these problems, a natural and noninvasive diagnostic method was developed by Shirai using a radioisotope injection combined with Visual Sexual Stimulation (VSS) in early 1970. The changes in the penile blood flow can be accurately interpreted by monitoring the radioisotope activity curve thereby, the difference between organic and psychological ED can be distinguished.^{10,11} We modified Shirai's technique and developed AVS-penogram to obtain a radioisotope penogram and the different types of ED have been diagnosed successfully using this technique for more than 10 years.¹²⁻¹⁴

Sildenafil is recently developed oral agent used for treating ED, and has revolutionized the treatment of ED. ED is mediated by the nonadrenergic noncholinergic neurotransmitter nitric oxide (NO) as well as its secondary messenger cyclic guanosine monophosphate (cGMP), which relaxes cavernosal smooth muscle. Sildenafil exerts its pharmacological action by inhibiting Type 5 phosphodiesterase; thereby increasing the cGMP concentration.¹⁵⁻¹⁸ The therapeutic efficacy of Sildenafil has been reported to be in the range of 75 to 92% of patients regardless of types of. However, most of these were categorized using the International Index of Erectile Function (IIEF).^{15-17,19,20} This is a well recognized tool for measuring erectile dysfunction but it is a self-administered type of questionnaire and is therefore subjective.²¹ There are few objective reports about the effects of Sildenafil.

To objectively investigate the therapeutic efficacy of Sildenafil, we have developed the SS (Sexual stimulation)-Penogram procedure, which utilizes a radioisotope and VSS to observe a

natural physiologic erectile process and any changes after the administration of Sildenafil.

MATERIALS AND METHODS

Subjects

Subjects used in this study were 104 males who were over 20 years of age and who had an ED more than 6 months in duration without any definite abnormalities. All had difficulty in achieving or maintaining a satisfactory sexual relationship.

The baseline studies included a complete blood count, urinalysis, and hormonal profiles. The major exclusion criteria were 1) a penile anatomical derangement such as a severe corporal fibrosis, 2) erectile dysfunction due to a loss of desire, 3) elevated serum prolactin levels (more than 3 times the normal level) or diminished serum testosterone levels (i.e., 20% lower than the normal lower limit in morning samples), 4) major psychotic problems (such as a major depression or schizophrenia), 5) chronic alcohol consumption or drug abuse, 6) a known history of major hematologic, kidney or liver disease 7) a recent cerebrovascular accident or a myocardial infarction (within the previous 6 months).

Methods

SS-penogram

After injecting ^{99m}Tc-RBC 15mCi via the antecubital vein, 30 minutes of sexual stimulation in the form of adult erotic video tapes was provided to induce a natural erection. The supine position the scrotum and inner thighs were shielded by a lead plate in order to enhance the visibility of the penile blood flow. Baseline measurements of the penile blood flow were measured and recorded by a computerized gamma camera every 15 to 30 seconds for 5 minutes. Forty minutes after administering 25 - 100 mg of Sildenafil, another penogram was taken for 30 minutes in a similar manner.

Analysis of activity curve

The analysis of the activity curve was described

previously.¹⁴ In short, Type I (i.e., normal; showing a 5 min or more peak erectile response with an induction period of 1 to 6 min), Type II-A (the impossible type; showing a less than 2 times the basal radioactivity), The Type II-B (the unstable type; showing less than 5 min peak erectile response), and Type II-C (the delayed type; showing a delay of more than 15 min after the start of sexual stimulation). The patients were grouped according to their response after Sildenafil administration. The effect of Sildenafil was assessed by comparing the radioactive activities between the 7th and 22nd minutes and any changes in the Type highlighted by the penogram.

Classification in the SS-penogram

The responses after Sildenafil treatment according to the radioisotope activity curve (RI) and its area under the curve during the 15 minutes from 7-22 minutes were categorized into 4 groups; 1) The Excellent response group; These showed an improvement or a greater than a 50% increase in the RI area after Sildenafil treatment. 2) The good response group; There was less than a 50% and a greater than 20% increase in the RI area after Sildenafil treatment. 3) The Borderline group; these showed less than a 20% change in the RI area after Sildenafil administration. 4) The Non-response group; These showed a worsening or a greater than 20% decrease in the RI area after Sildenafil administration. The therapeutic efficacy of Sildenafil was interpreted by SS-penograms both before and after administering Sildenafil.

Age Related response in the SS-penogram

The patients were grouped into those who were under 30's (low risk), over 50's (high risk), and those who were between age 30' and 50's (intermediate risk group), and their responses after administering Sildenafil were evaluated using the SS-penogram.

Statistical analysis

The data was analyzed using the SAS version 6.04 (SAS System, North Carolina, USA) program, a Chi-square test and Logistic regression analysis. P values < 0.05 were regarded as being statistically significant.

RESULTS

Patient characteristics

The mean age of patients was 44.9 ± 10.2 (23-68) years.

Their marital status was: unmarried 13, divorced 6, remarried 5, and deceased spouse 4. Seventy six patients (73.1%) were in stable relationships. The mean duration of marriage was 19.9 ± 9.6 (1-42) years, and the mean age of the spouse was 41.8 ± 8.4 (28-64) years.

Activity curves of the 1st and 2nd session SS-penogram

For the first penogram, Type I was found in 12 patients, Type (II-A) was found in 6, Type (II-B) was found in 73, Type (II-C) was found in 1 and complex (II-B + C) types were found in 4 patients. After the second administration of Sildenafil, Type I was found in 46, II-A was found in 10, II-B was found in 46 and the complex type was observed in 2 patients. The proportion of the Type I increased in the second penogram compared to the first examination.

Response to SS-penogram

The responses after Sildenafil administration were categorized into the following:
 A: Excellent response group (56 patients - 53.9%)
 B: Good response group (23 patients - 22.1%)
 C: Borderline group (15 patients - 14.4%)
 D: Inhibited response group (10 patients - 9.6%)

Examples of each group are shown in Fig. 1. A-D. When the clinical efficacy was determined according to the percentage of Excellent and Good response groups, Sildenafil was found to be effective in 76% (79/104) of patients.

Response to SS-penogram by age

The therapeutic efficacies of Sildenafil in patients under 30's, in 40's or over 50, were 79.4%, 67.7%, and 80.5%, respectively. No statically significant differences were noted ($p = 0.198$, Table 1). The proportion of the Excellent response groups with increased age in the patients over 50 was not

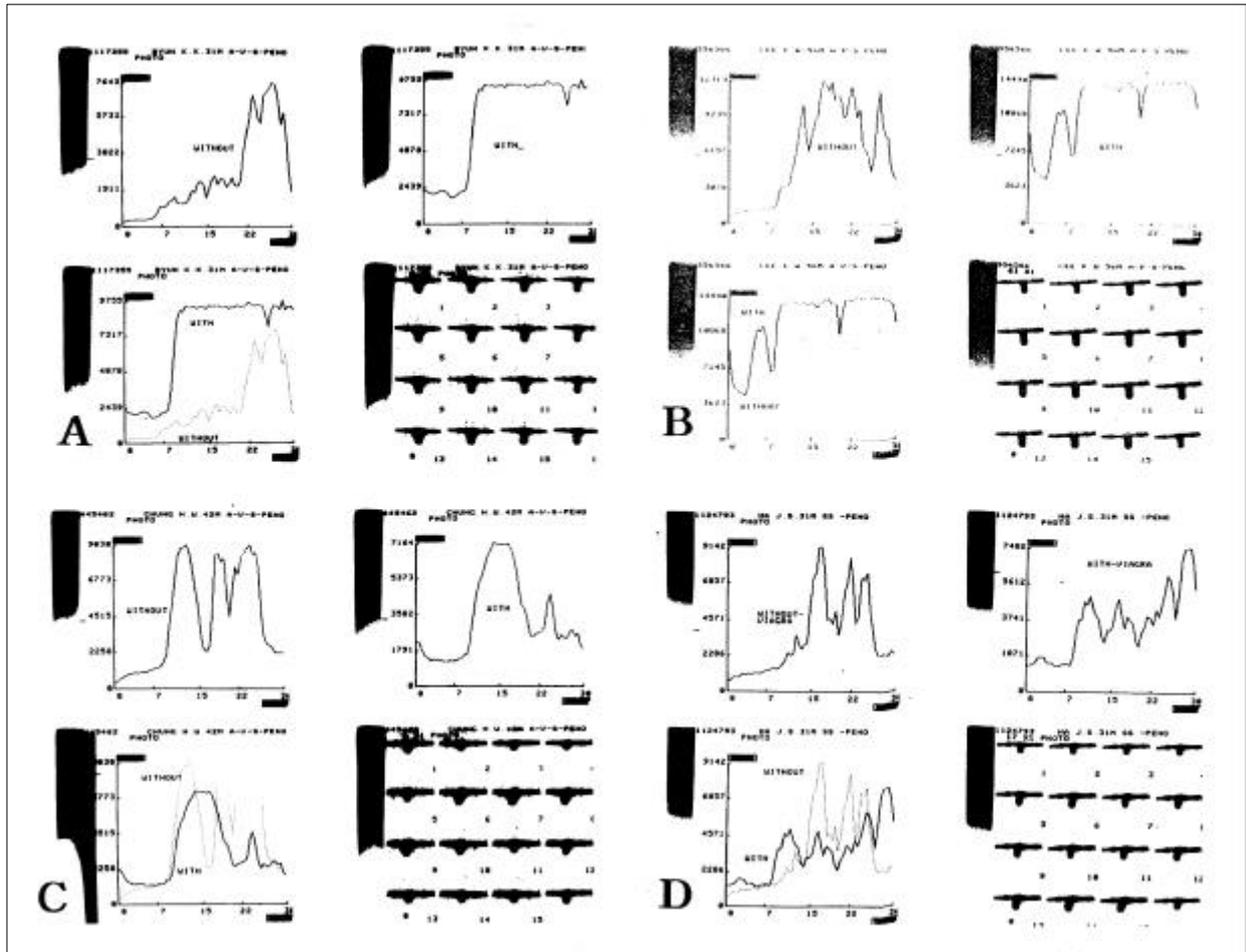


Fig. 1. Example of an SS-penogram. (A) Excellent response group, (B) Good response group, (C) Borderline group, (D) Non-response group.

statistically significant ($p = 0.382$). Logistic regression analysis showed that age was not a contributing factor to the response on the SS-penogram after Sildenafil administration (odds treatment ratio = 1.012, $p = 0.596$, Table 1).

DISCUSSION

In diagnosing ED, various aspects of the male erectile physiology that encompass the vascular, endocrine, central and autonomic nervous systems, psychological, and penile erectile systems must be evaluated. Consequently different treatment modalities are needed for each individual patient with ED.

The treatment of ED has consisted of pharmacological injection therapy, vacuum devices, or

penile prosthesis implantation but all of these produce erections that are far from the natural state. However, the oral agent used for erectile dysfunction, Sildenafil (Viagra), has revolutionized the treatment of erectile dysfunction, enabling patients to have erections on demand.¹⁸ Erectile dysfunction is mediated by nitric oxide (NO) and its secondary messenger, cyclic guanosine monophosphate (cGMP), which helps relax the cavernosal smooth muscle. There are 11 types of phosphodiesterases in the human body, and 2-5 types exist in penile tissue.²² Type 5 phosphodiesterase is unique in the fact that it is primarily involved in penile erection. It is modulated by the cGMP concentration. Sildenafil exerts its pharmacological action by inhibiting type 5 phosphodiesterase, thereby increasing the cGMP concentration.¹⁵⁻¹⁸

Table 1. Comparison of the Results of SS-penogram According to Age

Group*	Excellent response [†]	Good response	Borderline	Non-response	Total
Group 1 (≥ 39)	15 (44.1%)	12 (35.3%)	4 (11.8%)	3 (8.8%)	34
Group 2(40-49)	19 (55.9%)	4 (11.9%)	8 (23.5%)	3 (8.8%)	34
Group 3 (≤ 50)	22 (61.1%)	7 (19.4%)	3 (8.3%)	4 (11.1%)	36
Total	56 (53.9%)	23 (22.1%)	15 (14.4%)	10 (9.6%)	104

*The efficacy of Sildenafil on the SS-penogram did not correlate with age ($p = 0.198$).

On the logistic regression analysis, the relationship between the efficacy group and the age group was not significant (odds ratio=1.012, $p=0.596$).

[†]Excellent response group on the SS-penogram did not correlate with age ($p = 0.382$).

In this study, 76% (79/104) of patients demonstrated satisfactory results with Sildenafil on the SS-penogram, but 9.6% (10/104) of patients showed no response. In the latter group, the erectile response was inhibited rather than promoted, which suggests that these patients might have erections by some other mechanism. Clinically, these patients should be candidates for other oral agents, injections, or surgery rather than increasing the Sildenafil dosage.

Most therapeutic reports on Sildenafil are based on the International Index of Erectile Function (IIEF), consisting of a 15-question survey comprising 5 independent domains. It is a well-recognized tool for measuring erectile dysfunction but it suffers from inevitable subjectivity.²¹ There are some objective reports on the effects of Sildenafil, which illustrates the need for additional unprejudiced research.

The SS-penogram results in this study using radioisotopes were in agreement with the information from the patient questionnaires, and exhibited reproducible results. The results generally represent the penile physiologic state of most patients. Therefore, it is recommended for the preliminary screening of all patients with ED who have been considered for Sildenafil treatment. It is particularly suitable for young patients with psychological origins for their ED. However it is not appropriate for patients with a high threshold for erotic videotapes, poor health, and severe psychological inhibitions.

Unstable types were the most commonly found activity curves both before and after Sildenafil administration.¹³ In the first penograms, Sildenafil was relatively non-effective in Type I and II-B, but

highly effective in the impossible type. In the normal patients the area under radioactivity curve was rather large and the changes according the Sildenafil treatment were difficult to demonstrate.

Age was not a factor in the SS-penogram, which is not surprising. The therapeutic efficacy as determined by the SS-penogram was 76% and this correlates well with the reports from other studies. Thus, the SS-penogram is a noninvasive and physiologic test, and can objectively demonstrate changes in the penile blood flow, which can be used to determine the therapeutic efficacy of the treatment. Clinically, a SS-penogram can evaluate patients with ED, and can also be used in the new therapeutic trials using other new agents for treating ED. It can also be utilized in impotence clinics by screening patients who have ED and to determine the plausibility of using Sildenafil and other therapies before initiating treatment.

Our results with the SS-penogram on Sildenafil agree well with the results of other studies. However, further larger scale trials are needed to confirm the data. The SS-penogram should be used along side other agents for ED to determine its response objectively.

1) An SS-penogram can be used to accurately evaluate the natural erectile status in both sexual stimulation and pharmacological stimulation.

2) The therapeutic efficacy of Sildenafil as interpreted by the SS-penogram revealed augmented erectile capabilities in 76% of patients (79/104) but no response in 9.6% (10/104), which correlated with their clinical characteristics. No differences according to age were noted.

Further evaluation is warranted in the inhibitory group, which is not based on any severe

organic dysfunction.

3) Those men who showed no response to the Sildenafil challenged SS-penograms did not show any clinical improvement. In these patients other therapeutic modalities such as other oral and self-injection agents and surgical therapy should be considered.

4) The SS-penogram offers the most objective erectile response after any therapeutic trial. Thus, a primary challenge by any remedy for ED can greatly assist in determining the optimal treatment.

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