

LONG-TERM INTRACAVERNOUS THERAPY RESPONDERS CAN POTENTIALLY SWITCH TO SILDENAFIL CITRATE AFTER RADICAL PROSTATECTOMY

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ABSTRACT

Objectives. To assess whether long-term users of intracavernous (IC) injections after radical prostatectomy can switch to oral therapy with sildenafil citrate.

Methods. Forty-nine patients (mean age 60.9 years) with erectile dysfunction after radical prostatectomy were identified as long-term users of IC injections (3.7 ± 1.9 years). These patients received open-label treatment with sildenafil citrate (50 to 100 mg) for a minimum of 4 weeks or five attempts. The primary outcome measure of our study was assessed by the Sexual Health Inventory of Men (SHIM) questionnaire (International Index of Erectile Function-5 [IIEF]). A successful switch was prospectively defined as erection sufficient for vaginal penetration after sildenafil use and compliance to therapy. Patients were designated as responders or nonresponders on the basis of their ability to achieve vaginal penetration.

Results. Of 49 patients, only 36 agreed to receive oral open-label sildenafil (50 to 100 mg) for a minimum of 4 weeks or five attempts. Prostaglandin E₁ (PGE₁) was used in 70% and triple therapy (PGE₁, papaverine, and phentolamine) in the remaining 30%. Of the 36 patients, 15 (41%) successfully switched to sildenafil and discontinued IC injections. When the results were stratified by the type of IC solution, patients with high-dose triple therapy had a poor success rate of switch (7%) compared with patients using PGE₁ treatment (67%). Of the 36 patients, 14 (38%) found sildenafil ineffective and continued using IC injections. Patients who switched to oral therapy had had a greater ($P < 0.001$) total mean SHIM (IIEF-5) score with IC injections than those who did not switch (12.3 ± 7.8 versus 20.0 ± 4.9). Of the 36 patients, 7 (19%) found sildenafil alone to be suboptimal but continued using it, enhancing the efficacy of IC injections alone. The three predictive factors for a successful switch were high preoperative SHIM (IIEF-5) score, high post-IC injection SHIM score, and type of IC medication used (PGE₁ alone versus high-dose triple therapy).

Conclusions. Long-term users of IC injection therapy can potentially switch to sildenafil citrate with acceptable sexual satisfaction. Patients will accept a lower degree of sexual satisfaction as measured by the IIEF-5 (SHIM) score if oral therapy is effective. UROLOGY 63: 532–538, 2004. © 2004 Elsevier Inc.

Dennis and McDougal¹ were first to document the use of intracavernous (IC) therapy using prostaglandin E₁ (PGE₁) in previously potent radical prostatectomy (RP) patients with success rates of 85%. A study by Rodriguez Vela *et al.* in 1997

found that IC PGE₁ injection provided adequate rigidity in 95% of their patients.² Penile injections appear to be as effective in patients who have undergone non-nerve-sparing surgery as in patients with erectile dysfunction (ED) who have undergone nerve-sparing procedures. Thus, the efficacy of injections appears to be independent of the type of prostatectomy and the IC medication regimen used.³

Despite its high degree of effectiveness, patients often do not accept penile injections. Studies have shown that compliance rates are poor, ranging from 11% to 70%.^{4–13} Dropout rates in many series exceeded 40%.⁹ Factors that compromise the success of therapy include the pain associated with the

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injection, difficulty in reproducing a successful injection, and penile fibrosis.¹³

Although nonoral treatments (vacuum constriction device [VCD], medicated urethral system for erections [MUSE], and IC injections) have acceptable efficacy rates (33% to 68%), they also have high discontinuation rates (50% to 80%).³ The reasons for dissatisfaction include insufficient response to therapy, unacceptable side effects, or the feeling of anxiety associated with using the device or injections. Not surprisingly, when oral therapy was introduced, many patients switched from the traditional treatments to sildenafil citrate.^{3,14}

Even before sildenafil became available, patients with ED strongly preferred the least invasive form of therapy, such as oral medication.¹⁵ As a result, questions have arisen about the feasibility of switching patients with ED who are using IC PGE₁ injection therapy to an oral agent such as sildenafil citrate.^{3,14-16} Currently, it is unclear whether patients who have used IC injections long term can switch to oral therapy.

This study was conducted to determine whether patients with ED after RP successfully treated with IC injection therapy with PGE₁, alone or in combination with papaverine and phentolamine, could successfully switch to oral sildenafil citrate. Various parameters to predict which long-term users of IC injections after RP could successfully switch to oral therapy with sildenafil citrate were also assessed.

MATERIAL AND METHODS

PATIENT RECRUITMENT

The Cleveland Clinic Institutional Review Board approved this study, and all patients provided written informed consent. We obtained and reviewed the surgical records of a single surgeon (C.Z.) from August 1997 to October 2001. During that time, the surgeon performed RP on 450 sexually active patients with localized prostate cancer. After a mean follow-up of 9 months (range 6 to 12), 306 patients (68%) experienced severe ED, with no patient able to achieve vaginal penetration. All 306 patients who sought treatment for ED were initially evaluated by a comprehensive sexual history, laboratory evaluation, and physical examination. At that time, the patients were offered standard ED treatments, including a VCD, IC injection, or MUSE. The patients who had not received preoperative or postoperative hormonal therapy or radiotherapy, who were not using any concurrent form of ED treatment, and who did not have any contraindications to the use of sildenafil citrate (eg, ischemic cardiovascular disease or use of oral, sublingual, or transdermal nitrates) were prescribed the oral drug. Of the 306 patients, 102 chose IC injection therapy, 100 preferred treatment with sildenafil citrate, 30 preferred MUSE, and 74 agreed to a trial with a VCD.

The mean follow-up period for all 102 patients choosing IC injections for the treatment of ED after RP was 4 ± 2.2 years, and the mean patient age was 60.4 ± 6.3 years. Nerve-sparing (unilateral or bilateral) RP had been done in 59 patients (58%) and non-nerve-sparing procedures in 43 patients (42%). Of the 102 patients, 62 (61%) used PGE₁ alone, and 40 (39%) used either low-dose or high-dose triple therapy. The surgeon

recorded the anatomic status of the neurovascular bundle at surgery.

Overall, 59 (68%) of 102 patients achieved and maintained erections sufficient for sexual intercourse and 49 (48%) continued long-term therapy, with a mean use of 3.7 ± 1.9 years. Of the 102 patients, 53 (52%) discontinued IC therapy after a mean use of 14.5 months for the following reasons: insufficient erections, 18 patients (33%); preference for oral therapy, 17 (32%); fear of injections, 6 (11%); troublesome procedure, 6 (11%); loss of partner, 4 (8%); priapism, 1 (1%); and natural return of erections, 1 patient (1%). When excluding patients who preferred oral therapy to IC injection, who had a loss of partner, or a natural return of erections, the long-term compliance to IC injections was 70.6% (71 of 102).

Patients completed the long form of the International Index of Erectile Function (IIEF-15) questionnaire in the office before (preoperative, baseline) and at mean interval of 9 months (range 6 to 12) after RP during their follow-up visit (with C.D.Z.) at the Glickman Urological Institute, Cleveland Clinic Foundation. All patients were followed up at 6 to 9-month intervals. We retrospectively stratified the 49 long-term IC users according to the type of nerve-sparing RP procedure they had undergone: bilateral/unilateral nerve sparing in 37 (75%) and non-nerve-sparing in 12 (25%). Our patients had used IC injections for 3.7 ± 1.9 years, indicating chronic ED and representative of men in a urologic practice who are using effective and therapeutic doses of IC injections to manage ED after RP.

Before receiving the open-label trial of sildenafil citrate, patients had experienced sexual intercourse two times per week with IC injections in the prior month. Sildenafil citrate was prescribed for 4 weeks or for a minimum of five attempts. All long-term IC users switched to open-label treatment with sildenafil, reflecting the clinical practice situation. Sildenafil was prescribed at a dose of 50 mg, with a titration to 100 mg if needed to get a positive response. Patients were instructed to take one sildenafil tablet (100 mg) approximately 1 hour before sexual activity, as per the manufacturer's instructions. Patients were requested to have had adequate foreplay before sexual intercourse.

SURVEY AND DATA ASSESSMENT

The primary outcome measure of our study was assessed by the IIEF-15 questionnaire among the proportion of patients using IC alone, those who successfully switched to sildenafil, and those using a combination of IC injection and sildenafil therapy. A successful switch was prospectively defined as erections sufficient for vaginal penetration after sildenafil use and compliance to therapy. The patients were designated as responders or nonresponders on the basis of their ability to achieve vaginal penetration.

The data from the IIEF-15 questionnaire were condensed into the IIEF-5 questionnaire, which is an abridged five-item version of the IIEF-15 questionnaire, referred to as the Sexual Health Inventory of Men (SHIM). The SHIM is a validated, multidimensional, self-administered questionnaire that is a sensitive indicator of changes in erectile function. It is scored from 1 to 5: 1, never/occasionally; 2, less than one half the time; 3, sometimes/one half the time; 4, more than one half the time; and 5, almost always. The total IIEF-5 score was calculated by totaling the response to all five questions.^{17,18}

A second questionnaire (the Cleveland Clinic Post Prostatectomy Questionnaire) was used to determine the sexual satisfaction of the patient's partner. The partners were specifically asked how often they were satisfied with intercourse and how often the patient was able to achieve and maintain an erection. This questionnaire was scored from 1 to 5: 1, never/occasionally; 2, less than one half the time; 3, sometimes/one half the time; 4, more than one half the time; and 5, almost

always. Total spousal satisfaction was calculated from these questions and expressed as a percentage.¹⁶

To be included in the study, participants must have completed the office training, completed the IIEF-15 questionnaire, and reported satisfactory home use of IC injections for at least 2.5 years. Men were excluded if they received preoperative or postoperative hormonal therapy, radiotherapy, or any concurrent form of therapy for ED.

STATISTICAL ANALYSIS

The data are presented as the mean values and percentages as summary statistics. Skewness and kurtosis were used to evaluate the distribution of the results. The methods consisted of a comparison of scores of the patients using IC therapy long term and after the switch to oral sildenafil citrate using mean values. The number of patients discontinuing treatment for multiple reasons was calculated as a percentage of the total. In addition to the Wilcoxon tests, chi-square tests were used to compare categories. A two-tailed significance level of $P < 0.05$ was used for statistical tests, and all tests were performed with Statistical Analysis System, version 8.0, software.

RESULTS

Of the 49 patients, 36 agreed to take oral open-label sildenafil (50 to 100 mg) for a minimum of 4 weeks or five attempts. Nerve-sparing (unilateral or bilateral) RP had been done in 27 of these patients (75%) and non-nerve-sparing RP in 9 (25%). The median frequency of IC use in this subgroup was four times per month (25% to 75% interquartile range two to eight). PGE₁ alone (10 or 20 $\mu\text{g}/\text{mL}$ in normal saline) was used in 70%, low-dose triple therapy (5.88 $\mu\text{g}/\text{mL}$ PGE₁ plus 0.59 mg/mL phentolamine, and 17.65 mg/mL papaverine) in 16%, and high-dose triple therapy (20 $\mu\text{g}/\text{mL}$ PGE₁ plus 1 mg/mL phentolamine and 30 mg/mL papaverine) in the remaining 14%.

Of these 36 patients, 15 (41%) successfully switched to sildenafil and discontinued IC injections. Table I shows the demographics and dosing parameters of the 15 patients who changed from IC injection therapy to oral sildenafil. When the results were stratified by the type of IC solution, patients with high-dose triple therapy (20 $\mu\text{g}/\text{mL}$ PGE₁, 1 mg/mL phentolamine, and 30 mg/mL papaverine) had a poor success rate of switch (7%) compared with patients using PGE₁ treatment (67% overall; 53% [8 of 15] for those using 10 $\mu\text{g}/\text{mL}$ in normal saline; and 13% [2 of 15] for those using 20 $\mu\text{g}/\text{mL}$ in normal saline; $P < 0.003$). Fourteen patients (38%) found sildenafil to be ineffective and switched back to IC injections. The remaining 7 patients (19%) found sildenafil alone to be suboptimal but used it to enhance the efficacy of the IC injections. Table II shows the total mean IIEF-5 scores in patients using IC alone, those switching to sildenafil, and those using combination therapy (IC plus sildenafil citrate). Table III shows the comparison of the various variables predicting the successful switch from IC to oral silden-

TABLE I. Characteristics of patients who successfully switched from IC injections to oral sildenafil citrate

Characteristic	Value
Patients (%)	41 (15/36)
Mean age (yr)	60.9
Mean duration of erectile dysfunction (yr)	4 \pm 2.2
Duration of therapy with PGE ₁ (yr)	3.7 \pm 1.9
Radical prostatectomy type (%)	
Nerve sparing	60 (9/15)
Non nerve sparing	40 (6/15)
IC injection therapy type (%)	
PGE ₁ alone	
10 or 20 $\mu\text{g}/\text{mL}$ in normal saline	67 (10/15)
10 $\mu\text{g}/\text{mL}$ in normal saline	53 (8/15)
20 $\mu\text{g}/\text{mL}$ in normal saline	13 (2/15)
Low-dose triple therapy	26 (4/15)
5.88 $\mu\text{g}/\text{mL}$ PGE ₁ + 0.59 mg/mL phentolamine + 17.65 mg/mL papaverine	
High-dose triple therapy	7 (1/15)
20 $\mu\text{g}/\text{mL}$ PGE ₁ + 1 mg/mL phentolamine + 30 mg/mL papaverine	
Sildenafil dose (%)	
50 mg	26.7 (4/15)
100 mg	73.3 (11/15)

KEY: IC = intracavernous; PGE₁ = prostaglandin E₁.

afil citrate. Patients who switched to oral therapy had a greater mean SHIM (IIEF-5) score before surgery (23.3 \pm 3.4 versus 19.9 \pm 2.6) and while using IC injections (20.0 \pm 4.9 versus 12.3 \pm 7.8) than those who did not switch ($P < 0.001$). Partner satisfaction with IC injections was also greater for the partners of patients who successfully switched to sildenafil than for those who could not switch ($P < 0.03$). The three predictive factors for a successful switch were high preoperative SHIM (IIEF-5) score, high postinjection SHIM score, and type of IC medication used (PGE₁ alone versus high-dose triple therapy).

COMMENT

Our study was designed to assess the success rate of patients with ED after RP who were switched from IC injections to sildenafil citrate. Our data showed that of the 36 long-term users of IC injection who agreed to receive oral open-label sildenafil, 15 (41%) were able to switch to sildenafil citrate with acceptable sexual satisfaction.

Of our 102 post-RP patients, 69 (68%) were satisfied with IC injection therapy and 49 (48%) chose to continue with the therapy long term (3.7

TABLE II. SHIM (IIEF-5) scores: IC alone, switching from IC to sildenafil citrate, and combination therapy (IC + sildenafil)

Variable	IC Injections Alone (n = 14)	Successful Switch to Sildenafil (n = 15)	Combination (IC + Sildenafil) (n = 7)
Q5, maintenance ability	4.24 (4-5)	2.6 (2-3)*	4.64 (4-5)
Q15, erection confidence	3.96 (3-4)	2.22 (2-3)*	4.23 (4-5) [†]
Q4, maintenance frequency	4.28 (4-5)	2.54 (2-3)*	4.64 (4-5)
Q2, erection firmness	4.12 (4-5)	2.36 (2-3)*	4.27 (4-5)
Q7, intercourse satisfaction	3.61 (3-4)	2.45 (2-3)	4.80 (4-5) [†]
Total IIEF-5 score	20.21 (20-25)	12.17 (10-15)	22.58 (20-25)
Spousal satisfaction [‡] (%)	71.8	60.7	72.8

Key: SHIM = Sexual Health Inventory in Men; IIEF = International Index of Erectile Function; IC = intracavernous; Q = question. Data presented as the mean, with the range in parentheses, unless otherwise noted.

Each IIEF domain scored 0-5: 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; total IIEF-5 score calculated by totaling and taking mean of response to all five domains of IIEF-5.

* P < 0.05 vs. IC alone and combination therapy.

[†] P < 0.05 vs. IC alone and switch to sildenafil.

[‡] Spousal satisfaction is percentage of spouse/partner who responded positively to questionnaire.

TABLE III. Factors predicting successful switch from IC injections to oral therapy

Variable	Failed Switch to Oral Treatment (n = 14/36)	Successful Switch to Oral Treatment (n = 15/36)	Univariate P Value
Mean age ± SD (yr)	63.6 ± 5.27	60 ± 6.3	0.71
Hypertension (%)	36	33	0.73
Diabetes (%)	12	2	0.07
Coronary heart disease (%)	11	6	0.04*
Pretreatment IIEF-5 score	19.9 ± 2.6	23.3 ± 3.4	<0.001*
IIEF-5 score after RP	3.8 ± 3.3	4.7 ± 3.7	0.10
Time from RP to IC	2.3 ± 1.1	2.6 ± 1.2	0.17
IIEF-5 score after IC	12.3 ± 7.8	20 ± 4.9	<0.001*
Spousal satisfaction (%)	52	75	0.03*
Nerve sparing (%)	55	63	0.44

Key: IC = intracavernous; IIEF = International Index of Erectile Function; RP = radical prostatectomy.

* Statistically significant.

± 1.9 years). However, excluding those with a preference for oral therapy (n = 17), loss of a partner (n = 4), and a return of natural erections (n = 1), the long-term compliance rate with IC injections was 70.6% (71 of 102). The type of RP surgery (bilateral nerve sparing, unilateral nerve sparing, and non-nerve sparing) and type of regimen (single-agent therapy, high-dose triple therapy, or low-dose triple therapy) did not affect the efficacy of this therapy.

Our satisfaction and compliance rates are similar to those of Mulhall *et al.*⁵ and Purvis *et al.*⁷ Using an institutional questionnaire, Mulhall *et al.*⁵ found a good response in 75% of their patient group using PGE₁, which included patients with ED of all etiologies. They reported an attrition rate of 31% during a 38-month period. Purvis *et al.*⁷ found that 87% of their patient sample (which included patients with ED caused by a variety of etiologies) was fully or partially satisfied with IC injections.

The discontinuation rate in their study was 58% during 2 years.⁷

Cost, penile discomfort, and patient-partner problems were the major reasons for discontinuation in the study by Mulhall *et al.*⁵ A lack of efficacy was the primary reason for discontinuation in 1 (14.1%) of 7 patients. In the study by Purvis *et al.*,⁷ the lack of spontaneity, penile discomfort, and cost of therapy were the main reasons for dissatisfaction. Inadequate rigidity or lack of efficacy was the primary reason for discontinuation in 18% of the patients.⁷ The primary reasons for discontinuation in our study were inadequate erections and a preference for oral treatment with sildenafil citrate. As in the studies by Mulhall *et al.*⁵ and Purvis *et al.*,⁷ we found adverse side effects to be an infrequent reason for discontinuing treatment.

Our patients had used IC injections for a mean of 3.7 ± 1.9 years, indicating chronic ED and representative of those in a clinical practice situation

who are using an effective and therapeutic IC injection dose. Our data showed that of the 73% long-term users of IC injection who agreed to try oral open-label sildenafil, 41% (15 of 36) could potentially switch to sildenafil citrate with acceptable sexual satisfaction.

When the results were stratified by the type of IC solution, patients using high-dose triple therapy had a poor success rate of switch (7%) compared with patients using PGE₁ treatment (67%). Thus, it seems likely that the dose and type of IC medication can predict the success in switching to sildenafil citrate. Furthermore, most (53% [8 of 15]) of the patients who successfully switched were using less PGE₁ per dose. The study performed by Bechara *et al.*¹⁹ showed that triple therapy is more effective than high-dose PGE₁ alone in achieving erections suitable for penetration. In our study, more patients who were using PGE₁ alone successfully switched to sildenafil compared with those using high-dose triple therapy, which could be because this subgroup of patients may have had less severe ED and thus could be treated with low doses.

Although injections usually show better efficacy than sildenafil citrate, they are associated with discomfort and anxiety, which weigh heavily in patients' preference for oral therapy.^{10,20} As seen in our study, patients will accept a lower degree of sexual satisfaction as determined by the IIEF-5 (SHIM) score if oral therapy is effective (12.17 versus 20.21). Sildenafil citrate is noninvasive and discrete and facilitates erection only in response to sexual stimulation.²¹ As a result, questions have arisen about the feasibility of switching patients with ED after RP who are using IC PGE₁ therapy to an oral agent such as sildenafil citrate.^{3,14–16} We analyzed the variables predicting the successful switch from IC to oral sildenafil citrate. Patients who successfully switched to oral therapy had a greater SHIM (IIEF-5) score before surgery and a greater SHIM score while using IC injection therapy. The three predictive factors for a successful switch were high preoperative SHIM (IIEF-5) scores, high post-injection SHIM scores, and type of IC medication used (PGE₁ alone versus high-dose triple therapy; Table III).

Of the 36 patients who tried sildenafil, 14 (38%) found it to be ineffective and continued to perform IC injections at a frequency of 4.8 times per month, with efficacy similar to the preoperative sexual score. The regular follow-up and comprehensive training that was offered to our patients probably supported this continuity. We believe that periodic follow-up combined with encouraging realistic expectations increases patient compliance and lowers the attrition rate.

Although sildenafil citrate has been very successful in treating ED, intracavernous penile injections

with PGE₁ alone^{1, 2} or in combination with papaverine and phentolamine³ continue to be an important therapeutic option for patients who do not benefit from oral agents. Although the use of an oral agent such as sildenafil citrate as a first-line agent is optimal, this option in post-RP patients depends on the presence of one or two neurovascular bundles.^{3,21,22} Patients who have undergone non-nerve-sparing RP and those in whom oral therapy has failed will require other options such as IC injections.^{5–7} Additional study is required to determine whether other agents (eg, nitrodonors, forskolin, vasoactive intestinal peptide, and moxisylyte) alone, or in combination, can provide better efficacy and long-term compliance.^{23–25}

Of the 36 patients who tried sildenafil, 7 (19%) found sildenafil use alone to be suboptimal but continued using it, enhancing the efficacy of the IC injections. A recent area of interest has been the use of combination therapy for ED after RP when, individually, therapies are ineffective. The individual treatments have limited compliance and high discontinuation rates, which can lead to a lack of interest in sexual rehabilitation. Thus, combination therapy may be more efficacious in salvaging patients who desire noninvasive therapy but in whom a single-treatment modality fails. Our study showed that sildenafil can augment the response rate when used in combination with IC injections.

Although penile injection therapy is often not routinely advised in the early postoperative period because of penile discomfort or patient anxiety or lack of interest, some evidence has shown that "early rehabilitation" of the penis is necessary to prevent lasting ED. During the neurapraxia that follows nerve-sparing RP, early cavernous injection therapy may potentially maintain function. The neurapraxia, in our experience, may persist for 6 to 24 months. This concept has been supported by a study by Montorsi *et al.*²⁶ in 1997, who demonstrated that early postoperative IC injection limited the development of hypoxia-induced tissue damage and produced an overall improvement in the recovery of spontaneous erections. Because sildenafil citrate has shown limited effect in the early postoperative period, the use of IC injections during that time may become an important pharmacologic stimulus for nerve regeneration for post-RP patients.²⁷ Afterward, with nerve recovery, patients may ultimately switch to oral therapy once the period of neurapraxia resolves. Additional confirmatory studies are necessary to support this concept of early penile rehabilitation.

Recently, Padma-Nathan *et al.*²⁸ showed that 27% of post-RP patients treated with nightly sildenafil starting 1 month after surgery showed spontaneous erections compared with only 4% in a placebo group. Thus, during the early period of

neurapraxia that follows RP, urologists should consider promoting early penile rehabilitation with oral and nonoral therapies to prevent intracorporeal fibrosis and maintain sexual interest. The early use of MUSE (intraurethral PGE₁), VCDs, and intracavernous injections and sildenafil citrate could sexually rehabilitate and enhance the return of natural erections after RP. Our study showed that patients who were long-term users of IC injection therapy could successfully switch to sildenafil citrate with acceptable sexual satisfaction. Therefore, patients who are successfully treated with standard nonoral therapy should be offered the option of using oral therapy.

CONCLUSIONS

Long-term users of IC injection therapy can potentially switch to sildenafil citrate with acceptable sexual satisfaction. Patients will accept a lower degree of sexual satisfaction as determined by the IIEF-5 (SHIM) score if the oral therapy is effective. Patients who successfully switched to oral therapy with sildenafil citrate had greater SHIM (IIEF-5) scores before surgery and while using IC injections than those who could not switch. Some long-term IC injection users (20%) who found sildenafil citrate ineffective alone continued to use combination therapy of IC and sildenafil citrate to enhance their sexual satisfaction.

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