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Original Research

Delineating patient errors in an intracavernosal injection program

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Abstract

Background: Intracavernosal injection therapy (ICI) is a well-established therapeutic strategy for men with erectile dysfunction. Complications are often related to patient error when performong ICI.
Aim: The objective of this study was to examine patient errors in an established patient training program for performing ICI and identify factors that could predict major errors.
Methods: Patients enrolled in our ICI program are trained on technical aspects, and dose titration is begun. Patients are given explicit instructions during training, both verbally and in written form. Records were reviewed for men using ICI for ≥6 months. Multivariable analysis was used to define predictors of major errors.
Outcomes: Errors were listed as minor (zero-response injection, penile bruising, expired medication) and major (errors potentially leading to priapism: dose self-titration, double injecting).
Results: Overall, 1368 patients met the inclusion criteria and were included in the analysis. The mean patient age was 66 ± 22 (range 29-91) years. Regarding education, 41% of patients had graduate-level education, 48% had college education, and 11% high school education. Mean follow-up was 3.2 ± 7.6 (range 0.5-12) years. The agents used were trimix (62%), bimix (35%), papaverine (2%), and prostaglandin E1 monotherapy (1%). At least 1 error occurred during self-administration in 42% of patients during their time in the program. Errors included zero response to medication due to technical error (8% of patients), penile bruising (34%), use of an expired bottle (18%), self-titration (5%), and double injecting (4% of patients); 12% of men committed ≥1 error during their time in the program. On multivariable analysis, independent predictors of the occurrence of a major error included: young age, graduate-level education, and <12 months of injection use.
Clinical implications: To the best of our knowledge, this is the first reported study to investigate ICI errors and risk factors. The identification of factors predictive of major errors allows for more tailored and intensive training in this subset of patients.
Strengths and limitations: Strengths of this study include a large patient population (1386 men) with a considerable follow-up time. Additionally, the rigorous training, education, and monitoring of the participants, as well as the use of formal definitions, enhances the accuracy and reliability of the results. Despite the strengths of the study, recall bias may be a limitation concern.
Conclusion: The majority of patients were error free, and the majority of the errors were minor in nature. Major errors occurred in <10% of patients. Younger age, graduate-level education, and less experience with ICI were independent predictors of major errors.

Keywords: errors; intracavernosal injections; erectile dysfunction; outpatient setting; trimix; bimix.

Introduction

In the early 1980s, intracavernosal injection (ICI) was introduced as the primary treatment for erectile dysfunction (ED) and remained the gold standard until the late 1990s, when oral phosphodiesterase 5 inhibitors became available. Nowadays, ICI is considered a second-line treatment for ED and is a particularly important tool in penile rehabilitation programs for men who have undergone radical prostatectomy and have not achieved satisfactory results with oral phosphodiesterase 5 inhibitors.[1-3]

Therapy via ICI involves injection directly into the corpora cavernosa of medications such as papaverine, phentolamine, prostaglandin E1 (PGE1), or a combination of these drugs. Trimix is one of the most used medication combinations for intracavernosal injections, and consists of a mixture of papaverine, phentolamine and PGE1.[2,3] Bimix is anothermedication mixture in which papaverine and phentolamine are combined and is preferably used in patients with hypersensivity to PGE1, seen most commonly in patients with autonomic neuropathy.[4]

Therapy with ICI is known to be highly effective and safe for treating ED. Studies have shown high satisfaction rates among patients, and the therapy generally has an acceptable side-effects profile. Minor side effects include bruising and pain at the injection site, while the most severe side effects include cavernosal smooth-muscle fibrosis and priapism.[5,6]

Priapism, which is an erection lasting over 4 hours, is a rare but serious adverse event associated with ICI therapy. Trimix has been reported to cause priapism in the range of 0.5%-7.1% of patients. Prompt diagnosis and management are crucial to prevent irreversible smooth-muscle damage, which may result in fibrosis that can lead to the development of venous leak. Clinical experience suggests that most priapism cases are the result of major errors in self-injection, despite patients being educated on proper technique.[1-3,7,8]

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To ensure the safety and effectiveness of ICI therapy, it is essential for patients to adhere to the instituted safety guidelines, which is made possible by thorough patient education along with rigorous training in the clinic, close monitoring, and regular outpatient follow-up to assess treatment response and dose titration.

However, despite the efforts to deliver safe and efficient ICI care, our clinical experience and the literature indicate that patient errors largely stem from either misunderstanding of or noncompliance with the program guidelines. The objective of this study was to examine patient error patterns in an established ICI program and identify factors that might predict major errors.

Methods

Study population

The study cohort consisted of men who were enrolled (IRB number, 16-459) in our penile injection therapy clinic program for at least 6 months and who were sexually active. For training, patients attended two training sessions at the clinic where the technical aspects were taught and dose titration is begun led by advance practice (nurse) practitioners,. Patients are given written instructions[9,10] and are seen every 6-12 months once they are enrolled in the program. The trimix mixture used was papaverine 30 mg/mL, phentolamine 1 mg/mL, and PGE1 10 μg/mL, while the bimix mixture was papaverine 30 mg/mL and phentolamine 1 mg/mL.

Patients were given the following explicit instructions during training, both verbally and in written form: (1) the target erection is penetration rigidity for $\leq$90 minutes; (2) apply pressure on the injection site to limit bruising/hematoma risk; (3) avoid self-titration of the medication dose; (4) never inject a second time if no response occurs to the first injection; (5) avoid double-injecting (a second injection within a 24-hour period); and (6) if using trimix, change the medication bottle at least every 6 months. Patients are forewarned that they may be discharged from the program for persistent failure to comply with the ICI program guidelines.

All patients in our injection therapy program are followed up for 6 months after initial training and then annually thereafter. During the interview with the clinician during follow-up, all of the aforementioned ICI errors are reviewed by use of an injection therapy checklist. Thus, the 6-month follow-up interview is a structured assessment performed in an a priori–defined fashion.

Errors

Errors in ICI performed by patients were categorized as minor or major. Errors deemed minor were the following: a zero-response injection (after a successful injection in the office), penile bruising, or using an expired medication. Major errors included those that might lead to priapism, specifically dose self-titration and double injecting.

Priapism

Priapism was defined as a self-reported penetration hardness erection lasting $\geq$4 hours. Patients were instructed to take pseudoephedrine 120 mg by mouth if they had a penetration hardness erection lasting 2 hours, to call us at 3 hours, and to be in the emergency room by the 4th hour.

Statistics

Multivariable analysis was conducted in an effort to define possible predictors of a major error occurrence. Factors included in the model were patient age, partner status, duration within the program, education level, number of vascular comorbidities, and race. Univariable analysis was first performed to define potential predictors. All factors significant at less than the P value = .20 level moved forward into the multivariable model.

Results

Patient population

Overall, 1368 patients met all inclusion criteria and were analyzed. The mean (SD) patient age was 66 (22) (range 29-91) years. With regard to education, 41% of patients had a graduate-level education, 48% had a college education, and 11% had a high school education. Other data were that 82% of patients were White and 79% were partnered or married. The comorbidity profile included: hypertension in 49% of patients, hyperlipidemia in 52%, diabetes in 11%, coronary artery disease in 9%, and obstructive sleep apnea in 37% of patients. Unfortunately, we did not have data on income. The mean (SD) follow-up period was 3.2 (7.6) (range 0.5-12) years. The distribution of agents used was trimix in 62% of patients, bimix in 35%, papaverine in 2%, and PGE1 monotherapy in 1% of patients.

Error profile

At least 1 error was made by 42% of the patients during their time in the program (Table 1). Errors included zero response to injection due to technical error in 8% of patients, penile bruising in 34%, use of medication from an expired bottle in 18%, self-titration of medication dose in 5%, and double-injection in 4% of patients. Univariable analysis results are shown in Table 2. On multivariable analysis, independent predictors of the occurrence of a major error included young age (odds ratio [OR], 1.4; $P < .05$), graduate-level education (OR, 4.7; $P < .01$), injection use <12 months (OR, 1.6; $P < .01$) (Table 3).

Discussion

Therapy with ICI is reliable and highly effective for ED, and the safety of ICI has been demonstrated in several studies.[1-3,6] Despite being considered a second-line treatment nowadays with the advent of PDE5i, ICI has a high satisfaction rate for its users, at least those in a structured training program. Priapism is the most serious of the adverse effects of ICI and most commonly results from patient errors in ICI technique or noncompliance with guidelines.[1-3]

Our results showed that about one-half (42%) of our patients committed at least 1 minor error during the time in the ICI program. Most of the errors that occurred during the program were considered minor in nature, but 9% of the participants committed a major error. Among the major errors that occurred during the study period, self-titration and double injecting were equally reported. According to our search, much to our surprise, there exists almost no other literature on this topic despite the frequency of ICI use among ED patients internationally. Coombs et al.[3] reported that of the 7 patients who had priapism in their study, 86%

Table 1. Patient errors.

Error type		No. (%) of patients (n = 1386)	
Minor	Zero response	111 (8%)	582 (42%)
	Penile bruising	471 (34%)	
	Expired medication	249 (18%)	
Major	Self titration	69 (5%)	125 (9%)
	Double injecting	55 (4%)	

Table 2. Univariable analysis of predictors of a major intracavernosal injection error.

	Odds ratio	95% CI	*P* value
Patient age <40 years	2.2	1.8-3.9	.01
Graduate-level education (vs other)	7.0	3.5-8.2	<.01
Duration in ICI program <12 months	1.9	1.8-6.0	.01
Partner status (Y)	1.2	0.7-3.2	.22
Education level (graduate vs other)	1.1	0.4-3.4	.45
Education level (high-school vs other)	1.2	0.6-2.4	.54
White vs other	1.5	0.7-2.5	.44
Number of comorbidities	1.1	0.5-1.5	.8

Abbreviation: ICI, intercavernosal injection; Y, yes.

Table 3. Multivariable analysis of predictors of a major ICI error.

	OR	95% CI	*P* value
Patient age < 40 years	1.4	1.1-2.6	<.05
Graduate-level education (vs other)	4.7	2.1-5.2	<.01
Duration in ICI program <12 months	1.6	1.4-3.9	<.01

Abbreviation: ICI, intercavernosal injection.

reported self-adjustment of the dose. We have shown that young patients (<40 years-old), shorter duration in the ICI program (<12 months), and higher education level were predictors of a major error by patients.

Our finding that shorter duration in the ICI program predicted a major error by a patient when performing ICI is in accordance with Coombs et al., who showed that 86% of priapism events in their study patients occurred within a mean duration of 10 months of treatment. During the initial months of the program, patients are learning how to correctly inject correctly, while undergoing dose titration.

Results showed that younger patients (<40 years old) also tended to make more mistakes than older patients in our practice, perhaps suggesting that younger men are more prone to risk-taking or may have difficulty retaining the information provided. Our data showed that more highly educated patients (graduate level) also commited more errors during ICI self-injection than patients with lower levels of education, particularly in regard to self-titration. Of the 5% of patients who self-titrated, fully 80% were healthcare professionals (nurses, nurse practitioners, physicians, dentists, pharmacists). We propose that such healthcare personnel may deliberately be noncompliant and perhaps are judging themselves to be better at making their own medical decisions.

The strengths of this study include a large study population (1386 men), considerable follow-up time (mean duration >3 years), rigorous patient training and patient monitoring, and the use of a formal definition of patient errors. Despite the strengths of the study, recall bias is not an insignificant limitation. Furthermore, we may have defined errors differently from some centers, and the designations we report here are specific only to this program. However, we believe these data will be informative for all penile injection program coordinators and staff.

Overall, rigorous training and strict program guidelines are important for a safer ICI program. Dangerous complications can be avoided most of the time by using proper technique, careful dose titration, and patient monitoring. Regular follow-up with patients likely increases patient compliance and enhances overall safety. Although our educational and monitoring program has changed only slightly in response to these data, we have developed a patient education video and look forward to presenting outcome data on the use of this video in the near future.

Conclusion

The majority of patients in our ICI program were error free, and the majority of the errors were minor in nature. Major errors occurred in less than 10% of patients. Younger patient age, graduate-level education, and less experience with ICI were independent predictors of the occurrence of major errors.

Author contributions

T.P.F.: Writing—original draft. P.T.: Data curation, writing—original draft. Y.O.: Data curation. J.N.: Conceptualization. N.W.: Data curation. J.P.M.: Conceptualization, methodology, supervision, writing—review & editing.

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Conflicts of interest

J.P.M. works as a consultant for the Roman company and is also the editor-in-chief for the *Journal of Sexual Medicine*.

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