ORIGINAL RESEARCH

Predictors of successful erectile function using intracavernosal injection in post-prostatectomy men with erectile dysfunction

Yotam Veredgorn[1], Ziv Savin[2], Ron Marom[1], Haim Herzberg[3], Amihay Nevo[1], Ofer Yossepowitch[1], Snir Dekalo[1]

[1]Department of Urology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Department of Urology, Mount Sinai, New York, United States; [3]Department of Urology, Soroka Medical Center, Beer Sheva, Israel

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ABSTRACT

INTRODUCTION: Intracavernosal injections (ICI) are commonly used to treat erectile dysfunction (ED) in men following radical prostatectomy (RP). Predictors of treatment success are still unclear. Our objective was to explore the relationship between various clinical and pathologic parameters and the achievement of satisfactory erections with ICI following RP.

METHODS: This is a prospective study of men following RP with bilateral neurovascular bundle preservation who experienced ED refractory to treatment with phosphodiesterase type 5 inhibitors (PDE5I) at a minimum of six months after surgery. Three escalating dosages of TRIMIX were used consecutively (5 mg papaverine, 0.5 mg phentolamine, 10 mcg alprostadil; 10 mg papaverine, 1 mg phentolamine, 20 mcg alprostadil; 17 mg papaverine, 1 mg phentolamine, and 30 mcg alprostadil). Erection Hardness Scale (EHS) and International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) were used for functional assessments.

RESULTS: Thirty-four patients were stratified by their EHS scores and Trimix dosages: low-dose full responders (n=12), intermediate-dose full responders (n=10), high-dose partial responders (n=7), and high-dose failures (n=5). Twenty-nine patients (85%) reported on satisfactory erectile function with ICI. The ICIQ-SF scores were the only parameter that correlated significantly with successful erectile response, with median scores of 0, 3.5, 11, and 16 for the respective groups above (p=0.001). Univariate logistic regression demonstrated a significant association between ICIQ-SF scores and partial or non-response (odds ratio 1.3, 95% confidence interval 1.1–1.5, p=0.002).

CONCLUSIONS: ICI is an efficient therapy for achieving satisfactory erections following RP in PDE5I-resistant men. Sustainable urinary incontinence is a strong predictor of poor response to therapy.

INTRODUCTION

Erectile dysfunction (ED) is a common and often disconcerting consequence of radical prostatectomy (RP), a surgical procedure frequently employed in the treatment of localized prostate cancer.[1] The incidence of ED post-RP ranges from 20–90%, depending on factors such as nerve-sparing techniques, preoperative ED assessment scores, and definitions of erectile function. Additionally, erectile recovery post-surgery can be delayed, sometimes lasting up to 18 months for baseline erectile function to resume.[2,3]

Introduced as a monotherapy by Virag in 1982,[4] intracavernosal injections (ICI) therapy has evolved to include combination regimens with several different compounds.[5] Currently, ICI is considered one of the accepted options for the treatment of ED. Phosphodiesterase type 5 inhibitors (PDE5Is) are typically the first-line therapy for ED due to their ease of use and effectiveness; however, for patients who have undergone RP and do not respond adequately to PDE5Is, ICI remains a common and valuable treatment option.[6]

Despite the widespread use of ICI among men following RP, data is lacking regarding the optimal dosage and clinical parameters that may predict successful outcomes. Moreover, while studies have identified a correlation between nerve preservation, ED, and urinary incontinence after RP,[7,8] the interaction between the latter and response to therapy with ICI remains elusive.

In this study, we investigated a range of variables and their relationship to the efficacy of ICI in a very selected PDE5I-resistant population,

out of large contemporary cohort of men after robotic-assisted RP (RARP). Specifically, we investigated patient characteristics that may impact treatment response and elucidated the optimal medication dosages required to achieve satisfactory erections in each group of patients.

METHODS

Participants

After institutional review board approval, we prospectively enrolled consecutive patients who underwent RARP with bilateral neurovascular bundle preservation from January 2022 to December 2023 and continued to experience significant ED despite effective PDE5I treatment at least six months after their operation. Preoperatively, all patients reported on erectile function considered satisfactory for intercourse. Men who did not undergo bilateral nerve-sparing based on their preoperative tumor characteristics and those with any level of penile tumescence reported at initial consultation after the surgery (Erection Hardness Scale[9] [EHS]>1) were excluded.

After receiving informed consent, each of the study participants completed two questionnaires: 1) a baseline assessment using the EHS, a single-item scale questionnaire that assesses erectile function based on penile rigidity; and 2) the Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF)[10] questionnaire evaluating the frequency, severity, and impact on quality of life (QoL) of urinary incontinence. Demographic, clinical, perioperative, and pathologic information regarding these patients were collected.

Intervention protocol

All patients enrolled in the study were treated with incremental doses of ICI following a standardized protocol. Initially, each syringe contained 5 mg of papaverine, 0.5 mg of phentolamine, and 10 mcg of alprostadil. If the response was unsatisfactory, the dose was titrated up to 10 mg of papaverine, 1 mg of phentolamine, and 20 mcg of alprostadil. If adequate response was still not achieved, a final dose of 17 mg of papaverine, 1 mg of phentolamine, and 30 mcg of alprostadil was administered intracorporeally until satisfactory erections were obtained. Each patient was monitored in the clinic for at least three hours post-injection, allowing objective evaluation of response using the EHS. After each increase in ICI dose, an additional EHS score was obtained. The primary endpoint was an EHS score of 4, defined as success and indicative of a fully rigid erection.

Statistical analysis

The cohort was stratified into four distinct categories based on the combination of ICI dosage and treatment response determined by the EHS score. Continuous variables were summarized using the median and interquartile range (IQR) and compared between groups using the Kruskal-Wallis test. Categorical parameters were compared using Fisher's exact test. A box plot was used to graphically represent ICIQ-SF scores by group. Pearson and Spearman's correlation tests, receiver operating characteristics (ROC) curve, area under the curve (AUC), Kolmogorov-Smirnov metric, and logistic regression models were applied to identify factors associated with a response. A p-value of <0.05 was considered statistically significant. All analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between January 2022 and December 2023, 34 men agreed to participate in the study. All patients had erectile function sufficient for intercourse preoperatively, had undergone RARP with bilateral nerve-sparing, had attempted PDE5i treatment, and had an EHS score of 1 upon enrollment before the intervention. Patients were divided into four distinct response categories based on their final EHS score and ICI dosage: low-dose full responders, with EHS score of 4 after injection of the lowest dose (n=12); intermediate-dose full responders, with EHS score of 4 after injection of the second dose (n=10); high-dose partial responders, with EHS score of 3 after injection of the highest dose (n=7); and high-dose failures, with EHS score of 2 or less after injection of the highest dose (n=5). For 29 patients (85%), the ICI treatment resulted in erections satisfactory for sexual intercourse (EHS of 3 or 4). None of the patients who required the highest dose of TRIMIX achieved an EHS score of 4 (Figure 1).

The clinical and pathologic characteristics of the men in our cohort are presented in Table 1. The overall median age was 66.5 years (IQR 61–70), and the overall median time from surgery to enrollment was 14 months (IQR 12.25–16). The median ICIQ-SF score for the entire cohort upon enrollment was 4 (IQR 0–11). Age, time from surgery, adjuvant or salvage radiation therapy, International Society of Urological Pathology (ISUP) pathologic score, involvement of the surgical margins, and pathologic stage were similar across all ICI response groups. Positive surgical margins were more prevalent among the high-dose partial responders and

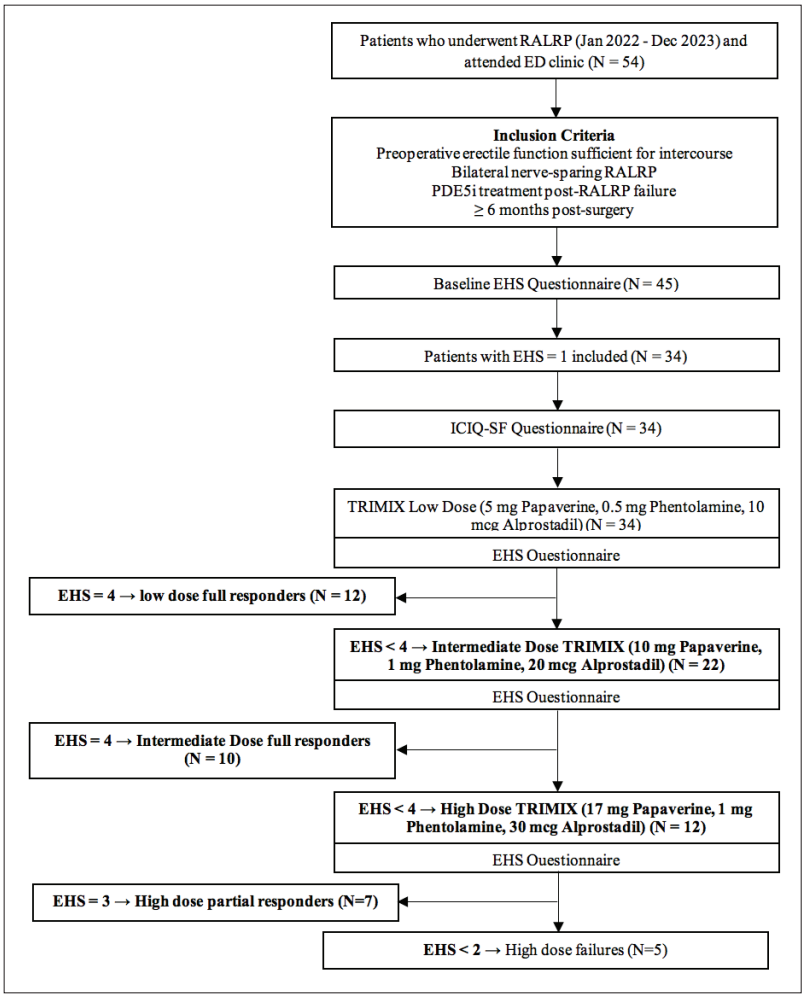

Figure 1. Flow chart of study selection. ED: erectile dysfunction; EHS: Erection Hardness Scale; ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form; PDE5i: phosphodiesterase type 5 inhibitors; RALRP: robot-assisted laparoscopic radical prostatectomy.

high-dose failures, albeit this difference was not statistically significant (p=0.1).

ICIQ-SF scores were significantly different among the different categories, as patients with better ICI responses had lower ICIQ-SF scores (i.e., better recovery of postoperative urinary continence). The median ICIQ-SF scores for each predefined ICI response group were as follows: 0 (IQR 0–3) for low-dose full responders, 3.5 (IQR 1–6) for intermediate-dose full responders, 11 (IQR 7–12) for high-dose partial responders, and 16 (IQR 13–16) for high-dose failures (p=0.001) (Figure 2).

ICIQ-SF scores were found to correlate with the response category, demonstrating a moderate-to-strong Pearson correlation coefficient of 0.68 (95% confidence interval [CI] 0.44–0.82, p<0.001). No other factors were found to be correlated with ICI response categories (Supplementary Table 1; available at *cuaj.ca*).

When dividing patients into full responders (EHS=4, n=22) and partial responders/non-responders (EHS<4, n=12), ROC curve analysis identified the ICIQ-SF score as a significant predictor of response, with an AUC of 0.88 (95% CI 0.76–1, p<0.001) and an optimal cutoff of 5.5 to predict partial/non-response (sensitivity 92%, specificity 82%). Univariate logistic regression demonstrated a significant association between ICIQ-SF scores and partial/non-response (odds ratio [OR] 1.3, 95% CI 1.1–1.5, p=0.002). Additionally, an ICIQ-SF score ≥6 was associated with a more than fourfold increase in the likelihood of partial/non-response (OR 49, 95% CI 4.8–501.7, p<0.001).

There was one incident of priapism following ICI documented in a 65-year-old man with an ICIQ-SF score of 0, who responded to the low dose of TRIMIX (5 mg papaverine, 0.5 mg phentolamine, and 10 mcg alprostadil) with EHS score of 4. The priapism lasted 5.5 hours and was resolved with phenylephrine in the emergency room. No other side effects were noted.

DISCUSSION

While ICI is a common treatment alternative for post-prostatectomy ED, predictors of its anticipated success remain scarce. This study evaluated the relationship between various clinical and pathologic parameters and the achievement of satisfactory erection with ICI. It found that urinary incontinence following RP, as indicated by a high ICIQ-SF score, was the only independent predictor of ICI failures, even at high dosages. Moreover, by applying a standardized ICI dose-escalating paradigm, we were able to achieve satisfactory outcome in the majority (85%) of patients while avoiding substantial side effects and maintaining a negligible rate of unwarranted priapism.

Over the years, ED rates have improved with developments in nerve-preservation techniques and the introduction of robotic surgeries.[6] Despite this improvement RP still results in damage to the cavernous nerves and blood vessels.[11] ED remains a significant morbidity, with rates ranging from 14–69% at 12 months following nerve-sparing RARP in earlier studies and up to 83% according to a more contemporary study,[12] significantly impacting QoL. The introduction of PDE5I has had certain impact on ED recovery, yet 30–45% of patients will still experience inadequate erectile function after an appropriate PDE5I attempt and often seek a better solution.[6,13]

With response rates of up to 90% and high patient satisfaction, ICI has become a viable treatment option.[14] Yet, ICI may incur several notable side effects, namely priapism, pain, ecchymosis, and hematoma formation.[15]

Table 1. Baseline clinical, pathologic, and functional characteristics stratified by the four response categories

Variable	Low-dose full responders (n=12)	Intermediate-dose full responders (n=10)	High-dose partial responders (n=7)	High-dose failures (n=5)	Total (N=34)	p
Age (years)	64 (60.5, 68.3)	67.5 (64.8, 69.8)	69 (63.5, 71)	60 (59, 70)	66.5 (61.3, 70)	0.57
ISUP	2 (2, 3)	2.5 (2, 3)	3 (2, 3)	3 (3, 3)	3 (2, 3)	0.67
Stage						
T2	5 (41.7%)	2 (20%)	2 (28.6%)	2 (40%)	11 (32.4%)	0.45
T3a	5 (41.7%)	8 (80%)	3 (42.9%)	3 (60%)	19 (55.9%)	
T3b	2 (16.7%)	0 (0%)	2 (28.6%)	0 (0%)	4 (11.8%)	
Positive surgical margins	1 (8.3%)	0 (0%)	2 (28.6%)	2 (40%)	5 (14.7%)	0.11
ICIQ-SF	0 (0, 3)	3.5 (0.8, 5.8)	11 (7, 12)	16 (13, 16)	4 (0, 11)	0.001
Time from surgery (months)	14 (11.3, 17.5)	15.5 (13.3, 16)	14 (13, 14.5)	13 (12, 14)	14 (12.3, 16)	0.38
Previous radiation	1 (9.1%)	1 (11.1%)	2 (33.3%)	0 (0.0%)	4 (12.9%)	0.48

Continuous variables are presented as medians (IQR) and categorical as n (%). ICIQ-SF: International Consultation on Incontinence Questionnaire-Short Form; ISUP: International Society of Urologic Pathology; IQR: interquartile range.

Compliance to therapy remains challenging, with studies indicating that more than half of patients discontinue treatment within five years. The reasons for discontinuing ICI therapy vary and can include ineffective erections, price, discomfort or pain, needle anxiety, a preference for different treatments, disinterest, or the loss of a partner.[16]

The optimal dosing schedule for ICI has not been established. Many physicians prefer to start with low dosages to minimize adverse effects, gradually increasing the dose until satisfactory erections are achieved; however, this method requires slow titration, and many patients may experience failures with lower doses, potentially leading to discontinuation. Conversely, prescribing higher doses can result in unwarranted priapism and its associated complications.[17]

We offer a stepwise escalation protocol that ensures both efficacy and safety, benefiting up to 85% of selected patients. This highlights the significant role of ICI in managing post-RP ED as an alternative to oral medications.

Incontinence is another major morbidity following RP, affecting 80% of patients,[18] with more than 50% remaining incontinent beyond 12 months.[12] While the pathophysiologic mechanism leading to postprostatectomy incontinence is unclear, an association with recovery of erectile function has been suggested.[18,19]

The bulbocavernosus and ischiocavernosus muscles play a crucial role in this context. These muscles surround the corpus spongiosum and partially encircle the corpora cavernosa, aiding erectile potency by constricting venous outflow and directly elevating intracavernosal pressure (ICP). Anatomical studies have shown that the anterior fibers of the bulbocavernosus muscle radiate to encircle the corpora cavernosa and insert into the tunica albuginea, while the ischiocavernosus muscles encapsulate the corpora cavernosa, contributing to penile rigidity during erection.[20-22]

Enhancing the tone and bulk of the pelvic floor musculature with pelvic floor exercises (PFEs) has been

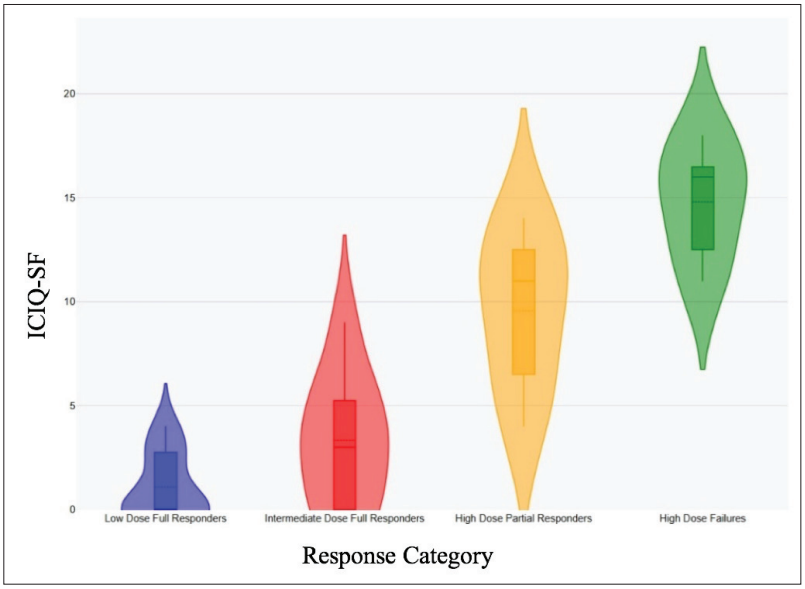

Figure 2. Violin plots of International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) scores according to response categories.

shown to significantly improve erectile function. Clinical trials have reported that PFEs can normalize erectile function in 40% of men with ED and improve it in another 35%. In one study, men who performed PFEs in conjunction with lifestyle counseling experienced significant improvements in the International Index of Erectile Function (IIEF) scores, overall satisfaction, and pelvic floor muscle strength compared to those who received lifestyle counseling alone.[23]

This pelvic floor theory aligns with our observed correlation between the extent of urinary incontinence and the response to ICI. Damage to the pelvic floor muscles, along with some degree of nerve injury — even when the neurovascular bundles are adequately preserved — may contribute to both ED and urinary incontinence after RP, with the severity of one potentially reflecting the other.

Previous studies have evaluated ED after RP using either the IIEF score or the EHS.[22,24] We chose to use the EHS because, unlike the IIEF, it allows for the assessment of erectile function by simple and objective clinical means, independent of sexual intercourse or a partner.[25] We believe that this study can aid physicians in the ED clinic by providing valuable insights for counseling and prescribing ICI treatment after RP. It can help tailor the protocol and dosage of ICI for each patient, ensuring a swift and effective response to therapy while minimizing side effects. In addition to prescribing an initial higher dose to incontinent patients, it can assist in setting realistic expectations regarding the success of the treatment.

Limitations

This study has limitations, most notably the small sample size of only 34 patients, which is a significant limitation that affects the generalizability of the findings. To achieve sufficient statistical power for the univariate analysis, patients were grouped into two categories rather than four. Despite this adjustment, the results appear robust. Further studies with larger cohorts are needed to validate and strengthen these conclusions. The inclusion criteria did not specifically address biochemical recurrence, leading to some patients receiving salvage radiation therapy while others did not. Although the number of patients receiving radiation was limited for statistical significance, it seems that radiation did not significantly impact the overall outcome.

CONCLUSIONS

Despite advancements in surgical techniques, ED remains a substantial morbidity post-RP, impacting QoL. Our study demonstrates that ICI may lead to satisfactory erections in a high proportion of incontinent patients resistant to oral therapy if an adequate dose is applied. The severity of post-prostatectomy urinary incontinence is a significant predictor of poor response to ICI for ED. This correlation underscores the potential benefit of integrating pelvic floor muscle rehabilitation into post-RP management. Furthermore, it offers valuable insights for tailoring ED treatments post-RP and helps in setting realistic patient expectations.

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This paper has been peer-reviewed.

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CORRESPONDENCE: Dr. Yotam Veredgorn, Department of Urology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; yotamvered@gmail.com