Effect of bulbospongiosus muscle injection with botulinum-A toxin for treatment of primary premature ejaculation. A preliminary results of randomized controlled trial

Ahmed Ghaith (dr_ahmedfayez@yahoo.com)
Tanta university hospitals
Khaled Almekaty
Maged Ragab
Ayman Rashed
Ayman Hagras
Ayman Ghoneem
Amr Abdel Raheem
Cairo university  https://orcid.org/0000-0002-5505-9291
Mohamed Zahran

Article

Keywords: Premature Ejaculation Profile, botulinum-A toxin, bulbospongiosus muscle, intravaginal ejaculatory latency time, primary premature ejaculation

Posted Date: July 10th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3128533/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Additional Declarations: There is NO conflict of interest to disclose.

Version of Record: A version of this preprint was published at International Journal of Impotence Research on February 2nd, 2024. See the published version at https://doi.org/10.1038/s41443-024-00831-8.
Abstract

Background:

Premature ejaculation is a common sexual disorder that significantly impacts the quality of life for both men and their partners. Various treatment options have been explored, including behavioral techniques, selective serotonin reuptake inhibitors (SSRIs), and local anesthetics. However, the outcomes of these treatments have been inconsistent for many patients.

This study aimed to evaluate the effectiveness and safety of injecting botulinum-A toxin into the bulbospongiosus muscle for treating premature ejaculation (PPE) in Egyptian patients.

Materials and methods:

Sixty patients with PPE were randomly assigned prospectively to two groups: one receiving botulinum-A toxin injections and the other receiving saline injections as a placebo. The injection was done under US guidance to localize the site of bulbospongiosus muscle.

Results:

After the follow-up period, 57 patients completed the study. Initially, there were no significant differences between the two groups in terms of age, baseline Intravaginal Ejaculation Latency Time (IELT), Premature Ejaculation Profile (PEP) score, or partner satisfaction.

Throughout the study, there were no statistically significant differences between the two groups in terms of IELT, PEP score, or female partner satisfaction at 1, 3, and 6 months after the intervention. However, the treatment group did show a significant increase in the median PEP score at 1 and 3 months compared to baseline. Unfortunately, no significant change was observed at 6 months, and there was no improvement in IELT or female partner satisfaction at any of the time points.

Conclusion:

While the treatment was found to be safe, this study did not demonstrate significant efficacy of botulinum-A toxin injections into the bulbospongiosus muscle for managing PPE symptoms when compared to a placebo. Further research with larger sample sizes is needed to validate these findings and explore alternative treatment options for PPE.

Introduction

Primary premature ejaculation (PPE) is considered the commonest sexual disorder affecting men with an estimated prevalence of 20–40%. [1] Many definitions have been proposed for PPE, the most accepted is the International Society for Sexual Medicine (ISSM’s) which consider PE “ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration from first sexual
experiences (lifelong premature ejaculation) + Negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy”. [2]

However, there is no doubt that PPE negatively affects the quality of life of the patient and his partner. Proper assessment of this problem in an objective validated way has always been a challenge. [3]

Treatment also varied from behavioral techniques, selective serotonin reuptake inhibitors (SSRIs) and local anesthetics with very variable outcome, unsatisfactory for many patients. New lines have been always evolving trying to address this resistant category of patients such as injection of the glans penis with filler or neurectomy of the dorsal nerve of the penis. [1]

Herein, we assess a new line of treatment for PPE which theoretically can inhibit the stereotyped rhythmic contractions of the bulbospongiosus muscle during the reflex of ejaculation using botulinum-A toxin in a prospective, randomized, double-blind, placebo-controlled study.

**Methods**

**Study design:**

A single center prospective randomized study was conducted at the Andrology Unit of Tanta University in Egypt between November 2020 and November 2022 to evaluate safety and efficacy of botulinum-A toxin injection into the bulbospongiosus muscle in the treatment of primary premature ejaculation in a sample of Egyptian patients.

**Ethical statement:**

The study was conducted in accordance with the declaration of Helsinki. The study was approved by the institutional review board of Tanta university (IRB approval number: 34296/11/20). Informed consent was confirmed.

**Eligibility criteria:**

Patients with PPE who were not suffering from bleeding tendencies, hypersensitivity to Botulinum toxin A or muscular weakness as myasthenia gravis; were considered for this study. Those suffering from PE secondary to erectile dysfunction, genital infection or psychic stress were excluded.

**Measurements:**

All patients were evaluated by medical history (age, medical co-morbidities, onset of the condition, duration, previous medications), physical examination to exclude any anomalies in the external genitalia. Also, they were objectively evaluated using intravaginal ejaculatory latency time (IELT), scores of the Premature Ejaculation Profile (PEP) and female partner’s satisfaction were assessed using a 1 to 5 Likert scale where 1 is very dissatisfied, 2 is dissatisfied, 3 is neither satisfied nor dissatisfied, 4 is satisfied and 5 is very satisfied.
Randomization:

Eligible patients have been asked to stop any medical treatment that could affect their sexual function e.g., phosphodiesterase 5 inhibitors (PDE5i) and medications for PPE; for at least 1 month before injection as well as 6 months thereafter. Patients were randomized to receive bulbospongiosus muscle injection of 100 U botulinum-A toxin at 10 U/ml (group I, test) and the same volume of saline (Group II, control). Independent randomization (in 1:1 ratio) was conducted by a third party (not involved in the study) using a computer-generated random table with stratification according to botulinum or placebo. The treating physicians were aware of the randomization, whilst patients were unaware of the randomization.

Intervention:

The injection was done in lithotomy position, under US guidance using the superficial probe to localize the site of injection (bulbospongiosus muscle). No anesthesia was required as the injection was well tolerated by all patients. Injection was done under complete aseptic condition, in 2 points, one on each side of the midline in order to infiltrate the right and left muscles. To ensure accuracy of infiltration, injection was done under US guidance. (figure1)

Measured outcome:

The primary outcome was to assess the effect of the injection of botulinum toxin in the BS muscle on the PE status. This was performed by reporting changes in IELT, PEP before treatment and 1, 3 and 6 months thereafter. We considered an increase of PEP 4 points as an improvement.

The second outcome is to assess female partners’ satisfaction changes at one, three and six months after the injection.

The third outcome is to assess the safety of the drug injection by reporting the adverse events (AE) reported early and late after injection.

Statistical analysis

Continuous variables were expressed as median and interquartile range (IQR) and categorical variables were expressed as number and percentage. Mann-Whitney U test was used to compare the median of used scores between both groups at different interval. Chi-square test was used to compare the percentage of PE improvement between groups. Measuring the mean difference changes at different times in each group was performed by paired sample t test. Statistical analysis was performed using IBM SPSS software v. 21. A P value of <0.05 was taken to indicate statistical significance.

Results
A total of 60 patients have been enrolled in the study: 30 in each group. However, 57 completed the follow up protocol and the other 3 were excluded. Figure 2 shows the flowchart of the study population.

At baseline, there were no statistically significant differences between both groups in terms of patients’ and partners’ age, baseline IELT, PEP or partner satisfaction.

At the 1, 3 and 6 months post intervention follow up visits, there was no statistically significant difference in the IELT, PEP score and female satisfaction between both groups. (Table1)

However, in the treatment group, the median (IQR) PEP score increased significantly after 1 month with a mean difference of 1.6 and 95% CI of (0.7-2.5), $P=0.001$ and after 3 months with a mean difference of 0.9 and 95% CI of (1.07-1.69), $P=0.02$. Whereas insignificant change was noted at 6 months, with a mean difference of 0.13 (95% CI of -0.6- 0.4, $P=0.6$). In the control group however, there was no significant change of the PEP score at 1, 3 or 6 months post injection. (table1)

Further analysis of the Botox group at 1 month, 5 patients (17%) showed PEP improvement as compared to none in the placebo group ($p= 0.02$). After 3 and 6- months: only 2 (7%) showed maintained improvement in the Botox group ($P=0.1$) (Figure3). Regarding the IELT and the female partner satisfaction, there was no statistically significant improvement at either of the 3 time points.

Adverse events were observed in 3 cases (5%) of the study population. One patient in the treatment group suffered from mild erectile dysfunction which lasted for 1 month, where there was a reduction in his rigidity but he was still able to have penetrative sex. Another patient in the same group reported post-micturition dribbling which occurred from day 4 after injection and lasted for 2 months. One patient in the control group, developed mild urethral bleeding post injection which stopped spontaneously after 2 days.

**Discussion**

PE is common male sexual dysfunction associated with negative consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy. Men with PE and their female partners are more likely to report low satisfaction with their sexual relationship. [4]

The exact aetiology of PE is unknown. Anxiety, penile hypersensitivity and 5-hydroxytryptamine (HT) receptor dysfunction have been considered as possible causes. [5-7]

Despite of its serious negative psychological and quality of life consequences, few men seek treatment. This is owing to the embarrassment of patients to discuss their sexual life and the belief that there is no treatment for PE.

Treatment options for PE include various behavioral and sexual therapy techniques, pharmacotherapy, and combination treatment (Pharmacotherapy with behavioral therapy). Some of them have variable outcomes and are unsatisfactory for many patients.
Pharmacotherapy of PE includes either dapoxetine on-demand or using topical desensitising agents such as lidocaine/prilocaine spray. Off-label SSRI antidepressants and off-label tramadol are other alternatives. [8]

Dapoxetine is a short-acting SSRI and is currently the only EMA-approved (European Medicine Approval) oral drug for treatment of PE. DPX is associated with a 3- to 4.3-fold increase in IELT over baseline. Carson et al concluded in a meta-analysis of three large placebo-controlled trials. [9]

Several studies support the therapeutic effect of daily SSRIs on PE. It was reported that SSRIs increase the geometric mean IELT by 2.6-13.2-fold. [10]

The use of local anesthetics to delay ejaculation is the oldest form of pharmacological therapy for PE. However, they are often criticized for not being optimized for PE. [11]

A recent meta-analysis by Liu et al concluded that local anesthetics were best among the other treatment options for PE including SSRIs, dapoxetine, PDE5Is and tramadol. [12]

Behavioral therapy such as stop start and squeeze techniques, allows the patient to delay ejaculation, increase sexual confidence, and reduce anxiety. In a systematic review done by Cooper et al, they found that behavioral therapy appears to improve IELT when compared with placebo in two out of four studies. [13]

In other studies, behavioral therapy had no significant differences when compared with SSRIs.[14, 15]

The lack of a definitive treatment for PPE causes patient disappointment because a tablet or spray/cream is needed for every sexual intercourse. In a study by Park et al; 79.1% of patients stopped treatment within 6 months and 90.1% at 2 years, the authors concluded that novel effective therapies are required. [16]

The emission and expulsion phases refer to the two stages of male sexual response that occur during ejaculation. During the emission phase, the vas deferens, seminal vesicles, and prostate gland contract to move semen into the urethra, where it is held until the expulsion phase. During the expulsion phase, the muscles at the base of the penis, known as the bulbospongiosus and pubococcygeus muscles, contract rhythmically to propel semen out of the body. The emission and expulsion phases of ejaculation are controlled by different parts of the nervous system and involve a complex interplay of neurotransmitters, hormones, and muscle contractions. The emission phase is under the control of the sympathetic nervous system, while the expulsion phase is under the control of the somatic nervous system. [17-19]

Ejaculation is a spinal cord reflex, which is constituted by emission and expulsion phases. During expulsion, rhythmic contractions of the bulbospongiosus and ischiocavernosus muscles propel semen antegrade through the bulbar and penile urethra.
Botulinum A toxin is a neurotoxin which has revolutionized the management of numbers of lower urinary tract dysfunction.

It binds to the nerve endings that control muscle contractions and prevents the release of acetylcholine. This results in temporary paralysis of the targeted muscles. The effects of BTX-A typically last for several months before the nerve endings regenerate and muscle function returns. [20]

In 2010, use of botulinum A toxin for treatment of lifelong PE was contemplated. It was thought that injection of botulinum A toxin injection in bulbospongiosus muscle will inhibit rhythmic contractions and may prolong ejaculatory latency. [21]

In 2014, Serefoglu et al. injected botulinum-A toxin percutaneously into the bulbospongiosus muscles of male rats. They reported an increase in ejaculatory latency times. But the difference in post-treatment ejaculatory latency between botulinum A toxin injection and saline was not statistically significant. [22]

The only clinical trial used injection of botulinum A toxin in bulbospongiosus muscle as a treatment of primary PE was done by Li et al in 2018. They randomly assigned 70 patients with PE to a treated (100 U botulinum A was injected) and a control group (saline was injected). The trial group showed a significantly longer IELT (intravaginal ejaculatory latency time) at 4 weeks after treatment compared to the control group, and also had significant improvement in PEP-ejaculation scores, PEP-sexual satisfaction, PEP-PE-related distress, and PEP-PE-induced difficult relationship with the partners. The female partners of the treated group also showed significant improvement in sexual satisfaction scores. [23]

In our current study, we used botulinum A toxin for treatment of 30 patients with PPE and compared them to other 30 received placebo. The results in this current study showed no significant changes regarding the IELT, PEP or partner satisfaction between both groups. However, there was a significant improvement in the PEP score in the treatment group compared to baseline. The improvement in the PEP score was not associated in improvement in the IELT because albeit the statistical significance, these changes were not clinically significant as clinical improvement should be at least 4-point increase in the PEP score.

At 1 month, 5 patients (17%) showed improvement in the treated group compared to none in the placebo group (P= 0.02). After 3 and 6- months: only 2 (7%) showed maintained improvement in the Botox group (P=0.1), the median (IQR) PEP score was 1.6 and 0.9 at 1 month and 3 months respectively. Whereas insignificant changes were noted at 6 months, with a mean difference of 0.13, P=0.6). The 5 patients who had statistically significant improvement in the PEP score did not report any clinically significant changes as per their IELT score and refused any suggestion of reinjection.

It is important to note that the injection of Botox into the bulbospongiosus muscle only affects the expulsion phase of ejaculation. This means that while it can prevent the ejaculate from being expelled to the outside, it does not stop the emission of semen into the posterior urethra.
Based on the findings of our conducted study, we did not observe significant clinical improvement with this treatment approach and it can be concluded that inhibiting pelvic floor muscle contraction through Botox injection into the bulbospongiosus muscle does not provide substantial clinical improvement in terms of ejaculation.

The adverse effects were observed in 6 cases (17.65%) in Li et al trial. While adverse effects in our study were reported in 3 cases (5%) of the study population. 2 patients in the treated group suffered from loss of rigidity during erection and post voiding dribbling. And one patient in control group had mild bleeding per urethra which stopped spontaneously. All patients reported normal ejaculation, no drippling of ejaculation was detected in any patient.

To the best of our knowledge, this is the second study in the literature investigating the effect of Botulinum A toxin injection into the bulbospongiosus muscle for treatment of PPE and the first to deny its clinical efficacy. Limitations of our study include short follow up period and small sample size.

**Conclusions**

The administration of botulinum-A toxin into the bulbospongiosus muscle appears to be a safe approach, but it has not demonstrated significant clinical effectiveness in treating PPE when compared to a placebo. Nevertheless, additional studies involving larger sample sizes may be necessary to confirm this finding and explore alternative and innovative treatment options.

**Declarations**

**Conflict of interest:**

All authors declare that no conflicts of interest.

**Funding:**

This research has not received specific aid from agencies from the public sector, commercial sector or non-profit entities.

**Acknowledgement:**

None

**Authors’ contribution:**

Study concept and design: Kh. Elmekaty, Amr Abdel Raheem and Maged Ragab.

Acquisition of data: Kh. Elmekaty, A. Ghaith, Ayman Hagras and Ayman Rashed.

Analysis and interpretation of data: Kh. Elmekaty, A. Ghaith and M. Zahran.
Drafting of the manuscript: Kh. Elmekaty, A. Ghaith, Ayman Hagras, Ayman Ghoneem and M. Zahran.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Kh. Elmekaty, and M. Zahran.

Obtaining funding: None.

Administrative, technical, or material support: All authors.

Supervision: Kh. Elmekaty, Amr Abdel Raheem, A. Ghaith and Maged Ragab.

Other: None.

References


20. Kuo HC. Clinical application of botulinum neurotoxin in lower-urinary-tract disease and dysfunctions: Where are we now and what more can we do? Toxins 2022, 14, 498.


Table

Table 1: Study outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Botox (group A)</th>
<th>Control (group B)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>39 (32.7-42)</td>
<td>39 (30.7-44)</td>
<td>0.9</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female age</td>
<td>33 (28-39.7)</td>
<td>32.5(28-40)</td>
<td>0.6</td>
</tr>
<tr>
<td>Co-morbidities*</td>
<td></td>
<td></td>
<td>09</td>
</tr>
<tr>
<td>DM</td>
<td>1 (3.3%)</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>2 (6.7%)</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td>1 (3.3%)</td>
<td>1 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>IIEF</td>
<td>23 (21-24)</td>
<td>23 (22-24)</td>
<td>0.6</td>
</tr>
<tr>
<td>Baseline IELT</td>
<td>27.5 (13.5-46.2)</td>
<td>40 (23.7-60)</td>
<td>0.06</td>
</tr>
<tr>
<td>Baseline PEP</td>
<td>2(1.7-4)</td>
<td>3(2-4)</td>
<td>0.3</td>
</tr>
<tr>
<td>Baseline female satisfaction</td>
<td>2(1-3)</td>
<td>2(1.7-3)</td>
<td>0.07</td>
</tr>
<tr>
<td>1-month IELT</td>
<td>31(14.7-48.5)</td>
<td>44.5(25-61)</td>
<td>0.09</td>
</tr>
<tr>
<td>1-month PEP</td>
<td>3.5(1.7-5.2)</td>
<td>2(2-4)</td>
<td>0.1</td>
</tr>
<tr>
<td>1-month female satisfaction</td>
<td>2(1-3)</td>
<td>2(1.7-3)</td>
<td>0.2</td>
</tr>
<tr>
<td>3-month IELT</td>
<td>30(12.7-48.5)</td>
<td>42.5(23.7-62)</td>
<td>0.08</td>
</tr>
<tr>
<td>3-month PEP</td>
<td>3(1-4.2)</td>
<td>2(1.75-3)</td>
<td>0.1</td>
</tr>
<tr>
<td>3-month female satisfaction</td>
<td>1.5(1-3)</td>
<td>2(1-3)</td>
<td>0.6</td>
</tr>
<tr>
<td>6-month IELT</td>
<td>26.5(14.7-45.5)</td>
<td>41(25.7-60)</td>
<td>0.06</td>
</tr>
<tr>
<td>6-month PEP</td>
<td>2.5(1-3)</td>
<td>2(1-3)</td>
<td>0.9</td>
</tr>
<tr>
<td>6-month female satisfaction</td>
<td>1.5 (1-3)</td>
<td>2(1.7-3)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

Figures
Figure 1

US pattern of bulbospongiosus muscle
Figure 2

Flowchart of study population
Figure 3

PEP changes in both groups