Original Article

Effectiveness of Frenulum Subcutaneous Injection of Botox in the Treatment of Premature Ejaculation

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Abstract

Background: Premature ejaculation (PE) is one of the most prevalent yet under-treated sexual dysfunctions. Current treatment methods have proven insufficient, with no single approach being universally effective. Alternative therapies, such as Botulinum neurotoxin-A injections, are being explored to address the inadequacies of conventional treatments. **Aim of the Study:** To evaluate the effectiveness of frenular and ventral glans penis intradermal injections of 50 IU Botulinum neurotoxin-A in patients with PE who have not responded to traditional therapies. **Patients and Methods:** A clinical trial involving 200 male patients with complaints of PE, dissatisfied with standard treatments due to either side effects or lack of efficacy. All patients received frenular and ventral glans penis intradermal injections of 50 IU Botulinum neurotoxin-A. Intravaginal ejaculatory latency time (IELT) was measured before and after the treatment using a stopwatch. **Results:** The IELT increased significantly post-treatment. Before injection, IELT ranged from 1 to 4 minutes (mean 1.86 minutes), while post-injection it ranged from 1 to 45 minutes (mean 10.6 minutes). The statistical analysis showed a significant improvement in IELT (p=0.001), indicating that Botulinum neurotoxin-A significantly extended the IELT in patients with PE. **Conclusion:** Frenular and ventral glans penis injection of Botulinum neurotoxin-A improves IELT and enhances sexual quality of life in patients with PE. However, further research is needed to identify factors that could optimize the treatment's efficacy and make Botulinum neurotoxin-A a recommended option for PE management.

Keywords: Premature Ejaculation (PE), Clinical Trial, Treatment, Botulinum Neurotoxin-A Injection.

Introduction

Premature ejaculation (PE) is one of the most prevalent male sexual dysfunction syndromes; it is estimated to affect between 4-39 % of all men globally.[1] The "Diagnostic and Statistical Manual of Mental Disorders" defines PE as "ejaculation occurring, without control, on or shortly after penetration and before the person wishes it, causing marked psychological distress."[2] IELT, known as the period from penetration into vagina to ejaculation, when it happens before 2 minutes or before penetration which is also defined as premature ejaculation.[3]

The "International Society for Sexual Medicine" has described PE, including IELT, as follows: "Ejaculation that always or nearly always occurs before or within about one minute of vaginal penetration; inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy."[4] It's also defined by the "American Urological Association" (AUA) as ejaculation which happens " sooner than desired, either before or shortly after penetration, causing distress to either one or both partners."[5] WHO defines premature ejaculation: as a reduced ability to control ejaculation sufficiently for both partners to enjoy sexual interaction. [6] In the last two or three decades the management of PE has expanded from behavioral psychotherapy to drug treatment. Several neurotransmitters and receptors have been found to be involved in regulation of ejaculation and

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they form the basis of pharmacotherapy for PE namely, serotonin, dopamine, oxytocin, norepinephrine, GABA, and NO.[7] Impotency or premature ejaculation is the most prevalent sexual dysfunction affecting men. Ejaculatory latency time is therefore not standard and is defined within considerable cultural and socio-economic framework. The introduction of Sexual Medicine helps to understand better the disorder as the PE is not considered as a mere psychogenic disorder anymore but is considered in terms of pathophysiological cause. This led to the coming up of new ways of treating PE in the society.[8] The major limitation of medical therapies of PE is the tendency of the condition to relapse after discontinuation of medication. Despite the fact that these treatments have been testified to have no side effect and they are very effective for most of the PE patients they still hope to find the permanent solution. Currently, there are no indications for surgical management of PE as in the present; however, there are several surgeries that have been performed for many years particularly in Asian countries.[9] Thus, the presented data analysis[10] allows to conclude that this treatment that consists in the injection of botulinum-A toxin into the bulbospongiosus muscle is safe and provides for the enhancement of the ejaculation duration in rats without affecting the other types of sexual activity and ejaculation. The current management of PE includes Behavioural therapy tricyclic antidepressant, selective serotonin reuptake inhibitors, local anaesthesia, selective phosphodiesterase inhibitors. This study has also discovered that many of the PE treatments are either experimental or are only utilized for non-medical purposes. New treatments are of course necessary to counter this frustrating sexual dysfunction.[11]

PE is one of the most frequent sexual disorders in males that is defined as the difficulty in controlling the time of ejaculation during intercourse. This condition may cause substantial psychological problems, interpersonal dysfunction, and a diminished well-being.[12] Many of the therapies that are used in the management of PE such as behavioral therapy, topical anesthesia, and the drugs have been found to offer temporary or poor relief to patients. However, literature search on clinical trials has failed to provide any adequate evidence that will show the efficacy and safety of this method. Thus, the aim of this trial is to evaluate the effectiveness and safety of frenulum subcutaneous Botox injection for the treatment of PE. The objective of this research is to determine the effectiveness of Botox injected under the frenulum for the treatment of PE. To determine the level of satisfaction of the patients on the improvement in the act of sexual performance after the above treatment. PE is one of the most widespread pathologies which substantially decreases the quality of life of the affected men and their sexual partners.[13] Existing interventions sometimes prove to be ineffaceable and therefore new solutions for the management of this condition are warranted. PE has been treated with numerous models of management including medications and surgery, and now Botox, a proven neuromodulator in other fields of medicine might be a unique approach in the management of PE. In this case, by administering Botox injection to the frenulum it would be possible to delay the ejaculation by reducing sensitivity which is the primary cause of PE among men. This study is important as it aim to establish a new way of treating this disorder in a bid to enhance the health and well-being of men with PE.

Literature Review

Premature Ejaculation Diagnostic Tool

1. They include satisfaction concerning sexual activities or conditions, personal distress that may be associated with ejaculation, ability to control ejaculation and interpersonal concern about it.[6]
2. Index of Premature Ejaculation (IPE): The above theory comprises of three factors; control, sexual satisfaction, and distress.[14]
3. 'Premature Ejaculation Diagnostic Tool(PEDT) questionnaire' specifically used for screening, consists of 5 items measure (frequency, in ability to control, distress, minimal stimulation, and personal difficulty).[15,16]

Classification of PE

PE classified into two types as primary and secondary:

- Primary or lifelong PE is considered when the man experiences early ejaculation, in 80% of cases within 30-60 seconds or in 20% of the cases within 1-2 minutes of intercourse.[17]
- Secondary or Acquired PE: previously normal ejaculatory history experienced by a man at some point in his life when he develops early ejaculation.[17]

Physiology of Ejaculation

The ejaculatory process is a complicated process and it involves the sensory areas of the brain and the spinal cord, the sensory receptors, afferent and efferent pathways, and motor areas. Some of the chemicals involved in ejaculation are "serotonin, dopamine, norepinephrine, acetylcholine, GABA, oxytocin, and nitric oxide".[18-20] The ejaculation consists of two phases: Emission and expulsion; emission phase is a physiological process in which many structures in the male reproductive system are involved such as distal epididymis, seminal vesicles, vas deferens, prostatic urethra, prostate gland as well as the bladder neck. CA is supplied by sympathetic nerves of T10- L2, which results in contraction of smooth muscle in the bladder neck and thereafter, prevent the back flow of the ejaculate into the bladder. Following this, prostatic secretions which is rich in acid phosphatase, citric acid and zinc is added in the prostatic urethra with the secretion of vas deferens. Further fluids sourced from Cowper's and periurethral glands make up the ejaculate and these include the "prostatic fluid (10% of total volume), vasal fluid (10% of total volume), seminal vesicle fluid (75–80% of total volume) and fluid from Cowper's and periurethral glands (also referred to as the glands of Littre)".[21,22] Expulsion phase after emission comprises of elimination of these products via "urethral

complex, bladder neck and pelvic striated muscles". It comprises the relaxation of the external urinary sphincter, contraction of which is followed by colonic contractions of different muscles under somatic innervation (S2 to S4).[23-27] Expulsion entails the ejection of the products of emission through the urethra with the assistance of coordinated contraction of the bladder neck, urethra and the pelvic striated muscles. The expulsion phase follows the emission phase. These are achieved by the relaxation of the "external urinary sphincter while the bladder neck is closed followed by contractions of the prostate, levator ani, transverse perineal muscles, bulbospongiosus muscle, ischiocavernosus and is mediated by somatic efferent fibers S2 to S4".[23-25] The tactile stimuli to the genital area (penis) give somatosensory sympathetic tactile input through the dorsal nerve of the penis which is a branch of the pudendal nerve (S2, S3, S4) {this is why we inject botox to desensitize the hyperexcitable frenular skin area, to the sensory cortex of brain and then stimulate Hypothalamic medial preoptic area and brainstem (nucleus paragigantocellularis) giving the Efferent output to the lumbosacral spinal cord then to penis for ejaculation. The ejaculatory response involves contributions from the somatic, sympathetic, and parasympathetic nervous systems. Normally, the sympathetic nervous system is involved in the emission phase while the somatic nervous system is involved in the expulsion phase.[28] Among many neurotransmitters involved in ejaculation, dopamine and serotonin have an essential role, the dopamine via D2 receptors fastens ejaculation whereas serotonin delays or inhibits it.[29,30] Many 5-HT serotonin are present in the brain and the spinal cord (5HT1a,5HT2a,5HT1b,5HT2b...etc). Men complaining of premature ejaculation can have hypersensitivity of 5HT1a and/or hyposensitivity of 5HT2c.[31] The Free nerve endings, known for their incomplete Schwann cell investment and irregular neurotubules and neurofilaments, constitute 80-90% of axon terminals in distal frenulum and the glans penis. These nerve endings exhibit high sensitivity to touch, temperature, and vibration sensation. Notably, heightened sensitivity to vibration has been strongly associated with premature ejaculation (PE).[32,33]

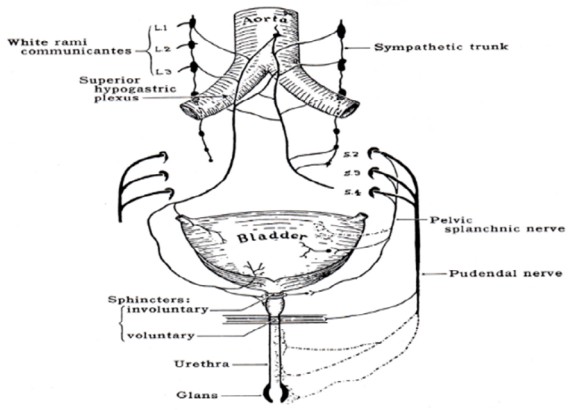

Figure 1: The Innervation of the Urogenital Area.
Source: Koraitim[34]

Other Modalities of Treatment of PE

Squeezing technique by squeezing the penis between the glans and shaft for about 30sec just before ejaculation, another method is to masturbate 30 min before sex.[35] Local anesthetics such as pilocaine and /or Lidocaine as a gel, cream, or spray.[36] Selective serotonin reuptake inhibitors (SSRI) Paroxetine, and on-demand Dapoxetine, Phosphodiesterase type 5 inhibitors (PDE5), Tricyclic antidepressants (TCA), Tramadol, and alpha-adrenergic blockers.[37-39]

Botulinum Toxin

BTX belongs to the group of neurotoxins, which is synthesized by the bacterium Clostridium botulinum and some other similar bacteria. This neurotoxin immobilizes the release of acetylcholine, a neurotransmitter, from axon endings at neuromuscular junctions. Infection with this bacterium results in botulism, a serious illness.[40] The toxin comes in seven distinct types, denoted as types A through H (labeled as A-G). Despite these types that are distinguished on the basis of antigenicity and serology, they are structurally related. Human botulism is affected mostly by the types "A, B, E" and, in few cases, F while the types C and D are more common in animals.[41,42] Firstly, Botox molecule is produced in a form of a single linked chain which molecular weight is 150 kilodalton. It is later cleaved to undergo a Di chain molecule with a disulfide bond or at a physiological cleavage site. It is composed of a light chain with molecular mass of approximately 50 kD (amino acids 1-448) and which is a zinc (Zn2) endopeptidase. This endopeptidase is covalently bound at the amino terminus and, such as tetanus toxin, it has a proteolytic role. The large chain is 100 kD (amino acids 449-1280) and is cholinergic specific helping in the interaction of the toxin with presynaptic receptors. Besides, it is also involved in the movement of the light chain through the endosomal membrane.[43-45]

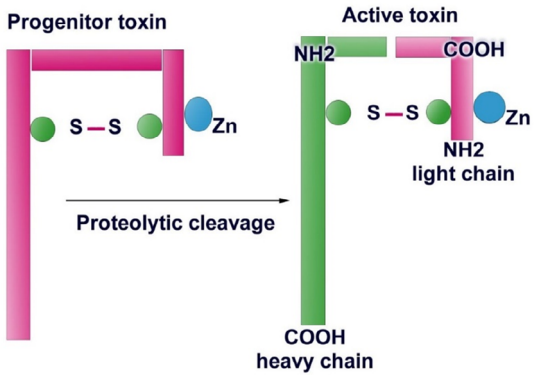

Figure 2: The Light and Heavy Chain of BTX Molecule

Source: Frevert[43]

Mechanism of Action

As for the way of its action, botulinum toxin interacts with nerves and inhibits the proteins which are essential

for their activation. First, it acts on nerves that use the chemical called acetylcholine as the transmitting agent. When it gets to the nerve terminal, the toxin is internalized into a vesicle in the neuron. This vesicle then penetrates deeper into the cell and as it does so, it becomes acidic and so a part of the toxin is activated. This activation leads to the toxin moving into the vesicle membrane and into the cytoplasm of the target cell. Once inside the cytoplasm, the toxin cleaves SNARE which in a way inhibits the ability of the cell to release vesicles containing neurotransmitter thus stopping nervous conduction.[46,47]

Treatment of Premature Ejaculation

The two most frequent methods used in behavioral therapy are the 'stop and start' method popularized by Semans in 1956[48] as well as the 'squeeze' technique which was devised by Masters and Johnson in 1970.[49]The above techniques were established to have been effective in most situations. However, couples may be repulsive to the use them, with some of the women not even willing to press the partner's penis and some couples, who are not ready to pause the sexual activity and intimacy once started. These techniques target on how the focusing can be distracted and how the sexual entertainment or interest that may decrease general sexual satisfaction.[11] Procedural interventions, Psychotherapy and pharmacotherapy and have been purported to have some level of effectiveness. There is good evidence that SSRIs and local anesthetics can be used for off-label treatment of PE due to the fact that erection latency time rises consistently. Education and mental health assessments are still incorporated in the management of PE despite lack of many published studies on these interventions.[50] Many treatment approaches have been studied in DE; there are scarce evidence regarding psychotherapy, pharmacologic intervention, and/or PVS as treatments. Treatment of PE was done with the help of behavioral methods and selective serotonin reuptake inhibitors, selective serotonin re-uptake inhibitors and local anesthetics have been attributed to the following are characterized by variable results, which are not satisfactory for many patients.[51] Among them, some have been always developing to try and assist in dealing with this resistant patients of such category as; injection of the glans penis with filler and neurectomy of the dorsal nerve of the penis.[52] Thus, injection of Botulinum A-toxin into "Bulbospongiosus muscle (BS)" can prevent the stereotyped rhythmic contractions during the reflex of ejaculation.[51]

Patients and Methods

A single-blind, placebo-controlled clinical trial is applied at the outpatient urological clinic, Medical City in Baghdad /Ghazi AL-Hariri Teaching Hospital over a period from May 2016 to December 2021.

Inclusion Criteria

- A potent married, sexually active man, who presented to the outpatient urological clinic at Ghazi Al-Hariri Teaching Hospital complained of Premature Ejaculation and proved to fulfill the definition of PE was involved in this study. (PE is defined as ejaculation in less than one or two minutes with an inability to delay it and the dissatisfaction and frustration of the patient and his partner. IELT is measured by a stopwatch from the moment of vaginal penetration to the time of intra-vaginal ejaculation.)
- Patients who have a history of failed multiple measures to treat their PE like local anesthetics, squeezing methods, SSRI, Tramadol, citalopram …. etc.

Exclusion Criteria

- The study excluded patients with erectile dysfunction, low libido, neurological and psychological, hyperthyroidism, DM, hypertension, alcoholics, and chronic use of steroids.
- Exclusion criteria were investigated through detailed medical history, local physical examination, assessment, and Laboratory tests including FBS, TFT, Hormonal assay, and CBC.

Procedure

The number of participants taken for this study are 200 (n=200), all participants underwent preliminary assessment, including IELT, physical, and laboratory assessment. Educate the patients how to use the stopwatch to measure IELT to avoid variability and false negative or positive results. patient and his partner were instructed to not pause intercourse and to not use condoms, local anesthetics or take SSRI, or TCA, and to not consume alcohol. Scheduled visits to the patients programmed, every 3 months for 4 or 5 times and contact them also by phone, follow their IELT, and ask if there are any undesirable side effects.

Results

The overall number of Study patients in this study was 200 males complaining from premature ejaculation.

Age

This is presented in table and figure (3) The age distribution of study patients is shown as follows; The age of study patient was between 20 and 49 years with the average of 31 years. Five years and SD= ± 6.95 years. The majority of the study patients was in age group below 30 years with a proportion of 43.4%.

Table 1: The Study Patients' Distribution by Age.

Age (Years)	No. (n=200)	Percentage (%)
< 30	87	43.4
30 – 39	80	40.0
≥ 40	33	16.5

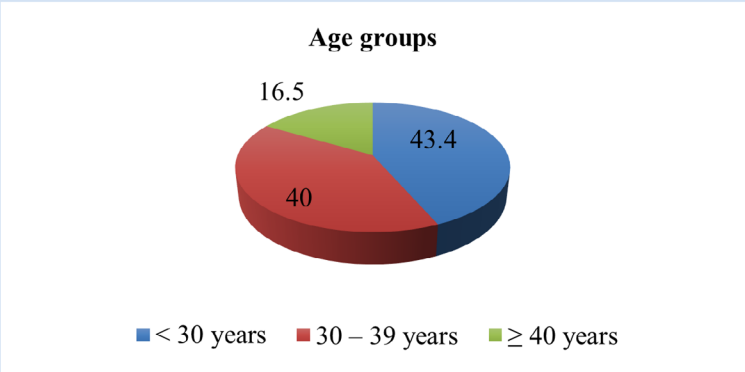

Figure 3: The Study Patients' Distribution by Age.

Cause of Premature Ejaculation

The study patients' distribution by the cause of premature ejaculation is presented in the table and figure (4). We observed that 80% of study patients had primary cause for premature ejaculation.

Table 2: The Study Patients' Distribution by the Cause of Premature Ejaculation.

Variable	No. (n=200)	Percentage (%)
Cause of premature ejaculation		
Secondary	40	20.0
Primary	160	80.0

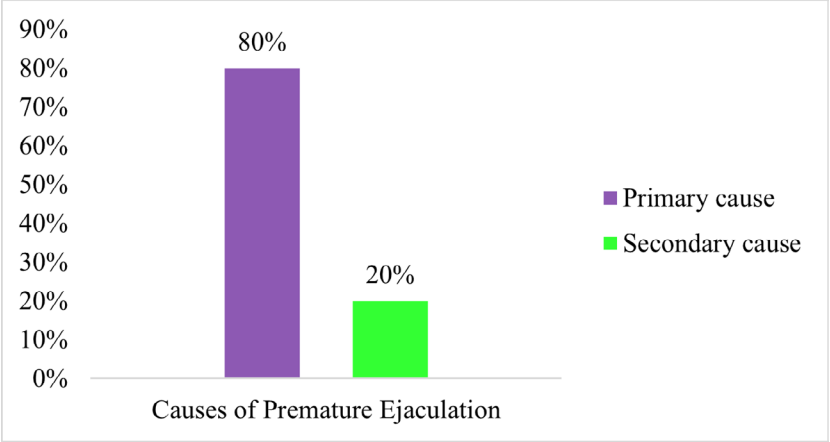

Figure 4: Distribution of Study Patients by Cause of Premature Ejaculation.

IELT before and after Injection

Table 3 compared the baseline IELT before the injections with the IELT after receiving the injections.

• Before injection: The duration of IELT was varying from "1 to 5 minutes" with a mean of 1.82 minutes and SD of "±0.987 minutes".

• After injection: The time taken as IELT was ranging from "1 to 48 minutes" with a mean of 13.9 minutes and SD of "±6.95 minutes".

Therefore, from the above results, it can be stated that there are differences in the mean value of IELT before injection and after injection (P<0. 001).

Table 3: The Differences between IELT before and after Injection.

IELT	Mean	Std. Deviation	P-Value
Before injection	1.82	0.987	**0.001**
After injection	13.9	6.95	

In the study, there were 200 male patients diagnosed of PE, aged between 20 to 49 years with a mean age of 31.5 years. The largest number of the patients, 43.4% were below thirty years of age, 40% were aged between thirty and thirty-nine years and 16.5% of those who are 40 years and above. This distribution shows that premature ejaculation is a common problem among young men especially those who are below 30 years. Concerning

the etiology of PE, it was established that 80% of the participants in the study suffering from primary premature ejaculation, that begins at the initial sexual practices. The remaining 20% had secondary premature ejaculation which is experienced after some time of normal sexual activities. An inference can be made from these results that primary PE is a more prevalent condition among the patient group. An important part of the investigation was also a consideration of changes in the Intravaginal Ejaculatory Latency Time (IELT) before and after the treatment carried out with the injection. The IELT before treatment was between one and five minutes with mean IELT of 1.82 minutes and SD of ± 0.987 minutes, after injection IELT was ranging from one to 48 minutes with a mean of 13.9 minutes and SD of ± 6.95 minutes. The substantial rise in IELT which was statistically proved by a highly significant p-value of 0. 001, They also make use of the treatment for prolonging of ejaculation time. Based on these studies, it can be recommended that the injection treatment was able to elicit a positive change on patients' ejaculatory control and provided a lot of improvement in the management of premature ejaculation.

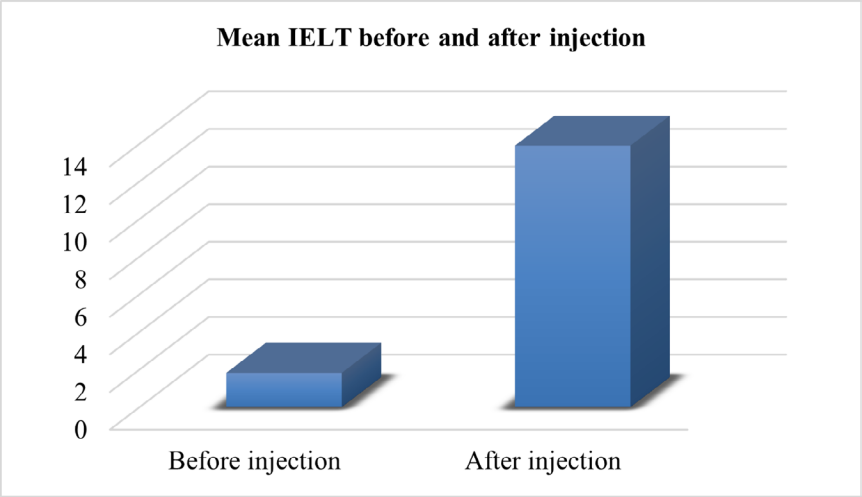

Figure 4: Mean IELT before and after Injection.

Discussion

Premature ejaculation (PE) is a common sexual disorder that affect the sexual life of patient and his partner. May defined, as ejaculation occurring without control to delay it make the patient and his partner unsatisfied and frustrated with short IELT. PE classified to primary PE (Lifelong when the patient suffers from PE from onset of puberty), and secondary PE (when the patient has previous normal IELT and develop PE later in his sexual life). PE treated over many years by different modalities like Psychosexual treatment (stop and start method, Master and Johnson squeezing method and masturbation before coitus), Topical anesthetic creams and sprays (lidocaine and pilocarpine), SSRI (Dapoxetine, paroxetine, serteraline, fluoxetine), PDE5 Inhibitors (Tadalafil, sildenafil). According to Gul *et al.*[53], currently available standard therapies are behavioral therapies, topical anaesthesia, dapoxetine and other SSRIs. Majority of the pharmacotherapeutic interventions aim at neurotransmitters that play a part in the ejaculation process for example serotonin and oxytocin. However, these treatments have minor efficiency and only reduce the ejaculation latency time and PE reoccurs when the treatment is ceased. Therefore, there is a need to come up with a treatment for PE and there is active research that is undertaken to come up with the best PE therapy. The use of topical anesthetics and SSRIs have been shown to be both effective and safe in a myriad of well conducted controlled trials. There are current preclinical and clinical investigations on new generation of SSRIs.[53] According to the study,[54] It can be supposed that, if Botulinum toxin-A is injected at the level of the prostate and bulbourethral muscles, inhibition of the muscular contraction during the ejection phase of ejaculation will be prevented. As a result, conclusions proposed in the study concluded that injection of botulinum toxin-A in the root of the penis and ischiocavernosus muscle can be recommended for PE treatment.[54] In our research we choose Botulunium Toxin for many reasons, a neurotoxin that desensitize the dermal somatoreceptors in the hyper excitable distal frenulum and ventral glans of the penis.

1. Does not affect the degree of rigid tumescence and pleasure of orgasm for patient and partner as occur with Psychotherapeutic measures (start and stop method, squeezing Master and Johnson method, masturbation before coitus).
2. More potent desensitization than local anesthetic creams and sprays, and the Botox desensitization effect doesn't affect the sense of whole penile skin as it directed only to distal frenulum and ventral glans penis (doesn't affect the orgasm of male) and doesn't cause vaginal numbness (losing female orgasm) as all these adverse effects occurred with local anesthetic medications.

3. Botox need to be injected one time every 6 – 8 months (according to biodegribility of drug, not similar to local anesthetic which need to be applicated before every intercourse.
4. As botox injected locally, it doesn't cause systemic side effects like SSRI (nausea, dizziness, dry mouth, headache, diarrhea, insomnia), PDE5Inhibtors (headache, flushing, runny nose, stomach pain, Bach pain and sometimes may sudden drop blood pressure).

In this clinical trial study, we found that IELT increase significantly after injection of Botox to patient with primary PE their ages below 30 years old (43.4%), and mean IELT increase in this study from 1.82min to 13.9 min, which revealed a significant P value (0.001), So we can recommend the Botox injection to distal frenulum and ventral glans penis as one of effective treatment for premature ejaculation.

Implications of the Study

Therefore, this clinical trial has implications for the management and treatment of premature ejaculation (PE) especially among the young patients. On this basis, the present study indicates that Botox injections into the distal frenulum and ventral glans is a feasible treatment for primary PE and the significant increase in IELT from 1. 82 minutes to 13. 9 minutes. That is why the treatment seems to be rather effective for young male patients diagnosed with lifelong PE, as the majority of patients in this study were under 30 years old. The p-value of 0. 001 also indicates the effectiveness of this intervention and may provide clinicians with a new treatment option for patients thus enhancing their sexual health and quality of life in case of this condition. Injections of Botox may be considered as non-surgical treatment option to other medical and behavioral treatments of PE.

Limitations and Future Research of the Study

However, there are few limitations, which are as follows: First, the study was conducted on the participants were below 50 years; therefore, the results cannot be generalized to elderly people who also suffer from PE. Further, they did not study the effects and safety of the Botox injections in the long run on this sensitive area of the body; thus, the impact of the treatment in the long-term is uncertain. Another limitation is that of sample size which comprised of 200 patients only and may not represent the general population. Thus, future studies should attempt to overcome these limitations by enrolling more extensive samples of patients at various age ranges and patients with secondary PE or with psychological factors involved in the disease development. Such studies as longitudinal research could help establish safety and effectiveness of Botox for the treatment of PE in the long run. Comparative studies could also look at how Botox compares with other therapeutic approaches such as behavioral therapy, oral medication or other surgical procedures. The exact way through which Botox inhibits control of ejaculation also requires further research as well as the possibility of multiple sessions or the use of Botox together with other treatment methods. Such efforts would assist in arriving at a better understanding of the treatment modality for PE and in designing treatments to meet specific patient needs.

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None

Conflict of Interest

None

Ethical Committee Approval

235 in 13/4/2016

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