ORIGINAL ARTICLE

Hyaluronic Acid Versus Botulinum Toxin Type A Injection in the Treatment of Premature Ejaculation: Comparative Study

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Abstract

Background: ***Premature ejaculation (PE) is the most prevalent type of male sexual dysfunction. Possible causes of premature ejaculation include abnormalities in nerve conduction, higher penile sensitivity, hereditary susceptibility, and serotonin receptors.***

Aim and objectives: ***To evaluate the efficacy and safety of hyaluronic acid injection and botulinum-A toxin injection in the treatment of premature ejaculation.***

Subjects and methods: ***This randomized clinical study included 60-patients collected from outpatient clinics for andrology at Al-Azhar University Hospitals. The patients were divided into two equal groups: (A) and (B) each involving 30-male patients with premature ejaculation. Group-A was given botulinum A and Group-B was given hyaluronic acid.***

Results: ***Statistically significant difference regarding control of ejaculation and patient satisfaction in patients injected with BTX. On the other hand, all the results of PEP were statistically significant in patients injected with HA. The mean IELT post-injection was 5.58 minutes, with a mean among patients who received BTX of 3.87 minutes and among those who received HA of 7.3 minutes. This difference is statistically significant. No side effects were reported other than pain in 80% cases of HA injection and 20% of cases of BTX injection.***

Conclusion: ***Botulinum toxin A and hyaluronic acid have been shown to be effective in managing premature ejaculation. However, hyaluronic acid has a higher effectiveness than botulinum toxin A in treating premature ejaculation.***

Keywords: Botulinum toxin A; Hyaluronic acid; Premature ejaculation

1. Introduction

Premature ejaculation (PE) is the most prevalent type of male sexual dysfunction.[1] According to the World Health Organization (WHO), premature ejaculation is defined as "the inability to delay ejaculation sufficient to enjoy a sexual relation." This behavior can be seen when ejaculation happens before or just after intercourse starts, or when there isn't enough of an erection to allow for intercourse to begin.[2] causes of premature ejaculation include abnormalities in nerve conduction, higher penile sensitivity, hereditary susceptibility, and serotonin receptors.[3] One possible organic cause of premature ejaculation is penile hypersensitivity; however, many individuals who experience primary premature ejaculation and find relief with local anesthetics also suffer from penile hypersensitivity.[4]

Secondary premature ejaculation describes when the problem first appears in adulthood, while primary premature ejaculation describes when the problem has been present since puberty.[5] Medications that enhance brain serotonin signaling decrease ejaculatory frequency. Paroxetine and dapoxetine are examples of SSRIs, or selective serotonin reuptake inhibitors. Remedies following medicine discontinuation are also a major drawback of medical treatment for premature ejaculation.[4]

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Botulinum toxin injections can be used to treat PPE.[6] The perfect filler for soft-tissue augmentation would be affordable, nonmigratory, long-lasting (but resorbable), easy to use, stable after injection, nonpyrogenic, noninflammatory, nontoxic, and biocompatible. It would also be nonmigratory and nonresorbable.[7]

The aim of this study was to compare the efficacy of hyaluronic acid injection and botulinum-A toxin injection in the treatment of premature ejaculation.

2. Patients and methods

This randomized clinical study included 60 male patients collected from the outpatient andrology clinic. The patients were divided into two equal groups: (A) and (B), each including 30 patients with primary premature ejaculation. The patients were recruited from October 2021 to April 2023.

Inclusion criteria:

Presenting with primary premature ejaculation, a stable heterosexual relationship for more than 3 months, age 25 years or older, and married

Exclusion criteria:

History of premature ejaculation with treatment less than 2 months, patients taking hormonal replacement therapy, patients with erectile dysfunction, history of drug abuse, patients with chronic debilitating diseases, e.g., liver cell failure, renal failure, or severe uncontrolled diabetes, patients on chemotherapy or radiotherapy, and patients with a history or known hypersensitivity to any of the hyaluronic acid preparations.

Ethical considerations:

Informed written consent was obtained from all patients before enrolment in the study. The study medical research committee approval number is MD117.

Procedure

Full history taking as regard: age, duration of marriage, occupation, sexual history, onset, course and duration of premature ejaculation, intravaginal ejaculation latency time (IELT), sexual satisfaction of both (patient and his wife), drug intake, smoking index (a unit for measuring cigarettes consumption over a long period and was calculated using the following formula: smoking index=CPD×years of tobacco use), surgical and medical history of any illness. Full clinical examination: including general, abdominal, and local examination of the penis (glans and shaft), scrotum, both testicles, epididymis, vas deferens, and digital rectal examination (to exclude prostatitis). Premature Ejaculation Profile (PEP) questionnaire before injection and in follow-up after injection. Each item on the PEP questionnaire is typically rated on a Likert scale ranging from 1 to 5. depending on the specific wording of the items.[8] Group-A patients were injected with botulinum toxin A into the bulbospongiosus muscle in the perineum bilaterally for each patient. Group-B patients were injected with hyaluronic acid at the coronal of the glans penis for each patient. Evaluation was performed after two months. Control or improvement of premature ejaculation, which was evaluated by calculation of IELT measured by a stopwatch used by the patient himself.

Statistical analysis:

The data was collected and tabulated via Microsoft Excel 2019. Data were then presented and statistically analyzed by using the Statistical Package for the Social Sciences (SPSS) software version 27. Descriptive statistics included means, percentages, ANOVA test, chi-square test, and t-test according to the type of data. Analytical statistics included logistic regression. The test of generalizability was the p-value. A value of<0.05 for p was set to determine the statistical significance of results.

3. Results

Table 1. Patient demographic and medical history data.

VARIABLE		TOTAL	GROUP-A (BTX)	GROUP-B (HA)	P-VALUE
NO.		60	30	30	---
AGE IN Y (MEAN+SD)		47.48+6.68	48.83+8.57	46.13+3.67	0.148
DURATION OF MARRIAGE IN Y (MEAN+SD)		17.35+8.87	19.87+11.09	14.83+4.90	0.043
SMOKING HISTORY	Index (mean+SD)	9.17+9.07	7.00+8.77	11.33+9.00	0.045
	Duration in y (mean + SD)	9.80+10.48	6.67+9.44	12.93+10.68	0.007
INTERCOURSE PER WEEK (MEAN+SD)		1.77+0.95	1.70+0.95	1.83+0.95	0.555
MEDICATIONS (%)	No	66.7	46.7	86.7	0.658
	Insulin	5.0	10	0	
	Oral hypoglycaemic	5.0	10	0	
	Antihypertensive	23.3	33.3	13.3	
DM (%)		18.3	36.7	0	<0.001
HTN (%)		26.7	40.0	13.3	0.033
SURGERY (%)		5.0	10.0	0	0.083
MALE DOMINANCE (%)		77	76.7	80	0.666
SUFFICIENT INTIMACY (%)		86.9	86.7	90	0.004

*p-value shows statistically significant difference when <0.05

Table (1) shows patient demographic data and medical history data, with a total of 60 patients in the study divided into 2 groups; BTX and HA groups, each of which contains 30 patients. Mean age of patients was 47.48 years, with mean duration of marriage was 17.35 years. Mean smoking index among patients was 9.17 cigarettes per day, with mean duration of smoking was 9.8 years.

The majority of patients had no history of DM (81.7%), HTN (73.3%), history of surgery (95%), nor medication use (45%). The mean intercourse frequency per week was 1.77. There was male dominance in 77% of cases (76.7% in group-A and 80% in group-B). Sufficient intimacy was reported in 86.9% of cases (86.7% in A and 90% in B). There is statistically significant difference between

patients' group who received BTX and those who received HA regarding duration of marriage, smoking index, smoking history, history of DM, history of HTN, and sufficient intimacy.

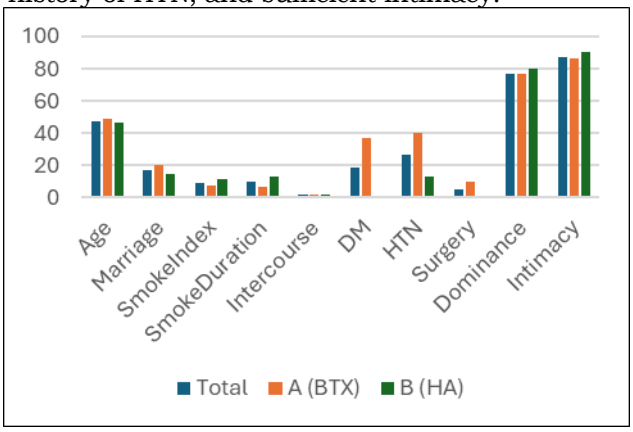

Figure 1. Patients Demographic Data

Table 2. PEP Questionnaire results before injection

ITEM (MEAN±SD)	TOTAL	GROUP-A (BTX)	GROUP-B (HA)	P-VALUE
EJACULATION CONTROL	2.32±0.73	2.37±0.72	2.27±0.74	0.184
DISTRESS	1.83±1.08	1.83±1.08	1.83±1.08	0.999
PATIENT SATISFACTION	2.00±0.82	2.00±0.82	2.00±0.82	0.999
PARTNER SATISFACTION	1.33±1.12	1.33±1.12	1.33±1.12	0.999
TOTAL	7.48±3.47	7.53±3.51	7.43±3.48	0.184

*p-value shows a statistically significant difference when <0.05

Table (2) shows patients' premature ejaculation profile before injection using PEP questionnaire. The mean score of ejaculation control was 2.32, with a mean of 2.37 among BTX group and 2.27 among HA group. The mean score of distress was 1.83 in both groups. The mean score of patient satisfaction was 2 in both groups. The mean score of partner satisfaction was 1.33 in both groups. All the results were statistically insignificant.

Figure 2 shows that, the mean score of ejaculation control was 6.53, with a mean of 5.63 among BTX group and 7.43 among HA group. For distress was 2.62, with a mean of 1.73 among BTX group and 3.5 among HA group. For patient satisfaction was 6.37, with a mean of 5.47 among BTX group and 7.27 among HA group. For partner satisfaction was 2.52, with a mean of 1.6 among BTX group and 3.43 among HA group. All results were statistically significant.

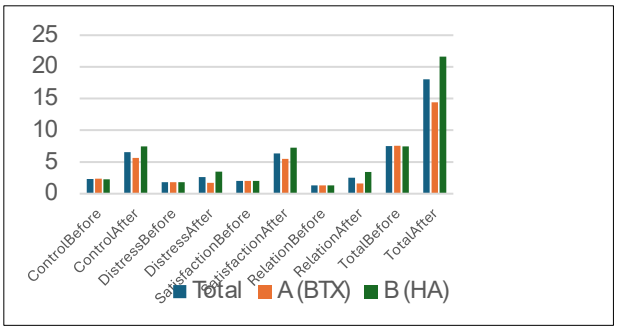

Figure 2. PEP Questionnaire before and after injection

Table 3. Comparison between PEP Questionnaire results before and after BTX injection

ITEM (MEAN±SD)	BEFORE	AFTER	P-VALUE
EJACULATION CONTROL	2.37±0.72	5.63±0.89	<0.001
DISTRESS	1.83±1.08	1.73±0.87	0.639
PATIENT SATISFACTION	2.00±0.82	5.47±0.57	<0.001
PARTNER SATISFACTION	1.33±1.12	1.60±0.97	0.301
TOTAL	7.53±3.51	14.43±3.00	<0.001

*p-value shows statistically significant difference when <0.05

Table (3) shows comparison between PEP scores before and after BTX injection. The mean score of ejaculation control was 2.37 before and 5.63 after BTX injection. The mean score of distress was 1.83 before and 1.73 after BTX injection. The mean score of satisfaction was 2 before and 5.47 after BTX injection. The mean score of partner satisfaction was 1.33 before and 1.6 after BTX injection. Results showed statistically significant difference regarding control of ejaculation and patient satisfaction.

Table 4. Comparison between IELT before and after BTX injection

ITEM (MEAN±SD)	BEFORE	AFTER	P-VALUE
IELT IN MIN	1.78±0.63	3.87±0.97	<0.001

*p-value shows statistically significant difference when <0.05

Table (4) shows comparison between IELT before and after BTX injection. The mean IELT was 1.78 before and 3.87 after BTX injection. This difference is statistically significant.

Table 5. Comparison between IELT before and after HA injection.

ITEM (MEAN±SD)	BEFORE	AFTER	P-VALUE
IELT IN MIN	1.23±0.49	7.30±0.84	<0.001

*p-value shows statistically significant difference when <0.05

Table (5) shows comparison between IELT before and after HA injection. The mean IELT was 1.23 before and 7.3 after HA injection. This difference is statistically significant.

comparison of mean IELT improvement

between BTX and HA groups. The mean improvement in IELT in BTX group was 2.08 min, while it was 6.07 min in HA group. The effect size was 84%. This difference is statistically significant, (figure 3).

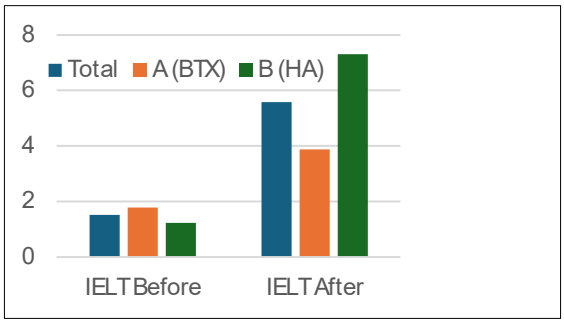

Figure 3. IELT Comparison before and after injection.

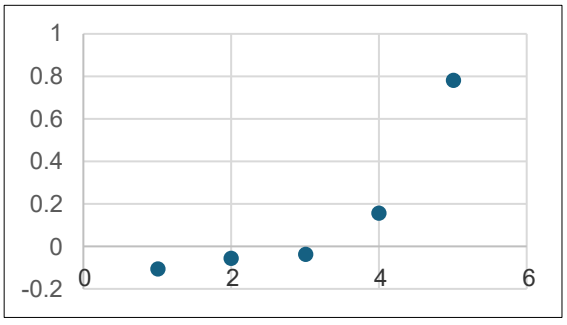

Figure 4. Regression coefficient of each independent factor against post-injection IELT.

4. Discussion

Premature ejaculation (PE) is characterized by an uncontrollable early ejaculation during sexual activity, affecting at least a third of the global male population.[9] Ejaculation occurs when sensations are transmitted through the autonomic nerves to the glans penis, received by multiple receptors. These sensations are influenced by the threshold and accessibility of stimuli to these receptors. Reduced accessibility of stimuli from the receptors to the central nervous system makes it more difficult to experience sensation. This mechanism underpins PE treatment strategies, which aim to suppress stimulus distribution and increase the stimulation threshold at local receptors to the central nervous system.[10]

Various drug therapies, such as local anaesthetics, selective serotonin reuptake inhibitors, and tramadol, have been employed to treat PE.[11] The expected outcome after injection depends on the patient's self-confidence gained from the positive results of the applied procedure. They may reduce the need for further intervention, as well as medical treatment. In this study, the medical history of patients showed that only 36.7% of BTX group had a history of DM, 40% of BTX group and 13.3% of HA had a history of HTN, and 76.7% of BTX group and 33.3% of HA group had a history of medication use, with oral hypertensive being the most used medication in both groups. In the Shaher et al.,[12] study, only 10.6% of patients had HTN. In the Almekaty et al.,[13] study, only 3.3% of patients had DM, and 6.7% had HTN. This can be explained by the older age of patients participating in this study, which increases the prevalence of chronic illnesses such as DM and HTN, and concurrently, medication use.

In this study, the mean intercourse frequency per week was 1.77. Male dominance was observed in 77% of cases (76.7% in group A and 80% in group B). Sufficient intimacy was reported in 86.9% of cases (86.7% in A and 90% in B). To the best of our knowledge, there is no evidence in the literature supporting this finding. Further research is needed to investigate the relation between components of sexual relationships and premature ejaculation.

There was a statistically significant difference between the patients in the BTX group and the HA group in this study regarding history of DM, history of HTN, and sufficient intimacy. Regarding IELT, in this study, the mean IELT was 1.78 min before and 3.87 min after BTX injection. This difference was statistically significant. In Shaher et al.,[12] study, the mean IELT was 35.79 sec before and 60.36 sec 3 months after BTX injection. In the Almekaty et al.,[13] study, the mean IELT was 31.4 seconds before and 33 seconds 3 months after BTX injection.

In the current study, the mean IELT was 1.23 before and 7.3 after HA injection. This difference was statistically significant. In Chen et al.,[14] study, the mean IELT was 124.7 sec before and 325.8 sec 3 months after HA injection. In Alahwany et al.,[15] study, the mean IELT was 33.5 seconds before and 73 seconds 1 month after HA injection.

The current study showed that the mean improvement in IELT in the BTX group was 2.08 min, while it was 6.07 min in the HA group. The effect size was 84%. This difference was statistically significant. The regression analysis showed that the improvement in IELT was dependent only on injection type. This indicates that HA was more efficient in improving IELT in patients with PE. This finding is consistent with the comparison of findings from previous studies that investigated the effect of BTX and HA, as mentioned before.

Regarding PEP, in this study, there was statistically significant improvement only regarding ejaculation control and satisfaction in the BTX group. However, there was evident statistically significant improvement in ejaculation control, distress, satisfaction, and relationship difficulties in HA group, indicating that HA was more efficient than BTX in the

treatment of PE, which was hypothesized before the beginning of the study. The mean total PEP score was 7.53 before and 14.43 after treatment in BTX group, and 7.43 before and 21.63 after treatment in HA group.

In Shaher et al.,[12] study, the mean PEP score was 5.49 before and 7.19 after 3 months of BTX injection. In the Almekaty et al.,[13] study, the mean PEP score was 2.3 before and 2.9 after 3 months of BTX injection. This is consistent with the current study results and indicates low efficacy of BTX in the treatment of PE. However, in Chen et al.,[14] study, the mean PEP score was 3.747 before and 12.91 after HA injection. This result was consistent with the current study, indicating the efficacy of HA in PE treatment.

Additionally, in Alahwany et al.,[15] study, the mean AIPE score was 15.6 before and 20.9 after HA injection. Despite using different index to follow up the efficacy of HA, the results were consistent with the current study in proving efficacy of HA in the treatment of PE.

In this study, there was a significant difference in patient satisfaction between the groups treated with botulinum toxin (BTX) and hyaluronic acid (HA), with HA demonstrating a higher satisfaction rate. This aligns with findings from previous studies. For instance, results showed an increase in satisfaction scores (PEP questionnaire results) from 2.0 to 7.27 in the HA group, compared to a smaller increase from 2.0 to 5.47 in the BTX group. Other studies have similarly indicated that HA injections often yield better outcomes in terms of satisfaction and symptom relief for patients with premature ejaculation (PE).

The effectiveness of HA over BTX might be due to HA's potential for sustained effect on increasing intravaginal ejaculation latency time (IELT), with an increase of about 6.07 minutes in the HA group versus 2.08 minutes in the BTX group. This difference has been attributed to HA's ability to provide longer-lasting mechanical effects by adding volume, thereby enhancing ejaculation control and overall satisfaction. This is consistent with studies by Chen et al.,[14] and Alahwany et al.,[15] both of which support HA's efficacy in treating PE and its positive impact on patient satisfaction.

Regarding complications, pain was reported as the primary side effect, with 80% of HA patients and 20% of BTX patients experiencing pain. This higher rate of pain in HA treatments could be due to the larger volume and viscosity of HA injections, which may cause greater discomfort compared to BTX. However, this side effect was generally manageable, and no severe complications were observed in either group, suggesting that both HA and BTX are relatively safe treatment options for PE.

Based on the results of the current study and previous studies, it can be concluded that BTX and HA proved efficacy in the management of PE. However, HA has higher efficacy than BTX in PE treatment.

4. Conclusion

We can conclude that HA is more efficient than BTX in the treatment of PE. However, more research is needed to generalize the utilization of this procedure to help more patients.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

References

1. Feige AM, Pinsky MR, Hellstrom WJ. Dapoxetine for premature ejaculation. Clin Pharmacol Ther. 2011; 89(1): 125-128.
2. Crowdis M, Leslie SW, Nazir S. Premature Ejaculation. In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 30: 2023.
3. Abou-Elhamd AS, Selim A, Rahman YA. Gross, Histological and Scanning Electron Studies on the Bulbourethral Gland of Donkey (Equus asinus) during Different Seasons. Journal of Advanced Veterinary Research. 2021; 11(3): 147-157.
4. Althof SE. Treatment of rapid ejaculation: Psychotherapy, pharmacotherapy, and combined therapy (pp.212–240). In S.R. Leiblum (Ed.), Principles and practice of sex therapy (4th ed.). NY: Guilford.2007.
5. Parnham A, Serefoglu EC. Classification and definition of premature ejaculation. Transl Androl Urol. 2016; 5(4): 416-423.
6. Li ZT, Li YF, Zhang Y, et al. Zhonghua Nan Ke Xue. 2018; 24(8): 713-718.
7. Moon du G, Kwak TI, Kim JJ. Glans Penis Augmentation Using Hyaluronic Acid Gel as an Injectable Filler. World J Mens Health. 2015; 33(2): 50-61.
8. Patrick DL, Giuliano F, Ho KF, et al. The Premature Ejaculation Profile: validation of self-reported outcome measures for research and practice. BJU Int. 2009; 103(3): 358-364.
9. Kosseifi F, Chebbi A, Raad N, et al. Glans penis augmentation using hyaluronic acid for the treatment of premature ejaculation: a narrative review. Transl Androl Urol. 2020; 9(6): 2814-2820.
10. Kim SW, Paick JS. Peripheral mechanisms of premature ejaculation. International Journal of Impotence Research. 2004;16(1): 2-7.
11. Wang WF, Chang CH, Chen CS. Pharmacotherapy for premature ejaculation. Journal of the Chinese Medical Association. 2017; 80(5): 283-288.
12. Shaher H, Noah K, Abdelzaher M, et al. Is bulbospongiosus muscle botox injection safe and effective in treating lifelong premature ejaculation? Randomized controlled study. World J Urol. 2024; 42(1): 218.
13. Almekaty K, Ghaith A, Ragab M, et al. Effect of bulbospongiosus muscle injection with botulinum-A toxin for treatment of lifelong premature ejaculation; a randomized controlled trial. Int J Impot Res. 2024; 36(8): 864-868.
14. Chen K, Li Q, Xu T, et al. Hyaluronic acid injection to coronal sulcus of the penis for the treatment of premature ejaculation: a retrospective observational study. BMC Urol. 2023; 23(1): 55.
15. Alahwany A, Ragab MW, Zaghloul A, et al. Hyaluronic acid injection in glans penis for treatment of premature ejaculation: a randomized controlled cross-over study. Int J Impot Res. 2019; 31(5): 348-355.