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ARTICLE

Hyaluronic acid injection in glans penis for treatment of premature ejaculation: a randomized controlled cross-over study

Amr Alahwany[1] · Mohamed W. Ragab[1] · Ahmed Zaghloul[1] · Hamed Abdallah[1] · Taymour Mostafa[1]

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Abstract

This randomized controlled cross-over study aimed to assess the efficacy and safety of glans penis injection with hyaluronic acid (HA) in treating premature ejaculation (PE). A total of 30 patients with PE were randomly allocated into two groups: group 1 ($n = 15$) which was subjected to glans penis HA injection and group 2 ($n = 15$) which was injected with saline as a control then both groups were subjected to follow-up at 1 week and 1 month after injection. These subjects were evaluated by intra-vaginal ejaculation latency time (IELT) and the Arabic validated index of premature ejaculation (AIPE). After a wash-out period, cross-over and re-evaluation of both groups were carried. Additionally, patients with reported improvement after 1 month of HA injection ($n = 20$) were subjected to extended evaluation by IELT at 3, 6, and 9 months intervals. Two-way repeated measures ANOVA indicated significant improvement after HA in comparison with saline across the follow-up periods ($F(1.66: 91.37) = 24.85$, $p = 0.001$). Post-hoc Bonferroni test indicated no significant difference after 1 week period in comparison with baseline IELT, but a significant difference after 1 month of injection in comparison with baseline IELT ($p < 0.001$) and after 1 week ($p < 0.001$). After 1 month of HA, IELT increased by a median of 2.6 folds while 1.1 folds increase was observed after 1 month of saline injection. Total AIPE scores improved significantly after HA injection compared with baseline ($p = 0.003$) and saline scores ($p = 0.002$). Reported adverse effects were minimal and self-limited. It could be concluded that glans penis injection with HA for treatment of PE is a safe method that ensures a modest but significant increase in IELT and improves couple sexual satisfaction.

Introduction

Premature ejaculation (PE) is a commonly reported male sexual complaint, with high prevalence in the male population, which varies according to its applied definition and the study populations [1, 2]. PE prevalence rates were estimated to be 20–40% with a detrimental impact on the quality of life for both the patients as well as their partners [3, 4].

On-demand treatment with dapoxetine, off-label use of daily selective serotonin re-uptake inhibitors (SSRIs), on-demand topical anesthetics, behavioral, and combination therapy are currently considered the first line therapies for lifelong PE (LL PE), while etiology-specific therapy is recommended for the management of acquired PE (A PE) which may be also combined with the aforementioned treatment modalities [5–7]. The main limitations of these available PE treatment options include; systemic side effects and recurrence of PE after their withdrawal [5].

According to the studies of Kim et al. [8], Abdallah et al. [9], and Littara et al. [10] regarding PE; hyaluronic acid (HA) can be injected into the dermis of the glans penis just above the nerve terminals. This injection was hypothesized to create a barrier that reduces the intensity of tactile stimuli reaching sensory receptors of the glans penis. However, available studies in this context were uncontrolled, used definitions for PE that did not cover all PE dimensions and evaluated PE by non-validated questionnaires. Therefore, these drawbacks may limit the generalizability of studies' findings and do not confirm that the improvement is due to the sole effect of HA itself [11].

This single blinded randomized controlled cross-over study aimed to assess the efficacy and safety of glans penis injection with HA in treating PE.

✉ Mohamed W. Ragab
dr.wa2el@gmail.com

[1] Department of Andrology, Sexology & STIs, Faculty of Medicine, Cairo University, Cairo, Egypt

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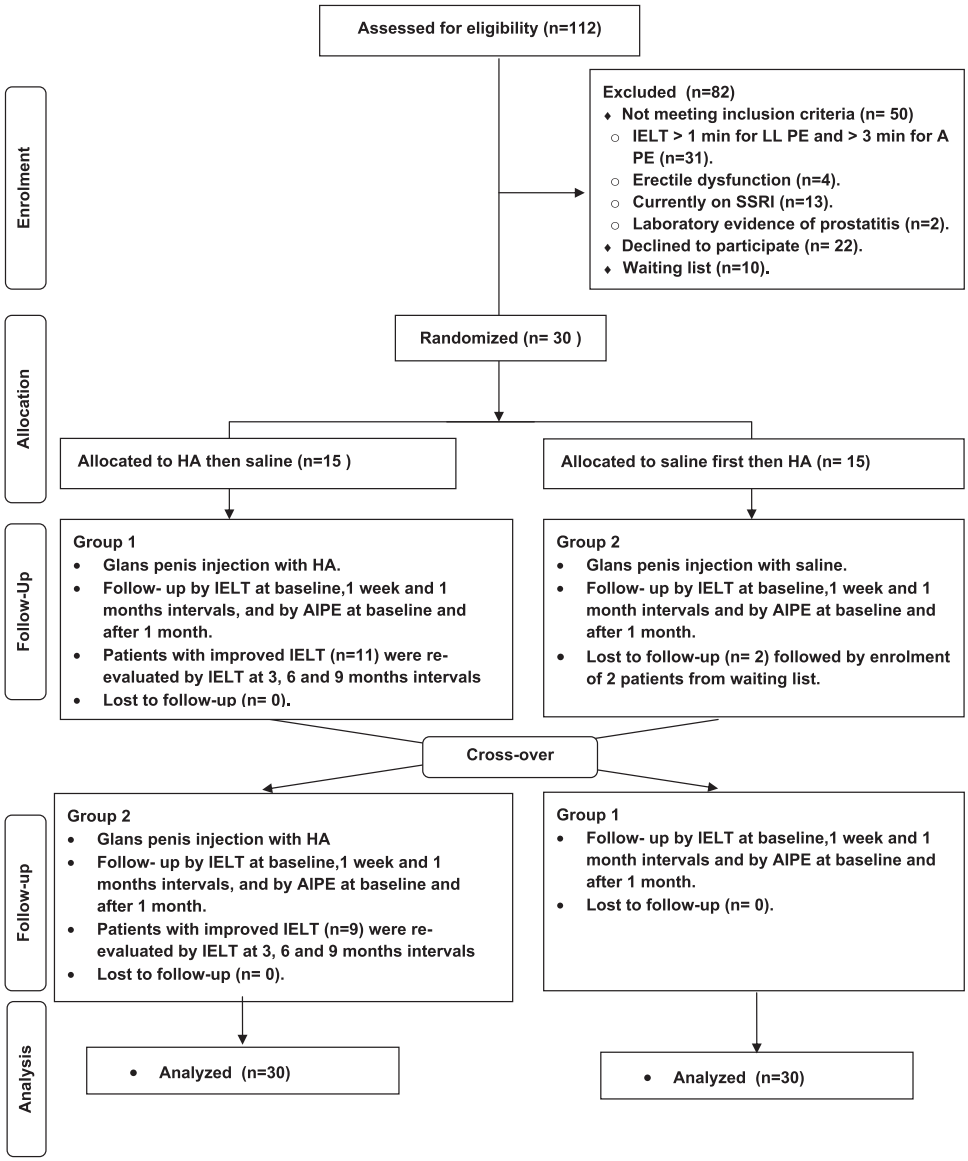

Fig. 1 Flow diagram of the study according to Consolidated Standards Of Reporting Trials (CONSORT) 2010

Materials and Methods

This prospective randomized controlled crossover study was carried out in the University hospital from August 2016 to March 2018 after ethical IRB approval and signed informed consents obtained from all participants. A total of 112 patients complaining from PE were recruited to participate in this study. Out of these men, 50 patients were ineligible for participation and 22 patients refused to be enrolled. Forty patients accepted enrollment and fulfillment of follow-up visits as described in Fig. 1. All included patients fulfilled the criteria of PE definition according to the second Ad Hoc International Society of Sexual Medicine (ISSM) committee for the definition of premature ejaculation [12, 13]. These criteria involved occurrence of ejaculation in patients with LL PE within 1 min from vaginal penetration in all or almost all occasions starting from the first sexual experience, and within 3 min in patients with acquired A PE, along with inability to delay ejaculation on all or nearly all vaginal penetrations, with negative personal consequences, such as distress, bother, frustration, and/or avoidance of sexual intimacy. Finally, patients were allocated to one of each group (30 patients vs. 10 waitlist), then the 30 patients were randomly allocated to one of two groups (Gr1 vs. Gr2) and similar procedure was done to the waitlist group. Random allocation was done using IBM SPSS software version 21 (SPSS Inc., Chicago, IL, USA).

Hence, 21 patients with LL PE and 9 patients with A PE were involved. All study participants were screened for erectile dysfunction (ED) prior to enrollment by the Arabic version of sexual health inventory [14]. All included

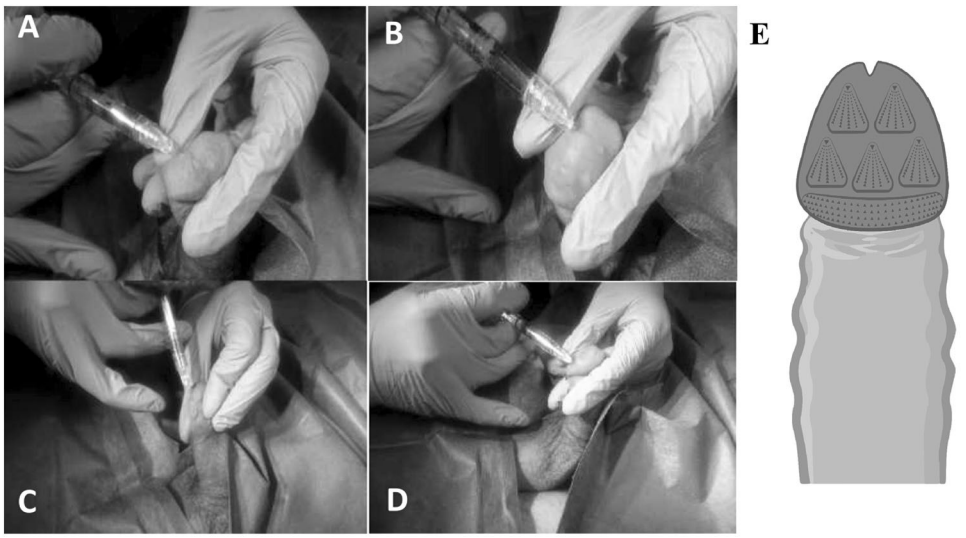

Fig. 2 Glans penis augmentation with hyaluronic acid gel; **a**, **b** injection mid-way between the corona and urethral meatus, **c** injection under the frenulum, **d** injection in corona glandis, **e** illustration of injection sites in glans penis. An informed consent was obtained from the patient for publishing the photos of the procedure

patients had normal erection, stable heterosexual marital relationship, normal total serum testosterone, prolactin and thyroid stimulating hormone levels and had no symptoms of prostatitis or history of drug abuse, psychiatric disorders and/or related medications. All participants were previously circumcised. Ten patients with LL PE were previously treated with selective serotonin re-uptake inhibitors (SSRI), six of them reported intolerable nausea or dizziness, while four patients reported unsatisfactory response. Three out of the five patients with A PE reported previous treatment with SSRI with unsatisfactory outcome.

These 30 subjects were randomly assigned into 2 groups. The first group (Gr1, $n = 15$) received a topical anesthetic agent for 30 min (Emla cream; lidocaine 25 mg, prilocaine 25 mg, Astra Xeneca, Mississauga, Canada) followed by injecting two prefilled 1 ml syringes of cross-linked HA with 30 G needle (Teosyal® PureSense Global Action 25 mg/ml, Teoxane Laboratories, Geneva, Switzerland) using multiple puncture technique as described by Abdallah et al. [9] with minor modifications. HA was injected at two circular levels: one at the level of corona and the second one mid-way between the corona and urethral meatus. Six injections were injected at coronal level and four in the second level, each injection was 0.2 ml into deep dermis (Fig. 2). These patients were followed up at intervals of 1 week by Intra-vaginal ejaculation latency time (IELT) and at 1 month by IELT and Arabic index of premature ejaculation (AIPE) questionnaire. The second group (Gr2, $n = 15$) received, by the same method, 2 ml saline injection as controls and were evaluated as group 1.

In Gr1, after a wash out period of a total of 18 months after HA injection, a cross-over of the treatment method to saline was carried out with follow-up as previously mentioned. The period of 18 months was chosen according to the estimated manufacturer longevity of Teosyal® (range 2–18 months) [15].

The evaluation was done by measuring IELT, the validated AIPE and occurrence of adverse effects. IELT was measured by a partner held stopwatch and the AIPE score was obtained by interviewing patients for fulfillment of the seven-items AIPE questionnaire [16]. According to AIPE score, PE severity is classified into; severe PE (7–13), moderate PE (14–19), mild to moderate PE (20–25), mild PE (26–30), and no PE (31–35) [16].

After HA injection, the patients were directly interviewed at 1 week and 1 month follow-up intervals. After saline injection in Gr2, the patients were directly interviewed at 1 week and 1 month intervals, and cross-over was carried out after 1 month. Patients with reported improvement in IELT after HA injection in both groups were subjected to further re-evaluation by measuring IELT at 3, 6, and 9 months intervals. In Gr2, 2 patients dropped out interviewing at 2 and 4 months being omitted from the study including another 2 patients from the waiting list. None of Gr1 patients were dropped out.

Statistical analysis

Statistical analysis and drafting of graphs were performed using IBM SPSS version 21(SPSS Inc., Chicago, IL, USA) and Graph Pad Prism 5.01 (Graph Pad Software Inc. LaJolla, CA, USA). Kolmogorov-Smirnov test for normality was used to assess data distribution. Accordingly, if data were found to be normally distributed, the results were expressed as means ± standard deviation (SD) whereas abnormally distributed data were expressed as median (range). Comparison between categorical data was performed using X^2 test. Comparison between continuous variables was performed using paired sample *t*-test or

Table 1 Descriptive data of the investigated groups

	Total ($n = 30$)	Group 1 ($n = 15$)	Group 2 ($n = 15$)	p value
Age (years)	33.3 ± 5.3	34.0 ± 4.9	32.1 ± 5.6	0.33[b]
Duration of stable relation (months)	9.5 (2–108)[a]	9 (3–108)[a]	10 (2–96)[a]	0.78[c]
Type of PE				
Lifelong (%)	21/30 (70)	11/15 (73.3)	10/15 (66.7)	0.69[d]
Acquired (%)	9/30 (30)	4/15 (26.7)	5/15 (33.3)	
Ante-portal ejaculation (%)	5/30 (16.7)	3/15 (20)	2/15 (13.3)	0.62[d]
IELT (seconds)	33.5 ± 14.8	30.0 ± 14.9	32.1 ± 15.2	0.59[b]
AIPE questionnaire				
Q1	3.3 ± 0.85	3.4 ± 0.74	3.33 ± 0.96	0.31[e]
Q2	4.27 ± 0.45	4.4 ± 0.51	4.13 ± 0.35	0.22[e]
Q3	1.6 ± 0.62	1.6 ± 0.63	1.53 ± 0.52	0.59[e]
Q4	1.37 ± 0.49	1.4 ± 0.51	1.33 ± 0.49	0.71[e]
Q5	1.43 ± 0.5	1.47 ± 0.52	1.4 ± 0.41	0.71[e]
Q6	1.43 ± 0.5	1.53 ± 0.52	1.33 ± 0.49	0.46[e]
Q7	2.17 ± 0.53	2.13 ± 0.52	2.2 ± 0.56	0.91[e]
Total score	15.63 ± 2.13	15.93 ± 2.12	15.33 ± 2.17	0.3[e]

Data expressed as mean ± SD

PE premature ejaculation, *AIPE* Arabic index of premature ejaculation, *IELT* intravaginal ejaculation latency time

[a]Data are expressed as median (range)

[b]Paired sample *t*-test

[c]Mann–Whitney test

[d]Chi-square test

[e]Wilcoxon signed rank test

$p < 0.05$ considered significant

Mann–Whitney *U* test. Measured IELT was not normally distributed. Hence, data were transformed to log 10. Repeated measures two-way ANOVA test was used to study the interaction between groups and different time of measurements. The model used the two groups (HA and saline) as independent variable and time (1 week and 1 month follow-up) as a dependent variable. Bonferroni test was used for adjusted pair-wise comparisons between measured IELT after HA and saline at different time points. Wilcoxon signed rank test was done to compare ordinal data. A p value < 0.05 was considered as significant for all applied tests.

Results

Intra-vaginal ejaculation latency time

Baseline values of IELT showed non-significant differences between Gr1 and Gr2 (Table 1).

As described in Table 2, two-way repeated measures ANOVA indicated significant improvement after HA in comparison with saline across the follow-up periods ($F(1.66: 91.37) = 24.85$, $p = 0.001$). Post-hoc Bonferroni test indicated that there was no significant difference after 1 week period in comparison with baseline IELT, but a significant difference after 1 month of injection in comparison with IELT in both baseline ($p < 0.001$) and 1 week follow-up ($p < 0.001$).

Twenty patients (67%) reported improvement from baseline IELT at the follow-up after 1 month of HA injection, while the remaining patients enrolled in this study ($n = 10$, 33%) did not report an improvement in IELT at 1 month follow-up visit. Re-evaluation of this subgroup of patients at 3, 6, and 9 months interval showed steady decrease of measured IELT but all were significantly higher than the baseline IELT (Fig. 3).

Arabic index of premature ejaculation questionnaire

Prior to enrollment in the study, four patients had severe PE, 25 had moderate PE and 1 patient had mild to moderate PE according to AIPE with a mean score of 15.6. After 1 month of HA injection, AIPE increased significantly to 20.9. Out of 25 patients with moderate PE before treatment, 5 patients had no PE after HA injection, and 9 patients had only mild

Table 2 IELT after HA and after saline at follow-up of 1 week and 1 month periods

	HA			Saline			Difference between HA & saline at 1 month follow-up		
Follow-up period by IELT	IELT (seconds)	Difference from baseline	Median fold change from baseline	IELT (seconds)	Difference from baseline	Median fold change from baseline	Difference between HA & saline at 1 week follow-up	*F* value	*p* value[a]
1 week	40 (0–80)	+3 (−23.0–48.0)	1.1	35 (0–80)	+3.5 (−17–41)	1.2	−4.5 (−44–50)	24.85	**0.001**
1 month	73 (0–240)	+53 (−15–187)	2.6	32 (5–58)	+0.5 (−15–21)	1.1	45 (−30–185)		

Data expressed as median (range)

IELT value of 0 s represents anteportal ejaculation

IELT intra-vaginal ejaculation latency time, *HA* hyaluronic acid

[a]Two-way repeated measures ANOVA

$p < 0.05$ considered significant (in bold)

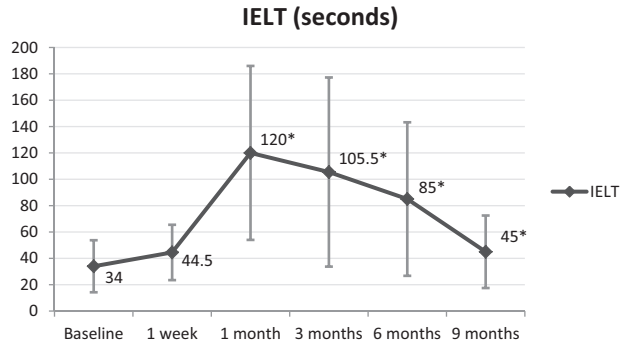

Fig. 3 Extended evaluation of IELT in the sub-group of 20 patients with improved IELT over baseline after 1 month of HA injection. IELT illustrated as median and inter-quartile range at baseline and after 1 week, 1, 3, 6, and 9 months of HA injection. Repeated measure ANOVA followed by post-hoc Bonferroni test for pair-wise comparisons with baseline. *significant difference from baseline

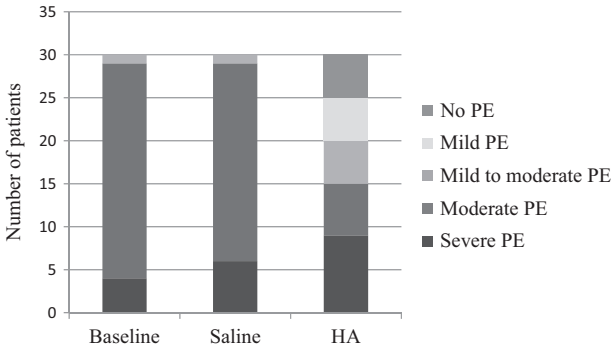

Fig. 4 Changes in categories of PE according to AIPE score after 1 month of treatment with HA and saline in compare with baseline

PE according to AIPE categorical classification. The category of PE severity measured by AIPE in patients with severe PE ($n = 4$) did not improve after either HA or saline injections. Fig. 4 demonstrates categories of PE according to AIPE score after 1 month of treatment with HA and saline in compare with baseline. Within AIPE, scores of Q3–7 improved significantly after HA injection but not after saline injection compared with baseline scores (Table 3).

Adverse effects

Adverse effects were reported in 6/30 patients (20%) of the patients after 1 week of HA injection; 3 patients had gradually decreasing local discomfort at the injection sites, 2 patients had glans penis ecchymosis, and 1 patient had irregular blanched papule from superficial HA injection. All adverse effects were resolved spontaneously at the next presentation (after 1 month of HA injection). No systemic or permanent effects were observed throughout the follow-up period. Saline injection resulted only in injection-site ecchymosis in 1 patient.

Table 3 Baseline individual and total scores of AIPE, after 1 month of HA injection and after 1 month of saline injection for patients involved in the study ($n = 30$)

AIPE	Explored domain	Baseline	HA	p value (HA vs. baseline)	Saline	p value (saline vs. baseline)	p value (HA vs. saline)
Q1	Sexual desire	3.4 ± 0.9	3.6 ± 0.9	0.28	3.3 ± 0.7	0.41	0.09[a]
Q2	Erectile function	4.3 ± 0.5	4.3 ± 0.5	0.56	4.1 ± 0.6	0.34	0.52[a]
Q3	Ejaculatory latency	1.6 ± 0.6	2.8 ± 1.3	**0.001**	1.7 ± 0.6	0.32	**0.001**[a]
Q4	Control over ejaculation	1.4 ± 0.5	2.5 ± 1.4	**0.001**	1.4 ± 0.6	0.48	**0.001**[a]
Q5	Sexual satisfaction	1.4 ± 0.5	2.6 ± 1.5	**0.001**	1.5 ± 0.6	0.32	**0.002**[a]
Q6	Partner satisfaction	1.4 ± 0.5	2.4 ± 1.4	**0.001**	1.5 ± 0.5	0.16	**0.002**[a]
Q7	Associated distress	2.2 ± 0.5	2.8 ± 1.6	**0.019**	2.1 ± 0.6	0.48	**0.016**[a]
Total score		15.6 ± 2.1	20.9 ± 7.9	**0.003**	15.5 ± 2.3	0.84	**0.002**[a]

AIPE Arabic index of premature ejaculation, *HA* Hyaluronic acid

[a]Wilcoxon signed rank test

$p < 0.05$ is considered significant (in bold)

Discussion

The current study showed that HA injection could significantly increase IELT compared with saline injection, and this increase could persist up to 9 months. This outcome can be explained by reduced sensation threshold of the glans penis as previously illustrated by Kim et al. [8] study. These researchers demonstrated significant increases of vibratory threshold after glans penis augmentation with HA that have the ability to absorb water to form highly viscous hydrated polymers [17], which is speculated to act as a barrier between sensory nerves in glans penis and external stimuli [8, 18]. HA–which is a member of glycosaminoglycans family– is present in the extracellular matrix of dermis, epidermis, and stratum corneum. The physiological role of HA involves expansion of the extracellular matrix. This role is facilitated by the macromolecular nature of HA and its high capacity of water-binding [19]. The native HA molecule has a short half-life in skin (~12 h), but its longevity can be expanded to several months by cross-linkage of HA molecules [15, 19].

Overall, the IELT has been improved by a median of 2.6 folds after 1 month of glans penis HA injection. This was evident in 20/30 (66.7%), whom IELT increased over the baseline value. In these patients, the mean IELT increased from a median of 34 sec before HA injection to 120, 105.5, 85, and 45 s at 1, 3, 6, and 9 months follow-up intervals, respectively. Kim et al. [8] reported similar improvement after 6 months of HA injection in a group of 65 patients with primary PE from a mean of 96.6–281.9 s. Similarly, Abdallah et al. [9] reported improved IELT in 49 patients after glans penis augmentation with HA from a mean of 127.2–462.6 and 319.2 s after 1 and 3 months respectively but they included patients with different inclusion criteria (self-reported IELTs of ≤2 min in >70% of coital attempts). Another uncontrolled study by Littara et al. [10] on 110 male patients with PE reported improved IELT from a mean of 88.34 to 293.14 s after 6 months from HA injection. The mean baseline IELT ranged around 88 s whereas this high baseline IELT resulted in higher IELT after HA injection compared with our patients. The observed difference between the end-result IELT of these studies can be attributed to the higher severity of PE included in our study with lower baseline IELT confined to baseline IELT <1 min and <3 min in patients with LL PE and A PE respectively.

Several validated questionnaires for PE evaluation were described in the literature. AIPE is a sensitive validated questionnaire for diagnosis of PE [20]. This questionnaire evaluates seven domains (Q1–Q7) as described in Table 3. Each domain is scored by 1–5 ordinal points. Patients' and partners' sexual satisfaction, which were evaluated by Q5 and Q6 of AIPE respectively, both showed significant score increase after HA injection but not after saline injection after 1 month of treatment in the current study. In concert with our findings, Kim et al. [8] reported improved patient's satisfaction (measured by 4 grades scale) in 49/65 (75%) patients and in 32/52 (62%) participated partners. Similar findings were observed by Littara et al. [10] who reported significant improvement of the 6 grades self-reported score used to evaluate patients' and partners' satisfaction over sexual performance. They observed a mean baseline patients' score of 1.2 before HA injection and 5.3 (6 months) after injection whereas the mean partners' sexual satisfaction score improved from 1.3 to 5.1.

Adverse reactions observed in six out of 30 patients were merely self-limiting ecchymosis and injection-site discomfort. HA injections for treatment of PE did not affect other domains of sexual functions. One patient had a

superficial papule from superficial HA injection that resolved spontaneously. Allergic reactions were not reported. This could be explained by the fact that HA is a polysaccharide that shares the same chemical and molecular composition in all species and naturally found in the intercellular matrix of dermal layers of the skin, therefore, it does not create foreign body reactions. Although, there were rare case reports of allergic reaction after HA injection for facial cosmetic purposes [21, 22], the safety and feasibility of in glans penis injection with HA was previously confirmed by experimental trials in dogs and rabbits [23]. Additionally, Kim et al. [8]. and Littara et al. [10] did not observe any adverse effects in their cohorts following HA injection. In their study, Abdallah et al. [9] reported mild adverse effects in ~30% of patients in the form of mild pain and bullae formation at the injection site. However, allergic reaction after a second exposure of HA injection cannot be precluded based on the findings of this study.

In 20/30 (66.7%) patients, improvement in measured IELT values after HA injection have been observed and were extended for >9 months. This durability is mostly attributed to the cross-linkage of HA molecules which limits the degradation process of HA [24]. Kwak et al. [25] concluded that the long-term improvement of IELT after HA injection could persist for up to 5 years.

Nevertheless, the reported mean fold increase of IELT after HA remains inferior to that reported previously form other PE treatment modalities: (a) paroxetine (8.8 folds), (b) clomipramine (4.6 folds), (c) sertraline (4.1 folds), and (d) fluoxetine (3.9 folds) [26]. However, HA injection got the advantage of being injected once every 9–12 months, absence of systemic side-effects and absence of negative consequences on sexual desire or fertility. Furthermore, the reported fold increases of IELT in our study after 1 month of HA injection in glans penis (2.6 folds) is almost the half of that reported after local anesthetic agent: 5.6 folds [27] but this increase is sometimes accompanied by loss of penile sensation and decreased vaginal sensitivity [5].

Although a significant improvement was observed in the median IELT after glans penis HA injection, this improvement remains below the threshold of 3–4 fold increase; which is anecdotally considered the lower limit of clinical success of PE treatment intervention [11].

The study sample size limits drawing a solid conclusion regarding the efficacy of HA injection for treatment of PE. Despite this small sample size, a significant improvement after HA injection could be observed. An another limitation is that AIPE questionnaire was developed mainly as a diagnostic tool for PE rather than a scale for treatment responsiveness, yet this validated questionnaire remains a sensitive tool for evaluating of PE [11, 28].

Conclusions

From these assembled results, it could be concluded that that glans penis injection with HA is a safe method that ensures a modest long-term significant increase in IELT, improves ejaculatory control and ameliorate couple satisfaction over their sexual intercourse. However, its role is limited in patients with severe PE and inconsistently of patients' improvement. Further studies are recommended for evaluation of long-term safety and efficacy as well as the effect of repeated injections.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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