

The efficacy of hyaluronic acid in treating premature ejaculation: A systematic review and single-armed meta-analysis

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Abstract

Aim: To evaluate the efficacy of hyaluronic acid (HA) injection in treating patients with premature ejaculation (PE).

Methods: Matching interventional studies from MEDLINE, CENTRAL, and CINAHL. Outcomes were intravaginal estimated latency time (IELT), glandular circumference, satisfaction score, and adverse event rate. Data were assessed with Open Meta Analyst, DerSimonian and Laird random-effects model.

Results: Ten interventional studies, three double-armed, with low to moderate bias risk, revealed significant differences in baseline IELT and 1, 3, and 6-month post-hyaluronic acid injection, with mean differences of 217.035 (95% CI, 89.330–344.739), 161.513 (95% CI, 37.262–285.764), and 196.350 (95% CI, 142.314–250.386) seconds. Glandular circumference increased by 10.956 mm (95% CI, 3.314–18.598) after six months.

Conclusion: Hyaluronic acid successfully extended IELT in premature ejaculation patients at one, three, and six months post-treatment with no severe side effects. It also enhanced glandular size and sexual satisfaction for patients and their partners.

Keywords

Intravaginal ejaculation latency time, glandular circumference hyaluronic acid, premature ejaculation

Introduction

As one of the most common sexual dysfunctions, premature ejaculation (PE) has been a major sexual problem among men worldwide. Its prevalence is estimated to be around 20–30% globally, and some reviews has reported up to 75% of men encountered this problem (Carson and Gunn 2006). To these dates, the universally accepted diagnostic criteria of premature ejaculation have not been

established. The American Urological Association Guidelines 2020 (AUA) defined PE as poor ejaculation, associated bother, and ejaculation within about 2 minutes after the initiation of penetrative sex. Furthermore, the AUA classified PE as primary (lifelong) and acquired (secondary) PE. In primary PE, ejaculation occurs within 30–60 seconds, measured from the beginning of penetration to ejaculation. In acquired PE, there is a markedly reduced ejaculation latency time from prior experience of about

50% or approximately within 2–3 minutes from penetration to ejaculation (Shindel et al 2022).

PE has been known to affect the quality and satisfaction of sexual intercourse, even causing distress and anxiety to the patient and their partners (Kempeneers et al. 2018). To add to this problem, the exact cause of PE has not been established yet, rendering it challenging to treat the condition. However, biological and psychological risk factors are thought to play a role. Biological factors that potentially contribute to PE include abnormal serotonin levels, abnormal hormone levels, inflammation or infection of the prostate or urethra, and psychological factors, including depression, stress, anxiety, history of sexual repression, and sexual abuse (Kalejaiye et al. 2017; Zhang et al. 2019). Therefore, a wide range of treatment modalities have been applied, including behavioral therapies, psychological therapies, and pharmacological therapies such as the use of antidepressants (e.g., tricyclic antidepressants and serotonin reuptake inhibitors), topical anesthetics, phosphodiesterase-5-inhibitors, and opiate analgesics (e.g., tramadol) (Martin and Shindel 2020). The side effects and recurrence after drug cessation have been the main problem of these pharmacological therapies. Thus, procedural treatments have been performed, such as selective dorsal neurectomy and hyaluronic acid (HA) injection (Perri et al. 2022).

The treatment with hyaluronic acid injection is a technique in which HA is injected into the dermis of the glans penis approximately above the dorsal nerve terminals, creating a barrier between the dorsal nerve branches and the skin. This barrier diminishes the tactile stimuli, reaching the sensory receptors of the glans penis, thus; resulting in penile analgesia and a slower ejaculatory reflex (Alahwany et al. 2019). A pilot study including 60 patients with PE reported a significant increase in intravaginal ejaculation latency time (IELT) after one month of receiving a single injection of 2 ml HA (from 2.12 ± 1.16 minutes to 7.71 ± 7.86 minutes) (Abdallah et al. 2012). Ahn et al., reported an increase in penile girth in 32 subjects within 24 weeks after using HA filler, as well as an increased satisfaction level without any serious adverse effects reported (Ahn et al. 2022). Similarly, Abdelazeem and Esawy also reported increased intravaginal latency time, glandular circumference, and patients' and partners' satisfaction levels at the 6-month follow-up after HA injection (Abdelazeem and Esawy 2019). Another study on 38 patients reported a positive long-term effect of HA injection after five years (Kwak et al. 2008). In contrast, several studies found a markedly decrease in IELT at a 3-month follow-up, suggesting that HA injection only provides a temporary solution to PE. In addition, the patient's satisfaction level was also found to be the same as the baseline at a 3-month follow-up (Kewei et al. 2022). Furthermore, Shebl et al., have also reported that although the patients' satisfaction at three months reached approximately 70%, their partners' sexual satisfaction at three months was less than 50% (Sterne et al. 2016).

Although HA injection might be a promising approach to treating PE, the same benefit of HA injection in treating PE remains inconclusive. Therefore, we performed a systematic review and meta-analysis of available randomized-clinical trials to obtain more conclusive information regarding the efficacy of HA injection in treating patients with PE.

Methods

Description of condition and intervention

We tried to evaluate the efficacy of hyaluronic acid in improving the condition of premature ejaculation patients. Therefore, the clinical questions for this meta-analysis were created as follows:

Table 1. Clinical questions.

Aspects	Criteria
Population	<ul style="list-style-type: none"> All patients with premature ejaculation, regardless of their race/ethnicity Aged 20–65 years old and have a stable sexual intercourse No history of the acquired nor congenital penile disorder (e.g., micropenis, concealed penis, severe phimosis, and Peyronie's disease; previous penile) No history of penile surgery, including PGE and insertion of a penile prosthesis Free of psychiatric disorder
Intervention	Hyaluronic acid given parenterally to the patient's penis
Comparison	Normal saline*
Outcome	Primary outcomes: <ul style="list-style-type: none"> Intravaginal ejaculation latency time (IELT) Glans circumference Secondary outcomes: <ul style="list-style-type: none"> Satisfaction score Adverse events

*Comparison between the baseline and after-treatment outcomes for single-arm studies.

Database searching and literature screening

We conducted ED-related works of literature searching on three electronic databases (MEDLINE, CENTRAL, and CINAHL), using five search engines (Pubmed, Cochrane, EBSCOHost, ProQuest, and EMBASE) from October to November 2022. We used PICOS to facilitate study tracing and identify the suitability of the observational study we encountered. Keywords selection was based on the specifications of each search engine (Table 1). All studies appearing on search engines are compiled in a database developed with the Endnote X9 application for Macintosh.

Study selection

Our systematic review is based on preferred reporting items for systematic reviews and meta-analysis (PRISMA) statements. The inclusion criteria for this review include the following:

- Cohort /RCT/case-control study according to PICO (clinical question)
- English written
- The full-text article is available; and
- Published in the last 15 years.

To maintain that our review is free of performance bias, we conducted a subgroup analysis regarding the above

inclusion. Meanwhile, the exclusion criteria include (1) Any studies in the form of systematic or meta-analysis, literature review, case reports, case series, editorial letters, studies on animals, and/or (2) studies in the process of peer review (not yet published).

Any articles found from the search were then filtered to remove duplications. Then, the authors of this review conducted an eligibility assessment for all articles, based on the titles and abstracts. Each author screened articles by reading the selected manuscripts, and any discrepancies were resolved by discussion.

Data extraction and outcome of interest

Studies that have passed the selection stage will be extracted from our database, which includes study characteristics, year of publication, study design, types of HA, and the outcomes of each study. The IELT outcomes and penile circumference were compared before and after the HA injection. Adverse event outcomes and patient satisfaction were assessed descriptively in the observation period of each study.

We used the mean \pm standard deviation of each result to be pooled in the forest plot computation using the Open Meta Analyst application. Studies with high heterogeneity were analyzed using the DerSimonian and Laird random-effects model.

Assessment of methodologic quality

This systematic review includes RCTs, cohorts, and case-control studies. The quality of the RCT study was

assessed by the Cochrane risk-of-bias tool for randomized trials (RoB 2). For cohort studies, we use the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool to assess the risk of bias (Littara et al. 2013). Only minimal and moderate quality studies were included in the pooled effect estimate calculation.

Results

Literature search

We found 76 articles on the first search (hit), of which 23 were duplicated manuscripts and these 23-manuscripts were removed. A total of 53 articles were included (based on the title and abstracts) to be proceeded for screening process. Of these 53 articles, ten articles followed the systematic review of PICO and they were selected. Then, we analysed these ten studies further by seeking at the full-text articles, and we found none of these manuscripts met the exclusion criteria. The PRISMA flowchart is displayed by the following Fig. 1 during our search.

Study characteristics

That the ten prospective interventional studies were selected (based on the inclusion criteria), only one manuscript was published before 2010 which is a study conducted by Kwak et al., in 2008. The total samples calculated from the selected manuscripts were 613 pa-

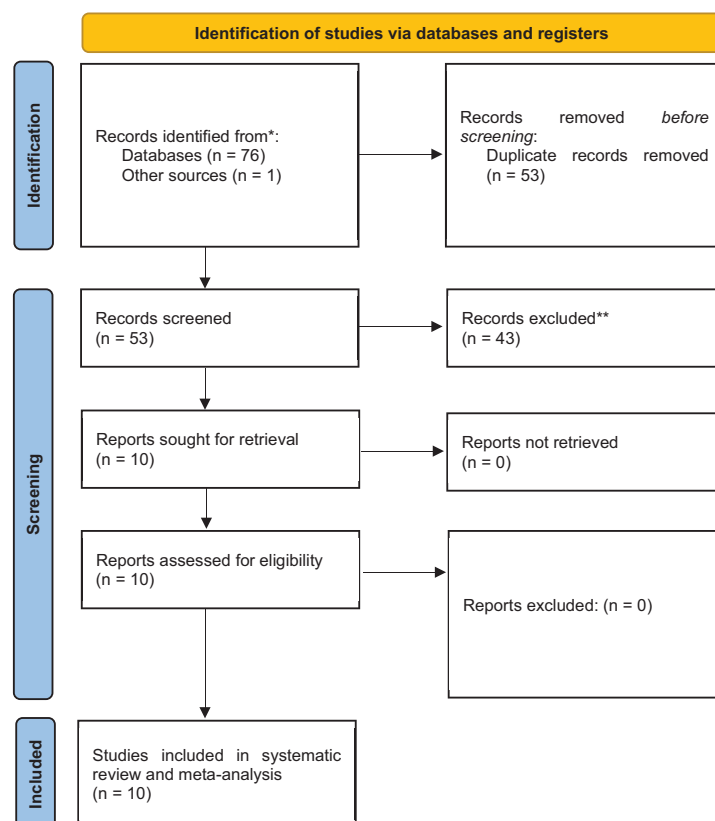


Figure 1. PRISMA flowchart describing the process for identifying included articles.

tients and was summarized in Table 3. There is a reasonably heterogeneous variation in hyaluronic acid (HA) dosage between among all studies, which is a volume range of 1–3 mL. In the selected manuscripts, the HA injection is performed into the glans penis. Although almost all of the studies report satisfactory outcomes after HA injection, the types of instruments used vary widely. Therefore, the outcomes are presented narratively in Table 2.

Risk of bias from included studies

Since all selected studies are in prospective trials, the Cochrane Risk of Bias (RoB) assessment was used to evaluate the risk of bias. Only one study showed a high risk of reporting bias as the authors did not report an outcome mentioned in the method section (Abdelazeem and Esawy 2019). Most of the studies did not mention how they measured the IELTS, and some also did not use validated questionnaires to evaluate the patient or partners' satisfaction rate after intervention as seen in Fig. 2.

Intravaginal estimated latency time (IELT)

All the selected articles reported a significant increase in the latency time in the first month after HA injection. Studies conducted by Abdallah et al. (2011) and Kewei et al. (2022) reported that IELT increased to more than four times compared to the baseline. However, the changes in latency time from baseline in both of the two studies were highly heterogeneous ($I^2 = 99.68\%$, $p < 0.001$). Overall, there was a significant difference between the IELT baseline and 1-month after HA injection with treatment mean of 217.035 seconds (95% CI, 89.330–344.739) as seen in Fig. 3.

Changes in latency time in three months after treatment were reported in 6 studies as seen in Fig. 4. In this 3-months of observation, these studies also reported a significant difference in latency time compared to those in the baselines. The pooled treatment mean was recorded at 161.53 seconds (95% CI, 37.262–285.764) with $p < 0.001$, and high heterogeneity among studies were found ($I^2 = 99.7\%$).

Table 2. Literature finding's result.

Database	Keywords	Hit
Pubmed	(((((IELT[Title/Abstract]) OR (latency[Title/Abstract])) OR (intravaginal latency[Title/Abstract])) AND (((penile girth[Title/Abstract]) OR (glandular circumference[Title/Abstract])) OR (penile circumference[Title/Abstract]))) AND (acid, hyaluronic[MeTerms SH])) AND (((premature ejaculation[Title/Abstract]) OR (rapid ejaculation[Title/Abstract])) OR (early ejaculation[Title/Abstract]))	3
Cochrane	"premature ejaculation" in Title Abstract Keyword AND "hyaluronic acid" in Title Abstract Keyword AND "IELT" OR "intravaginal latency" OR "satisfaction" OR "penile girth" OR "glandular circumference" in Title Abstract Keyword - (Word variations have been searched)	6
EBSCO	premature ejaculation AND hyaluronic acid AND (IELT	10
Host	OR latency time OR satisfaction OR penile girth OR glandular circumference)	
EMBASE	('premature'/exp OR premature) AND ('ejaculation'/exp OR ejaculation) AND hyaluronic AND ('acid'/exp OR acid) AND (((ielt OR 'latency'/exp OR latency) AND ('time'/exp OR time) OR 'satisfaction'/exp OR satisfaction OR penile) AND girth OR glandular) AND ('circumference' /exp OR circumference)	10
Proquest	(Premature Ejaculation) AND (Hyaluronic Acid) AND (IELT OR latency time OR satisfaction OR penile girth OR glandular circumference) Filter: article	47

Table 3. Characteristics of the study included in this systematic review.

No.	Author	N	Design	Intervention	Primary Outcomes	Secondary Outcomes
1	Abdallah et al. (2011)	60	SA	2 mL HA (1.54 mg/mL)	IELT 1 and 3 months	–
2	Abdelazeem et al. (2019)	20	SA	3 mL HA (not mentioned)	IELT 1, 3, and 6 months	Patient satisfaction (AIPE Q5–Q6); Adverse event
3	Kewei et al. (2022)	85	SA	0.8–2.4 mL HA	IELT 1, 3, and 6 months	Patient satisfaction (Self rated 0–3); Adverse event
4	Kwak et al. (2008)	38	SA	2 mL HA (Per lane)	IELT 6 months; Glandular circumference (GC) increment 6 months; Vibratory threshold	Patient satisfaction; Partner satisfaction (%)
5	Littara et al. (2013)	171	SA	1 mL HA (33 mg/mL)	IELT 6 months; GC 6 months	Patient satisfaction; Partner satisfaction (self-rated 1–10)
6	Perri et al. (2022)	31	SA	8 mg HA	PEDT and IELT 1, 2, and 3 months	Patient satisfaction (IIEF-5)
7	Sakr et al. (2022)	34	SA	2 mL HA (not mentioned)	IELT 1, 3, 6, and 12 months	Patient satisfaction (%); Adverse event
8	Ahn et al. (2021)	64	DA	2 mL HA (23 mg in total)	IELT 6 months; Penile Girth 1, 3, and 6 months	Patient satisfaction (self-rated 1–5); Adverse event
9	Alahwany et al. (2019)	30	DA	1 mL HA (25 mg/mL)	IELT 1 week and 1 month; AIPE score 1 month; PE category changes after 1 month	Patient satisfaction (AIPE); Adverse event
10	Shebl et al. (2021)	80	DA	2–4 mL HA (23 mg/mL)	IELT 1, 3, and 6 months; GC 1, 3, and 6 months	Patient satisfaction; Partner satisfaction (%)

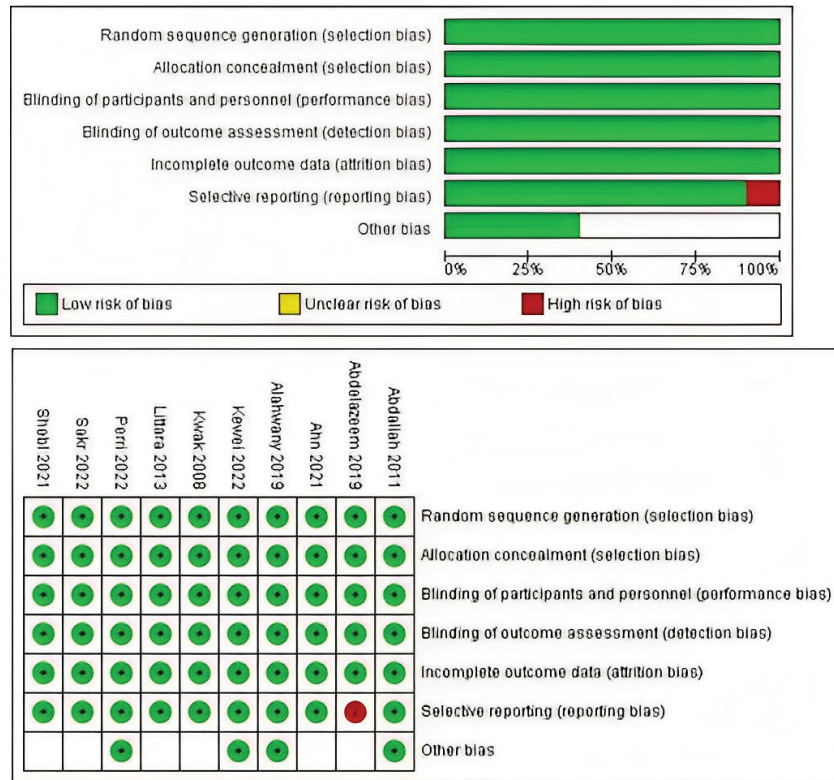


Figure 2. Risk of bias assessment results via Cochrane Risk of Bias analysis (RoB).

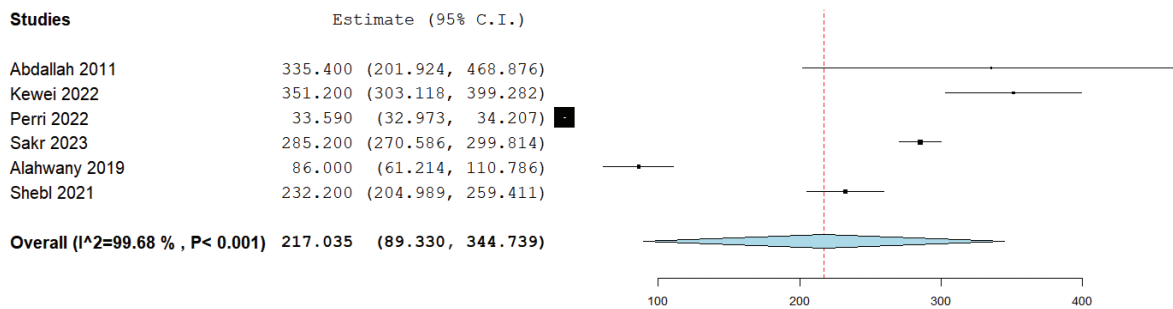


Figure 3. Comparison of IELT between baseline and 1-month after treatment.

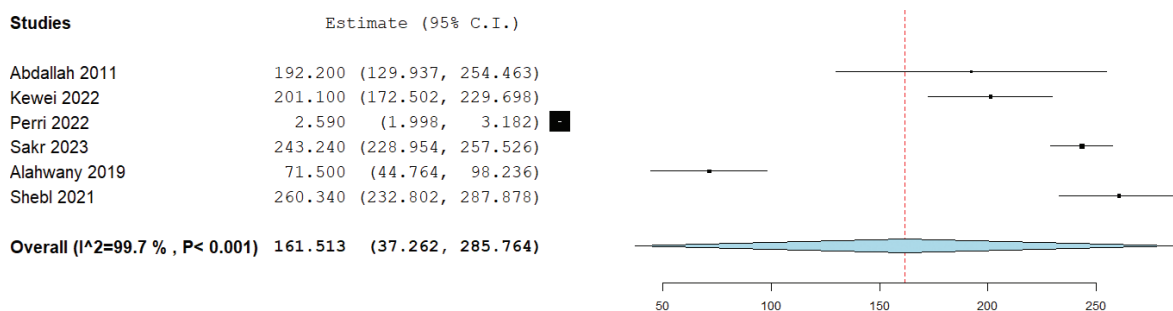


Figure 4. Comparison of IELT between baseline and 3-months after treatment.

At six months of post-injection, IELT scores were found to decrease gradually from 1 and 3 months in all studies. However, the IELT score remained higher than the baseline 196.350 seconds (95% CI, 196.350–250.386, $p < 0.001$). What needs to be underlined is that there is a vast variation in the IELT value among studies, both in baseline data and 6-month after treatment data (seen in Fig. 5). Thus, heterogeneity among studies below was found to be high ($I^2 = 99.78\%$).

Glandular circumference

All studies evaluating the glandular circumference demonstrated a significant increase compared to those in the baseline results. Shebl et al. (2021) and Ahn et al. (2021) reported a gradual increase in glandular circumference during the first and third months after treatment. Moreover, Kwak and co-workers have also reported an increase

by 16.58 ± 0.85 mm in the circumference in 6-months of post-treatment. Overall effect calculation using the forest plot shows a significant difference in glandular circumference between the baseline and six-months after treatment ($p < 0.001$), as shown in Fig. 6.

Satisfaction rate

Each study reported a satisfaction rate (for both patients and their partners) in a different outcome measure shown in Table 4 below. Only a study conducted by Perry and team (2022) have reported a decrease in satisfaction rate, although the IELT score increased significantly. The rest of the studies reported an increase in satisfaction rate compared to those in the baseline.

Studies	Estimate (95% C.I.)
Abdelazeem 2019	104.160 (100.556, 107.764)
Kewei 2022	157.500 (131.601, 183.399)
Kwak 2008	292.500 (273.753, 311.247)
Sakr 2023	243.240 (228.954, 257.526)
Littara 2013	204.800 (203.166, 206.434)
Ahn 2021	150.000 (2.391, 297.609)
Shebl 2021	198.170 (156.940, 239.400)
Overall ($I^2=99.78\%$, $P < 0.001$)	196.350 (142.314, 250.386)

Adverse event

Off all selected manuscripts, the post-operative side-effects were found to be minimal after the HA administration. Abdallah et al. (2011) reported the occurrence of pain and bullae formation at the injection site (28.57%), which then resolved in a matter of days without any additional medication. On the other hand, Kewei et al. (2022) reported the incidence of skin necrosis and vascular embolism in 1.2% and 2.4% patients after receiving HA treatment, respectively. A month after the treatment, these two complications had been in complete resolution with treatments. In overall, there were no systemic complications or organ failure due to the adverse events after the treatment as seen in Fig. 7.

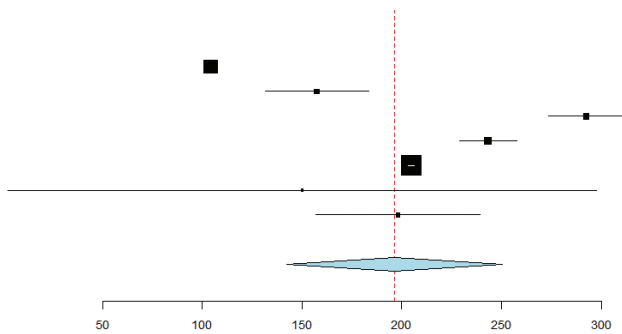


Figure 5. Comparison of IELT between baseline and 6-months after treatment.

Studies	Estimate (95% C.I.)
Abdelazeem 2019	15.100 (14.634, 15.566)
Littara 2013	15.840 (15.659, 16.021)
Shebl 2021	11.760 (10.159, 13.361)
Ahn 2021	1.130 (0.711, 1.549)
Overall ($I^2=99.93\%$, $P < 0.001$)	10.956 (3.314, 18.598)

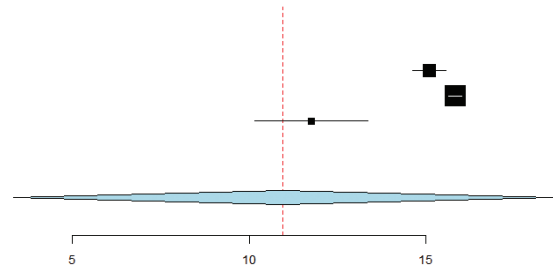


Figure 6. Comparison of glandular circumference between baseline and 6-months after treatment.

Studies	Estimate (95% C.I.)	Ev/Trt	Ev/Ctrl
Ahn 2021	0.667 (0.119, 3.726)	2/32	3/32
Alahwany 2019	6.000 (0.768, 46.870)	6/30	1/30
Shebl 2021	0.727 (0.327, 1.616)	8/40	11/40
Overall ($I^2=NA$, $P=0.144$)	1.067 (0.561, 2.029)	16/102	15/102

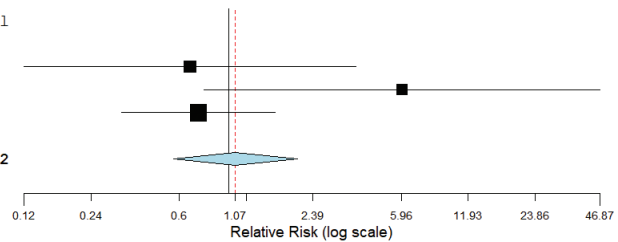


Figure 7. Comparison of adverse event rate between HA and the control groups.

In this review, only three studies directly compared the adverse events of HA administration with placebo groups, which have previously been demonstrated to have no harmful effects on the human bodies. Measurement of the overall effects reported by each study via the Mantel-Haenszel fixed-effect model showed no differences in the proportion of adverse events between the HA and control groups (relative risk for HA group of 1.067 (95% CI, 0.561–2.029)). Heterogeneity among studies was not significant ($p = 0.14$).

Discussion

This meta-analysis attempts to present the usefulness of injectable hyaluronic acid (HA) in improving the latency time of those with premature ejaculation (PE). The PE can be defined as a sooner ejaculation that happens uncontrollably during sexual activities, affecting at least a third of global male population (Kosseifi et al. 2020). Ejaculation itself occurs during a sensation distributed within the autonomic

Table 4. Outcomes of each study.

No.	Author	Age	IELT	GC	Adverse event	Patient satisfaction	Partner satisfaction
1	Abdallah et al. (2011)	38 + 55	Base: 127.2 + 69.6 1-M: 462.6 + 471.6 2-M: 319.2 + 211.2	NR	28.57%	NR	NR
2	Abdelazeem et al. (2019)	32.5 + 5.9	SA	Base: 90.5 + 0.7 6-M: 105.6 + 0.8	0%	Base: 1.6 + 0.07 6-M: 6.2 + 0.08 P<0.05	Base: 1.48 + 0.06 6-M: 5.5 + 0.07 P<0.05
3	Kewei et al. (2022)	32.2 + 5.3	Base: 321.6 + 210.6 1-M: 120 + 66.21 3-M: 325.8 + 71.26 6-M: 282.2 + 62.38	NR	25.81%	Base: 0.604 1-M: 3.16 3-M: 2.81 6-M: 2.613 P<0.05	NR
4	Kwak et al. (2008)	37.7 + 4.62	Base: 84.2 + 36.1 6-M: 376.7 + 57.73	6-M increment: 16.58 + 0.85	0%	6-M: 76.32%	6-M: 65.79%
5	Littara et al. (2013)	32.78 + 0.33	Base: 88.34 + 3.14 6-M: 293.14 + 8.16	Base: 98.51 + 0.71 6-M: 114.35 + 0.66	0%	Base: 1.2 + 0.04 6-M: 5.3 + 0.07 P<0.001	Base: 1.3 + 0.05 6-M: 5.1 + 0.09 P<0.001
6	Perri et al. (2022)	40.5 + 2.60	Base: 38.65 + 1.21 1-M: 72.24 + 1.27 3-M: 41.24 + 1.17	NR	0%	Base: 51.5 + 2.29 1-M: 53.88 + 1.89 6-M: 48.13 + 1.6 P>0.05	NR
7	Sakr et al. (2022)	41.72 + 8.50	Base: 37.83 + 11.01 1-M: 323.03 + 42.06 3-M: 281.07 + 41.05	NR	10%	6-M: 83.33%	6-M: 70%
8	Ahn et al. (2021)	40.47 + 12.12	Base: 321.6 + 210.6 6-M: 471.6 + 283.8	Base: 81.75 + 9.86 1-M: 109.25 + NA 3-M: 107.47 + NA 6-M: 104.33 + NA	6.25%	Base: 2.13 + 0.55 3-M: 3.45 + 1.03 6-M: 3.25 + 1.11 P<0.05	NR
9	Alahwany et al. (2019)	33.3 + 5.3	Base: 34 + 20.35 1-M: 120 + 66.21 3-M: 105.5 + 71.89 6-M: 85 + 59.54	NR	20%	Base: 15.93 + 2.12 1-M: 20.9 + 7.9 P = 0.03	NR
10	Shebl et al. (2021)	39.73 + 8.97	Base: 44.8 + 8.84 1-M: 277 + 123.86 3-M: 305.14 + 125.36 6-M: 242.97 + 132.75	Base: 96.89 + 1.58 1-M: 107.92 + 7.12 3-M: 108.65 + 4.92 6-M: 104.62 + 3.85	20%	1-M: 64.86% 3-M: 70.27% 6-M: 78.38%	1-M: 54.05% 3-M: 48.65% 6-M: 59.46%

nerves to the glans penis, received by number of receptors. Moreover, this sensation is influenced by the threshold and accessibility of the stimuli to these receptors. The lower the accessibility of stimuli from the receptors to the center would be difficult to experience, which formed difficulties in sensation. This mechanism becomes the basis for the reason of PE treatment that aims to suppress the distribution of stimuli as well as increasing the threshold of stimulation at local receptors to the central nervous system. (Kim et al. 2004).

The HA acts as a bulking agent, blocking accessibility and inhibiting tactile stimulation to reach the nerve receptors (Kim et al. 2004). By being injected into the dermis of the glans penis just above the nerve terminals, this would prolong the latency time in PE patients (Kim et al. 2004) HA is also a glycosaminoglycan with a significant component which is stable, non-toxic, non-allergenic, and non-inflammatory. Thus, HA is a safe chemical substance with excellent long-term effectiveness (Zucchi et al. 2022)

Various studies have reported the effects HA on IELT, such as Abdallah and team (2011) reported a nearly 4-fold increase in IELT from baseline (Abdallah et al. 2012). Similarly, Kewei and co-workers (2022) found improvements in the IELT score from baseline within 1-month, 3-month, and 6-month after treatment by injecting the HA into two

sites (glans penis and around the coronary sulcus). Even more, a more extreme increase in IELT score that was up to 8-fold from baseline at 1-month after treatment has been reported by Sakr et al. (2022) from 37.83 ± 11.01 to 323.03 ± 42.06 seconds (Kosseifi et al. 2020).

The IELT score variously occurs and gradually decrease after treatments. Compared to the baseline, a gradual decrease appears at three and six months of post-treatments. No studies have reported an improvement in IELT in three months after injection, compared to those in 1-month post-treatment. Similarly, at 6-month after treatment, the latency time would also decrease; nevertheless, the scores have never been to reach the baseline level. The highest decrease of latency time was reported by Alahwany et al. (2019) after 6 months of treatment, from 120 ± 66.21 seconds (1 month after treatment) to 85 ± 59.54 seconds. This figure seems to be continuously declining at 9-months after treatment to only 45 seconds (baseline time was 34 ± 20.35 seconds). However, a significant difference was still recorded on 9-month after treatment (Alahwany et al. 2019).

Glandular circumference (GC) was also found to be higher than the baseline. This increase in GC was assumed to have correlation with an increase in satisfaction of the

patients and their sexual partners. Littara and co-workers (2013) have found a more than 4-fold increase in sexual satisfaction scores compared to the baseline scores at 6-months after treatment. The same study also found an increase in glandular circumference from 98.51 ± 0.71 mm to 114.35 ± 0.66 mm at 6-months after treatment (El-Hamd et al. 2019). Similarly, Kwak et al. (2008) reported an increase of GC by 16.58 ± 0.85 mm at 6-months after treatment (Kwak et al. 2008).

However, Shebl et al. (2021) and Kwak et al. (2008) have reported low rates of sexual satisfaction. There were 76.32% of satisfaction in the patients and 65.79% in their partners, while under 60% of both patients and their partners were found after 1-month to 6-months of post-injection, respectively. The feeling of sexual satisfaction at 3-month after treatment was found in almost a half of patient partners (Kewei et al. 2021). It should be underlined that the studies used instruments to measure sexual satisfaction, which was not scientifically validated. Perri et al. (2022) used the IIEF questionnaire to measure sexual satisfaction. Overall and Intercourse satisfaction were reported to have increased at 1-month and 2-months after treatment in this study. Sexual satisfaction is multifactorial, and latency time and glandular circumference are not the only influencing factors. Therefore, the instrument for successful premature ejaculation, defined as ejaculation occurring earlier than expected, should be assessed based on latency time.

One of the limitations in the administration of HA as a minimally invasive procedure is a direct risk after injection during the preparation of glans penis. None of the selected studies reported any serious adverse events as it is reported by Ahn et al. (2021) that showed post-injection inflammation in small number of patients (6.3%), which

has been resolved by conservative therapy alone (Ahn et al. 2022). Abdallah and team (2011) recommended the multiple puncture techniques to reduce the number adverse events, which showed a smaller number of the adverse-event rate for 26.9% (30.4% for the fan technique) (Abdallah et al. 2012).

This meta-analysis has succeeded in providing an overview of the efficacy on injectable HA in improving patient's conditions with PE. There was a significant increase in IELT up to 6-months after treatment, an increase in glandular circumference, and an increase in satisfaction scores based on scientifically validated instruments. This therapy also has a low risk of complications. However, some weaknesses need to be highlighted in this meta-analysis, (1) a high heterogeneity among studies suggest various outcomes compiled in forest plots, required a random-effect of measurements, (2) differences in types of punctures may lead to various results, (3) the strength of HA is also varied in among studies. Thus, these three features would appear to have different results and outcomes, experienced by both the patients and their sexual partners.

Conclusion

Hyaluronic acid effectively increased the IELT of patients with premature ejaculation at one, three, and six months after treatment without any serious adverse events. This therapy also increased glandular circumference and sexual satisfaction with the patient and the patient's sexual partner. Further studies evaluating sexual satisfaction with validated instruments were needed to ensure that hyaluronic acid provides practical patient benefits.

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