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Effects of One-Shot Hyaluronic Acid Injection in Lifelong Premature Ejaculation: A Pilot Study

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Abstract: The therapeutic management of premature lifelong ejaculation (PE) ranges from behavioral therapy to pharmacological and surgical treatments. Hyaluronic Acid (HA) injection into the glans penis is a non-surgical procedure, intended to reduce glans hypersensitivity, improving the intravaginal ejaculation latency time (IELT). HA injection can be performed through different techniques that, although safe and effective, rarely can cause local complications. In this pilot uncontrolled study, we tested the effectiveness of a new technique based on a single HA injection into the frenulum of the glans, to improve IELT in a sample of patients affected by PE. We observed a significant increase of the IELT after one (median 73.3, IQR 66.2–79.9 s) and two months (66.2, 63.1–73.9) that gradually decreased at three months, remaining still significantly higher than at baseline (34.8, 30.9–37.4). PEDT and IIEF questionnaires significantly improved compared to baseline in the first two months of follow-up ($p < 0.001$). In conclusion, the preliminary results emerging from this pilot uncontrolled study, highlight the effectiveness of this one-shot HA injection approach, although a larger sample and longer follow-up time are needed to standardize the procedure.

Keywords: premature lifelong ejaculation (PE); intravaginal ejaculation latency time (IELT); hyaluronic acid (HA); HA injection

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1. Introduction

Premature ejaculation (PE) is the most common type of ejaculation dysfunction, affecting about 5−10% of the male population. According to the International Society of Sexual Medicine's (ISSM) Guidelines, PE is a male sexual dysfunction characterized by: (i) ejaculation that always or nearly always occurs before or within about 1 min of vaginal penetration from the first sexual experience (lifelong premature ejaculation) OR a clinically significant reduction in latency time, often to about 3 min or less (acquired premature ejaculation); (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; (iii) negative personal consequences, such as distress, bother, frustration, and/or the "avoidance of sexual intimacy" [1].

The etiopathogenesis of PE is multifactorial, as psychological and many biological factors have conventionally been responsible for this [2]. Therefore, many therapies could be applied, including behavioral therapy, topical anesthetics, antidepressants, such as serotonin re-uptake inhibitors and tricyclic antidepressants, phosphodiesterase-5 inhibitors, and opiate analgesics, such as tramadol [3]. However, the recurrence after withdrawal and the local and systemic adverse effects resulting from the pharmacological treatments, are sometimes unacceptable for patients [4,5]. In addition to pharmacotherapies, procedures

can be used to reduce glans hypersensitivity and improve the intravaginal ejaculation latency time (IELT), such as the selective dorsal neurectomy and the hyaluronic acid injection into the glans penis [6]. The latter is a technique in which hyaluronic acid (HA) is injected into the glans to create a barrier between the skin and the dorsal nerve branches, providing penis analgesia and slowing the ejaculatory reflex [7]. The gland augmentation with HA is a feasible and safe technique, but not frequently applied for both its technically challenging aspects (fan technique or multiple puncture technique) and yet unproven outcomes because most of the studies lack long-term follow-up; furthermore, the available studies have been conducted according to extremely heterogenous inclusion and exclusion criteria [7,8]. Finally, the proper patient selection is crucial, as this procedure should be used among patients in which pharmacotherapy has failed. Therefore, large randomized prospective studies are required to confirm the safety of this procedure and to verify its efficacy over the long time.

In this pilot study, we have tested the efficacy of a new technique based on a single HA injection into the dermis at the level of the frenulum of the glans, to improve IELT in a sample of patients affected by lifelong premature ejaculation.

2. Materials and Methods

2.1. Patients

All the outpatients with lifelong PE attending the Andrology Unit of Magna Graecia University of Catanzaro and the CURE2CHILDREN foundation in Florence between January and December 2021 meeting the recruitment criteria were enrolled in this study. PE was defined according to the ISSM definition and PE severity was assessed using the Premature Ejaculation Diagnostic Tool (PEDT), a five-item unidimensional measure that captures the major aspects of ejaculation status diagnosis: control, frequency, minimal stimulation, distress, and interpersonal difficulty [9]. Inclusion criteria were a stable heterosexual relationship for at least 12 months. Exclusion criteria were a history of medication that can affect ejaculation six months before the beginning of the study, a history of drug abuse and/or alcoholism, current major psychiatric disorder, erectile dysfunction, or other forms of sexual dysfunction. IELT, a measure defined as the time between the start of vaginal intromission and the start of intravaginal ejaculation, was evaluated for each couple, which received instructions on the IELT measurement techniques, in which partners were to activate the supplied stopwatch on vaginal penetration during sexual intercourse and to stop the stopwatch on either intravaginal ejaculation or withdrawal without ejaculation. Baseline IELT was defined as average IELT measured during the four weeks before HA injection.

At the baseline, all patients showed (i) a formal IELT < 1 min in most of the sexual attempts (>75%), (ii) a PEDT score > 11, and (iii) an IIEF score above 22, after written informed consent. IELT, PEDT, and IIEF-5 questionnaires, plus a satisfaction interview, were performed at 30, 60, and 90 days after treatment. Furthermore, all patients were instructed to immediately report any discomfort or pain.

Serum total testosterone, prolactin, FSH, LH, PSA, glycemia, total cholesterol, HDL, LDL, triglycerides, and hemoglobin were assessed before enrolling. No other medication of psychotherapy was allowed during the study period.

2.2. Hyaluronic Acid Injection

The present study was performed according to the Helsinki declaration. All patients signed the informed consent. Eight milligrams of hyaluronic acid sodium salt (IBSA), without local anesthesia, were injected with a 27 G needle at the level of the dermis of the frenulum of the prepuce, corresponding to a triangle that we have named **MONAVER** (abbreviation from inventors, **Mon**daini-**Aver**sa), as reported in Figure 1. After the injection, a light compressive dressing was applied to the penis for 24 h. All patients completed the VAS SCALE for pain (data not shown).

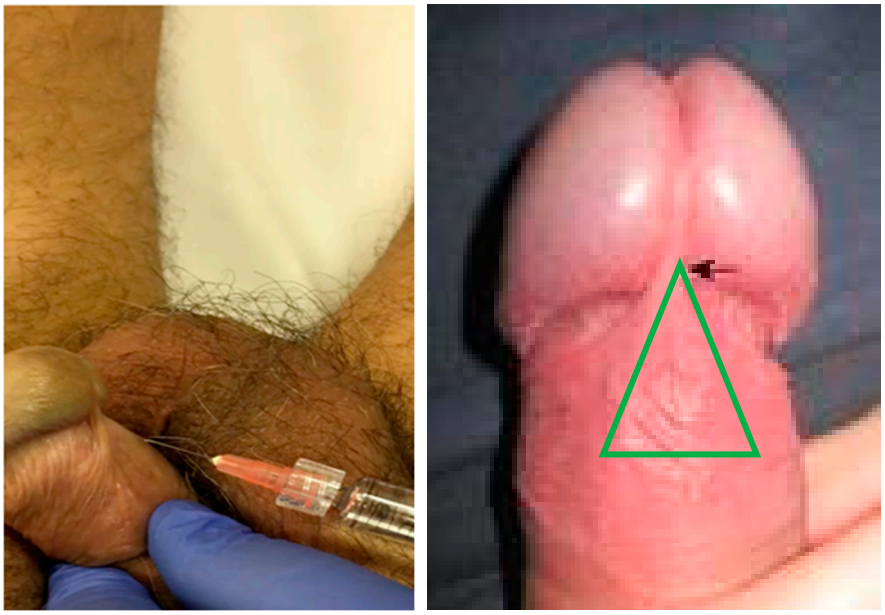

Figure 1. HA gel injection technique (**left panel**) into the MONAVER Triangle area (**right panel**).

Ejaculation-delaying techniques, condoms or topical anesthetic cream, and behavioral therapy were not permitted. Sexual activity was forbidden for 24 h after the procedure.

2.3. Statistical Analysis

Data are presented as median (IQR). Pairwise comparisons of results at follow-up visits versus baseline values were made using the Wilcoxon signed-rank test and calculating the fold increase of the IELT geometric mean [10], Bonferroni correction was applied to adjust *p*-values for multiple comparisons. A *p*-value of 0.05 was considered significant. All statistical analyses were performed with R (v. 4.2.1, R Foundation for Statistical Computing, Vienna, Austria).

3. Results

Thirty-one patients were enrolled, and Table 1 shows their characteristics at baseline. The median age was 40 years (IQR 36.5–45.5). The majority of patients were overweight, with no alterations in glucose and lipid profile. Moreover, all patients showed normal levels of gonadotropins, prolactin, total testosterone, TSH, and PSA. No significant report of pain at VAS SCALE was reported (data not shown).

3.1. HA Injection Effect on IELT

As showed in Table 2 and Figure 2, the IELT resulted significantly higher at 30 ($p < 0.001$), 60 ($p < 0.001$), and 90 days after HA treatment ($p < 0.05$) when compared to baseline levels.

Differences in IELT ranged from 50 to 11 s after 30 days (87% mean IELT increase) and from 46 to 4 after 60 days (65% mean IELT increase) from treatment, with 21 (67.7%) and 18 (58.1%) patients showing at least a 75% IELT improvement after 30 and 60 days, respectively. Even if statistically significant, IELT measurements after three months from treatment (7% mean IELT increase) resulted in similar values to IELT baseline values, ranging from 13 to −7 s.

3.2. PEDT and IIEF Questionnaires before and after HA Injection

Table 3 shows the results of the PEDT and IIEF questionnaires at baseline and each follow-up visit.

Table 1. Characteristics of the enrolled patients.

	Median (IQR)
Age (years)	40 (36.5–45.5)
Glucose (mg/dL)	89 (83.5–96)
BMI (Kg/m^2)	25.8 (24.15–26.85)
HGB (gr/dL)	14.8 (14.15–16.3)
Total Cholesterol (mg/dL)	200 (195.5–211.5)
HDL Cholesterol (mg/dL)	57 (48–66)
LDL Cholesterol (mg/dL)	120.8 (104.8–135)
Tryglicerid (mg/dL)	96 (83–146)
LH (mUI/mL)	5.5 (4.75–6.15)
FSH (mIU/mL)	6.4 (5.3–7.75)
TT (ng/dL)	418 (322–534)
PRL (ng/mL)	7.7 (4.89–12.15)
PSA (ng/mL)	2.54 (1.94–3.04)
TSH (μIU/mL)	2.56 (1.14–3.62)

Table 2. IELT mean and median values at baseline and 30, 60, and 90 days after HA injection and relative increase.

Days	**Geometric Mean (SD)**	**Median (IQR)**	**Folder Increase (95% CI)**	***p***
Baseline	38.65 (1.21)	40 (33–44)	-	-
30	72.24 (1.27)	79 (62–85.5)	1.87 (1.84–1.9)	<0.0001
60	63.75 (1.35)	72 (47–80.5)	1.65 (1.58–1.72)	<0.0001
90	41.24 (1.17)	41 (37.5–45.5)	1.07 (1.05–1.08)	0.018

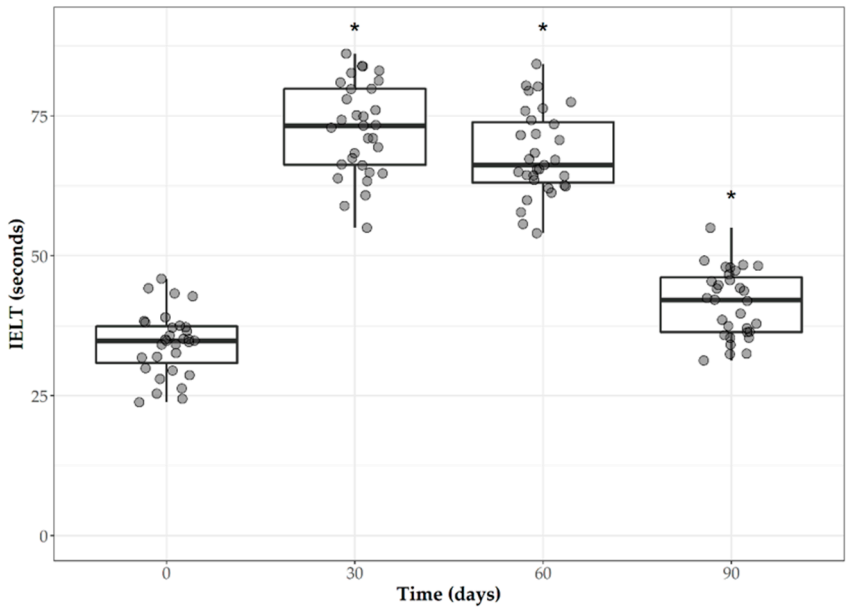

Figure 2. IELT before (0) and 30, 60, and 90 days after HA injection. * < 0.001 vs. baseline.

Table 3. Score of PEDT and IIEF questionnaires at different study protocol times. * < 0.001 vs. baseline.

	Baseline	30 Days	60 Days	90 Days
PEDT	14 (13–15)	12 (11–13) *	12 (11–13) *	15 (13–15)
IIEF	52 (47–51)	54 (50.5–57)	51 (49–53)	48 (45.5–51)
Erectile Function	29 (26–28)	27 (26–28)	27 (25.5–27)	26 (25–27.5)
Orgasmic Function	7 (5–6.5)	6 (5–7)	5 (5–6)	5 (5–6)
Sexual Desire	7 (6–7)	6 (6–7)	6 (5–7)	6 (5–7)
Intercourse Satisfaction	6 (5–7)	10 (6–11) *	7 (6–8) *	6 (5.5–7)
Overall Satisfaction	3 (3–4)	5 (5–6) *	6 (4–7) *	4 (4–5)

PEDT results were significantly lower ($p < 0.001$) after 30 and 60 days from HA treatment. IIEF showed a similar pattern trend toward improvement only after 30 days after the injection. Taking into account IIEF sub-scores, only Intercourse Satisfaction ($p < 0.001$) and Overall Satisfaction ($p < 0.001$) showed significantly higher values, while the Erectile and Orgasmic Function, as well as the Sexual Desire and Orgasmic sub-scores, did not seem influenced by the HA treatment. No data regarding aesthetic improvement reported after HA injection are available.

4. Discussion

In this pilot study, we observed that a single injection of HA at the frenulum of the prepuce promoted a significant increase of IELT at three-months follow-up in a small cohort of patients affected by premature lifelong ejaculation. The procedure was very well tolerated and without adverse reactions. Furthermore, the self-rated patients' and partners' sexual satisfaction, defined by PELT and IIEF questionnaires, significantly improved compared to baseline during the observational period.

It has been reported that, although lifelong PE is usually considered to be associated with emotional distress, it may be due to 5-HT2C hyposensitivity and or 5-HT1A hypersensitivity, but also to peripheral penile hypersensitivity [11–13]. On-demand dapoxetine is the first approved medication for treating lifelong PE, and although its effectiveness and safety have been proven by randomized and placebo-controlled trials, the rate of treatment discontinuation is high, mainly because of relapsing after drug withdrawal and side effects [14–17]. Furthermore, the Genetics of Sex and Aggression study in Finland suggested that 28% of phenotypic variance in PE may be related to genetics, and, hence, although to date no association between life-long PE and serotonin transport polymorphisms has been found, it is reasonable that the poor responsiveness to SSRI could depend on the genetic background of the patient [18,19]. For these reasons, over the past few years, a growing interest has been developed in the non-surgical approaches for PE treatment, in particular towards the use of HA injection, which represents a less invasive and easier approach compared to the selective dorsal neurectomy.

The hyaluronate molecule, besides being highly polar, water-soluble, and hypoallergenic, is an efficient lubricant, making it the ideal candidate for increasing soft tissue volume and being used as a filler. The injection of HA as a bulking agent within the glans dermis represents a local treatment for PE, intending to act as a barrier inhibiting the tactic stimuli, thus delaying the ejaculatory reflex [20]. Different techniques, all needing local anesthesia, are commonly used to inject HA into the glans: the "fan technique", by which HA is injected subcutaneously at one-third from the tip of the glans toward the coronal sulcus by rotating the needle to both sides during the injection, and multiple puncture technique, where multiple points of entry are created starting from proximal one-third of the glans along the coronal sulcus together with the frenulum [7]. Although safe, few complications following this procedure have been described, most of which can resolve spontaneously without further side effects, although they can cause negative psychological effects on the patients [21].

In the current pilot study, we adopted a new and fast technique, in which a single dose of HA was injected at the frenulum of the prepuce, and it was painless, such that it

did not require local anesthesia. The goal of this technique is not so much to induce the aesthetic glans augmentation but to reduce/inhibit the prepuce stimuli, thus delaying the ejaculatory reflex and strongly reducing the onset of penile complications. As reported in Figure 2, in this study, we observed a significant increase in IELT after one month, as well as in PEDT and IIEF subscales regarding satisfaction (Table 3), and, even if we observed a gradual decrease in IELT, at three months post-injection IELT reported by patients was still significantly higher than baseline. Our preliminary results agree with previous studies obtained by using different techniques of HA injection; in particular, to date, three prospective single-arm studies [20,22,23], one randomized non-controlled trial [24], and one randomized controlled trial [25] demonstrated that HA treatment improved IELT, that it was safe and well-tolerated, showing lasting effects up to 6–12 months follow-up and with reported side effects ranging from 0% to 30% across all studies [26].

Even though it is a pilot study, we are aware that it has some limitations: first, it is an uncontrolled study, and needs a validation results vs. matched placebo. Furthermore, the sample size of enrolled patients is too small; therefore, it will be increased to demonstrate the safety and the effectiveness of this new technique. Finally, to date, we do not perform a follow-up time sufficient enough to allow asserting that the increased IELT, observed up to three months, is maintained over time, at least up to 6–12 months. The latter information is crucial, as we believe that our procedure is less invasive, painless, and almost without complications for the patient, compared to the procedures adopted in previous studies; therefore, the patient may not be reluctant to repeat this procedure over the time, according to standardized time intervals.

5. Conclusions

We demonstrate for the first time that a single HA injection at the MONAVER triangle of the penis can improve IELT in men with lifelong premature ejaculation. This represents the first demonstration that a mini-invasive procedure may represent an alternative to oral SSRI administration, especially in patients where polypharmacy or reluctance make treatment decision very difficult. Differently from other techniques, this one has the advantage to permit the patients to resume sexual activity after 24 h from the procedure with immediate benefits on IELT. Whether repeated injections over time may yield some additional advantage is under current investigation and results are warranted.

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Data Availability Statement: Not applicable here.

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Conflicts of Interest: The authors declare no conflict of interest.

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