



Hyaluronic Acid Treatment Modalities of Premature Ejaculation

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Abstract

Background: Hyaluronic acid (HA) or hyaluronan is a linear nonsulphated glycosaminoglycan found commonly in the vertebrate extracellular matrix (ECM). It forms a strikingly viscoelastic matrix, which in part serves as a medium for connective tissue cells and it has been implicated in chondrogenesis and cartilage homeostasis, embryonic development, immunomodulation, wound healing, and a variety of disease processes, including arthritis, malignancies, and pulmonary and vascular disease, together with other immune and inflammatory disorders. Hyaluronic acid in specific is now used in the form of gel injections which were injected in the dermis of the penile skin just above the nerve terminals, allowing to achieve a volume sufficient to prevent Premature ejaculation and reduce the intensity of stimuli reaching sensory receptor's. Study evaluated the effect of hyaluronic acid in 60 men affected by PE, demonstrating that (IELT) increased 1 month after the injection of the compound in their penis. Multiple studies showed that HA injection could significantly increase the intra-vaginal latency time (IELT) (2.43- to 4.46-fold), and this increase could persist for long term (up to 5 years)

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Introduction

Premature ejaculation (PE) is a highly prevalent male sexual dysfunction that is often neglected, presenting a currently unmet therapeutic need. The classification of PE has historically been varied and at times ambiguous, contributing to inaccurate prevalence estimates. This review uses the International Society for Sexual Medicine (ISSM) definition of PE, which includes reduced ejaculatory latency, lack of control and associated negative personal consequences. Patient assessment and management options differ depending on the classification of PE and it is the role of the clinician to appropriately classify patients and be aware of the correct management strategies. This review provides an overall background of PE in terms of classification and underlying physiology, patient assessment and management strategies along

with the scientific rationale for treatment. Patients with lifelong and acquired PE are most likely to benefit from combination therapy of pharmacological treatment in the form of selective serotonin re-uptake inhibitor dapoxetine, psychosexual behavioural therapy and psychological therapy. **(1).**

Diagnosis of PE is based on the patient's medical and sexual history. History should classify PE as lifelong or acquired and determine whether PE is situational (under specific circumstances or with a specific partner) or consistent **(2).**



Patient Management

The management of a patient presenting with PE will depend on the cause and classification of PE. It is therefore important for the clinician to firstly determine if there is an underlying cause for the PE. Common underlying causes include concurrent erectile dysfunction, sexual performance anxiety and interpersonal relationship problems. The underlying cause of premature ejaculation should be managed first, followed by secondary treatment of PE if the symptoms do not remediate after treating the primary causes. It is also important during the management stage to set treatment goals with each patient and partner if appropriate, in order to better guide therapeutic actions. (2).

Hyaluronic acid (HA) or hyaluronan is a linear nonsulphated glycosaminoglycan found commonly in the vertebrate extracellular matrix (ECM)(3). It forms a strikingly viscoelastic matrix, which in part serves as a medium for connective tissue cells and it has been implicated in chondrogenesis and cartilage homeostasis, embryonic development, immunomodulation, wound healing, and a variety of disease processes, including arthritis, malignancies, and pulmonary and vascular disease, together with other immune and inflammatory disorders(4).

Hyaluronic Acid Structure:

Hyaluronic acid is a straight-chain glycosaminoglycan (GAG). It is the only GAG not attached to a core protein, and of the major GAGs, it is the only one not sulfated. It is a β -chain polymer composed entirely of repeating disaccharides of β -D-glucuronyl-(13)-N-acetyl-D-glucosamine connecting through β (14) linkages (5).

Hyaluronic Acid Function:

Increasing data suggest that HA may be involved in a number of functions within cells. HA was present intracellularly in locations such as the nucleus, rough endoplasmic reticulum, and caveolae(6)

Hyaluronic acid is present in the ECM, on the cell surface, and inside the cell. It is useful therefore to broadly divide the functions of HA into those associated with the organization of the ECM, those associated with a formation of a HA coat on the cell surface, those associated with receptor-mediated signaling, and those associated with the intracellular presence of HA (7)

In addition to its functions in tissue hydration and assembly of matrices, HA exerts influences on cell behavior by interacting directly with the cell surface, leading to signal transduction and cytoskeletal rearrangements.

HA interacts with the cell in at least two ways: by binding to cell surface receptors, such as CD44 and RHAMM, or by sustained attachment to HA synthase across the plasma membrane (8).

Hyaluronic acid has also been implicated in regenerative processes such as wound healing and as a key mediator of the immune process (9).

Hyaluronic Acid Degradation:

Despite the increasing importance of HA in biology (and the recognition of its extraordinarily rapid rate of turnover, surprisingly little is known about the degradation of HA. A 70-kg individual has 15 g of HA, a third of which turns over daily. Between different tissues, rates of turnover vary widely (5).

Hyaluronic acid polymers are degraded into monosaccharides by three enzymatic reactions.

Hyaluronidases (Hyal) degrade HA polysaccharides to oligosaccharides, which are



further digested into glucuronic acid (GlcA) and N-acetylglucosamine (GlcNAc) by β -D glucuronidase and β -N-acetyl-D-hexosaminidase, respectively (10)

Hyaluronic acid degradation and removal in the body occurs via two clearance systems: one is in the lymphatic system, which accounts for 85% of the HA turnover and another system is hepatic, accounting for 15% of the total body HA turnover (11)

Hyaluronic acid injection in glans penis for treatment of premature ejaculation:

Mechanism of action:

The human glans penis is covered by stratified squamous epithelium and a dense layer of connective tissue parallel to the dermis of typical skin. The papillary dermis is continuous with and blends into the dense connective tissue forming the tunica albuginea of the corpus spongiosum of the glans penis. Free nerve endings are present in almost every dermal papilla, and also the most numerous nerve terminals are scattered throughout the deeper dermis(12),the injection of HA to the deep dermal layer act as volume sufficient barrier that prevent or decrease the tactile nerve stimulus from reaching free nerve ending in the deep dermis (13)

Results:

Hyaluronic acid (HA) derivatives are the most widely used biodegradable fillers in both Europe and the USA (14) .

Hyaluronic acid in specific is now used in the form of gel injections which were injected in the dermis of the penile skin just above the nerve terminals, allowing to achieve a volume sufficient to prevent Premature ejaculation and reduce the intensity of stimuli reaching sensory receptor's (15) .

Study evaluated the effect of hyaluronic acid in 60 men affected by PE, demonstrating that (IELT)

increased 1 month after the injection of the compound in their penis (16) .

Multiple studies showed that HA injection could significantly increase the intra-vaginal latency time (IELT) (2.43- to 4.46-fold), and this increase could persist for long term (up to 5 years) (17).

In another study twenty-three patients (46.9%) received injection by the fan technique, while 26 patients (53.1%) received it through the multiple-point technique. The mean IELT increased significantly from 2.12 ± 1.16 to 7.71 ± 7.86 min, after 1 month of injection and then dropped to 5.32 ± 3.52 min, but still remaining significantly higher than the baseline values ($P < 0.001$) (13)

Furthermore, another study reported positive results in a 5-year long-term study in which hyaluronic acid gel was injected in 38 men. They demonstrated that IELT decreased if compared to 6-month follow-up, but it was still higher if compared with the pretreatment period. The patients and their partners reported high satisfaction for the procedure consisting in 76% and 63%, respectively(5).

In a 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 (IELT) and the Arabic validated index of premature ejaculation (AIPE). (18) .

After a wash-out period, cross-over and re-evaluation of both groups were carried(18) .

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 , a significant difference after 1 month of injection in comparison with baseline IELT ($p < 0.001$) and after 1 week ($p < 0.001$). **(18)** .

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**(18)** .

A significant difference found by **AmrAlahwany et al. (18)** 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 **(18)** .

Injection techniques:

1-Fan shape technique and one third technique:

Kim et al. (19) applied a glans penis augmentation under local anesthesia, after 30 min local application of Emla (lidocaine and prilocaine), 2 cc of injectable HA gel, 27-gauge needle is used to inject parlanes at proximal one-third from tip of glans to coronal sulcus ensuring that the needle is placed subcutaneously. Thin by fan shaped technique HA is injected. After injection of Perlanes, undulation of glandular surface was supplemented by injection of Restylanes via 30-gauge needle. 20 mg/mL of stabilized HA gel is the concentration used in both parlanes and Restylanes. The difference between the products is the size of the gel particles. Approximate number of gel particles is 100,000/mL in Restylanes and 1,000/mL in

Perlanes. The suppliers Advice 30-gauge needle for injecting Restylanes into the mid to upper part of dermis and 27-gauge needle for Perlanes that is injected in the deep layer of the dermis **(20)**

Same HA method was used by **Kwak et al. (17)**. without describing the details of the surgical procedure **(17)**. **Abdallah et al. (13)** in the other hand adopted tow techniques.

2-Multiple puncture technique:

This technique was developed to allow more uniform distribution of the injected material. Using a 27-gauge needle, multiple points of entry were created starting from proximal one-third of the glans along the coronal sulcus together with the frenulum after application of the topical anesthetic. At each point, only 0.25 mL was injected**(13)**

3-Three circle technique:

Littara et al. (15) performed local anesthesia by injecting with a 28-G needle containing 1 mL of 1% lidocaine and prilocaine.

The circumference of the glans penis was divided into three circles, from the base of the glans at a 1-cm distance from each other. The circles were then divided into quarter circles.

An injection containing 1 mL HA, Variofill, was performed in the deep dermis into every quarter circle with a 27-G needle for a total of 12 injections performed in a single session.

4-The two-circle technique:

In 2019, **Alahwany et al. (18)** modified the technique used by **Abdallah et al. (13)** Under topical anesthesia (30 min of Emla cream), two prefilled 1 ml syringes of cross-linked HA were injected with 30 G needle (Teosyal) using multiple puncture technique 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 performed at



coronal level and four in the second level, each injection containing 0.2 mL into deep dermis. All participants were previously circumcised.

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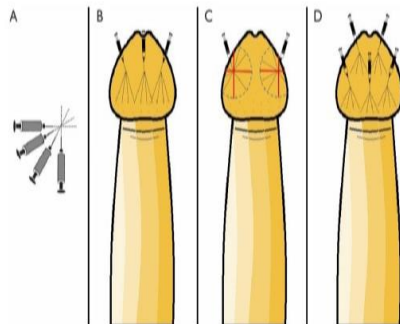


Figure (1):Injection techniques. (A) The fan technique; (B) (19) one-third technique; (C) the three circles technique; (D) the two circular levels technique

5-five puncture technique:

Xylocaine Jelly 2%: lidocaine 20 mg (Aspen, Sweden) was applied to the skin as a local anesthetic for 30 minutes before the injection of 2 ml hyaluronic acid (HA; STYLAGE® IPN Like TECHNOLOGY, VIVACY Laboratories, Paris, France) in glans penis via 30-gauge needle using new five-puncture technique. The glans penis was divided by a horizontal line into two halves; the distal half was divided by a vertical imaginary

line into two compartments, and the proximal half was divided into three compartments by two vertical imaginary lines, the above-mentioned design was used to ensure the

maximum equal distribution of the HA with least number of injections; each compartment was injected in the deep dermis with 0.4 ml HA with total 2ml over the glans(21).

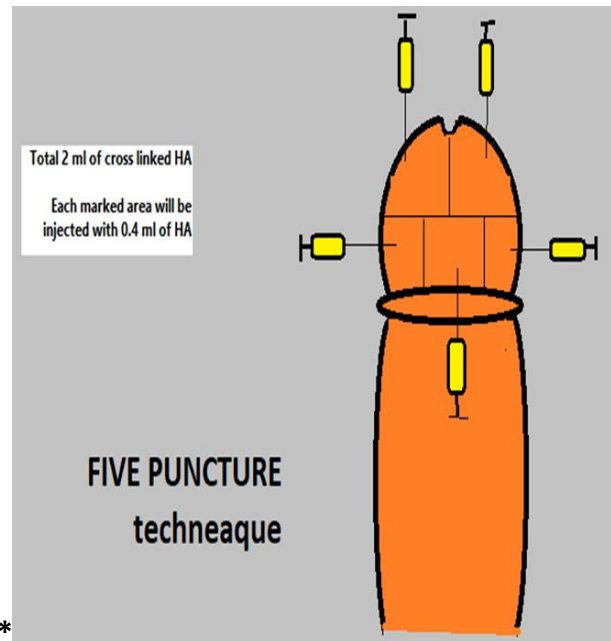


Figure (2) five puncture technique (21).

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