

ORIGINAL ARTICLE

Treatment of premature ejaculation by glans penis augmentation using hyaluronic acid gel: a pilot study

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Summary

Premature ejaculation (PE) is by far the most common male sexual complaint, with millions of men affected all over the world. It is estimated that up to 20–30% of all men may be suffering from various forms of PE. A variety of filler materials are widely used nowadays for soft tissue augmentation. The appropriate filler can restore symmetry, volume and create a smooth skin surface. The aim of this pilot study was to evaluate the therapeutic effect of hyaluronic acid gel injection in patients with PE. Sixty men with self-reported PE who were referred to our outpatient andrology clinic (between January 2007 and January 2008) were included in this study. Participants were randomly assigned using random sampling numbers into two distinct groups. Group A ($n = 30$) received a single injection of 2 ml of hyaluronic acid gel (Hyalift 3.5% micronised hyaluronic acid) using the previously described fan technique. Group B ($n = 30$) received a single injection of 2 ml of hyaluronic acid gel using the multiple puncture technique. 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 intravaginal ejaculation latency time (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. Results from our present pilot study demonstrated the usefulness of the application of hyaluronic acid dermal fillers in the treatment of PE; however, further investigations in large cohorts with longer follow-up are definitely needed to obtain more consistent results.

Introduction

Premature ejaculation (PE) is by far the most common male sexual complaint, with millions of men affected all over the world. It is estimated that up to 20–30% of all men may be suffering from various forms of PE (Bejma & Hellstrom, 2007). Historically, there has been much debate on the accurate definition of PE. Nowadays, most sexual medicine specialists prefer to follow well-constructed and evidence-based definitions of PE formatted by international organizations, such as the international Society for Sexual Medicine (McMahon *et al.*, 2008) and the American Psychiatric Association the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition

(DSM-IV-TR) (American Psychiatric Association, 2000). While these definitions, indeed, differ in their wording, however, they have certain common features: the relatively short time interval between penetration and ejaculation; diminutive or absence of voluntary control of ejaculation; and negative consequences, such as distress.

Multiple treatment modalities exist for PE, including pharmacological, behavioural, combination therapy and, very recently, acupuncture (Hellstrom, 2011). Several placebo-controlled reports have confirmed the efficacy of the selective serotonin-reuptake inhibitors (SSRIs), whether used daily or on-demand, as first choice of treatment in PE. For example, paroxetine, sertraline and fluoxetine are all used nowadays in patients with PE (Arafa & Shamloul,

2007; Hosseini & Yarmohammadi, 2007; Althof *et al.*, 2010). However, none of these SSRI have gained official license to be used in patients with PE worldwide. Interestingly, dapoxetine, a new SSRI with a short half-life, has become available in some countries for on-demand treatment of Feige *et al.* (2011). Other oral drugs tried for the treatment of RE include tricyclic antidepressants, phosphodiesterase-5 inhibitors and tramadol but with little supportive evidence to recommend further wide-scale usage (Althof *et al.*, 2010).

A variety of filler materials are widely used nowadays for soft tissue augmentation. The appropriate filler can restore symmetry, volume and create a smooth skin surface. Filler materials can be classified according to biodegradability into two categories: biodegradable (resorbable and nonpermanent) fillers that include collagens, hyalans and fat and nonbiodegradable (nonresorbable and permanent) fillers that include silicone, calcium hydroxylapatite, polymethylmethacrylate, polylactic acid and polyalkylamide (Jordan, 2003).

The aim of this pilot study was to evaluate the therapeutic effect of hyaluronic acid gel injection in patients with PE.

Patients and methods

Sixty men with self-reported PE who were referred to our outpatient andrology clinic (between January 2007 and January 2008) were included in this study. All men were circumcised, heterosexual and sexually active with no other sexual disorder. Patients with chronic psychiatric or systemic diseases, such as diabetes mellitus; with hypertension; with alcohol or substance abuse; or who used any medications were excluded. None of the men had received any treatments for PE previously. This study was approved by our local institutional ethics committee. Informed consent was obtained from all study participants.

The intravaginal ejaculation latency time (IELT) and the DSM-IV TR criteria (American Psychiatric Association, 2000) were used to assess PE before and after treatment. Men were recruited with self-reported IELTs of ≤ 2 min in $>70\%$ of coital attempts. IELTs before and after treatment were calculated using a partner-held stopwatch. Participants were randomly assigned using random sampling numbers into two distinct groups. Group A ($n = 30$) received a single injection of 2 ml of hyaluronic

acid gel (Hyalift 3.5% micronised hyaluronic acid) using the previously described fan technique (Kim *et al.*, 2004) where a topical anaesthetic cream Emla[®] (lidocaine 25 mg, prilocaine 25 mg, Astra Xeneca, Mississauga, Canada) is applied for 30 min and 2 cc of injectable hyaluronan (HA) gel (Hyalift[®], Aesthetic Dermal, Spain) was injected via 27-gauge needle. Injection needle was pushed subcutaneously at the proximal one-third from tip of glans penis to coronal sulcus, and thereafter, the needle is rotated to both sides to inject the material. Group B ($n = 30$) received a single injection of 2 ml of hyaluronic acid gel using the multiple puncture technique where the HA gel is injected using 27-gauge needle but with multiple points of entry starting from proximal one-third of the glans along the coronal sulcus together with the frenulum after application of the topical anaesthetic. At each point, only 0.25 ml was injected. This technique was developed by our group as it has the advantage over the fan technique in that it allows more uniform distribution of the injected material. Also, on the basis of our experience, this technique is associated with less pain, because the size of the bulla created is smaller than that created using the fan technique. IELTs of all patients were recorded before 1 month prior to the start of therapy and 1 and 3 months after the injection. Post-injection adverse reactions were also reported.

Computer software package spss 15.0 (IBM Corp., Armonk, NY, USA) was used in the analysis. For quantitative variables, mean standard deviation/range, minimum and maximum were presented. Frequency and percentages were presented for qualitative variables. Mann-Whitney and Wilcoxon signed ranks tests were used to estimate the differences in quantitative variables. Chi-square test was used to estimate differences in qualitative variables.

Results

Only 49 (81.6%) of 60 patients completed the study, while 11 patients dropped out during the follow-up period. The mean (SD) age of all patients was 38 ± 8.55 years (22–54). Table 1 illustrates the demographics of all patients. 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

Table 1 Demographics of all patients (mean \pm SD, range)

Patient's Age (years)	Partner's age (years)	Marriage duration (years)	Intercourse Frequency/week	Duration of PE (min)
38 ± 8.55 (22–55)	32.9 ± 8.8 (18–50)	10 ± 7.6 (1–29)	2 ± 1.1 (0.5–40)	1.9 ± 1.1 (0.5–55)

PE, Premature ejaculation.

then dropped to 5.32 ± 3.52 min, but still remaining significantly higher than the baseline values ($P < 0.001$) (Table 2). There were no significant differences between both groups concerning IELT recorded at baseline and 1 and 3 months after injection (Table 3). Seven patients had complications with multiple puncture technique, and seven patients had complications with the fan technique. The percentage of complications was 30.4% for the fan and 26.9% for the multiple puncture techniques. Complications included mild pain and bullae formation at site of injection. None of the complications opted any patient out of the study.

Discussion

Despite poor understanding of premature ejaculation, the main pathophysiology of premature ejaculation is a complex psychological phenomenon. The effects of glans penis augmentation using filler might be the results of reduced sensation of glans penis by the formation of barrier for stimuli to access the receptor and increased self-esteem (Kim *et al.*, 2004). Injectable soft tissue substitutes provide an affordable, nonsurgical alternative for correcting contour defects and soft tissue augmentation. The ideal filling substance for soft tissue augmentation should be biocompatible, nonantigenic, nonpyrogenic, noninflammatory, nontoxic, easy to use, stable after injection, nonmigratory, long lasting but absorbable, natural looking and not too expensive (Elson, 1995). A ubiquitous component of all mammalian connective tissues, HA is a

naturally occurring polysaccharide, in the same chemical and molecular composition in all species; in the intercellular matrix of dermal layers of the skin of all species, therefore, it is highly biocompatible to use animal sources in humans without creating foreign body reactions (Larsen *et al.* (1993). The material used in this study is based on HA, which has already been used in its native form as an implant for more than 20 years and in millions of individuals without causing adverse reactions. In this study, there were no serious adverse reactions in all cases.

Although the efficacy of HA was proved in various fields, the existence of potential space, technical feasibility and long-term residence should be identified to use injectable HA gel in augmentation of glans penis. The feasibility of glans penis augmentation by injectable HA in an animal experiment was previously demonstrated (Moon *et al.*, 2002). In that study, HA gel was easily injected into the Beagle dogs via 27-gauge needle for elastic glans and showed long-term residence in the lamina propria.

In this human study, it was not difficult to inject HA into the dermis of glans penis because of its elastic nature. Most clinicians are familiar with the fan technique, which is frequently used to make subcutaneous bulla for skin test of hypersensitivity and for easy dissection of subcutaneous tissues. Another technique we used is the multiple puncture injection carrying the advantages of more surface area coverage, frenulum injection, with more volume of the material injection. In contrary, as it was suggested, pain was less with the multiple puncture. Disadvantages of the multiple puncture technique include longer injection time and higher risk of bruising, which was found in seven cases in the study and resolved completely within few days. In this study, the effect of the injected material was maintained until 3 months with significant difference in IELT, when comparing before and after 3 months of injection. The slow digestion of this gel shows that stabilisation of the material through cross-linkage is able to increase its longevity several 100-folds compared to the natural polymer, without decreased biocompatibility. The implant has a property of degradation but has a characteristic of isovolemic degradation. The isovolemic degradation keeps the gel always in balance with water in the tissue, and this increased capacity to bind water of a less concentrated hyaluronan network, allows maintaining the correction even in low concentrations of the materials. In this study, 1 and 3 months post-injection ejaculatory latency was significantly increased compared with pre-injection baseline mean IELT ($P < 0.001$). Kim and colleagues (Kim *et al.*, 2004), in a similar study, evaluated their study subjects 6 months after injection. The IELT increased from 1.6 to 5.5 mins. There was no significant difference regarding the mean IELT

Table 2 IELT (min): baseline, 1 and 3 months post-injection of all patients ($n = 49$)

	IELT (mean \pm SD), range
Baseline	2.12 ± 1.16 (0.5–5)
After 1 month	7.71 ± 7.86^a (0.5–30)
After 3 months	5.32 ± 3.52 (0.5–20) ^{a,b}

IELT, Intravaginal ejaculation latency time.

^a $P < 0.001$ versus baseline.

^b $P < 0.001$ versus 1 month.

Table 3 Shows mean IELT (min) before and 1 month after injection by both techniques

	Fan ($n = 23$)	Multiple puncture ($n = 26$)
	23	26
IELT (baseline)	2.39	1.96
IELT (1 month post-injection)	7.4	7.9

IELT, Intravaginal ejaculation latency time.

between fan and multiple-point injection techniques. This may be explained by the fact that the same gel amount was injected by both techniques. It seems that multiple puncture technique has the possibility of injecting easier more amounts of filler as compared to the fan technique.

The advantages of this technique over local anaesthetic creams or the use of condom is the long-term effect obtained without decreasing the pleasure of intercourse or the risking the potential of decreased level of sensation and excitation of the female when using the anaesthetic creams. Also, many couples do not prefer to use condoms as they interfere with the sensation, pleasure and spontaneity of sexual intercourse.

Limitations of our study include the absence of a placebo group and the limited number of study participants. Results from our present pilot study demonstrated the usefulness of the application of hyaluronic acid dermal fillers in the treatment of PE; however, further investigations in large cohorts with longer follow-up are definitely needed to obtain more consistent results.

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