

Effects of glans penis augmentation using hyaluronic acid gel for premature ejaculation

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The main limitation of medical treatment for premature ejaculation is recurrence after withdrawal of medication. We evaluated the effect of glans penis augmentation using injectable hyaluronic acid (HA) gel for the treatment of premature ejaculation via blocking accessibility of tactile stimuli to nerve receptors. In 139 patients of premature ejaculation, dorsal neurectomy (Group I, $n = 25$), dorsal neurectomy with glandular augmentation (Group II, $n = 49$) and glandular augmentation (Group III, $n = 65$) were carried out, respectively. Two branches of dorsal nerve preserving that of midline were cut at 2 cm proximal to coronal sulcus. For glandular augmentation, 2 cc of HA was injected into the glans penis, subcutaneously. At 6 months after each procedure, changes of glandular circumference were measured by tapeline in Groups II and III. In each groups, ejaculation time, patient's satisfaction and partner's satisfaction were also assessed. There was no significant difference in preoperative ejaculation time among three groups. Preoperative ejaculation times were 89.2 ± 40.29 , 101.54 ± 59.42 and 96.5 ± 52.32 s in Groups I, II and III, respectively. Postoperative ejaculation times were significantly increased to 235.6 ± 58.6 , 324.24 ± 107.58 and 281.9 ± 93.2 s in Groups I, II and III, respectively ($P < 0.01$). The percentage of postoperative satisfaction in both patient and his partner was 68% (17/25) and 44% (7/16) in Group I, 80% (39/49) and 66% (25/38) in Group II and 75% (49/65) and 62% (32/52) in Group III, respectively. Maximal glandular girth was significantly increased from 9.16 ± 0.59 to 10.95 ± 0.4 cm in Group II and 8.95 ± 0.54 to 11.67 ± 0.71 cm in Group III, respectively. These results suggest that glandular augmentation with injectable HA gel is a safe and effective modality to reduce sensory of glans penis. Long-term follow-up for residual volume and efficacy should be requested to establish its precise therapeutic potentials in premature ejaculation.

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Introduction

Current treatment choice for premature ejaculation is medical treatment. The main limitation of medical treatment for premature ejaculation is recurrence after withdrawal of medication. Patients with primary premature ejaculation have penile hypersensitivity, which provides further implications for an organic basis of premature ejaculation.¹ In hypersensitivity of glans penis, various topical agents were applied, but the efficacies are still

controversial. Dorsal neurectomy is also created to decrease the sensitivity of glans penis.² Dorsal neurectomy is not an established treatment of penile hypersensitivity ejaculation due to the uncertain pathophysiology, invasiveness and side effects, for example, numbness paresthesia, pain for neuroma, Peyronie's disease and even erectile dysfunction. Despite these limitations, dorsal neurectomy is still performed in selective patients who do not respond to conventional treatment of premature ejaculation. Major contributing factors of sensory in glans penis are distribution of dorsal nerve, number of receptor, threshold of receptor and accessibility of stimuli to the receptor. Creation of barrier by bulking agent that inhibits the tactic stimuli to reach receptor may be effective in premature ejaculation. In the last decade, hyaluronic acid (HA) has been shown to possess many properties that suggest its value in several medical applications, particularly in ophthalmology, orthopedics, and soft-tissue aug-

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mentation with proven efficacy and safety.³⁻⁵ Recently, we also reported the feasibility of injectable HA gel in augmentation of glans penis *in vivo*.⁶ We performed this study to evaluate the effect of glans augmentation using injectable HA gel (Perlane[®], Q-Med, Uppsala, Sweden) for the treatment of premature ejaculation via blocking accessibility of tactile stimuli to nerve receptors.

Materials and methods

Patients

In all, 139 patients of primary premature ejaculation were recruited to this study. In 25 patients of Group I, dorsal neurectomy was carried out. In Group II of 49 patients, dorsal neurectomy with glandular augmentation using injectable HA gel was carried out. In 65 patients of Group III, glans penis augmentation by injectable HA gel was carried out.

Dorsal nerve neurectomy

Under local anesthesia with 1% lidocaine, circumcised incision was made at 2 cm proximal from coronal sulcus. Dorsal branch of dorsal nerve was cut at one side and lateral branch and ventral branch of the other side were cut under magnification.

Glans penis augmentation using injectable HA gel

Under local anesthesia, 30 min after topical application of anesthetic cream Emla[®] (lidocaine 25 mg, prilocaine 25 mg, Astra Xeneca), 2 cc of injectable HA gel (Perlane[®], Q-med, Uppsala, Sweden) was injected via 27-gauge needle. Injection needle was indwelled subcutaneously at proximal one-third from tip of glans to coronal sulcus; thereafter, HA

gel was injected by Fan technique (Figure 1). After injection of Perlane[®], undulation of glandular surface was supplemented by injection of Restylane[®] (Hyaluronic acid gel, Q-med, Uppsala, Sweden) via 30-gauge needle. Both Restylane[®] and Perlane[®] are injectable HA gel and have the same composition of 20 mg/ml of stabilized HA gel. The difference between the products is the size of the gel particles. The molecular weight of HA in its pure form can be determined. However, HA in its pure form is not stabilized. Injectable HA gel is chemically modified HA product to increase its longevity in the tissue and to form a gel. It is not relevant to talk about molecular weight, as it cannot be determined for a stabilized gel. Approximate number of gel particles is 100 000/ml in Restylane[®] and 1000/ml in Perlane[®], respectively. For this reason, Q-med recommends 30-gauge needle to inject Restylane[®] into the mid to upper part of dermis and 27-gauge needle to inject Perlane[®] into the deep layer of the dermis.

Evaluation

At 6 months after each procedure, ejaculatory latency, vibratory threshold of glans penis using a biothesiometer (Bio Medical Instrument Co., USA), patient's satisfaction and partner's satisfaction were compared, respectively. In Groups II and III, changes of glandular diameter were measured by tapeline to compare the net increase of maximal glandular circumference after augmentation of glans penis. Patient's subjective visual estimation of glandular size was requested to assess the residual volume of implants. The patients estimated the visual analogue scale from Grades 0 to IV: Gr 0, no residual volume; Gr 1, less than 25% of initial volume; Gr 2, less than 50%; Gr 3, less than 75%; Gr 4, more than 75% or nearly same as initial volume, respectively. Patient's satisfaction was also evaluated from Grades 0 to 4: Gr 0, very dissatisfied; Gr 1, moderately dissatisfied; Gr 2, about equally satisfied and dissatisfied; Gr 3, moderately satisfied; Gr 4, very satisfied, respectively. Partner's satisfaction was also

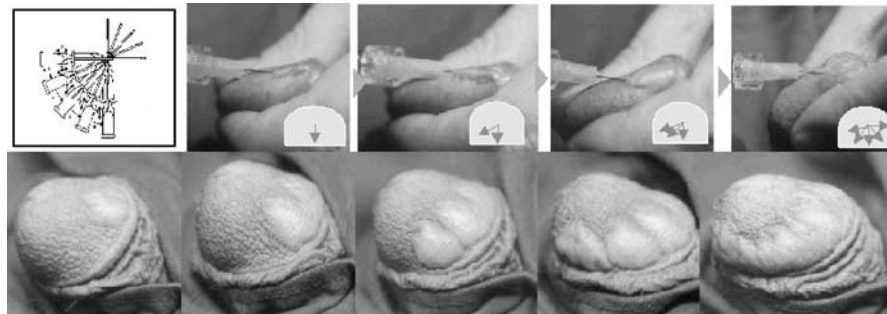


Figure 1 Injection needle was indwelled subcutaneously at proximal one-third from tip of glans to coronal sulcus; thereafter, HA gel was injected by Fan technique.

evaluated by telephone survey. Any adverse reactions were also evaluated.

Results

The mean age of patients was 43.2 (25–67) y in Group I and 41.8 (28–70) y in Group II, 42.1 (27–66) in Group III, respectively (Table 1). In all groups, postoperative ejaculatory latency and vibratory threshold were significantly increased compared to preoperative value (Table 1). There were no significant differences of ejaculatory latency and vibratory threshold among three groups. Maximal glandular circumference was significantly increased compared to basal circumference of 9.16 ± 0.59 cm in Group II ($P < 0.01$) and 9.95 ± 0.54 cm in Group III ($P < 0.01$) at 6 months after injection, respectively. The net increase of maximal glandular circumference after glans augmentation was 15.41 ± 0.82 mm in Group II and 16.58 ± 0.85 mm in Group III, respectively (Table 1, Figure 2). There was no significant difference between both groups. In patient's visual estimation of glandular volume after augmentation in Groups II and III, Gr 3 (more than 50% of injected volume) and Gr 4 (more than 75% of injected volume) was 26.5%, 61.2% in Group II and 24.6%, 65.2% in Group III, respectively. The mean grade of visual estimation was 3.49 in Group II and 3.55 in Group III, respectively. There was no significant difference in both groups. The percentage of postoperative satisfaction (Gr 3, 4) was 68% in Group I, 88% in Group II and 75% in Group III,

respectively. The mean grade of patient's satisfaction was high in Group II ($P > 0.05$). In Group II, mean postoperative ejaculatory latencies were 358.6 s in satisfied (Gr 3, 4) patients and 293.5 s in dissatisfied (Gr 0, 1) patients, respectively. In Group III, mean postoperative ejaculatory latencies were 331.5 s in satisfied (Gr 3, 4) patients and 288.9 s in dissatisfied (Gr 0, 1) patients, respectively. In Groups II and III, mean postoperative ejaculatory latencies of satisfied patients were significantly higher than those of dissatisfied patients, respectively ($P < 0.01$). In responding partners, postoperative satisfaction of partner was 44% (7/16) in Group I, 66% (25/38) in Group II and 62% (32/52) in Group III, respectively. There was no abnormal reaction in area feeling, texture and color. In most cases, initial discoloration by glandular swelling recovered to normal within 2 weeks in Groups II and III. Postoperative consistency of glans penis was natural without deformity and maintained through 6

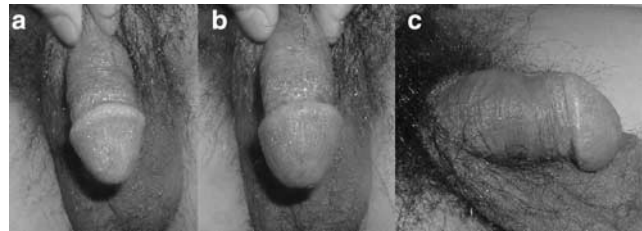


Figure 2 Representative figures of glans penis augmentation using injectable HA gel. Before augmentation, multiple tiny skin fold and smooth indentation from the tip of glans to proximal glans are clearly seen in dorsal view (a). After augmentation, indentations at the back of glans are elevated and skin folds are disappeared in dorsal view (b) and lateral view (c).

Table 1 Characteristics and parameters of all patients

	Group I	Group II	Group III
No. of pts	25	49	65
Age (y)	43.2 (25–67)	41.8 (28–70)	42.1 (27–66)
EL (s)			
Pre	89.2 (30–150)	101.5 (25–180)	96.5 (35–210)
Post	235.6 (210–430)*	324.2 (220–480)*	281.9 (250–420)*
VT (mA)			
Pre	4.14 (3–7)	4.38 (3–7)	4.54 (3–7)
Post	9.95 (8–12)*	9.80 (8–12)*	9.10 (8–12)*
GC (mm)	—	15.41 (13–16)	16.58 (12–17)
Pt's estimation (Gr)	—	3.49 (2–4)	3.55 (2–4)
Pt's satisfaction	68% (17/25)	80% (39/49)	75% (49/65)
Partner's satisfaction	44% (7/16)	66% (25/38)	62% (32/52)
Adverse reaction (%): numbness (6), paresthesia (4), pain for neuroma (3), Peyronie's disease (1)	24% (5/25)	20% (9/45)	0% (0/65)

Data are expressed as mean and min/max range.

Group I: dorsal neurectomy; Group II: dorsal neurectomy with glandular augmentation; Group III: glandular augmentation.

EL: ejaculatory latency, VT: vibratory threshold, *: $P < 0.01$.

GC: net increase of maximal glandular circumference.

Estimation of glans volume (Grades 0–4): Gr 0, 0%; Gr 1, less than 25%; Gr 2, 25–50%; Gr 3, 50–75%; Gr 4, 75–100% compared to initial volume.

months in Groups II and III. There were no signs of inflammation and no serious adverse reactions in all cases of Group III. In five patients of Group I and nine patients of Group II, numbness (6), paresthesia (4), pain for neuroma (3) and Peyronie's disease (1) occurred.

Discussion

Injectable soft-tissue substitutes provide an affordable, nonsurgical alternative for correcting contour defects and soft-tissue augmentation. Several materials have been used for this purpose, including paraffin, silicone and collagen.^{7,8} Paraffin and silicone create intense foreign body reactions and are known to migrate from injection sites. Collagen includes rapid degradation, which necessitates frequent reinjection and infrequent but significant hypersensitivity reactions.⁹ In recent years, implant materials have also been found to migrate to the lung and the brain.¹⁰ It is therefore advantageous to use degradable materials. 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 reabsorbable, natural looking and not too expensive.^{11,12}

A ubiquitous component of all mammalian connective tissue, HA (hyaluronan) 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.^{13–15} 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 y 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. Previously, we reported the feasibility of glans penis augmentation by injectable HA in animal experiment.⁶ In our 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 so difficult to inject HA into the dermis of glans penis. The nature of human glans penis is elastic and we developed the Fan technique. Most surgeons are already familiar with this technique, which is frequently used to make subcutaneous bulla for skin test of hypersensitivity and for easy dissection of subcutaneous tissues. In our animal study, we already revealed the potential space of lamina

propria in glans penis. Although the long-term residual volumes were not measured, the implants were well maintained until 1 y in this study. We used five-grade scale system. For more accurate estimation of glandular volume, 10-grade scale may be useful, but 10-grade scale is more demanding for patients. Through five-grade scale, patient's self-estimation of long-term residence was fairly good in both groups. The slow digestion of this gel shows that stabilization 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. Another advantage is easy supplementation by reinjection in cases of long-term volume loss. Like other fields of soft-tissue augmentation, there was no serious adverse reaction in this study. There was no abnormal reaction in area feeling, texture and color. In most cases, initial discoloration by glandular swelling recovered to normal within 2 weeks. In most patients, local application of anesthetic cream was sufficient, but a few presented penile pains.

Hypersensitivity of glans penis as a cause of premature ejaculation is still controversial. The skin of human phallus is innervated by the dorsal nerve of the penis (DNP). The main trunk of DNP is composed of two different populations of axons.¹⁶ The first group traveling along the dorsal midline and terminating in the glans. The other group of fibers radiated from the main trunk over the lateral and ventral aspects of the penile shaft with branches to the corpus spongiosum and urethra. At 1–2 cm proximal to the corona glandis, the DNP dorsal trunk divided into two to three nerve bundles. The DNP and its branches along the shaft run just beneath the skin and fascia, the main branches within the glans are 3–6 mm from the epithelial surface. The extent of nerve fibers, including in dorsal neurectomy, is important in postoperative sensory of glans penis. To avoid excessive sensory loss, dorsal branch at one side and ventral and lateral branches on the other side were excised in this study. Despite our efforts, numbness (6) and paresthesia (4) developed in 10 of 74 patients with dorsal neurectomy, while no patients presented sensory loss in 65 patients of glandular augmentation alone. Halata and Munger¹⁷ studied the sensory of the human glans penis. The human glans penis is covered by stratified squamous epithelium and a dense layer of connective tissue equivalent to the dermia of typical skin. The papillary dermis blends into and is continuous with the dense connective tissue forming the tunica albuginea of the corpus

spongiosum of the glans penis. The most numerous nerve terminals are free nerve endings present in almost every dermal papilla, as well as scattered throughout the deeper dermis. Genital bulbs are present throughout the glans, but are most numerous in the corona and near the frenulum. Considering the studies of Yang¹⁶ and Halata,¹⁷ injectable implants can be successfully injected into the dermis of glans penis just above the nerve terminal. In this study, injectable HA gel was easily injected into the dermis of glans and effectively decreased the sensory of glans penis. However, implants were not injected into the frenulum and corona glandis due to technical difficulty. In this study, the authors anticipated the additive effect of neurectomy with augmentation as measured by postoperative ejaculatory latency. In some patients, additive effects were seen but postoperative ejaculatory latency of Group II was not significantly different from those of Groups I and III. It maybe presumed that each neurectomy or glandular augmentation alone was enough to decrease glandular hypersensitivity. In each group, postoperative ejaculatory latency of satisfied patients was significantly higher than those of dissatisfied patients. Glans penis augmentation has additional benefit in premature ejaculation. The increased self-esteem and self-confidence from enlarged glans may act positively. Our study shows that dorsal neurectomy is effective in selective patients of premature ejaculation. However, major limitations are invasiveness, side effects and possibility of further sensory loss in longer period. Glans penis augmentation by injectable HA gel is not harmful and as effective as dorsal neurectomy in decreasing sensory of glans penis.

Conclusion

These results suggest that glandular augmentation with injectable HA gel is a safe and effective modality to reduce sensory of glans penis. Augmentation of glans penis is a promising treatment for hypersensitivity of glans penis in premature ejaculation patients. Long-term follow-up for residual volume and efficacy should be requested to estab-

lish its precise therapeutic potentials in premature ejaculation.

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