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Hyaluronic acid injection in the glans penis for the treatment of refractory premature ejaculation: A prospective, controlled study

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Abstract

We aimed to demonstrate the safety and efficacy of hyaluronic acid (HA) injection in the glans penis for the treatment of persistent premature ejaculation (PE). Eighty patients with persistent PE were divided equally into two groups. In group A, patients underwent HA injection by four-inlet injection technique, while in group B, patients were subjected to saline injection in glans penis by the same method as a control group. Patients were followed up for six months. At the end of follow-up, the IELT significantly improved in the HA injection group, as compared to the baseline values and control group. The maximal glandular circumference significantly increased at the 1st, 3rd and 6th month of follow-up. The rate of patient satisfaction with sexual intercourse was 64.9%, 70.3% and 78.4% at the 1st, 3rd and 6th month of follow-up, respectively. Besides, the partner satisfaction with sexual intercourse was 54.1%, 48.6% and 59.5% at the 1st, 3rd and 6th month of follow-up, respectively. In conclusion, HA injection may represent a promising treatment modality for persistent PE.

KEYWORDS

glans augmentation, hyaluronic acid, premature ejaculation

1 | INTRODUCTION

Premature ejaculation (PE) is the most common self-reported male sexual disorder estimated to occur in approximately 5% of men in the general community. The treatment of PE by medications that increase serotonin expansion in the brain has been successfully used. These incorporate specific serotonin reuptake inhibitors (SSRIs) for on-demand or day by day use, such as paroxetine, dapoxetine and clomipramine. Ejaculatory dysfunction typically begins in improvement within a week of starting the SSRIs. Nonetheless, SSRIs can lead to various forms of sexual disorders, such as anorgasmia, erectile dysfunction and decreased libido. Topical anaesthetic therapy, behavioural and combination treatment are recently believed to have a role in the treatment of PE. Alternatively, treatment of the cause is considered for the management of acquired PE (Althof, 2014).

Recently, the injection of bulking agents was proposed as a promising modality for PE; it acts by creating a barrier between the skin and nerve terminals to prevent tactile impulses from reaching receptors (Kosseifi et al., 2021). Such barrier can lead in return to decreased sensation in the glans penis and increased self-confidence due to the advantage of broadened glans (Moon et al., 2015).

However, the currently published studies, which assessed the injection of bulking agents, were applied to cases with PE. Thus, there is a lack of available data concerning the application of injectable agents in patients refractory to standard therapy. In this trial, we considered only refractory cases to explore whether hyaluronic acid (HA) injection can be considered as the last line therapy for the management of persistent PE (Kosseifi et al., 2021). The current study assessed the safety and efficacy of HA injection in the glans penis for the management of permanent PE.

2 | PATIENTS AND METHODS

2.1 | Study populations

We conducted a prospective, randomised, controlled study on 80 male patients with self-reported persistent PE, who failed to respond to any treatment (who failed to respond to continuous or in-demand intake of Dapoxetine, A combination of dapoxetine and behavioural treatment or other antidepressants for at least three months).

All patients were recruited from the outpatient clinics of Urology and Andrology Departments of Al-Azhar and Cairo University hospitals through the period from January 2017 to July 2020. Eligible patients were divided into two equal groups: A (patient group) and B (control group) each included 40 male patients. In group A, patients underwent HA injection by four-inlet injection technique, while in group B, patients were subjected to saline injection in glans penis by the same method as a control group. Eligible patients were randomly allocated by a computer software program (www.Randmizer.org), and allocation sequences were done by opaque closed envelopes.

The sample size was calculated using G* power version 3.1 for Windows. The expected difference between the study and control group was obtained from previous similar studies. This research achieved the approval of the Institutional Review Boards of Al-Azhar and Cairo University. All participants signed written informed consent before the study initiation.

2.2 | Inclusion and exclusion criteria

Adult (18–60 years old), sexually active, male patients were included if they were as follows: married once, well-educated, circumcised, heterosexual and presented with refractory PE, whether it was lifelong or acquired. Patients were included if they had a history of failed response to any optimisation measures for the treatment of PE. The PE was defined as self-reported intravaginal ejaculatory latency time (IELT) of ≤1 min from vaginal penetration in ≥50% of coital activities. Patients were taught to calculate IELT at least three times before starting the study by using a patient-held stopwatch. All patients underwent a one-month cessation period of any treatment before starting the injection of HA in the glans penis. All eligible patients should have normal serum testosterone, prolactin and thyroid hormonal profiles.

We excluded patients with history of erectile dysfunction, other sexual or ejaculatory disorders (such as retrograde ejaculation, secondary premature ejaculation or puberty disorders), acute or chronic prostatitis, debilitating diseases (such as liver cell failure, renal failure or severe uncontrolled diabetes), pelvic or spinal surgical operations, chemotherapy, radiotherapy, psychological drugs, drug abuse, penile prosthesis, penile deformity and/or hypersensitivity to any of HA preparations.

2.3 | Pre-injection evaluation

Before the injection, we collected the following data from eligible patients: age, duration of the marriage, profession, sexual history, infertility, PE characteristics, IELT, sexual contentment of both patient and his wife, drug intake, surgical and medical history of any illness, and International Prostate Symptom Score (IPSS) to exclude symptoms of prostatitis. General and systemic examinations were carried out, including examination of the penis (glans and shaft) with measurement of maximal glandular circumference, scrotum, both testicles, epididymis, vas deference and digital rectal examination. Evaluation of erectile function was assessed by the International Index of Erectile Function (IIEF) score and penile duplex.

2.4 | Injection Technique

Local anaesthetic spray (lidocaine spray), Xylocaine gel or cream (EMLA; Astra Zeneca) that contains a eutectic mixture of 2.5% lidocaine and prilocaine were applied to the glans penis for 30–45 min before injection. In the HA injection group, we applied a total of four injections of 2 – 4 ml of 23 mg/ml HA gel (Revofil Ultra Volume Body Contour Gel, Caregen Co.,) with a 27-G needle. The needle was injected subcutaneously at the coronal sulcus and frenulum through four inlet points, three for the coronal sulcus (right, dorsum and left sides) and the fourth for the frenulum, all in a retrograde pattern (Figures 1 and 2). The control group received an injection of normal saline (0.9%) solution by using a 27-G needle in the same technique.

Photographs of the glans penis were taken before and after the injection and evaluated. Patients were followed up in the first week after the injection for any changes in the injection site, one month, three and six months after the injection. The following items were evaluated during the follow-up period:

1. The IELT, which was measured by a stopwatch used by the patient himself.
2. Sexual satisfaction of both patient and his wife. The sexual satisfaction was evaluated by a four-grade scale: Grade 1 represented a very dissatisfied participant (0%–25%); Grade 2 represented a moderately dissatisfied participant (up to 50%); Grade 3 represented a moderately satisfied participant (up to 75%); and Grade four represented a very satisfied participant (>75%). In order to get the satisfaction of the partners who were unable to attend for evaluation, the partner contentment was asked by Whatsapp and telephone.
3. Maximum glandular circumference (MGC), which was measured by a tapeline plus.
4. 4Any other local changes or complications at sites of injection e g: discoloration, ulceration, necrosis or infection.

2.5 | Statistical analysis

Data were collected, coded, revised and entered into the Statistical Package for Social Science (IBM SPSS) version 20. Chi-square test was used in the comparison between two groups with qualitative data. An independent *t* test was used in the comparison between two groups with quantitative data and parametric distribution. The

FIGURE 1 Injection technique of hyaluronic acid in the glans penis. (a) Injection of the frenulum by Hyaluronic acid. (b) Injection of coronal sulcus. (c) Appearance of the glans after immediate injection. (d) Appearance of the glans after 3 months

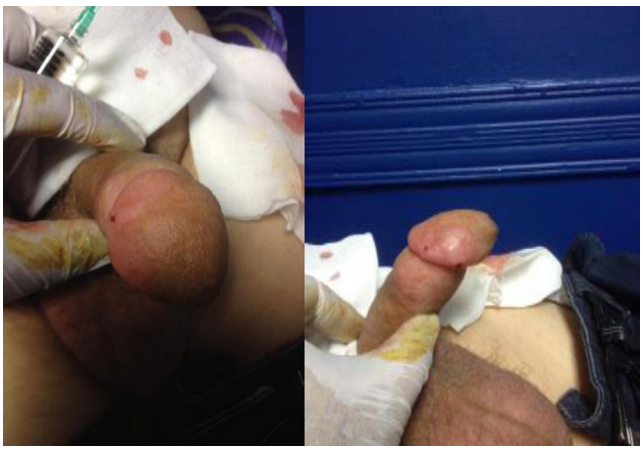

FIGURE 2 Bleeding from injection site controlled by gentle compression

comparison between more than two groups with quantitative data and parametric distribution was done by using the one-way analysis of variance (ANOVA) test. Post hoc test (Least significance difference) was used for multiple comparisons between different variables. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following: $p > .05$: Nonsignificant (NS); $p < .05$: Significant (S); $p < .01$: Highly significant (HS).

3 | RESULTS

A total of 80 male patients with refractory PE were enrolled. Of the 80 male patients, six patients (three in each group) were lost during the follow-up and were excluded from the study. Two patients in the HA group were lost after injection and the other one after the 3rd month; in the control group, but one patient was lost after the 1st month and the other two after the 3rd month.

The mean age of the patients was 39.73 ± 8.97 years old in the HA group and 36.83 ± 10.11 years old in the control group (Table 1).

In the HA group, 64.9% of the patients were satisfied (grade 3–4) throughout the study period; while in the control group, only 13.5% of the patients were satisfied (grade 3–4) (Table 4).

At the baseline, there was no statistically significant difference between the studied groups as regards IELT. During the 6-month follow-up period, IELT improved significantly, compared to the baseline values and the control group; there was a highly statistically significant difference (*p*-value < .001) between the studied groups as regard IELT at one, three and six months after the injection (Figure 3) (Table 2).

The maximal glandular circumference significantly increased at one, three and six months after the injection (Table 3). The patients' satisfaction with sexual intercourse was 64.9%, 70.3% and 78.4% at one, three and six months after the injection, respectively (Table 4). The partners' satisfaction with sexual intercourse was 54.1%, 48.6% and 59.5% at one, three and six months, respectively (Table 5). There was a statistically significant difference (p-value < .001) between all studied groups as regard female satisfaction, but no statistically significant difference between satisfaction at one, three, and six months. All complications that occurred during the study were few, mild, temporary and tolerable. Pain was felt by most patients during injection and disappeared within a few minutes after the procedure. Bleeding from the injection site (points of entry) was managed by simple compression for a few minutes and good haemostasis. Bruising and ecchymosis resolved spontaneously in about one-week post-injection.

4 | DISCUSSION

Drug therapy is considered as the current optimal treatment for PE. However, the main drawback of drug therapy is the high rate of recurrence after withdrawal. There is a controversy regarding glans penis hypersensitivity as a cause of PE. Recent observations showed that many patients with primary PE, who responded to local anaesthetics, had penile hypersensitivity, which provides further support for an organic aetiology of PE (Xin et al., 1996).

The current study revealed that the injection of HA can be productively utilised for PE treatment, achieving a remarkable increase in IELT. After six months of HA injection, the IELT was still remarkably higher in comparison with baseline values (from 44.8 ± 8.84 s at baseline to 277 ± 123.86 s at one month, 305.14 ± 125.36 s after 3 months and 242.97 ± 132.75 s after six months). The MGC was remarkably increased after six months of follow-up (from 83.68 ± 10.67 mm before treatment to 106.78 ± 7.66 mm at one month, 106.517 ± 19 mm at 3 months and 102.14 ± 6.61 mm at 6 months).

The linear threading technique was introduced as a simple and effective injection technique; however, it requires multiple punctures, which can lead to mucosal tearing, bleeding and outflow through the needle site. Afterwards, the fan technique was introduced as a Fewer needle punctures technique. In both techniques, the injection needle was passed subcutaneously at one-third of the distance proximally from the tip of the glans to the coronal sulcus. The human glans penis is elastic and easily injected in the dermis like a skin test of hypersensitivity (Moon et al., 2015).

The multiple puncture technique was utilised by Abdallah et al., in 2012 and compared with the fan procedure in their pilot study. The multiple points of the entrance were started from the proximal one-third of the glans along the coronal sulcus including the frenulum and only 0.25 ml was injected at each point. The multiple puncture technique has an advantage over the fan technique in that it allows more regular distribution of the injected substance, with less pain, because the extent of the bullae generated is smaller than those formed using the fan technique (Abdallah et al., 2012).

To avoid subsequent discoloration, pressure necrosis and excessive volume of injection, an initial injection of 2 ml of injectable HA gel via a 27-G needle and supplemental injection of Restylane via 30-G needle at two weeks after the initial injection was recommended by (Kim et al., 2003).

In our study, patients received a single injection of 2–4 ml of HA gel with a 27-G needle that pushed subcutaneously at the coronal sulcus and frenulum through four inlet points, all in a retrograde pattern. In concordance with Abdallah et al., the injection was concentrated only on suspected highly sensitive area at the coronal sulcus and frenulum through four inlet points all in a retrograde pattern through four points to avoid unnecessary injection.

Injectable materials can be effectively injected into the dermis of the glans penis just above the nerve terminal to produce a barrier delaying tactile stimuli from reaching receptors. Thus, it may be effective in the management of PE. Moreover, glans penis augmentation (GPA) is less injurious than invasive dorsal neurectomy, but the choice of suitable patients is required. GPA is less invasive, does not affect erectile function, and not permanent as dorsal neurectomy (Moon et al., 2015).

Our present findings are consistent with Abdallah et al., Kim et al., Moon et al., and Kwak, who reported a significant increase in the IELT after GPA in patients with PE. However, these studies pointed to the possibility of decreased sensation for a long time (Abdallah et al., 2012; Kim et al., 2003; Kwak et al., 2008; Moon et al., 2015). But, there is a difference in our controlled study in injection technique and patient selective criteria (only refractory cases).

A total of 38 patients were monitored by Kwak et al. (2008) for five years to assess the longstanding significance and side effects of GPA in PE. Vibratory threshold and IELT were significantly lower at five years, compared to the 6th month values, but still remained above baseline. Moreover, the satisfaction rate at five years was up to 76%, and the patients who were satisfied at six months generally stayed satisfied at the five-year follow-up.

Another uncontrolled study by Kim et al. (2004). reported parallel improvement in 65 patients after six months of HA injection with primary PE.

In our study, the IELT was improved after one month of glans penis HA injection. This was manifest in 64.9% of the patients,

TABLE 1 Comparison between patient group & control group as regards demographics

Variable	Patient (n = 40)		Control (n = 40)		p value
	Mean	*SD*	Mean	*SD*	
Age	39.73	8.97	36.83	10.11	.201
Wife age	33.03	7.60	31.25	6.25	.283
Marriage period in years	7.32	1.32	6.24	1.23	.191
Injected volume in Cm	2.51	0.40	2.78	1.25	.216

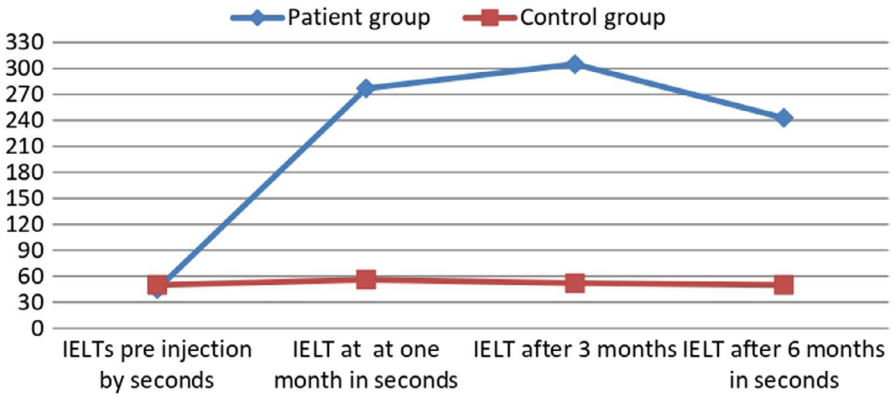

FIGURE 3 IELT (in s) pre- and post-injection in comparison with the control group

TABLE 2 Post Hoc test (LSD least significant difference) for comparison between IELTs (at 0, 1, 3 and 6 months) in all studied groups

		0 VS 1	0 VS 3	0 VS 6	1 VS 3	1 VS 6	3 VS 6
Patients group	*p* VALUE	<.001	<.001	<.001	.612	.017	.004
Control group	*p* VALUE	.254	.095	.011	.595	.155	.372

TABLE 3 Glandular circumference pre- and post-injection in comparison with the control group

		Patient		Control		
Variable		Mean	*SD*	Mean	*SD*	*p* value
Glandular circumference pre-injection in millimetre		96.89	1.58	97.17	2.19	.535
Glandular circumference post-injection in millimetre at one month		107.92	7.12	97.31	2.31	<.001
Glandular circumference at 3 months		108.65	4.92	97.37	2.35	<.001
Glandular circumference at 6 months		104.62	3.85	97.34	2.30	<.001
One-way ANOVA		<0.001		0.983		
0 VS 1	LSD[a]	9.199		0.268		
	p VALUE	.001		.789		
0 VS 3	LSD[a]	13.843		0.379		
	p VALUE	.001		.706		
0 VS 6	LSD[a]	11.298		0.326		
	p VALUE	.001		.745		
1 VS 3	LSD[a]	−12.691		0.111		
	p VALUE	.001		.912		
1 VS 6	LSD[a]	−2.480		0.056		
	p VALUE	.015		.955		
3 VS 6	LSD[a]	−3.924		0.055		
	p VALUE	.001		.954		

[a]Post Hoc test. LSD: least significant difference for comparison between glandular circumference (at 0, 1, 3 and 6 months) in all studied groups.

whose IELT improved over the baseline value. In these patients, the mean IELT increased from 44.81 ± 8.8 s before HA injection to 277.03 ± 123.86, 305.14 ± 125.36 and 242 ± 132.75 s at one, three and six months follow-up intervals, respectively.

In a previous uncontrolled study by Littara and coworkers on 110 male patients with PE, the authors reported increased IELT from a mean of 88.34 to 293.14 s after six months from HA injection. The mean baseline IELT ranged around 88 s, whereas, in the current study, the selected patients have IELT <one minute (Littara et al., 2013).

Alahwany et al. (2019) reported improvement in IELT after following up a total of 30 patients in a randomised, controlled and

TABLE 4 Comparison between patient group & control group as regards patient satisfaction

variable		Patient		Control		*p* value
		No	%	No	%	
Patient satisfaction at one month	Satisfied	24	64.9%	5	13.5%	<.001
	Unsatisfied	13	35.1%	32	86.5%	
Patient satisfaction at 3 months	Satisfied	26	70.3%	6	16.2%	<.001
	Unsatisfied	11	29.7%	31	83.8%	
Patient satisfaction at 6 months	Satisfied	29	78.4%	4	10.8%	<.001
	Unsatisfied	8	21.6%	33	89.2%	
1 VS 3	Chi-square test	0.247		0.107		
	p VALUE	.619		.743		
1 VS 6	Chi-square test	1.662		0.126		
	p VALUE	.197		.722		
3 VS 6	Chi-square test	0.637		0.463		
	p VALUE	.424		.496		

TABLE 5 Comparison between patient group & control group as regards partner satisfaction

Variable		Patient		Control		*p* value
		No	%	No	%	
Partner Satisfaction at one month	Satisfied	20	54.1%	4	10.8%	<.001
	Unsatisfied	17	45.9%	33	89.2%	
Partner Satisfaction at three months	Satisfied	18	48.6%	6	16.2%	.002
	Unsatisfied	19	51.4%	31	83.8%	
Partner Satisfaction at six months	Satisfied	22	59.5%	5	13.5%	.001
	Unsatisfied	15	40.5%	32	86.5%	
1 VS 3	Chi-square test	0.216		0.463		
	p VALUE	.642		.496		
1 VS 6	Chi-square test	0.220		0.126		
	p VALUE	.639		.722		
3 VS 6	Chi-square test	0.871		0.107		
	p VALUE	.350		.743		

cross-over study. The authors used Arabic validated index of premature ejaculation (AIPE) and reported minimal self-limited adverse effects, which was the same reported in our study. However, our study was different in inclusion criteria, study design, the method of injection used the multiple injection technique while in this study we used the four-point injection technique). Besides, they used Teosyal® (PureSense Global Action 25 mg/ml, Teoxane Laboratories). Furthermore, we did not use AIPE because it is used mainly in diagnosis more enthusiastically than treatment.

In the current study, the progress in 24/37 (64.9%) patients, in measured IELT values after HA injection has been detected at one month and were expanded for >6 months 29/37(78.4%). This resilience is mostly attributed to regular distribution and the persistence of HA molecules which limits the degradation process of HA on the other hand positive impact on the enlarged glans on self-esteem and self-confidence. long-term study carried out by Kim et al. (2004) concluded that the improvement of IELT after HA injection could persist up to 5 years.

Kim and colleagues demonstrated that there was no significant difference regarding the mean IELT between fan and multiple-point injection techniques. This may be explained by the fact that the same gel amount was injected by both methods (Kwak et al., 2008).

Hyaluronic acid by all explanations is a promising perfect filling substance for delicate tissue augmentation because it is simple to utilise, biocompatible, non-antigenic, non-pyrogenic, non-inflammatory, non-toxic, stable after infusion, non-transitory, durable, however, reabsorbable, regular looking and not very costly (Cairo et al., 2008).

Basal et al. (2010) reported that neuromodulation of the dorsal nerve by pulsed radiofrequency improves IELT, and no patients had any erection problems, penile hypoesthesia or pain after the procedure. Minimally invasive treatments of the dorsal nerve do not result in permanent sensory loss, but it needs more further studies to prove that procedure.

One of the points that need more investigation in our study is that in spite of the partners satisfaction was of a significant value, but still less than that of the patient, so interview of both partners and identifying the problem and sitting the expectations and eliminating any inter-relationship problems is very important in more satisfaction of the both partners. Abdallah et al. (2012) reported mild adverse effects in 30% of patients in the form of mild pain and bullae formation at the injection site. However, allergic reaction after a second exposure of HA injection cannot be precluded based on the findings of this study.

In our present results, the only Adverse reactions were detected in six out of 37 patients in form of injection site discomfort and just self-limiting ecchymosis in four patients out of 37 and. Mild to moderate tolerable burning pain felt by all patients and rapidly disappeared, Bleeding from points of entry occurred in 23 patients in group A, 18 patients in group B all stopped by gentle manual compression, Bruising and ecchymosis of the glans penis at the injection site observed in eight patients in group A & 11 patients in group B. No post-injection ulceration, infection, necrosis, granuloma formation or hypersensitivity reactions were observed in any patients of the study. This may be due to the reality that HA is a polysaccharide that shows the same chemical and molecular structure in all kinds and naturally found in the intercellular matrix of dermal layers of the skin, therefore, it does not produce foreign body reactions (Larsen et al., 1993).

Kosseifi et al. (2021) reviewed the literature using PubMed over the last 20 years. Only Five studies were found. These studies showed that HA injection could significantly increase IELT (2.43- to 4.46-fold), and this increase could persist for long term (up to 5 years). No serious adverse reactions were reported besides transient discoloration and swelling of the glans that recovered to normal within 2 weeks.

In most cases of current study, the early discoloration of the glans penis is regained to standard within 2 weeks. No abnormal changes in area feeling, texture, colour, no signs of inflammation and no serious adverse reactions in all cases, with no glans deformity noticed and maintained through 6 months. So in current study, we utilised the four inlet puncture technique to pick out the suspected sensitive points in glans including the frenulum to decrease the unnecessary punctures, possibility of ecchymosis, volume of injected materials and gaining long-term effect without diminishing the pleasure of intercourse or the risk of likely decreased level of sensation but further studies with long follow-up were definitely needed to compare the effectiveness of different methods of injection and winning more reliable results. Finally, we acknowledge some limitations of our present study. Firstly, the sample size was small. Secondly, more follow-up was necessary to assess possibility of repeated injection and long-term negative impact on penile morphology.

5 | CONCLUSION

In the present study, HA injection in glans penis using the least puncture manoeuver was safe and effective in satisfaction of 78,4% of men with early ejaculation who failed to respond to any treatment (IELTs of ≤1 min from vaginal penetration in ≥50% of coital activities) furthermore remarkable increase in IELT and partner satisfaction. So, it may be a hopeful and promising treatment for persistent PE. However, there is a need for large scale multicentre controlled studies with long follow-ups to validate our present findings.

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None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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