
The Possibility of Hyaluronic Acid as a Therapeutic Option for Peyronie's Disease: Systematic Review

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ABSTRACT

Peyronie's disease (PD) is a progressive, non-malignant disorder affecting the penile connective tissue, characterized by fibrous plaque formation leading to penile curvature and functional impairment. This study aimed to evaluate the effectiveness of hyaluronic acid (HA) as a therapeutic option for PD. A systematic review was conducted following PRISMA guidelines and utilizing the PICOT framework. Articles were sourced from PubMed, ScienceDirect, ProQuest, Wiley, and Google Scholar, focusing on studies published between 2012 and 2022 in English and with full-text availability. Six studies were analyzed, including cohort studies and clinical trials. The findings revealed that intralesional HA injections significantly reduced plaque size, improved penile curvature, and enhanced erectile function, as measured by the International Index of Erectile Function (IIEF). HA's anti-inflammatory and antioxidant properties, along with its ability to remodel collagen, contributed to these outcomes. Compared to other treatments, such as verapamil, HA demonstrated superior efficacy with minimal side effects. The discussion highlights HA's potential as a non-surgical treatment that addresses both physical symptoms and improves patient satisfaction. In conclusion, HA offers a promising, effective, and safe therapeutic alternative for PD, addressing critical gaps in the current management of the disease.

INTRODUCTION

Peyronie's disease (PD) is progressive and non-malignant disorder of the penis affecting the connective tissue in the penis, specifically the tunica albuginea of the corpus cavernosum. It is characterized by the development of fibrous islands and plaque, leading to an abnormal curvature of the penis during erection (Sandean & Lotfollahzadeh, 2020). This curvature results from the hindered expansion of the tunica albuginea, caused by the presence of fibrosis and plaque. However, the exact mechanism responsible for the formation of this scar tissue remains elusive., but it is believed to involve repeated micro-trauma during sexual activity followed by abnormal wound healing in susceptible individuals (Feyisetan, 2023).

Prevalence rates of Peyronie's disease ranging from 0.4% to 20.3% have been reported, and over 10% of men in the United States are reportedly affected by Peyronie's disease. As with many sexual disorders, it understandably triggers significant distress among patients. This distress arises from both the physical deformity and the functional impairment brought about

by the condition (Cilio et al., 2024). Consequently, it significantly diminishes patients' quality of life, with reported rates of significant depression reaching up to 48%. Recent estimates of its prevalence range from 3.2% to 8.9%. These differences can be attributed to various factors such as the age, race, and co-morbidities of the studied population. Additionally, it is likely that Peyronie's disease is under-reported due to personal embarrassment and a lack of awareness about the condition among the general population (Bilgutay & Pastuszak, 2015).

Conservative treatment of Peyronie's disease primarily targets patients in the early stage, characterized by acute inflammation. Surgical intervention is typically reserved for cases where the disease has stabilized for at least 12 months, aiming to correct curvature and facilitate satisfactory intercourse (Capece et al., 2023). Non-operative treatment options for Peyronie's disease include oral pharmacotherapy, intralesional injection therapy, and various topical treatments. Among these, injecting pharmacologically active agents directly into penile plaques is considered the most effective treatment option, as current evidence discourages the use of oral and topical agents (Abdel Fattah et al., 2024).

Additionally, various other therapies have been utilized in the past for Peyronie's disease, including oral treatments such as potassium para-aminobenzoate (Potaba), pentoxifylline, vitamin E, colchicine, tamoxifen, carnitine, and phosphodiesterase type 5 inhibitors. Intralesional treatments, such as steroids and verapamil, have also been explored. However, the outcomes from these treatments have shown contrasting results. Consequently, the European Association of Urology guidelines do not recommend their clinical use (Dr. Claudio et al., 2023).

Hyaluronic acid has demonstrated effectiveness in reducing scar formation and counteracting the effects of substances that induce inflammation and oxidative stress. Due to these properties, it is widely utilized in various medical applications, including cosmetic surgery (for treating wrinkles and scars) and orthopedics (for intra-articular therapy in osteoarthritis). Its therapeutic efficacy and feasibility in treatment cycles have been well-established (Zucchi et al., 2016).

Recent advancements in the understanding of Peyronie's disease (PD) have highlighted the multifactorial nature of its pathophysiology, where inflammation, oxidative stress, and abnormal collagen deposition play pivotal roles. While the exact mechanisms behind plaque formation remain unclear, evidence suggests that these processes lead to fibrosis of the tunica albuginea, resulting in penile deformities. The psychological burden of PD cannot be overlooked, as it often leads to significant emotional distress, anxiety, and reduced quality of life for patients. Current treatment options, particularly intralesional injections, have shown varying degrees of success. Hyaluronic acid (HA), a naturally occurring glycosaminoglycan with potent anti-inflammatory and tissue remodeling properties, has gained attention as a potential therapy. Despite its widespread use in dermatology and orthopedics, HA's application in PD is still emerging, necessitating robust clinical evaluation to determine its efficacy and safety.

Addressing PD in its acute inflammatory stage is critical, as early intervention can mitigate disease progression and prevent severe complications. Intralesional therapies, including verapamil and collagenase, have been explored but often present limitations in effectiveness or safety. Hyaluronic acid, by counteracting inflammatory mediators and oxidative stress, offers a novel therapeutic approach targeting the underlying pathophysiology of PD. Additionally, HA's ability to promote collagen remodeling and tissue regeneration could significantly improve penile curvature and erectile function, filling a critical gap in PD management. This study aims to systematically review the existing literature to evaluate HA's therapeutic potential, emphasizing its impact on plaque size, penile curvature, and patient-reported outcomes.

Previous studies have primarily focused on conservative treatment options for Peyronie's disease, such as intralesional therapies including steroids, verapamil, and collagenase. Notably, research by Zucchi et al. (2016) demonstrated the efficacy of HA in reducing plaque size and penile curvature. Other studies, such as those by Favilla et al. (2017) and Gennaro et al. (2015), provided preliminary evidence supporting HA's ability to enhance erectile function and decrease plaque rigidity. However, existing research often lacks comparative analysis with other treatment modalities, creating an opportunity to explore HA's distinct mechanisms of action and its long-term therapeutic outcomes.

Peyronie's disease significantly impacts quality of life, with high rates of psychological distress and functional impairment. Despite its prevalence, many patients experience suboptimal outcomes due to limited effective treatment options. Addressing this gap with evidence-based interventions like HA is crucial for improving both physical and emotional well-being.

While numerous studies have investigated various intralesional therapies, the comparative efficacy of HA against other treatments remains underexplored. Additionally, there is insufficient data on the long-term outcomes of HA in diverse populations and clinical settings.

This study provides a focused evaluation of HA's role in reducing penile plaque size, curvature, and functional deficits, distinguishing it from alternative therapies by emphasizing its anti-inflammatory and tissue-remodeling properties.

The research aims to assess the clinical efficacy and safety of HA as an intralesional therapy for Peyronie's disease, examining its impact on plaque size, penile curvature, and erectile function.

Findings will guide clinicians in selecting effective, non-invasive treatment options, improving patient outcomes and reducing the need for surgical intervention in Peyronie's disease management.

This study underscores the importance of integrating HA into clinical practice, highlighting its potential to revolutionize the therapeutic approach to Peyronie's disease, thereby enhancing patient care and satisfaction.

RESEARCH METHOD

We conducted a systematic review of the literature to assess the effectiveness of hyaluronic acid in treating Peyronie's disease. Our review adhered to the Preferred Reporting Items for Systematic Reviews (PRISMA) and question formulation using PICOT. Statement guidelines to ensure transparency and rigor in the review process.

Literature search

A comprehensive literature search using a combination of keywords, including MeSH terms and free text words such as 'Hyaluronic acid', 'peyronie disease', and 'Curvature penis'. The databases searched included MEDLINE, EMBASE, and the Cochrane Library (CENTRAL and CDSR), with searches conducted up to 2014. Additionally, we sought additional articles from the reference lists of the included studies to ensure a thorough review of the literature

Selection criteria

We included studies focusing on Peyronie's disease in adult patients. This encompassed case reports, case series, observational studies, non-randomized studies, and randomized trials published in English. Additionally, conference abstracts, letters to editors, commentaries, and editorials were also considered for inclusion. However, studies related to obstetrics and gynecology were excluded from our review. Similarly, studies pertaining to urinary tract conditions and dermatology were also excluded.

Data Collection

For eligible studies, we recorded study information such as first authors, study site, inclusion and exclusion criteria, sample size, and aim of the studies. We utilized a standardized form for data entry, focusing on the following areas: (1) Urological manifestations of Peyronie's disease, (2) Effectiveness of hyaluronic acid in treating Peyronie's disease, (3) Side effects associated with intralesional agents used in treatment.

RESULTS AND DISCUSSION

The PRISMA flow diagram depicted in Figure 1 illustrates the process of study selection. Initially, a total of 105 records were identified through the literature search, with no additional records sought from reference lists. After removing duplicates, 80 records remained. Subsequently, 9 records were excluded during the initial screening process. Additionally, 20 studies were excluded because the full text was not available, 30 studies did not address the research question, and 15 studies were not in English. Ultimately, 6 records met the inclusion criteria and were included in the review.

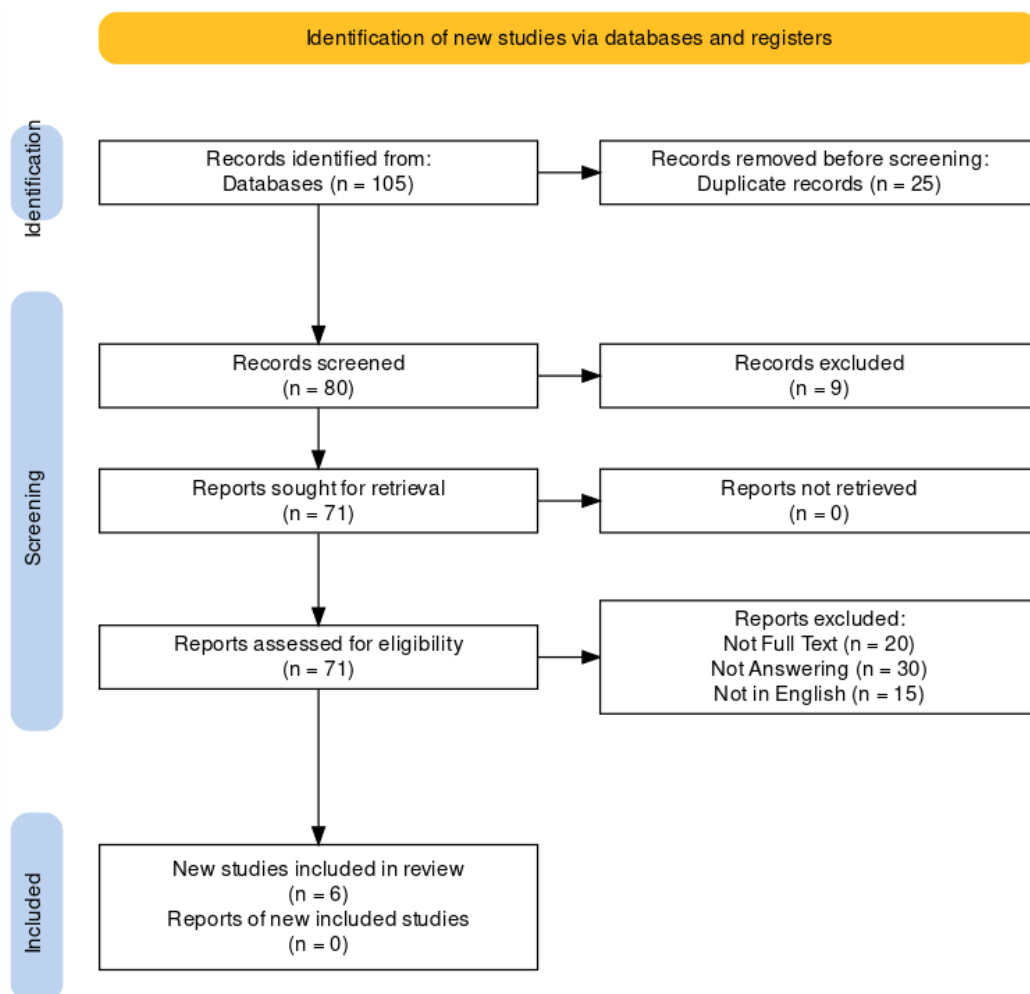


Figure 1. PRISMA Diagram of studies

Table 1. Summarised the study characteristics of the 6 studies

Author	Design	Sample	Objective	Result
Cirigliano et al, 2022	Original Studies	18	Safety and efficacy of intralesional injections of hyaluronic acid (IIHA) in the treatment of Peyronie's disease	The median penile curvature at baseline was 55. showed a decrease in the angle of curvature by a mean of 13.33 ± 8.57 degrees. A statistically significant improvement in IIEF- Intercourse Satisfaction
Gennaro et al, 2015	Original Studies	83	Evaluate the effectiveness of local treatment with injectable hyaluronic acid (HA) for patients with Peyronie's disease	All treated PD patients had experienced three statistically significant outcomes: reduction in plaque size (-93.7% , $p < 0.0001$); improvement in penile curvature (-9.01° , $p < 0.0001$); and improvement in penile rigidity (mean IIEF score $+3.8$)
Cocci et al, 2022	Cohort Studies	244	Illustrate the clinical outcomes after 2 years of follow-up in patients that received intralesional HA or verapamil for PD.	The median curvature was 25.0° at 3 months, For VAS score, the median change in Group A was -4.0 (IQR, $-4.0, -5.0$, $p < 0.01$) after 3 months
Zucchi et al, 2016	Original Studies	65	To assess the efficacy of intralesional injection of hyaluronic acid in patients affected by Peyronie's disease.	Mean plaque size was 10 mm (range $\frac{1}{4}$ 3e30 mm), mean penile curvature was 30(range $\frac{1}{4}$ 0e50), and mean IIEF-5 score was 20 (range $\frac{1}{4}$ 0e25), with slight to moderate erectile dysfunction
Marino et al, 2023	Original Studies	23	Evaluate the safety and the efficacy of a new protocol based on intraplaque injection of cross-linked hyaluronic acid plus modeling and stretching	Nineteen out of 21 patients (90%) showed a reduction in the degree of curvature by a mean of $11.9 \pm 7.3^\circ$. A statistically significant improvement in IIEF - Intercourse satisfaction domain
Fattah et al, 2024	Original Studies	42	Analyze and contrast the effectiveness and safety of intralesional HA in the acute stage of PD with that of verapamil injection	The penile curvature was significantly decreased at 12 weeks after therapy in contrast to baseline in group A ($34.1 \pm 6.77^\circ$ vs. $24.7 \pm 9.72^\circ$, $p = 0.005$), and was significantly decreased at 12 weeks after therapy compared to baseline in group B

Characteristics of the Study

Population

All studies included in the review focused exclusively on male patients diagnosed with Peyronie's disease who had undergone treatment with hyaluronic acid. The total sample size across these studies was comprised of 475 male patients.

Intervention

All of the research conducted was aimed at evaluating the effectiveness of hyaluronic acid on Peyronie's disease and its associated clinical manifestations. Some of the studies focused on evaluating the impact of hyaluronic acid on Peyronie's disease by measuring plaque size, as seen in the studies by Cirigliano et al., Gennaro et al., and Zucchi et al. Others assessed the reduction in penile curvature, such as in the studies conducted by Zucchi et al., Marino et al., and Fattah et al. Additionally, certain studies, like those by Zucchi et al. and Marino et al., investigated changes in erectile function using measures like the International Index of Erectile Function (IIEF). Only one study discussed the Patient-Reported Impact of Glycemic Outcomes (PIG1 Quest).

Clinical outcomes

Effectiveness of hyaluronic acid in reducing plaque size in Peyronie's disease show indicating a significant therapeutic effect. Cirigliano et al. (13.33%), Gennaro et al. (93.7%) and Zucchi (2mm). Penile curvature present findings regarding the degree of reduction such as Zucchi et al. (decrease 10 mm), Marino et al (11.9 mm), Fattah et al. (9.4 mm). Enhancing erectile function in Peyronie's disease, Zucchi et al. (increase of 1 point), Marino et al. (increase 2.35 points).

Discussion

Hyaluronic acid (HA) is known to counteract the effects of inflammatory cytokines and reduce oxidative stress. In the context of Peyronie's disease (PD), cytokine release and ROS overproduction contribute to the activation of NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells), leading to collagen overproduction and the formation of penile plaques. Given HA's anti-inflammatory and antioxidant properties, it is hypothesized to have beneficial effects on PD. While local injections of HA have been utilized over the past decade to enlarge the glans penis, our study represents the first attempt to employ HA in the treatment of PD (Cirigliano et al., 2022).

Three studies examining the effectiveness of hyaluronic acid in reducing plaque size in Peyronie's disease offer varying perspectives. Cirigliano et al. (2022) reported a modest decrease of 13.33%. In contrast, Gennaro et al. (2015) observed a substantial reduction of 93.7%, indicating a significant therapeutic effect. Zucchi et al. (2016) provided a different insight, noting a reduction of 2mm in plaque size. These findings collectively suggest that hyaluronic acid may have a varying impact on plaque size reduction, with Gennaro et al.'s study indicating particularly promising results compared to the other studies (Gennaro et al., 2015).

HA possesses anti-inflammatory properties that can help reduce inflammation associated with Peyronie's disease. Inflammation plays a significant role in the development and progression of penile plaques. By reducing inflammation, HA may help limit the growth and size of these plaques. Beside, Excessive collagen deposition is a hallmark of Peyronie's disease and contributes to the formation of penile plaques. HA has been shown to inhibit collagen production, potentially preventing the growth of plaques and reducing their size over time. HA can influence tissue remodeling processes by promoting the degradation of abnormal collagen fibers and facilitating the deposition of new, healthy tissue. This remodeling effect may contribute to the reduction of plaque size in Peyronie's disease (Andrea Cocci et al., 2022).

In exploring the impact of hyaluronic acid on penile curvature in Peyronie's disease, several studies present findings regarding the degree of reduction. Zucchi et al. reported a decrease of 10 mm, indicating a notable improvement in penile curvature. Similarly, Marino et

al. observed a slightly larger reduction of 11.9 mm, suggesting a significant therapeutic effect. Fattah et al. provided further evidence, reporting a decrease of 9.4 mm, supporting the efficacy of hyaluronic acid in addressing penile curvature associated with Peyronie's disease. These studies collectively indicate a consistent trend toward reduction in penile curvature with the use of hyaluronic acid (Favilla et al., 2017).

Penile curvature in Peyronie's disease is often caused by the presence of fibrous plaques within the tunica albuginea of the penis. HA may facilitate plaque remodeling by promoting the breakdown of abnormal collagen fibers and the deposition of new, healthy tissue. This remodeling process could potentially lead to a reduction in plaque size and stiffness, thereby reducing penile curvature (A Cocci et al., 2020). HA is a hydrophilic molecule that attracts and retains water molecules. By hydrating the tissues in the penis, HA may help to soften and loosen the fibrous plaques, making them more pliable and less rigid. This increased flexibility could contribute to a reduction in penile curvature (Virag et al., 2017).

In assessing the effect of hyaluronic acid treatment on erectile function in Peyronie's disease, Zucchi et al. observed a modest increase of 1 point in erectile function scores. Conversely, Marino et al. reported a more substantial improvement, with erectile function scores increasing by 2.35 points. These findings suggest a potential benefit of hyaluronic acid treatment in enhancing erectile function among patients with Peyronie's disease, with Marino et al.'s study indicating a more pronounced improvement compared to Zucchi et al.'s findings.

Peyronie's disease can lead to penile deformity and plaque formation, which may impede blood flow to the penis, resulting in erectile dysfunction (ED). HA treatment, by promoting tissue remodeling and reducing plaque size and stiffness, may improve blood flow to the penis, facilitating erections. PD also has significant psychological impact on affected individuals, leading to anxiety, depression, and reduced sexual confidence. By improving penile curvature and erectile function, HA treatment may alleviate psychological distress and improve overall sexual satisfaction (Capoccia & Levine, 2018).

CONCLUSION

The utilization of hyaluronic acid (HA) in the treatment of Peyronie's disease (PD) presents a multifaceted approach with promising outcomes. HA's anti-inflammatory and antioxidant properties offer potential benefits in reducing inflammation, limiting plaque growth, and promoting tissue remodeling, ultimately contributing to a reduction in plaque size and penile curvature.

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