Original Article

Efficacy and Safety of Intralesional Hyaluronic Acid versus Control or Verapamil in Acute-Phase Peyronie's Disease: A Systematic Review

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ABSTRACT

Background: Acute-phase Peyronie's disease (PD) is challenging to treat because management is often delayed until the stable phase. Evidence for conservative therapies remains limited, and no previous systematic review has specifically evaluated intralesional hyaluronic acid (HA). This systematic review evaluates the efficacy and safety of intralesional HA compared with control or verapamil in acute-phase PD.

Methods: This review was conducted in accordance with the PRISMA 2020 guidelines and registered. Six databases (PubMed, ProQuest, SAGE Journals, EBSCOhost, EuropePMC, and Wiley Online Library) were searched from inception, and trial registries were screened for ongoing studies. Two reviewers independently screened titles, abstracts, and full texts against pre-specified PICOS eligibility criteria, with disagreements resolved by a third reviewer. Eligible prospective trials (randomised and non-randomised) reported on penile curvature, plaque size or volume, erectile function (International Index of Erectile Function, IIEF), penile pain (Visual Analogue Scale, VAS), or patient-reported outcomes. Risk of bias was assessed in duplicate using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool for randomised and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool for non-randomised studies, and the certainty of evidence was rated using GRADE.

Results: The search identified 287 records; after duplicate removal, 193 were screened and 23 full texts assessed, of which four prospective studies (two randomised controlled trials and two non-randomised prospective studies; 582 patients) met the inclusion criteria. The two RCTs were rated at low overall risk of bias (RoB 2.0) and the two non-randomised studies at moderate overall risk of bias (ROBINS-I), mainly owing to confounding and participant selection. Intralesional HA was associated with improvements in penile curvature (reductions of approximately 4.6–9.5° versus control or verapamil, including a 9.01° [46.1%] reduction versus an untreated control), plaque size or volume (up to a 93.7% reduction in plaque volume versus progressive growth in untreated patients), and erectile function (IIEF gains of approximately 1.0–3.8 points). HA showed a favourable safety profile with no major adverse events. However, several outcomes—including plaque-size reduction and IIEF change in some trials—did not reach statistical significance over verapamil, and the evidence base is small and clinically heterogeneous.

Conclusion: Intralesional HA is a potentially effective, non-surgical option for acute-phase PD, yielding improvements in curvature, plaque size, pain, and erectile function with an excellent safety profile. However, the overall certainty of evidence is limited by the small number of included studies, methodological heterogeneity, and short follow-up; findings should therefore be interpreted with caution. Large-scale, multicentre RCTs with standardised protocols, extended follow-up, and evaluation of combination therapies (e.g., with phosphodiesterase-5 inhibitors) are required before HA can be integrated into clinical guidelines.

***Keywords*:** Hyaluronic Acid; Peyronie Disease; Intralesional Injection; Penile Curvature; Erectile Dysfunction.

Implications for Practice:

- Intralesional hyaluronic acid shows a consistent, low-certainty signal of benefit for reducing penile curvature, plaque burden, and pain in acute-phase Peyronie's disease; whether this translates into a reduced future need for surgery has not been directly evaluated in the included studies and remains a hypothesis for future trials rather than a demonstrated outcome.
- Current evidence identifies hyaluronic acid as a promising investigational option for acute-phase Peyronie's disease that warrants confirmation in adequately powered, multicentre randomised trials before it can be considered for formal guideline integration.
- Standardised, cost-effective hyaluronic acid treatment pathways should be explored in resource-limited and diverse healthcare settings to improve equitable access to non-surgical care.

Introduction

Peyronie's disease (PD) is an acquired, non-malignant wound-healing disorder of the penile tunica albuginea characterised by localised, inelastic fibrotic plaque formation (Abdel Fattah et al., 2024). These plaques prevent normal tissue expansion during erection, resulting in penile curvature, painful erections, narrowing, and structural instability. Modern epidemiological data indicate that PD is far more common than previously assumed, currently affecting approximately 3% to 9% of the adult male population (Al-Thakafi & Al-Hathal, 2016). The clinical presentation of PD consistently imposes a severe dual physical and psychological burden on patients. Physically, progressive plaque formation and severe penile angulation impair penetrative intercourse and frequently co-occur with structural or vasculogenic erectile dysfunction. Psychologically, the resulting anatomical deformity leads to profound emotional distress, clinical depression, reduced self-esteem, and relationship difficulties, thereby severely compromising the patient's overall quality of life (Moisés Da Silva et al., 2022).

Historically, standard therapeutic interventions have been deferred to the chronic, stable phase of PD, which is characterised by plaque calcification and the complete resolution of active pain. During this late phase, surgical options such as corporoplasty with plication or plaque excision/incision with grafting are considered the gold standard for correcting severe functional curvature (Nehra et al., 2015; Salonia et al., 2025). However, these stable-stage strategies are associated with significant patient dissatisfaction and poor acceptance. Plication procedures inherently shorten the contralateral normal tunica albuginea, resulting in permanent penile shortening, which is psychologically devastating and highly unacceptable to many patients (Chung et al., 2011). Furthermore, non-surgical late-stage therapies such as intralesional collagenase *Clostridium histolyticum* carry risks of

serious adverse events and do not recover the penile length lost during the untreated active stage (Gelbard et al., 2013). Consequently, there is an urgent clinical mandate to move away from stable-stage rescue toward proactive early-stage intervention (Moisés Da Silva et al., 2022).

To date, conservative management of acute-phase PD remains poorly standardised. Intralesional verapamil has been the most widely used off-label agent, yet major guidelines note that its efficacy in reducing penile curvature is inconsistent and that no intralesional agent other than collagenase *Clostridium histolyticum* carries a strong recommendation (Nehra et al., 2015; Salonia et al., 2025; Bella et al., 2018). Prior systematic reviews and narrative syntheses of intralesional therapy for PD have largely combined active- and stable-phase populations or focused on collagenase, and none has specifically evaluated intralesional hyaluronic acid (HA) restricted to the acute phase (Khooblall et al., 2023; Douroumis et al., 2024). The present review therefore does not update a previous HA-specific synthesis but rather addresses a clear evidence gap by isolating the acute-phase HA evidence and appraising it systematically.

Conceptually, the rationale for HA during the active phase rests on its biological properties. HA is a high-molecular-weight glycosaminoglycan that, through interaction with the CD44 receptor, exerts anti-inflammatory and antifibrotic effects, dampening pro-inflammatory cytokine expression and down-regulating the transforming growth factor-beta 1 (TGF-β1) pathway that drives myofibroblast differentiation and disorganised extracellular matrix deposition (Khooblall et al., 2023; Herati & Pastuszak, 2016). Intervening during the acute inflammatory phase therefore provides a biologically plausible window to halt progressive fibrosis before permanent scarring and calcification occur.

This question carries particular relevance in low- and middle-income countries, including Indonesia, where access to collagenase *Clostridium histolyticum* and to specialised reconstructive surgery is limited by cost and availability. A safe, low-cost, office-based conservative option that reduces progression and the future need for surgery would have substantial clinical and health-policy value in such settings.

Accordingly, this review was guided by the following structured research question (PICOS): in adult men with acute-phase Peyronie's disease *(Population)*, does intralesional hyaluronic acid injection *(Intervention)*, compared with no-treatment control or intralesional verapamil *(Comparator)*, improve penile curvature, plaque size or volume, erectile function, and pain while maintaining an acceptable safety profile *(Outcomes)*, as reported in prospective clinical trials *(Study design)*? On this basis, this systematic review evaluates the efficacy and safety of intralesional HA injection compared with control or verapamil in acute-phase Peyronie's disease.

Methods

Protocol And Registration

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021) and the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al., 2019). A systematic review methodology was chosen because the available evidence comprises a small number of heterogeneous prospective trials whose findings have not previously been integrated for the acute phase; a transparent, reproducible synthesis was therefore required to appraise the

consistency and certainty of the evidence rather than to generate new primary data. The protocol was registered. The review was structured to answer the PICOS question stated above.

Eligibility Criteria

Eligibility criteria were structured according to the PICOS framework. Population: adult men with acute-phase PD; Intervention: intralesional HA injection; Comparator: a no-treatment control group or an active comparator (intralesional verapamil); Outcomes: at least one of penile curvature, plaque size or volume, erectile function (IIEF), penile pain (VAS), or patient-reported outcomes such as the Patient Global Impression of Improvement (PGI-I); and Study design: prospective clinical trials (randomized and non-randomized). Retrospective studies, reviews, editorials, case reports, and animal experiments were excluded. No restriction was placed on publication year. Only peer-reviewed studies published in full text in English were eligible; conference abstracts and unpublished reports were excluded to ensure adequate methodological detail for appraisal. These criteria were chosen to capture the highest-quality prospective evidence specific to the acute phase while minimizing the recall and selection biases inherent in retrospective designs.

Information Sources

A systematic search was executed across six major electronic databases: PubMed, ProQuest, SAGE Journals, EBSCOhost, EuropePMC, and Wiley Online Library. The databases were searched from inception to 2026. In addition, the WHO International Clinical Trials Registry Platform and ClinicalTrials.gov were searched to identify ongoing or unpublished trials, and the reference lists of all included articles were hand-searched (a limited grey-literature step) to retrieve additional eligible studies.

Search Strategy

The search combined Medical Subject Headings (MeSH) and free-text keywords for the intervention and the condition. The full Boolean string applied in PubMed was: ("Hyaluronic Acid"[Mesh] OR hyaluronan OR "sodium hyaluronate" OR "HA") AND ("Penile Induration"[Mesh] OR "Peyronie* disease" OR "penile fibromatosis" OR "penile curvature") AND (intralesional OR injection OR infiltration). This string was adapted to the syntax of each database. A study-design filter limiting results to clinical trials and prospective studies in humans was applied where available, and the strategy was validated by confirming that all studies known a priori to be eligible were retrieved.

Selection Process

All identified records were imported into EndNote 20 for de-duplication. Two reviewers then independently screened titles and abstracts against the eligibility criteria using a shared, software-assisted screening workflow. Before formal screening, the reviewers completed a calibration exercise on a random sample of records to align their application of the criteria. Full texts of potentially relevant articles were then retrieved and assessed independently. Inter-reviewer agreement at the full-text stage was quantified using Cohen's κ (κ = 0.5). Disagreements at either stage were resolved by consensus or, when necessary, by consultation with a third independent reviewer.

Data Collection Process

Data were extracted in duplicate using a standardised extraction template. The template was pilot-tested on one included study and refined before full extraction to ensure consistent capture of all data items.

Extracted fields included study design, baseline patient characteristics, intervention protocol (dose and frequency), reported outcomes, and follow-up duration. Variables were recorded as dichotomous or continuous where available, or as "not reported" when missing. Extractions were cross-checked between the two reviewers, with discrepancies resolved by discussion; where key data were missing or unclear, the corresponding authors of the primary studies were to be contacted for clarification.

Data Items

The pre-specified primary outcome was the change in penile curvature (degrees). Pre-specified secondary outcomes were plaque size (mm) or plaque volume, erectile function (IIEF-5 or IIEF-15), penile pain (VAS), patient-reported improvement (PGI-I), and treatment-related adverse events. Where studies reported outcomes at multiple time points, the longest available follow-up was used for synthesis. No imputation was performed for missing summary statistics; outcomes not reported by a given study were treated as "not available" and excluded from the corresponding synthesis rather than assumed to be null.

Study Risk of Bias Assessment

Risk of bias was assessed at the study level independently and in duplicate, with disagreements resolved by discussion. Randomized controlled trials were appraised using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which evaluates the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Non-randomized studies were appraised using the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool, which addresses confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. Reporting bias was considered within the selective-reporting domain of each tool and, where feasible, by comparing reported outcomes against registered protocols. Domain-level judgements are summarised in Table 2 and Table 3 and displayed as a traffic-light plot in Figure 2.

Synthesis Methods

Because the included studies differed substantially in comparator (no-treatment control versus verapamil), treatment protocol, follow-up duration, and outcome-measurement methods, a meta-analysis was not appropriate and would have produced a spuriously precise pooled estimate; a structured narrative synthesis was therefore performed, informed by the Synthesis Without Meta-analysis (SWiM) framework. Studies were grouped a priori by outcome domain (penile curvature, plaque size or volume, erectile function, pain, patient-reported improvement, and safety), and within each domain results were tabulated and compared for the direction and consistency of effect. For the qualitative component, a content-analysis approach was used: each study's results, statistical methods, and conclusions were coded against the predefined outcome domains, candidate themes were developed iteratively from these codes, and credibility was supported by independent coding by the second reviewer and resolution of discrepancies by consensus. Clinical and methodological heterogeneity across the four studies was assessed qualitatively before this decision, following SWiM guidance: the comparator differed (no-treatment control in one study versus verapamil in three), HA dose and injection schedule differed (a 6-month, 30-injection 20 mg regimen versus 8–12-week, 16 mg

regimens), follow-up ranged from 3 to 30 months, and plaque burden was measured on non-equivalent scales (two-dimensional size in millimetres versus three-dimensional volume). Because these differences act on both the direction and the precision of effect estimates simultaneously, a formal statistical test of heterogeneity (e.g., I^2) was judged unlikely to be informative with only two to four studies per outcome and was not undertaken. A restricted subgroup meta-analysis comparing HA against verapamil only (Favilla et al., 2017; Cocci et al., 2021; Abdel Fattah et al., 2024) was considered, since these three studies share a common active comparator; however, they still differ in design (two RCTs, one non-randomised), HA dosing schedule, and follow-up duration, and pooling only three small, heterogeneous studies risked producing an unstable and potentially misleading summary effect. This option was therefore not pursued, but it is acknowledged as a reasonable alternative and is flagged as a priority for an updated meta-analysis once further trials are available.

Certainty Assessment (GRADE)

The certainty of the body of evidence for each outcome domain was rated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. The resulting certainty ratings are presented in the GRADE summary-of-findings table (Table 5). Because the assessment is based on a small number of studies, the ratings should be regarded as preliminary and confirmed by the authors against the full GRADE criteria before publication.

For penile curvature, certainty was rated down for risk of bias because two of the four contributing studies were non-randomised (Gennaro et al., 2015; Cocci et al., 2021) and were judged at moderate overall risk of bias on ROBINS-I (Table 3), principally reflecting confounding (D1) and participant-selection (D2) concerns, and for imprecision because individual study samples ranged from 42 to 164 patients per comparison, with confidence intervals not consistently reported and effect sizes (4.6–9.5°) spanning a range wide enough to straddle both clinically important and clinically marginal benefit. For plaque size or volume, certainty was rated down for inconsistency because two studies found HA superior to verapamil on formal statistical testing (Gennaro et al., 2015; Abdel Fattah et al., 2024) while two others found a numerically larger but non-significant reduction with HA (Cocci et al., 2021: 1.80 mm vs 1.36 mm; Favilla et al., 2017: 1.50 mm vs 1.20 mm), for risk of bias on the same grounds as above, and for imprecision given the small per-study samples and non-significant between-group differences in two of the four studies. For erectile function (IIEF), certainty was rated down for inconsistency because the between-group difference against verapamil was non-significant in one RCT (Favilla et al., 2017) despite a significant within-group HA effect elsewhere (Cocci et al., 2021; Gennaro et al., 2015), and for imprecision because only three of the four studies reported this outcome and sample sizes per comparison were small. For penile pain (VAS), certainty was rated down for imprecision and incomplete reporting because outcome instruments and reporting formats were not standardised across studies, precluding quantitative comparison of effect magnitude. Across all domains, indirectness was not considered a separate downgrading factor because population, intervention, and outcome definitions were judged sufficiently aligned with the review question, and publication bias could not be formally assessed (e.g., by funnel plot) given the small number of

studies, but is discussed qualitatively in the Discussion in relation to the limited number of contributing research groups.

Results

Study Selection

The initial search across six databases identified 287 records. After removal of duplicates (n = 94), 193 unique records were screened by title and abstract, of which 170 were excluded. Full texts of 23 potentially eligible articles were assessed, and 19 were excluded because of retrospective design (n = 8), absence of acute-phase data (n = 6), no intralesional HA intervention (n = 3), or lack of quantitative outcome reporting (n = 2). Four prospective studies met all inclusion criteria: two were double-blind randomised controlled trials (RCTs) and two were non-randomised prospective studies with contemporaneous comparison groups. The study-selection process is summarised in **Figure 1**, and the reasons for full-text exclusion are detailed in **Table 1 and Table 6.**

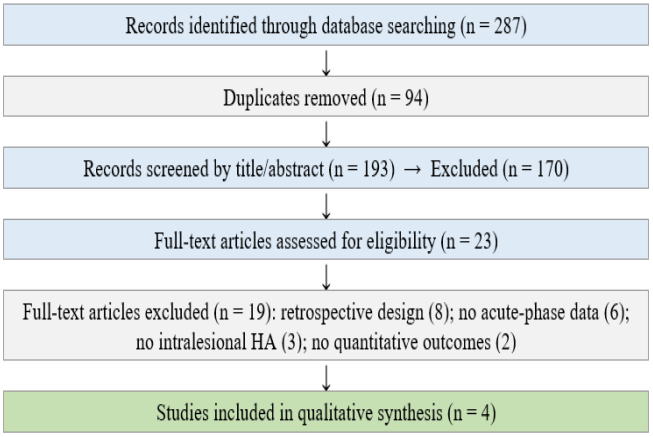

Figure 1. PRISMA 2020 flow diagram of study selection.

Table 1. Characteristics of included studies.

Study (Year)	Design	Follow-up (month)	HA protocol	Comparator	n (HA/Ctrl)	Mean age, y (HA/Ctrl)
Gennaro et al. (2015)	Non-randomised prospective	12 (up to 30)	20 mg HA, 30 infiltrations over 6 mo	No-treatment control	83/81	56.6/56.3
Favilla et al. (2017)	RCT, double-blind, multicentre	3	16 mg/2 mL HA (0.8% Na salt), 12 wk	Verapamil 10 mg/5 mL	63/69	55.1/57.5
Cocci et al. (2021)	Non-randomised prospective, open-label	3	16 mg/2 mL HA (0.8% Na salt), 8 wk	Verapamil 10 mg/5 mL	125/119	53.9/55.6
Abdel Fattah et al. (2024)	RCT, double-blind	3	16 mg/2 mL HA (0.8% Na salt), 12 wk	Verapamil 10 mg/5 mL	21/21	51.3/52.8

HA, hyaluronic acid; RCT, randomised controlled trial. Values are baseline characteristics. Erectile function (IIEF) and baseline plaque and curvature values per group are reported in ***Table 4.***

Risk of Bias in Studies

For the two RCTs, the RoB 2.0 assessment indicated a low overall risk of bias across all domains. The two non-randomised studies appraised with ROBINS-I were judged to have a moderate overall risk of bias, driven principally by potential confounding and participant-selection issues. The low overall RoB 2.0 rating for both RCTs reflects that each reported an adequate, concealed randomisation procedure, blinding of participants and outcome assessors, complete or near-complete outcome data at

the pre-specified follow-up, and a pre-specified outcome set consistent with the published protocol; however, both trials enrolled small samples (n = 132 and n = 42) over a short three-month follow-up, and neither trial report provided sufficient detail to fully exclude subtle deviations from the intended intervention (e.g., strict verification of injection-site blinding). These limitations did not meet the threshold for a "some concerns" or "high" RoB 2.0 rating on any individual domain under the tool's signalling questions, but they are reflected instead in the imprecision downgrade applied at the outcome level in the GRADE assessment (**Table 5**) rather than in the study-level risk-of-bias judgement. For the non-randomised studies, the moderate confounding (D1) rating reflects that neither study used statistical adjustment (e.g., propensity matching or multivariable regression) to account for baseline differences between comparison groups. This concern is most pronounced for Gennaro et al. (2015), whose control group comprised patients who declined treatment rather than a matched or randomly allocated comparator; because self-selection into the untreated arm may itself correlate with disease severity or health-seeking behaviour, the confounding and participant-selection domains for this study should be interpreted as approaching the boundary between "moderate" and "serious," and the corresponding GRADE certainty for outcomes drawing on this study (**Table 5**) already reflects this by incorporating a risk-of-bias downgrade rather than treating the ROBINS-I rating as fully reassuring. Domain-level judgements are presented in **Table 2** (RoB 2.0) and **Table 3** (ROBINS-I); a traffic-light plot is provided in **Figure 2.**

Table 2. Risk-of-bias assessment of randomised controlled trials (Cochrane RoB 2.0).

Study	D1 Randomisation	D2 Deviations	D3 Missing data	D4 Measurement	D5 Reporting	Overall
Favilla et al. (2017)	Low	Low	Low	Low	Low	Low
Abdel Fattah et al. (2024)	Low	Low	Low	Low	Low	Low

D1–D5 correspond to the five RoB 2.0 domains.

Table 3. Risk-of-bias assessment of non-randomised studies (ROBINS-I).

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Cocci et al. (2021)	M	M	L	L	L	M	L	Moderate
Gennaro et al. (2015)	M	M	L	L	M	M	L	Moderate

L, Low; M, Moderate. ROBINS-I domains: D1 confounding; D2 selection of participants; D3 classification of interventions; D4 deviations from intended interventions; D5 missing data; D6 measurement of outcomes; D7 selection of the reported result.

Results of Syntheses

Results are presented by outcome domain. Across domains, the four studies consistently favoured intralesional HA in the direction of effect, but the magnitude and statistical significance of the advantage over verapamil varied, and several between-group comparisons were not statistically significant.

Penile Curvature

All studies reported improvement in penile curvature with intralesional HA. In direct comparison with verapamil, one RCT reduced curvature from 34.1° to 24.7° at twelve weeks, significantly greater than the verapamil group's reduction from 36.2° to 30.8° (Abdel Fattah et al., 2024). A non-randomised study reported a median curvature decrease of 9.5° with HA versus 4.5° with verapamil (Cocci et al., 2021). In a multicentre RCT, the verapamil group showed no significant change, whereas the HA group experienced a mean 4.6° decrease, with HA strongly associated with achieving a ≥10° reduction on multivariate analysis (Favilla et al., 2017). Compared with a no-treatment control, HA produced a mean reduction of 9.01° (46.1%) over twelve months, while untreated patients worsened progressively (Gennaro et al., 2015). The direction of effect was therefore consistent across all four studies, although the comparators and effect magnitudes differed.

Plaque Size and Plaque Volume

Intralesional HA reduced plaque burden, but its superiority over verapamil was inconsistent. Versus a no-treatment control, HA achieved a 93.7% mean reduction in plaque volume at twelve months, whereas untreated patients showed progressive growth (a 145.9% mean increase at six months) (Gennaro et al., 2015). In one RCT, HA significantly reduced plaque *size* from baseline at twelve weeks while verapamil did not, yielding a significantly smaller plaque in the HA group (Abdel Fattah et al., 2024). In contrast, two comparative studies found that the greater numerical plaque-size reduction with HA did not reach statistical significance versus verapamil: 1.80 mm versus 1.36 mm (Cocci et al., 2021) and 1.50 mm versus 1.20 mm (Favilla et al., 2017). The plaque outcome thus illustrates clear inconsistency between studies, with HA superior to no treatment but not consistently superior to verapamil.

Erectile Function (IIEF)

Erectile function, assessed by the IIEF-5 or IIEF-15, improved with HA in all reporting studies. In one RCT, both treatments improved IIEF-5 significantly from baseline (HA +1.78; verapamil +1.46), but the between-group difference was not statistically significant (Favilla et al., 2017). A non-randomised study found a significant IIEF gain with HA (median +1.0) but no significant change with verapamil (Cocci et al., 2021). In the controlled observational cohort, HA produced a mean IIEF increase of 3.8 points (21.1%) at twelve months, and erectile dysfunction resolved completely in 48.1% of HA-treated patients who had baseline dysfunction (Gennaro et al., 2015); Abdel Fattah et al. (2024) did not report IIEF. Erectile-function results were therefore favourable for HA overall but, as with plaque size, the advantage over verapamil was not consistently statistically significant.

Penile Pain (VAS) and Patient-Reported Improvement (PGI-I)

Where reported, penile pain (VAS) decreased with HA, and the included studies consistently described greater pain relief and higher patient satisfaction with HA than with verapamil or no treatment. Favilla et al. (2017) additionally used the Patient Global Impression of Improvement (PGI-I), with patients reporting greater improvement following HA. Pain and patient-reported outcomes were not uniformly quantified across studies, limiting formal comparison.

Safety

Intralesional HA demonstrated a favourable safety profile across all four studies, with no major adverse drug reactions, injection-site haematomas, or local tissue atrophy reported, supporting

good patient compliance. Individual-study outcome estimates are summarised in **Table 4,** and the certainty of evidence for each domain is reported in **Table 5.**

Table 4. Summary of outcomes by study and domain.

Study	Outcome	HA group	Comparator	Between-group result
Abdel Fattah (2024)	Curvature	34.1° → 24.7°	36.2° → 30.8° (verapamil)	Favours HA (significant)
Cocci (2021)	Curvature	Median −9.5°	Median −4.5° (verapamil)	Favours HA
Favilla (2017)	Curvature	−4.6°; assoc. with ≥10° reduction	No significant change (verapamil)	Favours HA
Gennaro (2015)	Curvature	−9.01° (−46.1%)	Progressive worsening (untreated)	Favours HA
Gennaro (2015)	Plaque volume	−93.7% at 12 mo	+145.9% at 6 mo (untreated)	Favours HA
Abdel Fattah (2024)	Plaque size	Significant ↓ from baseline	No significant ↓ (verapamil)	Favours HA (significant)
Cocci (2021)	Plaque size	−1.80 mm	−1.36 mm (verapamil)	No significant difference
Favilla (2017)	Plaque size	−1.50 mm	−1.20 mm (verapamil)	No significant difference
Favilla (2017)	IIEF-5	+1.78	+1.46 (verapamil)	No significant difference
Cocci (2021)	IIEF	Median +1.0 (significant)	No significant change (verapamil)	Favours HA
Gennaro (2015)	IIEF	+3.8 (+21.1%); ED resolved in 48.1%	Untreated control	Favours HA
All studies	Safety	No major adverse events	—	Favourable for HA

HA, hyaluronic acid; IIEF, International Index of Erectile Function; ED, erectile dysfunction; mo, months. Confidence intervals and exact p-values were not consistently reported in the primary studies; insert from source where available.

Table 5. GRADE summary of findings and certainty of evidence.

Outcome	Studies (design)	Summary of finding	Certainty	Reasons for downgrading
Penile curvature	4 (2 RCT, 2 NRS)	HA reduces curvature more than control/verapamil (≈4.6–9.5°)	Low	Risk of bias (NRS); imprecision (small samples)
Plaque size / volume	4 (2 RCT, 2 NRS)	HA reduces plaque; superiority over verapamil inconsistent	Low	Inconsistency; imprecision; risk of bias
Erectile function (IIEF)	3 (1 RCT, 2 NRS)	HA improves IIEF; vs verapamil inconsistent	Low	Inconsistency; imprecision
Penile pain (VAS)	Mixed reporting	HA alleviates pain	Low	Imprecision; incomplete reporting
Safety / adverse events	4	No major adverse events with HA	Moderate	Imprecision (small total sample)

RCT, randomised controlled trial; NRS, non-randomised study; GRADE certainty: High, Moderate, Low, Very low.

Table 6. Full-text studies excluded, with reasons.

Reason for exclusion	n
Retrospective design	8
Absence of acute-phase data	6
No intralesional HA intervention	3
Lack of quantitative outcome reporting	2
Total excluded at full text	19

Discussion

The medical management of PD during its acute inflammatory phase remains one of the most challenging frontiers in reconstructive urology (Moisés Da Silva et al., 2022; Nehra et al., 2015). This systematic review synthesises the clinical evidence on intralesional HA in patients with active-phase PD. The included randomised and non-randomised prospective trials consistently demonstrate that early intervention with intralesional HA is associated with improvements in key objective and subjective parameters, including reduction of plaque size or volume, correction of penile curvature, alleviation of pain, and preservation or recovery of erectile function (Abdel Fattah et al., 2024; Cocci et al., 2021; Favilla et al., 2017; Gennaro et al., 2015).

Biochemically, the therapeutic rationale for HA lies in its capacity to modulate the inflammatory cascade that drives progression toward irreversible fibrosis (Khooblall et al., 2023; Abdel Fattah et al., 2024). Peyronie's plaque formation begins with mechanical microvascular injury followed by sustained local inflammation and up-regulation of transforming growth factor-beta 1 (TGF-β1), a primary driver of myofibroblast differentiation and disorganised collagen and extracellular matrix (ECM) deposition (Al-Thakafi & Al-Hathal, 2016; Herati & Pastuszak, 2016; Somers et al., 1989). Exogenous HA, a high-molecular-weight glycosaminoglycan, exerts anti-inflammatory control by interacting with CD44 and the receptor for hyaluronan-mediated motility (RHAMM), inhibiting pro-inflammatory cytokines (interleukin-1, interleukin-6, tumour necrosis factor-alpha) and down-regulating the TGF-β1 pathway (Khooblall et al., 2023; Gennaro et al., 2015). By counteracting these mediators during the hypercellular acute phase, HA may limit disorganised collagen deposition and stabilise the tunica albuginea before permanent calcification occurs (Khooblall et al., 2023; Abdel Fattah et al., 2024).

Placed within the wider evidence base, these findings complement—rather than contradict—the established literature on intralesional therapy for PD. Collagenase *Clostridium histolyticum* remains the only intralesional agent with phase-3 randomised support and regulatory approval, although its pivotal IMPRESS trials enrolled predominantly stable-phase patients and it is costly and not widely available (Gelbard et al., 2013; Lipshultz et al., 2015; Yang & Bennett, 2016). Evidence for collagenase specifically in the acute phase remains limited (Nguyen et al., 2017), and major guidelines continue to regard most other intralesional options, including verapamil, as having inconsistent efficacy (Nehra et al., 2015; Salonia et al., 2025; Bella et al., 2018; Osmonov et al., 2022). Intralesional HA has also shown benefit in the stable phase in retrospective series (Cilio et al., 2024). Against this backdrop, the present review adds focused, acute-phase evidence suggesting that HA is a biologically plausible and well-tolerated early option, while underscoring that it has not yet been tested at the scale of collagenase.

The comparative data compiled here indicate a benefit of intralesional HA over verapamil in the direction of effect (Abdel Fattah et al., 2024; Favilla et al., 2017; Cocci et al., 2021). While verapamil has long been used off-label for its capacity to reduce

calcium-dependent collagen transport, its effect on penile curvature has been inconsistent (Favilla et al., 2017). In one RCT, HA significantly reduced plaque size at twelve weeks whereas verapamil did not (Abdel Fattah et al., 2024), and in a multicentre RCT HA—but not verapamil—was associated with a clinically meaningful curvature reduction (Favilla et al., 2017). Cocci et al. (2021) similarly reported a larger median curvature decrease with HA.

It is equally important, however, to interpret the non-significant findings honestly. Although HA was numerically superior to verapamil for plaque-size reduction in both Cocci et al. (2021) and Favilla et al. (2017), these between-group differences did not reach statistical significance, and the between-group IIEF difference in Favilla et al. (2017) was likewise non-significant. In other words, HA's clearest advantage is over no treatment, whereas its superiority over active verapamil is suggested but not consistently demonstrated. These non-significant results are most plausibly explained by limited statistical power in small samples and by methodological heterogeneity across the trials. The studies differed in comparator (no-treatment control versus verapamil), HA protocol and dose (a 6-month, 30-injection 20 mg regimen in Gennaro et al. versus 8–12-week, 16 mg regimens elsewhere), follow-up duration (3 months versus 12–30 months), and outcome-assessment methods (two-dimensional ultrasonographic plaque size versus three-dimensional volume; IIEF-5 versus IIEF-15). Such heterogeneity affects both the magnitude and the apparent significance of effects and is the principal reason a quantitative meta-analysis was not performed.

Accordingly, the overall certainty of this evidence is low for most efficacy outcomes (Table 5), reflecting the small number of studies, the contribution of two non-randomised designs, imprecision, and between-study inconsistency. The potential for reporting bias cannot be excluded, as protocol pre-registration was not consistently documented across the primary studies, and the small literature increases the risk that null comparisons are under-reported. From an implementation perspective, an inexpensive, office-based agent such as HA could be especially valuable in low- and middle-income settings, including Indonesia, where collagenase and reconstructive surgery are often inaccessible; however, real-world adoption will depend on local drug availability, training in intralesional technique, cost-reimbursement structures, and culturally sensitive counselling, all of which warrant context-specific evaluation.

Implications and limitations

Scientific Contribution

To our knowledge, this is the first systematic review to focus exclusively on intralesional HA in the acute/active phase of PD, appraising it against both passive observation and an active comparator using RoB 2.0, ROBINS-I, and GRADE. By restricting inclusion to prospective trials, it minimises the recall and selection biases inherent in retrospective analyses and provides a transparent, reproducible evidence map for an under-studied clinical window. This novelty should, however, be read alongside an important caveat: the entire acute-phase HA evidence base currently rests on only four studies, several of which share overlapping author groups and a common 16 mg/2 mL HA formulation and dosing philosophy. This concentration within a relatively small research network raises the possibility that current effect estimates could reflect, in part, shared centre-specific practices, patient populations, or outcome-assessment conventions rather than a fully

generalisable treatment effect, and it limits external validity across other healthcare systems. Independent replication by unrelated research groups, ideally across different geographic and healthcare-system contexts, is therefore needed before the magnitude of benefit reported here can be considered a stable estimate rather than one that may be revised, in either direction, as further studies accumulate.

Clinical Significance

The consistent direction of benefit across curvature, plaque burden, and erectile function, combined with an excellent safety profile, supports consideration of intralesional HA as a proactive, non-surgical option worth evaluating further during the acute phase. It should be emphasised, however, that none of the included studies directly assessed surgical avoidance, long-term preservation of penile length, or a reduction in future reconstructive-surgery rates; the demonstrated outcomes are limited to short-to-medium-term changes in curvature, plaque size or volume, pain, and erectile function (Abdel Fattah et al., 2024; Gennaro et al., 2015), and any downstream benefit for surgical avoidance or length preservation remains a plausible but as-yet-untested hypothesis.

Limitations

Several limitations temper these conclusions. First, only four studies (582 patients) met inclusion, two of which were non-randomised, introducing confounding and selection bias—particularly Gennaro et al. (2015), whose voluntary no-treatment control may have favoured the intervention arm. Second, treatment protocols, HA concentrations, follow-up durations, and outcome measures were heterogeneous, precluding meta-analysis and limiting the definition of a standardised regimen. Third, most active-comparator trials used a short three-month follow-up, leaving long-term durability uncertain; only Gennaro et al. (2015) provided longer data. Fourth, and most importantly for interpretation, the certainty of evidence is low for most efficacy outcomes, and the small evidence base limits generalisability across populations and healthcare settings.

Future Research Priorities

First, large-scale, multicentre, double-blind RCTs with extended follow-up of at least 12–24 months are needed, using standardised HA formulations (molecular weight and concentration, e.g., 16 mg/2 mL highly purified sodium salt) and standardised dosing frequency and cycle number to establish an evidence-based infiltration protocol while maintaining cost-effectiveness. Second, head-to-head comparisons of HA against other acute-phase conservative modalities (e.g., low-intensity extracorporeal shockwave therapy or vacuum/traction devices) and evaluation of combination therapy are warranted; because phosphodiesterase-5 inhibitors (PDE5i) possess independent antifibrotic properties via increased cyclic guanosine monophosphate and TGF-β1 down-regulation, trials combining daily low-dose PDE5i with intralesional HA could reveal clinical synergy. Third, integrating molecular and translational biomarkers (e.g., TGF-β1, matrix metalloproteinases, tissue inhibitors of metalloproteinases) with therapeutic response would help identify the PD phenotypes most responsive to early, non-surgical intervention and refine patient selection (Herati & Pastuszak, 2016).

Relevance to Practice

The findings identify intralesional hyaluronic acid as a promising, well-tolerated investigational option for acute-phase Peyronie's disease, but the low certainty of evidence for most efficacy

outcomes means it is not yet ready for routine adoption or formal guideline recommendation. Clinicians and institutions considering its use should do so within research or closely monitored context, pending confirmation in adequately powered multicentre randomised trials. Should such trials confirm benefit, future implementation would also need to account for cost-effectiveness and accessibility across diverse healthcare settings so that non-surgical care can eventually reach patients in resource-limited environments.

Conclusion

In summary, intralesional hyaluronic acid is a promising, non-surgical option for acute-phase Peyronie's disease, with evidence from prospective studies showing consistent improvements in penile curvature, plaque size or volume, erectile function, and pain, an excellent safety profile, and benefit that is clearest relative to no treatment and suggestive—though not consistently significant—relative to verapamil; however, because the certainty of evidence is limited by only four small, heterogeneous studies, these findings should be interpreted with caution and confirmed by large-scale, multicentre RCTs with standardised protocols and extended follow-up before HA is integrated into clinical guidelines.

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CrediT Authorship Contributions Statement

Abdur Rahman Faqih Al Jundi: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Visualization.

Raden Danarto: Conceptualization, Methodology, Validation, Supervision, Writing – Review & Editing.

Nur Budiono: Investigation, Resources, Data Curation, Project Administration, Writing – Review & Editing.

Conflicts of Interest

There is no conflict of interest.

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