available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review

Editorial by XXX on pp. x–y of this issue

Clinical Efficacy of Injection and Mechanical Therapy for Peyronie's Disease: A Systematic Review of the Literature

Giorgio Ivan Russo^{a,*}, Uros Milenkovic^b, Wayne Hellstrom^c, Laurence A. Levine^d, David Ralph^e, Maarten Albersen^b

^a Urology Section, Department of Surgery, University of Catania, Catania, Italy; ^b Department of Urology, University Hospitals Leuven, Leuven, Belgium;

^c Department of Urology, Tulane University School of Medicine, New Orleans, LA, USA; ^d Department of Urology, Rush University Medical Center, Chicago, IL, USA; ^e St Peters Andrology Centre and The Institute of Urology, University College London Hospital, London, UK

Article info

Article history:

Accepted July 7, 2018

Associate Editor:

Jean-Nicolas Cornu

Keywords:

Collagenase *Clostridium histolyticum*
Hyaluronic acid
Interferon α -2b
Intralesional therapy
Penile curvature
Penile traction
Peyronie's disease
Vacuum device
Verapamil

Abstract

Context: Conservative therapies for Peyronie's disease (PD) aim to treat early-stage disease by improving clinical outcomes such as penile curvature, penile length erectile dysfunction, and pain.

Objective: To summarise the available evidence regarding injection and mechanical therapies for PD treatment.

Evidence acquisition: An extensive search of Medline, Embase, and Scopus databases retrieved English-language articles up to 15 May 2018. The systematic review protocol was registered on PROSPERO (CRD42017077050). Inclusion criteria were as follows: adults with early or chronic PD receiving treatment with injection therapy, penile traction, or a vacuum device.

Evidence synthesis: Fifty-two articles were selected according to the inclusion criteria—17 comparative studies and 35 cohort studies—analysing the effects of calcium channel blockers (verapamil, nifedipine), collagenase *Clostridium histolyticum* (CCH), interferon α -2b (IFN α -2b), hyaluronic acid (HA), onabotulinum toxin A, thiolcolchicine, penile extender devices, and vacuum devices. Qualitative data from these studies suggest a clinically significant effect of CCH and IFN α -2b injection therapy to decrease penile curvature and conserve penile length. Verapamil and HA performed well in single-arm or case-control studies. Studies of penile traction and vacuum devices in patients with PD demonstrated some benefits in terms of curvature and penile length but only in small, underpowered, nonrandomised studies. Studies of onabotulinum toxin A injections or thiolcolchicine showed significant improvements in penile curvature, but only in studies of single-arm or case-control design.

Conclusions: CCH and IFN α -2b injected into stable PD plaques can decrease penile curvature; CCH can also improve penile length. However, based on available data, strong conclusions cannot be drawn for other treatments, including calcium channel blockers, HA, or mechanical therapies.

Patient summary: Our systematic review of injection therapies provides evidence for improvements in penile curvature for patients with Peyronie's disease. No robust evidence is available to support the use of other local treatments including calcium channel blockers, hyaluronic acid, or mechanical therapies.

© 2018 European Association of Urology. Published by Elsevier B.V. All rights reserved.

* Corresponding author. Urology Section, University of Catania, Via Santa Sofia 78, 95125, Italy. Tel. +390953782710.

E-mail address: giorgioivan1987@gmail.com (G.I. Russo).

<https://doi.org/10.1016/j.eururo.2018.07.005>

0302-2838/© 2018 European Association of Urology. Published by Elsevier B.V. All rights reserved.

Please cite this article in press as: Russo GI, et al. Clinical Efficacy of Injection and Mechanical Therapy for Peyronie's Disease: A Systematic Review of the Literature. Eur Urol (2018), <https://doi.org/10.1016/j.eururo.2018.07.005>

1. Introduction

Peyronie's disease (PD) is a progressive fibrotic disorder of the tunica albuginea that causes penile deformity, making sexual intercourse difficult. It can result in significant psychological stress for patients and partners alike. PD occurs in ~22.4–25.7 per 100 000 men, with the highest incidence in men aged 50–59 yr [1]. Current conservative therapies for PD aim to treat patients in the early stages of the disease. Several options are available, including oral pharmacotherapy, intralesional injection therapy, topical treatments and penile extender and vacuum devices [2]. The rationale for intralesional therapy is based on the inflammatory and fibrotic aetiopathology of the disease [1,3].

Level 1 evidence regarding intralesional and local mechanical treatment is currently lacking, and outcomes of different studies are difficult to compare owing to heterogeneity between protocols. Injection therapies have become popular to reduce penile pain (PP), plaque size (PS), and/or penile curvature (PC). In 2013, collagenase *Clostridium histolyticum* (CCH) was introduced as the first (and to date only) Food and Drug Administration- and European Medicines Agency-approved treatment option for PD [4,5]. CCH has been shown in consecutive randomised controlled trials (RCTs) to reduce PC in men with PD [6]. However, a plethora of intralesional therapies are being offered to patients, despite a lack of efficacy data. Studies of local injectables and mechanical therapies for PD have produced contradictory results, and poor study design, including lack of placebo, limited number of participants, short-term follow-up, and different outcome measures, make it difficult to draw recommendations for the use of these therapies in a real-life setting [7].

Based on these limitations, this systematic review summarises and critically interprets the available evidence regarding injection therapies, penile extenders, or vacuum pump device use for the treatment of PD.

2. Evidence acquisition

An extensive search of Medline, Embase, and Scopus databases was conducted to retrieve English-language articles published up to 15 May 2018 (PROSPERO registration [CRD42017077050]). Search terms are shown in the Supplementary material and the protocol was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [8].

Retrieved studies had to include adults with early or chronic PD receiving injection therapy or treatment with a penile extender or vacuum device.

Retrospective studies, prospective clinical studies with single-arm design, or comparative, placebo-controlled clinical trials were included in the qualitative analysis. Congress meetings, editorial comments, and review papers were excluded. Studies describing surgical interventions and oral therapy alone were excluded from the analysis. Other exclusion criteria were as follows: case reports,

extracorporeal shock wave therapy, and full texts not available in the English language.

Two reviewers (G.I.R. and U.M.) independently assessed the eligibility of the identified papers (96% agreement), and any disagreements were discussed with a third reviewer (M.A.).

The primary end point of this systematic review was clinical efficacy of PD therapies to reduce PC; secondary end points were changes in PS, erectile function (EF), PP, and penile length (PL). Studies were included if at least one of the previously listed end points were assessed. In case of studies that included the same patient cohort but conducted assessments at different time points, the most recent study has been included.

3. Evidence synthesis

3.1. Literature search results

After removing duplicates, a total of 407 studies were identified by the literature search and independently screened. Of these articles, 52 fit the inclusion criteria and were further assessed for eligibility (Fig. 1): 17 comparative studies [6,9–23] and 35 noncomparative studies [3,24–59] (Tables 1 and 2). Two studies that included investigation of oral + verapamil therapy were included, and one included interferon α -2b (IFN α -2b) injection versus IFN α -2b + Vit. E versus oral Vit. E; however, only the study arms that investigated injection therapy as a single treatment modality were assessed [3,31]. The overall characteristics of included studies are listed in Tables 1–5.

3.2. Risk of bias assessment

The risk of bias in all included RCTs was evaluated according to the Cochrane Collaboration risk of bias tool [60]. For nonrandomised studies, we used the ROBINS-I tool to address the methodological quality [61].

Overall, the risk of bias of RCTs was deemed to be low (Fig. 2), whereas the risk was moderate or critical for nonrandomised studies in measurement of outcomes and selection of the reported results (Fig. 3).

3.3. Efficacy data in comparative studies

3.3.1. Calcium channel antagonists: verapamil or nifedipine

A total of nine studies evaluated the clinical efficacy of verapamil; seven were randomised [10,13,16,17,19,21,22] and two were nonrandomised (Table 1) [9,20].

Only two prospective nonrandomised studies were identified.

Only one study by Rehman et al. [19] compared 10 mg of intralesional verapamil injection with placebo (saline solution), demonstrating a reduction of PC from 37.7° to 29.6° for verapamil compared with a reduction from 33.6° to 31.4° for placebo. Furthermore, verapamil was also superior to placebo in terms of PS reduction and preservation of EF.

Fig. 1 – PRISMA flow diagram.

ESWT = extra corporeal shock wave therapy; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.

Soh and coworkers [21] performed a randomised placebo-controlled study to investigate the effects of 10 mg nicardipine injections versus placebo. This study showed no effect on PC but showed an effect on PP.

Three studies used a randomised, double-blind, placebo-controlled, partial cross-over design to compare verapamil applied using transdermal electromotive administration (TEA) with placebo + TEA [13], verapamil versus verapamil + TEA [16], and verapamil + TEA versus orgotein + dexamethasone [17]. Of these, the first one was not able to show a statistical PC improvement in either group [13], whereas the second [16] did not report PC as an outcome of the study; however, PP (assessed by a visual analogue score [VAS]) decreased significantly after verapamil + TEA [16]. The third study demonstrated an improvement in PC in both the verapamil + TEA and the orgotein + dexa-

methasone groups, but the study did not perform intergroup analysis [17].

Favilla and colleagues [10] compared intralesional verapamil with hyaluronic acid (HA) injection, showing a significant reduction in PC in men treated with HA (-4.60°) compared with baseline and the verapamil group, in which no effect was observed. An RCT by Toscano et al. [22] compared verapamil (5 mg) with thiocolchicine (4 mg), showing a significant improvement in PC in both groups compared with baseline. However, no intergroup comparison was performed.

Abern et al. [9] compared verapamil + penile traction + oral pentoxifylline and L-arginine (group I) with verapamil + oral pentoxifylline and L-arginine (group II), demonstrating significant decreases in PC in both groups (group I: 44.4° vs 33.4° ; group II: 36.6° vs 21.5°). However, intergroup

Table 1 – Characteristics of selected original publications on calcium channel blockers identified by systematic literature review

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
<i>Comparative studies</i>							
Abern et al (2012) [9]	Prospective nonrandomised	Verapamil + penile traction + oral pentoxifylline and L-arginine (group I) vs verapamil + oral pentoxifylline and L-arginine (group II)	39 (group I); 35 (group II)	44.4° ± 27.5° (group I); 36.6° ± 18.5° (group II)	10 mg verapamil every other week for a total of 24 wk + oral L-arginine 1 g b.i.d. and pentoxifylline 400 mg t.i.d. + penile traction (2–8 h daily)	33.4° ± 25.3° (group I); 21.5° ± 19.3° (group II)	p = 0.03 (group I); p < 0.01 (group II)
Favilla et al (2017) [10]	Randomised	Verapamil vs HA	69 (verapamil); 63 (HA)	90.5° ≥ 30° (verapamil); 95.7° ≥ 30° (HA)	Intralesional verapamil injection (10 mg in 5 ml of normal saline) weekly for 12 wk; intralesional HA injection (0.8% highly purified sodium salt HA 16 mg/2 ml) weekly for 12 wk	0.0° ± 0.0° (verapamil); 4.60° ± 5.63° (HA)	p < 0.001 (HA); p < 0.001 HA vs verapamil
Greenfield et al (2007) [13]	Randomised	EMDA verapamil (group I) vs EMDA placebo (group II)	23 (group I); 19 (group II)	43.5° ± NR (group I); 51.1° ± NR (group II)	10 mg verapamil in 4 ml saline solution + Mini-Physionizer device (2.4 mA for 20 min twice weekly) for a total of 3 mo	34° ± NR (group I); 43° ± NR (group II)	NS
Mehrsai et al (2013) [16]	Randomised	Verapamil vs TEA verapamil	30 (verapamil); 30 (TEA)	NR	6 weekly doses of 10 mg verapamil + 4 mg dexamethasone diluted in 2 ml distilled water by TEA or intralesional injection	NR	–
Montorsi et al (2000) [17]	Randomised, double-blind, placebo-controlled, partial cross-over design (group I); uncontrolled (group II)	EMDA 8 mg of orgotein + 8 mg of dexamethasone + 120 mg of lidocaine (group I) vs EMDA verapamil (group II)	40 (group I); 40 (group II)	30° (range: 20–45°, group I); 30° (range: 20–45°, group II)	9 sessions (3 times a week for 3 wk; sessions administered every other day) a duration of 20 min each	20° (range: 0–45°, group I); 20° (range: 0–45°, group II)	p < 0.05 (both groups vs baseline)
Rehman et al (1998) [19]	Randomised	Verapamil vs placebo	7 (verapamil); 7 (placebo)	37.71° ± 9.3° (SEM; verapamil); 33.57° ± 9.7° (SEM; placebo)	10 mg/1 ml of verapamil; dosage 10–27 mg	29.57° ± 7.3° (SEM; verapamil); 31.43° ± 8.9° (SEM; placebo)	p < 0.07 (verapamil vs placebo)
Shirazi et al (2009) [20]	Prospective nonrandomised	Verapamil vs control	40 (verapamil); 40 (control)	49.71° ± 9.3° (verapamil); 45.57° ± 9.7° (control)	10 mg of verapamil in 10 ml of distilled water twice weekly for 12 wk	47.57° ± 7.3° (verapamil); 43.43° ± 8.9° (control)	p = 0.91 (verapamil vs control)
Soh et al (2010) [21]	Randomised	Nicardipine vs placebo	32 (nicardipine); 30 (placebo)	NR	10 mg nicardipine (in 10 ml of distilled water) biweekly in 10 wk with a total of six sessions	NR	p = 0.13 nicardipine vs placebo
Toscano et al (2006) [22]	Randomised	Thiocolchicine vs verapamil	13 (thiocolchicine); 12 (verapamil)	46.77° ± 16.48° (thiocolchicine); 50.42° ± 10.97° (verapamil)	2 ml injection containing 4 mg of thiocolchicine; 2 ml of a solution containing 5 mg of verapamil	36.23° ± 15.78° (thiocolchicine); 42.08° ± 13.08° (verapamil)	p = 0.019 (thiocolchicine); p = 0.012 (verapamil)

Table 1 (Continued)

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
<i>Single-arm studies</i>							
Bennett et al (2007) [27]	Prospective nonrandomised	Verapamil	94	50° (±28°)	6 intralesional injections (10 mg in 5 ml saline) every 2 wk	47° (±35°)	NS
Cavallini et al (2007) [29]	Prospective nonrandomised	Verapamil 10 mg/4 ml (group I); verapamil 10 mg/10 ml (group II); verapamil 10 mg/20 ml (group III)	27 (group I); 24 (group II); 26 (group III)	28.1° (±13°; group I); 27.2° (±11.1°; group II); 29.4° (±13.6°; group III)	5–6 injections every 2 wk. for a total of 12 sessions	23.4° ± 11.8° (group I); 20.5° ± 8.9° (group II); 15.8° ± 7.7° (group III)	NS
Dell'Atti (2015) [31]	Prospective nonrandomised	Verapamil	23	21.24° (range 11–27°)	1 injection/wk for 12 wk	19.8° (NR)	NS
Favilla et al (2013) [3]	Prospective randomised	Verapamil 10 mg in 5 ml (group I); verapamil + oral antioxidants (group II)	52 (group I); 53 (group II)	47.9° (9.12; group I); 49° (8.81; group II)	1 injection/wk for 12 wk	Change: –10.86° (±9.5°; group I); 11.97° (±8.55°; group II)	p < 0.05 (group I); p < 0.05 (group II)
Heidari et al (2010) [34]	Prospective nonrandomised	Verapamil	16	17.18° (±16.52°)	Verapamil 10 mg/cm ² every 2 wk for a total of 6 injections	12.5° (±13.4°)	p < 0.01
Levine et al (2002) [40]	Prospective nonrandomised	Verapamil	156	NR	10 mg in 10 ml saline every 2 wk, with a total of 12 injections	79 patients reported decreased curvature; 41% grade 1 (<30°) improved; 68% grade 2 improved; 62% grade 3 improved	p < 0.01
Levine (1997) [38]	Prospective nonrandomised	Verapamil	38	NR	10 mg in 10 ml saline every 2 wk, with a total of 12 injections	50% of grade 1 (<30°) improved; 57% of grade 2 improved; 46% of grade 3 improved	NR
Levine et al. (1994) [41]	Prospective nonrandomised	Verapamil	14	48° (range: 10–90°)	10 mg verapamil in 10 ml saline	21° (range 10–35°)	NR
Moskovic et al (2011) [44]	Prospective nonrandomised	Verapamil	131	40° (max. 150°)	10 mg verapamil in 5 ml saline intralesional injections once every 2 wk, for a total of 6 injections	26% patients improved (mean 17° [5]); 62% unchanged	NR
Wolff et al. (2015) [55]	Prospective nonrandomised	Verapamil	60	37.3° (±13.3°)	6 verapamil injections 15 mg in 6 ml saline, once every 3 wk	21° (±13°)	p < 0.05
b.i.d. = bis in die (twice daily); EMDA = electromotive drug administration; HA = hyaluronic acid; NR = not reported; NS = not significant; SEM = standard error of the mean; TAE = transdermal electromotive administration; t.i.d. = ter in die (three times daily).							

Table 2 – Characteristics of selected original publications on IFN-2b identified by systematic literature review

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
<i>Comparative studies</i>							
Hellstrom et al (2006) [14]	Randomised	IFN α -2b vs placebo	53 (IFN α -2b); 50 (placebo)	49.9° $\pm$ 2.4° (IFN α -2b); 50.9° $\pm$ 2.5° (Placebo)	Intralesional injections of 5 $\times$ 10 ⁶ IU IFN α -2b in 10 ml saline weekly for a total of six injections	36.4° $\pm$ 2.1° (IFN α -2b); 46.4 $\pm$ 2.2° (placebo)	p < 0.001 (IFN α -2b); p < 0.01 IFN α -2b vs placebo
Kendirci et al (2005) [15]	Randomised	IFN α -2b vs placebo	19 (IFN α -2b); 20 (placebo)	48.75° $\pm$ 4.41° (IFN α -2b); 47.75° $\pm$ 2.84° (Placebo)	Intralesional injections of 5 $\times$ 10 ⁶ IU IFN α -2b in 10 ml saline weekly for a total of six injections	36.75° $\pm$ 4.53° (IFN α -2b); 44.10 $\pm$ 3.02° (placebo)	p < 0.001 (IFN α -2b); p < 0.01 IFN α -2b vs placebo
Inal et al (2006) [63]	Prospective	IFN α -2b vs oral Vit. E vs IFN α -2b + oral Vit. E	NR	33° $\pm$ 10.3°	5.0 $\times$ 10 ⁶ U per 12 wk	31.5° $\pm$ 9.7°	p > 0.05
Yafi et al (2015) [23]	Retrospective comparative	IFN α -2b + penile traction (group I); IFN α -2b (group II)	112	42.3° (SD 20.8; group I); 42.2° (SD 14.6; group II)	Biweekly injections of 2 $\times$ 10 ⁶ IU IFN α -2b + > 2 h traction daily	Change of –8.1° (SD 16; group I); –9.9° (SD 11.8; group II)	NS
<i>Single-arm studies</i>							
Ahuja et al (1999) [24]	Prospective nonrandomised	IFN α -2b	21	NR	1 injection 0.1 ml	37.2% improvement ($\pm$ 30.65%)	NR
Astorga et al (2000) [26]	Prospective nonrandomised	IFN α -2b	34	NR	10 $\times$ 10 ⁶ IU in 10 ml saline twice weekly for 14 wk	NR	–
Brake et al (2001) [28]	Prospective nonrandomised	IFN α -2b	23	32° (range 20–50°)	3 times a week for 3 wk (2 $\times$ 10 ⁶ IU)	Only improved in 1 patient	NR
Dang et al. (2004) [30]	Prospective nonrandomised	IFN α -2b	21	NR	Biweekly injections (2 $\times$ 10 ⁶ IU) for 6 wk	14 patients improved >20%	NR
Judge and Wisniewski (1997) [36]	Prospective nonrandomised	IFN α -2b	13	45° (range 30–75°)	3 times a week for 3 wk (1.5 $\times$ 10 ⁶ IU)	12° (NR)	NR
Polat et al (1997) [47]	Prospective nonrandomised	IFN α -2b	15	10 patients <30°; 5 patients >30°	3 times a week for 2–4 wk (3 $\times$ 10 ⁶ IU)	10 patients with <30° recovered completely; all other patients improved 10–20°	NS
Stewart et al (2015) [51]	Retrospective	IFN α -2b	131	NR	Biweekly injection (2 $\times$ 10 ⁶ IU) for 6 wk	34.1° ($\pm$ 21.6°)	NR
Wegner et al (1995) [53]	Prospective nonrandomised	IFN α -2b	25	16.6° (range 7–65°)	1 $\times$ 10 ⁶ IU of IFN α -2b weekly for 5 wk	NR	–
Wegner et al (1997) [54]	Prospective nonrandomised	IFN α -2b	30	10° (range 0–45°)	3 injections of 3 $\times$ 10 ⁶ IU of IFN α -2b	Improvement in 1 patient	–
IFN α -2b = interferon α -2b; IU = international unit; NR = not reported; NS = not significant; SEM = standard error of the mean.							

Table 3 – Characteristics of selected original publications on HA identified by systematic literature review

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
<i>Comparative studies</i>							
Favilla et al (2017) [10]	Randomised	Verapamil vs HA	69 (verapamil); 63 (HA)	90.5% $\geq 30^\circ$ (verapamil); 95.7% $\geq 30^\circ$ (HA)	Verapamil (10 mg in 5 ml of normal saline) weekly for 12 wk; intralesional treatment with HA (0.8% highly purified sodium salt HA 16 mg/2 ml) weekly for 12 wk	0.0° $\pm$ 0.0 (verapamil); 4.60° $\pm$ 5.63 (HA)	p < 0.001 (HA); p < 0.001 HA vs verapamil
Gennaro et al (2015) [12]	Prospective controlled	HA vs control	83 (HA); 81 (control)	21.52 $\pm$ 7.27 (HA); 21.88 $\pm$ 11.16 (Control)	30 injections in total over 6 mo of HA 20 mg. In the first 12 wk of treatment the injections were performed every 5 d whereas from the 13th week they were performed every 7 d	0.0° $\pm$ 0.0° (HA); +15.37° $\pm$ 16.00° (control)	p < 0.0001
<i>Single-arm studies</i>							
Lamprakopoulos et al (2000) [37]	Prospective nonrandomised	Hyaluronic acid	112	Curvature in 72.32% of patients	Hyaluronidase (1500 IU) every 2 wk and a total of 12 injections for each palpable plaque over a period of 5 mo	In 32.08% of patients, curvature resolved completely	NR
Zucchi et al (2016) [59]	Prospective nonrandomised	Hyaluronic acid	65	30° (range 0–50°)	10-wk cycle weekly injections (0.8% purified sodium salt HA 16 mg/2 ml)	20° (range 0–40°)	p < 0.01
HA = hyaluronic acid; NR = not reported.							

analysis was not performed. Shirazi et al. [20] performed a comparative study with a control group showing no benefit of verapamil injections on any of the end points.

Based on these data, the evidence is not robust enough to support the use of verapamil injections and does not suggest a meaningful improvement in PC compared with placebo. In fact, most of the studies investigating verapamil therapy did not perform direct statistical comparison between groups, leading to a high risk of bias.

3.3.2. Interferon α -2b

Three studies analysed clinical efficacy of IFN α -2b, two randomised versus placebo [14,15] and one retrospective study [23] (Table 2). In their randomised controlled study, Kendirci et al. [15] demonstrated superiority of IFN α -2b versus placebo for PC (36.8° vs 44.1°) but not for PS (3.45 vs 3.9 cm²). Furthermore, Hellstrom and colleagues [14] demonstrated a clinical benefit of IFN α -2b compared with placebo for PC (36.4° vs 46.4°) and PS (2.2 vs 3.6 cm²), but not for EF or PP.

A retrospective study by Yafi et al. [23] compared IFN α -2b + penile traction (group I) with IFN α -2b alone (group II). However, the authors did not demonstrate clinical benefit compared with baseline in either group in terms of PC or PL.

These data suggest that injection therapy with IFN α -2b improves PC, based on two randomised, placebo-controlled trials. However, the addition of traction failed to provide additional clinical benefit in terms of either PC or PL.

3.3.3. Hyaluronic acid

Gennaro et al. [12] compared injection of 20 mg HA with a control group of patients who received no treatment, showing that HA therapy stabilised PC at a 12-mo follow-up period after HA treatment (+0.0°), compared with the control group (+15.4°). HA injections also reduced PS (–0.73 mm³) and improved EF, according to the International Index of Erectile Function questionnaire 15 (IIEF-15; +1.24), compared with the control group. No differences were observed in the PP VAS (–1.66 HA vs –1.5 control; Table 3).

The efficacy of HA according to this non-placebo-controlled study seems to be limited, as no improvement in PC was reported. Moreover, the slight improvements in PS and EF do not translate into clinically significant benefits.

3.3.4. CCH

Two randomised prospective studies have compared CCH therapy against placebo [6,11]: one RCT compared CCH + vacuum + modelling with CCH + vacuum [18] and one prospective nonrandomised study compared CCH + penile traction with CCH alone [58] (Table 4). Gelbard and colleagues [11] first reported a subjective positive response to CCH therapy, demonstrating 36% and 4% improvements in PC after CCH and placebo, respectively.

In 2013, results from the IMPRESS I and II RCT demonstrated that CCH was superior to placebo in terms of percentage improvement in PC (–34% and –18.2%, respectively), EF (mean change in IIEF-15 of +1.0 and +0.4, respectively), and PL (0.4 and 0.2 cm, respectively), but not when considering PP [6].

Table 4 – Characteristics of selected original publications on CCH identified by systematic literature review

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
<i>Comparative studies</i>							
Gelbard et al (1993) [11]	Randomised	Collagenase vs placebo	22 (CCH); 27 (placebo)	Category 1 patients were characterised as those with a bend of $\leq 30^\circ$, and/or palpable plaque < 2 cm in extent. Category 2 patients displayed $30\text{--}60^\circ$ angular deformity and/or $2\text{--}4$ cm of palpable plaque in maximal dimension. Category 3 patients were those with $> 60^\circ$ angular deviation and/or > 4 cm of palpable plaque	6000 units for category 1, 10 000 units for category 2, and 14 000 units for category 3 patients	Subjective positive response. Overall: 36% (CCH) and 4% (placebo). Category 1: 100% (CCH) and 25% (placebo). Category 2: 36% (CCH) and 0% (placebo). Category 3: 13% (CCH) and 0% (placebo)	$p < 0.007$ (overall); $p = 0.03$ (category 2)
Gelbard et al (2013) [6]	Randomised	Collagenase vs placebo	401 (CCH); 211 (placebo)	$50.1^\circ \pm 14.4^\circ$ (CCH); $49.3^\circ \pm 14.0^\circ$ (placebo)	3 cycles of 2 injections of CCH (0.58 mg) with an interval of $\sim 24\text{--}72$ h between each injection	$33.1^\circ \pm 16.8^\circ$ (CCH); $40.0^\circ \pm 16.2^\circ$ (placebo)	$p < 0.0001$
Ralph et al. (2017) [18]	Randomised	Collagenase + vacuum + modelling (group I) vs. collagenase + vacuum (group II)	15 (group I); 15 (group II)	59.0 ± 15.0 (group I); 58.3 ± 12.2 (group II)	Two intralesional injections of CCH 0.58 mg separated by $\sim 24\text{--}72$ h for four cycles ~ 6 wk long + vacuum twice daily (morning and evening) from 14 ± 2 d after the second injection of CCH in each treatment cycle until the start of the next cycle	Change of $-23.7^\circ \pm 10.9^\circ$ (group I); change of $-23.3^\circ \pm 7.2^\circ$ (group II)	NS
Ziegelmann et al (2017) [62]	Prospective nonrandomised study	CCH + penile traction (group I) vs CCH (group II)	35 (group I); 16 (group II)	$55.7^\circ (\pm 19.3^\circ)$; group I); $50.8^\circ (\pm 19.8^\circ)$; group II)	2 CCH injections per series with 4 total series recommended + modelling with a flaccid penis for a minimum of 3 h daily	$16.1^\circ (\pm 14.9^\circ)$; group I); $20.8^\circ (\pm 15.3^\circ)$; group II)	$p < 0.001$ (group I); $p < 0.001$ (group II)
<i>Single-arm studies</i>							
Anaissie et al. (2017) [25]	Retrospective	CCH	77	$58.2^\circ (\pm 17.9^\circ)$	3 cycles of 2 injections of CCH (0.58 mg) with an interval of $\sim 24\text{--}72$ h between each injection	$41^\circ (\pm 17^\circ)$	NR
Cocci et al (2018) [64]	Prospective	CCH	15	135	3 intralesional injections of 0.9 mg of CCH performed at 4-wk intervals at the point of maximum curvature	$-19.07^\circ (-30.0^\circ; -15.0^\circ)$	$p < 0.01$

Table 4 (Continued)

Study	Design	Interventions	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
Goldstein et al (2017) [32]	Prospective nonrandomised	CCH	189	46.9° (±12°)	Maximum 4 cycles of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	Change –36.3% (±30.72%)	p < 0.01
Jordan (2008) [35]	Prospective nonrandomised	CCH	25	55.8° (range 15–75°)	3 injections 10 000 IU/0.25 cm ³ per injection administered over 7–10 d	Change –12.7° (NR)	p < 0.05
Levine et al (2015) [39]	Prospective nonrandomised	CCH	347	53° (14.82)	Maximum 4 cycles (each 6 wk) of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	34.7° (±15.36°)	p < 0.05
Nguyen et al (2017) [46]	Prospective nonrandomised	CCH	Acute phase 36 (group I); chronic phase 126 (group II)	60.6° (±18.5°; group I); 56.9° (±15.2°; group II)	Maximum 4 cycles (each 6 wk) of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	43.9° (±16°; group I); 41.3° (±15.3°; group II)	NS
Raheem et al (2017) [48]	Prospective nonrandomised	CCH + vacuum	53	54.17° (±15.38°)	3 cycles of 1 injection (0.9 mg) + vacuum	37° (range: 12–57°)	p < 0.01
Yang et al (2016) [56]	Prospective nonrandomised	CCH	49	49.3° (range: 30–100°)	Maximum 4 cycles (each 6 wk) of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	Change –15.4° (range: –10° to –60°)	p < 0.01
Ziegelmann et al (2016) [57]	Prospective nonrandomised	CCH	27	60° (20.1)	Maximum 4 cycles (each 6 wk) of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	37.4° (±21.2°)	p < 0.01
Ziegelmann et al (2017) [58]	Prospective nonrandomised	CCH	52	45° (range 35–70°; patient perceived)	Maximum 4 cycles (each 6 wk) of 2 injections of CCH (0.58 mg) with an interval of ~24–72 h between each injection	Change –15° (range: –5° to –30°)	p < 0.01

CCH = collagenase *Clostridium histolyticum*; NR = not reported; NS = not significant.

Table 5 – Characteristics of selected original publications on penile traction or onabotulinum toxin A identified by systematic literature review

Study	Design	Intervention	n	Baseline penile curvature	Treatment protocol	Post-treatment penile curvature	p value
Contero et al (2009) [33]	Prospective nonrandomised	Penile traction	19	31° (±1.55°)	600 g during the 1st month, 900 g during the 2nd month, up to 1200 g during the 5th and 6th months	27 (±2.79)	0.059
Levine et al (2008) [42]	Prospective nonrandomised	Penile traction	11	51° (range: 30–85°)	2–8 h/d for 6 mo, every 2 wk, extender rods were lengthened by 0.5 cm	Improvement in 33% of patients	NS
Martínez-Salamanca et al (2014) [43]	Prospective nonrandomised	Penile traction	55	33° (range: 10–90°)	6–9 h/d for 6 mo	13° (NR)	<0.05
Raheem et al (2010) [49]	Prospective nonrandomised	Vacuum device	31	47.6° (range: 10–95°)	10 min vacuum twice daily for 12 wk	67% improvement	<0.01
Muñoz-Rangel et al (2015) [45]	Prospective nonrandomised	Onabotulinum toxin A	22	32.95° ± 9.21°	100 IU	25° ± 9.38°	0.02

IU = international unit; NR = not reported; NS = not significant.

A study by Ralph et al. [18] compared CCH + vacuum + manual modelling with CCH + vacuum therapy, but failed to show a significant difference between these two approaches in terms of PC reduction, PP, or EF. Similarly, a prospective nonrandomised study by Ziegelmann et al. [62] compared CCH + penile traction with CCH alone. While the PC improved from baseline by 32.6% and 32.5% respectively, there was no significant difference in PC and stretched PL between both treatment groups.

In the IMPRESS I and II clinical trials, men treated with CCH demonstrated a significantly greater percentage reduction in PC (−34%) and improvement in patient-reported PD bother compared with those who received placebo (−2.8 ± 3.8 vs −1.8 ± 3.5). However, they also observed an 18% improvement from baseline in the placebo arm, presumably because of penile modelling. These findings raise questions regarding the putative role of penile modelling compared with placebo in improving outcomes in men with PD. Certainly, modelling seems to have an effect that is greater than the placebo effect observed in most randomised, placebo-controlled clinical trials. Further studies of CCH with or without penile modelling would be useful to better understand the roles of both these treatment modalities in improving PC.

3.4. Efficacy data of single-arm studies

3.4.1. Verapamil

A total of 12 studies have evaluated the clinical effects of verapamil using a single-arm study design [3,27,29,31,34,38,40,41,44,50,52,55] (Table 1). Five studies [3,34,40,52,55] demonstrated significant improvements in PC after 10 or 15 mg intralesional verapamil, although the protocols varied widely, ranging from six to 12 injections per week. Two articles showed no statistically significant benefit of verapamil injections on the primary end point of PC [27,31], nor was there a difference between groups where the authors dissolved 10 mg of verapamil into different volumes of saline (4, 10, and 20 ml) [29]. Three articles showed clinical improvements in PC after verapamil injections, but statistical significance was not reported, and so the evidence does not support the use of verapamil injections in PD [38,41,44].

Three studies demonstrated that verapamil 10 mg was beneficial in terms of the secondary end points of PS reduction [3], one of which also demonstrated improvements in EF [34] and one in PP [55]. Tuygun et al. [52] evaluated the efficacy of verapamil application using electromotive drug administration (EMDA) and showed a 10° reduction in PC after 20 20-min sessions at 3-d intervals over 2 mo. Finally, Riedl and colleagues [50] also evaluated verapamil 5 mg injection with EMDA, and showed a 16% improvement from baseline. However, the study was of poor quality, as statistical analysis was not performed.

Published data regarding injection therapy with verapamil show considerable heterogeneity, owing to the use of different dosage schedules. Moreover, the lack of placebo groups underpowers the studies, limiting their capability to provide strong efficacy data, either with or without the addition of EMDA.

Fig. 2 – (A) Risk of bias assessment in randomised studies and (B) summary in randomised studies: review authors' judgements about each risk of bias item for each included study.

Fig. 3 – Risk of bias assessment in nonrandomised studies according to ROBINS-I tool.
ROBINS-I = risk of bias in nonrandomised studies of interventions.

3.4.2. Interferon α -2b

IFN α -2b has been investigated in 10 separate single-arm prospective studies [24,26,28,30,36,47,51,53,54] (Table 2). However, the used treatment programmes varied widely across these studies, with doses ranging from 1 million international units (IU) to 10 million IU of IFN α -2b, and protocols ranging from 1 injection per week to 3 injections per week for a maximum of 14 wk. Only two studies presented characteristics of PC from baseline to final follow-up [36]. Judge and Wisniewski [36] reported an improvement in PC from 45° at baseline to 12° after IFN α -2b, whereas Polat et al. [47] supported the finding that IFN α -2b is more efficacious in smaller plaques. There was 100% recovery of the PC in patients with <30° of PC compared with baseline. Conversely, Inal et al. [63] could not confirm these results; there was no significant improvement in PC.

Secondary outcomes of plaque reduction, pain, and EF were reported in two studies [26]. Only the report of Astorga and colleagues [26] showed a significant reduction in PS from 56.7 to 12.7 mm. In a study on 21 patients, Dang and colleagues [30] demonstrated a statistically significant improvement in EF and PP in five and eight patients, respectively.

According to the ROBINS risk calculator, these studies are at a moderate risk of bias owing to a bias in the selection of the reported result. In fact, when analysing the primary outcome, we identified discrepancies in the measurement and statistical reporting of PC, making it difficult to draw any conclusions regarding the efficacy of IFN α -2b in single-arm studies.

3.4.3. Hyaluronic acid

HA therapy for PD has been investigated in only two prospective studies (Table 3) [37,59]. In a study in 2000, Lamprakopoulos and coworkers [37] administered 1500 IU HA every 2 wk, with a total of 12 injections to each palpable plaque over a period of 5 mo. The authors reported a complete resolution of PC in 32.1% of patients, resolution of plaque in 31.2% of men, and a reduction in PP in 97% of men. Statistical analysis was not reported in any of the comparisons.

In 2017, a multicentre study by Zucchi et al. [59] reported clinical outcomes of HA injections using a 10-wk cycle of weekly HA injections (0.8% purified sodium salt at 16 mg/2 ml). The authors demonstrated significant decreases in PC (30° vs 20°) and PS (20 vs 8 mm), and a slight difference in the IIEF-5 (20 vs 21) score.

3.4.4. CCH

A total of eight prospective single-arm studies [32,35,39,46,56–58], plus one retrospective single-arm study [25] have investigated the clinical efficacy of CCH for PD (Table 4). The treatment protocols exhibited considerable homogeneity between studies in terms of dosage (0.58 mg in all studies) and injection programmes, which ranged from three to four cycles of two injections with an interval of ~24–72 h between each injection. Only one study evaluated the effect of CCH therapy combined with a vacuum device [48]. Improvements in PC ranged from –22.6° to –12.7° in studies reporting significant

absolute changes [35,39,46,56–58], and –36.3% in the one study that reported a percentage decrease [32].

Raheem and colleagues [48] evaluated the effects of CCH therapy combined with vacuum pump device, and reported clinically and statistically meaningful improvements in PC compared with baseline (from 54.17° to 37°).

By contrast, Nguyen et al. [46] did not report any significant benefit of CCH injections, in patients with either early (60.0° vs 43.9°) or chronic (56.9° vs 41.3°) PD between baseline and the final follow-up point. Similarly, Anaissie and colleagues [25] did not demonstrate significant changes in PC after CCH injections.

Considering secondary outcomes, only Jordan [35] reported a significant reduction in plaque length (–0.941 inches) and width (–0.0129 inches), whereas Raheem et al. [48] reported an increase in IIEF-5 compared with baseline (23.75 vs 20.90).

The magnitude of improvement in PP reported across studies, evaluated with the use of the Peyronie's Disease Questionnaire—penile pain domain, ranged from –5.3 to –2.4 [32,39], and a reduction of –1.64 was described when CCH therapy was combined with a vacuum device [48].

For PL, only the study by Levine et al. [39] reported significant changes between baseline and final follow-up (10.6 vs 11.0 cm). The other three studies that reported PL did not demonstrate a significant benefit of CCH on this parameter [25,46,48].

A study by Cocci et al. [64] found that IIEF, PC, PS, PP, and PL significantly improved after treatment and observed a mean change of 19.1° of PC after treatment (three intralesional injections of 0.9 mg performed at 4-wk intervals).

3.4.5. Mechanical therapy

Four studies evaluated the efficacy of penile traction to treat PD [33,42,43,49] (Table 5). Three different treatment protocols were used across studies. Gontero and colleagues [33] administered 600 g during the 1st month and 900 g during the 2nd month, increasing to 1200 g during the 5th and 6th months; Levine et al. [42] described a minimum of 2 h for up to 8 h/d for 6 mo with the extender rods lengthened by 0.5 cm every 2 wk; Martínez-Salamanca and colleagues [43] used a programme of 6–9 h/d.

Gontero et al. [33] showed a slight, nonsignificant, decrease in PC from 31° to 27° after treatment, but improvements were not reported for the secondary outcomes.

Martínez-Salamanca et al. [43] performed a prospective nonrandomised study comparing penile traction with several types of oral therapies in the control group. This assessment has not been included in this systematic review. The authors demonstrated a decrease in PC from 33° to 13° after penile traction, and also reported improvements in the secondary outcomes of EF, PP, and PL after traction.

In 2008, Levine and colleagues [42] reported a 33% improvement in PC, but this outcome was not statistically significant owing to the small number of patients included in the study ($n = 11$). Moreover, 100% of patients reported some improvement in PL compared with baseline of 0.5–2.5 cm. No statistical significance was reported.

The use of a single-arm prospective design to investigate vacuum-pump-device therapy for PD was described by Raheem et al. [49]. The treatment protocol involved the use of the device for 10 min twice daily over a period of 12 wk. The authors reported 67% improvement in PC from a mean at baseline of 47.6°, as well as improvements in PP VAS (2.2 vs 1.1) and PL (+0.5 cm).

These data suggest that studies on penile traction and vacuum therapies are still heterogeneous to draw any conclusions, with a lack of comparative randomised studies, which could help better identify the benefit of traction in terms of functional outcomes.

3.4.6. Other treatments

Muñoz-Rangel and colleagues [45] investigated the role of intralesional injections of onabotulinum toxin A (100 IU) and reported significant changes in PC from 32.95° to 25°. Moreover, the authors also reported clinical and statistically significant benefits in terms of plaque thickness (0.34 vs 0.27 cm), IIEF-5 (16.18 vs 18.22) and PP VAS (from 3.36 to 1.14). A study regarding the use of thiocolchicine demonstrated significant improvements in PC, but provided only level 3 evidence using a single-arm or case-control design [22].

4. Discussion

In the present study, we systematically reviewed the literature investigating the use of injection therapy, vacuum devices, and penile traction therapy for the treatment of PD.

Among all retrieved articles, 12 (22.2%) were prospective randomised studies (level of evidence 1) and the remaining 42 (77.8%) had a case-control or a single-arm design, or were retrospective. These data provide no strong evidence that injection therapies, and traction and vacuum devices are effective for PD. Furthermore, assessment with the ROBINS calculator suggested that 51% of single-arm studies were biased in terms of measurement of outcomes and selection of reported results, which is considered a critical bias.

Regardless of these considerations, our analysis suggests a clinically meaningful effect of CCH and IFN α -2b injection therapies in decreasing PC and increasing PL; however, only one study showed a benefit of IFN α -2b in PS reduction.

For CCH therapy, the best support comes from two large phase III, randomised, double-blind, placebo-controlled studies (IMPRESS I and II) [6]. The results of these clinical trials showed that CCH can reduce PC up to 17° (or 34%), as well as improve the pain symptoms of PD and PL in some studies.

In addition to these observations, CCH injection was shown to slightly increase PL (+0.4 cm), but these findings might be attributable to the concomitant modelling procedure, rather than to a direct action of the drug itself. Indeed, penile traction therapies, such as penile modelling, have been used historically to help straighten PC in PD, using either a stretcher or a vacuum device [33,49].

However, the study by Ralph and colleagues [18] that compared CCH + vacuum + modelling with CCH + vacuum

did not show a significant effect on PC (–23.7° vs –23.3°), suggesting that the role of penile traction therapies is not limited to a specific approach. The only evidence supporting the use of traction therapies comes from three studies [33,42,43], that reported clinical benefits from baseline to final follow-up; however, the data are not robust enough to drive specific recommendations.

Evidence to support clinical efficacy of verapamil and HA is weak, as few RCTs are available and data come mainly from case-control or nonrandomised clinical studies without placebo controls.

Previous research has demonstrated the efficacy of IFN- α 2b injections in many in vivo and in vitro studies [51]. Two randomised, placebo-controlled trials suggest a clinical benefit of IFN- α 2b regarding a reduction in PC, while PS improvement was seen only in one RCT. However, improvements in PC were only 17% and 22%, respectively, which certainly makes this an inferior injection therapy compared with CCH injections. Moreover, concerning the single-arm studies, many discrepancies in reporting measurements of PC and statistical analysis were found. They do not provide any valid additional information about the use of IFN- α 2b outside a clinical trial setting. However, in the rare case that the patient previously had a severe allergic reaction to CCH injections, IFN- α 2b can be considered as a safe, though less effective, alternative.

Level 1 evidence to support the use of calcium channel blockers comes from the RCTs by Rehman et al. [19] on verapamil and Soh et al. [21] on nifedipine. Other studies on calcium-channel blockers are either comparative (level 2 evidence) or single-arm (level 3 evidence) studies.

A study investigating different injection protocols at various doses (10 mg/4 ml, 10 mg/10 ml, and 10 mg/20 ml) was performed by Cavallini et al. [29], but did not reveal an advantage of any particular formulations. Verapamil injection has also been tested with EMDA, but its addition failed to demonstrate any clinical benefit [16].

Finally, studies of onabotulinum toxin A 100 IU injections [45] or thiocolchicine demonstrated significant improvements in PC, but provided only level 3 evidence in a single-arm or case-control design [22].

Despite these limitations, the current systematic review of the literature has enabled us to draw some specific recommendations on injection therapies, vacuum devices, or penile traction for PD.

5. Conclusions

This systematic review showed that intralesional injections of CCH and IFN α -2b improve PC in men with PD. Moreover, CCH can also improve PL, and IFN α -2b can reduce PS. No strong recommendations can be made for other treatments, including calcium channel blockers, HA, or traction therapies. Additionally, robust RCTs should be conducted to compare injection therapies with other treatments or placebo for those treatments for which evidence is currently weak.

Author contributions: Giorgio I. Russo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Albersen, Russo.

Acquisition of data: Milenkovic, Russo.

Analysis and interpretation of data: Milenkovic, Russo.

Drafting of the manuscript: Milenkovic, Russo, Albersen.

Critical revision of the manuscript for important intellectual content: Levine, Hellstrom, Ralph, Albersen.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Levine, Hellstrom, Ralph, Albersen.

Other: None.

Financial disclosures: Giorgio I. Russo certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.eururo.2018.07.005>.

References

- [1] Herati AS, Pastuszak AW. The genetic basis of Peyronie disease: a review. *Sex Med Rev* 2016;4:85–94.
- [2] Hatzimouratidis K, Giuliano F, Moncada I, Muneer A, Salonia A, Verze P. EAU guidelines on erectile dysfunction, premature ejaculation, penile curvature and priapism. 2017. <https://uroweb.org/guideline/male-sexual-dysfunction/>
- [3] Favilla V, Russo GI, Privitera S, et al. Combination of intralesional verapamil and oral antioxidants for Peyronie's disease: a prospective, randomised controlled study. *Andrologia* 2014;46:936–42.
- [4] Desai SS, Hentz VR. Collagenase *Clostridium histolyticum* for Dupuytren's contracture. *Expert Opin Biol Ther* 2010;10:1395–404.
- [5] Carson CC, 3rd, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of collagenase *Clostridium histolyticum* (CCH) for adults with Peyronie's disease (PD). *BJU Int* 2015;116:815–22.
- [6] Gelbard M, Goldstein I, Hellstrom WJG, et al. Clinical efficacy, safety and tolerability of collagenase *Clostridium histolyticum* for the treatment of Peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol* 2013;190:199–207.
- [7] Muller A, Mulhall JP. Peyronie's disease intervention trials: methodological challenges and issues. *J Sex Med* 2009;6:848–61.
- [8] Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [9] Abern MR, Larsen S, Levine LA. Combination of penile traction, intralesional verapamil, and oral therapies for Peyronie's disease. *J Sex Med* 2012;9:288–95.
- [10] Favilla V, Russo GI, Zucchi A, et al. Evaluation of intralesional injection of hyaluronic acid compared with verapamil in Peyronie's disease: preliminary results from a prospective, double-blinded, randomized study. *Andrology* 2017;5:771–5.
- [11] Gelbard MK, James K, Riach P, Dorey F. Collagenase versus placebo in the treatment of Peyronie's disease—a double-blind-study. *J Urol* 1993;149:56–8.
- [12] Gennaro R, Barletta D, Paulis G. Intralesional hyaluronic acid: an innovative treatment for Peyronie's disease. *Int Urol Nephrol* 2015;47:1595–602.
- [13] Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol* 2007;177:972–5.
- [14] Hellstrom WJG, Kendirci M, Matern R, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon α -2b for minimally invasive treatment for Peyronie's disease. *J Urol* 2006;176:394–8.
- [15] Kendirci M, Usta MF, Matern RV, Nowfar S, Sikka SC, Hellstrom WJ. The impact of intralesional interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. *J Sex Med* 2005;2:709–15.
- [16] Mehra AR, Namdari F, Salavati A, Dehghani S, Allameh F, Pourmand G. Comparison of transdermal electromotive administration of verapamil and dexamethasone versus intra-lesional injection for Peyronie's disease. *Andrology* 2013;1:129–32.
- [17] Montorsi F, Salonia A, Guazzoni C, et al. Transdermal electromotive multi-drug administration for Peyronie's disease: preliminary results. *J Androl* 2000;21:85–90.
- [18] Ralph DJ, Abdel Raheem A, Liu G. Treatment of Peyronie's disease with collagenase *Clostridium histolyticum* and vacuum therapy: a randomized, open-label pilot study. *J Sex Med* 2017;14:1430–7.
- [19] Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology* 1998;51:620–6.
- [20] Shirazi M, Haghpahan AR, Badiie M, Afrasiabi MA, Haghpahan S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol* 2009;41:467–71.
- [21] Soh J, Kawauchi A, Kanemitsu N, et al. Nicardipine vs. saline injection as treatment for Peyronie's disease: a prospective, randomized, single-blind trial. *J Sex Med* 2010;7:3743–9.
- [22] Toscano Jr L, Rezende MV, Mello LF, Paulillo D, Glin S. A prospective, randomized, single-blind study comparing intraplaque injection of thiocolchicine and verapamil in Peyronie's disease: a pilot study. *Int Braz J Urol* 2016;42:1005–9.
- [23] Yafi FA, Pinsky MR, Stewart C, et al. The effect of duration of penile traction therapy in patients undergoing intralesional injection therapy for Peyronie's disease. *J Urol* 2015;194:754–8.
- [24] Ahuja S, Bivalacqua TJ, Case J, Vincent M, Sikka SC, Hellstrom WJG. A pilot study demonstrating clinical benefit from intralesional interferon alpha 2B in the treatment of Peyronie's disease. *J Androl* 1999;20:444–8.
- [25] Anaissie J, Yafi FA, DeLay KJ, Traore EJ, Sikka SC, Hellstrom WJG. Impact of number of cycles of collagenase *Clostridium histolyticum* on outcomes in patients with Peyronie's disease. *Urology* 2017;100:125–30.
- [26] Astorga R, Cantero O, Contreras D, et al. Intralesional recombinant interferon alpha-2b in Peyronie's disease. *Arch Esp Urol* 2000;53:665–71.
- [27] Bennett NE, Guhring P, Mulhall JP. Intralesional verapamil prevents the progression of Peyronie's disease. *Urology* 2007;69:1181–4.
- [28] Brake M, Loertzer H, Horsch R, Keller H. Treatment of Peyronie's disease with local interferon- α 2b. *BJU Int* 2001;87:654–7.
- [29] Cavallini G, Modenini F, Vital G. Open preliminary randomized prospective clinical trial of efficacy and safety of three different

- verapamil dilutions for intraplaque therapy of Peyronie's disease. *Urology* 2007;69:950–4.
- [30] Dang G, Matern R, Bivalacqua TJ, Sikka S, Hellstrom WJG. Intralesional interferon- α -2b injections for the treatment of Peyronie's disease. *Southern Med J* 2004;97:42–6.
- [31] Dell'Atti L. Tadalafil once daily and intralesional verapamil injection: a new therapeutic direction in Peyronie's disease. *Urol Ann* 2015;7:345–9.
- [32] Goldstein I, Knoll LD, Lipshultz LI, Smith T, Kaufman GJ, McMahon CG. Changes in the effects of Peyronie's disease after treatment with collagenase *Clostridium histolyticum*: male patients and their female partners. *Sex Med* 2017;5:E124–30.
- [33] Gontero P, Di Marco M, Giubilei G, et al. Use of penile extender device in the treatment of penile curvature as a result of Peyronie's disease. Results of a phase II prospective study. *J Sex Med* 2009;6:558–66.
- [34] Heidari M, Nejadi JR, Ghate A, Delfan B, Iran-Pour E. Evaluation of Intralesional injection of Verapamil in treatment of Peyronie's disease. *J Pak Med Assoc* 2010;60:291–3.
- [35] Jordan GH. The use of intralesional clostridial collagenase injection therapy for Peyronie's disease: a prospective, single-center, non-placebo-controlled study. *J Sex Med* 2008;5:180–7.
- [36] Judge IS, Wisniewski ZS. Intralesional interferon in the treatment of Peyronie's disease: a pilot study. *Br J Urol* 1997;79:40–2.
- [37] Lamprakopoulos A, Zorzos I, Lykourinas I. The use of betamethasone and hyaluronidase injections in the treatment of Peyronie's disease. *Scand J Urol Nephrol* 2000;34:355–60.
- [38] Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. *J Urol* 1997;158:1395–9.
- [39] Levine LA, Cuzin B, Mark S, et al. Clinical safety and effectiveness of collagenase *Clostridium histolyticum* injection in patients with Peyronie's disease: a phase 3 open-label study. *J Sex Med* 2015;12:248–58.
- [40] Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol* 2002;168:621–5, discussion 625–6.
- [41] Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. *J Urol* 1994;151:1522–4.
- [42] Levine LA, Newell M, Taylor FL. Penile traction therapy for treatment of Peyronie's disease: a single-center pilot study. *J Sex Med* 2008;5:1468–73.
- [43] Martínez-Salamanca JI, Egui A, Moncada I, et al. Acute phase Peyronie's disease management with traction device: a nonrandomized prospective controlled trial with ultrasound correlation. *J Sex Med* 2014;11:506–15.
- [44] Moskovic DJ, Alex B, Choi JM, Nelson CJ, Mulhall JP. Defining predictors of response to intralesional verapamil injection therapy for Peyronie's disease. *BJU Int* 2011;108:1485–9.
- [45] Muñoz-Rangel CA, Fernandez-Vivar E, Banuelos-Gallo RA, et al. Minimally invasive therapy using intralesional onabotulinumtoxinA in Peyronie's disease. *Urol J* 2015;12:2105–10.
- [46] Nguyen HMT, Anaissie J, DeLay KJ, Yafi FA, Sikka SC, Hellstrom WJG. Safety and efficacy of collagenase *Clostridium histolyticum* in the treatment of acute-phase Peyronie's disease. *J Sex Med* 2017;14:1220–5.
- [47] Polat O, Gul O, Ozbey I, Ozdikici M, Bayraktar Y. Peyronie's disease: intralesional treatment with interferon alpha-2A and evaluation of the results by magnetic resonance imaging. *Int Urol Nephrol* 1997;29:465–71.
- [48] Raheem AA, Capece M, Kalejaiye O, et al. Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol. *BJU Int* 2017;120:717–23.
- [49] Raheem AA, Garaffa G, Raheem TA, et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. *BJU Int* 2010;106:1178–80.
- [50] Riedl CR, Plas E, Engelhardt P, Daha K, Pfluger H. Iontophoresis for treatment of Peyronie's disease. *J Urol* 2000;163:95–9.
- [51] Stewart CA, Yafi FA, Knoedler M, et al. Intralesional injection of interferon-alpha2b improves penile curvature in men with Peyronie's disease independent of plaque location. *J Urol* 2015;194:1704–7.
- [52] Tuygun C, Ozok UH, Gucuk A, Bozkurt IH, Imamoglu MA. The effectiveness of transdermal electromotive administration with verapamil and dexamethasone in the treatment of Peyronie's disease. *Int Urol Nephrol* 2009;41:113–8.
- [53] Wegner HEH, Andresen R, Knipsel HH, Miller K. Treatment of Peyronie's-disease with local interferon-alpha-2b. *Eur Urol* 1995;28:236–40.
- [54] Wegner HEH, Andresen R, Knipsel HH, Miller K. Local interferon-alpha2b is not an effective treatment in early-stage Peyronie's disease. *Eur Urol* 1997;32:190–3.
- [55] Wolff B, Peyronnet B, Cattarino S, et al. Intralesional injections for early Peyronie disease: standardized assessment and analysis of predictive factors for treatment response. *Urology* 2015;86:57–61.
- [56] Yang KK, Bennett N. Peyronie's disease and injectable collagenase *Clostridium histolyticum*: safety, efficacy, and improvements in subjective symptoms. *Urology* 2016;94:143–7.
- [57] Ziegelmann MJ, Viers BR, McAlvany KL, Bailey GC, Savage JB, Trost LW. Restoration of penile function and patient satisfaction with intralesional collagenase *Clostridium histolyticum* injection for Peyronie's disease. *J Urol* 2016;195:1051–6.
- [58] Ziegelmann MJ, Viers BR, Montgomery BD, Westerman ME, Savage JB, Trost LW. Self-reported clinical meaningfulness early in the treatment course predicts objective outcomes in men undergoing collagenase *Clostridium histolyticum* injections for Peyronie disease. *Urology* 2017;106:107–12.
- [59] Zucchi A, Costantini E, Cai T, et al. Intralesional injection of hyaluronic acid in patients affected with Peyronie's disease: preliminary results from a prospective, multicenter, pilot study. *Sex Med* 2016;4:E85–90.
- [60] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- [61] Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
- [62] Ziegelmann MJ, Viers BR, Montgomery BD, Avant RA, Savage JB, Trost LW. Clinical experience with penile traction therapy among men undergoing collagenase *Clostridium histolyticum* for Peyronie disease. *Urology* 2017;104:102–9.
- [63] Inal T, Tokatli Z, Akand M, Ozdiler E, Yaman O. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study. *Urology* 2006;67:1038–42.
- [64] Cocci A, Russo GI, Salonia A, et al. Predictive factors of patients' and their partners' sexual function improvement after collagenase *Clostridium histolyticum* injection for Peyronie's disease: results from a multi-center single-arm study. *J Sex Med* 2018;15:716–21.