ARTICLE

Safety and feasibility of percutaneous needle tunneling with platelet-rich plasma injections for Peyronie's disease in the outpatient setting: a pilot study

Ahmed S. Zugail[1,2]✉, Muaath Alshuaibi[1,3], Sandrine Lombion[4] and Sébastien Beley[1]

The objective of this study is to evaluate the safety and feasibility of the combined simultaneous percutaneous needle tunneling coupled with injection of platelet-rich plasma in the outpatient department for the treatment of Peyronie's disease. This prospective, non-randomized, cohort and preliminary study included patients who underwent this procedure from November 2020 to July 2022. The main outcome was an improvement in penile curvature. Fifty-four patients were enrolled and underwent 6 sessions under local anesthesia followed by vacuum therapy for the treatment of Peyronie's disease in our outpatient unit. The amendment of the curvature angle was significant with a median correction percentage of −44.40% interquartile range (−66.70 to (−39.70)), [*p*-value = 0.001, 95% CI (−29.76 to (−18.02)), paired Student's *t*-test]. The median pre-treatment curvature angle was 45° (40–75), and the median post-treatment was 30° (20–40). The median score for pain during the procedure was 3 (0–4.25) according to a 10-point visual analogic scale. After two hours, 20.37% of patients still had pain but none required any pain medication. 50% of patients had a minor hematoma and 75.93% patients reported penile ecchymosis. A single patient reported an injection site skin infection. In our experience percutaneous needle tunneling with platelet-rich plasma injections for Peyronie's disease in the outpatient setting is a safe, effective, and feasible treatment of penile deformity for PD.

IJIR: Your Sexual Medicine Journal (2024) 36:140–145; https://doi.org/10.1038/s41443-023-00744-y

INTRODUCTION

Peyronie disease (PD), or *induratio penis plastica*, is an ailment that occurs due to the development of fibrosis in the tunica albuginea (TA) layer of penis. This disease can cause progressive penile curvature and pain and/or erectile dysfunction (ED) in around 20% of patients [1]. In the absence of any treatment, the curvature may disappear in about 12% of patients [2].

While the cause is unknown, it appears to be a result of poor wound healing following penile damage in genetically susceptible individuals, with the most commonly accepted concept being exposure of the TA to repeated microvascular stress [3]. The frequency in the male population ranges from 0.4 to 9% [4–8]. PD results in curvatures, shortening, hourglass, or hinge deformities, and symptoms that can range from pain with erections and impossibility of sexual intercourse to ED [9]. All these symptoms lead to discomfort in the sexual activity of patients, often with psychological repercussions and marital difficulties that could influence their quality of life [4, 10–14].

Several oral treatments have been examined, but with inconsistent evidence of effectiveness and low levels of evidence [15]. Intraplaque injections of pharmacological substances have emerged as a treatment option for curvature, aiming to counteract TA fibrosis, which is the final product of the pathological process of PD, before the deposit of calcifications [16]. These injectables include verapamil, which requires numerous injections [17], Interferon-α2b [18], which remains off label, the debated use of hyaluronic acid (HA) [19], collagenase *Clostridium histolyticum* (CCH), which is expensive and not readily available the European Union [20], and botulinum toxin which is still under study [21]. The interesting improvement rates observed with these treatments are challenged by their side effects such as corporeal ruptures for CCH [22], flu-like symptoms for Interferon-α2b [23], or dizziness and nausea for verapamil [24]. Despite the fact that several drugs have been used for therapy, a consensus on the appropriate treatment is yet to be found.

To this day, surgery remains the first-line treatment to correct the deformity of this disease [25–27]. Although definitive resolution of PD often requires surgery, there are non-surgical alternatives that may achieve significant improvements, avoiding potential complications or sequelae such as ED and loss of penile length [28]. Among these alternatives, oral, topical or shockwave therapy treatments have yet to demonstrate clear efficacy [15].

New therapeutic strategies have recently emerged, aiming to repair tissue damage of the penis caused by PD. One of these strategies is the promising Platelet-rich Plasma (PRP) injections [29]. Although the use of PRP in urology is still in its infancy, it made its debut in other fields of medicine such as orthopedics and plastic surgery back in 1987 [14]. Studies have been

[1]Department of Urology, Clinique Turin, Groupe Almaviva Santé, Paris, France. [2]Urology Division, Department of Surgery, Faculty of Medicine in Rabigh, King Abdulaziz University, Jeddah, Saudi Arabia. [3]Department of Urology, Faculty of Medicine, University of Ha'il, Ha'il, Saudi Arabia. [4]Sandrine Lombion, EURL Slc, Chamesey, France.
✉email: zugail2@hotmail.com

Received: 3 December 2022 Revised: 18 July 2023 Accepted: 19 July 2023
Published online: 7 August 2023

conducted in these fields, discussing the safety and efficacy of PRP. However, despite more than 30 years of use, its physiological properties and effects remain poorly understood and controversial when it comes to autologous injections [14]. According to recommendations from the American Urological Association and Sexual Medicine Society of North America, PRP shows promising potential that still needs to be proven [14].

A better understanding of this emerging controversial modality is essential in guiding physicians dealing with patients suffering from PD. Administering this autologous biological product directly into the fibrotic plaque of the corpora cavernosa within the TA has the potential to alleviate fibrosis and effectively treat the disease. To this day, little to no information is known about the use of pure PRP in PD. PRP, along with its containing growth factors, is involved in many aspects of natural wound healing, such as chemotaxis, cell proliferation and differentiation, regulation of mitogenesis, angiogenesis, and metabolism [30, 31]. They also control and conduct synthesis, modification, and degeneration of extracellular matrix proteins. The coordination of these cellular and molecular processes is integral to proper wound healing and tissue regeneration [30, 31].

The aim of this study is to test the safety and feasibility of percutaneous needle tunneling (PNT) of the TA plaque with subsequent administration of PRP injections in the outpatient department. This combination henceforth termed PNT/PRP with vacuum therapy could lead to a more cost-effective treatment.

SUBJECTS AND METHODS

This prospective, non-randomized, cohort and preliminary study was conducted after obtaining approval from the Ethics Committee of Turin Hospital (Approval number: CT2022-74). The study adhered to the Helsinki protocols, and patients provided written, informed consent. This article was composed in accordance with the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for reporting cohort studies [32]. This study was intended to observe and analyze PNT joined with PRP injections of the plaque of PD in terms of safety, feasibility, and outcome.

We included all male consecutive patients of any age who complained of a penile curvature condition with difficulties during coitus related to the presence of a palpable TA plaque; indicative of PD. The exclusion criteria included patients receiving curative doses of any anticoagulation medication, patients with unstable plaques, curvatures that had no impact on sexual performance, and patients with ED not responding to treatment. The study was performed in our urology outpatient department and the study was completed in 21 months (from November 2020 to July 2022).

All patients were instructed to take personal penile photos in a fully erect state, capturing dorsal and lateral views, using their own personal devices. These photos served as a baseline for measuring the penile curvature angle, which was determined using a goniometer (Considered the gold standard).

The treatment protocol consisted of accomplishing 6 PNT/PRP, with each session scheduled 4 weeks apart. Penile vacuum therapy was initiated on day 14 after each session. The patient was positioned on a medical table in a supine decubitus position. The penis was disinfected using disinfection a chlorohexidine 0.5% solution. Local anesthesia (Lidocaine 2% [20 mg/mL], 5 mL) was administered using a 25 G × 5/8 (0.5 ×16 mm) subcutaneous needle, targeting the penile tissue layers before reaching the plaque zone.

PRP was prepared with RegenKit BCT-3 (Regen Lab, Le Mont sur Lausanne, Switzerland). This dedicated medical device consists of evacuated sterile tubes that are designed to isolate PRP from the other blood components by a single centrifugation, using a chemically inert thixotropic separator gel, that acts as a mechanical barrier between blood components, and a sodium citrate solution, that allows fully reversible anticoagulation of the biological sample. This system is automated and works in closed circuit. In brief, venipuncture is performed at the antecubital fossa with a blood collection set. A preset volume of 10 ml of blood is automatically collected into the tube that is labeled. The tube is then centrifuged for 5 min at a relative centrifugal force of 1500 × *g*, corresponding to speed of 3500 rounds per minute in a centrifuged equipped with 45° fixed angle rotor. During the centrifugation, the blood components are separated according to their relative density, whereas the separator gel becomes fluid, migrates upward, and inserts itself precisely between the blood components, thanks to its thixotropic ability and its specific density. When the centrifugation stops, the separator gel regains its original consistency and forms a physical barrier that isolates the platelets and the plasma in the upper part of the tube, while the red and white blood cells are entrapped in the lower part of the tube (Fig. 1). After gentle agitations of the tube, to put the platelets, that have sedimented on the surface of the separator gel, back in suspension in the plasma, the PRP is ready to use. This proprietary technology allows the preparation of 5–6 ml of a standardized leukocyte poor PRP, with a platelet concentration factor of 1.5–1.6 times the baseline value in blood and a very low contamination with red blood cells and pro-inflammatory white blood cells. This PRP is classified as P2-Bβ according to Delong PAW classification [33].

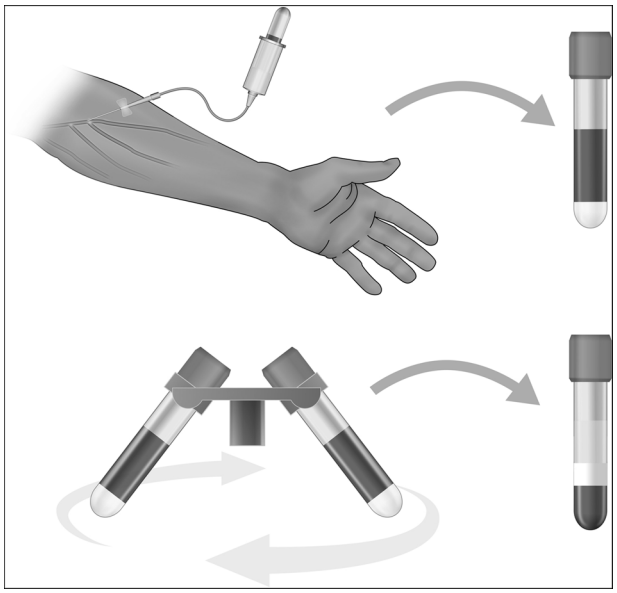

Fig. 1 Artwork that simplifies the process and production of Platelet-Rich Plasma (PRP). Withdraw of venous blood (Phlebotomy) is obtained using the butterfly needle system directly into a tube with negative pressure already containing an anticoagulant and a separator gel. The tubes are then labeled and centrifuged for 5 min at a speed of 3500 rounds per minute. The end result as shown is the PRP in yellow separated by the separator gel in white from the rest of the blood components (White and red blood cells) in red. Only the yellow part is used and transferred to a syringe.

The main procedure involved initiating PNT [34, 35]. This was accomplished by creating multiple pits and channels along the entire longitudinal axis of the plaque using a 25 G × 5/8 (0.5 × 16 mm) subcutaneous needle. The needle was connected to a syringe filled with PRP, and mini-doses of PRP were injected into the plaque until the syringe was empty (Fig. 2). PRP administration was completed in less than 5 min from its preparation for all patients.

Vacuum therapy was standardized; all patients were prescribed and educated on the use of a vacuum erectile devices (VED) (VACURECT™, Pretoria, South Africa) for daily use, 30 min each day, starting 14 days after the PNT/PRP session and continuing until the next session. After the procedure, a semi-compressive dressing was applied, and patients were instructed to remove it after 2 h. Sexual intercourse was prohibited for 24 h.

Patients were instructed to take the same photos as before the protocol for follow-up at day 28 after the sixth session. To minimize bias, all injections were administered by the same expert urologist. Pain levels were assessed during the PNT/PRP procedure, as well as at 2 and 24 h after the procedure, using a 10-point visual analog scale (VAS).

Statistical analysis was performed using the software SPSS for Windows version 18.0 (IBM, Armonk, New York, USA) and *p*-value of < 0.05 was considered statistically significant. Categorical variables were expressed as numbers and percentages, while quantitative variables were expressed by measures of central tendency, dispersion and spread. The changes in penile curvature angle within the group were compared using a one-sample paired Student's *t*-test.

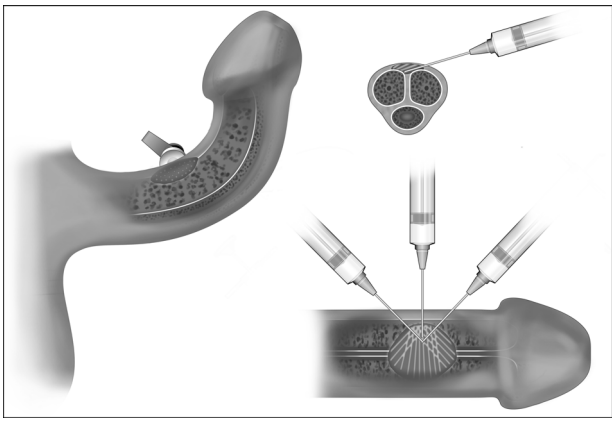

Fig. 2 Artwork of percutaneous needle tunneling technique. The idea is to create multiple crevasses and tunnels along the entire longitudinal axis of the plaque using a 25 Gauge × 5/8 inches (0.5 × 16 mm) subcutaneous needle. An injection of a total of 5–6 ml of PRP into the plaque.

RESULTS

Data was collected from 54 patients who were enrolled into our protocol. All patients completed the protocol and were compliant with penile vacuum therapy. Their median age in years was 47.50 interquartile range 40–55. The median duration of PD was 18 months (12–31.50). The penile curvature was stabilized in 47/54 (87.04%) patients upon consultation. Patients' demographics, past history and past ineffective treatment history are shown in Table 1. Blood thinners were taken by 9/54 (16.67%) patients; 7/54 (12.96%) were receiving a daily dose of 75 mg of acetylsalicylic acid and 2/54 (3.70%) were receiving a daily dose of 75 mg of clopidogrel. None of the patients stopped their blood thinners before PNT/PRP. Loss of penile length was observed in 40/54 (74.07%) with a median loss of 1.25 cm [1–3].

Plaque locations were as follows; dorsal distal third in 10/54 (18.52%), dorsal middle third in 9/54 (16.67%), dorsal proximal third in 3/54 (5.56%), right dorsolateral distal third in 4/54 (7.41%), right dorsolateral middle third in 3/54 (5.56%), right dorsolateral proximal third in 6/54 (11.11%), left dorsolateral distal third in 5/54 (9.26%), left dorsolateral middle third in 4/54 (7.41%), left dorsolateral proximal third in 4/54 (7.41%), right lateral middle third 1/54 (1.85%), left lateral distal third 1/54 (1.85%), left lateral middle third 2/54 (3.70%), left lateral proximal third 1/54 (1.85%), left ventrolateral proximal 1/54 (1.85%).

The median VAS score was 3 (0–4.25). 9/54 (16.67%) patients reported a pain of 6 or more. Two hours after PNT/PRP, pain was described in 11/54 (20.37%) but none required any pain medication and pain disappeared within 24 h in all patients. 41/54 patients (75.93%) reported penile ecchymosis and half the patients 27/54 reported a minor hematoma that disappeared spontaneously without further complications. A single patient (1.85%) reported an injection site skin infection which was cured with the help of oral antibiotics. No urinary symptoms were reported as a cause of PNT/PRP.

Penile curvature data is shown in Table 2. Comparing pre- and post-PNT/PRP with VED we found a significant improvement in curvature [p-value = 0.001, 95% CI (−29.76 to (−18.02)), paired Student's t-test].

DISCUSSION

Our protocol has demonstrated a significant correction of penile curvature angle deformity with minor complications, which is safe and feasible in the outpatient setting. Based on our results, this significance is both clinical and statistical.

Table 1. Patients' demographics, past history and past ineffective treatment history.

N	54
Age (Median (IQR))	47.50 (40–55)
Disease Duration (Median (IQR))	18 (12–31.50)
Degree of PC before treatment (Median (IQR))	45 (40–75)
Stabilized PC (*n* (%))	47 (87.04)
Past history (*n* (%))	
Smoking history	17 (31.48)
Diabetes mellitus	7 (12.96)
Type I	2 (3.70)
Type II	5 (9.25)
Hypertension	5 (9.25)
Dyslipidemia	5 (9.25)
Cardiac disease	2 (3.70)
Radical prostatectomy	2 (3.70)
Dupuytren's contracture	1 (1.85)
Autoimmune disease	3 (5.56)
HIV infection	0 (0)
Groin trauma	18 (33.33)
Blood thinners	**9 (16.67)**
Acetylsalicylic Acid 75 mg	7 (12.96)
Clopidogrel 75 mg	2 (3.70)
Past treatment	**31 (57.41)**
Vitamin E (Tocopherol)	17 (31.48)
NSAIDs	4 (7.41)
Pentoxifylline	3 (5.56)
Tamoxifen	1 (1.85)
Verapamil intraplaque injection	3 (5.56)
Steroid intraplaque injection	1 (1.85)
CCH intraplaque injection	2 (3.70)
VED	4 (7.41)
PTT	3 (5.56)
Both VED and PTT	1 (1.85)
LiST	3 (5.56)

N or n Number of patients, *IQR* Interquartile range, *PC* Penile curvature, *HIV* Human immunodeficiency virus, *NSAIDs* Non-steroidal anti-inflammatory drugs, *CCH* Collagenase *Clostridium histolyticum*, *VED* Vacuum erectile device, *PTT* Penile traction therapy, *LiST* Low-intensity shockwave therapy.

Surfing through the English and French literature, a study done by Virag et al. showed similar results; they evaluated the feasibility and efficacy of intralesional injections of autologous PRP combined with HA. Thirteen patients with deformity due to PD were included. The therapeutic protocol consisted of an intralesional injection every 15 days for 2 months under ultrasound guidance. The treatment was prepared from 2 tubes of 4 mL of whole blood previously containing HA. The mean follow-up was 9.3 months. In total, 10 of the 13 patients showed an average reduction of 30% in their initial curvature associated with a reduction in plaque size in 53% of cases. One hematoma was reported [29].

The withdrawal of CCH from the European Union [36] which obtained a Food and Drug Administration approval [20] as the only non-surgical treatment for PD motivated us to find an alternative in PRP. Approved by the European Medicines Agency in 2015, intralesional injection of CCH has demonstrated an

improvement in curvature in selected patients, sparing many of them from surgery [20, 37, 38]. Following its approval, several changes to the original drug-use protocol have been proposed, such as adding vacuum erectile devices (VED), decreasing the duration of the protocol, or increasing the amount of CCH for each injection, in order to improve treatment results and lower costs [39, 40].

In our case, the patients were instructed to use VED only after 14 days of the PNT/PRP session It was only fair to add VED therapy to our protocol to acquire better results synergistically, which is the number of days where PRP rests active in the lesions. Using VED might displace the PRP due to their suction effect which is absent in penile traction therapy [41–46].

Leriche described a technique in 2002, later named PNT, where plaque perforations using an 18-gauge needle as an alternative percutaneous treatment for PD that could improve the curvature itself [47]. We implemented the same technique in our protocol but with a finer needle while simultaneously injecting PRP. Although the exact effect of PNT on the plaque at the structural level is unidentified, we do not expect any histopathological changes other than a simple mechanical action that would enhance drug diffusion while creating microcracks that allow the plaque to be more malleable, so that traction therapy can achieve better results. Using a finer needle, in our opinion, will reduce iatrogenic trauma and post-interventional inflammation. PRP will counteract the harmful inflammatory processes and also signal an enhanced restorative response stabilizing the damaged plaque [48].

PRP is an autologous plasma with a supraphysiological platelet concentration in unit volume. It is produced from the centrifugation of whole blood that contains a 3 to 7 times higher platelet concentration compared to whole blood. It also contains growth factors related to wound healing and tissue repair such as platelet-derived growth factor, transforming growth factor, insulin-like growth factor, and epidermal growth factor, and plasma proteins enabling hemostasis and adhesion such as fibrin, fibronectin, and vitronectin [49–51]. PRP leads to the migration of macrophages, monocytes, and neutrophils as well as inhibiting the release of pro-inflammatory cytokines by suppressing the release of interleukin-1 from the macrophages [52, 53]. These therapies are being increasingly exploited in numerous medical settings, including dermatology, ophthalmology, cardiology, colorectal surgery, and plastic surgery [54]. PRP has been frequently used for orthopedic conditions such as bone and soft tissue trauma, inflammatory conditions, and chronic pain syndromes [54–56]. PRP has been employed as a primary therapeutic technique as well as a complement to other therapies in the hopes of enhancing wound healing, tissue regeneration, and angiogenesis. Despite the fact that most research on PRP injections have been limited and heterogeneous, they all show safety and effectiveness [48]. Additionally, the concept of autologous therapy may be particularly attractive to some patients [57]. Autologous treatment eliminates the necessity for immunosuppression and the fear of rejection. There are several circumstances in urology, as in many other specialties, where tissue regeneration is desirable [48]. Regenerative medicine is now a hot topic in medicine that could help stop the process and restore function. Stem cell therapy for PD has become a wide subject of research in animal studies with rising hopes for future treatments with adipose derived stem cells [29].

Limitation of our current research is the lack of a placebo group and the fact that we cannot exclude if the results are due to PNT or vacuum rather than PRP. Additionally, taking comparable photos by the patients is the most important criterion in evaluating curvature improvement which is also reliant on the quality of the erection. Also, self-photographs of the penis are not reliable in assessing penile curvature so the results may be affected by how they were taken. Despite these favorable results,

Table 2. Data of patients' penile curvature.

Variable	N	Nmiss	Mean	SD	Minimum	Maximum	25th Centile	75th Centile	Median
Curvature angle° before PNT/PRP with VED	54	0	53.98	23.19	15	115	40	75	45
Curvature angle° after PNT/PRP with VED	54	0	30.09	20.61	0	90	20	40	30
Curvature angle° difference pre- and post- PNT/PRP with VED	54	0	−23.88	21.49	−85	30	−30	−10	−25
Curvature correction percentage % pre- and post- PNT/PRP with VED	54	0	−40.17	42.96	−100	150	−66.70	−27.10	−44.40

N number of patients, Nmiss Missed patients, *SD* standard deviation, *PNT* percutaneous needle tunneling, PRP platelet-rich plasma, *VED* vacuum erectile device.

the sample size was small and should be augmented and dispersed in many medical centers to test reproducibility more efficiently. The strengths of the study include the fact that all injections were done by the same urologist, an expert in PD injections (CCH, verapamil, etc.). Moreover, we used the same tube brand from the Regen Lab SA, Geneva, Switzerland for all the patients to keep the same efficiency and safety. In conclusion, we believe PNT/PRP followed by VED is conceivably an effective, safe, and feasible treatment for penile deformity in PD that can be performed comfortably in the outpatient department.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

DATA AVAILABILITY

The data that supports the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

REFERENCES

1. Hellstrom WJ, Bivalacqua TJ. Peyronie's disease: etiology, medical, and surgical therapy. J Androl. 2000;21:347–54.
2. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. J Urol. 2006;175:2115–8.
3. Gonzalez-Cadavid NF. Mechanisms of penile fibrosis. J Sex Med. 2009;6:353–62.
4. Gelbard MK, Dorey F, James K. The natural History of Peyronie's disease. J Urol. 1990;144:1376–9.
5. La Pera G, Pescatori ES, Calabrese M, Boffini A, Colombo F, Andriani E, et al. Peyronie's disease: prevalence and association with cigarette smoking. A multicenter population-based study in men aged 50–69 years. Eur Urol. 2001;40:525–30.
6. Mulhall JP, Creech SD, Boorjian SA, Ghaly S, Kim ED, Moty A, et al. Subjective and objective analysis of the prevalence of Peyronie's disease in a population of men presenting for prostate cancer screening. J Urol. 2004;171:2350–3.
7. Lindsay MB, Schain DM, Grambsch P, Benson RC, Beard CM, Kurland LT. The Incidence of Peyronie's Disease in Rochester, Minnesota, 1950 through 1984. J Urol. 1991;146:1007–9.
8. Culha MG, Erkan E, Cay T, Yücetaş U. The effect of platelet-rich plasma on Peyronie's disease in rat model. Urol Int. 2019;102:218–23.
9. Levine LA, Larsen SM. Surgery for Peyronie's disease. Asian J Androl. 2013;15:27. ncbi.nlm.nih.gov/pmc/articles/PMC3739133/.
10. Rod X, Akakpo W, Roupret M. Efficacité et tolérance des traitements locaux en injections pour le traitement de la maladie de La Peyronie : revue de la littérature. Progs Urol. 2021;31:1072–9.
11. Burri A, Porst H. The relationship between penile deformity, age, psychological bother, and erectile dysfunction in a sample of men with Peyronie's Disease (PD). Int J Impot Res. 2018;30:171–8.
12. Terrier JE, Nelson CJ. Psychological aspects of Peyronie's disease. Transl Androl Urol. 2016;5:290–5.
13. Rosen R, Catania J, Lue T, Althof S, Henne J, Hellstrom W, et al. Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. J Sex Med. 2008;5:1977–84.
14. Alkandari MH, Touma N, Carrier S. Platelet-rich plasma injections for erectile dysfunction and peyronie's disease: a systematic review of evidence. Sex Med Rev. 2022;10:341–52.
15. Chung E, Ralph D, Kagioglu A, Garaffa G, Shamsodini A, Bivalacqua T, et al. Evidence-based management guidelines on Peyronie's disease. J Sex Med. 2016;13:905–23. https://pubmed.ncbi.nlm.nih.gov/27215686/.
16. Chong W, Tan RBW. Injectable therapy for Peyronie's disease. Transl Androl Urol. 2016;5:310–7.
17. Levine LA, Costabile RA. Is intralesional verapamil effective therapy for Peyronie's disease? J Urol. 2012 ;188:704–6.
18. Milam DF. Intralesional interferon-α2b improves penile curvature in Peyronie's disease. J Urol. 2015;194:1533.
19. Zucchi A, Costantini E, Cai T, Cavallini G, Liguori G, Favilla V, 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.
20. Levine LA, Cuzin B, Mark S, Gelbard MK, Jones NA, Liu G, 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.
21. Mohit K. H-22411: BOTOX® for Peyronie's disease. 2020. https://clinicaltrials.gov/ct2/show/NCT00812838.
22. Carson CC, Sadeghi-Nejad H, Tursi JP, Smith TM, Kaufman GJ, Gilbert K, 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. https://pubmed.ncbi.nlm.nih.gov/25818264/.
23. Hellstrom WJG, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. J Urol. 2006;176:394–8. https://pubmed.ncbi.nlm.nih.gov/16753449/.
24. Alizadeh M, Karimi F, Fallah MR. Evaluation of verapamil efficacy in Peyronie's disease comparing with pentoxifylline. Glob J Health Sci. 2014;6:23–30. https://pubmed.ncbi.nlm.nih.gov/25363175/.
25. Hatzimouratidis K, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Salonia A, et al. EAU guidelines on penile curvature. Eur Urol. 2012;62:543–52. https://pubmed.ncbi.nlm.nih.gov/22658761/.
26. Nehra A, Alterowitz R, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh JJ, et al. Peyronie's Disease: AUA Guideline. J Urol. 2015;194:745–53. https://pubmed.ncbi.nlm.nih.gov/26066402/.
27. Bella AJ, Lee JC, Grober ED, Carrier S, Benard F, Brock GB. 2018 Canadian Urological Association guideline for Peyronie's disease and congenital penile curvature. Can Urol Assoc J. 2018;12:E197–209. https://pubmed.ncbi.nlm.nih.gov/29792593/.
28. Larsen SM, Levine LA. Review of non-surgical treatment options for Peyronie's disease. Int J Impot Res. 2012;24:1–10. https://www.nature.com/articles/ijir201145.
29. Virag R, Sussman H, Lambion S, de Fourmestraux V. Evaluation of the benefit of using a combination of autologous platelet rich-plasma and hyaluronic acid for the treatment of Peyronie's disease. Sex Health Issues. 2017;1:1–8.
30. Werner S, Grose R. Regulation of wound healing by growth factors and cytokines. Physiol Rev. 2003;83:835–70.
31. Galliera E, Corsi MM, Banfi G. Platelet rich plasma therapy: inflammatory molecules involved in tissue healing. J Biol Regul Homeost Agents. 2012;26:35S–42S.
32. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The strengthening the reporting of observational studies in epidemiology (STROBE) statement. Epidemiology. 2007;18:800–4.
33. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: the PAW classification system. Arthrosc: J Arthrosc Relat Surg. 2012;28:998–1009.
34. Fernández-Pascual E, González-García FJ, Angulo J, Cerezo E, Quintana LM, Turo J, et al. Optimizing collagenase *Clostridium histolyticum* therapy for Peyronie's disease using a novel approach with percutaneous needle tunnelling. BJU Int. 2019;124:1055–62.
35. Fernández-Pascual E, González-García FJ, García-Criado E, Souto AD, Marcos D, Angulo J, et al. V04-07 How to improve your xiapex results in Peyronie's disease: the percutaneous needle tunnelling (PNT) technique. step-by-step surgical video. J Urol. 2019;201.
36. Ferretti L, Madec FX, Akakpo W, Methorst C, Carnicelli D, Terrier JE, et al. Recommandations pour l'évaluation et la prise en charge de la maladie de Lapeyronie : rapport du comité d'andrologie et de médecine sexuelle de l'AFU. Prog Urol. 2021;31:477–94.
37. Gelbard M, Goldstein I, Hellstrom WJG, McMahon CG, Smith T, Tursi J, 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.
38. Egui Rojo MA, Moncada Iribarren I, Carballido Rodriguez J, Martinez-Salamanca JI. Experience in the use of collagenase clostridium histolyticum in the management of Peyronie's disease: current data and future prospects. Ther Adv Urol. 2014;6:192–7.
39. Abdel Raheem A, Capece M, Kalejaiye O, Abdel-Raheem T, Falcone M, Johnson M, 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.
40. Fernández Pascual E, Carballo N, Cerezo E, Fraile A, Martínez Ballesteros C, Peinado F, et al. HP-09-003 Clinical outcomes of the use of Collagenase Clostridium Histolyticum (CCH) for peyronie's disease (PD). J Sex Med. 2017;14:e160–1.
41. Ziegelmann M, Savage J, Toussi A, Alom M, Yang D, Kohler T, et al. Outcomes of a novel penile traction device in men with Peyronie's disease: a randomized, single-blind, controlled trial. J Urol. 2019;202:599–610.
42. Moncada I, Krishnappa P, Romero J, Torremade J, Fraile A, Martinez-Salamanca JI, et al. Penile traction therapy with the new device 'Penimaster PRO' is effective and safe in the stable phase of Peyronie's disease: a controlled multicentre study. BJU Int. 2019;123:694–702.
43. Martínez-Salamanca JI, Egui A, Moncada I, Minaya J, Ballesteros CM, del Portillo L, 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. Ibrahim A, Gazzard L, Alharbi M, Rompré-Brodeur A, Aube M, Carrier S. Evaluation of oral pentoxifylline, colchicine, and penile traction for the management of Peyronie's Disease. Sex Med. 2019;7:459–63.
45. Raheem AA, Garaffa G, Raheem TA, Dixon M, Kayes A, Christopher N, et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. BJU Int. 2010;106:1178–80.
46. 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.
47. Khouaja K, Delmas V, Boccon-Gibod L. [Leriche technique for the treatment of La Peyronie's disease]. Prog Urol. 2004;14:586–9.
48. Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. Investig Clin Urol. 2018;59:61.
49. Anitua E, Andia I, Ardanza B, Nurden P, Nurden A. Autologous platelets as a source of proteins for healing and tissue regeneration. Thromb Haemost. 2004;91:4–15.
50. Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res. 1998;355S:S7–21.
51. Eppley BL, Woodell JE, Higgins J. Platelet Quantification and growth factor analysis from platelet-rich plasma: implications for wound healing. Plast Reconstr Surg. 2004;114:1502–8.
52. Pietrzak WS, Eppley BL. Platelet rich plasma: biology and new technology. J Craniofac Surg. 2005;16:1043–54.
53. Woodall J, Tucci M, Mishra A, Asfour A, Benghuzzi H. Cellular effects of platelet rich plasmainterleukin1 release from prp treated macrophages. Biomed Sci Instrum. 2008;44:489–94.
54. Andia I, Maffulli N. Platelet-rich plasma for managing pain and inflammation in osteoarthritis. Nat Rev Rheumatol. 2013;9:721–30.
55. Randelli P, Randelli F, Ragone V, Menon A, D'Ambrosi R, Cucchi D, et al. Regenerative medicine in rotator cuff injuries. Biomed Res Int. 2014;2014:1–9.
56. Xie X, Zhang C, Tuan RS. Biology of platelet-rich plasma and its clinical application in cartilage repair. Arthritis Res Ther. 2014;16:204.
57. Weiss RA. Autologous cell therapy. Facial Plast Surg Clin N Am. 2013;21:299–304.

AUTHOR CONTRIBUTIONS

Research conception and design: AZ, MA, SL and SB. Data acquisition: AZ, MA, and SB. Statistical analysis: AZ, MA, SL and SB. Data analysis and interpretation: AZ, MA, SL and SB. Drafting of the manuscript: AZ, MA, SL and SB. Critical revision of the manuscript: MA and SB. Supervision: SB. Approval of the final manuscript: AZ, MA, SL and SB.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICAL APPROVAL

They study was conducted after obtaining approval from the Ethics Committee of Turin Hospital (Approval number: CT2022-74). The study adhered to the Helsinki protocols, and patients provided written, informed consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41443-023-00744-y.

Correspondence and requests for materials should be addressed to Ahmed S. Zugail.

Reprints and permission information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.