ORIGINAL RESEARCH

Sildenafil 25 mg ODT + Collagenase *Clostridium hystoliticum* vs Collagenase *Clostridium hystoliticum* Alone for the Management of Peyronie's Disease: A Matched-Pair Comparison Analysis

Andrea Cocci, MD, PhD,[1] Gianmartin Cito, MD,[1] Daniele Urzì, MD,[2] Andrea Minervini, MD,[1] Fabrizio Di Maida, MD,[1] Francesco Sessa, MD,[1] Andrea Mari, MD,[1] Riccardo Campi, MD,[1] Marco Falcone, MD,[3] Marco Capece, MD,[4] Girolamo Morelli, MD,[5] Giovanni Cacciamani, MD,[6] Michele Rizzo, MD,[7] Chiara Polito, MD,[5] Bruno Giammusso, MD,[8] Giuseppe Morgia, MD,[2] Paolo Verze, MD,[4] Andrea Salonia, MD, PhD,[9] Tommaso Cai, MD,[10] Vincenzo Mirone, MD,[4] Nicola Mondaini, MD,[11] and Giorgio Ivan Russo, MD, PhD[2]

ABSTRACT

Introduction: The effectiveness of phosphodiesterase type 5 (PDE5) inhibitors over the conservative management of Peyronie's disease (PD) has been widely questioned.

Aim: To determine the role of sildenafil 25 mg film formulation twice a day (S25 b.i.d.) in the improvement of curvature after treatment of collagenase of *Clostridium hystoliticum* (CCH) in penile curvature owing to PD.

Methods: From April 2017 to April 2018, 161 consecutive patients were treated with S25 b.i.d. + CCH or CCH alone. Adjustment variables consisted of age, penile curvature, and the 15-question International Index of Erectile Function (IIEF-15) questionnaire at baseline using 1:1 propensity-score matching. Overall, 50 patients were considered subdivided into the following: 25 patients who received S25 b.i.d. + CCH (group A) and 25 who received CCH alone (group B). Patients received CCH injection using a shortened protocol and vacuum device in both groups.

Main Outcome Measure: The primary outcome of the study was the change in penile curvature after treatment, and secondary outcomes were the change in sexual function (IIEF-15) and in the Peyronie's Disease Questionnaire (PDQ) and its subscores, PDQ-PS (psychosexual symptoms), PDQ-PP (penile pain), and PDQ-SB (symptom bother).

Results: Overall, mean penile curvature was 47.0° (SD 21.88), the mean IIEF-EF (erectile function) was 23.56 (SD 4.10), and the mean PDQ was 27.06 (SD 13.55). After the treatment, we observed a mean change for penile curvature of 25.6 (SD 9.05) in group A and −25.6 (SD 9.7) in group B ($P < .01$), for IIEF-EF of 2.28 (SD 2.33) in group A and 1.36 (SD 1.77) in group B ($P = .03$), for PDQ-PS of −3.04 (SD 2.95) in group A and of −2.12 (SD 2.06) in group B ($P = .11$), for PDQ-PP of −1.0 (SD 4.48) in group A and of −0.88 (SD 2.04) in group B ($P = .60$), for PDQ-SB of −5.84 (SD 4.58) in group A and of −4.16 (SD 4.45) in group B ($P = .60$), and for Female Sexual Function Index of 3.8 (SD 2.45) in group A and of 2.72 (SD 2.28) in group B ($P = .14$). We found a rate of global satisfaction of 70.83% in group A and of 84.0% in group B ($P = .27$).

Clinical Implications: Addition of S25 b.i.d. to CCH is superior to CCH alone for improving penile curvature and erectile function.

Strength & Limitations: This is the first study comparing sildenafil + CCH vs CCH alone for the treatment of PD. Lack of randomization and direct verification of appropriate use of penile modeling could be considered limitations.

Received July 11, 2018. Accepted August 23, 2018.

[1]Department of Urology, University of Florence, Florence, Italy;
[2]Urology Section, University of Catania, Catania, Italy;
[3]Department of Urology, Molinette Hospital, University of Turin, Turin, Italy;
[4]Department of Urology, University of Naples, Naples, Italy;
[5]Cisanello Hospital, University of Pisa, Pisa, Italy;
[6]Department of Urology, University of Verona, Verona, Italy;
[7]Department of Urology, University of Trieste, Turin, Italy;
[8]Morgagni Clinic, Catania, Italy;
[9]Department of Urology, Urological Research Institute, Vita-Salute University, San Raffaele Scientific Institute, Milan, Italy;
[10]Department of Urology, Santa Chiara Regional Hospital, Trento, Italy;
[11]Andrology Center, Villa Donatello Hospital, Florence

https://doi.org/10.1016/j.jsxm.2018.08.012

Conclusion: In this study, combination therapy was superior in terms of penile curvature and erectile dysfunction improvement. **Cocci A, Cito G, Urzì D, et al. Sildenafil 25 mg ODT + collagenase *Clostridium hystoliticum* vs collagenase *Clostridium hystoliticum* alone for the management of Peyronie's disease: A matched-pair comparison analysis. J Sex Med 2018;15:1472−1477.**

Key Words: Induratio Penis Plastica; Peyronie's Disease; Penile Curvature; Treatment; Xiapex; Xiaflex

INTRODUCTION

Peyronie's disease (PD) represents a disease with negative impact, both from a physical and psychological point of view. Recent data suggest that 0.4−9% of the male population is afflicted, with a higher prevalence in patients with erectile dysfunction (ED) and diabetes.[1,2] The typical age of a patient is 55−60 years and is often accompanied by pain and ED. The etiopathogenesis of the disease remains largely unknown but may be a result of abnormal wound healing owing to minor coital trauma in a genetically susceptible individual.[3−6] The initial painful inflammation of the tunica albuginea is later replaced with the formation of fibrous plaques, which cause the classical penile deformity, shortening, and a variable degree of ED.[7]

Over the past decades, numerous medical protocols have been proposed, with no significant success. Intralesional collagenase *Clostridium histolyticum* (CCH) is the first US Food and Drug Administration−approved drug for the treatment of PD and has recently been licensed in Europe and the United Kingdom. It selectively degrades collagen types I and III in connective tissues. Gelbard et al[8,9] showed that 50−60% of patients exhibited a clinically significant (>20%) improvement in curvature, with a mean percentage reduction in penile curvature from baseline to between 30% and 40%.

The effectiveness of phosphodiesterase type 5 (PDE5) inhibitors over the conservative management of PD has been widely questioned. An early report by Ozturk et al[10] showed that PDE5 inhibitor administration may be beneficial in PD patients for both erectile function and pain reduction. The aim of the study was to determine the role of sildenafil 25 mg film formulation b.i.d. in the improvement of curvature after treatment of CCH in penile curvature owing to PD.

MATERIALS AND METHODS

This was a prospective, non-randomized, open-label clinical study of a cohort of 161 patients who were treated with sildenafil 25 mg film formulation twice a day (S25 b.i.d.) + CCH or CCH alone for PD, between April 2017 and April 2018. The post-treatment protocol during collagenase consisted in a modeling of the penis during erection to maximize the collagenase effect in terms of decreasing of the curvature. We administered sildenafil film formulation 2 times a day, once in the morning and once in the evening exactly 30 minutes before the modeling session (between 30 and 60 seconds of modeling). Patients aged ≥18 years, with dorsal or lateral penile curvature >30° and <90° and with stable disease were enrolled. Stable disease[1] and calcification level[11] were classified as reported previously. The calcification level was classified as absence of calcifications, low spots of perilesional calcifications, and high calcification, modifying the previous definition from Levine et al.[11]

Outcome Measures

The 15-question International Index of Erectile Function (IIEF-15)[12] questionnaire and the Peyronie's Disease Questionnaire (PDQ)[8] were collected at baseline. The angle of curvature was assessed during erection after an intracavernous injection of prostaglandin E1, and an ultrasonography had been performed. Partners were evaluated with the Female Sexual Function Index (FSFI) questionnaire.[13] The FSFI, used to assess the female sexual partner's sexual function, is a 19-item questionnaire for assessing the key dimensions of sexual function in women, with domains for desire or arousal, lubrication, orgasm, satisfaction, and pain. All parameters and questionnaires were evaluated before treatment (baseline) and at the end of treatment cycle (4 weeks after the last injection).

Patients received collagenase *Clostridium histolyticum* (CCH-Xiapex) injection using a new shortened protocol as reported previously.[1] Patients were advised to model and stretch the penis between injections, and to use vacuum therapy (Owen Mumford, Inc, Marietta, GA, USA, distributed by Medis, Rozzano, Italy), starting 24−48 hours after the CCH injection.

Statistical Analysis

Adjustment variables consisted of age, penile curvature, and IIEF-15 at baseline using 1:1 propensity-score matching.[14] Propensity scores were computed using a logistic regression model with the dependent variable defined as the odds of receiving CCH + sildenafil or CCH alone and the independent variables as age, penile curvature, and IIEF-15 at baseline. Subsequently, covariate balance between the matched groups was examined. Overall, 50 patients were considered, subdivided into the following: 25 patients who received S25 b.i.d. + CCH (group A) and 25 who received CCH alone (group B).

The Student independent *t*-test or Mann-Whitney *U* test was used based on distribution of variables. The chi-square test was used for categorical variables. Penile curvature decrease of 20° was considered treatment success. We then developed a

Table 1. Baseline characteristics of all subjects

Variables	N = 50
Age (y), mean (SD)	50.34 (13.59)
Duration (mo), median (IQR)	13.0 (3.34)
Calcification, n (%)	
None	19 (38.0)
Low	22 (44.0)
High	9 (18.0)
Localization of the plaque, n (%)	
Base and dorsal	16 (32.0)
Mid	20 (40.0)
Distal	14 (28.0)
Penile length, n (%)	
<10 cm	9 (18.0)
10–15 cm	28 (56.0)
>15 cm	13 (26.0)
Penile curvature (degree), mean (SD)	47.2 (21.88)
IIEF-15, mean (SD)	58.8 (7.72)
IIEF-EF, mean (SD)	23.56 (4.10)
IIEF-OF, mean (SD)	8.92 (1.34)
IIEF-SD, mean (SD)	8.58 (1.03)
IIEF-IS, mean (SD)	9.84 (2.70)
IIEF-OS, mean (SD)	8.42 (1.82)
PDQ-PS, mean (SD)	9.36 (4.60)
PDQ-PP, mean (SD)	3.06 (5.12)
PDQ-SB, mean (SD)	14.64 (7.64)
FSFI, mean (SD)	32.98 (6.35)

FSFI = Female Sexual Function Index; IIEF-15 = 15-question International Index of Erectile Function; IIEF-EF = International Index of Erectile Function (erectile function); IIEF-IS = International Index of Erectile Function (intercourse satisfaction); IIEF-OF = International Index of Erectile Function (orgasmic function); IIEF-OS = International Index of Erectile Function (overall satisfaction); IIEF-SD = International Index of Erectile Function (sexual desire); PDQ-PP = Peyronie's Disease Questionnaire (penile pain); PDQ-PS = Peyronie's Disease Questionnaire (psychosexual symptoms); PDQ-SB = Peyronie's Disease Questionnaire (symptom bother).

Table 2. Baseline characteristics in both groups after the pair matching

Variables	Group A (n = 25)	Group B (n = 25)	*P* value
Age (y), mean (SD)	49.4 (13.48)	50.32 (12.47)	.77
Duration (mo), mean (SD)	13.32 (4.03)	13.4 (6.11)	.59
Calcification, n (%)			.40
None	10 (40.0)	9 (36.0)	
Low	11 (44.0)	11 (44.0)	
High	4 (16.0)	5 (20.0)	
Localization of the plaque, n (%)			.30
Base and dorsal	10 (40.0)	5 (20.0)	
Mid	8 (32.0)	10 (40.0)	
Distal	7 (28.0)	10 (40.0)	
Penile length, n (%)			.22
<10 cm	6 (24.0)	4 (16.0)	
10–15 cm	16 (64.0)	13 (52.0)	
>15 cm	3 (12.0)	8 (32.0)	
Penile curvature (degree), mean (SD)	51.6 (23.12)	49.2 (21.58)	.76
IIEF-15, mean (SD)	57.24 (8.18)	58.08 (7.83)	.74
IIEF-EF, mean (SD)	22.92 (4.50)	23.44 (4.27)	.77
IIEF-OF, mean (SD)	8.72 (1.51)	8.8 (1.60)	.71
IIEF-SD, mean (SD)	8.32 (1.10)	9.0 (1.12)	.06
IIEF-IS, mean (SD)	9.68 (2.79)	9.4 (2.39)	.74
IIEF-OS, mean (SD)	7.84 (1.90)	8.08 (2.03)	.58
PDQ-PS, mean (SD)	9.24 (4.38)	9.16 (3.65)	.58
PDQ-PP, mean (SD)	3.24 (5.10)	4.48 (4.87)	.10
PDQ-SB, mean (SD)	15.28 (7.32)	11.76 (7.08)	.08
FSFI, mean (SD)	30.88 (6.29)	33.44 (5.86)	.08

FSFI = female sexual function index; IIEF-15 = International Index of Erectile Function; IIEF-EF = International Index of Erectile Function (erectile function); IIEF-IS = International Index of Erectile Function (intercourse satisfaction); IIEF-OF = International Index of Erectile Function (orgasmic function); IIEF-OS = International Index of Erectile Function (overall satisfaction); IIEF-SD = International Index of Erectile Function (sexual desire); IQR = interquartile range; PDQ-PP = Peyronie's Disease Questionnaire (penile pain); PDQ-PS = Peyronie's Disease Questionnaire (psychosexual symptoms); PDQ-SB = Peyronie's Disease Questionnaire (symptom bother).

multivariable model predicting success of therapy including significant variables. All statistical analyses were completed using Stata software, version 14 (StataCorp LP, College Station, TX, USA). A significance level of $P < .05$ was considered statistically significant.

RESULTS

Overall, mean penile curvature was 50.34° (SD 13.59), the mean IIEF-15 was 58.8 (SD 7.72), and the mean PDQ was 27.06 (SD 13.55) (Table 1). Group comparison after the pair matching is shown in Table 2. In particular, we did not find statistical differences regarding all variables.

After the study protocol, in group A we observed significant mean changes regarding penile curvature (25.6; SD 9.05), IIEF-15 (9.24; SD 5.42), IIEF-EF (erectile function; 2.28; SD 2.33); IIEF-OF (orgasmic function; 0.92; SD 1.15), IIEF-SD (sexual desire; 1.32; SD 1.18), IIEF-IS (intercourse satisfaction; 2.36; SD 1.98), IIEF-OS (overall satisfaction; 4.8; SD 12.63), PDQ-PS (psychological symptoms; −2.12; SD 2.06), PDQ-PP (penile pain; −0.88; SD 2.04), PDQ-SB (symptom bother; −4.16; SD 4.45), and FSFI (2.72; SD 2.28) (all $P < .05$).

Similarly, in group B we found significant mean changes for penile curvature (17.4; SD 6.63), IIEF-15 (7.8; SD 12.74), IIEF-EF (1.0; SD 1.26), IIEF-OF (1.2; SD 3.0), IIEF-SD (1.12; SD 3.00), IIEF-IS (1.92; SD 3.56), IIEF-OS (2.0; SD 3.95), PDQ-PS (−2.44; SD (2.24), PDQ-PP (−1.2; SD 3.67), PDQ-SB (−4.16; SD 3.41), and FSFI (3.8; SD 2.45) (Table 3). When comparing between groups, we found significant increase

Table 3. Mean changes from baseline to after treatment in both groups for penile curvature, IIEF-15 and subdomains and PDQ

Variables	Group A	Group B	*P* value*
Penile curvature (degree), mean (SD)	−25.6 (9.05)	−17.4 (6.63)	<. 01
IIEF-15, mean (SD)	9.24 (5.42)	7.8 (12.74)	<. 01
IIEF-EF, mean (SD)	2.28 (2.33)	1.0 (1.26)	<. 01
IIEF-OF, mean (SD)	0.92 (1.15)	1.2 (3.0)	.66
IIEF-SD, mean (SD)	1.32 (1.18)	1.12 (3.00)	.04
IIEF-IS, mean (SD)	2.36 (1.98)	1.92 (3.56)	.09
IIEF-OS, mean (SD)	4.8 (12.63)	2.0 (3.95)	<. 01
PDQ-PS, mean (SD)	−2.12 (2.06)	−2.44 (2.24)	.26
PDQ-PP, mean (SD)	−0.88 (2.04)	−1.2 (3.67)	.05
PDQ-SB, mean (SD)	−4.16 (4.45)	−4.16 (3.41)	.69
FSFI, mean (SD)	2.72 (2.28)	3.8 (2.45)	.20

IIEF-15 = 15-question International Index of Erectile Function; IIEF-EF = International Index of Erectile Function (erectile function); IIEF-IS = International Index of Erectile Function (intercourse satisfaction); IIEF-OF = International Index of Erectile Function (orgasmic function); IIEF-OS = International Index of Erectile Function (overall satisfaction); IIEF-SD = International Index of Erectile Function (sexual desire); PDQ-PP = Peyronie's Disease Questionnaire (penile pain); PDQ-PS = Peyronie's Disease Questionnaire (psychosexual symptoms); PDQ-SB = Peyronie's Disease Questionnaire (symptom bother).
*Group A vs group B.

of penile curvature ($P < .01$), IIEF-15 ($P < .01$), IIEF-EF ($P < .01$), and IIEF-OS ($P < .01$) in group B vs group A.

Overall, we observed 37 patients (74.0%) with a penile curvature improvement of at least 20° after the treatment. The median percentage penile improvement was 47.26% (SD 19.03). When comparing groups, the median percentage penile improvement was 53.84% (SD 14.19) and 40.68% (SD 21.16) ($P = .02$).

In particular, 23 (92%) and 14 (56.0%) belonged to groups A and B, respectively ($P < .01$). At the age-adjusted logistic regression analysis, we found that CCH + sildenafil treatment was associated with increased success in terms of penile curvature improvement (≥20°) (odds ratio [OR] 13.84; 95% CI 2.12−90.32; $P < .01$).

DISCUSSION

Until now, there has not been unanimous consent over the ideal management of PD. Although several pharmacologic treatments have been proposed over the past decade, only intralesional injection therapy and surgical treatment have proven to be effective enough in the management of penile curvature owing to PD.

To date, CCH represents the only licensed drug for the minimally invasive treatment of PD. CCH is a mixture of AUX-I and AUX-II clostridial collagenases, which have selective hydrolytic activity toward collagen types I and III, resulting in the reduction of PD plaques without damage to surrounding elastic tissue, vascular smooth muscle, or axon myelin sheaths. The safety and efficacy of CCH in the management of PD has already been evaluated in previous articles,[10,15−18] although we still do not have a standardization of the protocol around the world.

Herein, we present the first study demonstrating the efficacy and safety of sildenafil 25 mg film formulation associated with CCH penile intralesional injection in the management of PD. In particular, we found that CCH + S25 b.i.d. treatment was associated with increased success in terms of penile curvature improvement (≥20°; OR 13.84; 95%CI 2.12−90.32; $P < .01$). In addition, IIEF scores and its subdomains, as well, have improved. In fact, for groups A and B, IIEF-15 scores were 57.24 ± 8.18 and 58.08 ± 7.83, and after the treatment the scores improved 9.24 ± 5.42 and 7.8 ± 12.74 points, respectively, showing a statistically significant difference between the 2 arms ($P < .01$).

The effectiveness of PDE5 inhibitors over the conservative management of PD has been widely questioned. An early report by Ozturk et al[10] showed that PDE5 inhibitor administration has significant benefit in PD patients. These findings may be justified by the inhibition of PDE5, leading to elevation of cyclic guanosine monophosphate levels and activation of protein kinase G, which is involved in cell apoptosis and reducing collagen synthesis.[18−20] In fact, Valente et al[21] demonstrated on experimental rat PD models that long-term PDE5 inhibitors had antifibrotic effects by lowering collagen deposits, profibrotic factor secretion, oxidative stress, and myofibroblast counts. In a similar study, Ferrini et al[22] observed the effect of vardenafil in counteracting the formation of the PD plaque. These observations suggest that PDE5 inhibitor administration alongside CCH plaque injection might be beneficial in PD patients by acting into 2 different moments of collagen synthesis.

It is not well established whether PDE5 inhibitors could act also by enhancing the penile modeling. In our study, patients were instructed to stretch model the penis with the use of vacuum therapy. Nonetheless, the role of modeling and vacuum therapy in improving penile curvature in PD is still under debate.[23] Based on current available literature, it has been hypothesized that modeling in conjunction with CCH further reduces tunical restriction caused by the PD plaque.[23] Similarly,

very few data evaluated the efficacy of vacuum therapy as a combination therapy during CCH injections. A recent observational study evaluated CCH administration combined with vacuum therapy between injection intervals, demonstrating benefits in terms of penile curvature and length after treatment.[24]

Our study was not devoid of several limitations, including the non-randomized nature of the therapy, lack of direct verification of appropriate use of penile modeling, and small cohort size. Each of these factors might have introduced statistical bias and weakened the overall reliability of reported findings. Acknowledging these limitations, the present matched-pair comparison represents the largest series so far, testing the safety and efficacy of sildenafil 25 mg alongside CCH penile injection in the management of PD.

It is clear that a change in the treatment of PD is needed in the near future, and further studies focusing on the correct patient identification are a precise unmet need. Particularly, further well-designed studies must confirm these initial observations. Studies assessing the long-term effects of CCH therapy, its use in patients with ventral penile curvature or calcified plaque, and a larger series identifying predictors of optimal treatment success in different subgroups of PD patients would also be needed.

CONCLUSION

Although surgical management remains the gold standard for patients with dense plaque calcification or disabling ED, CCH now provides an effective minimally invasive treatment option for men with PD with a palpable plaque and penile curvature deformity of at least 30° at the start of therapy. In this observational, matched-pair comparison between S25 b.i.d. + CCH vs CCH alone, we demonstrated that combination therapy was superior than CCH alone in terms of penile curvature and ED improvement. Further studies and larger randomized clinical trials are needed to confirm these preliminary observations.

Corresponding Author: Giorgio Ivan Russo, MD, PhD, Urology, University of Catania, Via S. Sofia 78, Catania, Italy 95100. Tel: 003900953782710; E-mail: giorgioivan1987@gmail.com

Conflict of Interest: The authors declare no conflicts of interest.

Funding: None.

STATEMENT OF AUTHORSHIP

Category 1

(a) **Conception and Design**
Andrea Cocci; Giorgio Ivan Russo

(b) **Acquisition of Data**
Andrea Cocci; Gianmartin Cito; Fabrizio Di Maida; Francesco Sessa; Andrea Mari; Riccardo Campi; Marco Falcone; Marco Capece; Bruno Giammusso

(c) **Analysis and Interpretation of Data**
Andrea Cocci; Giorgio Ivan Russo

Category 2

(a) **Drafting the Article**
Andrea Cocci; Giorgio Ivan Russo

(b) **Revising It for Intellectual Content**
Daniele Urzì; Andrea Minervini; Giovanni Cacciamani; Michele Rizzo; Chiara Polito; Giuseppe Morgia; Paolo Verze; Andrea Salonia; Tommaso Cai; Vincenzo Mirone; Nicola Mondaini.

Category 3

(a) **Final Approval of the Completed Article**
Andrea Cocci; Giorgio Ivan Russo

REFERENCES

1. Cocci A, Russo GI, Briganti A, et al. Predictors of treatment success after collagenase Clostridium histolyticum injection for Peyronie's disease: Development of a nomogram from a multicentre single-arm, non-placebo controlled clinical study. **BJU Int 2018. In press.**
2. 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;15:716-721.**
3. Pryor JP, Ralph DJ. Clinical presentations of Peyronie's disease. **Int J Impot Res 2002;14:414-417.**
4. Bjekic MD, Vlajinac HD, Sipetic SB, Marinkovic JM. Risk factors for Peyronie's disease: A case-control study. **BJU Int 2006;97:570-574.**
5. Herati AS, Pastuszak AW. The genetic basis of Peyronie's disease: A review. **Sex Med Rev 2016;4:85-94.**
6. Ralph D, Gonzalez-Cadavid N, Mirone V, et al. The management of Peyronie's disease: Evidence-based 2010 guidelines. **J Sex Med 2010;7:2359-2374.**
7. Chung E, De Young L, Brock GB. Penile duplex ultrasonography in men with Peyronie's disease: Is it veno-occlusive dysfunction or poor cavernosal arterial inflow that contributes to erectile dysfunction? **J Sex Med 2011; 8:3446-3451.**
8. Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of Peyronie's disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. **J Urol 2013; 190:199-207.**
9. 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;12:248-258.**
10. Ozturk U, Yesil S, Goktug HN, et al. Effects of sildenafil treatment on patients with Peyronie's disease and erectile dysfunction. **Ir J Med Sci 2014;183:449-453.**
11. Levine L, Rybak J, Corder C, et al. Peyronie's disease plaque calcification—Prevalence, time to identification, and development of a new grading classification. **J Sex Med 2013; 10:3121-3128.**

12. Cappelleri JC, Rosen RC, Smith MD, et al. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. **Urology 1999;54:346-351.**
13. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): A multidimensional self-report instrument for the assessment of female sexual function. **J Sex Marital Ther 2000;26:191-208.**
14. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. **Stat Med 1998;17:2265-2281.**
15. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. **Urol Res 1982;10:135-140.**
16. Gelbard MK, James K, Riach P, et al. Collagenase versus placebo in the treatment of Peyronie's disease: A double-blind study. **J Urol 1993;149:56-58.**
17. French MF, Mookhtiar KA, Van Wart HE. Limited proteolysis of type I collagen at hyperreactive sites by class I and II *Clostridium histolyticum* collagenases: Complementary digestion patterns. **Biochemistry 1987;26:681-687.**
18. Nagayama T, Zhang M, Hsu S, et al. Sustained soluble guanylate cyclase stimulation offsets nitric-oxide synthase inhibition to restore acute cardiac modulation by sildenafil. **J Pharmacol Exp Ther 2008;326:380-387.**
19. Yildirim A, Ersoy Y, Ercan F, et al. Phosphodiesterase-5 inhibition by sildenafil citrate in a rat model of bleomycin-induced lung fibrosis. **Pulm Pharmacol Ther 2010;23:215-221.**
20. Cocci A, Capece M, Cito G, et al. Effectiveness and safety of oro-dispersible sildenafil in a new film formulation for the treatment of erectile dysfunction: Comparison between sildenafil 100-mg film-coated tablet and 75-mg oro-dispersible film. **J Sex Med 2017;14:1606-1611.**
21. Valente EG, Vernet D, Ferrini MG, et al. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. **Nitric Oxide 2003;9:229-244.**
22. Ferrini MG, Vernet D, Magee TR, et al. Antifibrotic role of inducible nitric oxide synthase. **Nitric Oxide 2002;6:283-294.**
23. Avant RA, Ziegelmann M, Nehra A, et al. Penile traction therapy and vacuum erection devices in Peyronie's disease. **Sex Med Rev; Epub ahead of print,** https://doi.org/10.1016/j.sxmr.2018.02.005.
24. Abdel Raheem A, 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;120:717-723.**