

# Complications and other concerns with intralesional injection therapy with collagenase clostridium histolyticum for Peyronie's disease

Laurence A. Levine

Department of Urology, Rush University Medical Center, Chicago, IL, USA

*Correspondence to:* Laurence A. Levine, MD, Professor of Urology, Rush University Medical Center, Chicago, IL, USA. Email: drlevine@hotmail.com.

*Provenance:* This is a Guest Editorial commissioned by Section Editor Yongde Xu, PhD (Department of Urology, First Hospital Affiliated to Chinese PLA General Hospital, Beijing, China).

*Comment on:* Yafi FA, Anaissie J, Zurawin J, *et al.* Results of SMSNA Survey Regarding Complications Following Intralesional Injection Therapy With Collagenase Clostridium Histolyticum for Peyronie's Disease. *J Sex Med* 2016;13:684-9.

Submitted Nov 09, 2016. Accepted for publication Nov 09, 2016.

doi: 10.21037/tau.2017.01.03

View this article at: <http://dx.doi.org/10.21037/tau.2017.01.03>

The article by Yafi *et al.* reports on a well-designed survey of Sexual Medicine Society of North America members regarding complications following intralesional injection with collagenase clostridium histolyticum (CCH) for Peyronie's disease (PD) (1). Only 100 of the 693 (14%) members responded to the report, which may be an indication of the limited adoption and/or experience with this drug as of the time of this survey. The side-effects reported are not surprising and correspond to the published reports from the CCH pivotal trials including that hematoma and ecchymosis are the most frequently observed adverse events following treatment with this drug (2,3). The extent and severity of these local side-effects are interesting given the small amount of fluid injected (0.25 cc) and the small needle used (27 gauge), as compared to intralesional verapamil or interferon where up to 10 cc's of fluid is injected using a 25-gauge needle (4,5). Ecchymosis is not an uncommon finding after injection with these drugs, but it is rare to have significant hematomas or blood blisters. Therefore, is there something peculiar to CCH that causes the more extensive ecchymosis and hematomas? It has been speculated that this occurs as a result of a local histamine response to the fragments of collagen released following injection of CCH. Since these complications are common following CCH injection, it would seem that the physician would be well-advised to inform the patient up-front that this is a likely side-effect of the drug and not necessarily one that should cause distress. The patient should know that the hematomas

and ecchymosis typically resolve without sequelae within 2 weeks after injection (2,3). Many physicians have suggested applying a post-injection compression dressing which is left on for 2–24 hours. As not all patients experience this problem, our approach has been that following initial injection, the patient is advised to manually compress the injection area for approximately 10 minutes, but if they do develop a significant ecchymosis, then on subsequent visits a gentle compression dressing with Coban should be applied overnight.

What was more significant in this survey was the relatively frequent incidence of corporal rupture reported by 34% of physicians at a median of 5 days from the last CCH injection. The most commonly reported cause of rupture was during vigorous intercourse in 38% but up to 31% had this occur during a spontaneous nocturnal/morning erection. As expected, these ruptures occurred in the area of the treated plaque and 67% of the responding physicians did explore the patient and repair the rupture. The patient information pamphlet does recommend “*waiting 2 weeks after the second injection before resuming sexual activity* (6).” But 44% of the noted corporal ruptures were found to occur beyond the 2-week window and no fractures occurred beyond the 30-day mark. The authors therefore suggest that patients should be counseled to “*exert caution and refrain from vigorous intercourse within the first 30 days after the second injection of the treatment cycle.*” This seems to be reasonable, albeit difficult to enforce advice. Interestingly,

no significant difference was noted in rates of post-rupture repair erectile dysfunction (ED), ability to have intercourse, change in penile curvature, or patient satisfaction versus those who were managed with surveillance. The current literature is pretty clear that patients who experience a non-CCH corporal rupture should have prompt surgical repair to reduce the likelihood of subsequent deformity and/or ED (7). This poses the question as to what is different about the ruptures that occur following CCH such that no significant difference was seen with respect to deformity or post-rupture ED regardless of surgical treatment and observation. Further experience may yield the answer.

The adverse events addressed in this article are certainly important and need to be recognized by the practicing physician and should be communicated to the patient as well. There are other issues which I believe warrant discussion here including treatment efficacy and cost of this drug. At this time, there is only one published non-industry supported post-approval treatment outcome report by Ziegelmann *et al.* which shows similar results to the IMPRESS trials with a mean measured curvature reduction of 23 degrees (38%) in 27 patients (8). We need more outcome data reports to help determine the characteristics of the optimum candidate for CCH. My personal observations in the clinic have revealed that too many men are receiving CCH without appropriate evaluation (i.e., no assessment of curve or plaque calcification) such that men with ventral curve, extensive plaque calcification, or no curve at all are receiving this expensive and relatively labor intensive drug protocol, where the likelihood of benefit is low in these groups. My impression is that those men who have a readily palpable plaque and have a discreet area of angulation rather than an elongated area of curvature are better candidates for CCH. The current recommended treatment protocol instructs the physician to inject only into the area of maximum curvature, which would not treat the secondary curvature. This may be in part responsible for suboptimal results in this patient population. In time alternate techniques for administering the drug may emerge including an increased dose or volume of the drug or multiple injection sites. Identification of other groups that may be either at higher risk for failure or better candidates for CCH will be most valuable in this era of cost containment as well as in an effort to avoid expensive and prolonged treatment which has a low rate of success. These parameters may include presence of calcification, ventral curvature, severe hourglass deformity, and a primary goal of penile length recovery. Certainly men with

pre-existing ED which is refractory to PDE5i therapy should not receive CCH as they will likely need penile prosthesis implantation to address their PD and ED.

Another important issue is the cost of this drug. These biological medications are expensive to manufacture and take through the FDA approval process. The price of CCH is around \$3,400.00 per injection with up to eight injections given over a 6-month course. Cordon *et al.* have authored a compelling and novel cost analysis which found that, according to their definition, one successful outcome with CCH is 8 times more costly than a single successful tunica plication procedure (9). Although cost is a clear issue, many men do not consider this a reason not to have treatment as the great majorities are not paying out of pocket. Another way to look at the decision as to whether a patient with stable PD should undergo surgery or CCH therapy is to compare the reported efficacy of CCH which according to the pivotal trials is around a 60% chance of experiencing a 25% or more reduction of curvature or a 34% mean reduction in curve versus a very high rate of near complete correction of curvature following an outpatient surgical procedure allowing return to sexual activity around 6 weeks post-operatively. I think that men with a severe curvature (i.e., >70 degrees) and/or severe hourglass deformity causing a hinge effect, should be aware of the limited benefit with CCH for this type of deformity. Clearly, the “gold-standard” treatment for PD has been, and remains surgery, as it is reliable and effective. Yet, patient preference will be the driving force particularly if insurance continues to pay for CCH.

Finally, credit is due to the manufacturers of CCH for creating a broad reaching advertising campaign which has increased the awareness of this, not so uncommon, disorder affecting up to 10% of men. The IMPRESS trials were also important to identify that the psychological bother of this disorder is critical to the patient and the practicing physician would again be well-advised to recognize and acknowledge this distress to the patients they see who present with PD.

### Acknowledgements

None.

### Footnote

*Conflicts of Interest:* The author is a consultant and speaker for Endo, Coloplast and Boston Scientific Corporations.

## References

1. Yafi FA, Anaissie J, Zurawin J, et al. Results of SMSNA Survey Regarding Complications Following Intralesional Injection Therapy With Collagenase Clostridium Histolyticum for Peyronie's Disease. *J Sex Med* 2016;13:684-9.
2. Gelbard M, Goldstein I, Hellstrom WJ, 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.
3. 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.
4. Levine LA, Estrada CR. Intralesional verapamil for the treatment of Peyronie's disease: a review. *Int J Impot Res* 2002;14:324-8.
5. Hellstrom WJ, Kendirci M, Matern R, 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.
6. XIAFLEX REMS for Peyronie's Disease. Available online: <http://www.xiaflexrems.com/peyronie.php>
7. Hatzichristodoulou G, Dorstewitz A, Gschwend JE, et al. Surgical management of penile fracture and long-term outcome on erectile function and voiding. *J Sex Med* 2013;10:1424-30.
8. Ziegelmann MJ, Viers BR, McAlvany KL, et al. Restoration of Penile Function and Patient Satisfaction with Intralesional Collagenase Clostridium Histolyticum Injection for Peyronie's Disease. *J Urol* 2016;195:1051-6.
9. Cordon BH, Hofer MD, Hutchinson RC, et al. Superior Cost-Effectiveness of Penile Plication vs Intralesional Collagenase Injection for Treatment of Peyronie's Disease Deformities. *Urology Practice* 2016. [Epub ahead of print].

**Cite this article as:** Levine LA. Complications and other concerns with intralesional injection therapy with collagenase clostridium histolyticum for Peyronie's disease. *Transl Androl Urol* 2017;6(1):120-122. doi: 10.21037/tau.2017.01.03