Commentary

Re: Results of SMSNA survey regarding complications following intralesional injection therapy with collagenase clostridium histolyticum for Peyronie's disease

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Provenance: This is a Guest Commentary 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.

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Expert summary of study

In this survey sent to the members of the Sexual Medicine Society of North American (SMSNA), Yafi *et al*. assessed the providers' experience with intralesional injection of collagenase *clostridium histolyticum* (CCh) for Peyronie's disease (PD). The anonymous, 33-question survey was sent to 693 members of SMSNA with valid email addresses and requested responses from CCh prescribers. The 100 responders (14.4% response rate), were relatively evenly distributed in their experience administering CCh injections with 36%, 23% and 41% of responders performing injections on ≤10 patients, 10–20 patients, and >20 patients respectively.

The providers' responses demonstrated variation in preferences for the delivery of CCh, as well as, diagnosis and management of complications. Two-thirds of providers apply some type of dressing in an effort to prevent hematoma formation. Severe hematomas were infrequently encountered, occurring in <10% of patients according to 73% of responders. In a subgroup analysis, hematoma formation was not affected by penile dressing application or anticoagulant use. Management of hematomas varied amongst providers with 63% observing, 20% applying a compressive dressing, 2% draining the hematoma, and 15% doing some combination of each. Corporal ruptures were encountered by one-third of providers, most of whom encountered a single rupture. Diagnosis of corporal rupture was made by history and physical exam alone by half of the providers. The remaining half of providers diagnosed the ruptures with MRI alone, ultrasound alone, or a combination. The ruptures occurred a median of 5 days (0.5–30 days) following injection and were usually following the second injection of a cycle. Two thirds of providers managed them surgically. Based on investigator recall only, there was no difference in erectile function following corporal rupture whether managed surgically or conservatively (1).

Expert's comments

PD is a dysregulation of wound healing that leads to deposition of an inelastic, collagenous plaque within the tunica albuginea, which results in penile curvature during tumescence that can impeded penetrative intercourse (2). CCh (Xiaflex; Endo Pharmaceuticals, Malvern, PA, USA) consists of two synergistic bacterial collagenases, AUX-I and AUX-II (3). In December 2013, the U.S. Food and Drug Administration (FDA) approved CCh as an intralesional agent for the treatment of PD. To be considered a candidate to receive the injection, the patient must have a palpable penile plaque and a ≥30 degree curvature.

The phase 3 clinical trials that preceded FDA approval, Investigation for Maximal Peyronie's Reduction Efficacy

and Safety Studies (IMPRESS) I and II, demonstrated both improvement in curvature and few serious adverse events. Mean curvature improved –17.0°±14.8° in the treatment group compared to –9.3°±13.6° in the placebo group. Of the combined 832 study subjects, 84.2% experienced an adverse event. The authors describe them as "*typically mild or moderate…approximately 79% resolved without intervention within 14 days*." (4). These adverse events included penile ecchymosis, penile swelling, penile pain, etc. Six serious adverse events were reported, 3 penile hematomas (0.4%) and 3 corporal ruptures (0.4%). The corporal ruptures were managed surgically. The hematomas were managed with observation, surgical exploration, or drainage (4). These results were further supported in a pooled analysis of the six clinical trials of CCh, in which 9 of 1,044 subjects (0.9%) developed serious adverse events, including 5 penile hematomas and 4 corporal ruptures, of which 4 (0.4%) required surgery (5).

Since FDA approval, there have been two, independent, prospective, post-market clinical trials that focus on curvature resolution, prevalence of adverse events and their management. Both studies have reported higher rates of penile hematoma and corporal rupture as compared to the IMPRESS I and II trials. Ziegelmann *et al.* reported 7/69 patients (10%) developed penile hematoma, which were defined as a palpable collection of blood product in the area of the penile injection (6). No corporal ruptures occurred during the study. Yang *et al.* reported penile hematoma in 5/49 patients (10.2%) and corporal rupture in 1/49 patients (2%). Penile hematomas were defined as penile bruising with a palpable collection (7).

In the index study, the authors provide further evidence that the occurrence rate of corporal rupture and severe penile hematoma may be higher than previously suspected. Admittedly, the difference in reported rates may be due to a lack of standardized definition of a severe penile hematoma. Ziegelmann *et al.* and Yang *et al.* reported similar rates of adverse events when employing a consistent definition for penile hematoma. Neither the Yafi *et al.* nor IMPRESS I and II trials provide definitions of severe penile hematoma. At least one episode of corporal rupture was seen by 34% of responders in the survey. Although not directly comparable, the reported rate is higher than would be expected based on the clinical trial corporal rupture rates of 0.4%. Because the index study is limited by recall bias, large prospective studies are needed to determine if bleeding complications and corporal rupture are more common than previously reported, or if higher rates are due to differences in nomenclature and diagnostic criteria.

Traumatic, or non-CCh-related, corporal rupture is considered a surgical emergency, requiring immediate repair in order to reduce the risk of erectile dysfunction and wound complications (8). To date, there is no data on the preferred diagnosis or treatment of CCh-related corporal rupture. The survey responders vary in their preferred methods of diagnosis. Half of the responders made the diagnosis with history and physical exam alone. The other half were evenly divided between MRI alone, ultrasound alone, or a combination of methods. The majority of responding providers treat both non-CCh-related and CCh-related corporal ruptures with surgical repair. However, one third of responders who had encountered a corporal rupture managed it conservatively and do not report any decline in erectile function. These results support the idea that CCh-related corporal ruptures may be physiologically different from their traumatic counterpart, making them more amenable to observation. However, these results must be interpreted with caution. Due to the methodology of the study, causal relationships cannot be made and bias cannot be excluded. More prospective studies are needed to answer the poignant questions posed by the authors.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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