

Peer Review File

Article Information: <https://dx.doi.org/10.21037/tau-22-746>

Review Comments (Round 1)

Reviewer A

Authors provide a helpful case report describing resolution of ejaculatory/pelvic discomfort symptoms in a patient with Zinner's syndrome. A few clarifications will be helpful to educate the readers before publication.

1) Case presentation - include whether cystoscopy was performed and the findings

A1: Thank you for pointing this out. Cystoscopy was not performed because the patient refused an invasive examination. This has been added to the Case presentation section in the revised version of the manuscript.

2) Line 88 - include what surgical treatments were offered

A2: A variety of procedures, from aspiration to surgical excision, were considered for this case. Based on this suggestion, the following has been added to the revised version.

“The need for management by use of percutaneous drainage and transurethral or transrectal aspiration, or a surgical procedure, either a laparoscopic or open vesiculectomy, was discussed with the patient, who expressed a desire to avoid invasive treatment as much as possible.”

3) Discussion - please include what other treatments specifically offered for Zinner's syndrome based on prior studies and in also in general for ejaculatory pain

4) Discussion - include how efficacious surgical treatments may or may not be for improving these symptoms and in this presentation

A3, 4: We appreciate these important suggestions. Surgical excision is the most common treatment and considered to be highly effective, since it eliminates the root of the pain. Furthermore, the rate of recurrence following that is lower as compared to other treatments. On the other hand, the level of difficulty of such a surgical procedure is high and there is a risk of complications. These points have been added to the Discussion section, as follows.

“Among those, a seminal vesiculectomy procedure, including open, laparoscopic, and robot-assisted approaches, is performed in nearly 60% of affected cases because of the advantage of less recurrence as compared to conservative management [3]. However, that report also noted that performance of a seminal vesicle resection is associated with high risk for surgical complications leading to erectile dysfunction and urinary incontinence.”

5) Discussion - discuss other commonly used alpha blockers (tamsulosin, alfuzosin) and why silodosin was chosen first

A5: We have added a description of $\alpha 1$ blockers widely used in Japan and rewrote the portion regarding why silodosin was chosen, as follows.

“There are three $\alpha 1$ -adrenoceptor subtypes ($\alpha 1A$, $\alpha 1B$, $\alpha 1D$) as well as $\alpha 1$ -adrenoceptor antagonists that target these receptors, ranging from subtype nonselective to those that act selectively. The previously described $\alpha 1$ adrenergic receptor subtype C was later found to be a variant of $\alpha 1A$ and then integrated into subtype A. The $\alpha 1A$ and $\alpha 1D$ receptors are present in prostate and bladder neck smooth muscle tissues, while $\alpha 1B$ is abundant in vascular smooth muscle. Presently, tamsulosin, silodosin, and naftopidil are $\alpha 1$ blocker drugs available in Japan for treating BPH. Of those, it is well known that silodosin has a high affinity for the $\alpha 1A$ receptor and naftopidil a strong affinity for the $\alpha 1D$ receptor, which is also distributed in the bladder.”

Reviewer B

This is a rare and interesting case report. It will be nice if author can comment / clarify / amend the manuscript according to the following suggestions.

1. How do authors think about the need of further evaluation methods such as seminal vesiculoscopy for evaluation of EDO and it will be better to add comments for this.

A1: Thank you for pointing this out. There was an abnormality in the semen findings, thus cystoscopy and vasospermography were considered, as noted by the reviewer. However, further invasive testing could not be performed because of lack of patient consent. This information has been added to the Case presentation section in the revised version of the manuscript.

2. Authors reported that a patient with Zinner syndrome whose ejaculation pain was successfully managed with silodosin. Is there any other case report or study in use of another $\alpha 1$ -adrenoceptor antagonist such as tamsulosin or alfuzosin for ejaculatory pain? If it is, it will be better to add comments for this.

A2: Thank you for pointing this out. To the best of our knowledge, this is the first report of an attempt to improve these symptoms with an $\alpha 1$ blocker. We recognize that this is an important point of the study.

3. In longer term follow-up, does this patient have no symptom recurrence?

A3: To date, there has been no recurrence of symptoms. We are not sure why, but judging by shrinkage of the cyst shown by MRI, EDO seems to have been improved, in part because of the silodosin treatment given. The following has been added to the revised Discussion section.

“Furthermore, since there was no recurrence of symptoms after the end of treatment and the seminal vesicle cysts showed a shrinking tendency, silodosin may have had some effect to improve EDO, though the mechanism is unknown.”

Reviewer C

This is an interesting case report of ejaculation pain due to Zinner's syndrome treated with silodosin, but there are several issues that need to be addressed.

- 1) The patient was a 37-year-old unmarried male; did the author adequately consider the risk of ejaculatory dysfunction with silodosin in a sexually active male? Please specify whether the author have provided fully informed consent.

A1: Thank you for noting these important points. A sufficient explanation was given and informed consent was obtained before the start of oral treatment. The following has been added to the revised version of the manuscript.

“After providing a full explanation of the risk of ejaculation disorder and orthostatic hypotension due to use of silodosin, the patient provided informed consent and the treatment was commenced.”

- 2) Please specify the prostate volume.

A2: As suggested, text regarding the prostate volume has been added to the revised Case presentation section.

- 3) If performed, please specify the findings of verumontanum on cystoscopy

A3: Unfortunately, a cystoscopy procedure could not be performed because the patient refused to undergo an invasive examination. We have added this information to the Case presentation section.

- 4) If silodosin relieves seminal vesicle contractions, the symptoms could recur when the drug is discontinued. Please discuss why symptoms did not recur.

- 5) Also, the author has not addressed the shrinkage of the right seminal vesicle gland on MRI 5 years later in Discussion part. EDO partially improved?

A4, 5: We appreciate the reviewer for these comments along with the very important question. As noted, it is very unclear why the symptoms did not recur after oral

administration. Although evidence is lacking at this time, EDO may have at least partially improved in the patient and silodosin might have had on role in that. The following sentence has been added to the revised Discussion section.

“Furthermore, since there was no recurrence of symptoms after the end of treatment and the seminal vesicle cysts showed a shrinking tendency, silodosin may have had some effect to improve EDO, though the mechanism is unknown.”

Reviewer D

The authors described a case of Zinner syndrome treated successfully with silodosin. The authors also performed a brief review of the condition and the mechanisms by which alpha antagonists may alleviate the symptoms. The case report is of good quality; however, there are a few points that deserve further attention.

1 - The manuscript should be reviewed by an English-speaking reviewer to improve the reading.

A1: A native speaker of English has checked the paper, including the revised portions.

2 - There are three subtypes of $\alpha 1$ -receptors (a,b and d), there is no c subtype. The once described c subtype was later found to be a subtype a variation. Please, review this topic

A2: Thank you for this important suggestion. The related sentence has been revised based on the advice of the reviewer, as shown following.

“There are three $\alpha 1$ -adrenoceptor subtypes ($\alpha 1A$, $\alpha 1B$, $\alpha 1D$) as well as $\alpha 1$ -adrenoceptor antagonists that target these receptors, ranging from subtype nonselective to those that act selectively. The previously described $\alpha 1$ adrenergic receptor subtype C was later found to be a variant of $\alpha 1A$ and then integrated into subtype A.”

3- Please, provide more data regarding the patient's semen analysis and fertility status. Was the ejaculate volume normal? Did he father a child?

A3: Thank you for these questions. The patient had not fathered a child, and semen volume and motility were abnormal. Semen findings and information regarding the lack of a child have been added to the revised Case presentation section.

Review Comments (Round 2)

The author has responded appropriately to the reviewer's request. However, the causative effect of silodosin in reducing pain due to cystic dilation of the seminal vesicle remains unclear. The failure to verify this point is a very significant limitation.

A: We appreciate the reviewer for these comments. As noted, it is a significant limitation that we have not been able to explain the detailed mechanism of silodosin for pain reduction due to cystic dilation of the seminal vesicle. We think it needs to be verified by further case accumulation.