Peer Review File

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Reviewer A

Comment #1

Start the commentary by evaluating the recent pregabalin randomized control trial prior to transitioning to the discussion of opioid reduction after ureteroscopy

REPLY: We thank the reviewer for the suggestion. We believe that first proving the framework in which our invited response should be read with in mind, such as on nonopioid pain management and the potential utility of gabapentinoids, allows the reader to better appreciate the points of our editorial. We have substantially revised the introductory paragraphs to place the trial in context and eliminated large portions of the discussion of opioid reduction after ureteroscopy, aligned with the spirit of the reviewer's suggestion.
Changes in the text: We have substantially revised the introductory paragraphs to place the trial in context and eliminated large portions of the discussion of opioid reduction after ureteroscopy.

Comment #2

Reduce verbosity to clearly focus on the message – pregabalin may reduce opioid use after ureteroscopy

REPLY 2: We have decreased the verbosity of this article for concision. We have made several clarifications to improve the flow of the article given the changes and edits presented.

Changes in text 2:
-Lines 32-33 clarified.
-Lines 38-39 clarified.
-Line 58 made concise.
-Lines 60-62 clarified for more precise description.
-Lines 63-64 clarified.
-Line 66 divided into two sentences to improve flow.
-Line 70-71 made concise.
-Lines 81-82 made consistent with lines 80-81 for consistency,
-Line 98 made concise
-Line 108 clarified.
-Line 110 clarified.
-Line 112 made concise.

-Line 114 clarified.
-Line 118 made concise.
-Line 121 made concise.
-Line 127 clarified.
-Line 132 clarified.
-Line 136 made concise.
-Line 136 made concise.
-Line 139 clarified.
-Line 144 changed to provided consistent emphasis on nonopioid management

Comment #3
The editorial should have a greater focus on why to include pregabalin (specifically) in an opioid free protocol

REPLY 3: We have expanded our literature seach regarding prior gabapentinoid use for stent pain discomfort. This is positioned as an introductory paragraph as opposed to being in the body of the text to further highlight gabapentinoid potential use.
Changes in text 3: Added new paragraph emphasizing recent literature search lines 42 – 55.

Suggested Rewrite:
Paragraphs 1, 2 should be eliminated (lines 23-40). Begin at line 41.

41 A recent single center prospective trial of preoperative pregabalin adds evidence to our understanding of pain management after ureteroscopy. Rosen and colleagues randomized 118 patients undergoing ureteroscopy to receive a single dose of pregabalin 300 mg versus placebo one hour before surgery. The primary outcome was visual analogue scores (VAS) at one hour after surgery. Secondary outcomes included postoperative pain scores on post-op days 3, 7, and 30, ED visits, and opioid intake.9

They found that patients who received pregabalin had more severe postoperative pain at one hour after surgery. When controlling for age and preoperative VAS, there were no differences between groups for all secondary outcomes. The authors concluded that single-dose of preoperative pregabalin offers no significant benefit to reduce post-ureteroscopy pain.
While this trial is notable for the "real world" design, there were summarily several factors which could have influenced the results. The primary outcome was 1 hour postoperative pain scores, which could be influenced by anesthesia medications. Gabapentin has a 6 hour half life, which would warrant consideration for additional time points for pain assessments prior to postoperative day 3. Stent dwell time was not included in the ANCOVA analysis as a controlled factor. Lack of a standardized pain medication pathway postoperatively could bias

the secondary outcomes. There was a higher oral morphine equivalent (OME) prescription in both groups than would be considered standard of care.
(continue now at line 59)
The routine use of opioids for post-ureteroscopy pain management is no longer emphasized. (move to line 68) Best practice guidelines recommend 0-5 tablets of oxycodone 5mg for uncomplicated ureteroscopy, laser lithotripsy and ureteral stent placement, and no opioids for stent free ureteroscopy.11 (move to line 80) Our institutional practice for routine ureteroscopic stone intervention utilizes an opioid free pharmacotherapy including acetaminophen, a nonsteroidal anti-inflammatory, plus alpha blockers and/or anticholinergics. (line 87) Forty percent of opioid overdoses in the United States may be attributed to prescription medications,12 and 6 percent of opioid naïve patients develop a dependency after exposure to the medication.13 Therefore, the refinement of protocols limiting opioids after ureteroscopy is vital to improving patient outcomes after ureteroscopy.
[insert paragraph here on why pregabalin is actually reasonable to include in postoperative pathways for pain control, despite the aforementioned negative study.]
(continue line 124)
While the pregabalin trial may have yielded a negative result, we do not believe that this study eliminates gabapentinoids as a pain adjunct entirely. A single, preoperative dose of pregabalin may not be optimized to yield demonstrable symptom relief. [Sentence or two suggesting an alternative prescription pathway including pregabalin that would reduce opioids, and why this pathway > single dose preop]. However, this study is an incremental step toward a larger evidence base upon which to strengthen opioid stewardship in urology.

REPLY 4: We appreciate the reviewer's suggestion. We have incorporated many of the changes in the other responses to this reviewer and other reviewers.

Reviewer B

Qi and Koo present a thoughtful overview of the potential role of gabapentinoids in controlling postoperative pain after ureteroscopic surgery. Overall, it is well written piece with only a few minor suggestions that I would recommend making:
- there is a large emphasis on the discouragement of the use of opioids, which is important, however detracts from the main message of this article which should be on the consideration of using gabapentinoids. In particular, I would recommend decreasing the amount of discussion relating to the opioid crisis which is a well-known issue already, (e.g. paragraph 5-6). Should the focus of this article be more relating to opioids, then the title should at least be revised to reflect as such.

REPLY:
We have deleted paragraph 1 (lines 23-31) to decrease the relative emphasis on opioids, and added a new paragraph (lines 42-55) regarding prior gabapentinoid use for stent pain discomfort to further emphasize the consideration of gabapentinoids.

- I know that the only primary evidence that has reviewed in this commentary piece is the study by Hosen et al. I believe if the purpose of this article is to reconsider the use of gabapentinoids, then a greater review of the literature is required to support its use in urological surgery. In particular, I know that there is other literature that is available that supports its for stent related symptoms (DOI: 10.1007/s11255-017-1561-7). The authors should consider expanding their review regarding the literature relevant to this topic.

REPLY:
We have expanded our literature seach in a new paragraph 2 (lines 42-55) regarding prior gabapentinoid use for stent pain discomfort. This is positioned as an introductory paragraph as opposed to being in the body of the text to further highlight gabapentinoid potential use.

Reviewer C

I commend the authors for this review of the literature and value the time and work spent on this manuscript. However, this manuscript does not add any additional value to the pre-existing literature. I recommend that the authors combine this review of the literature with a trial and statistics from their institution with a prospective trial of pregabalin.

REPLY:
We appreciate the reviewer's suggestion. As this manuscript was an invited editorial to a specific paper (Rosen et al), the inclusion of new trial data was outside the scope of the work. We agree that additional studies will help define the role for pregabalin, and we look forward to seeing such studies in the future.

Reviewer D

This is an excellent commentary on the recently described trial and I welcome it to the literature.

Line 59/60, grammar check please

REPLY:
We thank the reviewer for the suggestion. We have changed prior line 59-60 / revised draft line 81-82 to say “and 0–5 oxycodone 5 mg tablets for routine ureteroscopy and laser lithotripsy without stent placement” to maintain consistency and clarity with the wording of the previous line (“0–10 oxycodone 5 mg tablets for opioid-naïve patients undergoing routine ureteroscopy and laser lithotripsy with ureteral stent placement”).

Reviewer E

Important discussion points to put this study into context. Well written, concise, and impactful.

REPLY:
We thank the reviewer for the feedback.