Peer Review File

Article Information: https://dx.doi.org/10.21037/tau-21-41

Reviewer A

Overally great work with early animal in vivo studies which can be challening.

RESPONSE: We thank the reviewer the highly positive appraisal of our manuscript. We appreciate the constructive comments of the reviewer. As described in the detailed response below, we have revised the manuscript (with highlighted changes) to carefully address all of the comments.
NOTE: All line numbers mentioned below refer to the highlighted version of the manuscript, which shows the revisions.

A few minor revisions/clarifications:

Comment 1. There is mention of in vitro testing but no citation if these were previously published, or explanation of what specifically was done with placing them in a tube. If not previolsy published, I recommend sharing the methodology and results of the in vitro testing to complete the story and provide pictures of the testing apparatus

Reply 1: The preliminary in vitro testing mentioned briefly in the "Methods", subsection "Ureteral stent design and preparation" has not been published previously or separately. The testing was done informally, with an improvised apparatus. Because the apparatus was intended as a preliminary test, emphasis was placed on designing an effective, rather than "elegant" set-up, and photographs were not taken. However, a concise description of the methodology and results is now provided in the revised manuscript.

Changes in the text: We have modified the text to describe the methodology and results, in section "Methods", subsection "Ureteral stent design and preparation" (see Page 5, lines 112-122).

Comment 2. The methododlogy/technique for placing the stents fully intraureteral is not well explained. Are there radioopaque markers. The idea of an intraureteral stent is great, but being able to replicate among surgeons is in important

Reply 2: We particularly appreciate this comment. The stent itself is fully radiopaque, as seen for example in Figure 2. The stents were inserted into the pig cadaver and pig ureters using standard endourological methods, i.e., guidewire, radiopaque stent, and pusher. To achieve consistent positioning of the YotiCurl, we suggest that the urinary system first be delineated by either retrograde or antegrade pyelogram using contrast agent. Then, under fluoroscopy, the proximal tip of the YotiCurl should be located ~3 cm above the level of obstruction – either a stone or a stricture – before the sensor wire is withdrawn. This procedure will allow the spiral curls of the stent to be situated above and beneath the obstruction.

Changes in the text: We have modified the text to clarify that the stent itself is radiopaque (see Page 4, line 102; Page 6, line 159), and to further explain the proposed methodology used to ensure consistent placement of the stents in the ureters (Pages 8-9, lines 211-216).

Comment 3. THe IVF studies mentioned for evaluation of drainage are not well described. How long does it take to drain with the stent in place. Are there any comparison IVP in nonstented pigs to use a s a benchmark. Inclusion of some images here would also be helpful

Reply 3: On Day 3, at which point the right ureter was drained by the YotiCurl stent, contrast agent was injected intravenously. Within a few minutes, the contrast agent was observed simultaneously in both collecting systems, indicating no evidence of obstruction. Subsequently, on Day 5 and thereafter, with both YotiCurl stents in place, contrast agent was again injected and observed in the collecting systems as well as the bladder within minutes. These results indicate that no obstruction nor delay was apparent with both YotiCurl stents present.

Non-stented (control) pigs were not part of this initial, proof-of-concept study. As we note at the end of the Conclusions section, further testing on a suitably large number of animals, including control animals with conventional double-J stents and/or no stenting, is required to more fully evaluate stent function, and can now be justified on the basis of this proof-of-concept study.

Changes in the text: We have modified the text to provide more information on evaluation of drainage (see Page 7, lines 167-169 and lines 182-185).

Reviewer B

RESPONSE: We appreciate the constructive comments of the reviewer. As described in the detailed response below, we have revised the manuscript (with highlighted changes) to carefully address all of the comments.

NOTE: All line numbers mentioned below refer to the highlighted version of the manuscript, which shows the revisions.

Comment 1) In the discussion the authors state that patients with indwelling stents have significantly reduced QoL "presumably due mostly to the present of the anchors in the bladder and kidney, as well as to urine reflux to the renal collecting system. While there may be some irritation due to stent movement within the kidneys and bladder, and some level of reflux, more recent work has shown additional mechanisms including loss of peristalsis and excessive dilation of the ureter to also play a role.

Reply 1): We thank the reviewer for noting this point.

Changes in the text: We have modified the text to include these mechanisms, as suggested (see Page 10, lines 253-254).

Comment 2) The authors state that the stent curls will straddle any obstructing stone or stricture site. Given the perpendicular nature of the curls to the ureteral wall, is there not a likelyhood for a stricture to form by pushing between the curls and possibly a stone fragment becoming trapped in the lower curl resulting in obstruction?

Reply 2): We are certainly aware of these possibilities, but note that (i) the spiral curls enlarge (radially) sections of the ureter lumen over a length of 1-2 cm, so that ureter wall is "stretched" and stricture appears unlikely, and the (ii) the proof-of-concept experiment on two in vivo pig ureters did not display ureteral strictures. As we note at the end of the Conclusions section, further testing on a suitably large number of animals, including control animals with conventional double-J stents and/or no stenting, is required to more fully evaluate stent function, and can now be justified on the basis of this proof-of-concept study.

As for the possibility of a stone fragment becoming trapped in the lower curl, and resulting in obstruction – the likelihood appears very small: even if a stone fragment were to be trapped in the lower curl, the stent lumen itself allows urine drainage, and drainage can still also occur in the ureter lumen around the stone and curl.

Changes in the text: We have modified the text to recognize that these possibilities, as wells as others, require systematic analysis in large animal cohort testing, and then in human clinical trials (see Page 12, line 290; and Page 13, lines 319-321).

Comment 3) How do the authors propose the stents would be removed? This would either require a follow-up procedure to locate the stent within the ureter or a long tether would need to

be attached that would extend through the ureter, into the bladder (requiring cystoscopy for removal), or the tether would need to be left hanging out of the urethra. Given the increased risk for infection when a suture tether is left in place, the fact that the tether would reach into the ureter will significantly increase the risk for ascending infections as it provides bacteria direct access into the ureter and then the kidneys.

Reply 3): The reviewer asks how we propose that the stents will be removed. As described in the (original) manuscript in the "Methods", subsection "Ureteral stent design and preparation" , lines 98-101, "A standard suture is attached to the distal spiral …, similar to that used in commercially-available double-J stents, that extends into the bladder or through the urethra, to facilitate stent removal."

The reviewer then suggests that risk for infection increases with presence of a suture tether. We certainly agree with this, but note that the risk would appear no higher than with use of conventional double-J stents, with or without a tether, that may increase the risk for ascending infections by providing bacteria with direct access into the ureter and then the kidneys.

Changes in the text: We have added text to note the point regarding risk of infection (see Page 11, lines 273-275).

Comment 4) How do the authors explain the fact that the bottom curl seemed to change configuration and almost unravel? Is this intended? If not then this would suggest that the behaviour of the stent is unpredictable and unraveling of the top may result in stent migration.

Reply 4): The bottom curls, both of which are clearly visible in Figure 2, did not actually "change configuration and almost unravel". It is not clear to us why, or on what basis, the reviewer makes these statements. In fact, the positioning and configuration of the four (proximal, distal) spiral curls of the two stents inserted in the in vivo pig experiment remained essentially unchanged from initial insertion and opening until the completion of the experiment. As a result, there is no basis for the reviewer's suggestion that the behavior of the stent is unpredictable and/or that the proximal spiral might unravel. We understand that the manuscript may not have been sufficiently clear on this important point, and have added text to clarify.

Changes in the text: We have expanded the text to describe clearly that the positioning and configuration of the four (proximal, distal) spiral curls of the two stents inserted in the in vivo pig experiment remained essentially unchanged, from initial insertion and opening until the completion of the experiment (see Page 9, lines 220-222).

Comment 5) The authors state that only minimal ureteral dilation was observed. Considering that ureteral dilation is something that is "desired" especially in the context of an obstructed ureter. Is this not a limitation?

Reply 5): First and foremost, the YotiCurl stent is intended to relieve obstruction and enable free drainage of urine, while reducing the side effects of regular double-J stents. Dilatation by itself

does not confirm passing or migration of a stone. Other factors such as peristalsis and elasticity, as well as dilatation, also play a role in stone migration. Therefore, the fact that insertion of the YotiCurl stent results in mild (not "minimal") dilatation is not considered a drawback. Indeed, on the contrary, it was important to ensure that there was no hydroureter or otherwise extreme dilatation.

On the other hand, a potential advantage of the YotiCurl is that peristalsis may not be completely stopped. In such cases, this might encourage stone migration; but these aspects can only be tested in future clinical trials.

Changes in the text: We have modified our text accordingly (see Page 12, line 299, and Page 13, lines 319-321).

Comment 6) An additional limitation is the fact that the testing in a single pig does not allow for the assessment of renal function with respect to creatinine levels or even the comparison of dye passage into the bladder in non-stented pigs.

Reply 6): We recognize this point and mentioned the need for further testing, with both stented and unstented pigs, in the conclusions. We now expand the text to note that there is now justification to fully examine all aspects of the stent performance and all aspects of its impact on urinary tract function on a large animal cohort.

Changes in the text: We have modified the text as noted here (see Page 13, lines 331-332).

Comment 7) Encrustation is not something that is typically observed in pigs, so the visual observation that there was no encrustation on these stents is not relevant.

Reply 7): We agree that encrustation is not typically observed on stents in pigs, but the question still arises often when reporting on stent usage in pig and other animal experiments. For completeness, we prefer to retain the brief mention of this check.

Changes in the text: We have modified the text slightly to improve clarity, and to note explicitly that encrustation is not typically observed on stents in pigs (see Page 10, Lines 244-245).

Comment 8) Overall, the fact that the stent was tested in a single animal is a major limitation as there is no comparison to non-stented ureters for all parameters tested. At this stage publication seems premature.

Reply 8): We agree that a large animal cohort is desirable. We stated *explicitly*, in the title, Abstract, Methods, Discussion, and Conclusions, that the current study represents an *initial proof-of-concept*; and we then note that the results justify a systematic study on a large cohort of animals. For an initial study of this type, there is no real need to compare "all parameters tested" to non-stented ureters – in a control animal with no stent or other intervention of any

kind, there is no reason to expect discomfort, inflammation, hydronephrosis, or changes to drainage in the urinary tract. We emphasize that this study is, to the best of our knowledge, the *first consideration* and test of a *fully intraureteral* stent, ever since the initial use of ureteral stents was reported in 1967. After half a century, it seems remarkable that stent structure has remained virtually unchanged in terms of the kidney and bladder pigtail structures. On the other hand, we emphasize that entrenched thinking and fears regarding changes to ureteral stent design, which engender a considerable range of reasonable concerns, have led to a general reluctance to test different stent structure designs. *The proof-of-concept study presented here can be considered a significant step forward, suggesting for the first time that a fully intraureteral stent may be safe and effective.* As noted in the Conclusions, too, further testing on a suitably large number of animals, including control animals with conventional double-J stents and/or no stenting, is required to more fully evaluate stent function and all aspects of its impact on urinary tract function. Such testing can now be justified on the basis of this proof-of-concept study.

Changes in the text: We have modified the last paragraph of the Conclusions to further reflect this argument (see Page 13, lines 331-332).