

Peer Review File

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Reviewer A: The authors conducted a retrospective study using a multi-institutional database on urethroplasty outcomes and specifically report the outcomes for patients who perform CIC. Only 4/37 patients required a surgical reintervention for USD after a median follow-up of 3.1 years.

The authors are to be congratulated for this well written and comprehensive manuscript.

In my opinion, some minor revisions are necessary and could increase the quality of the manuscript.

Comment 1:

ABSTRACT

- In general: well written and informative.

- Conclusion: This conclusion is not supported by the data presented in the abstract/manuscript (first sentence: this is not a direct comparative study or a matched cohort analysis, so this conclusion cannot be drawn; second sentence: this is true, but not the content of the manuscript). I suggest using the conclusion of the full-text: 'Urethroplasty is suitable, safe and effective for patients dependent on CIC suffering from USD.'

Reply 1: Firstly, thank you for spending the time to read and provide comments. We have made the suggested change to the conclusion of the abstract

Comment 2: METHODS

- Line 47: Please define the start date of the database instead of 'prior to 2009', for instance, from 2000 until 2009. This may be relevant for systematic reviews and meta-analyses in the future.

Reply 2: So corrected line 47-48

Comment 3: - Line 61: As mentioned in the discussion (line 223), the 2 patients with stricture recurrence, but at a different location, were not considered a failure. If this is the case, the definition of functional success should be slightly adapted: '...who underwent repeat surgical treatment for a recurrent stricture at the site of original urethral reconstruction...'

Reply 3: Agree and appreciate this suggestions – so added

Comment 4: - Line 64: 'redo urethroplasty' is probably forgotten in this list.

Reply 4: Agree with oversight, corrected.

Comment 5: RESULTS

- Line 78: It would be interesting to know how many patients were in the original database (this would give an idea about the prevalence of this condition within a tertiary urethroplasty center): e.g. out of a 1000 urethroplasties, 37 patients met the inclusion criteria after excluding n for reason x, m for reason y, ...

- Line 118: The authors should specify how they investigated continence after surgery. I suppose by retrospective chart review without systematic use of questionnaires pre and postop. This needs further elucidation in the methods section or at least deserves attention in the limitations.

Reply 5: We have added to limitations as standard questionnaires of pre-and post-operative continence as well as other patient reported symptoms were not recorded. (page 11) In this specific patient population, PROM have not yet been validated to answer these questions:

The study represents a heterogeneous group of patients with varied reasons for being dependent on CIC presenting to genitourinary reconstructive experts. This represents a retrospective analysis with inherent bias, small sample size, without protocol for analyzing pre and postoperative continence or patient reported outcomes. Currently, bladder specific quality of life measurement tools for patients with neurologic conditions are heterogeneous and lack attention to the symptomatology of concomitant urethral stricture disease

Comment 6: DISCUSSION:

- Line 131: It deserves mentioning that indirect comparisons are hazardous, because many differences in patients, strictures, definitions of failure etc. may be present among different series and importantly impact the results of this comparison. For example: in this study, almost all patients returned to CIC, which could be considered a form of chronic dilation; it's hard to compare this patient subgroup to others.

Reply 6: We agree, which is why an extensive portion of the discussion is focused on this issue and controversy re: dilations: Line 164:

The data surrounding CIC is paradoxical as CIC may be used to decrease USD recurrence after DVIU but conversely may increase the risk of USD in the context of CIC for neurogenic bladder.

Comment 7: - Line 141: Don't enter new results in the discussion; use median as in the results section.

Reply 7: So corrected

Comment 8: - Line 164: How did the authors/surgeons deal with the fact that CIC was often continued until the operation? Did they use urethroscopy to identify the distal end of the stricture intra-operatively?

Reply 8: The decision regarding the extent of the urethral stricture was left to the discretion of each surgeon. For those given a pre-operative SPT, urethral rest may have allowed a more 'straightforward' identification. However, the data herein does not suggest a great advantage in this small series for pre-op SPT.

Comment 9: - Line 174-175: This was not mentioned in the results section. There appears to be no formal analysis or data to support this statement. It should be omitted.

Reply 9: Urethral rest and preop SPT is now highlighted in the results paragraph starting line 96:

Urethral rest with SPT was pursued in 15 (41%) patients for a median of 2 months (IQR: 1.25-5) prior to urethroplasty. Among included surgeons, 4 of 6 regularly retain SPT tubes post-operatively for up to 2 months to avoid CIC across a fresh urethroplasty whereas 2/6 restart CIC after acceptable post-operative RUG.

Comment 10: - Line 177: Don't enter new results in the discussion. Suggest to omit it or to mention it in the results section first.

Reply 10: Results are now emphasized regarding this issue starting on line 115: Ultimately, 4 patients required repeated surgical intervention, which equates to a 90% functional success rate. 32 (86%) patients returned to CIC for primary bladder management (Table 3), 5 (14%) are spontaneous voiders, 4 by Credé and 1 by condom catheter and 1(3%) continues to use indwelling SPT by preference. The patient's typical post-surgical CIC catheter size was 14 Fr (IQR: 12-14). Specific outcomes for patients with the longest strictures (10 cm, 15cm and 16 cm) were a return to CIC per urethra (n=1) and perineal urethrostomy with CIC (n=2) with 1 patient requiring dilation of their urethrostomy. 8 patients had an anatomic recurrence on cystoscopy, but no hindrance of CIC. The initial surgery type (and stricture lengths) for those requiring re-intervention were excision and primary anastomosis (2.5 cm & 1 cm), non-transecting urethroplasty (3 cm), and perineal urethrostomy (15 cm).

Comment 11: LIMITATIONS

- Should be added: small sample size, retrospective analysis with inherent bias, no systematic protocol for analyzing pre- and postoperative continence status.

Reply 11: These are excellent points and have been added to limitations section first line.

Reviewer B

Comment 1:

In general:

- edit and update all spelling mistakes; it makes it hard to read
- make it more fluent, change your sentence structure

Specific:

- please define your succes more in detail; 8 patients had cystoscopic recurrence, but you define success as fluent passage of a 17Fr cystoscope, thus in total 12 patients had recurrence -> success rate 70%?

Reply 1: Thank you for reading our manuscript and providing comments.

In this population, patients may regularly perform CIC (14 Fr catheter on average in this group) but anatomic recurrence was still noted on cystoscopy. For completeness, we have reported cystoscopic recurrences. But we measured and focused primarily on functional success rate given the lack of meaning for cystoscopic recurrence in this patient population. IE 4 patients required repeated intervention. Functional recurrence defined on line 62:

Functional recurrence was defined as any patient who underwent repeat surgical treatment for recurrent stricture at the site of the original reconstruction during the follow up period, including: urethral dilation, direct vision internal urethrotomy, repeat urethroplasty, creation of catheterizable channel, or urinary diversion.

Comment 2:

- median time of catheter removal postoperatively?
- were there failures after redo-urethroplasty/re-intervention?

Reply 2: To date no failures after re-intervetion.

Comment 3:

- what is your definition of incontinence after surgery? Which PROMs did you use?
- did you only assess incontinence? No uroflow, IPSS, UDI-6 questionnaires?
- what about quality of life?

Reply 3: We unfortunately do not have PROMs to report from this patient

population. Now summarized in limitations:

We lack a protocol for analyzing pre and postoperative continence or patient reported outcomes. Currently, bladder specific quality of life measurement tools for patients with neurologic conditions are heterogeneous and lack attention to the symptomatology of concomitant urethral stricture disease.

Comment 4: - are some techniques more prone to develop stricture recurrence?
Please use Kaplan-Meier graphs

Reply 4: Given the small numbers of included patients, and only 4 recurrences, we feel KM graphs will not add to the discourse.

Comment 5: - explain your statistics in detail

Reply 5: Simple descriptive statistics were used, category percentages, medians and IQR were calculated as one can see in table outputs 1-4.

Comment 6: - did all surgeons used the same surgical techniques? explain in detail

- grafts are defined in length and width, not only length

Reply 6: Surgeons performed a variety of techniques (Table 2) according to their clinical judgement, training, and expertise for each patient. Dorsal onlay, dorsal inlay, flap based, non-transecting, ventral and dorsal joint repair, anastomotic, and perineal urethroostomy were all included. Largest graft dimension was the recorded variable available.

Comment 7: - is a perineal urethroostomy defined as an urethroplasty or as an urinary diversion? explain in detail

Reply 7: PU was considered a urethroplasty and included as a repair type. (Table 2)

Reviewer C

Comment 1: The authors from the US TURNS group report on 37 male patients who regularly performed CIC due to different reasons and underwent urethroplasty for urethral stricture disease. This is an interesting descriptive manuscript on a rare condition.

I was surprised about the attribution of more than 40% of patients to “idiopathic strictures”. How were the authors able to assign such etiology in a patient who had performed CIC on a regular basis before surgery already (86% of all)?

Although the authors have defined CIC-related strictures in the results section, I

still believe that the repeated mucosal microtrauma caused by CIC may actually preclude the option of an idiopathic stricture in such patient population.

Reply 1: We appreciate your comments. Regarding the assignment of etiology, as you know it is extremely difficult to ascribe cause of USD even in a healthy male patient population given lack of biomarker or other objective metrics to back up intuition. The TURNs database records etiology of stricture based on physician entry of the database and herein we are simply reporting this characterization.

Comment 2: The authors should be commended to shed light on this understudied topic, but basically all conclusions are based on a presumable heavy selection bias. The discussion is nicely written and focuses on general issues in the context of CIC and patient suffering from neurogenic bladder and less on surgical technique or patient selection. An interesting question to ask would be how we can select those patients, who are adequate for urethroplasty and subsequent CIC. The authors more than once use the term “well selected patients”, however, it does not get quite clear how this selection was made. And this would be the really interesting part, (1) how to decide to opt for urethroplasty instead of diversion and (2) to elucidate what were the drivers to choose one surgical technique over the other. Otherwise, this would be “just” an interesting descriptive study showing that urethroplasty is feasible in CIC patients but does not really aid in making the right technical decision.

Reply 2: While we agree of your two points, the complex discussion between a patient and their physician in selecting diversion vs. urethroplasty would likely best be informed by qualitative analysis and not ascertained by chart review. For this group of expert surgeons, as we highlight, there are widely different strategies regarding catheter management, graft vs non-graft repairs, and speed to return to CIC. This data suggests that we cannot identify any specific winners or losers in technical strategy.

Reviewer D: The authors of this manuscript should be congratulated on making the effort to compile the outcomes on these challenging patients. The data on management of these patients is lacking, and this multi-institutional study fills a knowledge gap. The authors also do a good job of reporting the surgical technique utilized for the repairs, which adds to our understanding of what may be the best approach for the management of these patients.

Comment 1:

Title:

- Descriptive and clear

Abstract:

- Well written, clear, and concise

Introduction:

- Well written introduction. I agree that restoring catheterism in these patients is necessary, and worth the effort. There has been previous series by Chris Gonzalez approximately 10 years ago. Overall, previous data on the topic has shown worse success rates in these cases. Overall, this information is going to be useful for counseling patients.

Methods and Outcomes:

- Methods were well described

- Inherent to multi-institution study, there is a great deal of variability in the peri-operative care in this cohort. Would be interesting to see if certain institutions have better outcomes or less complications based on the use of SPT or delayed vs immediate resumption of CIC.

Reply 1: Appreciate your comments. We have a heterogeneous group with small numbers – conclusions should be drawn with caution. But as reported on line 118 use of grafts, no urethral rest appeared to affect outcomes.

Comment 2:

- The labeling of stricture to CIC only seems to be difficult. I feel that with a long enough duration of CIC and repeated instrumentation, all these patients suffer a negative sequelae leading to stricture disease. Not sure how much stock to put in the patient's recollection of specific instance of trauma. Just something to consider.

Reply 2: It is extremely difficult to ascribe cause of USD even in a healthy male patient population given lack of biomarker or other objective metrics to back up intuition. The TURNs database records etiology of stricture based on physician entry of the database and herein we are simply reporting this characterization.

Comment 3:

Discussion:

- Overall, the discussion is comprehensive and well written. No major comments.

- Line 181 – typo

- Line 190 – typo

Reply 3: So corrected

Reviewer E

Comment 1: A good paper that will add insights to how patients with urethral stricture disease are managed. Involving patients in this disease area could have been stronger and how the study data will help with in shared-decision making.

Reply 1: Thank you for your comments