

# Peer Review File

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## Reviewer A

This study aimed to evaluate the efficacy of ureteroscope assisted X-ray free ureteral stricture balloon dilation for ureteral strictures.

This technique has not been reported yet, however there are some issues to be discussed.

1. In the video, the authors performed the balloon dilation without the preparation of C-arm. It was a great job. But, I think that this technique has a risk of ureteral perforation due to imageless insertion of guidewire through the ureteral stricture, especially in the case of difficult ureter. To insert the guidewire safely, it is better to confirm x-ray under the ureteroscopic vision.

**Response:** Thanks for your friendly reminder. We all agree that X-ray plays an important role in the endourological procedure. In fact, despite that we preferred to perform the balloon dilation procedure without fluoroscopic assistance, we would always have a C-arm machine ready to help when necessary. However, under most circumstances, there was no need for the C-arm.

2, I think the success rate was quite high. In general, the success rate for ureteral stricture was 60-70% using insertion of dual ureteral stents after endoluminal incision and balloon dilation. What was the definition of surgical success?

**Response:** The definition of surgical success was disappearance of preoperative symptoms (including removal of preoperative catheter), relief of hydronephrosis (compared to preoperative ultrasound or CTU) and stable renal function (indicated by serum creatinine level or GFR in diuretic renal scan) (see in Page 7, line 117-120).

3, The authors commented that CTU was evaluated to determine the length of the stricture. However, it is difficult to measure the length of ureteral stricture using CTU, in case of severe hydronephrosis. And, the authors described the methods of measuring the ureteral stricture using ureteroscopy, but how accurately? I think it is difficult to measure it in a few millimeters.

**Response:** Your comments on the issue of measuring the length of ureteric stricture was very insightful, and it is true that both CTU and the method using ureteroscopy intraoperatively could not give a precise measurement of the exact ureteral stricture length. Thus, we have modified our description on the measurement of ureteric stricture as “roughly” (see Page 6, line 110). However, in this study, we didn’t have to verify the exact numerical value of the stricture length, and we only categorized it as

“less than 5mm”, “[5mm, 2cm]” and “over 2cm”. On evaluating preoperative CTU, If the stricture length is too long (over 2cm), we would recommend the patients take other treatment modality (open or laparoscopic surgery). During the operative procedure, we only roughly determined the length whether it is less or longer than 5mm to facilitate subsequent prognostic analysis.

4, The authors should show the split renal function.

**Response:** Thanks for your kind reminder, we added the data of split renal function (GFR result for diuretic renal scintigraphy) in the Table 1. However, since the study was retrospective, the data of diuretic renal scan were not available for all patients, and only 26/76 of patients’ GFR results were identified. However, we were planning to establish a prospective cohort of patients receiving balloon dilation and hoping the results could be presented one day.

5, This study included 76 cases, and multivariate analysis was evaluated using 8 subjects. The case number was too small to include 8 subjects for the multivariate analysis, statistically.

And in general, it was reported that the prognostic factors for postoperative stenosis recurrence were stricture length and split renal function. The authors should include split renal function, too.

**Response:** Thanks for your meticulous explanation in the multivariate analysis. We have taken counsel from the statistician in our university’s department of statistics. It is suggested that the case number should be at least 160 to include 8 subjects for the multivariate analysis. However, the statistician also believed that the choice of variables should also refer to clinical practice and those 8 subjects were important for prognostic study, moreover, with a “entry” method in COX regression model performed by IBM SPSS, the bias could be reduced to a certain extent. Thus, the multivariate analysis we performed was reasonable and it could also show some significance.

6, If the ureteroscope could not be passed through the stricture, what was the next strategy?

**Response:** If the ureteroscope could not be passed through the stricture, we would try another surgical strategy. If the patients were with nephrostomy tube, we would use the rendezvous technique, combing the antegrade and retrograde approach, under the fluoroscopic supervision. Once this failed or there was no nephrostomy tube, we would recommend the patients seek a more invasive surgery to address the issue.

7, The authors should describe the surgical methods in details. Which size of balloon dilation were used in this study?

**Response:** The balloon dilation catheter used in the study was a product of Bard Medical, and the product item name was “Dilation Catheters, Ureteroscopic Balloon, X-FORCE®, U30, with Inflation Device”, the diameter was 6Fr unexpanded and 30 Fr expanded, and the length was 6 cm. We have added this information in Page 9, Line 159.

## Reviewer B

line 63 - 'is always performed'

line 91-92 - evidence 'of' malignancy

**Response:** Thanks for your friendly reminder, we have corrected the language mistakes accordingly (See Page 5 line 74, Page 6 line 112).

how do you define / diagnose integrity of vascular condition?

**Response:** we define the integrity of vascular condition by patients' history. If the patients undergone a prior surgery involved the mobilization of ureter or periureteral tissue, such as ureteropyeloplasty, gynecological or pelvic surgery, and developed ureteral stenosis subsequently, then their vascular condition was defined as compromised (see Page 11, Line 202-205).

what is the brand and name of the balloon used?

**Response:** The balloon we used was a product of Bard Medical, and the product item name was "Dilation Catheters, Ureteroscopic Balloon, X-FORCE®, U30, with Inflation Device" (see Page 9, Line 159).

this is essentially doing balloon dilatation under direct endoscopic visualisation.

i agree that this method will not be possible for very tight pin hole stricture if only the wire can pass through the lumen.

also, op time may be longer without fluoroscopy because direct visualisation is required during balloon dilatation, as well as during stent placement. also, the need of bedside ultrasound to check upper end of DJ stents.

**Response:** Thanks for your review and approval, and we came into the situation that there was a very tight pin hole stricture and the guidewire could not be passed through, we would recommend the patients to choose another treatment modality. During the procedure, we also used a bedside ultrasound to check upper end of DJ stents.

## Reviewer C

The authors present a retrospective cohort analysis of 76 patients undergoing a fluoroscopy-free ureteral balloon dilatation in a single centre a median 22.5-month follow-up period. As the authors stated, there are some drawbacks to the use of intra-operative X-rays and have attempted to come up with a solution. The aim is to demonstrate the safety and efficacy of the technique.

There has been a published RCT by Mohey et al. in 2018. It would be interesting to see any additional value of this study.

Please find my comments below:

Title:

The title must clearly reflect the aims of your study: is it a feasibility study of a novel technique? Is it a safety and efficacy study. This needs to be clarified.

For example:

“Fluoroscopy-free minimally invasive ureteral stricture balloon dilatation: a retrospective safety and efficacy cohort study”

**Response:** We are grateful for your revision and the aim of this study is report of safety and efficacy study. We have changed the title into “Fluoroscopy-free minimally invasive ureteral stricture balloon dilatation: a retrospective safety and efficacy cohort study”.

Line 12:

The author state that all co-authors participated in the manuscript draft. Perhaps specify which part each author wrote. Abstract: author xyz, introduction: author yyy ect... This is to define the roles of authors 1., 2. and last author.

**Response:** The role the authors played in writing the manuscript was as follows. Y Peng, G Xiong and G Wang wrote the manuscript draft, specifically, Y Peng mainly focus in the Abstract, Introduction, Result and part of Discussion, G Wang and G Xiong mainly focus on the Method and part of Discussion. then the draft was transferred to XS Li, Xin Li, C Zhang, K Yang and L Zhou, these authors help to revise the manuscript.

Running Title

Again, shortly specify the aim of the study.

**Response:** We change into “The safety and efficacy cohort study of X-ray free balloon dilation” (see Page 2, Line 25-26).

Ethical approval:

Yes

Abstract: Needs re-writing

Background: please state the urgency of your study. Has this been previously covered in the literature?

**Response:** This method had not been previously reported in the literature, and we add this information in the text (see Page 3 Line 37)

Method: you stated that your aim to establish the safety and efficacy of this surgical approach. Please define your safety and efficacy criteria. How do you define success and failure rates?

I don't see the relevance of a prognostic analysis in this study.

Please finish the sentence with a full stop.

**Response:** Safety criteria was evaluated with perioperative and postoperative complication rate. Efficacy criteria was evaluated with success rate. The Definition of

success was disappearance of preoperative symptoms, relief of hydronephrosis and stable of renal function (see Page 3, line 50-51).

Results:

These do not reflect your aims.

How many patients were included? How many were excluded?

Clavien summary? Complication rates? Recurrence rates is actually 15/76 (20%) and failure rates is 2/76? You mentioned in the results (text) that success rate was 59/76 (78%).

(if all patients were included. You mentioned later in the manuscript that you excluded long strictures > 2 cm and yet up to 5cm strictures were analysed? Please clarify?

**Response:** Thanks for your review and we have re-written the results part of Abstract according to your suggestion. We added the information about the patients being included and excluded, Clavien summary, complication rates. (see Page 4, Line 54-61)

Additionally, for clarification, the success rate was 61/76, and failure rate was 15/76 (Seen Page 9, Line 162-164). The stricture length of patients included were all less than 2cm, and according to intraoperative findings, we categorized the patients into <5mm and [5mm, 2cm] group (I am afraid that you may have mistaken the 5mm with 5cm).

Conclusion:

To be able to conclude that the procedure is safe and efficient, you need to specify the complication rates and success rates in the result section of your abstract.

**Response:** We have added the complication rate and success rate was in the result section.

Introduction

Needs re-writing.

Lines 183-200 of the discussion should actually be in the introduction.

You need references to support the fact that X-ray under ureteroscopy is dangerous for both surgeon and patient. Please complete.

Lines 73-77: your statements require references.

Line 78: I would remove “precise” since your method with digital measurement of the stricture length was not.

**Response:** Thanks for your review, we have added some contents of Lines 183-200 into the Introduction section, however, in order to remain the succinct and logical flow of text, we did not move the whole part (see Page 5, Line 79-82). And according to your suggestion, we have added reference (see Page 17, Line 323-334). Moreover, we have removed the expression of “precise” and substitute it with “effective” (see Page 6, Line 92).

I made a quick search in Embase and several references were missing, just to name but a few. Please update.

1. Reus et al. World Journal of Urology 2019

2. Fluoroless-ureteroscopy for definitive management of distal ureteral calculi: randomized controlled trial

Mohey A., Alhefnawy M., Mahmoud M., Gomaa R., Soliman T., Ahmed S., Nouredin Y.A.

The Canadian journal of urology 2018 25:1 (9205-9209)

3. Endovisually guided zero radiation ureteral access sheath placement during ureterorenoscopy

Aghamir S.M.K., Salavati A.

Minimally Invasive Therapy and Allied Technologies 2018 27:3 (143-147)

There is already a RCT similar study. What is your study going to show that Mohey et al. have not?

**Response:** Thanks for your friendly reminder, we have read the reference article you mentioned and also made our own research on pubmed. The first article you suggested by Reus provide the information on long outcome of balloon dilation for both benign and post-malignant ureteral stricture, this piece of information was added to our reference, seen in (Page 17, Line 323-334).

As for the issue with the study of Mohey et al. Although both for the exploration of fluoroscopic free technique in endourological surgery, our study was quite indeed different from Mohey's. Our study focused on the balloon dilation procedure for the ureteral stricture, while Mohey's study focus on the ureterolithotripsy technique for distal ureteral stones. Furthermore, Mohey only deal with the distal ureteral without significant stenoses, while our study gives a step by step illustration of how to perform URS technique for ureter which condition is quite abnormal.

Methods

Needs re-writing

Please clarify the following:

- Number of included patients?
- Number of excluded patients.
- Success rate definition
- Failure definition
- Safety and efficacy criteria
- Symptoms: please specify (pain? Raised creatinine levels? Fever/hematuria?)

**Response:** Thanks for your kind reminder. We have re-written the Methods section. We added the information about the number of patients being included and excluded, Success definition, safety and efficacy criteria. Specifically, Success definition was the disappearance of preoperative symptoms (including removal of preoperative catheter), relief of hydronephrosis (compared to preoperative ultrasound or CTU) and stable of renal function (indicated by serum creatine level or GFR of diuretic renal scan). Safety and efficacy criteria were evaluated with perioperative and postoperative

complication rate. The main symptoms of patients with ureteral stricture were flank or abdominal pain, and some of them also presented with hematuria and transient fever.

Lines:

83. "Patients whose strictures were longer than 2 cm or who had evidence

84. 92 malignancy were recommended for other treatment modalities"...

I understand from the above that longer strictures were excluded from the study. I don't understand why in the patient characteristics section you included 20 patients with >5mm strictures. Please clarify.

**Response:** Thanks for your revision, and the language mistakes were corrected accordingly (see Page 6, Line 112-113).

Additionally, for **clarification**, these 20 patients you mentioned whose stricture length was between 5mm and 2cm and patients with stricture length longer than 2cm were recommended for other treatment method.

- I would like to have figure 1. With study flow chart to specify exclusion and inclusion.

**Response:** we have added a Figure 1 with study flow chart to specify exclusion and inclusion.

- Please specify which type of ureteroscope you used. These are the 2 I found produced by R. Wolf.

Needle Ureteroscope

8701.533 4.5/6.5 Fr., 5°, 315 mm Working Length OR

8701.534 4.5/6.5 Fr., 5°, 430 mm Working Length

- Please state the type of guide-wire used: Terumo? Ect..

- Specify the catheter size (F7 in the abstract)

- Specify which Balloon you used: make and length, I suppose 3 cm?

**Response:** The type of ureteroscope we used was Wolf needle ureteroscope, 8701.534 4.5/6.5 Fr., 5°, 430 mm Working Length.

The type of guidewire was from Bard Medical, The BARD® NICORE™ Nitinol guidewire.

The type of catheter was from Bard Medical, Ureteral Catheters, TIGERTAIL®, Flexible Open Tip, Non-ported Eye, Length 70cm, 6Fr.

The Balloon we used was Dilation Catheters, Ureteroscopic Balloon, X-FORCE®, U30, with Inflation Device", the diameter was 6Fr unexpanded and 30 Fr expanded, and the length was 6 cm.

- Why insert 2 JJ stents??? Rationale? Why 3 months? If I were a patient, I would decline 3 months with a stent. Routinely patients would have a stent up to 2 weeks post op. In this case, JJ stent related complications need to be investigated (pain, hematuria, visits to ER, infection ect...). How well did the patient tolerate 2x 7Fr stents? I think that is a big disadvantage to your study protocol, certainly not patient friendly.

- I think you should always have Fluoroscopy at the ready in the ER just in case.
- The adjustments made by the author to visually assess the stricture and correctly place the balloon seem time-consuming and not very accurate... I am not sure they are that easily learned and reproducible. Can you elaborate?

**Response:** We fully understand your worries about the dwelling of 2 DJ stents and some patients do report a hard feeling of the stents inserted in ureter. However, we made the protocol of 2 DJ stents rather than a single stent out of two reasons. First, two stents can further expand the stenotic ureter. Second, the space between the two stents give a better drainage, especially when the ureter was compressed.

Furthermore, the effect of two stents was supported not only by our own experience but also one RCT (Ibrahim, H. M., Mohyelden, K., Abdel-Bary, A., & Al-Kandari, A. M. (2015). Single versus double ureteral stent placement after laser endoureterotomy for the management of benign ureteral strictures: a randomized clinical trial. *Journal of endourology*, 29(10), 1204-1209.).

Additionally, based on our own experience, the learning curve of this procedure was approximately 5 cases, which was demonstrated by author Dr. Genyan Xiong and after the development of this procedure, most of balloon dilation performed by other surgeon in our center was X-ray free. Thus, we concluded that the procedure was easily learned and reproducible.

## Results

Needs re-writing

- Number of included patients
- Number of excluded patients
- Success rate% to revise if 20 patients were excluded, then the total number of included patients would be 56 not 76 if I understand correctly.
- Failure rates%

**Response:** the number of included and exclude patients was presented in Method section (see Figure1 and Page 6, Line 99-104), and the success rate and failure rate was illustrated in the Result section (see Table 2 and Page 10, Line 197 ). these 20 were included in the analysis as explained above.

- Please remove the prognostic table 2 as I don't see its relevance
- Add another Table 2. With Clavien Dindo detailed results in relation to the following criteria you outlined:
  - Please state post op complications related to JJ stents in situ.
  - Main stricture location (upper + middle vs. lower ureter) \*
  - Stricture length ( $\leq 5$ mm vs.  $> 5$ mm or multiple ureter stenosis)
  - Duration (months)
  - Surgery time (mins)
  - Simple dilation vs. dilation combined with ureteroscopic lithotripsy
  - Vascular intact vs. vascular compromise
- Add Table 3. with success rates and failure rates in relation to
  - Stricture length
  - Stricture location



- Stricture cause
- Surgical time
- Simple vs combined approach ect...

**Response:** Thanks for your revision, the prognostic table was created by a univariable analysis (chi-square or standard t test) to compare variable between successful and failed patients, and a multivariable survival analysis (COX regression model) to investigate potential variables related to time-dependent success rate. Therefore, the prognostic table was used to explore the factors that affect the surgical effect. With the table presented, we understood that “stricture length” and “vascular status” have a major impact on success rate, and then we could be better to counsel patients with ureteral stricture. Based on those reasons, we believed that the prognostic table deserved a chance to be reserved. (see Table 3.)

According to your suggestion, we added the detailed Clavien Dindo results and state post-operative complication rate related to JJ stents in Table 1 (It may be a little redundant to add another table 2 to accommodate those data.).

According to your suggestion, we also add a Table 2 showing the success rates and failure rates in relation to the criteria you suggested.

## Discussion

Needs re-writing

State the

- strengths of your study
- Weaknesses: which the authors have mentioned at the end of the discussion
- Since you identified its retrospective nature, I would invite you to compare your findings with those of the RCT. Has your study brought something new in comparison?
- Future perspective?

**Response:** we have rewritten the discussion section. The strengths of our study were that we provide a step-by-step illustration of X-ray free balloon dilation technique. And we also demonstrated the safety and efficacy of this procedure with our cohort. the future perspective was that we could validate this procedure with a larger cohort and observe its success rate in a long term.

Conclusion:

I think you wished to say:

In carefully selected patients with short, benign and uncomplicated strictures, the fluoroscopy-less minimal ureteral balloon dilatation can be a safe and effective (depending on the revised results above based on excluded patients) alternative, with less radiation hazards for both patient and surgeon.

**Response: Thanks for your revision. We** have rewritten the conclusion part according to your suggestion. (see Page 15, Line 298-301).