

Peer Review File

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Reviewer A

General comments

The authors evaluate the efficacy and safety of holmium laser enucleation of prostate (HoLEP) by using en-bloc and bladder neck preservation technique on benign prostatic hyperplasia (BPH) and the influence of this procedure on urinary and sexual functional outcomes. They concluded HoLEP by an en-bloc and bladder neck preservation technique can obtain good functional outcome with small injury and high efficiency, especially for patients who need to preserve normal sexual function and antegrade ejaculation.

It is very interesting that this technique preserved a high rate of retrograde ejaculation while retrograde ejaculation is very common in HoLEP and TUR-P.

The reviewer generally agrees with the conclusion.

However, there are several issues need to improve. The reviewer would like suggests several issues as follows;

1) Specific comments for revision

a) Major

#1 Please describe the bladder neck preservation technique in more detail. What is the difference between the normal HoLEP and the bladder neck preservation technique?

Reply 1: Thank you very much for these precious comments concerning our manuscript. Indeed, as you said, we did not describe the bladder neck preservation technique in adequate detail, which shown unclear information to the reviewers and might caused misunderstanding to the readers. So we supplemented related description in the methods section in revised version so as to describe this bladder neck preservation technique in more detail.

Changes in the text: Page 7-8, Line 118-141.

#2 If the en-bloc and bladder neck preservation technique could be safety, please describe the complications such as post-operative bleeding cases, TUC cases, transient urinary retention u after catheter removal cases, and incontinence rates at 6 and 12 months after HoLEP.

Reply 2: Thank you very much. This comment can make our research more substantial and valuable. We collected data about related complications and revised the Results section in the manuscript: The immediate postoperative outcomes were recorded. No major life-threatening complication was observed in the duration of hospital stay. The

reoperation rate due to prolonged bleeding or clot retention was 1.6% (11/704). No transurethral resection syndrome was observed during and after HoLEP. The mean duration of catheterization after surgery was 2.1 ± 1.5 days, and the mean hospital stay was 5.4 ± 3.6 days. Furthermore, the rate of urinary retention after first catheter removal was 4.8% (34/704). All patients were discharged without catheter. After catheter removal, mild urinary incontinence was observed in 38 patients (5.4%), while moderate incontinence was observed in 3 patients (0.4%). 12 patients (1.6%) still had mild incontinence at 6 months follow-up, and 4 of them (0.6%) had permanent mild incontinence until the last follow-up session (12 months after surgery). Two patients had anterior urethral stricture, and were resolved by urethral dilatation. No bladder neck contracture occurred.

Changes in the text: Page 10-11, Line 196-208.

#3 If you divide the patients who met the sexual function assessment criteria preoperatively into two groups by age, is there any difference in sexual functioning with age?

Reply 3: Thank you very much for this comment and suggestion. There indeed existed deficiencies in sexual function between age in sub-group from patients who met the sexual function assessment criteria. Actually, in subsequent study, we analyzed the influence of some parameters (include age) on sexual function in this cohort. Preliminary statistical analysis shown that age at survey was inversely correlated to IIEF score at follow-up; indeed patients reporting a decrease in IIEF scores were significantly older compared to those reporting a postoperative improvement of IIEF. We also tried to do univariate and multivariate analysis to test the association between predictors (for example, age, BMI, comorbidities, educational status, prostate volume and preoperative IIEF) and sexual function improvement or deterioration at long-term follow-up. At univariate analysis, younger age, lower prostate volume and a lower baseline IIEF score were positively associated with erectile function improvement after surgery. While at multivariate analysis, lower baseline IIEF scores emerged as an independent predictor of erectile function improvement at survey, whereas all other variables failed to predict improvement. But this is just preliminary results. The sample size is small, the follow-up duration is short, and the grouping is not precise enough. Therefore, we are further improving this research to be more convincing, which will be reported in future articles.

b) Minor

#1 The description of the results is duplicative of what is shown in the Table. Would you change the result part to be limited to the more important parts?

Reply 1: Thank you for your meticulous comments. We are sorry for the repetitive descriptions in the manuscript. We have deleted duplicative part and modified description in the revised manuscript to make the article more concise and easier to

read.

Changes in the text: Page 10, Line 191-192, 194-195.

#2 How does estimated blood loss (EBL) measure?

Reply 2: The EBL is a rough estimate based on the hemoglobin (Hb) test. Before surgery, the Hb concentration in peripheral venous of the patient was measured with a hemoglobin analyzer. After surgery, all flush fluid was collected and mixed in a container pre-placed with proper amount of heparin. Then 5 mL of the flush fluid was drawn to test the Hb concentration. The EBL was calculated according to the formula: $EBL (mL) = Hb \text{ concentration of flush fluid (g/L)} \times \text{volume of flush fluid (mL)} \div Hb \text{ concentration of preoperative peripheral venous blood (g/L)}$.

#3 p3, line57 Amongst these methods, holmium laser enucleation of prostate (HoLEP) is superior.

Would you describe what makes HoLEP superior?

Reply 3: Thank you very much. This statement is not accurate, so we described the advantages of HoLEP and modified the manuscript: Several new minimally invasive techniques have been developed to treat BPH/LUTS, including anatomical endoscopic enucleation of the prostate (AEEP), which first performed as holmium laser enucleation of prostate (HoLEP) (3). Improvements in technique and equipments have led to true anatomical enucleation of prostate of any size (4). When compared with TURP, currently the reference gold standard, patients undergoing AEEP benefit from a shorter catheterization time, shorter hospital stay, and fewer complications (5). Precisely because the well-documented superiority over the traditional therapies, including open surgery, TURP, and other plasma and laser modalities, HoLEP is widespread implemented. These benefits make HoLEP the procedure of choice for men seeking surgical relief for BPH related LUTS. Changes in the text: Page 4-5, Line 61-71.

#4 page7, line192-197

This part about the history of HoLEP is unnecessary.

Reply 4: We do agree with this comment. HoLEP has been introduced for more than 20 years, and it is a widely accepted surgical method. Therefore, the description of the history of HoLEP and the characteristics of holmium laser is superfluous. We have deleted this redundant description in the revised manuscript.

Changes in the text: Page 14, Line 263-269.

#5 page9, line226-227 By contrast, the improvement of erectile function was observed in many patients after surgery.

Please show and explain the data to explain.

Reply 5: Thank you for this comment. The expression of this part is indeed ambiguous. We modified the mistake in this section: In the present study, postoperative IIEF and EHGS scores showed slight improvement compared with those at preoperation, although the differences were insignificant ($P > 0.05$). These data showed that in most

patients, HoLEP slightly helped in improving erectile function, at least did not cause significant negative impact. That was to say, HoLEP caused unremarkable damage to erectile function.

Changes in the text: Page 16, Line 314-318.

#6 Table 2 should include a section indicating postoperative urinary incontinence rate.

Reply 6: Thank you for this comment. We have added the data of postoperative urinary incontinence at follow-up in Table 2, and described it in the Results section of the manuscript.

Changes in the text: Page 11, Line 202-206; Table 2.

Reviewer B

Comments:

1) The bladder neck preservation technique is not entirely clear to me and needs to be clarified to the reader. I would suggest contrasting non-bladder sparing technique to the authors' bladder sparing technique in the methods section to help us understand exactly how (or by how much) the bladder neck was preserved. The authors somewhat describe this in Lines 202-204 on Page 8, but a clear description of how this technique is unique would be helpful. A video would certainly be useful if possible.

Reply 1: Thank you very much for these precious comments concerning our manuscript. Indeed, as you said, we did not describe the bladder neck preservation technique in adequate detail, which shown unclear information to the reviewers and might caused misunderstanding to the readers. So we supplemented related description in the Methods section in revised manuscript so as to describe this bladder neck preservation technique in more detail. It is a good suggestion to use the operation video to explain, but due to the format and type of the manuscript, we did not upload it with the manuscript. If necessary, we can provide a complete video of the operation.

Changes in the text: Page 7-8, Line 118-141.

2) The authors should clarify in the Methods section how ejaculate volume and retrograde ejaculation were assessed. It appears from later in the discussion section that these are assessed by patient report, as opposed to an objective measure, which is what is commonly reported but should be explicitly stated. Additionally, the subjective reporting and assessment of something that could be objectively measured should be listed as a limitation of the study, if indeed these are being measured that way.

Reply 2: Thanks. Indeed, as you pointed out in this comment, it was a limitation of the present study. In China, due to relatively conservative traditional culture and viewpoint, the elderly are often reluctant to accept objective and assessments of sexual function and ejaculation function. We tried to use some objective indicators for evaluation, but fewer patients cooperated with the tests. It is difficult to accurately assess the ejaculate volume and retrograde ejaculation in such population. So for patients included in the

sexual function assessment group, we seted up a simple questionnaire, which contained questions as 'compared with preoperation, semen volume changes: increase, decrease, no change and no ejaculation'. The patients were required to select one of the options. If option 'no ejaculation' was selected, urine analysis and sperm detection will be carried out in the urine sample after ejaculation, to determine whether exist retrograde ejaculation. We roughly evaluate the change in ejaculation function in this way. It is a limitation of the present study which should be listed in the manuscript. So we clarified the assessment method for ejaculation detection in Methods section, and this limitation was supplemented in the Discussion section in the revised manuscript.

Changes in the text: Page 9-10, Line 174-180; Page 17, Line 346.

3) Page 4 Line 85 of Methods discusses Inclusion criteria for the sexual function assessment. I would suggest stating "patient with a partner" as opposed to "patient with a wife", unless marriage to a female was specifically documented and assessed. If patients were not married, or had non-female partners were they excluded?

Reply 3: Thank you. We agree with this comment. The inclusion criteria for the sexual function assessment should be expressed as "patient with a partner", which was more clearly. We have modified this statement the manuscript.

Changes in the text: Page 6, Line 101.

4) Page 7 Line 178 states "In the present study" when referring to a study of TURP. I imagine the authors meant to refer to reference 13, as opposed to the present HoLEP study. Please clarify.

Reply 4: We are very sorry for this mistake. This sentence do refer to the study of TURP which was involved in reference 13. We have modified this mistake the manuscript.

Changes in the text: Page 13, Line 246-247.

5) Lines 225-227 on page 9 appear to have contradictory information about the data in this manuscript, unless it is referring to another manuscript referenced before. It appears that in this present study there was no change in erectile function based on the results section. Please clarify.

Reply 5: Thank you for your meticulous comments. The expression of this part is indeed ambiguous. We modified the mistake in this section: In the present study, postoperative IIEF and EHGS scores showed slight improvement compared with those at preoperation, although the differences were insignificant ($P > 0.05$). These data showed that in most patients, HoLEP slightly helped in improving erectile function, at least did not cause significant negative impact. That was to say, HoLEP caused unremarkable damage to erectile function.

Changes in the text: Page 16, Line 314-318.

6) Line 230 on page 9 suggests an electrical current in the tissue created during HoLEP; the energy from the holmium laser is thermal, but not from an electrical current like monopolar or bipolar electrocautery. Please correct.

Reply 6: We are very sorry for the inconvenience caused by this mistake. We have corrected it in the revised manuscript. Thank you very much.

Changes in the text: Page 16, Line 323.

7) Lines 233-235 on page 9 talk about a smaller coagulation layer leading to less urinary tract irritation and higher quality of life - please provide a reference (or references) to substantiate these statements).

Reply 7: Thank you for this comment. We have added some description and references in the manuscript to substantiate these statements: The depth of coagulation plays an integral role in at least hemostasis and possibly other postoperative outcomes, for instance, a smaller coagulation layer leading to less urinary tract irritation and higher quality of life.

1. Maddox M, Pareek G, Al Ekish S, et al. Histopathologic changes after bipolar resection of the prostate: depth of penetration of bipolar thermal injury. *J Endourol.* 2012;26(10):1367–71.
2. Orihuela E, Pow-Sang M, Motamedi M, et al. Mechanism of healing of the human prostatic urethra following thermal injury. *Urology*, 1996;48(4): 600-8.

Changes in the text: Page 16, Line328-331; References 27-28.

Reviewer C

This is an emerging technique for AEEP and important casistics like this one are worth of publication.

The study design is retrospective and observational, however Authors correctly refer to STROBE Guidelines.

Herein the parts to be revised:

- Introduction line 58: please amend this sentence. The reference [3] is old and nowadays we speak of AEEP instead of a particular enucleation technique as no one appeared really superior. Please refere to those two papers

1. Pirola GM, Saredi G, Codas Duarte R, et al. Holmium laser versus thulium laser enucleation of the prostate: a matched-pair analysis from two centers. *Ther Adv Urol.* 2018;10(8):223-233. Published 2018 Jun 7.
2. Xiao KW, Zhou L, He Q, et al. Enucleation of the prostate for benign prostatic hyperplasia thulium laser versus holmium laser: a systematic review and meta-analysis. *Lasers Med Sci.* 2019;34(4):815-826.

Reply: Thank you so much for meticulous review and kind comments. These comments are very helpful for improving our paper. We have read these novel literatures carefully and we found they are very beneficial. We have amend the sentence in the revised manuscript according to the reviewers' comments and related papers. These literatures and opinions have also been cited in our revised manuscript to replace old ones.

Changes in the text: Page 4-5, Line 61-71.

- You should report eventual urinary incontinence, even if transitory (in results and

discussion section) and how it was assessed (clinical exam, pad test etc.)

Reply: Thank you very much. This is a good suggestion. We have supplement data of postoperative urinary incontinence immediately after catheter removal and during follow-up in Table 2, and also described it in the Methods and Results section of the manuscript.

Changes in the text: Page 11, Line 202-206; Table 2.

- The discussion is over-centered on sexual function, therefore changing the objective of the paper. You should focus more on urinary symptoms and relative questionnaires. Otherwise, the title of the article must be changed to orient readers on an evaluation of sexual function after en-bloc HoLEP.

Reply: Thank you very much for this comment. Indeed, we used too much sentences to discuss the impact of this modified HoLEP on sexual function. The objective of this study was to evaluate the efficacy and safety of this modified HoLEP and assess the influence on urinary and sexual functional outcomes. We focused on analyzing the influence of the modified technology over sexual function, which indeed deviated from the original purpose. Therefore, we modified the manuscript to describe the surgical technique in more detail. At the same time, we collected more detailed data about urinary symptoms and performed more detailed analysis and discussion in this aspect.

Changes in the text: Page 7-8, Line 118-141; Page 11, Line 202-206; Page 16, Line 328-331.

Reviewer D

1. HoLEP is the AUA and EAU procedure of choice for size independent prostates in surgical treatment for symptomatic BPH. It is also the treatment of choice with patients who are on anticoagulation. ThuLEP is the second most studies procedures in this category and is included with HoLEP. Much of your discussion compares your technique to TURP, you will need to compare your data to other HoLEP techniques in this study.

Reply 1: Thank you very much for these kind comments. They are very helpful for improving our paper. We added some comparisons between HoLEP and other techniques especially ThuLEP following the reviewer's suggestion in the Discussion section: Transurethral enucleation techniques have been described with almost all energy sources. HoLEP representing the original and by far the most widely evaluated method. In addition to HoLEP, numerous other energy therapies exist for treatment of BPH, including plasmakinetic enucleation of the prostate and Thulium laser enucleation of the prostate (ThuLEP). Few studies are available that directly compare HoLEP to these alternative modalities. Some studies showed that ThuLEP presents excellent vaporization and hemostatic capabilities with outcomes and complication rates similar to that of HoLEP (14). However, as a pulsed laser, HoLEP offers a "scar-

free” feature on the prostatic surface and makes the plane of enucleation easy to develop and follow, providing superior visibility with precise incision and dissection, as well as greater versatility to the urologists: patients undergoing endoscopic surgery for BPH frequently require cystolitholapaxy, tumor resection or stricture ablation, all of which can be accomplished using the holmium laser (15).

Changes in the text: Page 14, Line 269-280.

2. Was all the procedures done by one surgeon only? Single surgeon, single site, retrospective analysis of en-bloc enucleation with bladder neck sparing technique?

Reply 2: Thanks. All HoLEP procedures in our center were performed by the same experienced surgeon (MXX, the head of Urinary Continence Subspecialty in our department), who had >2000 surgical cases till now. In addition, patient management, follow-up, data collection and analysis are completed by other members of the team.

3. Does this data help you counsel your patients differently?

Reply: To some extent yes. According to our research and other published paper, we will focus on different points when communicating with patients and preparing for surgery. Generally, blood is not prepared before HoLEP surgery, and anticoagulant medicine is not stopped. The possibility of complications such as bleeding, transurethral resection syndrome and recurrence don't need special emphasis. In addition, the patients can be told that the expectation of outcome may be relative good, and the hospital stay is relatively short. However, It is certain that the routine risks of surgery still need to be informed to the patient, despite these data can give us more evidence and confidence in communicating with patients.

4. The biggest challenge for HoLEP is the learning curve. Is your en-bloc technique harder to learn than the two or 3 lobe technique? Can surgeons using other HoLEP technique transition into this technique easily? Number of cases to get competent?

Reply: Exactly as you said, the biggest challenge for HoLEP is the learning curve. Mastering the technique requires a long learning curve and substantial experience. This might be hampering the wider acceptance of HoLEP. The key point of a successful HoLEP lies in the mastery of the characters of instruments and accurate understanding of the anatomical structure of prostate. On this basis, there is no essential difference in the difficulty of HoLEP using one or two or 3 lobe technique. So the en-bloc technique does not increase the difficulty of operation or extend the learning curve. To our knowledge this is no report focus on the transition between different HoLEP techniques. But in the present study, all en-bloc HoLEP procedures were performed by an urologist skilled in the use of the conventional three-lobe technique. This suggests that switching to en-bloc HoLEP is simple. For a experienced surgeon skilled in conventional HoLEP, no more than 10 cases are required to switch to en-bloc HoLEP.

5. Bladder neck sparing techniques be performed with the 2 or 3 lobe technique. What are your thoughts on this? Any experience with this? Outcomes?

Reply: Thanks. Actually, there is no essential difference between en-block or 2 or 3 lobe technique in the process of enucleation, except dissecting order. This study is mainly about the technique of bladder neck preservation in combination with en-block enucleation of prostate. We think the bladder neck preservation technique can also be used in the 2 or 3 lobe prostate resection. In fact, before switched to en-bloc HoLEP, the surgeon in this study performed some conventional three-lobe HoLEPs used bladder neck preservation technique, despite the number was small. This initial experience might prove that bladder neck preservation technique can be used in different type of HoLEP. Since the number of cases is relatively small, there was no systematic analysis of outcomes in this population. But because these techniques are essentially the same, we think they are similar in functional outcomes. Of course, further research is needed to confirm this view.

6. Does this HoLEP technique reduce the time of transient Stress Incontinence?

Reply: Thank you very much. Compared to TURP, HoLEP removes more gland, especially at the apex of prostate. This leads to higher rate of transient incontinence after HoLEP than TURP, which has been confirmed by many comparative studies. The external urethral sphincter is the main structure for urinary control. Beyond that, the internal sphincter (including the bladder neck) can also contribute to some extent. The HoLEP by using bladder neck preservation technique could retain the internal sphincter, which may conduce to decrease the rate and degree of incontinence. We observed a rate of 5.4% incontinence after catheter removal, which was relatively lower compared to that reported in other studies. Moreover most of them recovered to normal continence within a short follow-up duration. Therefore, we think this HoLEP technique may reduce the time of transient incontinence. There is no doubt that further evidence is needed.

7. Patients seeking to maintain antegrade ejaculation usually choose other MIT options such as UroLift or Steam therapy or even Aquablation. Aside from urinary outcomes not being equivalent to HoLEP, are you offering this technique as an alternative to these MIT options to treat BPH and maintain antegrade ejaculation.

Reply: Thank you very much. Surgical manners for BPH induced LUTS that have been carried out in our center include TURP, HoLEP, plasmakinetic enucleation, greenlight PVP and prostate stent implantation. UroLift has not yet been launched in our center. We will explain the advantages and disadvantages of these treatment methods to patients before surgery. Due to medical insurance policy issues, greenlight PVP and prostate stent require more of their own medical costs, so patients often prefer HoLEP. In addition, in China, when patients seeking for surgical treatment, the main appeal is good urinary function, sexual function second. Therefore, surgeons and patients often choose surgical procedures with better urinary outcomes.

8. In my experience, the majority of patients who choose HoLEP are not generally

concerned about ejaculatory function but are more interested in a procedure optimal quality of life outcomes, durable, and has minimal risk of blood transfusion and urinary incontinence. HoLEP has already shown to fit this category. Should the en-bloc bladder neck sparing procedure be the option of choice for all HoLEP techniques?

Reply: Thank you very much. Indeed as you said, the majority of BPH patients who seeking for surgical treatment are more interested in urinary outcomes and safety. Ejaculatory function is not a main appeal in such population. But among the patients we have treated, someone had severe LUTS before surgery, which led to sexual dysfunction or complete no sexual desire. But after operation, following the relief of LUTS, the patient resumes normal sexual activities. This technique may contribute in such patients. In addition, the bladder neck preservation technique during HoLEP is not only conducive to the preservation of ejaculation function, but also to the urinary continence to some extent. For surgeons skilled in this technique, using the bladder neck preservation technique when performing en-bloc HoLEP does not increase the difficulty and extend operation time. So now we almost all adopt this method during HoLEP. Subsequently, We plan to further assess the value of this technique through a controlled study.