**Author’s response to reviews**

**Title:** Transurethral resection of ejaculatory duct combined with seminal vesiculoscopy for management of persistent or recurrent hemospermia in men with ejaculatory duct obstruction

**Authors:**

ZhengJu Ren (renzj5383@sina.com)

Bo Yang (603323687@qq.com)

DongLiang Lu (2393674230@qq.com)

ShengZhuo Liu (359115195@qq.com)

LuChen Yang (245923563@qq.com)

LinCun Wang (383139035@qq.com)

ZhuFeng Peng (969640269@qq.com)

LiangRen Liu (952651341@qq.com)

Qiang Dong (dong_qiang@mcwcums.com)

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**Author’s response to reviews:**

Dear Editors,

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Transurethral resection of ejaculatory duct combined with seminal vesiculoscopy for management of persistent or recurrent hemospermia in men with ejaculatory duct obstruction (BUCO-D-19-00208R1)”. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction in the manuscript, the revised part was marked as red. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. The main corrections in the paper are as flowing:

Responds to editor/reviewers Comments:

Editor Comments:
The quality of the English used throughout your manuscript does not currently meet our requirements, as there are several incorrect sentence constructions and grammatical errors throughout obscuring the message the authors want to convey. We recommend that you ask a native English speaking colleague to help you copy-edit the paper. If this is not possible, you may need to use a professional language editing service. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

Response: Thank you very much for your good suggestion, we have checked the manuscript carefully. In addition, we used “Editage” for help with English usage in revising our manuscript.

Reviewer reports:

Minato Yokoyama, M.D., Ph.D. (Reviewer 1): This article focused on the effectiveness and safety of TURED against hematospermia with EDO. Because there are little evidences of surgery against hematospermia, this study might shed light on the treatment of hematospermia. However, there are some issues to be addressed.

Major

1. As described by the authors, hematospermia is a self-limited and non-life threatening symptom in most cases. Therefore, it rarely requires surgical treatment. Readers would be interested in the proportion of patients receiving surgery in the number of the whole patients with hematospermia, or, in other words, the number of patients with hematospermia who did not receive surgery.

Response:

Thank you very much for your good suggestion. Hematospermia is a self-limited and non-life threatening symptom in most cases. Most of the patients get better by oral antibiotics, and only a small number of people with persisting or recurrent hematospermia came to our hospital seeking treatment. And most of the patients who came to our hospital require surgical treatment. Therefore, the proportion of patients receiving surgery in the number of the whole patients with hematospermia is unclear. This is an interesting idea, and we will try to investigate proportion of patients receiving surgery in the number of the whole patients with hematospermia. In addition, the study reported the proportion of patients receiving surgery is few. And in one study performed by Seiji Furuya, they reported 189 Japanese patients with hematospermia, 9 (4.76%) patients with persisting hematospermia for more than 1 year have been treated with transurethral endoscopic surgery.

2. As described, above, hematospermia is non-life threatening symptom in most cases. However, in middle-aged or older men, prostate cancer can be a cause of hematospermia. PSA value which should have been tested in those patients is to be described in the first paragraph of Results or Table 1.
Response: Thank you very much for your good suggestion. There were 28 older men who have tested PSA value. The MRI of these patients revealed no sign of prostate tumor. We have added the PSA value which have been tested in middle-aged or older patients in the first paragraph of Results. The revised part was marked as red.

3.In 7 of the 103 patients, hematospermia persisted even after the surgery. How were the additional treatments for the persistent hematospermia?

Response: Thank you very much for your good suggestion. Symptoms of hemospermia disappeared in 96 of the 103 (93.20%) patients after subsequent semen analysis one to three times during the follow-up period. The other 7 patients, hematospermia persisted after the surgery, however, the number of red blood cells in semen is less than before. The 7 patients was all treated with TURED combined with seminal vesiculoscopy, blood clots or small calculi in the prostate utricle or seminal vesicle were removed. The persisted hematospermia may due to the inflammatory and infectious. All the 7 patients were treated by oral antibiotics, and symptoms of hemospermia disappeared after 5-7days. We added the information in the section of result, and marked as red.

4. In the current study, patients received meticulous imaging studies such as TRUS and MRI. How was the concordance between the images and intraoperative endoscopic findings? Because this concordance might be the brand new information, it would be of great value to be reported.

Response: Thank you very much for your good suggestion. This is a very interesting idea. Before surgery, the TRUS and MRI can not detecte the blood clot, they only detected hematocele in the seminal vesicle. The blood clots were detected by seminal vesiculoscopy. Hematocele in the seminal vesicle were detected in all patients by TRUS and MRI. The calculi were detected in 32 patients by TRUS and MRI. We added this information in the result section of manuscript, and the revised part was marked as red.

Minor

1. The first sentence of the second paragraph in the Results section, i.e. "Semen analysis was performed preoperatively and 3 months after surgery on 90 out of the 103 patients. Semen analysis was performed preoperatively and 3 months after surgery on 90 out of the 103 patients", should be moved to the Methods paragraph.

Response: Thank you very much for your good suggestion. We have made correction according to your comments. “Semen analysis was performed preoperatively and 3 months after surgery on 90 out of the 103 patients.” was moved to the Methods paragraph, and marked as red.
Chien-lun Chen (Reviewer 2): This study reports a successful treatment outcome of a cohort of 103 patients with persistent or recurrent hematospermia from ejaculatory duct obstruction (EDO) who underwent transurethral resection of ejaculatory duct (TURED) and seminal vesiculoscopy. The post-op follow-ups reveal improved parameters without severe complications. The comments are as followings.

Major concerns:

1. In the background introduction, the authors indicate that EDO can be subdivided into congenital or acquired EDO. What is the percentage of this classification in this study cohort? How could they be classified clinically? Will there be any difference in treatment consideration? No such information could be found in the subsequent discussion.

Response: Thank you very much for your good suggestion. In theory, EDO can be subdivided into congenital or acquired EDO. Congenital causes of EDO include congenital atresia or stenosis of the ejaculatory ducts and Müllerian duct (utricular) or Wolffian duct (diverticular) cysts. Acquired EDO is often secondary to seminal vesicle calculi, postinflammatory scar formation at the prostate level, a history of indwelling urethral catheter use, urethral trauma, and previous transurethral surgery, such as bladder-neck incision or transurethral resection of the prostate (TURP). However, because the anatomical structure of distal genital tract is delicate and complicated, at present, congenital and acquired EDO cannot be clearly diagnosed in clinical practice. The relationship between obstruction, inflammation, and calculi was vicious. For example, the EDO patients with seminal vasicle calculi, there were no methods to identify the cause of EDO. The EDO may caused by inflammation and calculi, and the EDO also may be congenital EDO. Thus, we reported the percentage of cysts, calculi and blood clot in the EDO patients with persistent or recurrent hemospermia. Thanks again for your good suggestion.

Minor comments:

2. The treatment outcome has been overemphasized as making redundancy. It has been highlighted in the abstract and clearly described in the results. In the discussion, it was again reiterated 3 times, Page 8 line 45, As we found…; Page 11 line 3, in our study, all cases…; and Page 12 line 3, this is the first study to show….

Response: Thank you very much for your good suggestion. we have checked the manuscript carefully, and made correction according to your comments. The sentence “To our knowledge, the present study is the first report of TURED combined with seminal vesiculoscopy for the diagnosis and treatment in hemospermia patients with EDO. And we found symptoms of hemospermia disappeared in 93.20% (96/103) of our patients during the follow-up period. The ejaculate volume and percent motility of sperm were significantly increased. Except for one case with acute urinary retention and one case complaining about watery ejaculate, who both were reported during the follow-up period, no complications, such as epididymitis, retrograde ejaculation, urinary incontinence or rectal injury were observed.” was deleted.
3. Some mistyping needs to be corrected. Page 9 Line 54, "relieved". Page 21 Table 1, Follow-up duration, "months".

Response: Thank you very much for your good suggestion. We have checked the manuscript carefully, made correction according to your comments, and the revised part was marked as red.

4. Hematospermia, hemospermia, and haematospermia were used randomly in the manuscript which should be double-checked.

Response: Thank you very much for your good suggestion. We have checked the manuscript carefully, The hematospermia and haematospermia were changed as “hemospermia”, and the revised part was marked as red.

5. Page 7, Result, line 50, whereas semen PH and sperm concentration did not improve significantly. The "improve" should be "change" as the authors did not define the meaning of improvement.

Response: Thank you very much for your good suggestion. We have checked the manuscript carefully, made correction according to your comments, the "improve" was changed to "change", and the revised part was marked as red.

Bimalesh Purkait (Reviewer 3): According to author, this is a retrospective study. But author presented data and descriptions like a prospective study. Author should present like “all relevant data including history, investigations etc are collected and analyzed” rather than saying "patients were evaluated with ...." in methods section. Author should also mention how many pt underwent MRI, TRUS etc as it a retrospective collection of data?

Response: Thank you very much for your good suggestion. we have checked the manuscript carefully, made correction according to your comments, “Patients were evaluated preoperatively for detailed history, complete physical examination, hormone profiles (FSH, LH, PRL, E2, and testosterone levels), semen analysis, TRUS and MRI.” was changed as “All relevant data including detailed history, complete physical examination, hormone profiles (FSH, LH, PRL, E2, and testosterone levels), semen analysis, TRUS and MRI were collected and analyzed”. And all the relevant data of each patient were collected by us.

Did all patients had all investigations performed?

Response: Thank you very much for your good suggestion. The detailed history, complete physical examination, hormone profiles (FSH, LH, PRL, E2, and testosterone levels), semen analysis, TRUS and MRI were performed on each patient before surgery. The patients who underwent TURED combined with seminal vesiculoscopy had all investigations performed.
In introduction section, around line 50...

The relief of EDO itself may lead to improvements of symptoms and in some cases drainage of blood may be. Though relieving obstructions, does not remove stone without vesiculoscopy, dose seminal vesiculoscopy required in all patients even after removal of EDO??

Response: Thank you very much for your good suggestion. The relief of EDO itself may lead to improvements of symptoms in the milder cases. For EDO patients with persistent or recurrent hemospermia, the blood clots and calculi usually existed in the seminal vesicle. It is necessary to perform the seminal vesiculoscopy. Under the seminal vesiculoscope, we can do seminal vesicle irrigation, remove blood clots and calculi. More importantly, seminal vesiculoscopy could be considered to exclude malignancy, although the incidence is low.

Methods section line...22....any reason or basis for 4 weeks antibiotic treatment?

Response: Thank you very much for your good suggestion. For the anatomical position is special, effective concentration can't be reached by oral antibiotic in the short term, and the seminal vesicle inflammation usually associated with the bacterial prostatitis. If bacterial prostatitis existed, antibiotic treatment for 4 weeks is needed. If the patients experienced persistent or recurrent hemospermia did not improve by oral antibiotics for 4 weeks, the surgery treatment should be considered.

How many patients had evidence of calculus or blood clot detected on imaging preoperatively?

Response: Thank you very much for your good suggestion. Before surgery, the TRUS and MRI can not detect the blood clot, they only detected hematocel in the seminal vesicle. The blood clots were detected by seminal vesiculoscopy. Hematocel in the seminal vesicle were detected in all patients by TRUS and MRI. The calculi were detected in 32 patients by TRUS and MRI.

For calculus, 32 patients had evidence of calculus detected on imaging preoperatively.

Author should also mention how many patients had unilaterally or bilateral EDO with or without calculus or clots.

Response: Thank you very much for your good suggestion. There are 92 patients had unilaterally EDO and 11 patients had bilateral EDO. In these patients, 19 patients had calculus in left seminal vesicle, 13 patients had calculus in right seminal vesicle. The blood clots were found in the unilateral seminal vesicles. We added this information in the result section of manuscript, and the revised part was marked as red.

Overall writing is good, but author should improve the English language and grammatical aspect carefully.
Response: Thank you very much for your good suggestion, we have checked the manuscript carefully. In addition, we used “Editage” for help with English usage in revising our manuscript.

We deeply appreciate your consideration of our manuscript, and we look forward to receiving comments from the reviewers. In addition, we are sorry for the inconvenience brought to editor. The corresponding author’s email address "dong_qiang@mcwcums.com" is temporarily unavailable, if you have any queries, please don’t hesitate to contact me with "dqiang666@163.com".

Thank you and best regards.

Yours sincerely,

Corresponding author:

Name: Qiang Dong

E-mail: dqiang666@163.com
Fax: +86 028-85422547
address : West China School of Medicine/West China Hospital, Sichuan University, 37, Guo Xue Road, Chengdu 610041, Sichuan Province, China.