Author’s response to reviews

Title: Scrotal hemorrhage after testicular sperm aspiration may be associated with phosphodiesterase-5 inhibitor administration: a retrospective study

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Author’s response to reviews:

The authors’ response letter has been included as a supplementary file"

Response to Reviewers

Dear Editor,

Thank you very much for your comments and suggestions.

As suggested, we have made further revisions according to those review comments point by point. The paper has been revised significantly throughout the text.

I am looking forward to hearing from you soon.

With kindest regards,

Yours Sincerely

Yongtong Zhu

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REPLIES TO THE COMMENTS

Editorial Comments:

1. Can you please include a completed STROBE checklist as an additional file when submitting your revised manuscript

Reply: We have included a completed STROBE checklist as an additional file when submitting our revised manuscript.

2. We also ask that you add the study design and setting to the title of your manuscript.

Reply: We have added “a retrospective study” in the title of our manuscript. (Line 2)

3. We recommend that you copy edit your manuscript. You may wish to ask a native-English speaking colleague to help you do this.

Reply: Our manuscript has been edited and rewritten by a native English speaking colleague.

Reviewer 1:

1. There are syntax and grammar errors throughout the text. Editorial help is strongly suggested

Reply: Our manuscript has been edited and rewritten by a native English speaking colleague.

2. If patients are unable to produce sperm by way of masturbation, the authors report they are given a PDE5i, then TESA was performed if they were still unable. Were any of the procedures rescheduled due to patients being unable to produce sperm? Were the patients given pornographic material? Did any receive an intracavernosal injection?

Reply: Following the suggestion, it has been added

“given pornographic material,” (Line 212)

“Patients on intracavernosal injection treatment had high withdrawal rates. The most common reason for withdrawal was poor response to the therapy, followed by the inconvenience of use[6]. So they did not receive such therapy in our centre.” (Line 209-211)

3. The authors use the terms TESA and TESE interchangeably. These are 2 different procedures. One is a percutaneous aspiration and the other requires an incision. Which one was performed?

Reply: TESA was performed. “TESE” in (Line 100) has been corrected.
4. What were the causes of azoospermia in the control group? Why was sperm retrieval performed in this group with TESA as opposed to TESE or micro-TESE which would be more appropriate in these patients with smaller pockets of active spermatogenesis for sperm retrieval.

Reply: Following the suggestion, it has been added

“previously identified azoospermia, which contained obstruction azoospermia and non-obstruction azoospermia,” (Line 124-125)

“Patients in the drug group were all sperm retrieval performed by TESA successfully. In order to compare consistently, patients with prior epididymal sperm aspiration (PESA), testicular sperm extraction (TESE) or micro-TESE were excluded from this study.” (Line 126-129)

“Figure 1 The testicular sperm aspiration procedure” (Line 334)

5. It seems a little odd that the patients in the control group with known azoospermia had larger testicular volume as compared to the drug group which had sperm in their ejaculated sperm. Were the majority of patients in the control group obstructive patients? You would expect a certain amount of azoospermic patients to have smaller testicular volume, especially in the setting of testicular hypofunction.

Reply: Following the suggestion, it has been added

“The majority of patients in the control group were obstructive patients. While azoospermic patients who had smaller testicular volume (<8 mL), especially in the setting of testicular hypofunction, TESE or micro-TESE would be more appropriate in these patients.” (Line 190-193)

6. The testicular volume of patients in the drug group is particularly small for patients with sperm in the ejaculate. How were measurements made?

Reply: Following the suggestion, it has been added

“The testis size, character and the presence of testicular mass, or asymmetry was assessed via manual palpation and orchidometer.” (Line 170-171)

7. Good discussion on why PDE5i may cause hemorrhage.

Reply: Thank you.

8. While the coagulation factors were similar, were any patients on anti-coagulants, anti-platelets, taking NSAIDs?
Reply: Following the suggestion, it has been added in Discussion

“Patients were on anti-coagulants, anti-platelets, taking NSAIDs and ice scrotum may be beneficial after TESA.” (Line 252-253)

9. Were the patients asked about the level of activity following the procedures?

Reply: Following the suggestion, it has been added

“They were asked about light level of activity following the procedures, and abstained from strenuous exercise for 1 month.” (Line 145-146)

10. There are many variables that are not addressed by the authors that could've contributed to the rates of hemorrhage, and these should be discussed as limitations.

Reply: Following the suggestion, it has been added

“Most patients do not feel uncomfortable after TESA, and routine sonographic examination is not performed, and thus small areas of hemorrhage maybe overlooked.” (Line 201-204)

“The limitations of this study include its retrospective design. A prospective study should be done to validate our results.” (Line 239-240)

11. The authors recommend in the last paragraph that men who have difficulty producing a semen sample of the day of ART should be counseled about using ejaculated sperm for cryopreservation on an earlier date. While this is reasonable, all patients in the drug group had been able to produce ejaculated sperm twice prior to the procedure date. How could they then predict this ahead?

Reply: Following the suggestion, it has been added

“Although it is difficult to predict ahead who have difficulty producing a semen sample of the day of assisted reproductive technique, as all patients in the drug group had been able to produce ejaculated sperm twice prior to the procedure date. We should gain information by detailed inquiry.” (Line 253-256)

7. Conclusions should be toned down due to the limitations of this study.

Reply: Following the suggestion, Conclusion has been edited as

“In summary, the results of this study suggest that a PDE5i administration increases the risk of scrotal hemorrhage in men undergoing TESA, although the study design does not allow drawing
a conclusion of cause and effect. Given the potential risk of scrotal hemorrhage after the ingestion of PDE5i, it may be wise not to administer it to men in whom a TESA may be performed.” (Line 261-265)

Reviewer 2:

1. My critical issue with the study is that ultrasound was only performed after the physician suspected a hematoma on physical exam post procedure. This introduces significant bias and lack of certainty if there actually were many other patients that did not develop hematomas that were not detected by the clinician performing a 3d post procedure exam.

Reply: Following the suggestion, it has been added

“As ultrasound was only performed after the physician suspected a hematoma on physical exam post procedure. This may introduce significant bias and lack of certainty if there actually were many other patients that did not develop hematomas that were not detected by the clinician performing a 3 days post procedure exam. So it would be better to perform ultrasound exam at 3 days after TESA.” (Line 243-247)