Peer Review File

Article information: http://dx.doi.org/10.21037/tp-20-473

Reviewer #1

Comment 1: The English language should be professionally checked (first grammar mistake already in first sentence of the abstract [has vs. have], orchiopexy vs. orchidopexy), etc.

Reply 1: We are very sorry for the grammar mistakes! We have got a native English-speaking expert to check our manuscript from Editage. The grammar mistakes have been corrected (see Page 3, line 61). The word "orchidopexy" has been changed into "orchiopexy" (see Page 3, line 73; page 11, line 240; page 14, line 315).

Changes in the text: Page 3, line 61, line 73; page 11, line 240; page 14, line 315.

Comment 2: The methodology/statistical approach should be checked by a dedicated biostatistician.

Reply 2: Thank for your advice! The statistical approach has been checked by Shengli An, who is a professional biostatistician working in the Statistical Department of Southern medical university. He said there was a mistake in the Univariate analysis, "$p > 0.1$" should be changed into "$p < 0.1$".

Changes in the text: Page 8, line 180.

Comment 3: As several patient populations were excluded from the study (e.g. chromosomal abnormalities, etc.) the conclusion statement in the abstract should be changed accordingly, to ensure the ready is aware of this sub-section of patients with UDT.

Reply 3: We have revised the text according to your advice. We added the sentence "In patients with undescended testes, excluding those with chromosomal abnormalities and testicular nubbin" in the Abstract and the Conclusion section.

Changes in the text: Page 4, line 83-84; page 16, line 361-362.

Comment 4: Introduction. Incidence has previously been published for term and preterm boys and should be provided in more detail.

Reply 4: We are very sorry for the negligence of incidence in detail. We have added some data about incidence of full-term and preterm boys in the Introduction part.

Changes in the text: Page 4, line 96-98.

Comment 5: Line 85 is an over-simplification. Many children need no treatment or are served well with hormonal treatment. Also, the timing of orchidopexy and the different guidelines on this issue deserves to be mentioned.
Reply 5: We are sorry for over-simplification in the treatment of undescended testis. We have added some data on the hormonal treatment, surgical treatment, and the timing of surgery, according to the EAU guidelines and AUA guidelines.
Changes in the text: Page 4, line 98-100; page 5, line 101-102.

Comment 6: Methods. Does the Institutional Review Board approval include an ethics statement?
Reply 6: In our hospital, the Institutional Review Board includes ethics committee. Therefore, Institutional Review Board approval includes an ethics statement.

Comment 7: A table should be presented that directly compares patients with and without testicular atrophy and their accompanying clinical characteristics.
Reply 7: We has made a new table comparing patients with and without testicular atrophy as advised. The clinical characteristics are listed in the table (Table 2).
Changes in the text: Table 2.

Comment 8: Line 164: why were variables with $p > 0.1$ were included in subsequent multiple variable analysis?
Reply 8: We are very sorry for the writing mistakes. The sentence should be "variables with $p < 0.1$ were included in subsequent multiple variable analysis". It follows the statistical principle of multiple variable logistic analysis. We have change "$p > 0.1$" into "$p < 0.1$".
Changes in the text: Page 8, line 180.

Comment 9: How was "deferens anomaly" defined?
Reply 9: The "deferens anomaly" includes looping vas deferens, absence of vas deferens, and disjunction of testis and epididymis. We added the definition in the Methods section. For the purpose of precision, we have change "deferens anomaly" into "deferens and epididymis anomaly".
Changes in the text: Page 7, line 158-160.

Comment 10: Results. What was the timing of stages 1 and 2 for Fowler-Stephens procedure? This is essential information that should be provided to evaluate the potential delay and its contribution to subsequent atrophy development/persistence.

Reply 10: We are sorry for the negligence of timing in Fowler-Stephens procedure. The median age of stage II FSO was 3.52 years, and the time intervals between stage I and stage II were 6–8 months. We have added the data in the results section.
Changes in the text: page9, line 196-198.

Comment 11: What does the variable operating time in table 3 refer to exactly?
Reply 11: Operating time is defined as the time from skin incision to skin closure. In Table 3 (has been renamed Table 4), the OR of operating time is 0.992 (<1), which means the operating time increase, the atrophy rate may decrease. However, there is no significant difference (P =0.082).

Comment 12: For the comparison of surgical procedures, it is essential to eliminate pre-procedure atrophy (rate) as a confounder. Naturally, FSO is performed for intra-abdominal testes, which in itself has a high rate of TA (irrespective of surgical treatment)
Reply 12: It is true that intra-abdominal testis is a confounder for the comparison of surgical procedures. However, multiple logistic regression analysis can eliminate the confounder, and Staged FSO is an independent risk factor. For example, as showed in Table 1, the atrophy rate of FSO was 5 times higher than that of open orchiopexy (56.9% vs 10.8%), but in multiple analysis, the OR of two-stage was only 2.6 (Table 4), because the statistical analysis eliminates the confounding factor of testicular location.

Comment 13: Discussion: Essential literature on this topic has not been discussed or adequately mentioned, e.g. DOI: 10.1097/MD.0000000000005731 Jedrzejewski et. al on the role of ultrasound in the management of undescended testes before and after orchidopexy. This study specifically showed that atrophy in younger children but also even at older age (>8 years) is often followed by catch up growth if follow up is long enough. Please discuss.
Reply13: We are sorry for the inadequate discussion of this topic. Jedrzejewski et al. reported the testicular volume ratio increased after orchiopexy, which indicated that most undescended testis would have catch-up growth after long follow-up. We have discussed this topic and cited the article in the discussion section. It is the limitation of our study. Therefore, long-term follow up is needed, to get more precise result.
Changes in the text: Page 13, line 284-288.

Comment 14: Further, the difference between primary and secondary UDT should be mentioned and appropriate literature should be cited, e.g. “Multicenter Analysis of Acquired Undescended Testis and Its Impact on the Timing of Orchidopexy.” Boehme

P et al., J Pediatr. 2020 Aug;223:170-177.e3. doi: 10.1016/j.jpeds.2020.04.037. Epub 2020 Jun 9. PMID: 32532648

Reply 14: Thank for your constructive advice. In our study, the age for surgery in secondary UDT was older than primary UDT, but the atrophy rate was not statistically different between the two groups. We have added the issue in the section of discussion and added the data in the Table 1.

Changes in the text: Page 15, line 325-329; Table 1.

Comment 15: The discrepancy between this study's findings and those in the cited literature (lines 258-262) is mentioned but not discussed. Please discuss.

Reply 15: We have discussed the discrepancy according to your advice.

Changes in the text: Page 12, line 272-276.

Comment 16: The clinical outcome of TA should be mentioned and discussed (normal vs. sub-/infertility, paternal rate, etc.)

Reply 16: We are sorry for the inadequate discussion of the clinical outcome of TA. TA is associated with azoospermia and infertility in adulthood. Boys with one undescended testis have a lower fertility rate and the same paternity rate as those with bilateral normal testes. Boys with bilateral undescended testes suffer both lower fertility and paternity rates. We have cited two studies and EAU guidelines.

Changes in the text: Page 11, line 241-248.

Comment 17: As FSO was identified as an independent risk factor for TA, a specific discussion on the option to choose another surgical approach over FSO should be given. Please discuss for which patients FSO should – according to these new findings - be avoided, what the alternatives are and how these findings can change clinical practice.

Reply 17: For the intra-abdominal testis not amenable to regular laparoscopic orchiopexy, a novel technique of two-stage laparoscopic traction-orchiopexy may be an alternative, which has high success rate and low atrophy rate according to reports. This procedure preserves spermatic vessels, so it could reduce TA. I have modified our text as advised.

Changes in the text: Page 14, line 307-310.

<u>Reviewer #2</u>

Comment 1: English needs review

Reply 1: Thank you for your advice. We have got a native English-speaking expert to review our manuscript from Editage, which is a professional English language editing company.

Comment 2: Put the last sentence of introduction section in methods
Reply 2: We have revised our text as advised.
Changes in the text: Page 6, line 125-126.

Comment 3: Put the IRB number in beginning of methods section
Reply 3: We have put the IRB number in the beginning of methods section.
Changes in the text: Page 6, line 127-129.

Comment 4: The study is retrospective - In authors opinion what is the contribution of this paper to medical literature?
Reply 4: In our opinion, this study has the potential to assist surgeons in choosing the optimal surgical procedure in UDT, and in predicting the probability of TA after orchiopexy, in addition to helping answer parents' questions about TA. It has been listed in the discussion section (see Page 11, line 236-238).

Comment 5: The authors selected patients until 14 years old?
Reply 5: Yes. Because in our children's hospital, most patients were below 14 years.

Comment 6: Two important points are missing in methods : The authors measure the testis with USG but the measure during the surgical procedure will be important. The second point - Where the stitches in testis were done during the surgery? In the lower pole?
Reply 6: We are very sorry for the missing data in methods! (1) Since the surgeries were performed by different surgeons, some data about the measurement of testis during operation were lost. The data were not available for our study, so we used the data measured by ultrasound. (2) During the surgery, the testis was located into the dartos pouch, and the stitch was done in the lower pole of testis to the inferior wall of scrotum, to prevent testicular ascent.
Changes in the text: Page 7, line 167-169.

Comment 7: The authors classified the anomalies between testis and epididymis as a deferens anomaly? This is correct? There are several types of disjunction between testis and epididydimis.

Reply 7: We are very sorry for the incorrect name of anomaly. It is not appropriate. We have changed “deferens anomaly” into “deferens and epididymis anomaly” (see Page 7, line 158-160; page 13, line 289-293; Table 1,3,4,5).
The disjunctions between testis and epididymis consist of epididymal head non-fusion, epididymal tail non-fusion, and complete non-fusion. It is cited from the following study. E Rachmani el al, Complete testis-epididymis nonfusion anomaly: a typical association with cryptorchid testis. Urol Int 2012;89(3):355-7. doi: 10.1159/000342665. Epub 2012 Sep 28. I have added the data in the text (see Page 13, line 289-293).
Changes in the text: Page 7, line 158-160; page 13, line 289-293; Table 1,3,4,5.

Comment 8: Paper limitations are very important
Reply 8: Thank you for your suggestions! We have listed the limitation of this study in the discussion and conclusion sections.
Changes in the text: Page 16, line 356-359; page 16, line 366-367.