

## PEER REVIEW HISTORY

BMJ Paediatrics Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The effectiveness of penile ventral curvature correction and the trend of hypospadias repair: A prospective study of the national center in China
<b>AUTHORS</b>	Yang, Zhenzhen Li, Jiayi Liu, Pei Fang, Yiwei Wang, Xinyu Fan, Songqiao Li, Zonghan Shao, Zikun Xia, Yujie Wang, Zihong Liu, He Sun, Ning Song, Hongcheng Zhang, Weiping

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Dr. Peter Flom Peter Flom Consulting
<b>REVIEW RETURNED</b>	28-Apr-2023

<b>GENERAL COMMENTS</b>	<p>I confine my remarks to statistical and methodological aspects of this paper. I have a suggestion for what might be a better analysis.</p> <p>The statistics that were done are not wrong, but I think a change of variables might make everything clearer. Rather than look at initial curvature and amount of correction, which necessitates a rather cumbersome presentation of results, what if you look at a dependent variable of "proportion of correction" so that 100 would be a perfect result, 0 no change and a negative number a procedure that made things worse. Then you could use regression on that, with independent variables of initial condition (measured in whatever way is appropriate) and any other covariates that are important.</p> <p>You could use OLS regression and check its assumptions, but these are likely to be violated. If they are, then beta regression can be used. In R, this can be done with the betareg package. A good article on this method (which I think is underused) is here: <a href="https://pubmed.ncbi.nlm.nih.gov/16594767/">https://pubmed.ncbi.nlm.nih.gov/16594767/</a></p>
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<b>REVIEWER</b>	Dr. Fang Chen Shanghai Jiaotong University Affiliated Sixth People Hospital South Campus, Urology
<b>REVIEW RETURNED</b>	30-Apr-2023

<b>GENERAL COMMENTS</b>	The authors have made great efforts on describing their experience of different strategies for VC correction. The results are clear and convincing. But there is still one question should be argued. According to the article, there are 187 patients had residual curvature after UPT with the median preoperative VC of 60° (50°, 83°), they underwent subsequent DP to achieve the satisfactory straightening. The median residual VC showed that they still have severe VC, do you think DP is a proper method to this situation? As most long term studies of severe hypospadias show that DP run a high risk of VC recurrence, many surgeons choose ventral lengthening rather than DP when residual VC is over 30-45 degree. Could you give your opinion and experiences on this in the discussion?
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### VERSION 1 – AUTHOR RESPONSE

Reviewer 1

I confine my remarks to statistical and methodological aspects of this paper. I have a suggestion for what might be a better analysis.

Comments: The statistics that were done are not wrong, but I think a change of variables might make everything clearer. Rather than look at initial curvature and amount of correction, which necessitates a rather cumbersome presentation of results, what if you look at a dependent variable of "proportion of correction" so that 100 would be a perfect result, 0 no change and a negative number a procedure that made things worse. Then you could use regression on that, with independent variables of initial condition (measured in whatever way is appropriate) and any other covariates that are important.

You could use OLS regression and check its assumptions, but these are likely to be violated. If they are, then beta regression can be used. In R, this can be done with the betareg package. A good article on this method (which I think is underused) is here: <https://pubmed.ncbi.nlm.nih.gov/16594767/>

Response: We appreciate your suggestion to change the approach for analyzing the data, and we have conducted the statistical analysis based on the proportion of correction in each correction approach as you proposed. The results revealed that the median proportion of correction for degloving was 44% (IQR: 27%, 63%), for dorsal plication (DP) was 43% (IQR: 31%, 56%), and for urethral plate transection (UPT) was 33% (IQR: 18%, 50%).

Since both the independent and dependent variables are not normally distributed, and there is no linear correlation between them, the assumptions for OLS regression are not met. Consequently, using OLS regression would not be appropriate in this case.

Considering that we employed a systematic stepwise approach for VC correction, where each step builds upon the previous one, it is indeed challenging to compare the correction efficiency of different approaches directly. The efficiency of correction can be influenced by the preceding steps, making it difficult to make a fair and reasonable comparison.

Regarding the use of beta regression, we appreciate the suggestion and will consider it for comparing the efficiency of the different correction approaches. We will explore the `betareg` package in R, as recommended in the article you provided (<https://pubmed.ncbi.nlm.nih.gov/16594767/>). This method seems promising and can address the non-normal distribution of data. According to your suggestion, we attempted to perform beta regression on the data. We first calculated the contribution of different corrective steps (including degloving, DP, UPT) to the degree of curvature correction (ranging from 0 to 1). However, since beta regression requires the response variable (degree of curvature correction) to have a range that does not include 0 and 1, we excluded those data points (this step excluded all data points where complete curvature correction was achieved through degloving). As different corrective steps were performed on the same patients, the final sample size for beta regression was 915. The results of the beta regression are shown in the figure. It is important to note that there is a certain degree of progression between the different steps, for example, DP and UPT are not performed without degloving. Please confirm if there are any inaccuracies in the above content.

We would be grateful if you could further clarify our confusion. Thank you for your valuable input, and we will further investigate the feasibility of using beta regression for comparing the efficiency of the correction approaches.

Reviewer 2

The authors have made great efforts on describing their experience of different strategies for VC correction. The results are clear and convincing. But there is still one question should be argued.

Comments: According to the article, there are 187 patients had residual curvature after UPT with the median preoperative VC of 60° (50°, 83°), they underwent subsequent DP to achieve the satisfactory straightening. The median residual VC showed that they still have severe VC, do you think DP is a proper method to this situation?

Response: Thank you for your comments. We appreciate your feedback and apologize for any confusion caused by our previous expression. In our study, among the 187 patients who underwent urethral plate transection (UPT), it should be noted that they had residual curvature of 25° (15°, 30°) after the procedure, which was not explicitly mentioned in the manuscript. Subsequently, these patients underwent dorsal plication (DP) to achieve satisfactory straightening.

It is important to acknowledge that due to the short-term follow-up in our study, we were unable to obtain accurate statistics on the recurrence of ventral curvature (VC). Specifically, for the small proportion of patients with residual VC exceeding 30 degrees, it remains uncertain whether DP is an appropriate method. Further long-term follow-up and additional studies are necessary to evaluate the risk of VC recurrence in such cases.

We appreciate your attention to this aspect, and we will make sure to provide clearer explanations and additional details in future revisions of the manuscript.

Comments: As most long term studies of severe hypospadias show that DP run a high risk of VC recurrence, many surgeons choose ventral lengthening rather than DP when residual VC is over 30-45 degree. Could you give your opinion and experiences on this in the discussion?

Response: Thank you for your comments and bringing up the issue of ventral lengthening in the context of ventral curvature (VC) recurrence. You are correct that in many long-term studies of severe hypospadias, dorsal plication (DP) has been associated with a high risk of VC recurrence. As a result, many surgeons opt for ventral lengthening instead of DP when the residual VC is over 30-45 degrees.

In our study, DP was primarily utilized for VC less than 30 degrees after each step. However, in cases where the residual VC exceeded 30 degrees, DP was still performed because ventral lengthening was not a commonly practiced technique at our center during the time of the study. We acknowledge

the limitations of our approach and the potential benefits of ventral lengthening in reducing VC recurrence.

To address the concerns raised by the reviewer, we have included a revised description in the manuscript as follows: "In our center, ventral plate lengthening (VPL) is not commonly employed due to concerns about potential adverse effects, such as erectile dysfunction, hemorrhage, and scar healing of the albuginea incision, which lack sufficient long-term studies [4, 19]. The presence of bleeding during the incision or the need for closure with a flap or graft can impact surgical and postoperative urethral healing. A study conducted in 2017 reported achieving satisfactory straightening in all cases of severe hypospadias using UPT combined with DP, without the requirement for VPL in any patient [20]" (Lines 219-226).

We appreciate the reviewer for highlighting the limitations in our study and emphasizing the need for further assessment of ventral plate lengthening in future national multi-center, prospective randomized controlled studies. This point will be duly emphasized in the revised discussion section.

#### REFERENCES

4. Castagnetti M, El-Ghoneimi A: Surgical management of primary severe hypospadias in children: an update focusing on penile curvature. *Nature reviews Urology* 2022, 19(3):147-160.
19. Schlomer BJ: Correction of Residual Ventral Penile Curvature After Division of the Urethral Plate in the First Stage of a 2-Stage Proximal Hypospadias Repair. *Current urology reports* 2017, 18(2):13.
20. Pfistermüller KLM, Manoharan S, Desai D, Cuckow PM: Two-stage hypospadias repair with a free graft for severe primary and revision hypospadias: A single surgeon's experience with long-term follow-up. *Journal of pediatric urology* 2017, 13(1):35.e31-35.e37.

In conclusion, we extend our heartfelt appreciation for your valuable time and effort dedicated to reviewing our manuscript. We have taken great care to address and incorporate the suggestions and comments provided during this revision process. While we acknowledge the inherent limitations of our study, we firmly believe that our research holds significant scientific value. We sincerely hope that the revisions made will meet the standards for publication.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Dr. Peter Flom Peter Flom Consulting
<b>REVIEW RETURNED</b>	12-Jun-2023

<b>GENERAL COMMENTS</b>	<p>I am torn between "accept" and "minor revision" and leave it to the authors and editors to decide on whether another revision is needed.</p> <p>The authors have addressed most of my concerns. I suggested beta regression and the authors noted that they got an error because their dependent variable includes 0 and 1. This can be dealt with. See this thread</p> <p><a href="https://stats.stackexchange.com/questions/48028/beta-regression-of-proportion-data-including-1-and-0">https://stats.stackexchange.com/questions/48028/beta-regression-of-proportion-data-including-1-and-0</a></p> <p>for some ways of doing so.</p> <p>But, as I said in my first review, what they have done is not wrong, just not optimal.</p> <p>So .... The editors can decide.</p>
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<b>REVIEWER</b>	Dr. Fang Chen Shanghai Jiaotong University Affiliated Sixth People Hospital South Campus, Urology
<b>REVIEW RETURNED</b>	15-Jun-2023

<b>GENERAL COMMENTS</b>	I have read the reply to my questions from the authors and agree with their opinions in principle. I have no further questions and recommend this article to be published.
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#### **VERSION 2 – AUTHOR RESPONSE**

N/A