Peer Review File

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Reviewer A: Thank you very much for the opportunity of reading this exciting manuscript. PhimoStopTM could be useful in a well-matched group of patients suffering from phimosis, especially in the SARS-COV-2 pandemic. However, some points need revision:

Comment 1. Precise what you exactly mean by median-terms effects? What is the period? Please standardize this throughout the manuscript
Comment 2. How long was the follow-up duration? Please indicate in every part of the manuscript, from abstract to materials and method and results.
Reply 1 and 2. We agree with the reviewer that "medium-term effects" is not a good term to define follow-up. We removed the term throughout the manuscript, as a source of confusion. Conversely, we specified the exact follow-up time.
Change in the text: #40; #42; #150; #199; #253; #270.

Comment 3. Please expand the abbreviation RCTs #42; #245
Reply 3. Thank you for the advice. We modified both.
Change in the text: “RCT” was modified in “Randomized clinical trials” at #43, #270.

Comment 4. What do you understand by pathological phimosis in adults? Is there a different type of phimosis in this age group? In adults patients, phimosis is always caused by disease, especially lichen sclerosus
Reply 4. Pathologic phimosis, the adult form of phimosis, relates to a condition secondary to underlined pathological condition such as BXO and others (local scarring, chronic infection, etc) to differentiate from physiologic phimosis that is the form predominantly in the children. Pathologic phimosis is diffusely used in the literature as synonymous of acquired or secondary phimosis
Change in the text: None

Comment 5. Corticosteroids are only effective in phimosis caused by lichen sclerosus, but BXO=lichen sclerosus were exclusion criteria in this study. These results cannot be compared to your device.
Reply 5. While in paediatric patients corticosteroids are generally considered useful in phimosis management, in adult patients there is a lack of evidence. Nevertheless, in clinical practice is not unusual to use local corticosteroids as first-line therapy in adult phimosis, even without BXO diagnosis, because of the known antiproliferative and antifibrotic effects of those drugs. Moreover, BXO was not properly inserted as exclusion criteria because of the lack of histological diagnosis and in our case is better defined as “clinical BXO”
Change in the text: “BXO” was corrected in “clinical BXO” in the exclusion criteria in Table 1

Comment 6. Please be precise how did you perform BXO diagnosis? Did you make a histopathological examination or only clinical? (Table 1) There are some studies about discrepancies between clinical and pathological Diagnosis of LS in patients suffering from phimosis in the literature.
i.e
Czajkowski M, Żawrocki A, Czajkowska K, Kłącz J, Sokołowska-Wojdyło M, Biernat W, et al. Lichen Sclerosus and Phimosis - Discrepancies Between Clinical and Pathological Diagnosis and Its Consequences. Urology. 2021 Feb;148:274-9.
https://doi.org/10.1016/j.urology.2020.11.027
Reply 6. We agree with the reviewer that the lack of histological diagnosis made no possible the exact diagnosis of BXO. Moreover diagnosis based on clinical parameters often leads to wrong diagnosis. In our study we did not perform any histological exam and this make impossible exact diagnosis of BXO, but none of the patients enrolled had a suspicious BXO based on clinical parameters. For this reason we decided to correct BXO in clinical BXO in the exclusion criteria. We decided to discuss this topic in the Discussion section citing the article suggested (Czajkowski et al.)
Change in the text: "BXO" was corrected in "clinical BXO" in the exclusion criteria in Table 1. We insert the article by Czajkowski both in the Discussion (#259) and in the References

Comment 7. What about patients with phimosis caused by a short frenulum? Did you enrol this group of patients in the study?
Reply 7. Patients with short frenulum were enrolled in the study. Short frenulum was not considered an exclusion criterion.
Change in text: None

Comment 8. #Table 2. What were other comorbidities?
Reply 8. In Table 2 were reported the most frequent comorbidities (i.e., diabetes, hypertension and dyslipidaemia). "Other" comorbidities included: hypothyroidism (3 cases); Behçet's syndrome (1 case); retinitis pigmentosa (1 case); depression (2 cases); asthma (3 cases); hyperuricemia (2 cases); benign prostatic hyperplasia (4 cases).
Change in the text: Table 2 was modified specifying the "Other" comorbidities at the end of the table

Comment 9. Which version of MGSIS were used? MGSIS-5 vs MGSIS-7?
Reply 9. MGSIS 7 item has been used.
Change in the text: at #192, #237, #239 and Table 6 we specified MGSIS-7

Comment 10. It might be interesting to include complete questionnaires and results for each question. This would show which aspects have been particularly improved. (IIEF-5, EHS, MGSIS-?)

Reply 10. MGSIS-7 and EHS scores did not show any statistically significant differences compared to the baseline. For this reason, we decided to report only final score for all the questionnaires.
Change in text: MGSIS-7 replace MGSIS throughout the manuscript (at #192, #237, #239 and Table 6). No other modifications have been made

Comment 11. What does each score mean on the EHS scale? This is not clear to readers without enclosing individual questionnaires.
Reply 11. Reference for EHS is reported in the manuscript in order to understand what the different values mean. For MGSIS-7, EHS, IIEF-5 we prefer to report the references rather than specify every single questionnaire
Change in text: None

Comment 12. Please standardize the citation of tables in the text. Once it is "in Table" and sometimes it is (Table)
Reply 12. We modified as advised by the reviewer.
Change in text: every single Table was reported as “in Table…”

Comment 13. # 212 You could not use the phrase "Most patient" because in #162 ", A total of 85 patients were enrolled", and in Table 5 - 41 patients answer yes for the question about satisfaction after treatment. This is 41 from 85 enrolled, and it is 48%
Reply 13. The phrase “Most patient” was referred to PP (N = 71), and not to FAS population (N = 85). This is 41/71 (57%). To avoid confusion, the phrase was modified
Change in text: New phrase is “Among PP, most patient […]” (#224)

Comment 14. # 222 remove the repeat population because - PP is per protocol-population
Reply 14. Modified as advised.
Change in text: at #180, #219, #244 and Tables 4, 5 and 6

Comment 15. It is worth adding to the work a comparison with other circumcision devices and with the results of studies where patients were circumcised.
i.e
Lebina L, Milovanovic M, Otwombe K, Abraham P, Manentsa M, Nzenze S, et al. PrePex circumcision surveillance: Adverse events and analgesia for device removal. PLoS One. 2018;13(3):e0194271.
Gu C, Tian F, Jia Z, Li G, Meng Z, Xing W, et al. Introducing the Quill™ device for modified sleeve circumcision with subcutaneous suture: a retrospective study of 70 cases. Urol Int. 2015;94(3):255-61.
Czajkowski M, Czajkowska K, Zarańska K, Giemza A, Kłącz J, Sokołowska-Wojdyło M, et al. Male Circumcision Due to Phimosis as the Procedure That Is Not Only Relieving Clinical Symptoms of Phimosis But Also Improves the Quality of Sexual

Life. Sex Med. 2021 Apr;9(2):100315.
Reply 15. The article by Czajkowski is already in out list of references (13). We added the other two articles in the Introduction and consequently in the Reference section
Change in text: two new references were added (#67) and list of references was updated

Reviewer B

Comment 1. This paper is adequate. I suggest though to reduce the horrific collection of potential complications of circumcision in your introduction. The discussion should be more rational, i.e. usually circumcision is simple, safe and not a problem.
Reply 1. Thanks for your suggestion; we modified the text underlining the safety and simplicity of circumcision in most of the cases.
Change in text: Introduction was modified as suggested by adding the phrase "Usually, circumcision is a simple and safe surgical procedure. Nevertheless, is not devoid of complications […]" (#57). Thus, the list of potential complications (reported in literature, usually mild) should seem less horrific.

Comment 2. The aim of a 33% success rate of your device is rather moderate. For such an involved and time-consuming procedure, I would want a higher success rate of well above 50%.
Reply 2. 33% success rate was our primary endpoint; our study showed 52% overall success rate in PP population or 43.5% in the worst case scenario (FAS population). Anyway PhimoStop protocol is not to be considered "involved and time-consuming": application lasts few seconds, device must not be removed during micturition and scheme of application largely depends on patient's preference (night was the preferred moment).
Change in text: None.

Comment 3. The discussion on health care costs is also heavily biased. With all the number of outpatient visits etc your therapy is also quite expensive.
Reply 3. Cost-analysis was not part of the study objectives and is already reported in study limitations. Anyway, outpatient visit were limited to two: baseline/enrolment and 4-months follow-up. Nevertheless, it is reasonable to consider PhimoStop™ much less expensive for the NHS compared to circumcision considering that the cost of the device is around 100-150 Euros
Change in text: None

Comment 4. Finally. you should do a randomized trial between your device and circumcision. Only that would convince your readers.
Reply 4. We agree with the reviewer. Randomized clinical trial would be advisable in patients with mild/moderate phimosis. However identification of the primary

endpoint in such RCT could be challenging: a combined "trifecta" outcome efficacy/complication/cost would be probably necessary.
Change in text: Conclusion section has been modified as follows: " A randomized clinical trial comparing circumcision with Phimostop™ in patients with mild/moderate phimosis would be advisable, although the right primary endpoint in such trial would be a combination of efficacy, complications and cost" (from #270 to #273)

Reviewer C: Interesting topic but the paper has some problems.

Comment 1. Clarify your hypothesis before the objectives
Reply 1. The final part of the Introduction Section was modified to clarify the hypothesis of the study
Change in the text: "Hypothesis is that the use of a non-surgical treatment protocol, such as the novel minimally invasive device PhimStop™, could avoid circumcision in a significant number of patients with mild-moderate phymosis. Objective of the study was to prospectively assess the efficacy and durability of results of PhimoStop™" (from #76 to #79)

Comment 2. Include the IRB number in the first paragraph of material and methods section
Reply 2. We created a new paragraph in the Material and Methods section named "Ethics"
Change in the text: New paragraph 3.2 "Ethics" was created including the IRB number was inserted in (from #99 to #103). Consequently, we changed the numbering of the other paragraphs in the same section

Comment 3. The authors says: " Patients with phimosis grade >2 were excluded because of the impossibility to retract the prepuce sufficiently to apply PhimoStop" The patients submitted to device use has surgical indication? This is the key point of this paper - patients with true phimosis were excluded
Reply 3. According to Kikiros classification, phimosis grade ≤ 2 were considered "true phimosis". Patients with phimosis grade ≥ 3 were immediately enrolled for circumcision. To date, adult phimosis grade ≤ 2 are almost always enrolled for circumcision, given the lack of alternative strategies. We consider this management as potential "overtreatment" in some patients. The objective of the study is searching for a non-surgical alternative.
Change in text: none

Comment 4. Short follow up. A control group will be interesting
Reply 4. The lack of a control group is already reported in the "Discussion" Section as a study limitation (see #256).
Change in the text: None

Comment 5. A schematic drawing with the phimosis group will be interesting
Reply 5. Thank you for the suggestion
Change in text: a new figure was added (Figure 2)

Comment 6. In figure 1 include a picture showing the device in one or two patients
Reply 6. Unfortunately it is not possible because it needs specific consent from the patients that we did not collect.
Change in the text: None

Comment 7. Put all references in Journal Rules
Reply 7. Modified as advised.
Change in the text: References has been modified following Journal Rules

Comment 8. Suppress table 3
Reply 8. We suppressed Table 3. At the same time, we added Kikiros grade informations of PP in Table 2 because of the importance to know specific informations on phimosis grade between the enrolled patients
Change in the text: Table 3 was suppressed. Consequently, we changed the numbering of the other tables. Kikiros grade informations on PP were added in Table 2.

Comment 9. Put table 5 as a supplementary file
Reply 9. Modified as advised.