Peer Review File

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Reviewer A

Novoglan appears to be a safe, effective, and well tolerated method for treating adult phimosis.
I have some questions and concerns that I hope that the authors can address:

Comment 1:

There is industry involvement in the authorship, where Mr Andrew James, CEO of Platigo Solutions, is listed as one of the authors. May I know if Novoglan is used as standard of care in the two institutions, or it remains investigational? If it is investigational, then may I ask if the patients paid for the intervention, or is it industry sponsored? Did the 2 hospitals receive financial sponsorship from the company?

Reply:

Novoglan remains investigational in the institutions involved in the trial and the kits were provided by Platigo Solutions. The hospitals did not receive any other sponsorship from Mr Andrew James or Platigo Solutions.

Changes in the text:

The following sentence has been added to the Novoglan device section in the Methods section of the manuscript: “The Novoglan kits were provided for the study free of charge by Platigo Solutions Pty Ltd.” (Please see Page 6, Line 99)

Comment 2:

In the declaration of conflict of interest, there is inadequate description of how the Platigo Solution's staff involvement in the project as study administrators influence the study design, interpretation of results, or conclusions. What are the steps undertaken to mitigate the potential conflict of interest?

Reply:

Mr Andrew James as an employee of Platigo Solutions has provided Novoglan kits and training to the clinical staff on their use and is included as author for transparency. Mr Andrew James has reviewed the manuscript and approved its submission, however, in order to mitigate the potential conflict of interest, he did not make or recommend any edits and was not involved in the analysis or interpretation of the findings.

Changes in the text:

The following sentence has been added to the Conflict-of-Interest section of the Footnotes section: “Andrew James has reviewed the manuscript and approved its submission but did not make or recommend any edits and was not involved in the analysis or interpretation of the findings.” (Please see Page 15, Lines 340-341)

Comment 3:
The authors mentioned that 24 patients were required for statistical analysis. However, where all 20 screened patients agreed to consent for the study, the authors did not explain why they did not recruit a further 4 patients to satisfy the initial requirements.

Reply: The authors indeed aimed to recruit 24 participants, however, recruitment has been significantly delayed due to COVID restrictions and, after the interim review of the data from the first 20 participants, it was decided that further recruitment was not required given the size of the effect achieved.

Changes in the text:
The following sentence has been added to the Participants section of the Methods section: "Following an interim analysis after recruitment of the first 20 participants, a decision was made to analyse and publish the results given the size of the effect achieved." (See Page 7, Lines 118-119)

Comment 4:
I have slight concern over the definition of treatment efficacy. By definition, it would be prudent to use complete resolution of phimosis (Moreno, 2014) as the definite treatment outcome. This would correspond to Grade 6 in this article. Although all patients became grade 5 and 6, how many patients remain at grade 5, which would infer that they still had mild phimosis ("tight behind glans")?

Reply:
Indeed, not all patients achieved complete resolution of phimosis with tightness behind the glans persisting in 10 participants (50%) after the treatment. All patients, however, were able to fully retract the foreskin.

Changes in the text:
The last sentence of the first paragraph of the Treatment Efficacy section of the Results section now reads: "…all 20 patients have been assessed as either grade 5 or 6 at the final visit with 10 patients (50%) in each group." (Page 10, Line 214)

5) The procedure of twice daily, 10 min insertion of the device over a period of 4 to 8 weeks require a high degree of commitment. May I know the compliance of patients to this regime?

Reply:
During the Study Visits 2 and 3, patients were asked about the overall progress with the treatment and any problems with its use. While 95% reported the treatment progressing well, compliance was not directly monitored. The authors agree that treatment requires a high degree of commitment and aim to thoroughly assess treatment compliance in the next study.

Reviewer B

This paper presents the short term results of the Novoglan device that are predominantly focused on the safety and tolerability. There are few issues that need addressing.

Comment 1:

The term BXO should be replaced with lichen sclerosus (appropriate pathological description)

Reply: Authors agree that the term BXO should be replaced with lichen sclerosus.

Changes in the text:

The term BXO has been replaced with the term lichen sclerosus in the Introduction and Results sections and Table 4. (Page 5, line 64; page 10, line 204)

Comment 2:

Can the selection criteria be elaborated? Scarring of glans was an exclusion criteria. However, patients with Grade 1 or 2 Phimosis were included. How many patients were screened? Were these consecutive?

Reply:

Twenty consecutive patients were screened and enrolled with no patients being excluded. Only severe scarring of the glans was an exclusion criteria. While glans scarring is indeed difficult to assess with Grade 1 or 2 phimosis, none of screened patients had evidence of severe scarring of the glans during screening and none had it revealed after achieving foreskin retraction at the end of the treatment.

Changes in the text:

The first sentence in the Participants section in the Methods section now reads: "…where a total of 20 consecutive phimosis patients have been screened and enrolled." (Page 6, line 111-112)

Comment 3:

This study is for the adult population. However, a lot of the data such as grading of phimosis and other points in the discussion are based on the paediatric population. These populations remain quite distinct and should be mentioned clearly

Reply: The authors agree that there are important differences in adult and pediatric phimosis, however, the data on adult phimosis is very limited due to its lower prevalence.

Changes in the text:

The following sentence has been added to the Discussion section: "Due to higher prevalence of phimosis in children, some methods of phimosis treatment were validated in paediatric populations only and require careful interpretation and further assessment in adults." (Please see Page 13, Lines 290-291)

Comment 4:
It is unclear how the sample size was calculated? What were the primary, and secondary outcome measures, to decide the sample size?

Reply:
The sample size was determined using a power analysis to achieve a power of 0.8 in a paired-samples t-test with an alpha level of 0.05. Based on an expected standard deviation of 1.5 for the paired differences, the computed Cohen's d for the size effect of the paired-samples t-test was 0.67. Using all the above inputs, the minimum required sample size for the paired-samples t-test was calculated to be 18. The primary outcome measure for the study to decide the sample size was reduction of phimosis grade by at least 1 by the end of the treatment.

Changes in the text:
The following sentence has been added to the Statistical Methods section of the Methods section: "The sample size was determined using a power analysis to achieve a power of 0.8 in a paired-samples t-test with an alpha level of 0.05. Based on an expected standard deviation of 1.5 for the paired differences, the computed Cohen's d for the size effect of the paired-samples t-test was 0.67. Using all the above inputs, the minimum required sample size for the paired-samples t-test was calculated to be 18." (Page 9, lines 190-193)

Comment 5:
How were the partial responses assessed and standardised? E.g. reduction from phimosis level 3 to 4?

Reply:
The response to treatment was standardised using the 1 to 6 scale of foreskin retraction and detailed in the results section. The pre and post treatment foreskin retraction (Table 5) and degree-change (Figure 4) are shown in the results section.

Comment 6:
Were patient reported outcome measures formally validated prior to the adoption in this study?

Reply: The phimosis scale measurement was completed by consultant urologists. The questionnaires were custom designed for the study and have not been previously validated.

Changes in the text:
The following sentence has been added to the Methods section: "The Novoglan-01 Quality-of-Life Questionnaire has been specifically designed for this study." (Page 8, lines 148-149)

Comment 7:
Did any patients need extra training, to use the device, than the planned standard?

Reply: Patients were offered extra training during Study Visit 2 and 3, however, none of the participants requested it.

Comment 8:
It is mentioned that the device has been approved since 2006. Why has it not been adopted in the past?

Reply: Novoglan has been used by adults with phimosis since 2006, however its adoption by the guidelines has been limited by the lack of formal clinical trials.

Comment 9:
It is most important to have a long term data on the efficacy for foreskin preserving treatments. It is important that this point is discussed in detail in the discussion/limitation session. There are reviews available on other treatments. It would be useful to present the comparative data on the medical treatments (steroids) as well as the data from the other stretching devices.

Reply: The authors agree that long-term efficacy of phimosis treatment is crucial and needs to be assessed. The limitations section of the discussion section names lack of long-term follow up and indicates the plan for long-term follow up in the next study. The discussion section also mentions immediate and long-term efficacy of other conservative methods, however comparison is difficult given most existing data has been obtained in paediatric population.

Changes in the text:
The Discussion now reads: “The main limitations of this study were relatively low number of participants, and lack of long-term follow up data available at this stage as other conservative methods of phimosis treatment have been reported to suffer from phimosis recurrence.” (Page 14, lines 310-312)

Comment 10:
Some of the tables can be combined. E.g. tables 2, 5 and 6.

Reply: Authors agree that tables 5 and 6 can be combined.

Changes in the text: Tables 5 has been removed and percentages have been added to Table 6.

Comment 11:
Is there any health economic data available?

Reply: The authors do not currently have health economic data on Novoglan as a phimosis treatment. Novoglan treatment is, however, likely to be significantly more cost effective than circumcision, which requires the use of operating theatres and general anesthesia.

Reviewer C

Overall this paper represents a small cohort study on the safety and efficacy of the Novoglan-01 device. There are several points which can be better addressed to improve the overall quality of the manuscript

Comment 1:
The use of both the Kikiros scale and Phimosis scale is redundant and confusing. Consider limiting to use of one scale.

Reply: Authors agree that the use of both scales is not necessary and can be confusing.

Changes in the text:
The Kirikos scale has been removed from the manuscript. (Please see Table 2)

Comment 2:
Indicate which of the questionnaires were validated versus created for the purposes of this study alone.

Reply: Both Novoglan-01 Quality-of-Life Questionnaire, and Novoglan-01 Treatment Tolerability Questionnaire were specifically designed for the Novoglan-01 clinical study and have not been previously validated.

Changes in the text:
The methods section now reads: “participant’s quality of life was assessed using the Novoglan-01 Quality-of-Life Questionnaire, and participant’s perceived tolerability of the Novoglan product was assessed using the Novoglan-01 Treatment Tolerability Questionnaire, both of which were specifically designed for the Novoglan-01 clinical study.” (Page 8, lines 155-158)

Comment 3:
Line 45: unclear how only 90% improved but 100% were fully retractile

Reply: After the treatment all patients had either grade 5 (full retraction of the foreskin, tight behind the glans) or grade 6 (full and free retraction of the foreskin, no tightness behind the glans) foreskin retraction, meaning that all patients had fully retractile foreskin. Two patients (10%) with grade 5 retraction did not respond to treatment. They were able to fully retract the foreskin but it remained tight before and after the treatment.

Comment 4:
Please clarify that "quality of life" (starting line 210) refers to impact of phimosis on QoL and not use of the device. Upon initial read, it is unclear whether pain and discomfort in this section refers to use of the device or with phimosis.

Reply: The authors agree with this comment and added clarification to the text.

Changes in the text:

The first sentence in the quality-of-life section of the methods section now reads: “The effect of phimosis on patient’s quality of life was assessed before and after…” (Page 10, line 224-225)

Comment 5:
It is unclear why some results are reported with ranges (line 49, 255).

Reply: The ranges indicated different proportion of patients reporting side effects at different visits. The authors agree that this may cause confusion.

Changes in the text:
The single value of 15% has been left in the abstract and range was removed from the results section. The values can still be seen in the Table 8.

Comment 6:
Please clarify which side effects are considered "adverse events" "minor events" and "major events".

Reply: We did not classify side effects into minor and major events. Patients were specifically asked about minor side effects including pain and discomfort and monitored for serious adverse events as defined by the Therapeutic Goods Administration Medical device incident reporting & investigation scheme and included serious conditions that require hospitalisation, have risk of permanent damage, are life-threatening or leading to death.

Changes in the text:
The following sentence has been added to the Objective and Trial Design section: “The adverse events were defined as per the Therapeutic Goods Administration Medical device incident reporting & investigation scheme and included serious conditions that require hospitalisation, have risk of permanent damage, life-threatening or leading to death. (Please see https://www.tga.gov.au/resources/resource/guidance/medical-device-incident-reporting-investigation-scheme-iris).” (Page 7, lines 126-129)

Comment 7:
Please clarify line 281 "novoglan has been most effective in patients with more advanced phimosis." How does your data support this?

Reply: When assessing the efficacy of Novoglan treatment in terms of degree-improvement of the phimosis score, the highest efficacy was observed in patients with scores 1-3 with most patients (42.9%) having a four-degree improvement, 35.7% experiencing a three-degree improvement and 21.4% achieving a two-degree improvement. In the grade 4 phimosis group, 2 in 3 patients only achieved a one-degree improvement, while 2 in 3 patients with grade 5 phimosis did not respond to treatment at all. Similarly, grade 6 foreskin retraction has been achieved by 57 % (8/14) of patients in the 1-3 grade group and by 33.3% (2/6) of patients with grades 4-5.

Changes in the text:

The following sentence has been added to the Discussion section: “Grade 6 foreskin retraction has been achieved by 57% of patients with grade 1-3 disease and by only 33.3% of patients with grade 4 or 5 phimosis.” (Page 13, lines 297-298)

Comment 8:
Overall the authors report a 70% rate of pain being the same or WORSE with use of the device. This should not be glossed over just because the N is low.

Reply: The authors thank the reviewer for valuable input. On review of the data, we found that most of the patients that had no change in their pain level had no pain before and after the treatment. The description of findings has then revised to improve understanding. Out of 8 patients with pain, 6 reported improvements. Only 2 patients developed new slight pain/discomfort.

Changes in the text:
The Quality of life section now reads: “Out of 8 participants reporting slight or moderate general pain/discomfort at the First Visit, 6 participants reported reduction in general pain/discomfort, while 2 participants reported their level of pain/discomfort remained unchanged at the Final Visit. Two participants (10%) reported new slight general pain or discomfort at the Final Visit.”(Page 11, lines 227-229)

Comment 9:
Include percentages in figure 4, it is difficult to quickly receive the main message otherwise

Reply: Authors agree that percentages would improve Figure 4.

Changes in the text:
Percentages have been added to Figure 4.

Comment 10:
It is unclear how exactly the device works despite Figure 1 and 2. Is the balloon inflated on one side of the glans? Is the patient instructed to move the balloon to a different location with each application?

Reply:
The standard instructions for patients as well as the training given to the trial Nurse are to place the balloon in the same location, however, the clinician/nurse may recommend the application in slightly different locations based on patient preference.

Changes in the text:
The Novoglan device section in the Methods section now reads: “The Novoglan balloon is guided under the foreskin between the glans and the prepuce using a purpose moulded rod and placed in the same position every time.” (Page 6, lines 94-96)

Comment 11:

It should be reported how long each patient remained in the trial - did longer use associated with better results?

Reply: All patients were followed up for 6-8 weeks from the first study visit and had same treatment duration. It remains to be investigated whether longer treatment duration leads to better results.

Reviewer D

Novoglan-01 could be useful in a well-matched group of patients suffering from phimosis. However, some points need revision:

Comment 1:

Author's claimed that circumcision or surgical removal of the prepuce is the definitive treatment for adult phimosis. However, the essential part of male circumcision is the surgical removal of the prepuce. Please elaborate on these statements.

Reply: Apologies for confusion, the sentence has been rephrased.

Changes in the text: The first sentence has been rephrased and now reads: "At present, the only definitive treatment for adult phimosis is circumcision, which is a surgical removal of the prepuce" (Page 3, lines 34-35)

Comment 2:

Paragraphs 68-70 there is no citation. Please give the citation or mention that this is author's opinion. i.e

Czajkowski M, Czajkowska K, Zarańska K, Giemza A, Kłącz J, Sokołowska-Wojdyło M, Matuszewski M. 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. doi: 10.1016/j.esxm.2020.100315. Epub 2021 Feb 2. PMID: 33545503; PMCID: PMC8072165.

Reply: Authors would like to thank the reviewer for providing the reference and have added it to the text.

Changes in the text: The recommended reference has been added to the manuscript.

Comment 3:

In the article you should use different brackets. For citations you use (…) and for inclusion criteria (paragraph 109-115) the same (…). This is not clear.

Reply: Authors agree that the use of brackets in inclusion and exclusion criteria appeared confusing. The numbering has been removed from the recruitment criteria. Brackets may appear elsewhere in the text, however, as we believe that such styling of references and brackets in the text is dictated by the journal.

Changes in the text: Numbering has been removed from the Participants section in the Methods section. (Page 6, lines 112-117)

Comment 4:
Please be precise how did you perform lichen sclerosus diagnosis? Did you make a histopathological examination or only clinical? There are some studies about discrepancies between clinical and pathological diagnosis of LS in patients suffering from phimosis in the literature. Are LS in exclusion criteria. In one place authors mentioned that scares are exclusion criteria, contrary in table 4 – 7 patient had BXO.
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: We only used clinical diagnosis of LS and enrolled several LS patients as only severe scarring of the glans was an exclusion criteria. LS was not an exclusion criteria. We added a clarification that LS was diagnosed only clinically with no histopathological confirmation.

Changes in the text:
The following sentence has been added to the Patient recruitment and clinical characteristics section: “It is important to note that the diagnosis of lichen sclerosus was based only on clinical examination, which has been shown to be inaccurate in some instances (13).” (Page 10, lines 205-206)

Comment 5:
How long was the follow-up duration? Please indicate in every part of the manuscript, from abstract to materials and method and results.

Reply: Follow up for all patients was 6-8 weeks from the beginning of the treatment.

Changes in the text:
The following sentence has been added to abstract and results sections.
The abstract now reads: “The treatment involved twice daily 10-minute applications for a duration of 4-8 weeks with patient’s degree of phimosis assessed before and at 6-8 weeks after the initiation of the treatment" (Page 3, line 41-42)
The following sentence has been added to the Results section: “The degree of phimosis was assessed before the treatment and at the final visits at 6 to 8 weeks after the initiation of the treatment as a measurement of its efficacy.” (Page 10, lines 211-212)

Comment 6:
Why do you indicate frenuloplasty in table 4, despite the fact no patients enrolled on this study underwent frenuloplasty?

Reply: Prior frenuloplasty was a characteristic that we aimed to include in analysis for the study. We, however recruited no patients with frenuloplasty and agree that it can be removed from Table 4.

Changes in the text: Frenuloplasty has been removed from Table 4.