

# Peer Review File

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## Reviewer A

- 1) The title should reflect that per the methods section the authors specifically investigated hyaluronic acid, not glans augmentation generally.
  - ⇒ The title was modified by adding “using hyaluronic acid” in order to specify the investigated method.
  - ⇒ **Changes in the text:** line 1.
  
- 2) The authors repeat the common claim that PE is present in up to or over 1/3rd of men. Data suggesting such a high prevalence is derived from single item patient reported surveys that do not adequately address the presence of associated bother, lack of control, or markedly short latency. This misinterpretation of data has potentially serious consequences and should be avoided. A 5% or less prevalence has been reported as most consistent with Clinical PE per Althof 2014, please utilize correct data for the abstract and introduction.
  - ⇒ The suggested article has been reviewed and taken into consideration. The adequate changes were performed and Athof et al. report was cited and added in the references.
  - ⇒ **Changes in the text:** lines 28, 49-51, 233-235.
  
- 3) The abstract would be more useful if quantitative data on the number of published studies, success rates, and complication rates were included. Background is less important here; more important to convey a bulleted summary of what the authors found. Data on the mechanism is important but should be subordinate to actionable information and retained only in the manuscript if space is limited.
  - ⇒ The number of published studies as well as a general review of their effectiveness and their drawbacks was added in the abstract. However, since this article is not space limited, we thought it would be useful to keep the data on the mechanism, making it easier and faster for the reader to understand the paper.
  - ⇒ **Changes in the text:** lines 35-38.
  
- 4) The authors should consider and cite the newly published AUA definition of premature ejaculation. Please also consider reviewing this publication for additional details and context on PE.
  - ⇒ The new definition of PE according to the AUA guidelines 2020 by Shindel AW, et al was mentioned and cited.
  - ⇒ **Changes in the text:** lines 53-57, 241.

**5)** Please note that NVPE and PELD are provisional diagnoses and are not at this time widely accepted nor utilized. I would not include these as classifications official endorsed by ISSM, AUA, or DSM.

- ⇒ NVPE and PELD were removed from the manuscript as suggested.
- ⇒ **Changes in the text:** lines 59-60.

**6)** Consider further sub-division of the introduction into more discrete paragraphs focused on given topics. For instance, start a new paragraph when you discuss the theoretical neurotransmitter and nerve aspects of lifelong PE.

- ⇒ Two subdivision were added: the first explaining the theoretical neurotransmitter and nerve aspects of lifelong PE, and the second details the innervation of the penis and the glans.
- ⇒ **Changes in the text:** lines 64 and 66.

**7)** Include a citation supporting the statement that augmentation surgery is not recommended. Not recommended by whom? In general it is essential that citations be provided for nearly all statements, including those on therapies that are or are not recommended.

- ⇒ Both EAU 2020 (SEXUAL AND REPRODUCTIVE HEALTH section) and AUA (guideline statement 15 on PE) guidelines consider the injection of bulking agents (including HA) as experimental and requiring further safety and efficacy studies. This in fact was one of the reasons why we are writing this paper to shed light on this debatable topic. The 2 citations supporting this statement were added in the manuscript.
- ⇒ **Changes in the text:** lines 77-80 and 248-249.

**8)** A testable hypothesis may be included even for review papers such as this. What did the authors hope to prove or disprove? This should be stated as a refutable question at the end of the introduction.

- ⇒ The testable hypothesis is indeed the effectiveness and safety of penile glans augmentation using HA. But since we are writing a narrative review of literature (or narrative overview, also called unsystematic narrative review), we tried to follow the instructions provided by the journal through the article “Writing narrative literature reviews for peer-reviewed journals: secrets of the trade”. However, we modified the stated aim of the study in the introduction by adding “and to assess their safety and efficacy”.
- ⇒ **Changes in the text:** line 82.

**9)** Which specific narrative review check list was utilized? This information is better suited to the methods section.

- ⇒ According to TAU author’s guidelines, the sentence “We present the following article in accordance with the NARRATIVE REVIEW reporting checklist” must be added at the end of the Introduction section of Main Text. The checklist is that provided by the journal guidelines and was filled and sent at the time of re-submission.

**10)** Please include discrete time points, not “over the last 20 years” for the time period under investigation. IN other words, “1/1/2000-1/1/2020” or similar. Please also be

specific with how Boolean operators (eg “AND”, “OR”,) were applied in the search strategy.

Consider that absence of “glans augmentation” as a search term may have led to some papers being missed.

Details of the analysis conducted are insufficient. Who identified papers? Who made selections on which were to be further assessed? Who analyzed them? Was it more than one person? How were discrepancies resolved? Were inclusion/exclusion criteria specified a priori? Was quality assessed/graded? Please detail these. Also cite the narrative review checklist utilized in this section.

A wire diagram figure is typically included in the methods to detail how many studies were identified and how many were screened out at different phases of data acquisition and for what reason.

Did the authors consider checking sources other than Pubmed? Were reference lists of included articles reviewed?

⇒ The discrete time period precision was added.

The used combination of Boolean operators was as follow: “Premature ejaculation AND ((glans penis) OR (hyaluronic acid))”.

“Glans augmentation” itself was not used as a search term (not a MeSH).

The identification and selection of the articles was performed by 3 authors, however the assessment of the quality and the analysis was performed by all authors independently. No inclusion criteria were specified a priori and “case reports and comments” were excluded.

A flowchart was already done but was not included in the figures. It will be added as a referenced figure as requested.

The references from all the articles found were searched for further relevant literature, however the found articles were already present during the initial search.

⇒ **Changes in the text:** lines 86-91, a flowchart was sent as an attachment (Figure 1).

**11)** Were the data on physiological rationale collected as part of the pubmed search or is this background that was obtained otherwise?

⇒ The data of physiological rational were extracted from the article included in this review (it is in fact a part of the results).

**12)** The section on technique is interesting; it would be more useful if the authors consolidated this section into discrete paragraphs analyzing specific aspects of the procedure (e.g. a paragraph on how local anesthesia was done, a paragraph on formulation of HA used, a paragraph on injection location, a paragraph on any studies which enrolled uncircumcised men) and then cite data from each of the 5 papers within these paragraphs. What the authors have done by simply reviewing each paper individually is certainly easier but harder to interpret for the readers. A truly useful review will

synthesize, not simply regurgitate, data. To their credit the authors do a better job of this in the section on outcomes, where IELT for all studies is considered in a discrete paragraph...this format should be applied to the technique section.

- ⇒ The technique section was a bit challenging to write in a different way due to lack of details concerning the anesthesia (only 3 out of 5 studies mentioned the anesthesia used and only 1 study mentioned that all patients were circumcised), so our main focus was the detailed techniques (Needle gauge, amount, type and pattern) of HA injections.

**13)** Please include quantitative data on adverse reactions. What is “most” cases/patients? Cite absolute numbers and also percentages of the total study groups. Also noteworthy is that just 3 studies are cited, were AE reported in the other two?

- ⇒ The AEs of all the studies were added. However, the lack of precise data in these articles concerning the adverse reactions makes it impossible to include more quantitative data and analysis.
- ⇒ **Changes in the text:** lines 152, 158 and 159.

**14)** Comment is lacking on durability. What was the mean follow up of these studies? Was their degradation of ELT prolonging effect over time?

Comment is also lacking on other metrics for satisfaction. Were validated instruments used in any of these studies? Patient reported outcomes? Please include more detail on other aspects (survey responses, PRO, general assessment of efficacy, willingness to repeat or recommend therapy) relevant to patient satisfaction.

The figure is useful and the table provides much useful information. Specific items called out above do however merit consideration for mention in the text with either detail included or specific reference to the tables so the readers knows where to find the quantitative data.

- ⇒ Indeed, the different studies (except that of Kwak et al., 5 years follow-up) lack on durability and long term follow-up (this subject was added in the limitations in the discussion paragraph).

The patient was evaluated only in 2 studies using a non-validated instrument (from Grades 0 to 4: Gr 0, very dissatisfied; Gr 1, moderately dissatisfied; Gr 2, about equally satisfied and dissatisfied; Gr 3, moderately satisfied; Gr 4, very satisfied, respectively), this limitation was also added.

Most of the relevant information present in the table were mentioned in the results and discussion section. That of follow-up and patient satisfaction were added in the manuscript.

- ⇒ **Changes in the text:** lines 203 to 206.

## **Reviewer B**

1. The penile glans augmentation and glans penis augmentation was written. Please unify it into one.

- ⇒ Penile glans augmentation was removed and unified under “glans penis augmentation” only.
- ⇒ **Changes in the text:** lines 1, 163, 178, 199, 212.

**2.** ISSM guidelines do not recommend penile glans augmentation by HA injection for the treatment of PE because of possible sensory loss. So please add something about loss of sensory nerves to the outcomes.

- ⇒ ISSM guideline statement concerning the loss of sensory and thus sexual function was added.
- ⇒ **Changes in the text:** lines 77 to 80