Peer Review File

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Reviewer A

The editorial commentary on the PINNACLE Study, evaluating the Optilume® BPH Catheter System for treating lower urinary tract symptoms due to benign prostatic hyperplasia (BPH), provides a comprehensive analysis. The study's strengths include its randomized, sham-controlled design, significant improvements in symptoms, and flow rate with Optilume BPH. However, the commentary identifies limitations,

Clarity and Detail in Methodology Critique: While the commentary mentions limitations related to the study's focus on a specific prostate size range and potential biases, it could benefit from more detailed explanations or examples of how these factors might impact the study's findings.

We have added in the importance of considering various prostate volumes in trial design for the future, as currently the lack of subgroup analysis within the study does not provide indication on which patients may be post suitable. While this trial's inclusion criteria is comparable to other studies, we ultimately should include difficult anatomy for future studies as otherwise these patients may be neglected from potential novel therapies. Additionally, by having a subgroup analysis, we can better understand the degree of IPSS or SHEM improvement.

Changes in text: Line 124-127, 128-130

Broader Context and Comparisons: The commentary could include a more extensive discussion of how the Optilume BPH system compares to other treatments for BPH in terms of effectiveness, cost, and patient outcomes. This would provide a better understanding of the system's place in the broader landscape of BPH treatments.

To integrate the article with PMID: 36402815 into the commentary on the PINNACLE Study, you can highlight the comparison between different treatment modalities for large benign prostatic hyperplasia (BPH), specifically focusing on robot-assisted simple prostatectomy (RASP). Since the PINNACLE Study focuses on the Optilume BPH Catheter System, a novel minimally invasive surgical therapy, it would be insightful to juxtapose its results with those of RASP, as reported in this systematic review and meta-analysis.

Thank you for your suggestion of assessing the landscape of MIST in further detail. Unfortunately, the exact cost of the Optilume® BPH system has not been fully identified at this time, however previous costs of similar Optilume® technology in anterior urethral strictures are reported in our current piece. We look forward to contributing to the literature with health economic analysis of MIST. This is a great point as the burden of MIST technology on healthcare systems remain high given the proprietary patents. We must provide adequate access and equity to all our patients.

Thank you for your suggestions of RASP as a novel treatment for BPH. The meta-analysis is extremely well done and I thank you for sharing this great work. We have included this within our current analysis along with Aquablation. Comparisons to IPSS of Aquablation and RASP have been referenced.

Changes in text: Line 175-181, 111-116

Long-term Implications: The need for extended follow-up is mentioned, but the commentary could further emphasize the importance of long-term data in assessing the sustainability of treatment benefits and potential long-term side effects.

Great points regarding the importance of long-term outcomes. We have also discussed the impacts of future redo procedures that may appear. Given that MISTs are often only shorten term solutions, we need to document long term reoperative surgical difficulty. Such data may only be collected if long term follow up is conducted. We have included this now in the manuscript.

We have also discussed the potential molecular impacts of paclitaxel on prostate cells, along with raising uncertainty regarding the impacts of local chemotherapy on future treatment.

Changes in text: Line 156-173, 193-198

Clearer Conclusions: The final conclusion could be strengthened by summarizing the main points more concisely and clearly stating the potential impact of the study's findings on clinical practice.

The conclusion has been updated to further highlight the limitations of MIST trials along with the main findings of Optilume BPH in regard to IPSS and SHEM. Thank you once again for your suggestions.

Changes in text: Line 193-198

Reviewer B

Excellent commentary.

Thank you for your input and considerate review.

Reviewer C

In this editorial comment, the authors describe and reflect on the PINNACLE study,
"A Double-blind, Randomised, Sham-controlled Study Evaluating the Optilume BPH Catheter System for the Treatment of Lower Urinary Tract Symptoms Secondary to Benign Prostatic Hyperplasia"
I have the following suggestions / comments

Discrepancy between text and Table 1: IPSS > 13 (Table) vs IPSS > or = 13 in text (line 37)

Thank you for identifying this discrepancy, it is now updated. The correct answer should be greater or equal to 13 (i.e., IPSS ≥ 13).

Changes in text: Table 1 updated

Table 1: Median lobes >1cm were excluded (see Text line 113) - this should be added as exclusion criterion.

This has been removed from the text line as it was included in the study. Confusion arise from the study's initial Clinical Trial website.

IPSS improvement (%) is a possible outcome measure. Change in IPSS category could be more relevant. A % is subjective to initial value and does not represent the patient perspective. Has PINNACLE reported on that? if not, it could be a critique to the study.

IPSS improvement as measured by % change was an outcome measure in this piece, however IPSS category change was not reported. Raw IPSS change was included, an average of 10.7 at 3 months. It is unclear whether this resulted in clinically meaningful change of IPSS category. Patient reported outcomes are important and should be considered. We have added this to the manuscript.

It should be noted that the authors of PINNACLE do note the limitation that they only assessed men within a certain PV range, and with moderate or severe symptoms. The results may not be generalisable to all men.

Changes in text: Line 167-173

Spelling: line 66 (however was), 69 (improvements was), 107 (mixture of anesthetic technique)

However was → however appeared insignificant
Improvements was → improvement
Mixture → range of

The results on cross-over should be included in the paragraph at lines 73-75: how many did cross over at 3 months?

Added. Between three and six months, 1 patient in the Optilume arm received BPH medication and 1 was lost to follow up. In the control arm, 11 patients underwent a surgical procedure and 1 commenced BPH medication.

Changes in text: Line 78-82

The sentence "PINNACLE found..."(lines 98-100) is unclear
Thank you, changes accepted and expression revised.

Lines 117-118 are contradictory with lines 46-48. How can cross-over from the sham arm occur at 3 months if blinding of that arm is sustained for 12 months? The outcome of the sham arm is evaluated at 12 months?

Thank you for your insight and pick up here. It should be 12 months follow up of the intervention arm.

The blind was broken at 3 months for the sake of pursuing alternative therapy, only if the blinded patient has had a discussion with blinded site personnel about general treatment options. Additionally, the

subjects opting to cross over were required to continue meeting study eligibility criteria. Our current commentary critiques the uncertainty surrounding clinical equipoise. At 3 months, while blinding is still maintained for patients on control arm, it can be broken if patient require further intervention. Not all patients will be unblinded.

The cross over at 3 months did not impact the study as it did does not impact the primary outcome. The primary outcome was comparing the IPSS improvement from baseline to 3 months in the sham arm (thus, 3 months cross would not impact results), to improvement from baseline to 1 year in the Optilume BPH arm. The question of whether there is clinical equipoise here is uncertain.

Changes in text: Line 151-154

Lines 133-134: What would the authors recommend? Which patient is a good candidate for Optilume BPH?

While we eagerly await the long-term outcomes of Optilume® BPH, the authors believe that younger patients wanting to improve bothersome LUTS and avoid impacts to sexual function should be considered for this novel technology. There may also be a role for Optilume® BPH in comorbid patients wishing to avoid general anaesthesia.

Changes in text: Line 186-196

Reviewer D

I must say that the comments are accurate and pertinent. I would add that MIST are also interesting a new patient category which is the 45-55 years-old moderate LUTS patients who are willing to preserve their sexuality but are aware that they will need a further treatment for LUST in a future. Differently speaking, a moderate treatment with no side effects to a moderate functional impairment.

Thank you for your insight. This has been added now.

Changes in text: Line 191-196

Reviewer E

According to my opinion this comment should more critically discuss some aspects of the PINNACLE study
1. The authors should discuss whether the primary end-point of this study was met, i.e. whether this was a positive or negative trial. Although the IPSS difference was significant at three months, the 30% performance goal was not met.

From an efficacy standpoint, the primary outcome was met, resulting in a positive trial. Patients in the Optilume BPH arm not only had an improved IPSS (average 49%), it also met the pre-specified

performance of 30%. Similar results were seen in Qmax measures as well. However, when a margin of 25% super-superiority was incorporated, the significance was no longer maintained.

Changes in text: Line 69-76

2. The lack of PSA-data: if PSA does not change over 12 months after Optilume treatment, then it is very unlikely that the Optilume devices leads to a relevant prostate tissue destruction, thus questioning the long-term outcome.

Thank you for your review. PSA data is not routinely reported in BPH related trials, however it is a pertinent point regarding the impact of chemo-toxic medication on prostate cells, and consequent serum PSA. There remains a paucity of data of the short- and long-term effects of paclitaxel delivered via catheter. Additionally, if the paclitaxel only prevents central zone cells from further proliferation, then perhaps impact on PSA may not be great as other prostatic lobes may not be affected. We have acknowledged further clarification and understanding of paclitaxel in BPH management in the updated version. The extent of locally delivered paclitaxel on PSA goes beyond the scope of this piece.

Changes in text: Line 156-165

3. The long-term outcome is still unknown; more than two decades ago balloon dilatation of the prostate was introduced yet given up due to long-term efficacy; this needs to be discussed.

Agreed regarding long term outcomes. Phrasing has been modified from a "useful" tool to a "potential" tool in order to avoid any suggestion that it has proven effects at this time for long term LUTS relief. Reference to balloon dilatation has been added.

Changes in text: Line 105-107

4. The placebo-effect is striking in this study, both regarding IPSS and particularly Qmax improvement in the range of 5.5ml/sec. It is difficult to understand how a simple catheterization can lead on an Qmax improvement in this range after 3 months. This should be discussed.

Indeed. The median improvement in IPSS effect of the sham arm at 3, 6 and 12 months appear to be 8, 6.1 and 4.8 respectively. No predilatation catheter was inflated. IPSS change across follow up monotonically decreased in the sham arm however remained consistent in the intervention arm. While placebo achieved an 8 point reduction in IPSS at 3 months, there is uncertainty regarding the fundamental mechanism behind such improvement. We have further addressed this concern in our discussion. What is important to note is that even with the placebo effect in place, patients in the interventional arm reported superior outcomes.

Changes in text: Line 167-173

5. The first paragraph of this editorial should be modified to "Optilume BPH is another "potential tool". I believe that the data are too immature to conclude that it is "another useful tool".

Agreed – this is now updated. Thank you.

Changes in text: Line 186

Reviewer F

Thank you for providing this comment. It is very well written.

Thank you for your input and considerate review.

Reviewer G

Excellent synopsis and review of the cited study of Optilume balloon dilation for BPH. Wonderful addition to Translational Andrology and Urology, important insight for the reader base.

Thank you for your input and considerate review.