January 26, 2022

Re: “Relationship between Visual Analog Scale Pain Scores and Opioid Consumption after Total Hip Arthroplasty” (MS#: 72040)

Dear Editors of the *World Journal of Orthopedics,*

Thank you for your consideration of our manuscript, titled “Relationship between Visual Analog Scale Pain Scores and Opioid Consumption after Total Hip Arthroplasty” for publication in your journal. We thank the reviewers for theirs suggestions and comments. We have revised our manuscript accordingly. Please see below for our response to each comment. All changes made to the main manuscript are in red font. We appreciate your interest in our research.

Reviewer #1:

Comment 1.1: Overall good article and significant aspect of the prevailing problem brought out. Keywords: Opioids; Narcotics; Pain; Hip replacement; Total hip arthroplasty, Hip replacement and total hip arthroplasty, same – please change one

> **Response 1.1:** Thank you for bringing this to our attention. We have replaced the keyword “hip replacement” with “visual analog scale”.
>
> The revised keywords are listed on page 1, line 43.
>
> They now read as follows: “Opioids; Narcotics; Pain; Visual Analog Scale; Total hip arthroplasty”.

Comment 1.2: Please include the following references

1.) Perioper Med (Lond). 2018 Nov 22;7:25. doi: 10.1186/s13741-018-0105-8. eCollection 2018. Predictors of chronic prescription opioid use after orthopedic surgery: derivation of a clinical prediction rule. Daniel I Rhon 1 2 3, Suzanne J Snodgrass 3, Joshua A Cleland 4, Charles D Sissel 5, Chad E Cook 6

2.) How orthopedic surgeons can impact opioid use and dependence in shoulder arthroplasty. Chatha K, Borroto W, Goss L, Ghisa C, Gilot G, Sabesan VJ. JSES Int. 2020 Feb 5;4(1):105-108.

3.) The impact of state-mandated opioid prescribing restrictions on prescribing patterns surrounding reverse total shoulder arthroplasty.Sabesan VJ, Echeverry N, Dalton C, Grunhut J, Lavin A, Chatha K. JSES Int. 2021 May 6;5(4):663-666.

Can be quoted for reducing opioid use.

> **Response 1.2:** We appreciate the feedback and have added the following references to the manuscript.
>
> The first reference is cited on page 11-12, lines 274-279.

It reads, “Rhon et al. [51] found that the use of pain medication prior to surgery, younger age, female, lower socioeconomic status (education and household income), high health-seeking behavior, and presence of substance abuse, insomnia, or mental health disorders prior to surgery were all significant in predicting chronic opioid use after surgery. However, it is likely that a combination of these variables may provide a greater predictive value for determining the likelihood of chronic opioid following surgery.”

51. Rhon DI, Snodgrass SJ, Cleland JA, et al (2018) Predictors of chronic prescription opioid use after orthopedic surgery: derivation of a clinical prediction rule. Perioper Med 7:25. https://doi.org/10.1186/s13741-018-0105-8

The second reference is cited on pages 2-3, lines 67-69.

This sentences reads, “Although recent studies have highlighted a pattern of patients receiving excess opioid medication after undergoing various orthopedic procedures, there has been minimal evidence to suggest an optimal supply of pain medication postoperatively [16–23].

23. Chatha K, Borroto W, Goss L, et al (2020) How orthopedic surgeons can impact opioid use and dependence in shoulder arthroplasty. JSES Int 4:105–108. https://doi.org/10.1016/j.jses.2019.10.113

The third reference is cited on page 11, lines 254-257.

This sentence reads, “Implementing standardized, evidence-based opioid prescribing protocols may optimize the quantity of opioid prescriptions provided to patients and are particularly paramount for patients at risk for transitioning from short-term to long-term opioid therapy postoperatively [4, 16, 43–45].

45. Sabesan VJ, Echeverry N, Dalton C, et al (2021) The impact of state-mandated opioid prescribing restrictions on prescribing patterns surrounding reverse total shoulder arthroplasty. JSES Int 5:663–666. https://doi.org/10.1016/j.jseint.2021.04.009

Comment 1.3: LINE 26, 98; 105 out of 1142 THAs Only anterior approach. How many among the remaining were anterior approach, rest posterior? This could be a variable – please clarify

Response 1.3: A total of 1,142 primary THAs were performed at our institution within the period of interest, of which, 270 (24%) were performed by the senior author. Furthermore, 105 of the 270 THAs had available data for analysis and therefore were included in the study.

We have mentioned this in the limitations section on page 12, lines 296-298.

It reads, “All patients in this study underwent THA via the direct anterior approach by a single surgeon, thus our results may not be generalizable to patients who undergo THA via other surgical approaches.”

Comment 1.4: Line 152. Following discharge, patients are assessed for adequate pain control (and severity) at multiple time points. Please elaborate – telephonic review ? follow-up ?

Response 1.4: Thank you for your feedback. Patients were assessed for pain via telephone by clinical care coordinators as well as during their follow-up visits. We have added this to the manuscript for further clarity.

This can be seen on page 6, lines 155-156.

It reads, “Following discharge, patients are assessed for adequate pain control (and severity) at multiple time points via telephone and during scheduled follow-up visits.”

Comment 1.5: LINE 187 MAJORITY WERE FEMALE 63% TABLE 1
Geriatric - MAJORITY female and 58 > 65 years of age - bias, variable should be mentioned as a limitation.

Response 1.5: This is valid statement. We have added this bias to the limitations as recommended.

This can be seen on page 12, lines 293-294.

“The study population was majority female and age 65 years or older which causes inherent selection bias.”

Comment 1.6: What duration was the preop opioid usage, what precautions were taken, perioperative care different?

Response 1.6: The duration of preoperative opioid use was not collected through our survey. However, if a patient reported preoperative opioid use, a thorough medication reconciliation was performed and these patients were instructed to taper or discontinue opioid usage prior to undergoing surgery. All other aspects of preoperative care were similar.

This is mentioned in the manuscript on page 5 lines 131-133.

It reads, “Thorough medication reconciliation is performed and patients who are actively consuming opiates are advised and instructed to taper or discontinue its usage prior to undergoing surgery.”

Additionally, we have added the limitation of the lack of duration of preoperative opioid consumption to our manuscript.

This can be seen on page 13, lines 310-312.

It reads, “We did not quantify both opioid and non-opioid oral analgesic use such as meloxicam and aspirin according to oral morphine equivalent or collect duration of preoperative opioid use.”

Comment 1.7: No data on non-opioid usage in the opioid dependent group. Increased dosage non opioid attempted?

Response 1.7: Thank you for your feedback. We wanted to focus specifically on preoperative opioid users to help guide prescribing patterns for these patients. Our future work aims to establish cohorts based on opioid consumption; however, the present study was meant to provide impetus for further investigation in this group of patients. Although we do agree that more granular data is needed.

50.2% of the patients did not consume opioids after their procedure. This was highlighted in Table 4.

Table 4. Comparison of Mean Postop VAS Pain Score and Opioid Use (n=105)

	No Opioid Use (50.2%)	1 Opioid Pill (22.3%)	2+ Opioid Pills (27.5%)	*P-values
VAS Pain Score (SD)	3.48 (1.81)	4.30 (1.63)	5.32 (1.76)	<0.001

Comment 1.8: When were opioids added in the postoperative period? This information could be added for clarity and also a clear mention that there was no comparison with the non opioid group. Pain tolerance and other factors could be different across geriatric age group with various co morbidities.

Response 1.8: Our institution employs an opioid-sparing protocol for pain management using mostly non-opioid medications. Patient-controlled analgesia, as well as intravenous opioid administration, was strongly discouraged, except in rare situations of breakthrough pain when alternatives had been exhausted. We have added this to the manuscript.

This can be seen on page 6, lines 150-153.

It reads, “Postoperative pain management was accomplished using mostly non-narcotic medications. Patient-controlled analgesia, as well as intravenous opioid administration, was strongly discouraged, except in rare situations of breakthrough pain when alternatives had been exhausted.”

With regards to non-opioid patients, they were included in the study population as evidenced in table 4 in the above response. The confounders to pain tolerance are also mentioned in our limitation section.

The limitation section can be seen on page 12-14, lines 292-324

It reads, “This study is not without limitations. The retrospective nature of this study has the potential to introduce inherent bias. The study population was majority female and age 65 years or older which causes inherent selection bias. Both the opioid and pain surveys that were administered relied on self-reporting by the patients. Due to the nature of the self-reported survey, opioid dependence could be undetected in our study cohort. All patients in this study underwent THA via the direct anterior approach by a single surgeon, thus our results may not be generalizable to patients who undergo THA via other surgical approaches. Additionally, we excluded any patients who underwent revision of their primary implant or were hospitalized due to any postoperative complications. These patients may be the heaviest postoperative users of opioids due to a difficult and prolonged recovery resulting in higher pain intensity. Indeed, most patients included in the present study had a LOS of less than two days, and further analyses may benefit from addressing how lengthened in-patient

stays affect VAS and the subsequent prescription of opioids postoperatively. In addition, the pain threshold of each patient is different making the generalizability of our results relatively difficult. Although we accounted for all non-THA related pain indications, we could not quantify all possible pain events after surgery that could necessitate prescription opioid therapy. Theoretically, a patient could have obtained an opioid prescription after undergoing THA for an issue unrelated to their orthopedic procedure. Patients who have pre-existing psychiatric conditions, anxiety, and/or fear of pain may confound the data, as they are unlikely to show improvement in pain, regardless of pain score. We did not quantify both opioid and non-opioid oral analgesic use such as meloxicam and aspirin according to oral morphine equivalent or collect duration of preoperative opioid use. In addition, our analysis of PO opioid medication did not take into account IV opioids received perioperatively. This study only considered opioid intake; therefore, analgesics consumed by patients that may reduce the need for opioid intake could have possibly skewed the results. Furthermore, while VAS scores may be generalizable, an individual's immediate post-operative opioid consumption is dictated by subjective measures such as anaesthesia type could introduce confounding variables that are difficult to quantify [53]. Lastly, we did not account for patients who may have had unreported adverse effects (constipation, nausea, vomiting, hypotension, etc.) due to opioid consumption and stopped their intake during the postoperative periods evaluated in this study. Future investigations comparing multiple surgical approaches for THA and including patients from different regions of the country and various parts of the world would help further elucidate our findings. Despite these limitations, the results presented can aid surgeons' opioid prescribing patterns based on their patients' reported pain level following THA."

Comment 1.9: Line 225. opioid medications such as ibuprofen and acetaminophen to manage pain. Ibuprofen also has significant risks – cardiac, renal, gastritis. Other NSAIDs for short term – aceclofenac, etc

Response 1.9: We agree with your statement. NSAIDs present their own set of side effects. Contraindications for the use of NSAIDs should be assessed on an individualized basis based on prior medical history.

Comment 1.10: Please highlight opioid dependence could go undetected.

Response 1.10: Thank you for raising this point. We have added this concern to the manuscript.

This can be seen on page 12, lines 295-296

It reads, "Due to the nature of the self-reported survey, opioid dependence could be undetected in our study cohort."

Reviewer #2:

Comment 2.1: Firstly, logic relationship is not clear enough. There is no direct causal relationship between VAS scores fluctuations and opioid consumptions peri-operatively. The VAS scores fluctuations before and after surgery are normal physiological phenomenon. The pain is severe during two to three days post-operatively, because of acute surgical trauma.

And the pain will be relieved gradually as the healing process starts. As the pain intensity declined, opioid intake reduced, which is not difficult to understand. Therefore, I recommend that the title of the manuscript should be “The fluctuations of VAS scores and Opioid Consumption before and after Total Hip Arthroplasty”. Anyway, the knowledge gap of this manuscript exits, which is the time node of 15 days post-operatively, when the VAS score and opioid consumption decreased dramatically. That will be useful to guide opioid prescribing practices.

> **Response 2.1:** Thank you for your feedback. We have changed the title of the manuscript based on the recommendation.
>
> The title now reads, “The Fluctuation of Visual Analog Scale Pain Scores and Opioid Consumption Before and After Total Hip Arthroplasty”.

Comment 2.2: Secondly, various analgesics were administered, the author only used the number of opioid pills as the outcome. That is not rigorous. It would be better to take all the analgesics into consideration, convert analgesics into one kind of opioid equivalently, use the dose of the opioid as the outcome.

> **Response 2.2:** We appreciate your astute feedback and agree with the comments. We are working on a follow-up study which evaluates morphine milligram equivalents in a larger study cohort. The purpose of this study was to provide a general idea on the number of opioid pills patients were consuming and its relationship to their reported VAS pain scores. Due to the heterogeneity of opioid medications in this study it makes calculating MME difficult. However, we have mentioned this in our limitations.
>
> This can be seen on page 13, lines 310-312.
>
> It reads, “We did not quantify both opioid and non-opioid oral analgesic use such as meloxicam and aspirin according to oral morphine equivalent or collect duration of preoperative opioid use.”

Comment 2.3: Thirdly, this study is an observational study, and with no comparison group. As a cohort study, it would be better to have two groups or more with different exposure factors, only in this way can causal relationship be established. Strictly speaking, this is not a cohort study.

> **Response 2.3:** We agree with the feedback. We are working on a future study in which we established two cohorts based on opioid use to further establish a causal relationship between pain scores and opioid consumption.

Comment 2.4: Fourthly, the pain intensity several days after surgery fluctuates dramatically. Based on clinical experience, the pain is very severe one to two days after surgery, and gradually alleviated afterwards. The author set postoperative days 1-7 as a whole for analysis, this did not reflect huge internal changes within postoperative days 1-7. Better to divide postoperative days 1-7 further into postoperative days 1, postoperative days 2-3, postoperative days 4-7, and use opioid doses per-day as an outcome. That would have more reference value for clinicians.

Response 2.4: We agree with the feedback; however, given the number of patients in the present study, further division of the first 7 postoperative days would make the data too granular and statistically underpowered. For this reason we grouped the first week of the postoperative period since the pain levels are generally highest during this period.

Comment 2.5: Fifthly, apart from VAS score, some other outcome measures are recommended. Such as sleeping time, index of life quality and the like. These indexes also contribute to patient's recovery and satisfaction.

Response 2.5: Thank you for your feedback. We felt the addition of outcome variables was out of scope of the message of this manuscript. However, with more robust data, we plan on conducting future prospective studies evaluating sleep time and quality of life after THA. This study was done to provide impetus for future investigations on the topic.

Reviewer #3:

Comment 3.1: I am a little bit confused with the drafting scheme of the paper, and what you are looking for. Total hip arthroplasty is a major surgery (no doubt), but if you're looking to decrease opioid consumption, I have nothing against. Anyway, VAS (visual analogue scale) - which is already overconsumed as a measuring scale to the point of doubting its validity - will do little to decrease opioid consumption; if this is the desired outcome. You should instead propose other pain medications and compare efficacy in between groups.

Response 3.1: We appreciate your feedback. Although the VAS pain scale may be diluted due to its subjective nature it was the most feasible to collect. Our future work aims to establish cohorts based on opioid consumption; however, the present study was meant to provide impetus to establish and help guide opioid prescribing patterns. Although we do agree that more granular data is needed.

We have mentioned this in our conclusion on page 14, lines 334-336.

It reads, "However, without further research that considers other patient factors that influence pain severity, our understanding of the independent impact of pain on opioid consumption after THA remains uncertain."

Comment 3.2: You describe the anesthetic procedures; mentioning Propofol in the (pre)medication and sedation. THA was performed under spinal anesthesia? No doubt (recently, however...) that this can be the gold standard, and patients will suffer less from postoperative pain when compared with the general anesthesia group: Matsen Ko L, Chen AF. Spinal anesthesia: the new gold standard for total joint arthroplasty? Ann Transl Med. 2015 Jul;3(12):162. However, I still miss the point between VAS (?) and opioid consumption: decreasing this one might be an advantage of the form of anesthesia. As far as people still need pain killers after operation, please consider comparing different groups (different medications used; why not different forms of anesthesia - here again the discussion over the spinal or general one)

Response 3.2: We agree with the reviewer feedback as anaesthesia type plays a major role in postoperative pain management. We have added this to the limitations section and have cited the study mentioned by the reviewer.

This can be seen on page 13, lines 315-318.

It reads, “Furthermore, while VAS scores may be generalizable, an individual’s immediate post-operative opioid consumption is dictated by subjective measures such as anaesthesia type could introduce confounding variables that are difficult to quantify [53].”

53. Matsen Ko L, Chen AF (2015) Spinal anesthesia: the new gold standard for total joint arthroplasty? Ann Transl Med 3:162. https://doi.org/10.3978/j.issn.2305-5839.2015.06.12

Science Editor’s Comments:

Comment: The author's manuscript is well written, but is there a problem with the overall idea? For example, the author only uses opioids, so what about non-opioids.

Response: Thank you for your feedback. We wanted to focus specifically on preoperative opioid users to help guide prescribing patterns for these patients. As the opioid epidemic’s effect are still evident in the United States a lot of work is needed to help guide providers on the topic. Our future work aims to establish cohorts based on opioid consumption; however, the present study was meant to provide impetus for further investigation in this group of patients. Although we do agree that more granular data is needed.

Comment: In addition to the VAS score, some other outcome indicators are recommended. Such as sleep time, quality of life index, etc

Response: Thank you for your feedback. We felt the addition of outcome variables was out of scope of the message of this manuscript. However, with more robust data, we plan on conducting future prospective studies evaluating sleep time and quality of life after THA. This study was done to provide impetus for future investigations on the topic. Currently, we do not have this data available for us to add to this patient group.

Company Editor-In-Chief Comments:

Comment: Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: We appreciate you bringing this to our attention. All figures have been properly designated and organized in a PowerPoint format per the journal guidelines**.**

Comment: Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

(1) Requirements for Figures: Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file, and submit as "**72040-Figures.pptx**" on the system. The figures should be uploaded to the file destination of "Image File".

(2) Requirements for Tables: Please provide decomposable Tables (in which all components are movable and editable), organize them into a single Word file, and submit as "**72040-Tables.docx**" on the system. The tables should be uploaded to the file destination of "Table File".

> **Response:** All tables have been properly designated and organized in a single Word document per the journal guidelines. Thank you.

In addition to the above comments, all spelling and grammatical errors have been corrected.

We are grateful once again for your consideration. Thanks to the comments, the revised manuscript is significantly improved, and we hope that it will be acceptable for publication. We look forward to your positive response.

Sincerely,

The Authors