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Reviewer A

I would like to commend the author for their efforts to reduce opioid use following anterior lumbar interbody fusions. They present an intriguing MMPC protocol with potentially beneficial results. Below are few issues with this manuscript that should be addressed:

Comment 1: How were the patients selected to receive posterior hardware? The addition of posterior hardware would increase the patients postoperative pain significantly. This variable was never accounted for in the statistical analysis.

Reply 1: The patients all underwent single level ALIF as well as subsequent posterior fusion. We clarified this in the text by adding surgical procedure subsection in the Methods section as follows.

Changes in the text: Page 7, line 17- Page 8, line 14

Patients were placed in the supine position. The approach was transperitoneal for L5-S1 and retroperitoneal for the proximal levels. For the transperitoneal approach, a transverse incision was made between the umbilicus and the symphysis pubis. The exposed linea alba was vertically divided using monopolar diathermy. Peritoneum was bluntly perforated, and colon was retracted superiorly and laterally. The retroperitoneum was divided in the middle line, and the iliac arteries and veins are then retracted laterally, with the median sacral vessels double clipped and divided. The anterior disc space dissection is performed with a Kittner to avoid injury to the sympathetic nerves to reduce the risk of retrograde ejaculation.

Retroperitoneal approach was done using a left paramedian incision. The anterior rectus sheath was opened, and the rectus mobilized laterally. A retroperitoneal pocket was created bluntly to place a spinal Thompson retractor and blunt dissection carried out between the iliac vessels and psoas muscles.

Once the disc of interest was exposed, the disc was excised using a knife followed by Cobb elevator and endplate preparation tools. It was then dilated to accommodate a cage. The endplates were cleaned off all disc, and the posterior annulus was exposed. A cage was packed with an allograft and bone graft substitutes or extenders. It was impacted into the disc space with good fit and fixation. Patients were then positioned in the prone position and posterior fusion were performed in standard fashion.

Comment 2: It was stated that selected patients underwent single level fusions, but then in Table 1 there are 18% of the non-MMPC and 13% of the MMPC groups that received two level fusions. Once again, the addition of more surgery, outside of a single level

ALIF without posterior hardware, could potentially alter the amount of pain the patient experiences post operatively.

Reply 2: The patients all underwent single level ALIF. “Number of level fused” in Table 1 is for posterior instrumented fusion. The posterior fusion level is not statistically different between both groups as shown in the table. We clarified this in the Table 1.

Changes in the text: *Posterior fusion (Table 1 footnote)

Comment 3: What was the opioid status of the patient preoperatively? An opioid naive patient would require significantly less opioids to control their pain adequately. It doesn’t appear this was controlled for.

Reply 3: As Table 1 shows, preop opioid use (MME) is not different between the two groups.

Changes in the text: none

Comment 4: For the analysis of retrospective case series like this, univariate statistical analysis falls short because they are unable to account for the numerous confounding variables. For this study a multivariate regression would have been more appropriate.

Reply 4: The aim of the study is to compare in-hospital opioid consumption in patients undergoing ALIF using MMPC to those not on MMPC and the use of unpaired t-test is appropriate. Identifying factors associated with in-hospital opioid consumption is beyond the scope of this paper. In addition, the two groups are similar in terms of baseline characteristics.

Changes in the text: none

Comment 5: There is no sample size calculation presented in this manuscript. Given the number of potential variables that need to be accounted for, the sample size needed to successfully answer this question would likely be much higher than 108 patients included.

Reply 5: We added sample size calculation in the Method.

Changes in the text: Page 6, line 20- Page 7, line 1

The sample size calculation is based on the parameters $\alpha = 0.05$ (2-sided) and power: $1-\beta = 0.8$. With MMPC having a medium effect size of 0.5 on reducing postoperative opioid consumption the sample size was calculated to be 102.

Reviewer B

Comment 1: The discussion section briefly references other studies that have previously looked at postoperative opioid consumption, but should provide more interpretation of how their results fit in among these others. For example, how did the MMPC used in the current study differ from that used by others? Was there a significant difference in the protocol used by studies that found different results? This was essentially the primary outcome of the current study and deserves considerably more discussion.

Reply 1: We revised discussion as suggested.

MMPC was initially introduced in abdominal surgery and is currently used in orthopedic and spine procedures. Although some studies have shown that MMPC reduced opioid consumption (16, 25-27) other studies have not (28). A variety of agents are available for MMPC and have been studied to reduce postoperative opioid consumption. There are numerous reports detailing the efficacy of acetaminophen for postoperative pain management, showing reduced hospital stay, opioid consumption, and complication rate (29-31). Gabapentin also has been studied regarding its efficacy in the reduction of postoperative pain and opioid consumption (16, 32, 33). TAP block has been considered an effective analgesia for abdominal surgery (34, 35). These studies examined the efficacy of a single modality, with each medication having a significant benefit in reducing postoperative opioid consumption. Since our patients underwent ALIF and subsequent posterior fusion surgery, our regimen included a combination of oral agents and a TAP block. In our cohort and regimen, MMPC significantly decreased in-hospital opioid consumption (62%). Soffin et al. examined the efficacy of MMPC including pre-incisional TAP block, regularly scheduled non-opioid analgesics (gabapentin, acetaminophen, ketorolac) for ALIF and LLIF (36), which is similar to our study. They showed median MME was 57.5. The MMEs are much lower than those of our patients, which may be due to the difference in procedure. They evaluated patients undergoing ALIF/LLIF without posterior procedures whereas our patients all underwent posterior fusion. Also, their study did not have a control group, and sample size was small (n=32). In our study, we compared opioid consumption between MMPC and non-MMPC (control group) with relatively large size. Our finding provided a concrete evidence in the efficacy of MMPC regimen including TAP block. (Paragraph 1 in Discussion)

Comment 2: As mentioned above, a number of previous studies have examined the use of multimodal analgesia for lumbar fusion surgeries. The authors need to make a thorough case for the novelty and value of their study in the context of these previous works. In short: what new information or insight does this study provide? Specifically, the authors should address how their study is distinct from Soffin et al's 2019 study (<https://doi.org/10.1007/s00586-019-06081-3>) which also examined a multimodal analgesia protocol for ALIF.

Reply 2: Soffin et al. conducted a similar study. We referred to their results in the Discussion section.

Changes in the text: Page 10, line 22- Page 11, line 8

Soffin et al. examined the efficacy of MMPC including pre-incisional TAP block, regularly scheduled non-opioid analgesics (gabapentin, acetaminophen, ketorolac) for ALIF and LLIF (36), which is similar to our study. They showed median MME was 57.5. The MMEs are much lower than those of our patients, which may be due to the difference in procedure. They evaluated patients undergoing ALIF/LLIF without posterior procedures whereas our patients all underwent posterior fusion. Also, their study did not have a control group, and sample size was small (n=32). In our study, we compared opioid consumption between MMPC and non-MMPC (control group) with relatively large size. Our finding provided a concrete evidence in the efficacy of MMPC

regimen including TAP block. (Paragraph 1 in Discussion)

Comment 3: The statistical analysis section should include a more detailed description of the methods used, which variables were specifically compared and how this was done. The reasons a given statistical test was used should be outlined to give the reader a perspective on the data set and how this may impact the reported results.

Reply 3: We revised as suggested in the Method section.

Changes in the text:

Page 9, lines 2-3: Difference between groups were analyzed using Fisher exact test for categorical variables or Mann-Whitney U test for continuous variables.

Page 7, lines 11-14: We compared baseline demographic, surgical data (EBL, surgical time, level fused, and primary vs revision), and preoperative opioid use as all of these could affect postoperative pain and opioid use. We defined revision surgery as history of spine surgery involving the same level, such as pseudoarthrosis and adjacent segment disease.

Comment 4: An explanation of the ALIF procedure itself, its complications and the reason why certain MMPC medications were chosen and if this was influenced by the type of surgery (ALIF) should be included.

Reply 4: We clarified this in the text by adding surgical procedure subsection in the Methods section as follows. Also, the reason why certain MMPC medications were chosen was added in the regimen subsection in the Methods section.

Changes in the text: Page 7, line 17- Page 8, line 14

Patients were placed in the supine position. The approach was transperitoneal for L5-S1 and retroperitoneal for the proximal levels. For the transperitoneal approach, a transverse incision was made between the umbilicus and the symphysis pubis. The exposed linea alba was vertically divided using monopolar diathermy. Peritoneum was bluntly perforated, and colon was retracted superiorly and laterally. The retroperitoneum was divided in the middle line, and the iliac arteries and veins are then retracted laterally, with the median sacral vessels double clipped and divided. The anterior disc space dissection is performed with a Kittner to avoid injury to the sympathetic nerves to reduce the risk of retrograde ejaculation.

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Page 8, lines 19-22: This regimen is based the fact that patients undergoing combined

procedure typically complain of abdominal pain as well as back pain and spasm postoperatively. Therefore, we included TAP block in addition to standard pain medications such as cyclobenzaprine, gabapentin, and acetaminophen. (Regimen subsection in Methods)

Comments 5: A more thorough explanation of the “rate of revision surgery” should be provided; this variable is introduced with very little background and it’s unclear whether this is referring to the percentage of procedures in the current study that were revisions or the percentage of patients that went on to require revisions later. The authors should explain this variable and how this can potentially affect outcomes.

Reply 5: We defined revision surgery as prior fusion surgery, such as pseudoarthrosis and adjacent segment disease

Changes in the text: Page 7, lines 13-14

We defined revision surgery as prior fusion surgery, such as pseudoarthrosis and adjacent segment disease.

Comment 6: The conclusion following the discussion section is very similar to the abstract’s conclusion. It would be good to further expand upon the results, reiterate the importance of the study, and summarize the implications for clinical practice.

Reply 6: We revised as follows.

Changes in the text: Page 3, lines 16-19

We examined the effect of an MMPC regimen in patients undergoing single-level ALIF for degenerative conditions. Our regimen significantly reduced in-hospital opioid consumption. An MMPC may reduce risk of opioid dependence as a greater amount of initial opioid exposure is associated with greater risks of long-term use.

Comment 7: A clearer explanation and introduction of MME and other methods of collecting and quantifying clinical data should be included.

Reply 7: Method was revised as suggested.

Changes in the text: Page 7, lines 4-10

Postoperative opioids were administered based on doctors’ PRN order and pain severity. Total daily opioid consumption was calculated and converted to the morphine milligram equivalents (MMEs) as follows.

$$\text{MMEs} = \text{total dose (mg)} \times \text{MME conversion factor}$$

MME conversion factor is 0.1 for tramadol, 1 for morphine and hydrocodone, 1.5 for oxycodone, and 4 for hydromorphone. Then, MMEs of used opioids were added.