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Reviewer A

In this retrospective cohort study, the authors examined whether ACDF patients who received intra-operative liposomal bupivacaine LB (LB cohort) exhibited decreased post-operative opioid use and lengths of hospital stays (LOS) compared to ACDF patients who did not receive intra-operative LB (controls). Initial cohort included fifty-nine patients who received intra-operative LB and twenty-three who did not.

Findings: The LB cohort did not require fewer opioids on post-operative day (POD) 0, POD1, POD2, or throughout the hospital course after normalizing by LOS (total per LOS).

The number of cervical vertebrae involved in surgery, but not LB use, predicted opioid consumption on POD0, POD1, and total per LOS. For every vertebral level involved, 242 additional morphine milligram equivalents (MME) were consumed on POD0, 266 additional MME were utilized on POD1, and 130 additional MME were consumed in total per LOS.

The authors concluded that ACDF patients who received intra-operative LB did not require fewer post-operative opioids or exhibit a decreased LOS compared to controls.

Major concerns

What was the reason behind using liposomal bupivacaine in certain patients vs. others since the whole cohort of the patients was operated on by a single surgeon.

Reply: We agree that an explanation is warranted and thus have modified the text as follows: "The decision to utilize LB in some patients versus others was purely temporal. Beginning in 2018, the surgeon decided to incorporate the use of LB into his clinical practice; therefore, all ACDF patients in 2018 and 2019 received LB while those in 2016 and 2017 did not." (Page 4, lines 89-92).

While the authors are commended for controlling the bassline factors between the 2 groups, an important factor to be taken into account is that the pain threshold for the patients undergoing spine surgery can vary significantly. Including pre- and post-operative pain scores can minimize this confounding.

Reply: We concur that including preoperative and postoperative pain scores (e.g., VAS) would be beneficial; however, these data were not consistently captured in the electronic medical record both prior to and immediately following surgery. We have it featured as a limitation: "Another limitation from the involves the lack of post-operative pain scores, e.g., visual analog scale (VAS), due to their absence in the EMR. Future studies should include VAS scores which would further elucidate the possible role of

LB during ACDF." (Page 12, lines 277-278).

A study investigating this topic on post-operative opioid use should also include the previous history of opioid use of each patient. Patients who have received/ used opioids before might have developed dose-tolerance.
Reply: We completely agree. We re-reviewed every study patient's medical record for evidence of opioid usage prior to their surgery. While we were unable to quantify amounts in MME, we obtained documentation whether a patient had consumed any opioids prior to surgery or were entirely opioid naïve. No significant difference was found between groups. We have added this detail (and the accompanying statistics) to Table 2.

The number of patients included in the final analysis in each groups is small. The authors stated that "Due to the lack of literature 154 that both mimics the design of the present study and provides the data necessary for power 155 analysis, sample size was estimated to be between 15 to 69 patients per cohort (assuming α = 156 0.05 and β = 0.2) using the post-operative opioid consumption and lengths of stays reported in a previous retrospective cohort study.21"
Can the authors describe the power analysis in more details? I suspect that a larger sample size is required to detect the difference between the 2 cohorts.
Reply: Yes, the present study is unfortunately underpowered. While there are several methods to estimate sample size, we performed the calculation using means (16.0 and 24.1) and pooled standard deviation (16.8) derived from Kim *et al*. (2016). By convention, $\alpha = 0.05$ and $\beta = 0.2$, so we utilized those values. The calculation yielded a suggested sample size of n = 68 per cohort which was changed in the text (Page 7, line 154). This suggests that the present investigation is indeed underpowered; however, it should be noted that the study participants in Kim *et al*. were patients who underwent transforaminal lumbar interbody fusion, not ACDF. We were unable to find a previously published study that precisely replicated our methodology, and therefore, the calculation serves as only an estimate.

In Table 2, last row: How is the P value was calculated to be 1.000 while there is a difference in the "Readmission within 30 days" between the 2 groups? P value can have the value of 1.000 only if the outcome is "identical" in both groups.
Reply: Thank you for pointing this out. You are correct—the p-values for both "ICU Transfer" ($p = 0.651$) and "Readmission Within 30 Days" ($p = 0.910$) have been fixed.

Reviewer B

A simple but satisfying study was performed by the authors. A simple research question was investigated with correct interpretation of the data. I would only suggest to leave

the numbers out of the textual parts. It is unpleasant to read with all the numbers. I have no further suggestions and encourage publication of your article.

Reply: Thank you for the kind review. We have removed all numerical/statistical output from the text that can be found in the tables. We kept a few numbers that are not featured in the tables since the text is the only location that this information can be found. We hope that the reviewer finds this acceptable.

Reviewer C

It would help if you can explain the rationale why injecting LA just in the s/c will make any diffrencence in post op pain or opioid use ?

Reply: Thank you for your comment. You are correct that, because LB is infiltrated into the subcutaneous tissue of the wound, it primarily ameliorates surgical site (i.e., incisional) pain. There are several chief etiologies of discomfort following ACDF, including incisional pain, neck pain secondary to the bony work and insertion of the cage, and neurologic symptoms. Pain contributions from these three sources vary from individual to individual. While LB will not address the latter two, the goal is by decreasing the pain contribution from the incision, a patient's overall opioid needs will decrease.

Also please comment on what is main reason of pain after such surgery. What is the source of pain : bone, muscle , disc ?

Reply: Please see the reply to your question above.