Peer review file

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Reviewer A

Comment 1: Thoracotomy technique

Reply 1: We employ an almost exclusively serratus anterior- and latissimus dorsi-sparing postero-lateral thoracotomy approach.

Changes in the text: via *serratus anerior- and latissimus dorsi-sparing postero-lateral thoracotomy* approach (Page 8, Line 169-170)

Comment 2: Management of Thoracic Epidural

Reply 2: The thoracic epidural analgesia infusion was usually initiated at the end of the operation in order to avoid intraoperative hypotension. The infusates were either local anesthetic agent such as bupivacaine alone or in combination with either fentanyl or hydromorphone, at the discretion of individual acute pain anesthesiologist who placed the epidural catheter at the beginning of the case. The epidural narcotics were included in the MME calculation.

Changes in the text: "… managed by the regional anesthesia team. *Epidural analgesia typically was initiated at the end of the case with baseline infusion of bupivacaine with or without an opioid such as fentanyl or hydromorphone. The initial settings of epidural analgesia were routinely a basal infusion rate titrated to achieve optimal pain control and to avoid hypotension and a patient-control administration (PCA) option. (Page 9, Lines 195-199)*

Comment 3: Post-Discharge opioid usage

Reply 3: We would like to direct the reviewer to Table 4. In this table, the total post-discharge MME and the % of patients requiring schedule II and schedule IV at initial fill as well as at refill are summarized. A distinct pattern of opioid prescription at discharges emerges: almost all ERATS patients (98%) were given prescription for tramadol while nearly none (4%) in the pre-ERATS group were given tramadol. This reflects our ERATS-practice changing goals in which we aimed for opioid II-sparing oral analgesia. Fewer patients (50%) in the ERATS group required opioid II refills versus 100% of the pre-ERATS group. This reflects better education, less over-prescription, more attention to other types of discomfort such as neuralgia that frequently is describe by patient as "pain," and better management of pain with non-opioid and reliance on schedule IV). We did see that there was *LESS* refill in the pre-ERATS group (17%) versus 40% of the pre-ERATS group. The lower MME is a result of less opioids required. Tramadol is frequently prescribed as 50 mg q6hrs for 3 (60 MME); oxycodone is frequently

prescribed as 5 mg Q6hrs for 3 days (90 MME). We do agree that tramadol, even though classified as schedule II by the USA FDA, it is still a form of opioid and cautious use is of paramount importance. We do not indiscriminately prescribe it for protracted period of time. We believe that the lower MME is mainly attributable to using less potent opioids (tramadol instead of oxycodone) and to a lesser degree, fewer pills and fewer refills of both schedule II and schedule IV opioids.

Changes in text: none

Comment 4: Typographic error line 368 (This study has obvious many limitations)

Reply 4: Thank you for pointing out this omission, we do appreciate and apologize.

Change in the text: Correction: *This study has many limitations.* (Page 19, Line 438)

Reviewer B

Comment 1: Even though the progress in pain control was clear after implementation of ERATS concepts and the reduction of schedule II opioid use is important, the pain scores of control group (pre-ERATS) were unacceptably high. I have to say that these results came from inadequate use of epidural anesthesia in control group.

Reply 1: We do agree with the observation that the pain levels were high in the pre-ERATS epidural group. At our institution, a dedicated anesthesiologist manages thoracic epidurals within the acute pain service. Not all epidural catheters function perfectly; some provided perfect analgesia, some provided partial analgesia, some did not work well at all. With the two latter scenarios, intravenous and oral schedule II opioids were used as supplemental forms of pain control. Having an epidural, whether well-functioning or not, provided a "false sense of security" that postoperative pain is "managed" by mid-level care providers. Thoracic surgical team (attending staff and resident trainees) relied on the anesthesia team to manage and trouble-shoot epidural analgesia. Another aspect of thoracic epidural analgesia is orthotopic hypotension, which required a higher level of care in the intensive care unit with vasopressors. As mentioned in our discussion, an alternative postoperative pain management strategy such as those provided by ERATS, without reliance on thoracic epidural analgesia, mitigates this shortcoming. More importantly, as mentioned in our discussion, the surgical team takes the responsibility for patient's real-time pain management. Our data recapitulate previously reported results from other groups implementing similar ERATS protocols.

Changes in text: None.

Reviewer C

Comment 1: Add a paragraph to provide context to abstract.

Reply 1: We have added to the Background part of the abstract as suggested

Change in the text: Enhanced recovery after surgery protocol incorporates evidence-based practices of pre-, intra- and post-operative cares to achieve the most optimal surgical outcomes, safe on-time discharge, and surgical cost efficiency. Such protocols have been adapted for specialty-specific needs and implemented by a variety of surgical disciplines including general thoracic surgery. (Page 4, lines 65-69)

Comment 2: Avoid using colloquial description of data, such as "very comparable cohorts."

Reply 2: We agree with this suggestion.

Change in the text: *between the two cohorts. (Page 4, line 84)*

Comment 3: Do not provide explanations in the abstract.

Reply 3: Thank you for the suggestion, we will remove the explanation.

Change in the text: *Deleted: because tramadol (schedule IV opioid) was prescribed following protocol implementation. (Page 5, Line 88)*

Comment 4: A 2-fold increase can be 1% to 2% or 40% to 80%

Reply 4: We described the reduction of opioid use in terms of the magnitude of change. A 2-fold reduction means a reduction to half of the control. Similarly 5-fold and 10-fold reduction of post-discharge opioid use is present in the ERATS group.

To avoid any concerns, we will list the numbers for readers to see.

Change to the text: Results section of the abstract.

A significant reduction of in-hospital potent schedule II opioid use was noted following ERATS implementation (average MME: 10.5 [3.5-16.5] (ERATS) versus 19.5 [12.6-36.0] (pre-ERATS), median {IQR], p<0.0001). More importantly, a drastic reduction of total and schedule II opioid dispensed at discharge was noted in the ERATS group (total MME: 150 [100.0-330.0] versus 800.0 [450.0-975.0], p<0.0001and schedule II MME: 90.0 [0-242.2] versus 800.0 [450.0-975.0], p<0.0001; ERATS versus pre-ERATS respectively). (Page 4-5, Line 85-92)

Comment 5: Elimination of thoracic epidural and use of tramadol is more of a clinical decision than an observed phenomenon post-implementation of ERATS program.

Reply 5: We do agree with this comment. ***In our institution, it was a conscious decision and a part of our ERATS implementation to eliminate thoracic epidurals and to reduce reliance on schedule II opioids***. This is ***not*** a cause and effect. However, it does not diminish the significance of what we observed: decreased pain, decreased opioid use, and no more nuances with thoracic epidural analgesia. Since the submission of this manuscript, we continue to observe the salutary effects of ERATS for our thoracotomy patients.

Change in the text: none

Comment 6: Wordy sentence line 86-90.

Reply 6: We reviewed carefully lines 81 to 100, the entire first paragraph of the introduction. We cannot identify what the reviewer is referring to. The only possible run-on sentence is this sentence: " while the components of ERATS ….., plays an essential role".

Change in the text: none

Comment 7: The reviewer referred to the use of reference number 11.

Reply 7. We do agree with the reviewer. However, this paper by Kreb et al from University of Virginia is significant enough to deserve to be cited.

Change in the text: none

Comment 8: Were patients undergoing robotic surgery included?

Reply 8: As stated in the title and in the methods section on page 7, *only* patients undergoing elective same-day admit thoracotomy procedures were included in this study. Therefore, we absolutely did not include robotic patients in this study. There is no concern for giant bias.

Change in the text: none

Comment 9: Only 27 patients in the pre-ERARTS groups had reliable data post-discharge MME data; this is a source of limitation.

Reply: We did recognize this fact. We did address this as a limitation in the second to last paragraph in which we discussed limitations of this study. Would this bias be for or against our observation? There is no reason to believe that the first half of the pre-ERATS group would need significantly less post-discharge MME to eliminate the observed difference.

Change to the text: none

Comment 10: avoid using colloquial description " quite comparable."

Reply 10: Thank you, we will comply with this suggestion.

Change in the text: Line 241 … characteristics of the two cohorts **were similar.** (Page 13, Line 284)

Comment 11: Recommendation to mention in the text the incidence of complications.

Rely 11: Thank you, we will comply with this recommendation.

Change in the text: second paragraph of the result section. First sentence … over all incidence of *complications (pre-ERATS: 37.2% versus ERATS: 25.5) between the two groups. We also made an addition to the Table 2 by adding the percentage of no complications of 62.8% for pre-ERATS and 74.5% for the ERATS***.** (Page 13, Line 296-297)

Comment 12: In multivariate analysis, the analysis for LOS as continuous and categorical data (> 7 days) is redundant. Keep the first one. Describe in the methods sections how did you define your model and what variables to include.

Reply 12: Thank you for your observation. We understand how looking at different measures of the same outcome could be viewed as redundant. We removed the logistic model assessment of the length of stay and expanded the description of our non-parametric model for length of stay as a continuous outcome.

Change in the text: Line"Univariable and multivariable linear, low-rank splines and logistic regression models were used to measure primary end-point outcomes. *The low-rank regression splines were specified in the framework of generalized additive models and fitted to penalized likelihood estimation (GAMPL in SAS) to produce flexible nonparametric regressions and asses the relationship of ERATS on the total length of stay. The 95% confidence intervals were reported in the parametric models. In multivariable models, we adjusted for age, sex, and BMI. (Page 12, Lines 268-273).*

Change in table and text (method): Prolonged LOS >7 days was removed from table 3 and text starting from page 14, line 208.

Comment 13: Please include intervals in the multivariate analysis tables

Reply 13: Thank you for the very valuable statistical suggestions. We added 95% CI when it was appropriate for parametric models used with normally distributed data (complications and LOS). Additionally, we would like to bring the reviewer's attention to the fact that we used multivariable, not multivariate analysis. It is possible that these are commonly used as interchangeable terms, but in fact, they are very different. Please consider the folliwng reference. Hidalgo B, Goodman M. Multivariate or multivariable regression? Am J Public Health. 2013;103(1):39-40. doi:10.2105/AJPH.2012.300897

Change in Table 3: 95% CI levels were added.

Comment 14: In the discussion, include possible alternatives explanations for the association between variables, such as the progressive importance given by medical community to opioids prescription and over-use, other reasons to shorten LOS, possible changes in perception of patients' pain, etc.

Reply 14: Thank you for highlighting this important aspect. In order not to deviate greatly from the scope of the current manuscript, we have noted the role of the health care system in being detrimental to the opioid pandemic.

Change in discussion*: To put this in a broader context, in a study by Chen, et al. of 18,343 patients, 46% were prescribed opioids at hospital discharge. There was a trend of 36% over prescription in the thoracic service, demonstrating the concerning role of health care professionals in contributing to the opioid pandemic, particular since the surplus medication following surgery is the primary source of prescription diversion. Thus, it is imperative to understand how we can limit opioid use within the healthcare system while providing optimal outcomes. (Page 18/19, lines 430-436)*