

Peer Review File

Article information: <http://dx.doi.org/10.21037/apm-21-766>

Reviewer A

Comment 1: While there have been a number of ketamine for post-op pain studies in different surgical populations, it was certainly worth taking a look at the effect on VATS patients, since it has become the most common approach to intrathoracic surgery and it does have a very high incidence of long term post-op pain syndromes. I'm not surprised at your results after having reviewed many studies where multimodal anesthesia including regional anesthesia and ketamine were used. It appears that ketamine adds little to post-op analgesia when a regional anesthetic is used. I also think your discussion was right on point regarding your results and shortfalls of this study. There are many doses and routes of administration of ketamine and nothing has been standardized. The sample size was small but I think your results are valid. It would have been interesting to have given patients a bolus of ketamine before starting the infusion because had plasma levels of ketamine been measured, I believe they would have been very low, particularly in the shorter cases (which were the less complicated surgeries for the most part). In addition, continuing ketamine infusions post-op at a low dose may have been useful in determining whether the need for narcotic analgesic was lessened. So while I think this study is very limited, it provides some new information and can guide future studies that are more involved: using a larger sample size, bolus doses of ketamine prior to starting infusions and post-op infusions perhaps at different doses for 48-72 hours- longer than the TPVB would have lasted.

Reply 1: Thank you for your considerations reviewing this manuscript. We agree to all of the points that were mentioned and accepted that they are the limitations of our study. We have also added your comments about future studies into the discussion part.

Changes in the text: "Further studies using larger sample size with lobectomy

procedures and continuous postoperative infusion for longer period are required to conclude the effects of ketamine on postoperative pain and pulmonary function.” (See Page 16, Line 13-15)

Reviewer B

General comment

Comment 1: Authors found that ketamine infusion may benefit a little in patients undergoing VATS. They also performed paravertebral block. The additional effect by ketamine did not seem effective.

Reply 1: Thank you for reviewing this manuscript and give us useful comments. We have responded to each comment point by point.

Specific comments

Methods

Comment 2: Dexmedetomidine infusion - I think that dexmedetomidine infusion affect the pain score and opioid requirements in this investigation. Please mention this in the discussion part.

Reply 2: Thank you for your suggestion. We agree that dexmedetomidine infusion could have an effect on postoperative pain and opioid consumption. We have also included this point into the discussion.

Changes in the text: *“Moreover, all patients in our study were sedated with dexmedetomidine during TPVB. Dexmedetomidine is an alpha-2 adrenergic receptor agonist, which provides dose-dependent analgesia (48). Dexmedetomidine has been demonstrated as an effective adjuvant to opioids for postoperative pain after thoracic surgery (48-50). Although the doses administered in our study was low, intraoperative dexmedetomidine may have also decreased the postoperative pain, especially upon arrival at the PACU (51).” (See Page 14, Line24-25 and Page 15, Line 1-4)*

Comment 3: Ketamine dose - Authors should describe how the ketamine infusion dose was decided. Adequate reference may be necessary.

Reply 3: We have modified the discussion part in order to explain the reasons why the ketamine infusion dose was chosen, as well as their references, as you suggested.

Changes in the text: “Since the dose and mode of delivery varied greatly among the literatures, we have chosen the practical dose suggested by Gorlin et al., (0.1-0.3 mg/kg followed by 0.1-0.2 mg/kg/hour infusion) (37). Recent studies have demonstrated that single bolus dose of ketamine may be inefficient for postoperative pain (39,40) and continuous intraoperative infusion was recommended (41). We also determined to specifically evaluate whether the intraoperative ‘infusion only’ regimen would yield the same effect when subanesthetic ketamine was combined with multilevel TPVB. Our hypothesis was that VATS resulted in less pain and tissue injury compared to open thoracotomy, therefore, we aimed to examine the effect of low-dose intraoperative ketamine rather than postoperative ketamine infusion. As a result, intraoperative infusion of 0.2 mg/kg/hour of ketamine was adopted.” (See Page 13, Line 4-14)

Discussion

Comment 4: PFR - There was a difference of PFR between groups. I think that this is important result. Please discuss this point.

Reply 4: Thank you for this suggestion and we think the result is significant as well, therefore, we have added a paragraph to discuss this finding as suggested.

Changes in the text: “In our study, the patients in ketamine group had significantly less percent reduction of the 24-hour postoperative PFR from baseline compared to the control group. During early postoperative period, substantial impairment in the pulmonary function is frequently observed as a result of reduced lung volume, decreased lung compliance, respiratory muscles and diaphragmatic dysfunction after lung resection (55,56). Low dose ketamine may have a protective effect on postoperative pulmonary function by stimulating respiration and offset opioid-induced respiratory depression (57-59). As an NMDA receptor antagonist, ketamine can attenuate central sensitization and results in lower opioid requirement in order to achieve the same analgesia, thus, reducing the undesirable side effects (60). Ketamine also has bronchodilator effect and its sympathomimetic activity is known to relieve airways spasm (61). Mitchelet et al. demonstrated better postoperative pulmonary

function after lobectomy in patients receiving ketamine with morphine (1:1) via PCA when compared to PCA morphine alone on the first postoperative day (62). In their study, significant lower morphine consumption was demonstrated only after 36th hour following surgery and no difference in pain scores were reported during the first day. However, in our study, the benefit of ketamine on the postoperative PFR changes may have been confounded by the disproportion of the procedure types (lobectomy versus wedge resection). The higher proportion of patients underwent wedge resection in the ketamine group can result in less complicated surgery, shorter duration of anesthesia, and a more substantial lung volume preserved. Furthermore, ketamine infusion was not extended through the postoperative period and neither reduction in pain nor opioid requirement could be demonstrated. Further studies using larger sample size with lobectomy procedures and continuous postoperative infusion for longer period are required to conclude the effects of ketamine on postoperative pain and pulmonary function.” (See Page 15 Line 18-25 and Page 16 Line 1-15)

Figure 3

Comment 5: Correct the p-value (0.009).

Reply 5: Thank you for your correction. We have changed the p-value in Figure 3 as suggested.

Changes in the text: ($p = 0.090$) (See Figure 3)