Peer review file
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Reviewer A

Doi et al. described a randomized controlled trial on treatment fo postoperative neuropathic pain after thoracic surgery in their manuscript "Mirogabalin treatment of postoperative neuropathic pain after thoracic surgery: study protocol for a multi center, randomized, open-label, parallel-group intervention trial." There are couple of issues that needs to be addressed to improve the study

Comment 1: Please describe if the patients are going to be randomized based on the approach of pulmonary resection (i.e. thoracotomy, VATS, robot assisted).

Reply 1: *We will collect data related to the pulmonary resection approach; however, these data will not be used as a stratification factor. We consider that VAS at baseline is a more important factor than the surgical approach used; therefore, VAS will be used as a stratification factor.*

Changes in the text: Although the manuscript text already stated that data on surgical characteristics will be collected, we have made some minor changes for clarity (page 13, lines 253–254).

Comment 2: Please describe if the patients are going to be randomized based on extent of pulmonary resection (i.e. wedge, segment, lobe, pneumonectomy).

Reply 2: *Although we plan to collect data on the extent of pulmonary resection, these data will not be used as stratification factors.*

Changes in the text: We have clarified in the Methods subsection, "Randomization and interventions", that t*he stratification factors used in this study will be a VAS score of <60 mm vs. ≥60 mm at baseline and study site (page 12, lines 226–228).*

Comment 3: Please describe if the study is going to exclude those patients who are on chronic opioid pain medication, chronic NSAID medication or chronic pain medication.

Reply 3*: Patients using opioid medications and other prohibited concomitant medications will be excluded; however, patients will be allowed to use NSAIDS if needed.*

Changes in the text: We have not made any changes in the text as this is clearly stated on page 11, lines 217–222 and page 12, lines 229–232.

Comment 4: Please clarify the criteria that a patient may be deemed inappropriate by the investigator

Reply 4*: The exclusion criterion states "…any patient deemed inappropriate as a subject of the study by the investigator…", which refers to patients who may not be able to comply with the study requirements. For example, this could apply to patients who cannot attend the study visits at the hospital.*

Changes in the text: We made a minor change for clarity to the text on page 11, line 213.

Comment 5: What happens to patients if they enroll and the pathology shows that they will benefit from platinum doublet adjuvant chemotherapy?

Reply 5*: The exclusion criterion states "receipt of neoadjuvant chemotherapy within 2 months before surgery (to exclude chemotherapy-related neuropathic pain)." The reason for excluding these patients is that they may experience peripheral neuropathic pain secondary to platinum doublet adjuvant chemotherapy. If any patients were to require adjuvant chemotherapy with cisplatin, such patients would be discontinued from the study.*

Changes in the text: We have clarified at the end of the exclusion criteria paragraph that if any patient were to require adjuvant chemotherapy with cisplatin, such patients would be discontinued from the study (page 11, lines 214–216).

Comment 6: Why exclude the use of tramadol? Why not the use of hydrocodone and other narcotics?

Reply 6*: Conventionally, weak opioids, rather than potent opioids, are used for the regular management of neuropathic pain at the participating sites. As we state in the manuscript, the concomitant use of several therapies, including pregabalin and gabapentin, duloxetine, tramadol, platinum chemotherapy agents, probenecid and cimetidine, lorazepam, postoperative nerve block, surgical procedures, or any other intervention (e.g., electrical stimulation, radiation therapy) will be prohibited during the study as these therapies may affect the evaluation of treatment effectiveness.*
However, we will still collect data on the drugs used for pain control. Additionally, we will evaluate patients who used potent opioids and decide whether to include these patients in the statistical analysis.

Changes in the text: We believe this exclusion criterion is clear and thus have made no changes to the manuscript regarding this point.

Comment 7: The treatment arms are Tylenol + NSAID vs Tylenol +NSAID + microgabalin, what if in both arms the pain is not adequately controlled by the given medication. Are patients allowed to take additional medication? If so, which medication? If not, are patients suppose to suffer after surgery with inadequate pain control?

Reply 7*: If the given medication does not adequately control pain, the investigator will consider prescribing medications that are not listed among the prohibited concomitant medications. For patients in the conventional treatment group, the investigator will consider increasing the dose of concomitant drugs to treat pain if needed to achieve pain control. Nevertheless, patient pain control will prevail as per ethical standards. If patients require prohibited concomitant medications to manage their pain, they will be discontinued from the study.*

Changes in the text: We have added this explanation on page 12, lines 232–238).

Comment 8: What if patient develops side effect of microgabalin? How is the study going to handle that group of patients?

Reply 8: *In the case of adverse event onset, the investigator will assess each case individually and consider whether the patient should continue treatment at a maintained or reduced dose or if the patient should be discontinued from the study.*

Changes in the text: We have added this explanation on page 13, lines 261–264.

Comment 9: Please describe criteria for randomization. Are you using age, type of surgery, extent of pulmonary resection, gender, etc?

Reply 9: *Study site and visual analog scale scores for pain intensity at baseline with cutoffs of <60 mm vs. ≥60 mm will be used for patient stratification.*

Changes in the text: We have revised the text in the subsection "Randomization and interventions" to clarify the only two stratification factors we plan to use for analysis (page 12, lines 226–228).

Reviewer B

This is a well thought out, very interesting subject of postoperative neuropathic pain after lung surgery using mirogabalin. I have a few questions, comments below

Comment 1: It was unclear, if ALL lung resections are going to be included, it would be interested to differentiate in one group the VATS group, another group the Robotic group, and finally the OPEN arm, is there a plan to distinguish this?

Reply 1: *We will collect data on the approach used for pulmonary resection and we are considering conducting a subgroup analysis according to the type of approach. The details of the subgroup analysis will be included in the statistical analysis plan.*

Changes in the text: As details of the subgroup analysis according to the type of approach will be mentioned in the statistical analysis plan, we have not made any changes to the main text.

Comment 2: If you exclude all patients with epidurals and intercostal nerve blockade, will you accrue enough patients? The majority of patients do get some type of perioperative pain modality, what does your institutions currently do for VATS vs. open? Meaning is there going to be a selection biased for picking the "right" operative pain groups?

Reply 2: *Regardless of surgery type, extradural anesthesia and NSAIDs and/or acetaminophen are often used. If it is not possible to use extradural anesthesia, an intercostal nerve block is performed. Patients with a history of surgery involving extradural anesthesia or intercostal nerve block are not excluded from this study. Pain control is conducted based on each study site's decision. Our study aims to target patients who have moderate or severe postsurgical neuropathic pain regardless of the pain control approach used during surgery; therefore, there is no impact on study feasibility or patient selection. It is not ethical to limit pain control before study registration.*

Changes in the text: We have not made changes to the text in this regard

Comment 3: The designation of neuropathic pain is a little new to me and vague. Did the authors consider defining neuropathic pain more on a subjective questionnaire as opposed to physical pin prick sensation? I think it would be helpful if there is a questionnaire asking specifics about their pain and that may actually be more accurate then doing the pin prick sensation tests

Reply 3: *Neuropathic pain will be evaluated using a neuropathic pain diagnostic algorithm for subjective symptoms that includes a questionnaire and a pin-prick sensation test as an objective assessment of symptoms as per the grading system developed by the International Association for the Study of Pain Special Interest Group on Neuropathic Pain. Since it is not*

easy to diagnose postsurgical neuropathic pain, we standardized the procedure for multiple study sites based on expert opinion and the cited recommendations.

Changes in the text: We have added the above clarification to the "Study details" section (page 10, lines 192–196).

Comment 4: The POWER to the study seemed lower than I expected. With more than 10 institutions participating, do you think you can reach closer to 300 patients? Also the limitation may be in enrollment, b/c you won't have any of these patients with perioperative nerve blockade, PcA, or epidural, correct?

Reply 4*: As we have mentioned in the manuscript text, we have estimated the number of patients needed to ensure a power of 90% to detect the mean changes in VAS after 8 weeks of treatment with mirogabalin. The calculations yielded 126 patients in total. Considering dropouts, we plan to accrue 150 patients, 75 patients per group. These power calculations were based on previously reported results of pregabalin treatment for postthoracotomy pain (citation #26: Yoshimura N, et al. Effect of postoperative administration of pregabalin for post-thoracotomy pain: A randomized study. J Cardiothorac Vasc Anesth 2015;29:1567-72). Furthermore, we plan to include four additional medical institutions.*

Changes to the text: We have revised the planned number of participating medical institutions to 14 in the text (page 9, line 163) and Table S1.

Comment 5: This is a necessary study for sure, but one of the negatives, is that Neurontin although not FDA approved for postop neuralgia pain, works quite nicely and I imagine is much cheaper, have the authors thought about WHY mirogabalin versus just using what we always use in Neurontin?

Reply 5: *We cannot use gabapentin as this drug has not been approved for the indication of neuropathic pain in Japan.*

Changes in the text: We have not made any changes to the text in this regard.

Comment 6: What makes mirogabalin better than Neurontin? less toxic? more efficacious? Have authors thought about comparing Neurontin to mirogabalin? Is mirogabalin superior to all other gabapentinoids in preliminary studies?

Reply 6: *As there are no reports of studies directly comparing mirogabalin and gabapentin or pregabalin, which drug is more efficacious or less toxic remains unknown.*

Changes in the text: We have not made changes to the text in this regard.

Comment 7: Who will be conducting the follow up? nurses, surgeons, research associates?

What do you expect the response rate will be on the questionnaires and how do you plan to follow these patients and at what intervals?

Reply 7: *The follow-up will be conducted by the investigator or clinical research coordinators via interview during the study visits. In addition, investigators or clinical research coordinators will contact patients via telephone calls to encourage attendance to study visits, with the goal of ensuring high response rates during the study.*

Changes in the text: We have not made changes to the text in this regard.

Comment 8: I couldn't tell if there was a question on the survey whether they ask if the patient takes the mirogabalin and NEVER discontinues it for those 8 weeks, or if they stop taking it after one week, I assume you would exclude them from the study.

Reply 8: *Patients who discontinue mirogabalin within 8 weeks from the start of treatment will be discontinued from the study..*

Changes in the text: This information was added to the revised manuscript text (page 13, lines 249–250).

Comment 9: I worry about accrual in that case, b/c there may be a significant number of patients who don't tolerate the medications as in Neurontin, or take varying doses so not a uniform standardized population, and the effects of gabapentinoids sometimes take weeks and thus patients cease taking their meds when they don't see a dramatic improvement, this should be discussed as a possible limitation and how the authors will work around these things.

Reply 9: *We agree with the concern raised by the Reviewer. We will add this to the limitation paragraph when we report the results.*

Changes in the text: We have not made any changes to the text in this regard.

Reviewer C

In this manuscript, the authors outlined a multicenter, open-label, parallel-group interventional to address the role of microgabalin, a novel gabapentinoid to treat post-thoracic surgery neurogenic pain. This is a very timely study because, as stated by the authors, this condition is very prevalent after thoracic procedure's (either minimally invasive thoracoscopic procedures - VATS or robotic or open thoracotomy) and is the source of discomfort and frustration for patients with significant negative impact on quality of life and daily function.

The rationale for the study is well described and relevant to clinical practice. The design is sound as is the statistical consideration. the inclusion and exclusion criteria are well described.

Comment 1: do the authors equate CPSP with post thoracic surgery neurogenic pain? I would like to see a more explicit definition of "neurogenic pain".

Reply 1: *As we have stated in the Introduction, chronic postsurgical pain (CPSP) is defined as pain that continues for ≥3 months following the surgical procedure, while neuropathic pain is defined as pain resulting directly from a lesion or disease affecting the somatosensory system either at the peripheral or central level. Roughly, a third of patients who develop CPSP after thoracic surgery present a neuropathic pain component, which has been associated with more marked physical dysfunction and worse quality of life than CPSP without the neuropathic component.*

Changes in the text: We have now added the definition of neuropathic pain as stated by the NeuPSIG guidelines to the Introduction and added content explaining that CPSP can be accompanied by a neuropathic component (page 6, lines 93–98 and References #10 and #11).

Comment 2: Moreover, many practicing thoracic surgeons start gabapentin in the immediate preoperative period and continue immediately in the postoperative period. This study seems to start microgabalin after removal of chest tube.

Reply 2*: As a chest tube insertion has deleterious effects on intercostal nerve function (citation # 14: Miyazaki T, et al. Chest tube insertion is one important factor leading to intercostal nerve impairment in thoracic surgery. Gen Thorac Cardiovasc Surg 2014;62:58-63), patients who undergo lung resection will receive a clinical dose of mirogabalin in addition to conventional therapy for 8 weeks if they are diagnosed with neuropathic pain after the removal of the chest drain. This will be applied regardless of the type of surgical resection.*

Changes in the text: We revised the text to clarify why mirogabalin treatment is started after removing the chest drain and not before (page 8, lines 146–151).

Comment 3: A correctly stated by the authors, optimal management of acute pain in the immediate postoperative period is associated with less chronic postsurgical pain postoperative pain (CPSP); duration and severity. How do the authors control for the impact of the acute pain managements by different groups in this multi-institution study on the management of neurogenic pain?

Reply 3: *Although the management before the drain removal is not stipulated, the best approach will be selected for each group, upholding the inclusion and exclusion criteria (e.g., excluding patients receiving treatment for neuropathic pain before undergoing surgery). Nevertheless, many institutions offer conventional treatments to these patients.*

Changes in the text: We do not consider that any changes are needed in the text.