Peer Review File

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Reviewer A

Comment 1: The authors have not registered with PROSPERO.

Reply 1: Thank you for your valuable advice. We previously registered a meta-analysis with PROSPERO about a comparison between multimodal analgesia and single-use opioids. Based on the recommendation of clinicians, we selected this topic. However, after a careful search and screening, we found that the quantity and quality of literature did not meet our requirements.

Opioids have been used as the first-line medication for pain relief. However, their effects in treating neuropathic cancer pain are controversial. According to the World Health Organization three-step analgesic ladder, the combination of anticonvulsant drugs and opioids is recommended. In consideration of the first-line role of gabapentin in relieving neuropathic pain in non-cancer patients, we urgently wanted to investigate its effectiveness to combat neuropathic cancer pain.

Therefore, we changed research topic of meta-analysis and focused on the analgesic efficacy of gabapentin and opioids. The relevant modification of PROSPERO has been submitted and we are still waiting for approval.

Comment 2: It is unclear when and for how long the literature was reviewed.

Reply 2: Thank you for your carefulness. The search of literature was completed in January 2020 and literature published after January 2020 was not reviewed. The studies were screened from January 2020 through April 2020. The relevant content has been added in the revised manuscript.

Changes in the text: Page 7, Line 100; Page 7, Line 105-106.

Comment 3: There is no review formula.

Reply 3: Thank you for the valuable advice. Review formula is that two authors independently extracted data and made data extraction sheets. Data sheets were compared and judged by the third review author. This review formula has been added to the manuscript.

Changes in the text: Page 8-9, Line 136-138.

Comment 4: There is no ROB rating listed.

Reply 4: Thank you for the valuable suggestion. ROB rating provided by Cochrane is more suitable for random clinical trials (1,2). Considering that the selected literature in this meta-analysis consisted of case-control studies and cohort studies, we used Newcastle Ottawa Scale (NOS) to objectively assess the quality of literature. NOS was designed to evaluate case-control studies and cohort studies with a total score of 9 points (3). The related content has been added in the revised manuscript.

Changes in the text: Page 8, Line 135-136; Page 24, Line 401; Table 1.

References
1. Higgins J P T, Altman D G, Gøtzsche P C, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials[J]. Bmj, 2011, 343: d5928.
2. Higgins J, Green S. Cochrane Handbook for systematic reviews of interventions version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org.
3. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm.

Comment 5: What is "pain score"?
Reply 5: Thank you for your carefulness. Pain score indicates pain intensity which is also used by other researchers (1,2). To increase the readability of this article, we redefine pain score as pain intensity. Pain intensity is evaluated by Visual Analogue Scale (VAS), Numeric Rating Scale (NRS) or numerical scales designed by the investigators to assess pain sensation of patients. The related parts have been revised according to the advice.
Changes in the text: Page 8, Line 119-124; Page 8, Line 126-128; Page 9 Line 140-146; Page 10, Line 169;

References
1. Kelly A M. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain[J]. Emergency Medicine Journal, 2001, 18(3): 205-207.
2. Breivik H, Borchgrevink P C, Allen S M, et al. Assessment of pain[J]. BJA: British Journal of Anaesthesia, 2008, 101(1): 17-24.

Comment 6: The numbers in the table do not match the text.
Reply 6: Thanks very much for your carefulness. We have carefully checked the numbers in the table and main text. The mistake has been corrected in the revised manuscript.
Changes in the text: Page 8, Line 131-135; Page 24, Line 401; Table 1.

Reviewer B
Comment 1: The authors should clarify whether their definition of "Neuropathic cancer pain" is "Neuropathic pain in cancer patients" or "Cancer-related neuropathic pain". From reviewer's viewpoint, the authors may explore the former which includes both "cancer-related neuropathic pain" and "non-cancer-related neuropathic pain in cancer patients" and should write that their result included both of them. If the authors were going to investigate only the latter, they may redefine it and search again. The authors defined the subjects with neuropathic pain as having burning pain, shooting (electric-shock-like) pain, or allodynia, but did these definitions fill the criteria of diagnosis with neuropathic pain? The authors should select the literatures which use the

validated screening tool for neuropathic pain because of ascertainment bias. If there have been little literatures which use screening tool, the authors should report it.

Reply 1: Thank you for your constructive suggestion! According to your valuable suggestion, we defined neuropathic cancer pain in our article as neuropathic pain in cancer patients. Meanwhile, neuropathic pain in cancer patients included cancer-related neuropathic pain and non-cancer-related neuropathic pain. Gabapentin has been widely used to treat neuropathic pain in non-cancer patients, such as diabetes and herpes zoster patients (1,2). The majority of selected literature did not detailly provide the concurrent disease in our included patients. Therefore, in terms of non-cancer-related neuropathic pain, we mainly focused on neuropathic pain induced by anti-cancer treatment. However, owing to limited available data, we cannot perform subgroup analysis based on two types of neuropathic pain. Furthermore, we have searched the databases again, and no additional literature meets our criterion. Taken together, the studies whose patients suffered from cancer-related neuropathic pain or anti-cancer treatment-related neuropathic pain were taken into consideration.

After generalization of abundant literature, we define neuropathic cancer pain as follows: Neuropathic cancer pain was defined as pain on account of nerve injury or compression by a tumor lesion or anticancer treatment (i.e., chemotherapy, surgery, or radiation therapy), including at least one of the following symptoms or signs referred to the pain area: continuous sensory disturbance (e.g., dysesthesia, hyperesthesia, allodynia, burning pain), or incidental pain (e.g., shooting, lancinating pain) (3-5). The medical history, examination, and available imaging studies (e.g., computed tomography, magnetic resonance, or others) for each patient were also used to assist investigators to diagnose the type of pain (6). Some studies have identified concordance between the clinician diagnosis and pain assessment screening tool outcomes for Neuropathic Symptoms and Signs (LANSS), Douleur Neuropathique en 4 (DN4) or painDETECT (PDQ) in patients with cancer pain (7). Unfortunately, the majority of included studies did not mention the screening tools for the aid of pain diagnosis. Further research is needed to standardize and improve clinical assessment in patients with cancer pain (8). The related criteria of diagnosis has been added into the revised manuscript.

Changes in the text: Page 5, Line 54-59; Page7, Line109-113; Page 11, Line 194-196; Page 15, Line 259-270.

References

1. Backonja M, Beydoun A, Edwards K R, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial[J]. Jama, 1998, 280(21): 1831-1836.
2. Bader M S. Herpes zoster: diagnostic, therapeutic, and preventive approaches[J]. Postgraduate medicine, 2013, 125(5): 78-91.
3. Grond S, Radbruch L, Meuser T, et al. Assessment and treatment of neuropathic cancer pain following WHO guidelines[J]. Pain, 1999, 79(1): 15-20.
4. Martin, Lee Ann, and Neil A. Hagen. "Neuropathic pain in cancer patients: mechanisms, syndromes, and clinical controversies." Journal of pain and symptom

management 14.2 (1997): 99-117.
5. Vadalouca A, Raptis E, Moka E, et al. Pharmacological treatment of neuropathic cancer pain: a comprehensive review of the current literature[J]. Pain Practice, 2012, 12(3): 219-251.
6. La Cesa S, Tamburin S, Tugnoli V, et al. How to diagnose neuropathic pain? The contribution from clinical examination, pain questionnaires and diagnostic tests[J]. Neurological Sciences, 2015, 36(12): 2169-2175.
7. Mulvey M R, Boland E G, Bouhassira D, et al. Neuropathic pain in cancer: systematic review, performance of screening tools and analysis of symptom profiles[J]. BJA: British Journal of Anaesthesia, 2017, 119(4): 765-774.
8. Fallon M T. Neuropathic pain in cancer[J]. British journal of anaesthesia, 2013, 111(1): 105-111.

Comment 2: The authors included the records which permit to use other analgesic adjuvants such as steroids, antidepressants, anxiolytics, and muscle relaxants previously. These analgesic adjuvants were effective for neuropathic pain in cancer patients, weren't they? These drugs may cause of confounders.

Reply 2: Thank you for the valuable advice. To the best of our knowledge, there have been few studies that have previously reported definitive interactions of gabapentin with analgesic adjuvants, especially in the context of treating neuropathic cancer pain. First, for non-steroidal anti-inflammatory drugs, a combination of ibuprofen with gabapentin has been shown to achieve an increased efficacy in controlling post-injury pain (1). Moreover, the use of a combination of diclofenac with gabapentin has been shown to be more efficacious and safer than that of monotherapy in treatment of neuropathic pain in rats (2). Few studies were found about gabapentin combining with other non-steroidal anti-inflammatory drugs, including aspirin, acetaminophen, indomethacin.Second, for steroidal anti-inflammatory drugs, dexamethasone combining with gabapentin has been shown to relieve pain following tonsil surgery in children, but there has been no report on the efficacy of such a combination in relieving neuropathic cancer pain (3). Few studies were found about gabapentin combining with other steroidal anti-inflammatory drugs. However, several studies have suggested favorable effects of pain relief of gabapentin compared with those of steroids, including hydrocortisone and aldosterone (4).

In terms of the antidepressant drugs, the majority of the research works have focused on comparing gabapentin with other agents in the treatment of pain, pruritus and hot flashes, such as mirtazapine, venlafaxine (5-7). However, few researchers investigated the interaction of different antidepressant drugs with gabapentin, including paroxetine, fluoxetine and amfebutamone. Furthermore, a large proportion of anxiolytics also have effects on muscle relaxation, such as diazepam, carisoprodol, hydroxyzine. Similarly, we only found the related reference about the efficiency comparison of gabapentin with other anxiolytics or muscle relaxants. Taken together, the mechanisms and efficacies of a combination of gabapentin with other non-opioid analgesic drugs require further investigation, especially in the context of treating neuropathic cancer pain.

Furthermore, neuropathic pain in enrolled patients was not completely controlled with

opioids analgesics and other analgesic adjuvants. Although some of the selected studies permitted the usage of previous medication, the dose remained unchanged throughout the investigations. Based on the included study's design, the patients in three studies used other analgesic adjuvants such as steroids, antidepressants, anxiolytics, or muscle relaxants previously (8-10). Thus, we conducted a two-sample Kolmogorov-Smirnov test based on the mean difference of pain intensity in the above three studies compared with that of the other studies. The p-value of this analysis was 0.89, indicating a negligible influence of previous medication on pain relief. Despite a potential synergistic effect of gabapentin with other adjuvants, gabapentin likely played a dominant role in providing relief from neuropathic cancer pain.

The influence of other analgesic adjuvants on the therapeutic efficiency of gabapentin has been added in the section of Discussion.

Changes in the text: Page 7, Line 113-117; Page 13-15, Line 220-254.

References

1. Yoon M H, Yaksh T L. Evaluation of interaction between gabapentin and ibuprofen on the formalin test in rats[J]. Anesthesiology: The Journal of the American Society of Anesthesiologists, 1999, 91(4): 1006-1006.
2. Ibrahim M A, Abdelzaher W Y, Rofaeil R R, et al. Efficacy and safety of combined low doses of either diclofenac or celecoxib with gabapentin versus their single high dose in treatment of neuropathic pain in rats[J]. Biomedicine & Pharmacotherapy, 2018, 100: 267-274.
3. Amin S M, Amr Y M. Comparison between preemptive gabapentin and paracetamol for pain control after adenotonsillectomy in children[J]. Anesthesia, Essays and Researches, 2011, 5(2): 167.
4. Ghadami N, Barzanji A, Nasseri K, et al. Effect of gabapentin in comparison with hydrocortisone on postlaparoscopic cholecystectomy pain control[J]. Journal of family medicine and primary care, 2019, 8(2): 652.
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randomized controlled trial from the Gabapentin Cancer Pain Study Group[J]. Journal of clinical oncology, 2004, 22(14): 2909-2917.

Comment 3: In Results, the authors discussed the assessments and interpretations of their findings, but these should do in Discussions. Furthermore, in Discussion at line 185 to 200, the authors presented the background of this analysis which should be presented in Introduction. So, the authors should redesign their report. The values should be described to be consistent, such as the decimal point.

Reply 3: Thank you for your constructive suggestion and carefulness. The background of this analysis has been presented in the section of Introduction. The assessments and interpretations of our finds have been moved to Discussions. Our manuscript has been carefully revised and redesigned according to the comments.

Changes in the text: Page 5, Line 67-86; Page 13, Line 211-219; Page 12, Line 204.