The efficacy of gabapentin combined with opioids for neuropathic cancer pain: a meta-analysis

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Background: More than 30% of cancer patients experience neuropathic pain. Opioids, as standard pain-relief agents, cannot achieve satisfactory outcomes to treat neuropathic cancer pain due to drug resistance and side effects. Meanwhile, gabapentin, a third-generation anticonvulsant drug, has great potential in providing relief for neuropathic cancer pain. However, there is currently no sufficient evidence to support the efficacy of a combination of gabapentin and opioids in ameliorating neuropathic cancer pain. Hence, the aim of the present study was to explore the analgesic efficacy of gabapentin combined with opioids in treating neuropathic cancer pain.

Methods: PubMed, EMBASE, and Web of Science (Web of Knowledge) were searched for randomized controlled trials and prospective studies via the following keywords: "gabapentin", "opioid", "cancer", and "neuropathic pain". We used a scale of 0–10 (0 denoting no pain and 10 denoting the worst pain imaginable) to estimate pain intensity and utilized Review Manager 5.3 and Stata12 to analyze data.

Results: Seven studies meeting our criterion were selected from 110 records that were primarily searched. The mean difference of pooled pain intensity and the 95% confidence interval (CI) was –1.75 (–2.44, –1.07) (P value <0.00001; treatment group versus control group or time to outcome assessment versus baseline). The pain intensity of cancer patients after a combined treatment of gabapentin and opioids was significantly lower than that of patients receiving opioids alone.

Conclusions: Our meta-analysis showed that gabapentin combined with opioids effectively alleviated neuropathic cancer pain compared with that of opioids alone.

Keywords: Cancer pain; neuralgia; gabapentin; analgesics, opioid

Introduction

Neuropathic cancer pain is defined as pain resulting from nerve injury or compression by tumor infiltration 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) (1-3). Currently, opioid analgesics are regarded as the first-line drugs to alleviate pain intensity. However, opioids are unable to achieve satisfactory efficacies in relieving neuropathic cancer pain due to drug tolerance and adverse effects. Based on the World Health Organization three-step analgesic ladder, anticonvulsant drugs are suggested to be adjuvants to opioids for enhancing analgesic effects and/

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or reducing the side effects of opioids. Unfortunately, the efficacies of combinations of anticonvulsants and opioids in treating neuropathic cancer pain have not been sufficiently validated.

Gabapentin is an anticonvulsant drug that has been applied in the treatment of painful diabetic neuropathy, postherpetic neuralgia, and other types of neuropathic pain (4-7). At present, the acknowledged mechanism of alleviating neuropathic pain from gabapentin is associated with its functions in binding to α-2-δ subunits of calcium receptors located in the spinal cord and inhibiting the release of excitatory neurotransmitters (8-11). Meanwhile, the α-2-δ subunits of voltage-gated Ca^{2+} channels (VGCCs) play a prominent role in the onset of neuropathic pain (12). Furthermore, by inhibiting N-methyl-D-aspartate-receptor-induced excitotoxicity, gabapentin can also exert partial protective effects against glutamate-induced neuronal injury (13). It has been demonstrated that a combination of gabapentin and opioids significantly inhibits evoked dorsal-horn neuronal responses and relieves pain intensity, while administration of the drug alone lacks such efficacy (14). In terms of drug interactions, some studies have suggested that opioids are able to increase the absorption of gabapentin by reducing intestinal motility, which may partly explain the enhanced analgesic effects of a combination of gabapentin and opioids (15). However, the detailed mechanisms underlying interactions between opioids and gabapentin require further elucidation. Furthermore, the minimal adverse effects of gabapentin have promoted its wide clinical application, which is also an attractive characteristic for its use as an adjunctive analgesic with opioids (16,17).

Some researchers have reported a favorable combination of gabapentin with opioids in terms of relieving neuropathic cancer pain (18). However, other studies have suggested that the efficacy of this combination is not significant (16). Therefore, the current evidence of gabapentin as an adjuvant analgesic to opioids in alleviating neuropathic cancer pain is insufficient. Thus, it is of great importance and necessity to explore the efficacy of gabapentin combined with opioids in treating neuropathic cancer pain. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tcr-20-2692).

Methods

Search strategy

PubMed, EMBASE, and Web of Science were searched

for applicable studies according to the "PICOS" search principle. The search terms were "gabapentin", "opioid", "cancer", and "neuropathic pain", while "clinical trial" acted as the filter criterion. This literature search was completed in January 2020.

Criteria for screening studies

Types of studies and interventions
Randomized clinical trials and prospective studies were included in this meta-analysis, the contents of which were associated with the analgesic evaluation of gabapentin combined with opioids. Case reports, case series, observational studies, meta-analysis, and reviews were excluded. The studies were screened from January 2020 through April 2020.

Types of patients
The patients included in our present meta-analysis were over 18 years old and were confirmed as cancer patients with neuropathic pain. Patients diagnosed with neuropathic pain had one of the following symptoms or signs: burning pain, shooting (electric-shock-like) pain, or allodynia (19). The medical history, results of examinations and available imaging studies (e.g., computed tomography, magnetic resonance imaging) for each patient were also used to assist investigators to diagnose the type of pain (20). Some of the investigated patients who have previously used other non-opioid analgesic drugs—such as nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, antidepressants, anxiolytics, or muscle relaxants—were permitted to be included in the corresponding study if they had a constant therapeutic schedule. All included patients with neuropathic cancer pain took opioids for analgesia by default.

Types of outcomes
The primary outcome in this meta-analysis was pain intensity evaluated by the Visual Analogue Scale (VAS), Numeric Rating Scale (NRS), or numerical scales designed by the experimental team to assess pain intensity of patients (21). All the different pain intensity was converted to a range of 0–10, with 0 corresponding to "no pain" and 10 corresponding to "the worst possible pain".

Data extraction

We first concentrated on data regarding pain intensity at baseline and at the end of each study. The mean pain intensity, standard error, and changes in pain intensity were

extracted directly or calculated indirectly. Additionally, the doses of gabapentin and opioids, the duration of the study, and the number of participants, as well as the descriptions of the study methods and results, were also recorded. Of note, if a study was categorized as a randomized controlled trial, the number of patients was calculated as the sum of the numbers of patients in the control group and experimental group. If a study was a prospective controlled study, patient number was defined with the minimum value representing the number of patients that completed the study. The quality of each study was accessed by the Newcastle-Ottawa Scale (NOS) (22). The review procedure consisted of two authors independently extracting data and generating data-extraction sheets. Data sheets were then compared and judged by a third review author.

Statistical analysis

We used Review Manager 5.3 software to pool the mean change of pain intensity, as well as its standard error, across studies. If a study was categorized as a randomized controlled trial, the difference in pain intensity between the control group and experimental group was used to evaluate the analgesic efficacy. If a study was a prospective controlled study, the pain intensity at baseline was compared with that at the end point of the observational window. All data regarding pain intensity was converted into a range from 0 to 10. Due to the same evaluation criterion, we chose the mean difference mode in Review Manager 5.3 software.

I^2 was used to determine the degree of heterogeneity in our meta-analysis. If the heterogeneity was over 50%, the random-effects mode was selected, and the causes for high heterogeneity were explored by subgroup analysis. Otherwise, the fixed-effects mode was chosen. Stata12 software was used to analyze publication bias via a funnel plot, Begg's test, and Egger's test. A P value less than 0.05 was considered statistically significant.

Results

Literature search and description of studies

We primarily searched 110 records through PubMed, EMBASE, and Web of Science using keywords described in our Methods. After using EndNote X7 Software to remove duplicates, 29 records were removed, after which 81 records remained. Among the remaining records, 71 records did not meet our criteria after detailed screening. Thus, 10 studies

were preliminarily selected for further analysis. However, there were two studies from which we could not extract pain intensity, and one study was excluded as the similar research was updated by the same investigators, the updated study was included in our present meta-analysis. Finally, after excluding these studies, our present meta-analysis contained seven studies with publication dates ranging from 2002 to 2013, including two randomized controlled trials and five prospective controlled studies (*Figure 1*). The details and quality of each study are shown in *Table 1*.

Primary outcomes

After summarizing the mean changes of pain intensity from seven studies, the mean difference and 95% confidence interval (CI) of neuropathic cancer pain relief were –1.75 (–2.44, –1.07) (*Figure 2*). The P value was less than 0.00001, which indicated that the combination of gabapentin and opioids significantly relieved neuropathic cancer pain compared with that of opioids alone. However, I^2 was 99%, showing the high heterogeneity in our present meta-analysis. Thus, subgroup analysis was performed to find the origins of this heterogeneity.

First, we classified the seven included studies based on study types. Two subgroups were established, namely randomized controlled studies and prospective controlled studies, and the I^2 values reached 85% and 98%, respectively. However, the heterogeneity of studies was still at a high level. Different designs and durations in the two randomized controlled studies might be the major influence on heterogeneity. Furthermore, I^2 of the prospective controlled studies did not decrease significantly. Thus, we performed a more detailed subgroup analysis based on the number of patients in each study. To some extent, the scale of a study can indirectly reflect its validity and statistical power. The studies containing more than 20 patients at the end of the study observation period were defined as large-scale studies, whereas studies containing less than 20 patients at the end of the study observation period were defined as small-scale studies. The small-scale-study subgroup had much lower heterogeneity (I^2=0%), and the large-scale-study subgroup had higher heterogeneity (I^2=64%) (*Figure 3*). The heterogeneity of the large-scale-study subgroup was still over 50%, which may have been due to the different designs of studies. However, the decrease in I^2 following this subgroup analysis was reduced compared to the 98% heterogeneity of all prospective controlled studies, indicating that the number
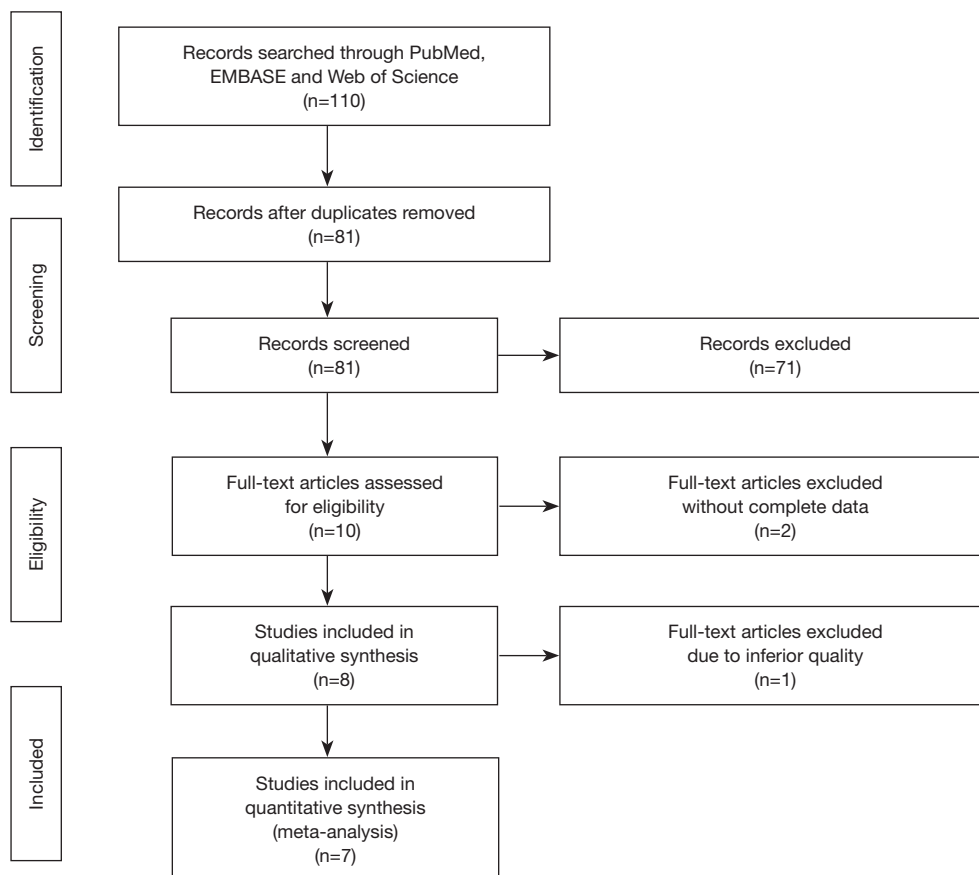
Figure 1 Flow of studies through selection process.

Table 1 Characteristics of included studies

First author	Year	Region	Design	Patient number	Gabapentin dose (mg/day)	Quality [0–9]
Arai (23)	2010	Japan	Single-center group	14	400	5
Banerjee (24)	2013	India	Open-label parallel group	40	600–1,800	7
Bosnjak (25)	2002	Serbia	Open-label single-center group	15	900–1,800	5
Caraceni (26)	2004	America	Double-blind parallel group	89	300–1,800	8
Mishra (27)	2012	America	Double-blind parallel group	60	900–1,800	8
Ross (3)	2005	United Kingdom	Open-label parallel group	41	400–1,200	6
Takahashi (16)	2010	Japan	Open-label single-center group	20	200–2,400	6

of patients was one of the main origins of heterogeneity. There was insufficient data for subgroup analysis based on the types of neuropathic pain induced by anti-cancer treatment or cancer progress, which may be another origin of heterogeneity. Overall, all the P values were less than 0.05 in the subgroups, suggesting that gabapentin may be

an effective adjuvant analgesic to opioids in the treatment of neuropathic cancer pain.

Publication bias

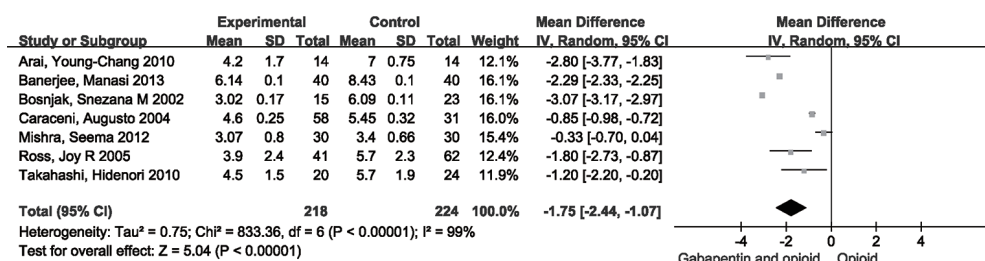Stata12 software was used to detect publication bias and

Figure 2 Forest plot of the combination of gabapentin and opioids to alleviate neuropathic cancer pain compared with opioids alone. CI, confidence interval.
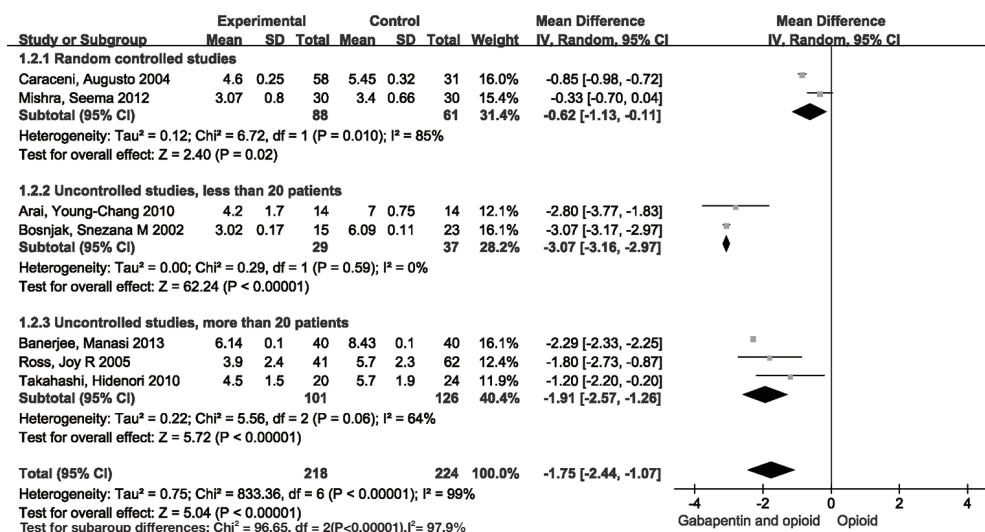

Figure 3 Subgroup analysis based on the number of patients. CI, confidence interval.

heterogeneity via Begg's test and Egger's test. The results of these tests demonstrated that our meta-analysis did not have significant publication bias, such that the P values of Begg's test and Egger's test (0.55 and 0.56) were each more than 0.05. For our funnel plot, some points were out of the limits of the 95% CI, which may have been attributed to high heterogeneity (*Figure 4*).

Discussion

Many studies have explored the efficacy of gabapentin combined with opioids in alleviating neuropathic non-cancer pain, but evidence to support the efficacy of this combination under cancer conditions has been lacking. Our present meta-analysis analyzed the analgesic efficacy of a combination of gabapentin and opioids for treating neuropathic cancer pain. Our results revealed that this

combination significantly alleviated neuropathic cancer pain, such that the mean difference in pain intensity was –1.75 (–2.44, –1.07). Furthermore, subgroup analysis based on the type of study and the number of patients also revealed that a combination of gabapentin and opioids was efficacious in alleviating neuropathic cancer pain. Additionally, our meta-analysis did not possess publication bias, further indicating the validity of our present findings.

However, influences from other non-opioid analgesic drugs—such as NSAIDs, steroids, antidepressants, anxiolytics, or muscle relaxants—may have existed in our present meta-analysis. 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 NSAIDs, a combination of ibuprofen with gabapentin has been shown to achieve an increased
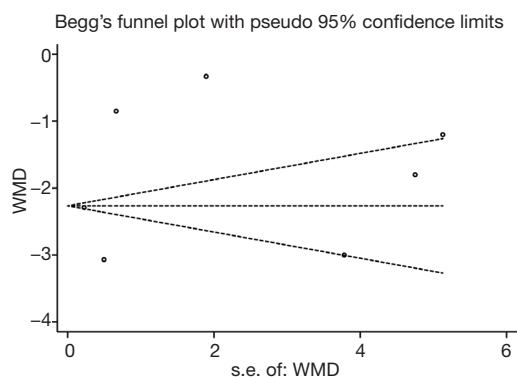
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Begg's funnel plot with pseudo 95% confidence limits

Figure 4 Begg's funnel plot of combination of gabapentin with opioids for neuropathic cancer pain treatment. WMD, weighted mean difference.

efficacy in controlling post-injury pain (28). Moreover, the use of a combination of diclofenac with gabapentin has been shown to be more efficacious and safer than that of monotherapy in treating neuropathic pain in rats (29). Second, for steroids, dexamethasone combined with gabapentin has been shown to relieve pain following tonsil surgery in children (30). In contrast, there has been no report on the efficacy of such a combination in relieving neuropathic cancer pain. However, several studies have suggested favorable effects of pain relief of gabapentin compared with those of steroids, including hydrocortisone and aldosterone (31). In terms of antidepressant drugs, the majority of the research works have focused on comparing gabapentin with other agents in the treatment of pain, pruritus or hot flashes, such as mirtazapine and venlafaxine (32-34). However, few researchers have investigated the interaction of antidepressant drugs or anxiolytics with gabapentin. 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.

In our present meta-analysis, neuropathic cancer pain in enrolled patients was not completely controlled with opioids or other analgesic adjuvants. Although some of the selected studies permitted usage of previous medication, the doses remained unchanged throughout the studies. Moreover, based on experimental designs of the included studies, patients in three studies previously used other analgesic adjuvants such as steroids, antidepressants, anxiolytics, or muscle relaxants (16,23,26). 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, our meta-analysis revealed that gabapentin likely played a dominant role in providing relief from neuropathic cancer pain.

There were also some limitations of our present meta-analysis. The number of collected samples was restricted. Additionally, the heterogeneity was high in this meta-analysis, which may have been caused by differences in experimental designs and the numbers of patients across studies, as indicated by our results of subgroup analysis. We also attempted to perform subgroup analysis based on the types of neuropathic pain induced by anti-cancer treatment or cancer progress, but the data was insufficient due to the small number of studies included in our meta-analysis. Thus, additional high-quality studies on this topic should be gathered to consolidate evidence for a preferable combination of gabapentin with opioids for treating neuropathic cancer pain. 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 (35). 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 assessments in patients with neuropathic cancer pain (36). Finally, multimodal analgesic efficacy deserves validation and application in the future.

Conclusions

This meta-analysis supports the enhanced analgesic efficacy of gabapentin combined with opioids, compared with that of opioids alone, in the treatment of neuropathic cancer pain. Hence, our findings may help to further guide clinical treatment of neuropathic cancer pain to improve the quality of life of cancer patients and to inspire researchers to further elucidate the mechanisms underlying the analgesic efficacy of gabapentin combined with opioids.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/tcr-20-2692

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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