Traditional herbal medicine for cancer pain: A systematic review and meta-analysis

Jung-Woo Lee a,1, Won Bock Lee a,1, Woojin Kim a, Byung-II Min a, b, HyangSook Lee c, Seung-Hun Cho d,∗

a Department of East-West Medicine, Graduate School, Kyung Hee University, Seoul 130-701, South Korea
b Department of Physiology, College of Medicine, Kyung Hee University, Seoul 130-701, South Korea
c Acupuncture and Meridian Science Research Center, College of Korean Medicine, Kyung Hee University, Seoul, South Korea
d Hospital of Korean Medicine, Kyung Hee University Medical Center, #1 Heogi-Dong, Dongdaemun-Gu, Seoul 130-701, South Korea
Available online 19 February 2015

KEYWORDS
Traditional herbal medicine; Cancer pain; Systematic review; Meta-analysis

Summary
Background: The effectiveness of traditional herbal medicine (THM) as an adjunctive therapy for cancer pain is unclear.
Objective: To assess the effectiveness of THM as an adjunctive therapy for cancer pain using randomized controlled trials (RCTs).
Methods: Five electronic databases, including those from the UK and China, were systematically searched for the period before September 2013. All RCTs involving the use of THM in combination with conventional cancer therapy for cancer pain were included.
Results: Twenty-four RCTs involving 4889 patients with cancer pain were systematically reviewed. Among them, nine studies of 952 patients reported a significant decrease in the number of patients with cancer pain in the treatment group. Four studies of 1696 patients reported a significant decrease in the degree of pain in the treatment group.
Conclusion: The results of these studies suggest that THM combined with conventional therapy is efficacious as an adjunctive therapy for patients with cancer pain. However, more research, including well-designed, rigorous, and larger clinical trials, are necessary to address these issues.
© 2015 Elsevier Ltd. All rights reserved.

∗ Corresponding author. Tel.: +81 02-958-9184; fax: +81 02 958 9183.
E-mail address: chosh@khmc.or.kr (S.-H. Cho).
1 Both authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ctim.2015.02.003
0965-2299/© 2015 Elsevier Ltd. All rights reserved.
Introduction

The International Association for the Study of Pain (IASP) is an international professional organization promoting research, education, and policies related to pain management. The often-quoted IASP definition of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” is derived from a 1964 definition by Harold Merskey. Although cancer encompasses multiple physical symptoms, the symptom of pain is often cited as most critical. Pain is one of the most common symptoms of cancer, and its intensity increases as the stage of cancer advances. A meta-analysis reported cancer pain in 64% of patients with metastatic disease, 59% of patients receiving antineoplastic therapy, and 33% of patients who had received curative cancer treatment. In Asia, traditional herbal medicine (THM) is frequently combined with Western approaches to treat cancer, usually in regimens that combine various traditional Asian herbs into one treatment strategy. Alternative medicine has been used to meet patient needs in lieu of or as an adjunct to conventional medicine. More than half of patients treated with traditional Asian herbs report effective relief of their symptoms, including pain. About 41–62% of patients with cancer use traditional Asian herbs as an alternative therapy. Clinical trials suggest that Asian THM may alleviate cancer pain with no adverse effects. However, a scientific evaluation of the effect of traditional Asian herbs on pain is lacking, and safety and toxicity are concerns.

The effectiveness of traditional Asian herbs is controversial among current practitioners of complementary alternative medicine. To date, no systemic review of the oral administration of traditional Asian herbs for cancer pain has been conducted. Thus, we conducted this systemic review to summarize and critically assess the evidence from randomized controlled trials (RCTs) showing that traditional Asian herbs are effective for reducing cancer pain. Indeed, several RCTs have reported that Asian THM is effective against cancer pain. Thus, we conducted this study as a follow-up to the systematic review conducted by Ling et al. to update research in this area.

Materials and methods

Search strategy

The following sources were searched from their inception to September 2013: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, the Allied and Complementary Medicine Database, and the Cumulative Index to Nursing and Allied Health Literature.

The reference lists of the articles were checked for further relevant publications, and experts were asked for information concerning any additional trials. An additional manual search for relevant journals, symposia, and conference proceedings was performed, and all identified publications were cross-referenced. When necessary, personal contact was made with the authors of the published studies to request additional data.


Study selection

We selected only articles on RCTs; quasi-randomized or non-randomized trials were excluded. We also excluded articles on animal or in vivo experiments. Studies in which THM was not orally administered were also excluded.
Studies using THM combined with conventional cancer therapy for the treatment group were included. We selected patients receiving conventional treatment such as radiotherapy or chemotherapy, placebo or microwave treatment, or no treatment as the control group.

Quality assessment

We (JWL and WBL) independently selected the endpoint data on the major outcome measures from each trial in studies evaluating THM. Details of this procedure have been explained elsewhere.7 We prefer continuous to binary data because most of the eligible trials reported continuous outcomes. We referenced the previous reviews8–9 in an open discussion. Summaries and quality assessments of all studies were completed by two reviewers following the detailed descriptions of these categories provided in the Cochrane Handbook for Systematic Reviews of Interventions.10 The following questions were assessed and answered by reviewers: (a) Was the allocation sequence adequately generated? (b) Was allocation adequately concealed? (c) Was knowledge of the allocated interventions adequately prevented during the study? (d) Were procedures to ensure blindness regarding outcome assessment adequate? (e) Were incomplete outcome data adequately addressed? (f) Were the results of the study free of selective outcome reporting? (g) Was the study apparently free of other problems that could put it at a risk for bias? This review used “Y,” “U,” and “N” to code responses to these questions; “yes” (Y) indicated a low risk of bias, “unclear” (U) indicated an uncertain risk of bias, and “no” (N) indicated a high risk of bias.

Statistical analysis

Study data were summarized using basic statistics and simple counts and means. The main purpose of the analyses was to quantify and compare the effects of THM combined with conventional cancer therapy (treatment group) with those of conventional cancer therapy alone (control group) on patients with cancer pain using only RCTs. The statistical analysis was performed using Review Manager 5.1 for Windows (The Nordic Cochrane Center). The odds ratios (ORs) for improvement on the visual analog scale (VAS) by number of persons, degree, and number of pain occurrences per day, with their 95% confidence intervals (CI), are presented individually for each trial. An OR <1 indicates a lower risk for the treatment than for the control group, and an OR >1 indicates a greater risk for the treatment than for the control group.

Results

Study description

An initial search identified 331 potentially relevant articles. Of these, only 2411–34 met our inclusion criteria and, thus, were subjected to our systematic review. Nine articles11,12,14,19,20,22,23,27,34 were in English, and 15 articles13,15–18,21,24–26,28–32 were in Chinese.

A total of 307 articles were initially excluded because they did not meet our inclusion criteria. Of these, 87 were excluded because they were duplicates of other articles or their titles clearly reflected their irrelevance. Additionally, 196 articles were excluded after an Abstract review. Ten additional articles were included after the review of references. Thirty-four additional articles were included after a more detailed evaluation of each article. Six studies were not RCTs, and 28 did not meet our inclusion criteria. As a result, 24 RCTs11–34 on THM orally administered for cancer pain were reviewed. The total number of subjects evaluated was 4889. Fig. 1 summarizes the search results based on a quality of reporting of meta-analyses flow diagram.35

Various cancers (breast, gastric, lung, colorectal, non-small cell lung, pancreatic, esophageal, stomach, cervical, uterine, kidney, leukemia, prostate, ENT, esophagus, bladder, submaxillary gland, bone, primary hepatic carcinoma, ovarian, gallbladder, renal, large intestine and middle/advanced stage of lung) were included in RCTs.

The intervention varied considerably across the trials. There are four kinds of comparisons. Herbs vs western therapy,16,21–24,26–28,31,33 herbs + western therapy vs herbs,13,15,17–20,22,23,27,34 herbs vs western therapy vs herbs + western therapy,12,14,25,29,30 and herbs vs none.11 All studies based the THM elections on Traditional Chinese Medicine theory. According to the Chinese medicine treatment method, strengthening Qi and eliminating pathogens often use botanicals, promoting blood circulation and removing stasis often use botanicals and animal products and promoting cytotoxic effect often use minerals. Various herbal medicines were used in the included RCTs; the botanical was commonly used, processed animal products were second commonly used and processed minerals were the less common. Key data are summarized in Table 1.

Traditional herbal medicine used for pain management

Three major kinds of traditional herbal medicine are usually used to control pain

1. Botanicals such as Corydalis Rhizoma, Ligusticum Rhizoma, Libanotus, Myrrha, Cynanchum Panniculatum Radix, Clematis Radix, Aconitum Radix, Aconitum Kusnezoffi Radix, Paeoniae Alba Radix, Carthami Flos, Paeoniae Rubra Radix, and Angelicae Pubescentis Radix.

2. Processed animal products such as Venenum Bufonis, Scorpion, Scolopendra, Eupolyphaga Steleophag, and Lumbricus.

3. Processed minerals such as Bornolium Syntheticum and Realgar.

Most of these are known in THM to relieve pain by promoting blood flow and qi circulation.

VAS improvement by number of persons

An analysis of improvement on the VAS based on nine13,15,17,18,20,28,30,32,33 of the 23 controlled trials revealed that a total of 495 (81.8%) patients in the treatment group (n = 605) and 169 (48.7%) members of the control group.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Type of cancer pain</th>
<th>Participants (n)/mean age (SD)/male (%) /country</th>
<th>Comparison treatment vs control/treatment frequency (treatment period)</th>
<th>Drugs</th>
<th>Outcome reported</th>
<th>Quality assessmenta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeong et al.11</td>
<td>Breast cancer, gastric cancer, lung cancer, colorectal cancer, other cancer</td>
<td>40/52.6 (11.4)/37.5/Korea</td>
<td>Herbs vs none /3 per day (2 weeks)</td>
<td>None</td>
<td>VAS p &lt; 0.05 prefer treatment</td>
<td>Y-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Tian et al.12</td>
<td>Non-small cell lung cancer</td>
<td>60/over 60 were 35%/50/China</td>
<td>Herbs vs herbs + chemotherapy vs chemotherapy/herbs: 2 per day (2 moths); chemotherapy: vinorelbine or gemcitabine 2 per month, cisplatin 1 per month (2 months)</td>
<td>Vinorelbine plus cisplatin, gemcitabine plus cisplatin</td>
<td>No significant difference</td>
<td>U-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Chen et al.13</td>
<td>Lung, liver, breast, gastric, pancreatic, esophageal, colorectal cancer</td>
<td>50/Treat: 54.6 (11.35), Control: 53.2 (10.28)/66/China</td>
<td>Western medicine + herbs vs western medicine/herbs: 3 per day (2 weeks); western medicine: 2-3 per day (2 weeks)</td>
<td>Indomethacin, tramal, morphine</td>
<td>VRS: p &lt; 0.05 prefer treatment</td>
<td>U-U-N-N-Y-Y</td>
</tr>
<tr>
<td>Wu et al.14</td>
<td>Lung, liver, colorectal, stomach, cervical, uterine, kidney, leukemia, prostate, ENT, breast, pancreas, esophagus, bladder, others cancer</td>
<td>2466/40-79 were 87%/50.7/China</td>
<td>Herbs + Taiwan herbal tonic vs hospital meals vs Taiwan herbal tonic/3 per day (1 week)</td>
<td>None</td>
<td>Hospital meals group, Taiwan herbal tonic group: pain p &lt; 0.05 significantly reduced herbs + Taiwan herbal tonic group: pain p &lt; 0.01 significantly reduced. 10 days after treatment herbs + Taiwan herbal tonic group: pain p &lt; 0.05 reduced, Taiwan herbal tonic group: pain p &lt; 0.05 reduced. Analgesic effect p &lt; 0.05 prefer treatment duration of analgesia p &lt; 0.01 prefer treatment Side effect p &lt; 0.01 prefer treatment</td>
<td>U-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Lin et al.15</td>
<td>Esophageal, gastric, liver, lung, breast, rectal cancer</td>
<td>60/Treat: 57.2 (14.6), Control: 55.8 (15.7)/61.7/China</td>
<td>Western medicine + herbs vs western medicine/4 per day (1 month)</td>
<td>Aspirin, tramal tablet, pethidine</td>
<td>Analgesic effect p &lt; 0.05 prefer treatment duration of analgesia p &lt; 0.01 prefer treatment Side effect p &lt; 0.01 prefer treatment</td>
<td>U-U-N-N-Y-Y</td>
</tr>
<tr>
<td>Shi et al.16</td>
<td>Liver, lung, gastric cancer</td>
<td>180/Treat: 48.9 (15.5), Control: 46.7 (14.8)/65/China</td>
<td>Herbs vs western medicine/2 per day (2 weeks)</td>
<td>Tramal</td>
<td>Time to pain relief p &lt; 0.01 prefer treatment</td>
<td>U-U-U-U-Y-Y</td>
</tr>
<tr>
<td>Author(s)</td>
<td>Patients and Cancer Type</td>
<td>Intervention Description</td>
<td>Outcome Measure</td>
<td>Conclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 17</td>
<td>Stomach, liver, lung, breast, colon, pancreatic, and submaxillary gland cancer (most metastatic)</td>
<td>Herbs + western medicine vs western medicine/herbs: 3 per day; western medicine: 2 per day (3 weeks)</td>
<td>Effect of pain relief $p &gt; 0.05$ no significant difference</td>
<td>U-U-U-U-Y-Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cao et al. 18</td>
<td>Bone cancer</td>
<td>Western medicine + herbs vs western medicine/4 per day (1 month)</td>
<td>Aspirin, tramal tablet, pethidine</td>
<td>Experimental group's percentage of reduction of pain 97.56%, control group's percentage of reduction of pain 92.68% $p &lt; 0.05$ prefer treatment. Pain $p &lt; 0.05$ significant difference</td>
<td>U-U-N-N-Y-Y</td>
<td></td>
</tr>
<tr>
<td>Tian et al. 19</td>
<td>Primary hepatic carcinoma</td>
<td>Herbs + HACE VS HACE + chemotherapy + western medicine/herbs: 1 per day (4 weeks)</td>
<td>MMC, THP, 5-Fu</td>
<td>U-U-N-Y-Y-Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lin et al. 20</td>
<td>Primary hepatocellular carcinoma</td>
<td>Microwave + herbs vs microwave/herbs: 3 per day (1 month), microwave: 1 per week (2 weeks)</td>
<td>None</td>
<td>Liver pain $p &lt; 0.01$ prefer treatment</td>
<td>Y-U-N-U-Y-Y</td>
<td></td>
</tr>
<tr>
<td>Li et al. 21</td>
<td>Liver, colon, head, pancreas, prostate, stomach, ovarian, gallbladder, renal, bladder cancer</td>
<td>Herbs vs western medicine/3 per day</td>
<td>Indomethacin</td>
<td>U-U-U-U-Y-Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wan et al. 22</td>
<td>Cancer</td>
<td>Herbs + acupuncture vs western medicine/eastern medicine: 1 per day (1 week), western medicine: i.m. 3 per day (1 week)</td>
<td>Bucinnazine</td>
<td>U-U-N-U-Y-Y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang et al. 23</td>
<td>Lung, gastric, liver, esophagus, large intestine cancer</td>
<td>Herbs + opioid analgesics vs opioid analgesics/2 per day (2 weeks)</td>
<td>Morphine hydrochloride sustainedrelease tablets</td>
<td>Frequency of pain, period of pain relief, time to pain relief $p &lt; 0.05$ prefer treatment</td>
<td>Y-U-N-U-Y-Y</td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>Type of cancer pain</td>
<td>Participants (n)/mean age (SD)/male (%)/country</td>
<td>Comparison treatment vs control/treatment frequency (treatment period)</td>
<td>Drugs</td>
<td>Outcome reported</td>
<td>Quality assessment</td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------------</td>
<td>------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>Lung, liver, gastric, colon, pancreatic cancer</td>
<td>60/Treat: 58.2 (7.3), Control: 58.9 (5.2)/58.3/China</td>
<td>Herbs vs western medicine/3 per day (1 week)</td>
<td>Diclofenac</td>
<td>Experimental group: percentage of pain reduction 90%, Control group: percentage of pain reduction 83.3% no significant difference. But degree of pain reduction, duration of pain, time to pain relief, extension of pain relief, tenderness etc. prefer treatment</td>
<td>U-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Liu et al.</td>
<td>Middle-late stage malignant tumor</td>
<td>81/30–75/37/China</td>
<td>Chemotherapy + herbs vs chemotherapy + herbs + moxibustion vs chemotherapy/herbs: 2 per day (1 week); moxibustion: 10 min per day (1 week)</td>
<td>CE-CAP, PVM, FAM, 5-FU + CF, CHOP, CMF, CAF</td>
<td>Chemotherapy group pain $p &lt; 0.05$ significantly reduced. chemotherapy + herbs group pain $p &gt; 0.05$ no significant difference. Herbs + moxibustion group pain $p &lt; 0.05$ significantly reduced. When compared with other group Chemotherapy group $p &lt; 0.01$, chemotherapy + herbs group $p &lt; 0.05$ prefer treatment</td>
<td>U-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Ma et al.</td>
<td>Gastric cancer</td>
<td>62/Treat: 53.1, Control: 52.8/79/China</td>
<td>Herbs vs western medicine/herbs: 3 per day (15 days); western medicine: 2 per day (15 days)</td>
<td>Analgesic drug</td>
<td>Effect of pain relief, duration of pain relief, VRS, Karnofsky $p &gt; 0.05$ no significant difference</td>
<td>U-U-U-Y-Y</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>Advanced pancreatic cancer</td>
<td>65/Treat: 54.6 (6.8), Control: 53.2 (7.6)/55.4/China</td>
<td>Herbs + arterial perfusion + chemotherapy vs chemotherapy/herbs: 1 per day (2 months); arterial perfusion: 1 per month (2 months)</td>
<td>Vinorelbine</td>
<td>No significant difference</td>
<td>U-U-N-U-Y-Y</td>
</tr>
<tr>
<td>Study</td>
<td>Primary/Diagnosis</td>
<td>Patients/Placebo/Doxorubicin/Chemo/Control</td>
<td>Intervention</td>
<td>Comparison</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>--------------------------------</td>
<td>--------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feng et al.²⁹</td>
<td>Primary liver cancer</td>
<td>80/53.8/68.8/China</td>
<td>Dexamethasone vs ginsenosides vs dexamethasone + ginsenosides vs placebo/2 per day</td>
<td>Dexamethasone Both experimental group p &lt; 0.05 prefer treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dexamethasone vs ginsenosides vs placebo/2 per day</td>
<td>Dexamethasone vs ginsenosides group: effect about (duration of symptoms, low bone mineral density) reported</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan et al.³⁰</td>
<td>Middle/advanced stage of lung cancer</td>
<td>250/59.6/76.4/China</td>
<td>Herbs + western medicine + Zhiling capsule vs western medicine + Zhiling capsule VS herbs + Zhiling capsule vs Pingxiao capsule/3 per day (2 weeks)</td>
<td>Herbs + western medicine + Zhiling capsule chest pain p &lt; 0.05, 0.01 prefer treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wei et al.³¹</td>
<td>Liver, lung, gastric cancer</td>
<td>200/Treat: 55.2 (10.1), Control: 54.2 (10.4)/60.5/China</td>
<td>Herbs vs western medicine /3 per day (5 days)</td>
<td>Paracetamol codeine phosphate, placebo drug None</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Effect of pain relief, duration of pain relief p &gt; 0.05 no significant difference</td>
<td>Effect of pain relief, duration of pain relief p &gt; 0.05 no significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al.³²</td>
<td>Middle-advanced pancreatic cancer</td>
<td>58/Treat: 48.2 (5.7), Control: 49.7 (4.1)/74.1/China</td>
<td>Radiation therapy + herbs vs radiation therapy/radiation: 5 per week (6 weeks); herbs: 2 per day (9 weeks)</td>
<td>Experimental group: abdominal pain 25 people among 30 people cured Control group: abdominal pain 16 people among 28 people cured p &lt; 0.05 prefer treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pan et al.³³</td>
<td>Liver, stomach, esophagus, liver, kidney, breast, nasopharyngeal, colorectal</td>
<td>400/Treat: 55.4 (12.6), Control: 57.5 (15.1)/66.8/China</td>
<td>Zhiling capsule vs Pingxiao capsule/3 per day (2 weeks)</td>
<td>Experimental group’s percentage of reduction of pain 83.9%, control group’s percentage of reduction of pain 11.6% p &lt; 0.001 significant difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chan et al.³⁴</td>
<td>Ovarian cancer</td>
<td>59/Treat: 52.9, Control: 51.5/0/China</td>
<td>Chemotherapy + herbs vs chemotherapy + placebo/herbs: 2 per day (6 cycles); chemotherapy: 3 weekly cycles (6 cycles)</td>
<td>Placebo, carboplatin, paclitaxel (Taxol)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(a) (1) Was the allocation sequence adequately generated? (2) Was allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately prevented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were reports of the study free of suggestion of selective outcome reporting? (6) Was the study apparently free of other problems that could put it at risk of bias? Key: Y, 'yes'; U, 'unclear'; N, 'no'. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see: http://www.textcheck.com/certificate/z9r5ZI.*
(n = 347) reported a complete or partial response. The percentage (%) of VAS decrease was evaluated by: (difference between VAS before and after treatment/VAS before treatment) × 100. Complete response and partial response was defined as scoring 91–100% and 61–90.9%, respectively. The results showed that concomitant THM therapy was significantly and positively correlated with VAS improvement in terms of number of persons reporting decreased pain; this was not the case for Western therapy alone (MD, −0.51; 95% CI, −0.94 to −0.08; p = 0.02).

The randomized-effects model was used because of the inter-trial heterogeneity of the results ($\chi^2$, 10.86 with 3 df; p = 0.01) (Fig. 3).

Discussion
This systematic review of 24 RCTs investigated the efficacy of treatment with both THM and conventional therapy for patients with cancer. This is the first systematic review including only RCTs that investigated the effect of THM as adjunct therapy for cancer pain. We conducted this systematic review after systematically reviewing the work of Ling et al., who included both non-RCTs and RCTs. This systematic review investigated the effect of adjunct THM therapy on a variety of cancers. Significant evidence has previously demonstrated the effect of THM in this regard.

The treatment group differed significantly from the control group when improvement on the VAS was measured by number of persons reporting decreased pain; this was not
clear in the review conducted by Ling et al. as it was not a meta-analysis. A similar result was found when improvement on theVAS was measured by degree. We have not added the funnel plot in this review because the meta-analyzed RCTs were not enough to exclude potential publication bias. We reviewed two articles that investigated the effect of THM on the number of pain occurrences/day in patients with cancer. Although the results were positive, the number of trials was too small to draw firm conclusions. Thus, these results should be interpreted with caution, and further investigation is necessary.

This systematic review had several limitations. First, the quality of the studies was not assessed completely. We used the "Risk-of-Bias" assessment tool included in the Cochrane Handbook to assess the quality of the studies included in this systematic review. As it is difficult to justify the subtle differences in each item using a qualitative method, we tried to assess each trial with regard to seven critical domains: randomization, allocation concealment, blindness of participants and personnel, blindness of outcome assessment, reporting of incomplete outcome data, selective-outcome reporting, and other biases. However, the risk-of-bias assessment may not be entirely objective.

Second, of 24 articles, only nine were written in English. The remaining 15 were written in Chinese, making it difficult for other researchers to follow up on the results of these studies.

The quality of the trials in this systematic review was generally weak; thus, further high-quality trials are needed to assess the effectiveness of THM for patients with cancer pain. And as treatment regimens varied in the studies included in the review this is an important limitation.

**Conclusions**

In conclusion, this systematic review demonstrated the significant effect of THM treatment combined with standard therapy versus standard therapy alone, as the former was associated with increased improvement on the VAS as measured by number of persons reporting improvement, degree of improvement, and number of pain occurrences per day. Additionally, more RCTs should be conducted to determine the role of THM in a variety of cancer therapies.

**Conflict of interest statement**

No authors have any conflict of interest to declare.

**Acknowledgements**

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government [MEST] (No. 2012-0005755).

**References**


