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REVIEW ARTICLE

A systematic review and meta-analysis on the use of traditional Chinese medicine compound kushen injection for bone cancer pain

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Abstract
Purpose Bone cancer pain presents a clinical challenge with limitations of current treatments. Compound kushen injection (CKI) is a well-known traditional Chinese medicine (TCM) formulation in treatment of patients with bone cancer pain. The objective of this study is to assess the efficacy and safety of CKI for bone cancer pain.
Methods A systematic literature search was conducted in nine databases until December 2012 to identify randomized controlled trials (RCTs) of CKI versus current western therapies for bone cancer pain. The primary outcome was total pain relief rate. The secondary outcomes were the quality of life and adverse events at the end of treatment course. The methodological quality of RCTs was assessed independently using six-item criteria according to the Cochrane Collaboration, and the level of evidence was assessed by the GRADE approach. All data were analyzed using Review Manager 5.1.0.
Results Seven RCTs with 521 patients from 2010 to 2012 were identified. Compared with radiotherapy or bisphosphonates, seven RCTs showed significant effects of CKI for improving pain relief in patients with bone cancer pain ($n=521$, risk ratio (RR)=1.25, 95 % CI (95 % confidence intervals (CI)), 1.13 to 1.38, $p<0.0001$)), three RCTs for improving Karnofsky scoring (KPS) increase rate ($n=305$, RR=1.62, 95 % CI, 1.32 to 1.99, $p<0.00001$), 1 RCT for increasing KPS scores ($n=78$, mean difference (MD)=10.43, 95 % CI 4.76 to 16.10, $p=0.0003$). 4 RCTs reported adverse effects in both the treatment and control groups. The patients treated with CKI achieved statistically significant reductions of incidences of leukopenia ($n=276$, RR=0.32, 95 % CI, 0.21 to 0.47, $p<0.00001$) and nausea ($n=78$, RR=0.15, 95 % CI, 0.06 to 0.34, $p<0.00001$). No severe adverse events were found and no treatment was stopped because of adverse events of CKI in the treatment groups. However, the studies were deemed to have a high risk of bias.
Conclusion This systematic review showed positive but weak evidence of CKI for bone cancer pain because of the poor methodological quality and the small quantity of the included trials. Future rigorously designed RCTs are required.

Keywords Traditional Chinese medicine · Kushen · Bone cancer pain · Clinical trial

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Introduction

Description of the condition

Pain is the first clinical symptom of cancer in a large population of cancer patients, particularly in advanced cancer

patients [1], which strongly affect the patients' quality of life. Tumor-derived, inflammatory, and neuropathic factors may simultaneously contribute to cancer pain, such as bone cancer pain [2].

Bone cancer pain does not exist as a single entity but is instead a combination of background and breakthrough pain. Breakthrough pain has been defined as "a transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain" [3]. Breakthrough pain can be divided into spontaneous pain at rest and incident pain (either volitional or nonvolitional) [4, 5]. Recent work has characterized the different components of bone cancer pain. Breakthrough pain was present in 75 % of cases of bone cancer pain. Patients with breakthrough pain had greater interference on aspects of life (mood, relationships, sleep, activity, walking ability, work, and enjoyment of life) than those with no breakthrough pain. Almost half of breakthrough pain episodes were rapid in onset (<5 min) and short in duration (<15 min). Forty-four percent of patients with breakthrough pain had pain that was unpredictable [6].These clinical characteristics make the successful treatment of bone cancer pain challenging. This has been supported by other studies that have shown that up to 45 % of patients with bone cancer pain report poor pain control [7, 8].

The underlying pathomechanism of bone cancer pain is largely unknown. Bone destruction, reactive muscle spasm, increased local and blood concentration of calcium ions, and the release of inflammatory mediators by tumor cells are all implicated in the pathomechanism [9]. Intraosseal tumor causes severe disintegration of the cortical and trabecular bone. This inevitably leads to fractures at a later stage, an occurrence seen in approximately 50 % of patients with bone metastases [10].

Description of the intervention

The current treatment options for bone cancer pain are wide-ranging and include external beam radiotherapy, opioid analgesia, nonsteroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, local surgery, and anaesthetic techniques. However, each of these treatment options is accompanied by limitations. Radiotherapy is the gold standard treatment of bone cancer pain, but with less effectiveness. Studies have shown that complete pain relief is only achieved in about 25 % of patients [11], whereas 50 % of patients will achieve 50 % pain relief [12]. Opioids are an effective therapy for background pain in bone cancer pain. However, their usefulness in breakthrough pain is unclear. Normal release oral morphine has, at best, an onset of action of about 30 min [13]. This means that in patients with rapid-onset, short duration breakthrough pain, normal release morphine will probably be ineffective. Furthermore, titration of opioids to doses that control episodes of breakthrough pain may result in unacceptable opioid side-effects [14]. Recently, rapid-onset opioids have been developed with the aim of mirroring the temporal features of breakthrough pain. As these products have only recently become available, their efficacy has yet to be fully demonstrated in clinical practice. Although NSAIDs are regarded by clinicians as an important drug in the treatment of bone cancer pain, they are limited by their adverse effects, such as gastric ulceration, hepatic dysfunction, myocardial infarction, and renal failure [15–18]. Bisphosphonates are used to reduce skeletal morbidity from bone metastases and for analgesia in bone cancer pain. Bisphosphonates act on osteoclasts both directly by inhibiting attachment, differentiation, and survival and also indirectly through effects on osteoblasts [19]. Although their efficacy in preventing skeletal events has been shown in some tumor groups, in the management of acute and chronic bone cancer pain, their role is less clear [20].

How the intervention might work

Bone cancer pain presents a clinical challenge with limitations of current treatments clearly evident. In China, acupuncture and traditional Chinese medicine (TCM) have been used to treat bone cancer pain for more than 2,000 years. In recent decades, patented TCMs have been widely used in cancer patients in both Western medicine hospitals and TCM hospitals. However, few studies have been published in English written journals that report the effectiveness and safety of many commonly used TCMs [21]. Therefore, confirmation of the effectiveness of TCM could have a great impact on bone cancer pain management worldwide.

It has been of great interest to evaluate TCM for management of bone cancer pain. In this paper, clinical studies were reviewed for one TCM formulation called compound kushen injection (CKI), also known as Yanshu injection, which contains extracts from two herbs, kushen (*Radix sophorae flavescentis*) and baituling (*Rhizoma smilacis glabrae*); the primary components are oxymatrine and matrine [22]. CKI was approved for the treatment of cancer by the State Food and Drug Administration of China in 1992. Since then, CKI has been used extensively throughout China for pain treatment in combination with conventional analgesics, chemotherapy, or radiotherapy. Preclinical studies indicate that CKI can reduce the expression of endothelial nitric oxide synthase, decrease the level of intracellular calcium, and inhibit inflammation in a murine model for cancer pain [23].

Why it is important to do this review

Owing to the significant health risk of bone cancer pain and the limitations of currently available conventional therapies, unprecedented attention has been attached to CKI in modern time due to its potential efficacy on bone cancer pain. There have

been a number of controlled studies over the past decade to evaluate the efficacy and safety of CKI for bone cancer pain in China [24–30]. Evidence-based medicine (EBM) is a strategy for the critical evaluation and uniform comparison of clinical trial data with conclusions according to predetermined efficacy criteria. However, there is still a lack of reliable scientific evidences for the application of CKI for bone cancer pain because many studies were classified as "not-so-good" study according to the Cochrane criteria. In a TCM reviewing process, researchers may need to include such papers to identify current problems and areas worthy of improvement and future development [31]. Therefore, it is worthwhile to undertake a systematic review of currently available randomized clinical trials (RCTs) using CKI as treatment for bone cancer pain.

Objective

Given the gap between the lack of scientific evidence for the efficacy of CKI and the growing use among the public possibly because of the limitations of conventional therapies available, the objective of current systematic review is thus to evaluate the clinical efficacy and safety of CKI for bone cancer pain.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines were followed during all stages of the design, implementation, and reporting of this systematic review [32].

Eligibility criteria

Types of studies Reports made for RCTs, irrespective of blinding, publication status and language. Quasi-randomized trials and nonrandomized studies were excluded for analysis. Trials with significantly skewed distributions of participants in groups that could not be explained by the randomization principle were also excluded.

Types of participants Trials included adult (18 years or older) participants of any ethnic origin who had cancer-related bone pain (as defined by commonly used verbal rating scales or questionnaires), which was assumed to be directly linked to cancer development, but not due to pre-existing pathologies or related to treatments, such as chemotherapy-induced neuropathic pain or procedure or surgery related pain.

Types of interventions The patients in the control group were given one of the following current western therapies: external beam radiotherapy, opioid analgesia, NSAIDs, or bisphosphonates. The patients in the treatment group were given CKI, regardless of treatment period and dosage of treatment, in addition to one of the current therapies which was similar to the control group.

Types of outcome measures The primary outcome was total pain relief rate. The reduction in pain intensity was measured using a visual analogue scale (VAS), verbal rating scale, or numerical rating scale (NRS). The intensity of pain was evaluated by the WHO standards [33] with NRS, and expressed as numerical numbers ranging from 0 (for no pain) to 10 (for extreme pain). The degree of pain intensity was determined and marked out by the patients themselves. In reference to the WHO standard [33], the effectiveness in cancer pain treatment was categorized into four grades: (1) complete remission (CR) denoted by completely no pain after medication; (2) partial remission (PR) denoted by evident alleviation of pain, with normal daily life and basically uninfluenced sleep; (3) mild remission denoted by pain that was alleviated but still distinct, and sleep that was interfered to a certain degree; (4) no palliation (NP) denoted by no alleviation of pain compared with that observed before medication. For the systematic review, the outcomes of "CR" and "PR" were considered successful treatments.

The secondary outcomes were quality of life and adverse events at the end of treatment course. Assessment of the patients' quality of life was estimated using Karnofsky scoring (KPS). The intensity of KPS was evaluated by the WHO standards [33] with VAS, NRS, or NRS, expressed as numeric numbers ranging from 0 (for worst) to 10 (for best). The KPS included appetite, sleeping, general activity, mental status, emotion, communication ability, and interest in life. The degree of KPS intensity was determined and marked out by the patients themselves. In reference to the WHO standards [33], the effectiveness of CKI on cancer pain treatment was categorized into three grades: (1) alleviation denoted by KPS scores that increased by greater than or equal to 10 after medication; (2) stabilization denoted by KPS scores that increased or decreased by less than 10 after medication; and (3) reduction denoted by KPS scores that reduced by greater than or equal to 10 after medication. For the systematic review, the outcomes of "alleviation" were considered successful treatments.

An assessment was made for the frequency and severity of the commonly expected adverse effects and divided into two levels: those severe enough to result in cessation of treatment and those that are mild.

Literature search

Nine databases were searched from their inception to December 2012. These included MEDLINE; four Chinese Medical Databases—China National Knowledge Infrastructure Database, VIP Database for Chinese Technical Periodicals, Chinese Biomedical Literature Database, and Wan-Fang Database; two

Korean Medical Databases–Korean Studies Information, and Data Base Periodical Information Academic; one Japanese Medical Database—citation information by the National Institute of Informatic; and Cochrane Controlled Trials Register (Issue 12, 2012).

The search terms used were based on two concepts, subject and disease. Subject search terms included "kushen" or "Yanshu" or "matrine." Disease search terms included various terms for bone cancer pain. The keywords for the terms indicating pain (e.g., pain and nociceptors) and presence of cancer or bone metastasis (e.g., neoplasms, cancer, and tumor). The two concepts were combined using the Boolean operator AND. Databases were also searched for ongoing trials, including Current Controlled Trials, the UK National Research Register, and Chinese medical journals that were not indexed in the electronic databases. Quality control was employed for all reports considered for analysis by screening for the reference list of relevant trials and identified reviews. In addition, we contacted experts in this field and relevant pharmaceutical companies for additional references or unpublished studies.

Study selection and data collection

Studies were selected by two independent reviewers ((Y. J. Bao and L. P. Yang)) according to the pre-determined inclusion criteria. And disagreements were resolved by a third reviewer(B. J. Hua).

Data were independently entered into an electronic database by the two reviewers (Y. J. Bao and L. P. Yang); instances where the two entries did not match, a third person (B. J. Hua) was involved for verification. The following data were independently extracted by two reviewers from eligible studies using pilot-tested data extraction forms: age and number of participants, male–female ratio, diagnosis criteria, treatment dosage and duration, side effects, and quality assessment item. Important missing data were obtained by contacting article authors whenever possible.

Quality assessment of the included randomized, controlled trials included sequence generation, allocation concealment, blinding of participants personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of biases [18].

The level of evidence was assessed by the GRADE approach (using GRADE pro 3.6) by two independent reviewers (Y. J. Bao and L. P. Yang) [34–37]. Disagreements were resolved by discussion between the two reviewers (Y. J. Bao and L. P. Yang), with consultation of a third reviewer (B. J. Hua or W. Hou) when necessary.

Data synthesis and analysis

Data analyses were performed using the statistical package Rev Man 5.1.0 (Cochrane Collaboration). Dichotomous data were presented as risk ratio (RR) and continuous outcomes as mean difference (MD), both with 95 % confidence intervals (CI). Subgroup analyses were conducted in terms of control type (e.g. radiotherapy, opioid analgesia, NSAIDs, and bisphosphonates). Heterogeneity among trials was tested using I^2 test and considered significant when I^2 was over 50 % or $p<0.1$. The random effect model was used for the meta-analysis if there was significant heterogeneity while the fixed effect model was used when the heterogeneity was not significant [38]. Publication bias was explored via a funnel-plot analysis.

Results

Search results

We identified 170 potentially relevant articles after duplicates removed. Through screening titles and abstracts, 105 were excluded because they were nonclinical trials, case reports, reviews, basic/mechanistic studies, or studies lacking the control group. We conducted full-text evaluation for the remaining 54 articles, and 37 articles were excluded for not meeting our inclusion criteria. Among them, 6 articles did not meet the inclusion criteria, 3 trials are duplicate publications, 28 articles are not about bone cancer pain. Finally, seven studies [24–30], involving a total of 521 participants, met our inclusion criteria. The screening process is summarized in a flow diagram (Fig. 1).

Study characteristics

A total of 521 participants were included in the seven studies (256 were in the control group, 265 were in the treatment group, and the ages ranged from 31 to 78 years old). All studies were conducted in China, published between 2010 and 2012, and performed in a single center. Only one trial [27] compared CKI with bisphosphonates to bisphosphonates individually. Six trials [24–26, 28–30] compared CKI with radiotherapy to radiotherapy individually. CKI was given in dilution at the time of treatment by using 250 mL of 5 % glucose injection or 250 mL of 0.9 % sodium chloride injection for intravenous administration.

The duration of studies lasted from 10 days to 8 weeks. All studies used the total pain relief rate as primary outcome. The quality of life was reported in five studies [26–30]. Adverse effects were reported in four studies [24, 25, 28, 29]. Detailed characteristics of included studies are listed in Table 1.

Risk of bias within studies

All of the included studies mentioned randomization, but only one study reported the method of random sequences

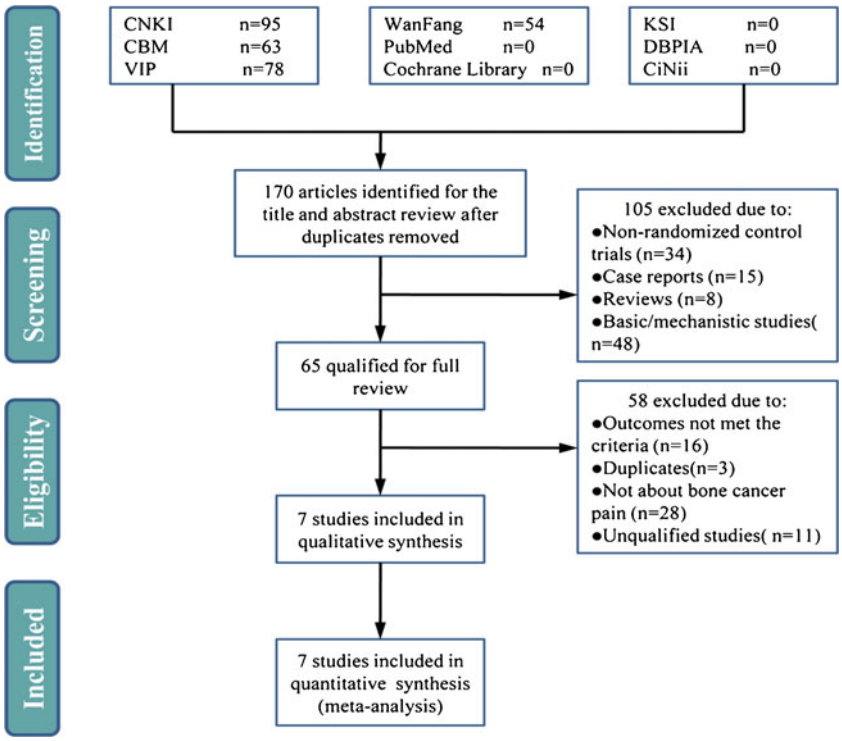

Fig. 1 PRISMA flow chart of literature retrieval and selection. *CNKI* China National Knowledge Infrastructure, *CBM* Chinese Biomedical Literature Database, *VIP* VIP Database for Chinese Technical Periodicals, *WanFang* Wanfang Database on Academic Institutions in China, *KSI* Korean Studies Information, *CiNii* citation information by the National Institute of Informatics

generation [28]. No study mentioned allocation concealment and blinding procedures. One report [28] recorded the loss to follow up, and no studies conducted intention-to-treat analysis. The dropout data were not reported in all of the included studies and selective reporting was found in all of the trials. In general, one RCT was deemed to have a unclear risk of bias and six RCTs were deemed to have a high risk of bias based on the Cochrane Risk of Bias tool (Table 2).

Evidence level

Based on the GRADE approach, evidence level for total pain relief rate in the trial of CKI with radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates individually was low. Evidence level for increased rate of KPS for one trial of CKI with radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates individually was also low. Evidence level for the incidence of nausea and leucopenia was low (Fig. 2).

Efficacy assessment

Total pain relief rate

All seven studies adopted the total pain relief rate to assess the clinical improvement. The fixed effect model was used for statistical analysis because heterogeneity was not significant ($p=0.57$, $I^2=0$ %). The combined effects of seven independent trial results showed that CKI could relieve pain in patients with bone cancer pain when compared with radiotherapy or bisphosphonates ($n=521$, RR=1.25, 95 % CI, 1.13 to 1.38, $p<0.0001$) (Fig. 3). A subgroup analysis was performed to explore whether the heterogeneity could be partially explained by the type of control group. The subgroup analysis indicated that no better improvements were observed after CKI treatment for any of the included types of control group (Fig. 3).

The funnel plot indicated existence of publication bias (Fig. 4).

Quality of life

KPS increase rate Data extracted from four studies [26–28, 30] showed no heterogeneity among trials (heterogeneity: $p=0.50$, $I^2=0$ %). The fixed effect model was used for statistical analysis. The combined effects of 4 independent trial results showed that CKI had improved the KPS increase rate in patients with bone cancer pain when compared with radiotherapy or bisphosphonates control ($n=305$, RR=1.62, 95 % CI, 1.32 to 1.99, $p<0.00001$) (Fig. 5a). A subgroup analysis was performed to explore whether the heterogeneity could be partially explained by the type of control group. The subgroup analysis also indicated that no better improvements were observed after CKI treatment for any of the included types of control group (Fig. 3).

KPS scores Wang [29] conducted a RCT to evaluate the efficacy and safety of CKI for bone cancer pain within 1 month of onset. Seventy-eight patients were randomly divided into experimental group ($n=40$) and control group ($n=38$). The

Table 1 Characteristics and methodological quality of included studies

Reference	Method	Subject (treatment/control)	Age (years; treatment/control)	Type of cancer pain	Interventions		Outcomes
					Control group	Trial group	
[24]	RCT, not blinded. Duration, 8 weeks	35/29	63.81±6.93/64.37±7.02	Lung and breast cancer	CKI at 30 mL iv once daily+bisphosphonates	Bisphosphonates	(1) Total pain relief rate, (2) KPS increase rate, and (3) side-effect
[25]	RCT, not blinded. Duration, 10 days	40/38	49.2±6.3 (22–76)	Lung, liver, gastric, breast, esophageal, nasopharyngeal, prostate, renal, ovarian, uterine, and cervix cancer	CKI at 12–15 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate, (2) KPS scores, and (3) side-effect
[26]	RCT, not blinded. Duration, 8 weeks	45/44	64 (37–76)/60 (38–75)	Lung , breast, esophageal, and prostate cancer	CKI at 20 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate and (2) KPS increase rate
[27]	RCT, not blinded. Duration, 10 days	46/46	52 (31–78)	Lung, breast, nasopharyngeal, prostate, and colon cancer	(1) CKI 20 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate, and (2) KPS increase rate
[28]	RCT, not blinded. Duration, 2 weeks	30/30	59 (42–77)/59(40–76)	Lung, breast, esophageal, prostate, rectal, and uterine cervix cancer	CKI at 20–30 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate, (2) KPS increase rate, and (3) side-effect
[29]	RCT, not blinded. Duration, 4 weeks	29/29	61 (45–78)	Lung , breast, esophageal, and prostate cancer	CKI at 20 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate and (2) side-effect
[30]	RCT, not blinded. Duration, 4 weeks	40/40	45 (36–78)	Lung, breast, nasopharyngeal, esophageal, prostate, and rectal cancer	CKI 20 mL iv once daily+radiotherapy	Radiotherapy	(1) Total pain relief rate and (2) side-effect

RCT randomized clinical trial, *F* female, *M* male, *CKI* compound kushen injection, *KPS* Karnofsky scoring, *iv* intravenous

Table 2 Quality assessment of included randomized controlled trials

Included trials	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Risk of bias
[24]	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	High
[25]	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	High
[26]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
[27]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
[28]	Table of random number	Unclear	Unclear	Unclear	No	No	Unclear	Unclear
[29]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High
[30]	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	High

experimental group received CKI plus radiotherapy, while only radiotherapy was given for control group for 1 month. Compared with only radiotherapy treatment, CKI plus radiotherapy showed significant effects for improving KPS scores at 1-month follow-up ($n=78$, MD=10.43, 95 % CI 4.76 to 16.10, $p=0.0003$) (Fig. 5b).

Adverse events

Specific adverse effects included leukopenia and nausea. Of the seven trials, four trials [24, 25, 28, 29] reported adverse effects. The treatment groups achieved a statistically significant reduction in the incidences of leukopenia ($n=276$, RR=0.32, 95 % CI, 0.21 to 0.47, $p<0.00001$) (Fig. 6a) and nausea ($n=78$, RR=0.15, 95 % CI, 0.06 to 0.34, $p<0.00001$) (Fig. 6b).

Only one case of rash resulting from CKI was reported in the treatment groups [27]. No severe adverse events were found and no treatment was stopped because of adverse events of CKI in the treatment groups.

Discussion

Summary of evidence

Seven studies with 521 individuals suffering from bone cancer pain were selected. The main findings of present study were that CKI could improve the total pain relief rate and quality of life of patients with bone cancer pain. Despite the apparent positive findings reported, there is insufficient evidence to

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CKI	Current western therapies	Relative (95% CI)	Absolute		
Total pain relief												
7	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	217/265 (81.9%)	168/256 (65.6%)	RR 1.25 (1.13 to 1.38)	164 more per 1000 (from 85 more to 249 more)	⊕⊕OO LOW	IMPORTANT
								67.4%		169 more per 1000 (from 88 more to 256 more)		
KPS increase rate												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111/156 (71.2%)	66/149 (44.3%)	RR 1.62 (1.32 to 1.99)	275 more per 1000 (from 142 more to 439 more)	⊕⊕OO LOW	IMPORTANT
								39.4%		244 more per 1000 (from 126 more to 390 more)		
Incidences of leukopenia												
4	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/139 (17.3%)	74/137 (54%)	RR 0.32 (0.21 to 0.47)	367 fewer per 1000 (from 286 fewer to 427 fewer)	⊕⊕OO LOW	IMPORTANT
								52.5%		357 fewer per 1000 (from 278 fewer to 415 fewer)		
Incidence of nausea												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	5/40 (12.5%)	32/38 (84.2%)	RR 0.15 (0.06 to 0.34)	716 fewer per 1000 (from 556 fewer to 792 fewer)	⊕⊕OO LOW	IMPORTANT
								84.2%		716 fewer per 1000 (from 556 fewer to 791 fewer)		

[1] Lack of blinding and allocation concealment

Fig. 2 Summary of GRADE on evidences of outcomes of Compound Kushen Injection (CKI) for bone cancer pain

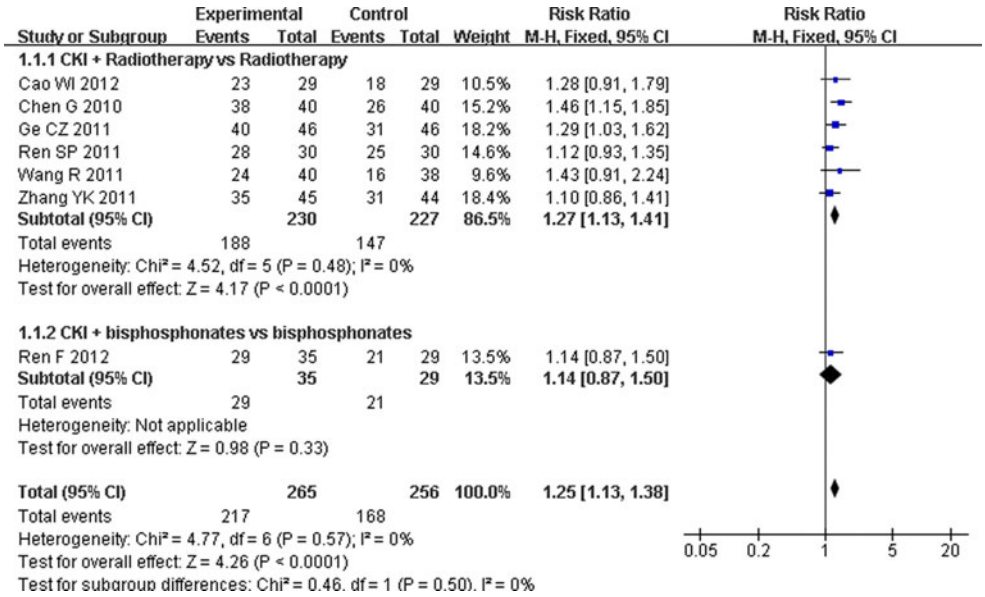

Fig. 3 Forest plot of comparison: compound kushen injection (*CKI*) plus radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates alone: total pain relief rate

support routine use of CKI for bone cancer pain due to the poor methodological quality and the small number of trials of the included studies. Of special interest was CKI with radiotherapy or bisphosphonates that reduced the incidence of side effects of radiotherapy or bisphosphonates. There were fewer side effects in the treatment groups and none of the effects was severe; no patients dropped out of their test trial due to the side effects of CKI, which indicated that CKI is safe for clinical use. However, the evidence is limited to make a conclusion on the issue of safety because only 57.1 % studies mentioned the adverse effects.

The transcription factor cAMP response element binding protein (CREB), which can be phosphorylated by multiple intracellular kinases in response to a vast range of physiological and pathological stimuli [39], has been suggested to contribute to the central sensitization associated with bone cancer pain [40]. It has been proposed that *N*-methyl-D-aspartate receptors (NMDA) activation-induced Ca^{2+} influx can trigger an early phase of CREB phosphorylation and a persistent phase of CREB phosphorylation is mediated by a delayed extracellular signal-regulated kinase (ERK) signal cascade, which is important to the development and maintenance of bone cancer pain [41]. Oxymatrine (OMT), a natural quinolizidine alkaloid, is the main basic constituents derived from the root of *Sophora flavescens*, which is also called "kushen." Recent study has been reported that OMT protects neurons through down-regulation of NR2B-containing NMDARs [42]. It has alao been reported that intraperitoneal injection of OMT could beneficially decrease the chronic constrictive injury (CCI)-induced mechanical allodynia and thermal hyperalgesia, antagonize the effect of NMDA, led to a marked decrease in NMDA NR2B, phosphorylation of ERK, and phosphorylation of CREB induced by CCI in the spinal cord in mice [43]. The observations indicate that regulation of NMDA NR2B receptor-ERK/CREB signaling maybe the targets for the antinociceptive effects of CKI for bone cancer pain.

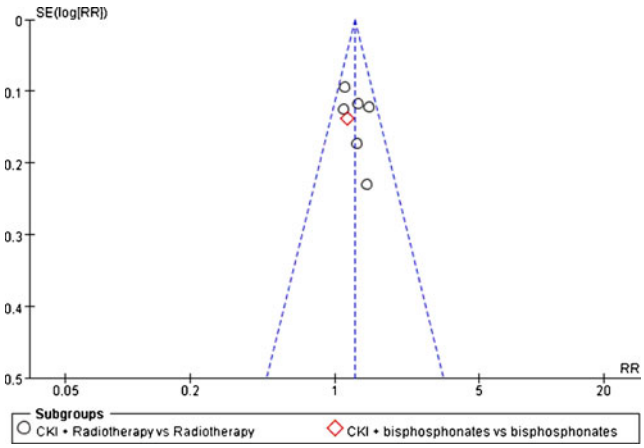

Fig. 4 Funnel plot of comparison: compound kushen injection (*CKI*) plus radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates alone

Limitations

A number of inherent and methodological weaknesses should be addressed. First, none of included studies had been registered. In September 2004, a statement requiring that all clinical trials must be registered was published by the members of the International Committee of Medical Journal Editors to be considered for publication [44]. Clinical trial registration will improve research transparency and ultimately strengthen the validity and value of the scientific evidence base.

Second, randomization is necessary to avoid selection bias. However, only 1 study [28] provided specific information on how the random allocation was generated. None of the included trials reported the allocation concealment. Indeed,

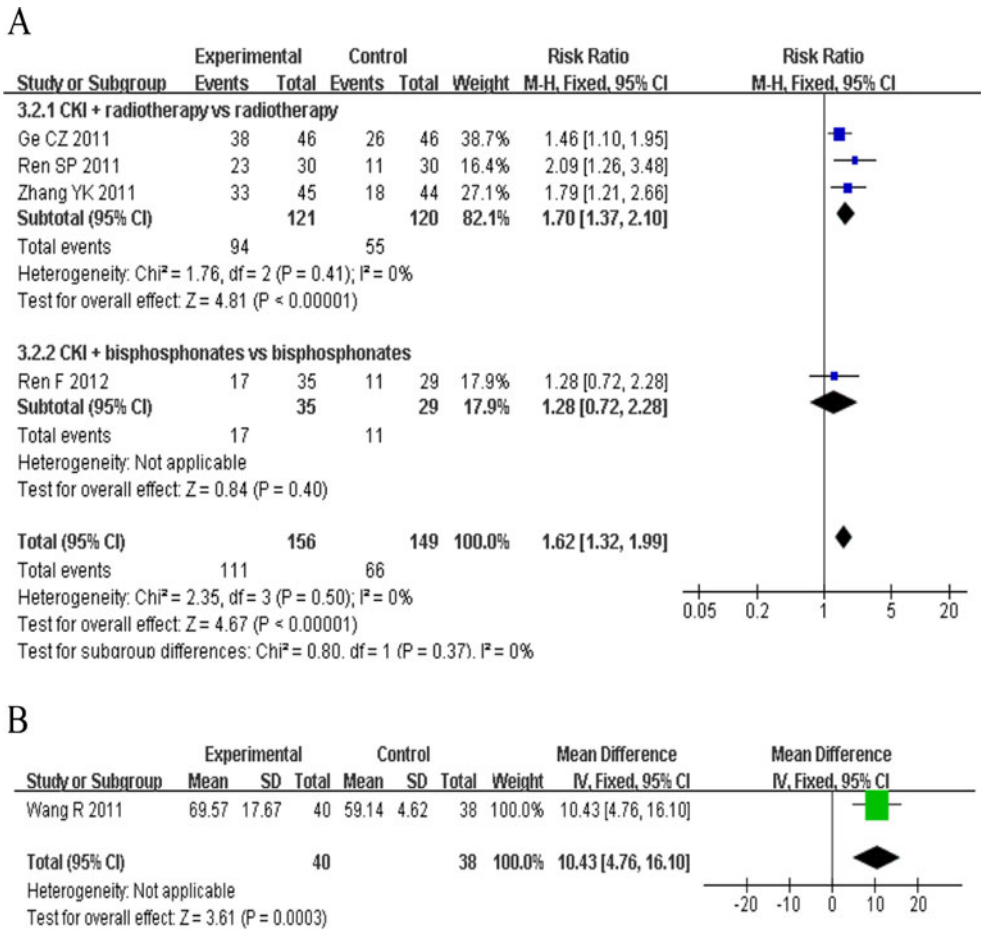

Fig. 5 Forest plot of comparison: compound kushen injection (*CKI*) plus radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates alone. **a** Karnofsky scoring (*KPS*) increase rate; **b** KPS scores

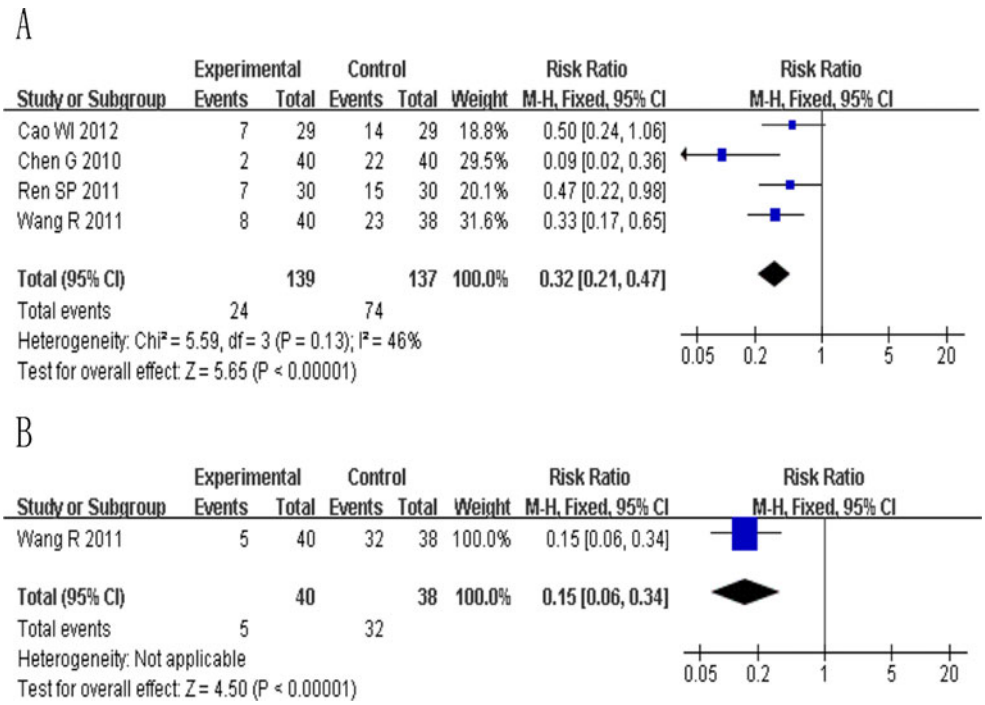

Fig. 6 Forest plot of comparison: compound kushen injection (*CKI*) plus radiotherapy or bisphosphonates versus radiotherapy or bisphosphonates alone. **a** Incidences of leukopenia; **b** incidences of nausea

inadequate allocation concealment leads to exaggerated estimates of treatment effect. None of the studies mentioned blinding and placebo controlled, which are likely to be influenced by either the placebo effect [45] or the observer bias. All of the trials evaluated the efficacy immediately after completing the treatment, and the period of follow-up was not long enough to evaluate the long-term effect of CKI treatment. The included studies were of relatively small sample sizes in individual trials. This may place their statistical analysis's validity in doubt. The results were likely to be underpowered.

Third, the primary outcome should be focused on the level of activities rather than a vague clinical effective rate. However, the common use of "clinical efficacy rate" as an ancillary outcome measure through subjective qualitative scores such as "clinical cure," "markedly effective," "effective," and "ineffective" in Chinese are not internationally recognized, and the validity and reliability of that was uncertain in assessing the outcome.

Forth, special attention should be paid to adverse effects. Safety is a fundamental principle in the provision of herbal medicines and herbal products for health care, and a critical component of quality control. However, there is a widespread misconception that "natural" always means "safe," and a common belief that remedies from natural origin are harmless and carry no risk among most consumers and patients. In fact, the health risks of herbal remedies include direct toxic effects, contamination such as with heavy metals or unlabeled pharmaceutical agents, drug interactions, and the indirect risk that an herb without demonstrable efficacy may impair, delay, or replace conventional treatments [46]. Therefore, World Health Organization (WHO) published WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems in 2004. In present systematic review, only four studies [24, 25, 28, 29] of the included trials reported whether any adverse events relevant to CKI were apparent in patients with bone cancer pain. Thus, all adverse events must be reported by the researchers participating in a clinical trial of CKI in the future.

Lastly, we made an effort to identify all relevant studies, including those in West and East. However, no study outside of China is another limitation that potentially limited the generalizability of the findings. Thus, another limitation was publication bias which was assessed by visual inspection of funnel plots. The funnel plot asymmetry suggests the possibility of publication bias. Vickers and colleagues [47] figured that some Asian countries including China publish unusually high proportions of positive results. Almost all the included RCTs claimed that the positive effect of CKI combined with radiotherapy or bisphosphonates is better than radiotherapy or bisphosphonates alone. Negative findings almost have not been reported. We tried to conduct extensive searches for unpublished material, but no unpublished "negative" studies were found. Therefore, we could not exclude the possibility that studies with negative findings remain unpublished.

Implication for practice

This systematic review provides moderate evidence for the effectiveness and safety of CKI as adjuvant therapy for bone cancer pain, and a clinical recommendation cannot be warranted because of the generally low methodological quality of the included studies (Fig. 2). CKI may have beneficial effects in the improvement of total pain relief rate and quality of life, and reduction of side effects, but this efficacy and safety remain to be further determined by methodologically rigorous trials.

Implication for research

CKI is widely used to treat bone cancer pain in China, but the available evidence is of low quality. Therefore, a judgment on whether CKI is effective cannot be made and more large RCTs are required with particular attention.

First, all of the included RCTs reported subjective symptom relief from the patients' baseline bone cancer pain status. Pain studies rely heavily on subjective patient reports because of the lack of objective measurement tools. Presently, there is no universally accepted tool to assess bone cancer pain in the palliative care setting [48, 49]. Until a validated objective measurement for pain is developed, attempts to use psychometrically validated subjective outcomes, such as a self-administered diary or a health-related quality-of-life questionnaire, a scientific and systematic approach to bone cancer pain assessment is necessary. This approach must involve extensive literature review, expert opinions and consensus, rigorous translation procedures and comprehensive validation [50]. The standard of bone cancer pain assessment could be enhanced using this methodology.

Second, the studies need to incorporate accepted standards for trial design and reporting. Specifically, these studies should be based on proper power calculations for sample size, use of optimal dose of CKI, homogeneity of bone cancer pain conditions under study, control for nonspecific effects and adhere to modern human research ethics.

Lastly, TCM needs EBM, but the evidence from EBM is not limited to RCTs. Innovative methodological studies are urged based on the characteristics of TCM theoretically and clinically. Several guidelines such as the CONSORT statement [51], CONSORTPRO extension [52], guidelines for RCTs investigating Chinese herb medicine [53], and CONSORT for TCM [54] should be used as a guideline when designing and reporting RCTs for TCM in the future.

Conclusions

CKI appears to be able to improve total pain relief and quality of life, and seems to have beneficial effects on reduction of side effects in patients with bone cancer pain compared with

radiotherapy or bisphosphonates. However, current evidence is insufficient to support the efficacy of CKI for bone cancer pain because the included studies were of generally poor quality and had small sample sizes, and the evidence level for low based on the GRADE approach.

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