Int J Clin Exp Med 2017;10(3):5788-5804
www.ijcem.com /ISSN:1940-5901/IJCEM0043040

Review Article

The efficacy of compound kushen injection in preventing and treating radiation-induced oral mucositis: a systematic review and meta-analysis

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Received October 28, 2016; Accepted December 15, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: Background: Oral Mucositis (OM) is a common complication of head and neck cancer with radiotherapy. Given the intractable complication with the radiotherapy of cancer, many patients seek additional prevention and treatment methods that may reduce the incidence, decrease pain, and improve the quality of life. Several randomized controlled trials (RCTs) have reported that Compound Kushen Injection (CKI), a traditional Chinese medicine injection, is efficient in OM. The purpose of this meta-analysis was to evaluate the clinical evidence for or against CKI as a treatment for OM. Methods: Our research registered in PROSPERO (International prospective register of systematic reviews). The registration number is CRD42016049460. We searched the following electronic databases: PubMed, Web of Science, EMBASE, CENTRAL, CNKI, CBM, VIP and Wan-fang Data databases from their inception to September 2016. Searchers were restricted to randomized controlled clinical studies of CKI to intervention for the treatment of OM and without language restrictions. The outcome measures were the grade of radioactive-stomatitis, the pain degree of radiation-induced oral mucositis; Healing time of impaired oral mucosal; The improvement rate for the quality of life, recent therapeutic evaluation of tumor. Used the Cochrane risk of bias to assess the methodological quality of all RCTs. Meta-analysis, sensitivity analysis, publication bias of data was applied RevMan 5.3 software (Cochrane Collaboration) and Stata software. Also, this meta-analysis is reported according to the Preferred Reporting Items or Systematic Reviews and Meta-Analyses (PRISMA) guideline strictly, and the level of evidence assessed by the GRADE approach. Results: We included 18 RCTs (n=1,647). All studies used an active control group. The quality for methodological of included studies was limited. We analyzed data from 18 studies reporting on the grade of radioactive-stomatitis (Relative Risk [RR] of 0.50, 95% CI (0.44, 0.57), P<0.0001). The degree of pain in radioactive-stomatitis included 4 studies, (RR=0.47, 95% CI (0.36, 0.61), P<0.0001). The healing time of oral mucosa included two studies, (RR=1.92, 95% CI (1.15, 2.68), P<0.0001). The improvement rate for the quality of life for adopting CKI described in all five included studies, (RR=1.36, 95% CI (1.17, 1.57), P<0.0001). The recent therapeutic evaluation of solid tumour included 9 studies, (RR=1.14, 95% CI (1.01, 1.30), P<0.0001). Conclusion: Current evidence considering insufficient to show that CKI is an effective treatment of radiation-induced oral mucositis. Such as limited patient numbers, the high risk of bias in the included studies, and reports on adverse effects. But it still provides a clinical choice for the prevention and treatment of OM. More precise studies are required.

Keywords: Radiotherapy, oral mucositis, compound kushen injection, Chinese medicine, head and neck cancer

Introduction

Most new cases of invasive head and neck cancers (HNC) are mainly taken radiotherapy (RT) as an adjunct to surgery, combined with chemotherapy, or as palliative care [1]. RT plays a critical role in the treatment of HNC [2]. Treatment intensification improved clinical outcome, but also increased toxicity effects in the treatment, heavily affect the quality of life of patients with HNC [3]. Oral mucositis (OM) is considered one of the most common complications associated

with HNC treatment [4, 5]. It occurs nearly all patients receiving head and neck radiation therapy with or without chemotherapy [6, 7]. The oral mucosa is a continuously updating of the organization, including a stratified squamous epithelium.

Radiation induces tissue injury at the cellular level, and those tissues most susceptible are those with a higher percentage of dividing cells [8]. Therefore, the oral mucosa is gradually thinned, and when the number of epithelial cells reaches a critical level, the mucosa breaks down due to erosion [9]. And the highest oral mucositis related symptoms would appear, like mouth pain, dryness, eating difficulties, dysphagia, swallowing difficulties [10]. So that patient often suffering malnutrition from mucositis, their energy expenditure increases during RT, promoting an energy deficit of 100 kcal/day and thus significant weight loss [11, 12]. A statistical analysis of the survey, OM has also involved interruption of treatment, placement of feeding tubes, and prolonged hospitalization [13]. How to reduce the OM patient's oral mucosa ulcer and the pain feeling has been a difficult task of the head and neck surgeons. Therefore, it is of great importance, and necessary for the prevention and treatment of oral mucositis when HNC patients are receiving radiotherapy. At present, there are some methods used in the clinic to less pain and symptoms for OM, such as take mechanical cleaning using traditional mouthwashes, use of anti-inflammatory and analgesic agents, use high-power narrow-band red light, use of ice cubes, and use of Traditional Chinese Medicine [14, 15].

However, the prevention and treatment of OM during cancer therapies remain unsolved problems, there are no explicit clinical guidelines currently, and the potential of various prophylactic and treatment methods are not significant. Therefore, scholars all over the world are seeking for ways to prevent and treat OM, but so far there is still no accepted effective method [16].

Traditional Chinese Medicines (TCMs) currently used in the treatment of tumor and alleviate related toxicity widely. Traditional Chinese Medicines are experience-based remedies derived from hundreds or thousands of years of clinical use in China [17]. It can be used in a single herb, prescription, and with another anti-tumor therapy selectivity. This treatment can kill tumor cells, is enhanced the quality of life of patients by systemic regulation [18-20]. Kushen is a kind of Traditional Chinese Medicine which as a prophylactic and treatment herb for solid tumors, inflammation and other diseases has a long history. It is the dried roots of Sophora flavescens Aition (Leguminosae) [21]. The traditional use of it is generally taken from dried plant root to make powder or decoction [22]. The contemporary use for Kushen usually combined with Baituling (Rhizoma Smilacis Glabrae) taking modern standardized Good Manufacturing Processes (GMP), made of a kind of combination formula-Compound Kushen Injection (CKI) also known as Yanshu Injection [23, 24]. It is essential to explore their underlying molecular mechanisms in a systematic fashion, previous studies have shown that it can inhibit tumor reproduction, metastasis, incursion, aggregation by downregulating the Wnt/β-catenin pathway and inducing apoptosis [25, 26], Wei *et al* have used the MCF-7 human breast cancer cell line as an initial in vitro model to identify CKI induced changes in gene expression [18, 27], the recent study identified novel lncRNAs and showed that many of them might be expressed as a response to CKI treatment [17]. And it possesses a variety of pharmacological actions, including reducing pain, anti-inflammatory, anti-viral, anti-fibrotic and some additional effects [28]. In addition, clinical studies have shown that CKI improved the quality of life by modulating the immune function and reduce the adverse reactions of radiotherapy and chemotherapy [29, 30].

In Traditional Chinese Medicine theory, radiotherapy injury belongs to the external cause of the "Three-factors Theory", itself is a kind of "fiery toxin" for the characteristics of the warm pathogen, this toxin from outside and outside the ferocious, burning skin friction, fluid, interaction cause the Yin depletion [31, 32]. And some clinical observation researches of Head and neck cancer after radiotherapy, making clustering analysis, analyzing the clustering result, studying the factors related to syndrome characteristics [33, 34]. The main features of the patients are approximately divided into four categories, as liver stagnation and spleen deficiency type, Qi and Yin insufficiency type, sputum and wet condensation, heat toxin blood

stagnancy type, referring to the "Diagnostics of Traditional Chinese Medicine" [35] and "Traditional Chinese Medicine Oncology" [36]. Discovered the main etiology and pathogenesis are heat toxin injury body fluid contact all the syndromes [37]. Moreover, with analysis of TCM theory, to prevent and cure OM, Compound Kushen Injection, which widely used at the clinic, is one of the great choices.

Our research registered in PROSPERO (International prospective register of systematic reviews). The registration number is CRD42-016049460. And then we had collected relevant researches, adopted Meta-analysis to quantitatively analyze the enrolled literature after the rigid screening, and conducted analysis from the aspects of multiple indicators such as the injury degree of the oral mucosa and the effective rate of the tumour short-term therapeutic effect evaluation. Hence, it was the purpose of this research to assess and analyze the evidence for or against the effectiveness of CKI as a prophylactic and treatment method for radioactive-stomatitis critically.

Materials and methods

Data sources

Naijun Yuan and Xianxin Yan worked independently searched the following electronic databases: PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure (CNKI), Taiwan Electronic Periodical Services, China Proceeding of Conference full-text database, Chinese Biomedical Database (CBM), VIP information database, and WanFang Data Information Site from their inception to September 2016. Searches were restricted to randomized controlled clinical studies of CKI to intervention for the treatment of radiation-stomatitis and without language restrictions. This study is reported by the Meta-Analyses (PRISMA) guideline and Preferred Reporting Items or Systematic Reviews strictly [38].

PubMed search strategy: Radiation-induced oral mucositis OR radioactive oral mucositis OR radioactive oral injury OR head and neck cancer radiotherapy OR cancer radiotherapy OR oral mucositis with anti-cancer therapy [Title/Abstract]; Compound Kushen OR Yanshu [Title/Abstract]; Randomized controlled trial OR randomized OR placebo [Title/Abstract].

Inclusion criteria

Type of study: All the study is randomized controlled clinical studies; Patients of study: 1. The patient must be approved by pathological examination, cytology or radiologically confirmed as head and neck cancer, and were first received radiotherapy; 2. In this process, did not accept other TCM therapies; 3. The baseline of treatment and control groups should be balanced and comparable; 4. Karnofsky performance status (KPS)>60 and expected survival time for more than three months.

Exclusion criteria

Non-randomized controlled clinical trials or trails in which CKI as combination therapy was not the only intervention to differ between the treatment and control groups; Duplicate studies; Studies only reporting summary or insufficient data and contact the author who does not reply; Patients of study: 1. If patients complicate with other oral diseases or other severe organ dysfunction, it is difficult to assess the extent of damage caused by radiotherapy; 2. The mode of administration by non-intravenous; 3. Patients with pregnancy and lactation of head and neck cancer to radiotherapy.

Outcome measures

The primary outcome measures were the grade of radioactive-stomatitis. This is an important condition for screening. Each of the inclusion of the RCT must have to contain the outcome.

The grade of radiation-induced oral mucositis: According to World Health Organization (WHO) Mucositis Scale. It is one of the simplest established grading systems that incorporate both subjective and objective criteria. According to the clinical examination four different stages can identify the grade has been given 0 to 4 mucositis scores [39]. Combined with the 0, 1, 2 scores of calculation for the mild damage, combined 3, 4 scores of the severe damage. And compared according to the severity. The second outcome measures were the pain degree of radiation-induced oral mucositis, healing time of impaired oral mucosal, the improvement rate for the quality of life, recent therapeutic evaluation of tumor, the length of hospital stay, the medical expenses of the patients. Included studies should contain at least one of the outcome measures.

Table 1A. The characteristics of included

Included trails	Sample size (T/C)	Age (T/C)	Interventions (T/C)	CKI Injected Dose	Duration	Outcome measures	Jadad scores	published language
LJP 2008 [49]	90/90	20~60	CKI and Radiotherapy/Radiotherapy	NS 250 ml + CKI 30 ml	5-7 w	1) The grade of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	4	Chinese
XQ 2008 [50]	68/68	47±11.45/49±13.78	CKI and Radiotherapy/Radiotherapy	GS 250 ml + CKI 20 ml	6 w	1) The grade of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	4	Chinese
ZMY 2009 [51]	32/32	28.6±74.3	CKI and Radiotherapy/Radiotherapy	NR	5-7 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM; 4) The improvement rate for quality of life; 5) Recent therapeutic evaluation of tumor.	3	Chinese
CYY 2010 [52]	35/35	45/46	CKI and Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	GS 250 ml + CKI 15 ml	6-7 w	1) The grade of radiation-induced OM; 4) The improvement rate for quality of life; 5) Recent therapeutic evaluation of tumor.	5	Chinese
HJQ 2011 [53]	30/30	NG	CKI and Radiotherapy/Radiotherapy	GS 200 ml + CKI 20 ml	5-7 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM;	4	Chinese
HWY 2011 [54]	43/42	(16~61) 35	CKI and VitC with Radiotherapy/VitC with Radiotherapy	NS 250 ml + CKI 20 ml	7 w	1) The grade of radiation-induced OM; 3) Healing time of impaired oral mucosal;	4	Chinese
SZT 2011 [55]	48/48	(27~72) 54/(26~70) 52	CKI and Radiotherapy/Radiotherapy	GS 250 ml + CKI 20 ml	6-7 w	1) The grade of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	7	Chinese
WJG 2011 [56]	41/37	(34~76) 57/(23~77) 53	CKI and Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	NS 250 ml + CKI 30 ml	42-63 d	1) The grade of radiation-induced OM; 4) The improvement rate for quality of life; 5) recent therapeutic evaluation of tumor	4	Chinese
WR 2011 [57]	30/30	NG	CKI and Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	CKI 20 ml	45 d	1) The grade of radiation-induced OM; 4) The improvement rate for quality of life;	7	English
ZRG 2012 [58]	30/30	(21~75) 51	CKI and gargle with the self-made mouthwash and Radiotherapy/Radiotherapy and gargle with the self-made mouthwash▲	GS 250 ml + CKI 30 ml	6 w	1) The grade of radiation-induced OM;	4	Chinese
FXX 2012 [59]	60/60	51.5±11.1/50.4±9.0	CKI and Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	NS 250 ml + CKI 20 ml	6-7 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM; 4) The improvement rate for quality of life; 5) Recent therapeutic evaluation of tumor.	5	Chinese
SHP 2014 [60]	56/56	(30~60) 43/(31~62) 42	CKI and Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	CKI 15 ml	6-7 w	1) The grade of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	7	Chinese
CHT 2015 [61]	40/40	43.56±7.89/42.49±8.13	CKI and gargle with the self-made mouthwash and Radiotherapy/Radiotherapy and gargle with the self-made mouthwash▲	NS 200 ml + CKI 20 ml	6 w	1) The grade of radiation-induced OM; 3) Healing time of impaired oral mucosal;	4	Chinese
LB 2015[62]	30/30	43/45	CKI with Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	NS 250 ml + CKI 20 ml	6 w	1) The grade of radiation-induced OM; 4) The improvement rate for quality of life; 5) Recent therapeutic evaluation of tumor	5	Chinese
WL 2015 [63]	60/60	47.8±12.7	CKI and self-made mouthwash▲ with Radiotherapy/Radiotherapy and self-made mouthwash▲	GS 250 ml + CKI 30 ml	6 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	4	Chinese

WPF 2015 [64]	56/56	(30~60)43/(31~62) 42	CKI with Radiotherapy and chemotherapy/Radiotherapy and chemotherapy	CKI 15 ml	6-7 w	1) The grade of radiation-induced OM; 5) Recent therapeutic evaluation of tumor.	7	Chinese
HQ 2016 [65]	36/36	52.15±10.17/52.26±10.13	CKI and CSVtB6 with Radiotherapy/ CSVtB6 with Radiotherapy	GS 250 ml + CKI 30 ml	4 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM;	6	Chinese
JYY 2016 [66]	42/40	(19~64) 50.6/(14~69) 47.8	CKI and self-made mouthwash▲▲ with Radiotherapy and chemotherapy/CKI and self-made mouthwash▲▲ with Radiotherapy and chemotherapy	NS 250 ml + CKI 20 ml	6 w	1) The grade of radiation-induced OM; 2) The pain degree of radiation-induced OM;	5	Chinese

Eighteen trials (n=1,647) conducted in China were included in this study. Self-made mouthwash▲: The mixture of NS (normal saline), lidocaine, dexamethasone. Self-made mouthwash▲▲: The mixture of Compound borax and NS, lidocaine, gentamicin and dexamethasone. CSVitB6: Cantharidin sodium vitamin B6 Injection (by Intravenous injection). NR: No report; W: Week; NS: Normal saline; GS: Glucose.

Table 1B. Quality score of selected studies (Jadad scores)

Study	Generation of allocation sequence	Allocation concealment	Double blinding	Withdrawals	Efficacy of Randomization	Total
LJP 2008 [49]	1	1	1	1	0	4
XQ 2008 [50]	1	1	1	0	1	4
ZMY 2009 [51]	1	1	1	0	0	3
CYY 2010 [52]	1	2	1	0	2	5
HJQ 2011 [53]	1	1	1	0	1	4
HWY 2011 [54]	1	1	1	0	1	4
SZT 2011 [55]	1	2	1	1	2	7
WJG 2011 [56]	1	1	1	0	1	4
WR 2011 [57]	1	2	1	1	2	7
ZRG 2012 [58]	1	1	1	0	1	4
FXQ 2012 [59]	1	1	1	0	2	5
SHP 2014 [60]	1	2	1	1	2	7
CHT 2015 [61]	1	1	1	0	1	4
LB 2015 [62]	1	2	1	0	1	5
WL 2015 [63]	1	1	1	0	1	4
WPF 2015 [64]	1	2	1	1	2	7
HQ 2016 [65]	1	2	1	0	2	6
JYY 2016 [66]	1	1	1	1	1	5

The pain degree of radiation-induced oral mucositis: According to the VAS rating scale, pain 0 points; Mild pain from 0 to 3 points; Moderate pain from 4 to 6 points; Severe pain 7 to 10 points. When calculating the moderate to severe pain together, pain and mild pain be aggregated [40].

Healing time of impaired oral mucosal.

The improvement rate for quality of life: KPS scores based on quality of life, increase 10 into improved reduction 10 is divided into decline, no change is stable. Quality of Life (QoL) and a stable rate=(steady improvement in the number of cases of + number of cases)/total cases 100% [41].

Recent therapeutic evaluation of tumor: Referring represent Response Evaluation Criteria in Solid Tumors are divided into CR, PR, SD, PD complete remission, partial remission, stable progress in these four kinds of evaluation, RR represents an efficiency=(CR + PR)/(CR + PR + SD + PD) *100% [42].

The length of hospital stay, the medical expenses of the patients: There no RCT included these outcomes.

Study selection and data extraction

Two reviewers worked independently, in duplicate, examining titles and abstracts to screen eligible RCTs. The full text of pertinent studies was retrieved and read to examine which studies met the inclusion criteria. If holding disagreements, we were resolved by discussion or by a third reviewer (Min Ma). Then two reviewers independently extracted the data including author, published time, outcome measures and the basic characteristics of the included studies of interventions. Also, included in the extraction of RCTs literature taken randomization, blinding, whether the lost and quit, whether balancing methodology baseline characteristics.

Validity assessment of included studies

Methodological quality included in the study based on the assessment of the risk of bias assessment tools recommended from Cochrane Collaboration in seven criteria, including selection bias divided to random sequences and allocation concealment, blinding participation and subjects, blinding outcome evaluation studies, inadequate outcome data, selective reporting of results, and other bias. Above quality standards, as are all of the standard “used/

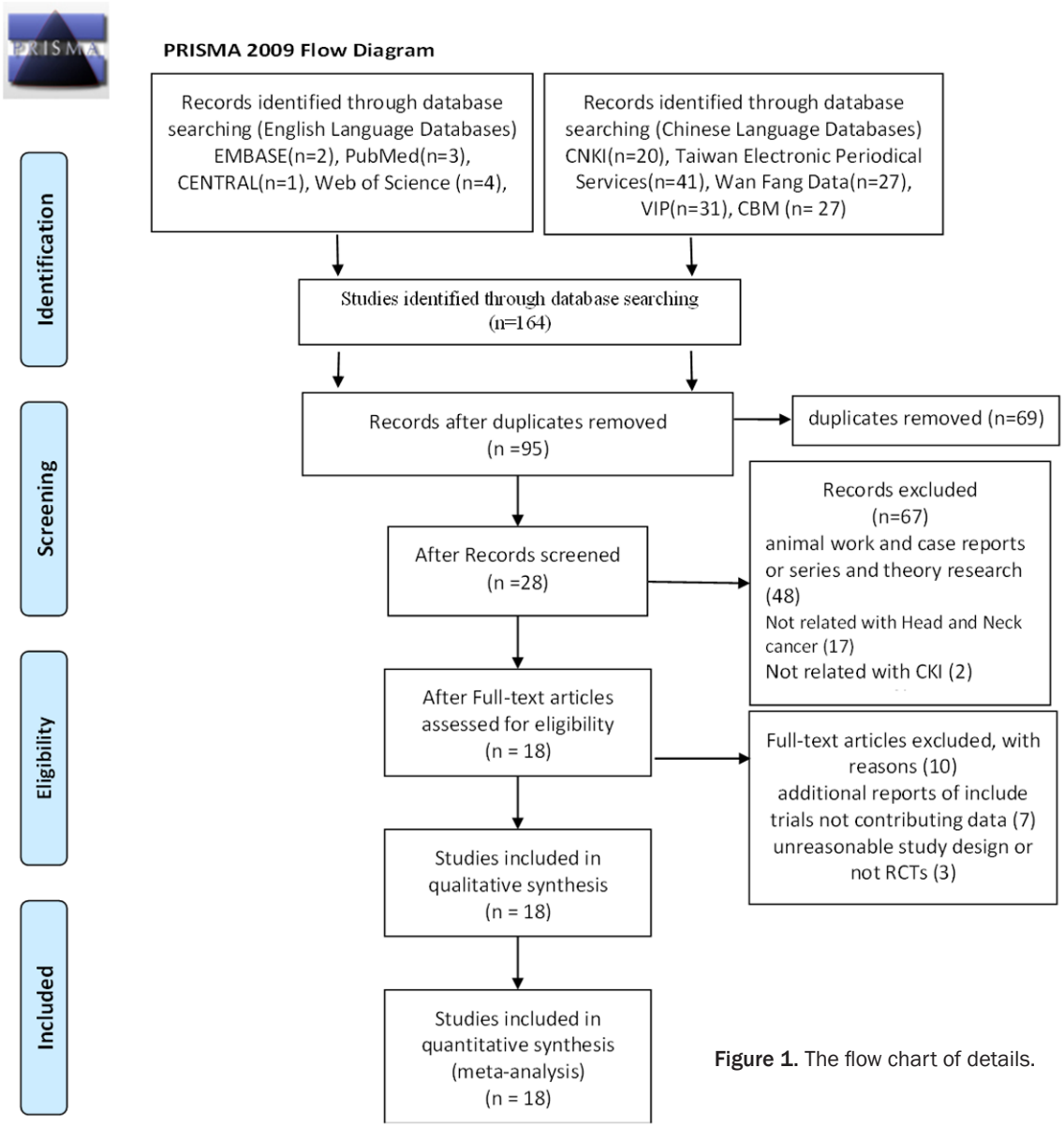

Figure 1. The flow chart of details.

sufficient", a small possibility of bias occurs, if one promising "unclear", there is a medium likelihood of a corresponding bias, if it is "not employed/insufficient", then there is a high degree of likelihood of a corresponding bias [43, 44]. Three reviewers individually evaluated the methodological quality of the included studies. And we also evaluated the quality using the modified Jadad scores (MJS). The established standard is evaluated through several aspects of RCTs: Generation of allocation sequence (2-computer-generated random numbers, 1-not described); Allocation concealment (3-central randomization, 2-sealed envelopes or similar, 1-not described or inadequate); Investigator blindness (2-identical placebo tablets or similar, 1-inadequate or not described, 0-no double-blinding), description of withdrawals and drop-outs (1-numbers and reasons are described, 0-numbers and reasons are not described), efficacy of randomization (2-pretreatment variables in tabular form, 1-balance of pretreatment variables mentioned but not in tabular form, 0-no information reported) [45, 46]. The quality scores based on the modified Jadad scores of each study was showed in **Table 1A**. Specific quality score of selected studies showed in **Table 1B**. Disagreements were resolved by discussion or arbitrated by an others reviewer (Min Ma) if necessary.

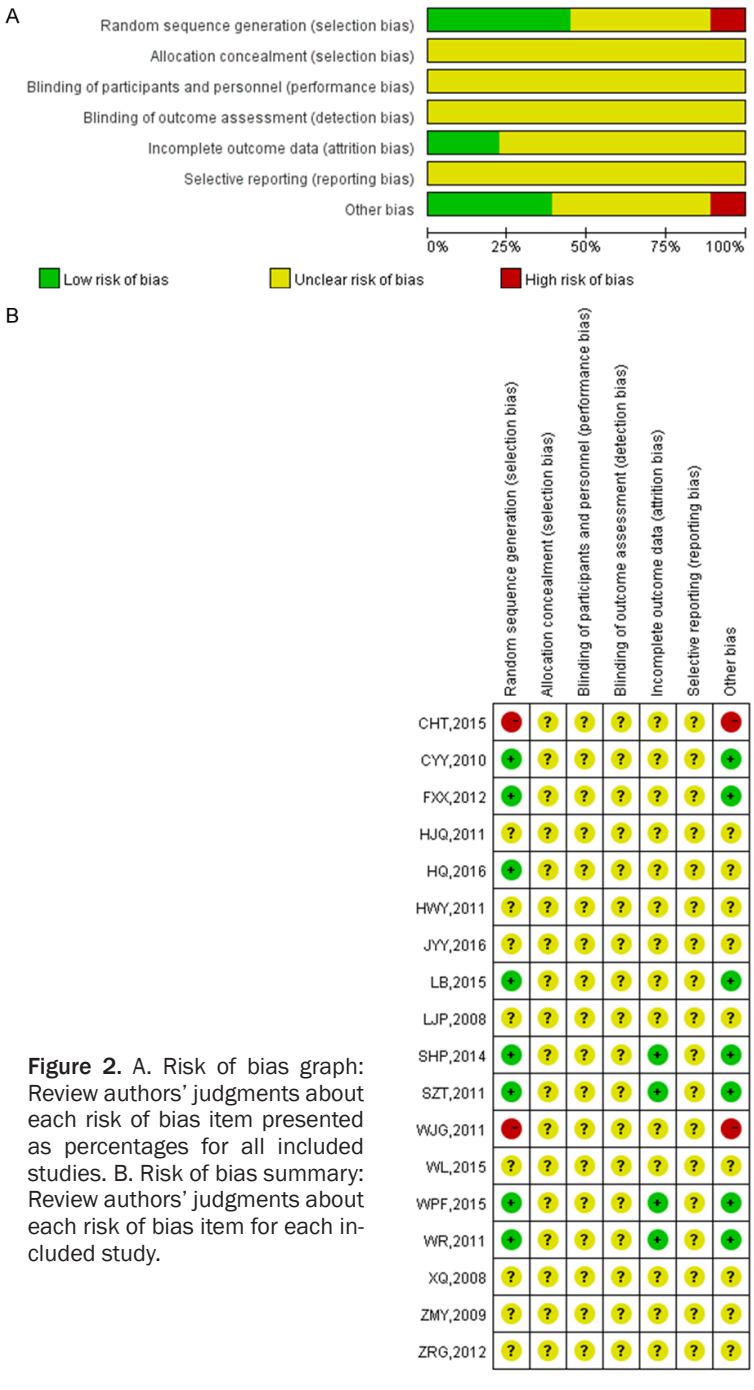

Figure 2. A. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages for all included studies. B. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study.

Statistical analysis and data synthesis

Used the RevMan5.3 software, the Cochrane Collaboration (Oxford, UK) offered, to conduct Meta-analysis. Performed prior to the merger statistics heterogeneity test, when $P \geq 0.1$ and $I^2 \leq 50\%$, considered among the plurality of homogenous study, it can be fixed effect model analysis and evaluation; when $P < 0.1$ and $I^2 > 50\%$ that prompt with considerable heterogeneity among studies, it should select the random effects model, and subgroup analysis according to sources of heterogeneity that may exist, and carefully explain the results of the analysis, when $P < 0.1$ and unable to determine the source of heterogeneity should discard Meta-analysis, only make a descriptive analysis. When analyzing dichotomous variables using relative risk (RR) as its effect size. Selectable measurement data mean difference (MD or WMD), standardized mean difference (SMD) as the effect size, and all analyzes were seeking the 95% CI [47, 48]. Funnel plots were utilized to detect publication bias.

Results

Retrieval results

We searched the following electronic databases: PubMed, EMBASE, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Chinese National Knowledge Infrastructure (CNKI), Taiwan Electronic Periodical Services, China Proceeding of Conference full-text database, Chinese Biomedical Database (CBM), VIP information database, and WanFang Data Information Site. The detail showed in **Figure 1**. Through stepwise screening, 18 articles were finally included [49-66]. They are included in these databases, and some articles are also included in several databases at the same time: 9 of these articles [49-51, 54, 58, 60-63] were included in four Chinese databases (CNKI, VIP, CBM and Wan fang database), 5 of these articles [52, 59, 64-66] at the same time by three Chinese databases (CNKI, VIP, and WangFang database) included, 2 of these articles [53, 56] were included in two databases (CNKI and VIP database) at the same time, one article [55] were

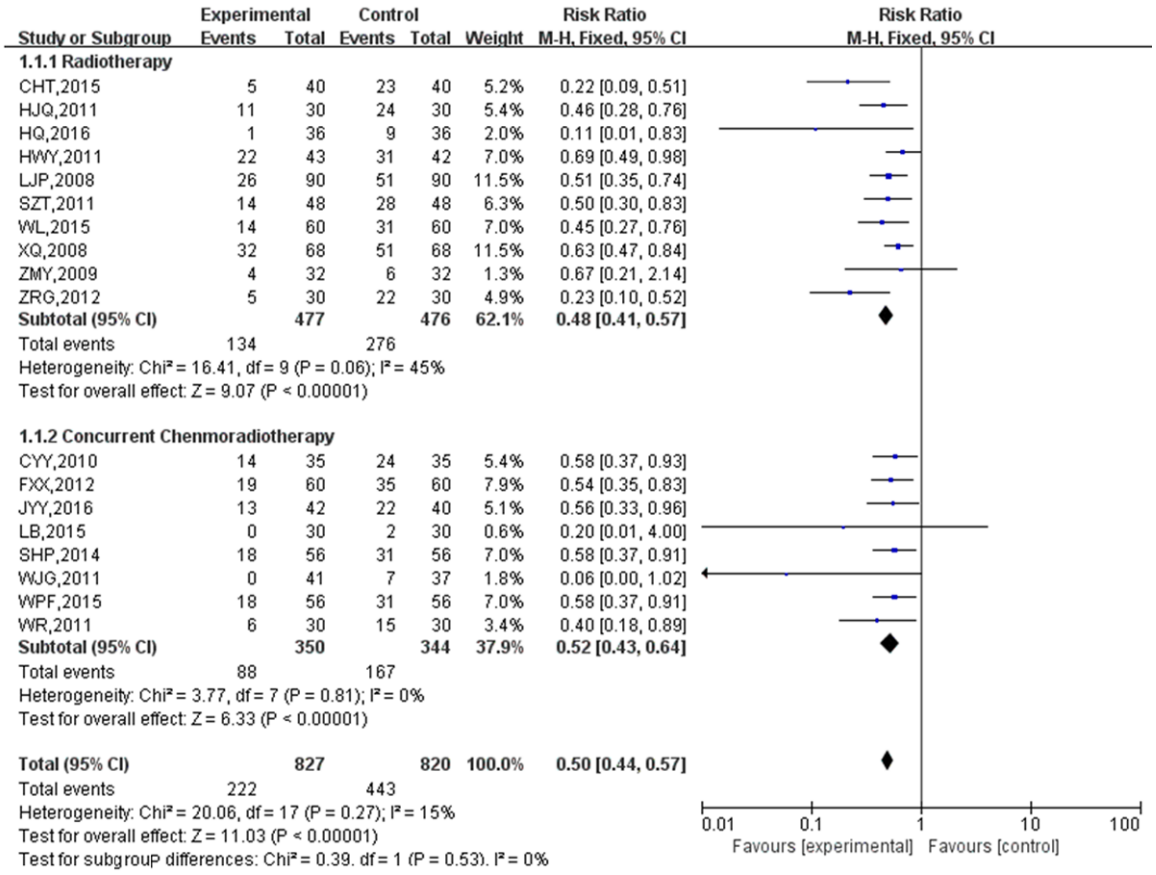

Figure 3. Forest plot of the grade of radiation-induced oral mucositis.

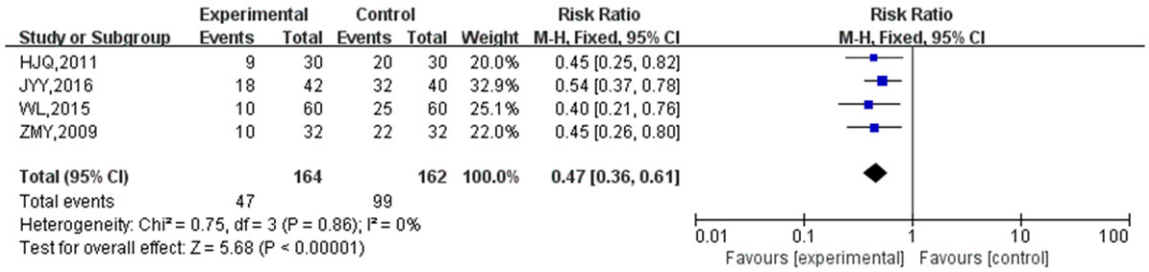

Figure 4. Forest plot of the pain degree of radiation-induced oral mucositis.

included in these two databases (VIP and WanFang database), one article [57] were included in PubMed.

The basic characteristics of included studies

Showed in **Table 1A** and **1B**.

Methodological quality of included articles

This study included 18 randomized controlled trials [49-66], baseline comparability was reported, and all of the random methods were adopted. There were five trials used simple random digital table method, one trail used the lottery, one used the envelope method, one based on odd or even week visit to the random allocation method, one was randomly grouped according to the order of admission and other trials have not mentioned the method of random grouping. All trials have not referred to the blind method and the distribution of the hidden situation. All trials were not mentioned the with-

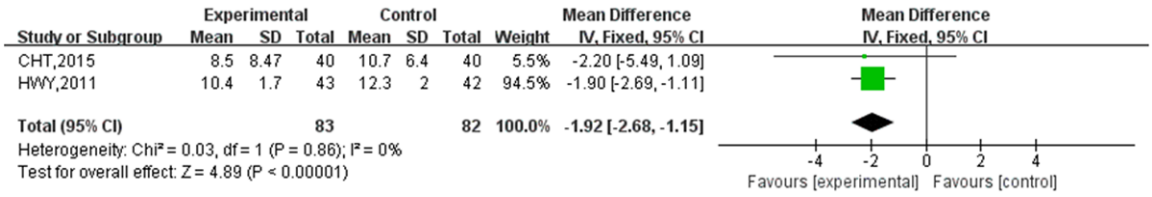

Figure 5. Forest plot of the healing time of oral mucosa.

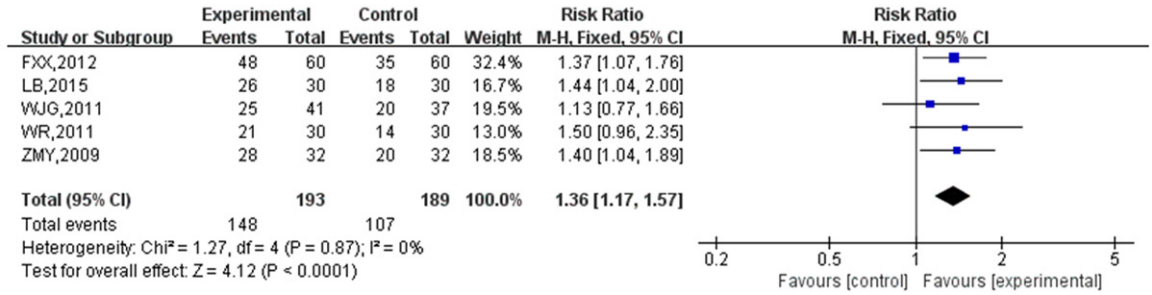

Figure 6. Forest plot of the improvement rate for quality of life.

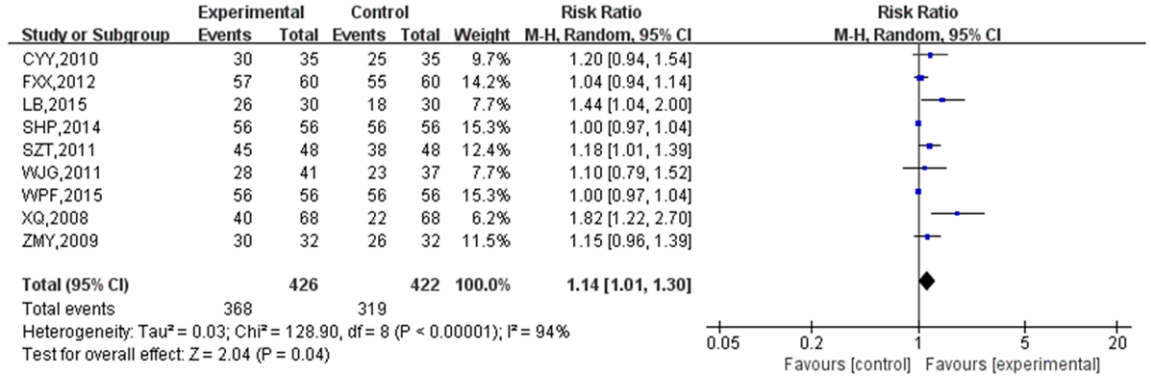

Figure 7. Forest plot of recent therapeutic evaluation of solid tumor.

drawal or quit of the treatment process; only 5 trials conducted a long-term follow-up. No intentional analysis (ITT) was also reported taking measures to ensure the compliance of the subjects. The risk of bias of information as showed in **Figure 2**.

Analysis of outcomes

The grade of radiation-induced oral mucositis: The grade of radiation-induced oral mucositis in whether adopt CKI was described in all 18 included studies [49-66] a total of 1,647 patients, including nasopharyngeal, laryngeal, paranasal sinus cancer, oropharyngeal cancer and other types of patients with nasopharyngeal carcinoma based. There are 827 cases in the test group, 820 cases of patients in the control group. Divided into two subgroups according to whether with the concurrent chemotherapy treatment measures, there was no evidence of significant heterogeneity in each subgroup (P=0.27, I^2=15%), so we used fixed effect model to analyze. See **Figure 3**. The severity of oral mucosa injury in the test group was significantly lower than the control group; the difference possesses statistical significance (RR=0.50, 95% CI (0.44, 0.57), P<0.0001).

The degree of pain of radiation-induced oral mucositis: We pooled data from four trials [51, 53, 63, 66] reporting on the degree of pain of

A

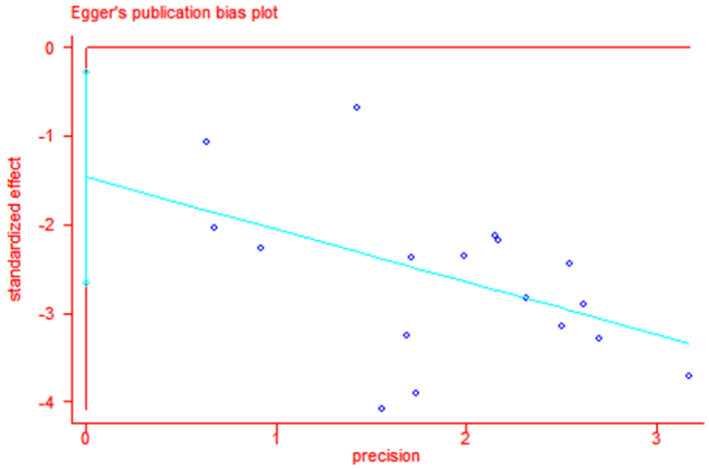

Figure 8. A. Egger's publication bias plot. B. Egger's test.

B

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	-.5912645	.2730831	-2.17	0.046	-1.170175	-.0123542
bias	-1.465575	.5651163	-2.59	0.020	-2.663568	-.2675815

radiation-induced oral mucositis among 326 patients. There are 164 cases in the test group, 162 cases of patients in the control group. We used fixed-effect model to analyze because no heterogeneity between studies (P=0.86, I^2=0%). See **Figure 4**. The results indicated that the degree of pain in the experimental group was significantly lower than the control group, and the difference is statistically significant. (RR=0.47, 95% CI (0.36, 0.61), P<0.0001).

The healing time of oral mucosa: We pooled data from two trials [54, 61] reporting on the healing time of oral mucosa among 165 patients. There are 83 cases in the test group, 82 cases of patients in the control group. We used fixed-effect model to analyze because no heterogeneity between studies (P=0.86, I^2=0%). See **Figure 5**. The results indicated that the healing time of text group significantly less than the control group and the difference is statistically significant. (RR=1.92, 95% CI (1.15, 2.68), P<0.0001).

The improvement rate for quality of life: The improvement rate for the quality of life for whether adopt CKI described in all 5 included studies [51, 56, 57, 59, 62], a total of 382 patients. There are 193 cases in the test group, 189 cases of patients in the control group. No evidence of heterogeneity between studies (P=0.87, I^2=0%), it can be fixed effect model to Meta-analysis. See **Figure 6**. The severity of oral mucosa injury in the test group was significantly lower than the control group, the rate of the experimental group was significantly higher than control group; The difference possesses statistical significance (RR=1.36, 95% CI (1.17, 1.57), P<0.0001).

Recent therapeutic evaluation of solid tumor: We pooled data from 9 trials [50-52, 55, 56, 59, 60, 62, 64] reporting on recent therapeutic evaluation of solid tumor among 848 patients. There are 426 cases in test group, 422 cases of patients in the control group. The heterogeneity test showed X^2=*128.90*, *P=0.004*, and I^2=*94%*, indicating large statistical heterogeneity between studies. Based on the heterogeneity test, the random-effects model was used to calculate. See **Figure 7**. The results showed that text group with higher efficiency than control group in the treatment of recent therapeutic evaluation of solid tumor, the difference possess statistical significance (RR=1.14, 95% CI (1.01, 1.30), P<0.0001). Because of the small number of studies included, no subgroup analyzes were performed. In addition, we analyzed the possible source of heterogeneity, that may exist a statistically significant difference between two groups.

Compound Kushen Injection for radiation-induced oral mucositis

Patient or population: patients with radiation-induced oral mucositis
Settings:
Intervention: Compound Kushen Injection

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk Control	Corresponding risk Compound Kushen Injection	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
the degree of OM	Study population		RR 0.53 (0.46 to 0.6)	1647 (18 studies)	⊕⊖⊖⊖ low[1,2]	
	540 per 1000	286 per 1000 (249 to 324)				
	Moderate					
	560 per 1000	297 per 1000 (258 to 336)				
the degree of pain for OM	Study population		RR 0.47 (0.36 to 0.61)	326 (4 studies)	⊕⊖⊖⊖ low[3]	
	611 per 1000	287 per 1000 (220 to 373)				
	Moderate					
	677 per 1000	318 per 1000 (244 to 413)				
the days of Oral mucosa healing		The mean the days of oral mucosa healing in the intervention groups was 1.92 lower (2.68 to 1.15 lower)		165 (2 studies)	⊕⊖⊖⊖ low[1,3]	
the improvement rate for quality of life	Study population		RR 1.37 (1.18 to 1.58)	382 (5 studies)	⊕⊖⊖⊖ low[1,3]	
	566 per 1000	776 per 1000 (668 to 894)				
	Moderate					
	583 per 1000	799 per 1000 (688 to 921)				
recent therapeutic evaluation of solid tumor	Study population		RR 1.14 (1.01 to 1.3)	848 (9 studies)	⊕⊖⊖⊖ low[1,3]	
	756 per 1000	862 per 1000 (763 to 983)				
	Moderate					
	792 per 1000	903 per 1000 (800 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] All trials were not referred to the blind method and the distribution of the hidden situation.
[2] Then Stata12.0 software was used to make egg's quantitative analysis,p<0.05, indicated the funnel figure had dissymmetry, possibly because publication bias existed and negative results was not published.
[3] The studies with limited patient numbers.

Figure 9. Grade evaluation: Compound Kushen Injection for radiation-induced oral mucositis.

Analysis of adverse drug reactions

There are two articles [65, 66] mentioned the adverse reactions of Compound Kushen injection, describing a small number of patients with mild nausea, vomiting, mild fever and skin itching (treatment group of 7 people, 4 people in the control group). The difference between the treatment group and the control group was not statistically significant, and there were no significant adverse reactions reported in other included studies, in addition, all studies have not resulted in the interruption of treatment because of the combined use of CKI, which suggests that CKI security is better. However, adverse drug reactions were not the focus of this review and would need further research.

Analysis of publication bias

Used RevMan5.3 software found the dissymmetry in publication bias funnel Figure base on preventive treatment radioactive-stomatitis with CKI, indicating small amplitude publication bias possibly existed. Then Stata 12.0 software was used to make egg's quantitative analysis, (as showed in **Figure 8A**, **8B**), *P<0.05*, indicated the funnel Figure had dissymmetry, possibly because publication bias existed and negative results were not published. Life quality stable rate: *P=0.098*, evaluation on recent curative effects: *P=0.754*, pain relief rate: *P=0.156*, and all indicating no publication bias. Only two studies recorded the oral mucosa injury time to be the outcome measure. Therefore, funnel

Figure and quantitative analysis were not performing. And, it is not absolute to analyze whether there existed publication bias by above analysis.

Evidence strength

Evidence strength based on the GRADE approach, evidence strength for Compound Kushen Injection reduces the degree of radiation-induced OM was low. Evidence strength for CKI reduces the degree of OM-related pain was low. Evidence strength for CKI reduces the times of OM healed were low. Evidence level for increased rate of QoL was also low. Evidence level for CKI increased the recent therapeutic elevation of the solid tumor was also low (**Figure 9**).

Discussion

Discussion summary of results

This Meta-analysis included 18 RCTs with a total of 1,647 patients. CKI has been widely used in China, many studies have demonstrated its clinical effect of adjuvant therapy of tumors, it can be used as an adjunct comprehensive cancer treatment [67, 68]. As treatment method with radiotherapy or/not combined chemotherapy to establish a subgroup, this analysis indicated: [RR=0.50, 95% CI (0.44, 0.57), P<0.0001]. In this study, others outcome measures were analyzed by Meta-analysis, indicating CKI can be used for tumor patients who need radiotherapy or chemotherapy by lowering the pain degree and reducing the duration of oral mucosal injury, meanwhile, it can improve the life quality stability rate of head and neck cancer patients who need radiotherapy and/not combined chemotherapy [RR=1.36, 95% CI (1.17, 1.57), P<0.0001], improve the efficacy of solid tumors [RR=1.14, 95% CI (1.01, 1.30), P<0.0001].

Limitations

In this study, there possibly had the following limits: (1) After the study was included in the document and evaluated by Cochrane system, most studies with lower methodological quality. (2) The included patients were all from China, affecting the validity and reliability of generalizing, which are related to less application of Chinese medicine injections in foreign countries; (3) The treatment methods for oral mucositis when HNC patients receiving radiotherapy is incompletion consistently, like conventional therapy and intervening measures (including drugs or treatment courses), therefore, increasing the heterogeneity among studies to some extent; (4) Only a few studies designed follow-up visit after taking drugs, therefore, lack of aftereffect studies make this study limited in clinical promotion and application; (5) In all included studies, only one study used TCM syndrome descriptions on HNC patients, so, TCM diagnosis and treatment descriptions were insufficient; (6) In addition, it is much to be regretted that there is no detailed comparison the length of hospital stay, the medical expenses of the patients after using CKI in all study.

In a word, based on the current research results, Compound Kushen Injection had more definite effect in treating radiation-induced oral mucositis, applicable to the clinical promotion and application. It also provides a new idea integrated Chinese and Western medicines in treating radioactive oral mucosa injury. The reporting of methodological issues was limited, more high-quality large samples, blind methods and randomized controlled trials should be provided to evaluate further and verify the curative effect of Compound Kushen Injection in preventing and treating oral mucosa injury resulted from radiotherapy or combined with chemotherapy on head-neck cancer patients.

Conclusion

These analyses demonstrate that CKI may significantly reduce the degree, related-pain, repairing time of radiation-induced OM; Also, increased the rate of the quality of life. It is likely that CKI combination with anti-cancer treatment also improves recent therapeutic elevation of the solid tumor. CKI should be provided with an integrative therapeutic option for oral mucositis which HNC patients are receiving RT, improve the quality of life and reduce suffering pain. However, we based on the GRADE approach to assessing evidence strength, the evidence of each evidence was low quality. Therefore, our findings must be interpreted with caution because of the low power and limitations of the research. Certainly, further rigorous, large-simple RCTs are essentially required to confirm these outcomes.

Acknowledgements

The current work was supported by National Natural Science Foundation Project of China (nos. 81673979, 81473688, 81173265, 8137-3314); Education Program of China for New Century Excellent Talents (no. NCET-13-0827); Traditional Chinese Medicine Administration Project of Guangdong Province, China (no. 20141070); Science and Technology Support Program of Guangzhou, China (nos. 2014J-4100104, 201605131227328); Science and Technology Planning Project of Guangdong Province, China (nos. 2014A020212672, 20-14A020210015, 2013B090500105); Natural Science Foundation Project of Guangdong Province, China (nos. 2016A030313114, 2015A-030313333); Jinan University scientific research cultivation and Innovation Fund/Special fund for basic research business of Central University (nos. 21615464, 21615412); Jinan University 2015 annual National College Students' innovation and entrepreneurship training programs (no. 201510559046).

Disclosure of conflict of interest

None.

Authors' contribution

Naijun Yuan, Guijuan Zhang and Xianxin Yan are joint Senior Author.

Abbreviations

CKI, Compound Kushen Injection; OM, Oral Mucositis; RT, radiotherapy; TCM, Traditional Chinese Medicine; CENTRAL, Cochrane Central Register of Controlled Trials; RCTs, randomized controlled trials; CNKI, Chinese National Knowledge Infrastructure; CBM, Chinese Biomedical Database; VIP, VIP information database; KPS, Karnofsky performance status; ITT, intentional analysis; NS, normal saline; T, tail; C, control; CsVitB6, Cantharidin sodium vitamin B6 Injection.

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