

Herbal medicine (Hyeolbuchukeo-tang or Xuefu Zhuyu decoction) for treating primary dysmenorrhea

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background: Primary dysmenorrhea is a condition characterized by painful menstrual cramps that usually occurs in the absence of any identifiable pathological condition among menstruating women, with the prevalence estimates varying between 45% and 95%. Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered as a standard treatment for primary dysmenorrhea; however, the failure rate of NSAIDs is often 20% to 25% and these drugs commonly cause adverse effects. In this review, we investigated the current evidence related to the effectiveness of Xuefu Zhuyu decoction (XZD) or Hyeolbuchukeo-tang, a traditional herbal formula, as a treatment for primary dysmenorrhea.

Methods: Literature search was conducted about randomized controlled trials (RCTs) for XZD on primary dysmenorrhea. PubMed, Cochrane Library, Embase, China National Knowledge Infrastructure Database, Oriental Medicine Advanced Searching Integrated System, and other Chinese, Korean, Japanese databases were searched up to December 20, 2017. Two independent reviewers extracted and assessed the data. The main outcome domains were visual analogue scale (VAS) score and response rate.

Results: Among 475 publications, 8 RCTs involving 1048 patients were finally included. Methodological quality of included RCTs was relatively low. In 4 add-on design studies, XZD plus western medication (WM) group showed better response rate as compared to the WM sole therapy (relative risk 1.18, 95% confidence interval [1.11, 1.25], $P < .01$). VAS score after the 3rd month of treatment in the XZD plus WM group was also lower than that in the WM group (mean difference -0.45 , 95% confidence interval $[-0.79, -0.12]$, $P < .01$). In 4 XZD versus WM design studies, XZD sole therapy showed better response rate than did WM sole therapy (relative risk 1.26, 95% confidence interval [1.06, 1.49], $P < .01$).

Conclusion: The existing trials showed a favorable effect of XZD for the management of primary dysmenorrhea. However, the efficacy of XZD on primary dysmenorrhea is not conclusive owing to the small number of studies and the high risk of bias. Large-scale, long-term RCTs with rigorous methodological input are needed to clarify the role of XZD for the management of primary dysmenorrhea.

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Abbreviations: AE = adverse event, CHM = Chinese herbal medicine, CI = confidence interval, MD = mean difference, NSAIDs = nonsteroidal anti-inflammatory drugs, PI = pattern identification, RCT = randomized controlled clinical trial, RR = risk ratio, TCM = traditional Chinese medicine, VAS = visual analogue scale, VIP = Chinese Scientific Journals Database, WM = western medication, XZD = Xuefu Zhuyu decoction.

Keywords: herbal medicine, Hyeolbuchukeo-tang, primary dysmenorrhea, systematic review, Xuefu Zhuyu decoction

1. Introduction

Primary dysmenorrhea is a menstrual disorder characterized by painful cramps that usually occurs in the absence of any identifiable pathological condition among menstruating women, with the prevalence estimates varying between 45% and 95%.^[1,2] Despite the high prevalence, dysmenorrhea is often poorly understood, treated, and even disregarded by health professionals and the women themselves, who may accept it as a normal characteristic of their menstrual cycle.^[3] However, dysmenorrheic pain is not only the primary cause of recurrent short-term school or work absenteeism among young women, but also the cause of a significantly reduced quality of life, low mood, and poor sleep quality during menstruation as compared to the women without primary dysmenorrhea.^[3]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are considered as a standard as well as an effective treatment for primary dysmenorrhea.^[4] However, the failure rate of NSAIDs is often 20% to 25%, and these drugs may be contraindicated or may not be tolerated by some women.^[4] In addition, NSAIDs commonly cause adverse effects, including indigestion, headaches, and drowsiness.^[4] Therefore, many women also seek alternative therapies to manage their menstrual discomfort including Chinese herbal medicine (CHM).^[5]

Traditional Chinese medicine (TCM) or Korean medicine identified blood stagnation as the main factor causing abdominal pain during menstruation.^[6] Blood stasis is one of the important pathological concepts in TCM since its concept was first documented in Huangdi Inner Classic. Additionally, it is one of the currently active and vibrant research domains in TCM.^[7,8] Generally, blood stasis is a significant pathological product due to stagnant blood.^[7,8] If blood stasis occurs within the body, characteristic symptoms such as pain in a fixed position, nyctalga, dark-purple coloring of the tongue or face, infraorbital darkness, sublingual varicosis, blood spots under the skin or tongue, or an astringent pulse can manifest.^[9] In clinical practice, many diseases such as ischemic heart disease, cerebral vascular accident, chronic gastritis, trauma, and dysmenorrhea can be related to blood stasis.^[10]

Hyeolbuchukeo-tang also known as Xuefu Zhuyu decoction (XZD) was the most frequently used formula in research focused on blood stasis in Korea.^[11] XZD is recorded in the book "Correction on Errors in Medical Classics" in 1830. The components of XZD include the followings: *Angelicae Sinensis Radix*, *Rehmanniae Radix*, *Persicae Semen*, *Carthami Flos*, *Aurantii Fructus*, *Paeniae Radix Rubra*, *Bupleuri Radix*, *Glycyrrhizae Radix et Rhizoma*, *Chuanxiong Rhizoma*, *Achyranthis Bidentatae Radix*, and *Platycodonis Radix*. There have been substantial randomized controlled clinical trials (RCTs) using XZD for primary dysmenorrhea, but no review focused on the use of XZD in the treatment of primary dysmenorrhea has been published yet. Therefore, in this review, we investigated the current evidence related to the effectiveness of XZD or Hyeolbuchukeo-tang, a traditional herbal formula, as a treatment for primary dysmenorrhea.

2. Materials and methods/design

We have followed a previously published systematic review protocol.^[12] A detailed explanation of the methodology has been described in the protocol. We have also registered the systematic review protocol. The trial registration number is CRD42016050447 in PROSPERO 2016.

2.1. Data sources and search strategy

Two independent reviewers (J L, H L) searched for the following databases from inception to December 20, 2017: The Cochrane Central Register of Controlled Trials, EMBASE (via OVID), Medline (via PubMed), Cumulative Index to Nursing and Allied Health Literature, and Allied and Complementary Medicine Database. Three Chinese databases Wanfang, Chinese Scientific Journals Database (VIP), and China National Knowledge Infrastructure Database were also searched. Six Korean medical databases (KoreaMed, DBPia, Oriental Medicine Advanced Searching Integrated System, Research Information Service System, Korean Traditional Knowledge Portal, Korean studies Information Service System) and 1 Japanese medical database (CiNii) were also searched. Clinical trial registries, conference proceedings, and relevant journals were manually searched. The search terminologies comprised of:

- (1) the disease or its symptoms (eg, pelvic pain, menstrual disorder, cramps, painful period, period pain, painful menstruation, menstrual pain, and dysmenorrhea)
- (2) intervention term (eg, Xuefu Zhuyu granule/decoction/formula/tang/capsule/pill/ tablet or Hyeolbuchukeo-tang).

The search strategy for each database was modified according to the database. The details of the search strategies are explained in supplementary 1, <http://links.lww.com/MD/C771>.

2.2. Eligibility criteria

We included the prospective, RCTs only. In Chinese articles, the randomization process was not described in detail, although the word "randomization" was used; we included such studies. Patients with primary dysmenorrhea were included in our review. Patients with secondary dysmenorrhea due to a specific pathological condition such as infection or endometriosis were excluded. In the intervention group, both XZD sole therapy or XZD adjunctive therapy (XZD plus other agent used for intervention) were included in our review. In addition, the control group intervention included no treatment or usual care or western medication (WM) sole therapy. Studies involving combined therapies such as XZD with acupuncture versus WM were excluded. "Head to head design" that compared XZD versus other traditional medicine interventions such as herbal medicine, moxibustion, or acupuncture were also excluded. The XZD is composed of 11 medicinal herbs. We also included modified XZD which contains less than 6 modified (50%) medicinal herbs. There was no restriction of language for

including the study in our review. Disagreement between the 2 reviewers was finally judged by a third independent reviewer (J J).

2.3. Data extraction

According to our previous protocol,^[12] data extraction form was prepared that included the information related to the study design, first author, country where the study was conducted, published year, language, clinical setting, age, number of patients as well as the dropout rate in the control group and the intervention group, diagnostic criteria, disease duration, disease severity, number of arms, type of XZD formulation, number of adverse events (AEs), composition and dosage of XZD, pattern identification (PI), treatment duration, follow up duration, control group intervention, and types of outcome variables. If the outcome variables were measured several times, we extracted the data at every time point. Two authors performed data extraction independently (H L, C K). Disagreement between the reviewers (H L, C K) was resolved by discussion among all authors. In case of ambiguous or insufficient data, we contacted the author of the article for further clarity.

2.4. Outcome measurement

In our previous systematic review protocol,^[12] visual analogue scale (VAS) score and response rate were the primary outcomes of our research. In Chinese articles, treatment response was usually divided into 4 categories viz. “Cured” (C), “Markedly improved” (M), “Improved” (I), and “No effect” (N). In our previous protocol, we defined 3 types of response rates viz. type I, type II, and type III. In type I category, “No effect” group was defined as a nonresponder group and the other group (C, M, and I groups) was defined as a responder group. In type II category, the responders were defined as those with more than 50% improvement in the symptoms while the nonresponders were defined as those with less than 50% improvement in the symptoms. The proportion of responders between the treatment and the control group in each type were compared. In our previous protocol,^[12] we also defined the response rate (type III), according to which any patient whose symptoms showed no change or showed worsening were classified into nonresponder group regardless of the treatment response category; while the others were classified into responders. However, in our review, type I and type III have the same meaning; therefore, we conducted the analysis with type I and type II categories only. In our previous protocol, quality of life and AEs were included as secondary outcomes. In addition to the predefined secondary outcomes, we also extracted the recurrence rate and the symptom score.

2.5. Assessment of risk of bias

A risk of bias about the included studies was conducted using the risk of bias assessment tool from the Cochrane handbook.^[13,14] Two independent reviewers (J L, C K) assessed the risk of bias into low, unclear, or high grade. If the disagreement was not resolved by a mutual discussion among the 2 reviewers, a final decision was made by the third reviewer (J J). We assessed the selection bias (random sequence generation and allocation concealment), the performance bias (blinding of participants and personnel), the detection bias (blinding of outcome assessment), the attrition bias (incomplete outcome data), the reporting bias (selective reporting), and other bias. A “high” risk

of bias was graded in case of random sequence generation assessment, where only the word “randomization” was used without any further explanation.

2.6. Statistical analysis and data synthesis for meta-analysis

To assist researchers, the effect size of every outcome variable was presented for related clinical trial protocol development. Review manager (V.5.3 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for data synthesis and meta-analysis. Outcome variables were combined according to the study design (add-on design or head to head design) and the type of outcome measure. Continuous outcome data were pooled and expressed as mean difference (MD) with a 95% confidence interval (CI). Binary outcome data were also pooled and expressed as risk ratio (RR) with a 95% CI. Heterogeneity among studies was evaluated by I^2 statistic and tested with a significance level of $P < .1$. The I^2 statistic indicates the proportion of variability among the included studies that cannot be explained by chance alone.^[15] Random effect model was used if the I^2 statistic value was $>50\%$, which indicates a substantial heterogeneity. If I^2 statistic value was $<50\%$, the fixed model was used. We also explored the source of heterogeneity. Subgroup analysis was performed separately depending on whether the PI was applied or not while prescribing XZD to the patient.

3. Results

3.1. Description of the included studies

A total of 475 studies were screened by electronic and manual searching. These studies were assessed for duplication and after removing the duplication, 175 articles were assessed by title and abstract after which 141 articles were excluded. The remaining 34 articles were assessed with full-text and 26 articles were identified as having an inappropriate design, disease, or intervention (Supplementary 2, <http://links.lww.com/MD/C771>). Eight articles were finally included for qualitative and quantitative analysis (Fig. 1). Thus, among 475 publications, 8 RCTs involving 1048 patients were finally included 4 studies were “add-on study design” that compared XZD and WM combination therapy group versus WM sole therapy group.^[16–19] In add-on study, the control group receives conventional treatment, while the experimental group receives XZD along with conventional treatment.^[20] Other 4 studies were “head to head study design” that compared XZD sole therapy versus WM sole therapy.^[21–24] We did not find any placebo-controlled trial. A summary of the included studies is shown in Table 1. The details of XZD treatment are described in Table 2.

3.2. Summary of the included studies and detailed information of XZD treatment

All studies were conducted in China and published in Chinese language. Four of these studies were outpatient studies and the others could not be identified. The number of participants was 524 in each group (treatment as well as the control group). The mean age of included patients ranged from 16.8 to 26.5 years. The average disease duration ranged from 1.6 to 7 years. One of the included studies used XZD Koufuye (oral liquid)^[22] and the other 7 studies used XZD decoction. The number of patients in each group ranged from 30 to 128. WM used by the patients in

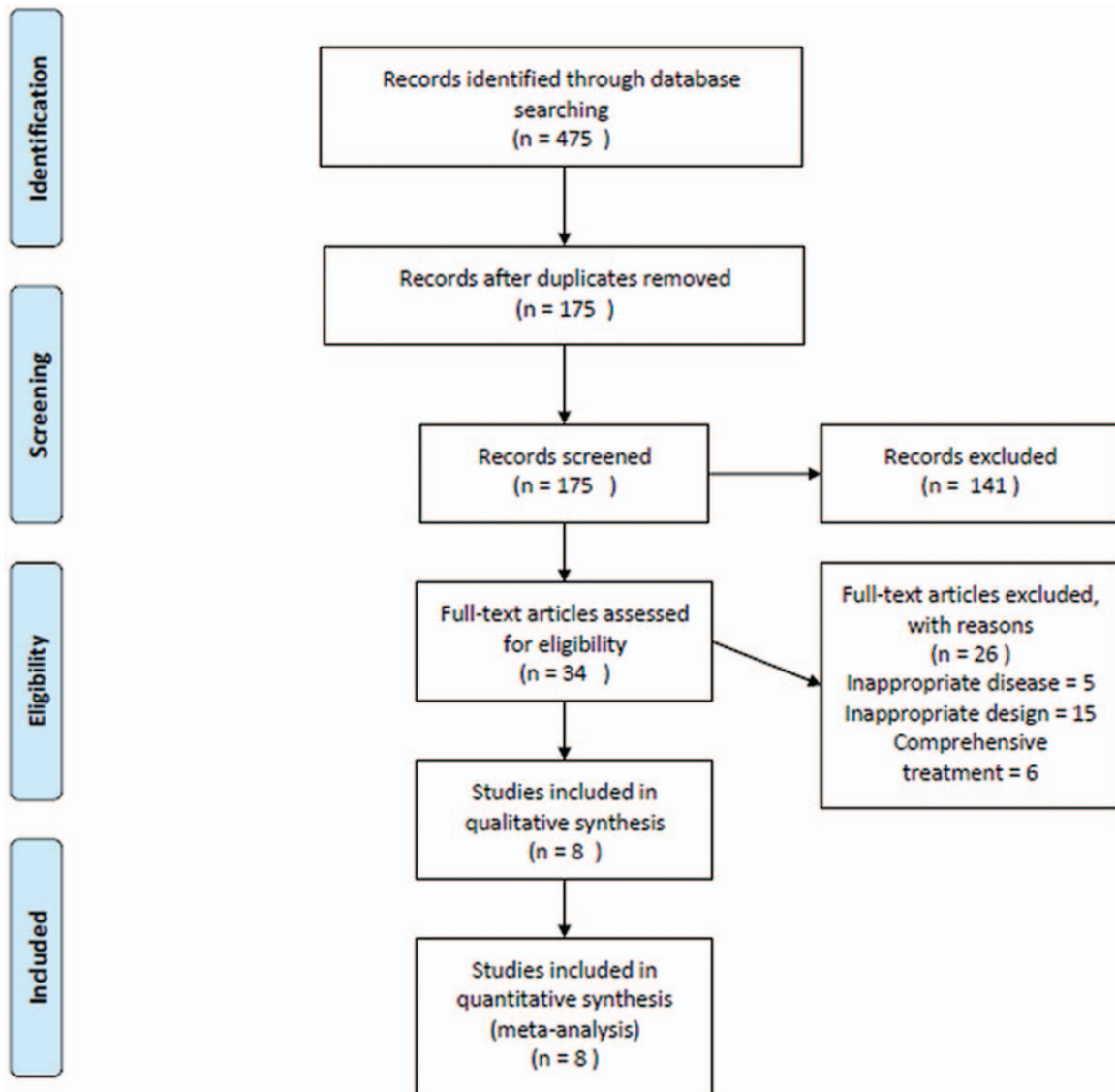


Figure 1. PRISMA flow diagram. PRISMA = preferred reporting items for systematic reviews and meta-analyses.

the studies were Fenbid, Oryzanol, Thiamine, Indometacin, Naproxen, Ibuprofen, or Diclofenac Sodium (Table 1).

Primary dysmenorrhea was diagnosed by pelvic sonography in 1 RCT.^[21] Four RCTs reported that they excluded secondary dysmenorrhea due to pelvic inflammatory diseases, endometriosis, or uterine fibroids, but they did not describe specific methods in detail.^[16,19,22,24] The other 3 RCTs did not mention how they diagnosed primary dysmenorrhea.^[17,18,23]

In 5 studies, XZD was prescribed only to the patients who were diagnosed with blood stasis due to qi stagnation according to the TCM PI.^[16,18,19,21,23] Modification of XZD according to PI or symptom was allowed in 6 studies.^[16,17,19,21,23,24] The total number of treatment cycles comprised of 3 cycles except for 1 study in which it was 6 cycles.^[22] However, the definition of 1 treatment cycle was somewhat different between the studies. The outcome assessment timing was 3 months from the start of the treatment except for 1 study for which it was 6 months.^[22] Furthermore, excluding 2 studies, an additional follow up assessment was conducted in all other studies.^[16,18,19,22–24] XZD is composed of 11 medicinal herbs. In our review, some studies

allowed modification of the medicinal herbs based on the PI or related symptoms. Therefore, the daily dose of the included medicinal herbs was slightly different from each other. The details of the XZD and its daily dose are presented in Table 2.

3.3. Risk of bias in the included studies

The overall risk of bias of the included studies was high or unclear. A graphical illustration about the risk of bias is shown in Figure 2. In random sequence generation, only 2 studies were graded as low as they mentioned about using random number table.^[16,19] Other studies that did not mention about random sequence generation were graded as high. Allocation concealment was not mentioned in any of the included studies and hence it was graded as unclear in all the studies. Placebo-controlled design trial was not included in any of the studies and hence the risk of bias accounting from the blinding of participants was graded as high in all the studies. The risk of bias accounting from the “blinding of outcome assessment” and “incomplete outcome data” were graded as unclear in all studies because none of the

Table 1

Summary of the included studies.

First author, yr	Country/ setting	Disease duration yrs; mean ± SD (range)/disease severity; [(n) mild /moderate/ severe]	Age, yrs; mean ± SD (range)	Treatment group (n)	Control group intervention (n)	Outcome	Effect size*	Adverse events (AEs)
Xuefu Zhuyou decoction (XZD) + western medication (WM) versus western medication (WM) Chou (2015) [16]	China/OPD	TG) 4.1 ± 2.2 (2–9) CG) 3.6 ± 2.1 (1–8) [17/28/19] [19/29/16]	TG) 26.5 ± 5.2 (16–41) CG) 25.8 ± 5.7 (16–39)	XZD decoction + WM (64)	Fenbid (64)	① Symptom score ② VAS ③ TRR [C/M/N]	① -3.78 (MD, 95% CI [-4.62, -2.94]) ② 1st, 2nd, 3rd mo 1 mo) -0.52 (MD, 95% CI [-0.73, -0.31]) 2 mo) -0.51 (MD, 95% CI [-0.67, -0.37]) 3 mo) -0.28 (MD, 95% CI [-0.43, -0.13]) ③ 1.15 (RR, 95% CI [1.02, 1.29]) [(TG) 28/24/10/2 (CG) 19/20/15/10]	TG) 7 [‡] CG) 10 [‡]
Wang (2013) [17]	China/ND	TG) 1.7 (0.3–4) [ND] CG) 1.6 (0.2–4) [ND]	TG) 18.6 (16–27) CG) 17.9 (15–26)	XZD decoction + WM (60)	Oryzanol, Thiamine, (if severe) Indometacin, Fenbid, Naproxen (60) [‡]	① TRR [M/N]	① 1.19 (RR, 95% CI [1.03, 1.36]) [(TG) 45/12/3 (CG) 24/24/12]	ND
Wu (2014) [18]	China/OPD	TG) 2.1 ± 0.3 (0.5–8) [21/23/7] CG) 2.3 ± 0.2 (0.8–7) [18/27/6]	TG) 22.5 ± 3.2 (16–31) CG) 23.1 ± 4.3 (18–33)	XZD decoction + WM (51)	Ibuprofen (51)	① TRR [C/M/N]	① 1.37 (RR, 95% CI [1.07, 1.59]) [(TG) 24/15/8/4 (CG) 9/15/12/15]	No AEs
Zhang (2015) [19]	China/ND	TG) 4.2 ± 2.4 (2–9) [34/56/38] CG) 3.5 ± 2.0 (1–9) [38/58/32]	TG) 25.4 ± 4.8 (17–40) CG) 25.3 ± 4.6 (17–41)	XZD decoction + WM (128)	Fenbid (128)	① Symptom score ② VAS ③ TRR [C/M/N]	① -3.83 (MD, 95% CI [-4.43, -3.23]) ② 1st, 2nd, 3rd mo 1 mo) -0.52 (MD, 95% CI [-0.67, -0.37]) 2 mo) -0.51 (MD, 95% CI [-0.61, -0.41]) 3 mo) -0.45 (MD, 95% CI [-0.79, -0.12]) ③ 1.15 (RR, 95% CI [1.06, 1.24]) [(TG) 57/47/21/3 (CG) 39/39/31/19]	TG) 7 [‡] CG) 10 [‡]
Xuefu Zhuyou decoction (XZD) versus western medication (WM) Huang (2014) [21]	China/OPD	TG) 2 (0.5–9) [21/27/8] CG) 4 (0.75–7) [19/30/7]	TG) 22 (16–31) CG) 24 (18–33)	XZD decoction (56)	Diclofenac Sodium (56)	① TRR [C/M/N]	① 1.26 (RR, 95% CI [1.03, 1.53]) [(TG) 25/16/8/7 (CG) 12/18/9/17]	ND
Li (2014) [22]	China/ND	TG) 1.9 ± 3.2 (ND) [9/12/9] CG) 1.9 ± 3.5 (ND) [10/13/7]	TG) 23.9 ± 9.1 (ND) CG) 24.7 ± 8.9 (ND)	XZD Koufuyue (30)	Indometacin (30)	① TRR [C/M/N] ② 6 mo recurrence rate	① 1.07 (RR, 95% CI [0.96, 1.20]) [(TG) 12/10/8/0 (CG) 1/14/13/2] ② 0.08 (RR, 95% CI [0.01, 0.60]) [(TG) 1 case (CG) 12 cases]	ND
Wang (2015) [23]	China/ND	TG) 7 ± 1.2 (0.4–6) [33/40/27] CG) 4.1 ± 1.4 (0.6–8) [38/42/20]	TG) 25.2 ± 1.1 (16–34) CG) 24.8 ± 1.3 (15–32)	XZD decoction (100)	Diclofenac Sodium (100)	① TRR [C/M/N]	① 1.34 (RR, 95% CI [1.14, 1.57]) [(TG) 31/29/27/13 (CG) 24/21/20/35]	TG) 1 CG) 9
Zhao (2016) [24]	China/OPD	All) 5.1 ± 3.2 (0.4–11) [14/32/24]	All) 16.8 ± 3.5 (13–28)	XZD decoction (35)	Symptomatic treatment of pain (35)	① TRR [C/M/N]	① 1.48 (RR, 95% CI [1.16, 1.89]) [(TG) 20/9/5/1 (CG) 1/8/14/12]	ND

Unit of disease duration: years. Treatment response is categorized as C (cured), M (markedly improved), I (improved), N (no effect). In this Table, total response rate (TRR) follows the definition of response rate type I in the manuscript. TRR is calculated as (C + M + I) * 100 / (C + M + I + N) which means proportion of patients showing any positive change. Dropout rate is not described in any trial.

AE = adverse event, C = cured, CG = control group, CI = confidence interval, I = improved, M = markedly improved, MD = mean difference, ND = no effect, ND = not described, OPD = out-patient department, RR = risk ratio, TG = treatment group, TRR = total response rate, VAS = visual analogue scale, WM = western medication, XZD = Xuefu Zhuyou decoction.

* Effect size was presented with mean difference (MD, 95% confidence interval [lower limit, upper limit]) in continuous variables or risk ratio (RR, 95% confidence interval [lower limit, upper limit]) in dichotomous variables.

† Zhang (2015) reported that visual analogue scale (VAS) of 3 month after treatment completion was significantly better in the treatment group, and 0.69 ± 0.44 in the control group, and 0.69 ± 0.44 in the treatment group. We tried to contact the author, however, we could not find the means of contact. Therefore, according to the conclusion of the article, we exchanged the values (control with treatment) and conducted a meta-analysis. The results based original data are also presented in {}.

‡ In case of psychiatric symptom, sedative medication was prescribed.

§ All the reported adverse events (AEs) were mild stomach discomfort.

Table 2

Details of Xuefu Zhuyu decoction (XZD) treatment.

First author, yr	XZD + WM treatment group				XZD sole treatment group			
	Chou (2015)	Wang (2013)	Wu (2014)	Zhang (2015)	Huang (2014)	Li (2014)	Wang (2015)	Zhao (2016)
Prescribed XZD only to patients diagnosed with blood stasis due to qi stagnation by pattern identification (PI)	Y	N	Y	Y	Y	N	Y	N
Modification by PI or symptoms	Y	Y	N	Y	Y	N	Y	Y
Treatment cycle	3	3	3	3	3	6	3	3
Definition of treatment cycle (when to take XZD)	-3 to 0	-3 to 10 d*	-3 to 0	-3 to 0	-5 to 0	-3 to +1	-5 to 0	-7 to +3
Outcome assessment timing, mo	3 mo	3 mo	3 mo	3 mo	3 mo	6 mo	3 mo	3 mo
Additional follow up duration, mo	3 mo	N	3 mo	3 mo	N	6 mo	3 mo	3 mo
Daily dose of included medicinal herbs (unit) g								
Angelicae Sinensis Radix†	9	12	15	15	15	ND	15	12
Rehmanniae Radix†	12	—	10	20	10	ND	10	15
Persicae Semen†	12	15	10	12	10	ND	10	10
Carthami Flos†	9	9	10	10	10	ND	10	8
Aurantii Fructus†	9	9	10	10	10	—	10	10
Paeniae Radix Rubra†	12	12	10	10	10	ND	10	15
Bupleuri Radix†	9	10	15	10	15	ND	15	10
Glycyrrhizae Radix et Rhizoma†	6	6	8	6	8	—	8	10
Chuanxiong Rhizoma†	8	15	10	10	10	ND	10	10
Achyranthis Bidentatae Radix†	9	10	12	15	12	ND	12	15
Platycodonis Radix†	9	10	10	9	10	ND	10	10
Medicinal herbs that are not included in the original XZD								
Corydalis Rhizoma			12		12		12	
Paeoniae Radix Alba								20
Salviae Miltiorrhizae Radix et Rhizoma								15
Poria								15
Atractylodis Macrocephalae Rhizoma								15
Zingiberis Rhizoma Praeparatum		12						

Definition of treatment cycle is as follows: For example, Zhao (2016) is expressed as -7 to +3. It means XZD treatment was started 7 days before menstruation. XZD medication was finished 3 days after menstruation. XZD was consumed twice a day.

d = day, mo = month, N = no, NA = not applicable, ND = not described. Used in the prescription but dosage was not known, PI = pattern identification, WM = western medication, XZD = Xuefu Zhuyu decoction, Y = yes.

* XZD decoction was started 3 days before menstruation and maintained for 10 days.

† 11 Medicinal herbs included in the original XZD prescription.

studies mentioned about these issues. In selective reporting, there were no previously published study protocols. However, 3 trials in which the outcome variables previously intended to analyze were reported in the article, were graded as low.^[16,19,23] Other articles were graded as unclear due to the lack of information. We could not assess any other bias, so they were graded as unclear in all the studies.

3.4. Outcome

There were 2 types of study designs:

(1) “add-on design study” that compared XZD plus WM combined therapy versus WM sole therapy.^[16-19]

(2) “head to head design study” that compared XZD sole therapy versus WM sole therapy.^[21-24]

In “add-on design studies,” VAS)^[16,19] symptom score,^[16,19] and response rate^[16-19] were used to examine the effect of XZD, while in “head to head design studies,” response rate^[21-24] and recurrence rate^[22] were used. We conducted a qualitative as well as quantitative analysis in each design (Table 1).

3.4.1. XZD plus WM combined therapy versus WM sole therapy (add-on design study)

3.4.1.1. Response rate (type I). Pooling the data from 4 add-on study design,^[16-19] the XZD and WM combined group showed significantly better response rate (type I) than the WM sole

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chou 2015	+	?	-	?	?	+	?
Huang 2014	-	?	-	?	?	?	?
Li 2014	-	?	-	?	?	?	?
Wang 2013	-	?	-	?	?	?	?
Wang 2015	-	?	-	?	?	+	?
Wu 2014	-	?	-	?	?	?	?
Zhang 2015	+	?	-	?	?	+	?
Zhao 2016	-	?	-	?	?	?	?

Figure 2. Summary of the risk of bias. +, low risk of bias; ?, unclear risk of bias; -, high risk of bias.

therapy group (RR 1.18, 95% CI [1.11, 1.25], $P < .01$; Fig. 3). We also conducted a subgroup analysis to check whether adopting PI affected the results. Three studies prescribed XZD only to those patients who were diagnosed with blood stasis due to qi stagnation by PI.^[16,18,19] In the “adopting PI group,”^[16,18,19] RR was 1.18 (95% CI [1.10, 1.25], $P < .01$). In the “not adopting PI group,”^[17] RR was 1.19 (95% CI [1.03, 1.36], $P = .02$). As both the groups showed statistical significance with 95% CI (overlapping), we could not find any difference between adopting PI versus nonadopting PI group in response rate (type I) by subgroup analysis.

3.4.1.2. Response rate (type II). Only 2 studies reported the proportion of patients who showed more than 50% of symptom improvement.^[16,19] the XZD and WM combined group showed significantly better response rate (type II, symptom improved more than 50%) as compared to the WM sole therapy group (RR 1.33, 95% CI [1.17, 1.52], $P < .01$; Fig. 4).

3.4.1.3. VAS. Two studies that prescribed XZD for 3 months reported VAS score every month.^[16,19] The XZD and WM combined group showed significantly lower VAS score as compared to the WM sole therapy group after the 1st month (MD -0.52, 95% CI [-0.64, -0.40], $P < .01$) and after the 2nd month (MD -0.51, 95% CI [-0.59, -0.43], $P < .01$). At the end of the 3rd month also, Zhang^[19] described that the treatment group showed significantly lower VAS score. However, as depicted in the table of the article, the VAS score was 0.69 ± 0.44 in the treatment group and 0.07 ± 0.40 in the control group. We predicted that the table may contain a writing error and hence we tried to contact the author. However, we could not find the e-mail on the homepage. Therefore, we concluded that the authors must have made a mistake. We exchanged the values of the treatment group with that of the control group and conducted a meta-analysis. Consequently, the VAS score at the end of the 3rd month in the treatment group was also significantly lower than that in the WM sole therapy group (MD -0.45, 95% CI [-0.79, -0.12], $P < .01$; Fig. 5).

3.4.1.4. Symptom score. Two studies reported the symptom score.^[16,19] The XZD and WM combined group showed significantly lower symptom score as compared to the WM sole therapy group (MD -3.81, 95% CI [-4.30, -3.32], $P < .01$; Fig. 6).

3.4.2. XZD versus WM (head to head design study)

3.4.2.1. Response rate (type I). Pooling the data from 4 head to head study design,^[21-24] the XZD group showed significantly better response rate (type I) as compared to the WM group (RR 1.26, 95% CI [1.06, 1.49], $P < .01$; Fig. 7). I^2 statistic was partially high (75%). Li^[22] used Koufuye form of XZD for 6 months. However, other studies used decoction form and prescribed it for 3 months only. To identify the origin of heterogeneity we excluded Li^[22] and conducted a meta-analysis again. The I^2 statistic decreased to 0%; however, the XZD effect persisted (RR 1.34, 95% CI [1.20, 1.50], $P < .01$; data not shown). We also conducted a subgroup analysis to assess whether adopting PI affects the results. There were 2 studies that adopted PI when prescribing XZD only to the patients who were diagnosed with blood stasis due to qi stagnation syndrome. In the “adopting PI group,”^[21,23] RR was 1.31 (95% CI [1.15, 1.48], $P < .01$) whereas in the “not adopting PI group,”^[22,24] RR was 1.24 (95% CI [0.83, 1.87], $P = .30$). “However, due to Li’s (2014) study, the heterogeneity in the “not adopting PI group” was high ($I^2 = 89\%$).

3.4.3. AEs. In “add-on design group,” 1 study reported no AEs,^[18] another study did not describe about AEs^[17] while 2 other studies reported AEs^[16,19] (Table 1). Fourteen AEs were reported in XZD + WM group and 20 AEs were reported in WM sole therapy group. In the meta-analysis, RR of AEs between the 2 groups were not significantly different (RR 0.70, 95% CI [0.37, 1.34], $P = .28$; Fig. 8). All the 34 AEs were mild stomach discomfort. In “head to head design group,” only one study mentioned about AEs.^[23] Only 1 AE occurred in the treatment group and 9 AEs occurred in the control group. RR of AEs was 0.11 (95% CI [0.01, 0.86]) in the XZD group.

4. Discussion

4.1. Main findings

Our systematic review and meta-analysis revealed that XZD sole or combined with WM appears to be more effective for pain relief

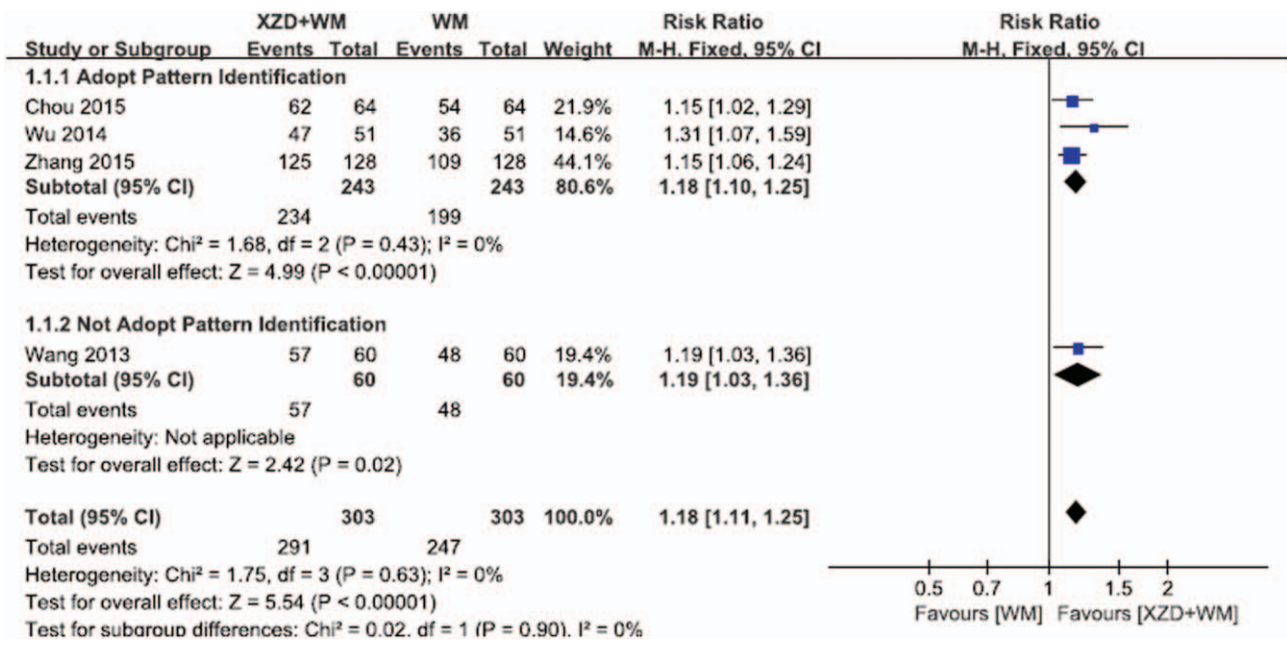


Figure 3. Forest plot of comparison: XZD plus WM versus WM, outcome: 1.1 Response rate type I. WM = western medication, XZD = Xuefu Zhuyu decoction.

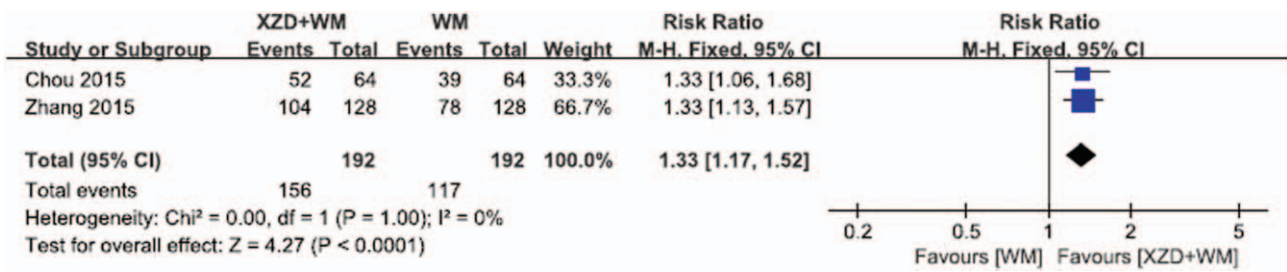


Figure 4. Forest plot of comparison: XZD plus WM versus WM, outcome: 1.2 Response rate type II. WM = western medication, XZD = Xuefu Zhuyu decoction.

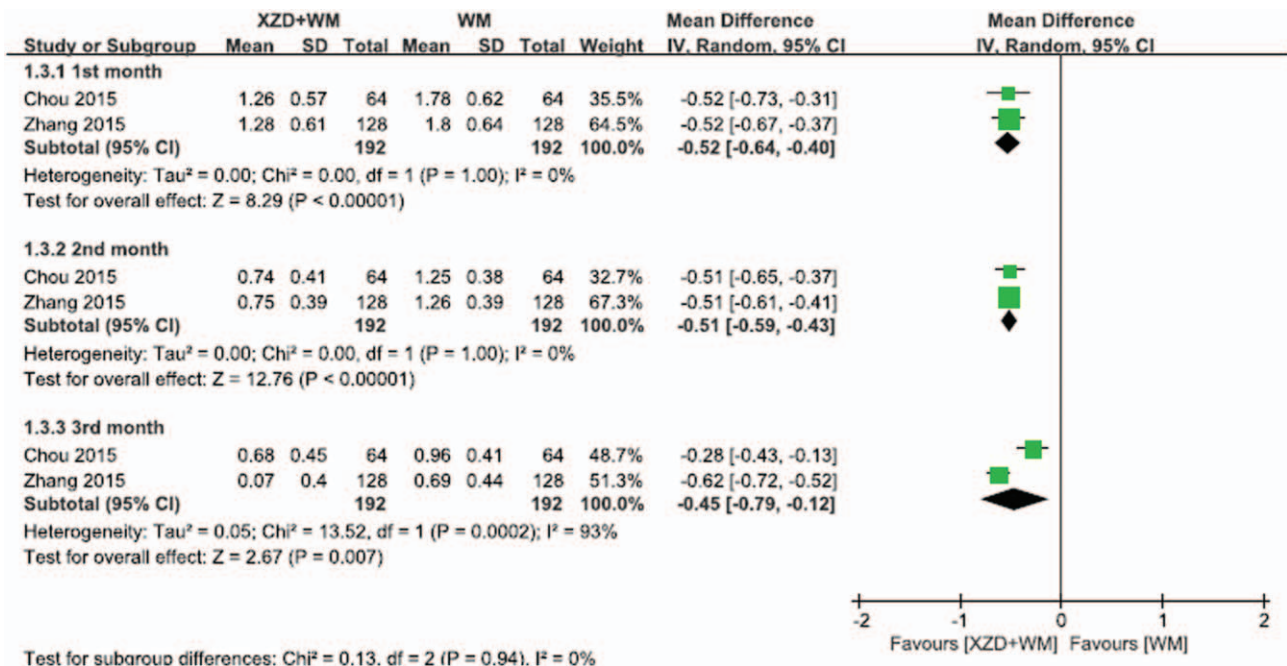


Figure 5. Forest plot of comparison: XZD plus WM versus WM, outcome: 1.3 VAS. VAS = visual analogue scale, WM = western medication, XZD = Xuefu Zhuyu decoction.

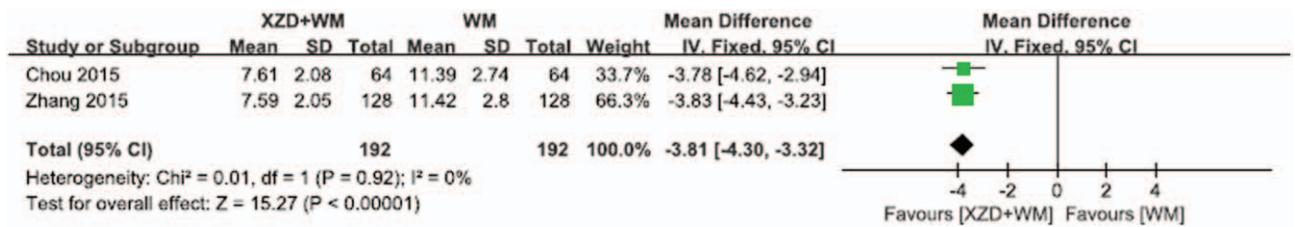


Figure 6. Forest plot of comparison: XZD plus WM versus WM, outcome: 1.4 TCM symptom score. TCM = traditional Chinese medicine, WM = western medication, XZD = Xuefu Zhuyu decoction.

over WM alone. However, the evidence was limited because of the generally high risk of bias of the included trials and poor reporting or validity of the herbal interventions. Furthermore, the total number of RCTs and the total sample size included in our analysis were not sufficient to draw a firm conclusion. Although reports on AEs were insufficient, there were few AEs associated with XZD as compared to WM.

4.2. The mechanism of XZD on dysmenorrhea

Our previous review has shown that the underlying molecular mechanisms of herbal medicines for dysmenorrhea are associated

with prostaglandin level reduction, suppression of cyclooxygenase-2 expression, superoxide dismutase activation and malonaldehyde reduction, nitric oxide, inducible nitric oxide synthase, and nuclear factor-kappa B reduction, stimulation of somatostatin receptor, intracellular Ca²⁺ reduction, and recovery of phospholipid metabolism.^[25] Especially, XZD is known to be associated with enhanced angiogenesis on vascular endothelial cells^[26] or reduced inflammatory substances,^[27] which are considered to be related with pathology or symptoms of dysmenorrhea.^[28,29]

These results also suggest the beneficial potentials of XZD on blood stasis, which is recognized as the main factor causing

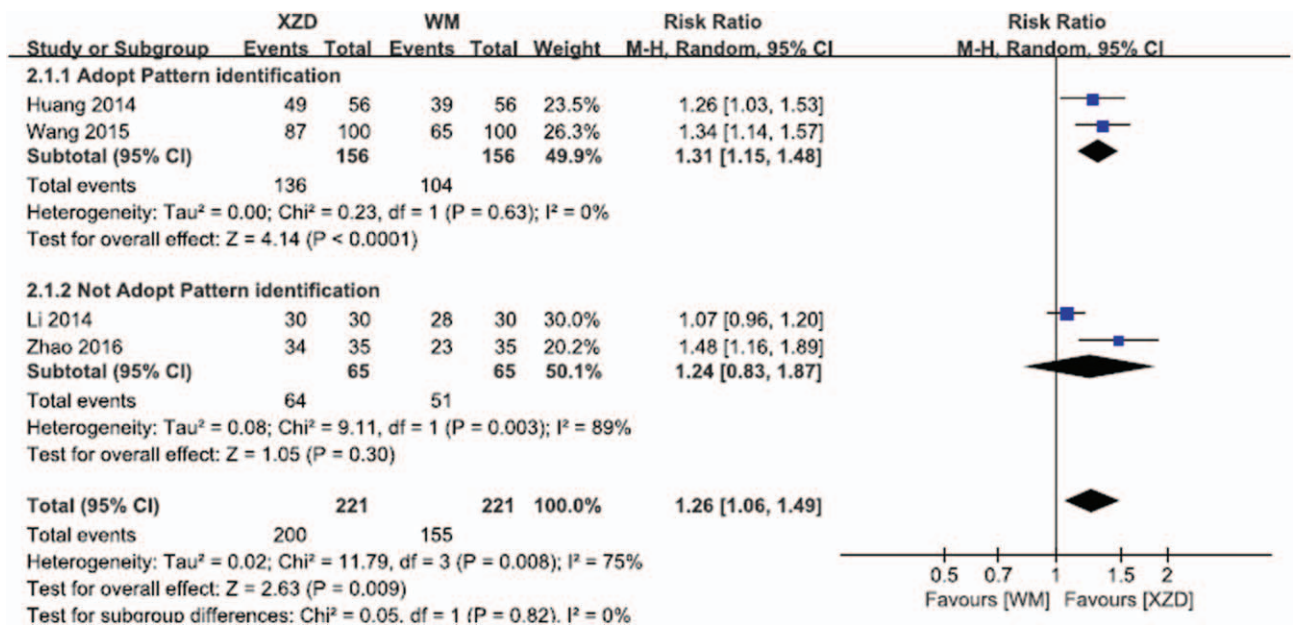


Figure 7. Forest plot of comparison: XZD versus WM, outcome: 2.1 Response rate type I. WM = western medication, XZD = Xuefu Zhuyu decoction.



Figure 8. Forest plot of comparison: XZD plus WM versus WM, outcome: 3 AE rate. AE = adverse event, WM = western medication, XZD = Xuefu Zhuyu decoction.

dysmenorrhea in traditional East Asian medicine theory.^[30] Especially in Chinese, Zhuyu has the meaning of removing blood stasis, and some decoctions having this on its name have been used for the treatment of various blood stasis-related diseases including dysmenorrhoea. In this regard, several herbal medicines including other “Zhuyu decoction,” Shaofu Zhuyu decoction, have been shown to be effective in treating dysmenorrhea.^[31–33] XZD has been considered to be one of those herbal medicines, which perform the function of promoting qi and activating blood to relieve the symptoms of blood stasis due to qi stagnation. And this decoction has been investigated in many pathological conditions related to blood stasis.^[34–37]

In our study, XZD has shown some beneficial potentials in treating dysmenorrhea and, considering previous studies, it may be associated with, at least partially, its anti-inflammatory activity, improving blood circulation, and antinociceptive effect as well as removing blood stasis.

4.3. Strengths and limitations

This systematic review had a predefined and explicit methodology. Also, the protocol for this systematic review was registered in PROSPERO for transparency. A comprehensive search was conducted in a variety of databases without language restrictions. Independent study selection, data extraction, and the risk of bias assessment by independent reviewers' minimized errors. Nonetheless, this systematic review had several limitations. Consistent with other systematic reviews on CHM, a major limitation of this report lies in the methodological flaws of the included studies. First, most of the included trials used the response rate as an outcome variable, which lacks reliability and validity and poses a risk of possible bias from the practitioner.^[32] Second, all of the RCTs were conducted in China and hence the generalization of these results may be limited. Third, the risk of bias in the present findings is generally considered high because most of the included studies were graded as having high risk and unclear risk of bias for the key methodological elements such as randomization, allocation concealment, and patient/outcome assessment. Another issue is the lack of standardization of herbal ingredients used in each study. The herbal medicine interventions are usually complex and highly variable, and hence a detailed report on the quality and preparation of the herbal medicine that follows the relevant reporting guidelines is important.^[38,39]

In our previous protocol, we have suggested several additional analyses. We conducted a subgroup analysis only for PI because the analyses for other factors were not applicable in our review. We planned to conduct the sensitivity analysis according to the quality of trials assessed by consolidated standards of reporting trials extension for herbal interventions.^[40] However, as the quality of included trials were low; we did not conduct the sensitivity analysis. Furthermore, as the number of included trials were less than 10, we did not assess a publication bias using either funnel plot or Egger method.^[14]

4.4. Comparison with existing literature

This systematic review showed that XZD alone or combined with conventional WM is effective for pain relief in women with primary dysmenorrhea. This is consistent with the findings of most other systematic reviews on CHM for primary dysmenorrhea.^[32,33,41] We tried to conduct subgroup analysis to assess whether adopting PI affects the results, so as to help physicians in their everyday practice. There is a tendency that PI

is effective when prescribing XZD to the patients who were diagnosed with blood stasis due to qi stagnation syndrome; however, no such conclusion can be drawn due to high heterogeneity observed in the “not adopting PI group” in head to head design.

4.5. Implications for research

To be used widely for pain relief in clinical practice, XZD should show superiority or safety over NSAIDs, which are considered as a standard treatment for primary dysmenorrhea. Future trials should use international standards and validated scales for pain such as VAS for evaluating the treatment effects because the response rate cannot represent the precise degree of improvement. We suggest evaluating VAS during the first 5 days of each menstrual cycle using a horizontal unmarked VAS of 0 to 10 cm (0 cm representing no pain; 10 cm, severe pain). Pain scores of painful days over the first 5 days of menstruation can be averaged at the screening and end of treatment cycles as overall-pain intensity.^[42,43] The average scores of the first 2 menstruation days can also be calculated to assess the most intensive menstrual pain. Data regarding the type and frequency of the intake of all drugs and the use of other remedies, as possible confounders, need to be collected along with the VAS pain intensity in the diary.^[42]

Moreover, the outcome assessment in a majority of the trials occurred immediately following the intervention period, and thus the information on the persistence of the effect of XZD could not be gathered. More studies focusing on a long-term follow-up are needed to examine the effectiveness of XZD for pain relief as well as to assess the sustainability of the effect. Further studies are also required not only to determine whether XZD effectively blocks the dysmenorrheic pain, but also, to assess the possibility of preventing and ameliorating the risk of the development of chronic pain disorders in adolescent girls.^[3]

5. Conclusions

The existing trials showed a favorable effect of XZD for the management of primary dysmenorrhea. However, the efficacy of XZD on primary dysmenorrhea is not conclusive owing to the small number of studies and the high risk of bias. Given the poor reporting and methodological flaws of existing studies, large-scale, long-term RCTs with rigorous methodological input are desirable to clarify the role of XZD for the management of primary dysmenorrhea.

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