Benefits of balneotherapy in the management of fibromyalgia syndrome: a systematic review and meta-analysis of randomized controlled trials

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Chun-Feng Cao
Yongchuan Hospital of Chongqing Medical University

Kun-Long Ma
Yongchuan Hospital of Chongqing Medical University

Qian-Lu Li
Yongchuan Hospital of Chongqing Medical University

Fu-Jun Luan
Yongchuan Hospital of Chongqing Medical University

Qun-Bo Wang
Yongchuan Hospital of Chongqing Medical University

Ming-Hua Zhang
Yongchuan Hospital of Chongqing Medical University

Hai Qiang Wang
Shaanxi University of Chinese Medicine

drwanghq@163.com Corresponding Author
ORCiD: https://orcid.org/0000-0002-7752-6217

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Abstract
Objective To assess the effectiveness of balneotherapy (BT) in the management of fibromyalgia syndrome (FMS). Methods The Cochrane Library, EMBASE, MEDLINE, and PubMed were thoroughly searched for relevant studies with a pre-specified searching strategy (from their inception to May 31st, 2019), to identify randomized controlled trials (RCTs) evaluating BT in FMS management. The primary outcomes were pain, Fibromyalgia Impact Questionnaire (FIQ), Tender Points Count (TPC), Beck’s Depression Index (BDI). A meta-analysis was performed to identify risk ration (RR) or standardized mean difference (SMD) where appropriate, 95%CI with random-effect and consistent models. Results Ten RCT studies with 611 participants were included. Pooled results showed that BT can benefit FMS with significant improvement reflected as, pain (SMD= -0.90, 95%CI [-1.37 to -0.42] I² =86%), FIQ (SMD= -0.81, 95% CI [-1.24 to -0.38] I² =84%), TPC (SMD= -0.88, 95% CI [-1.63 to -0.14] I² =91%) and BDI (SMD= -0.29, 95% CI [-0.53 to -0.05] I² =22%) at the end of treatment. However, there was no significant effect on BDI (SMD= -0.57, 95% CI [-1.40 to 0.26]) at follow up. Conclusion Based on 12 to 48 weeks observation, pooled evidence from RCTs indicates BT may reduce pain and improve the quality of life of patients with FMS. Definitive, large-sample studies are needed, with focus on long-term results and maintenance of the beneficial effects.

Introduction
FMS is a musculoskeletal disorder characterized by widespread skeletal muscle pain, accompanied by various symptoms, including fatigue, sleep disturbances, headache, morning stiffness, anxiety and depression [1, 2]. The prevalence of FMS is estimated at 1–2% in the general population. The disorder mainly affects women, with a incidence as six times higher than men [3]. Its treatment is usually complex [4] and unsatisfactory, thus being identified as a public health issue due to significant health expenditures. Consequently, FMS has been mainly presenting in a high rate of medical consultations and a high consumption of drugs [5].

Balneotherapy (BT) is a non-invasive alternative treatment to relieve musculoskeletal or neuropathic pain and stiffness, improving the quality of life amongst the elderly with musculoskeletal pain [6]. Defined as bathing in thermal mineral waters, BT contains extensive treatment mode, including SPA
therapy, physiotherapy, and exercise [7]. Previous randomized clinical trials (RCTs), meta-analyses and systematic reviews have shown its effectiveness in alleviating symptoms for patients with musculoskeletal disorders [8]. However, the effectiveness of BT is still in controversy given that the mechanisms of BT have not been fully understood. Nevertheless, studies on BT for FMS are disputable with potential as a source of bias, such as lack of double-blinded studies [9, 10]. As well, emerging studies on BT in FMS have not been analyzed in systematic reviews so far. Therefore, we conducted an updated meta-analysis to determine the efficacy of BT in FMS.

Methods
Since this is a systematic review, ethics committee approval is waived.

Protocol and registration
This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 (PRISMA-P) guidelines [11]. The systematic review has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number of CRD42019142187.

Inclusion and exclusion criteria
Studies were required to meet the following criteria: 1) target population were patients with FMS based on established criteria; 2) intervention method compared BT between only the pharmacological treatment or exercise; 3) primary outcomes include pain, tender points count (TPC), Beck's depression index (BDI), fibromyalgia impact questionnaire (FIQ); 4) methodological criteria were prospective RCTs; 5) publication of the study in full paper form.

We excluded retrospective studies, cohort studies, and clinical controlled studies. Two authors (CFC and KLM) screened the studies independently. An initial screening of titles and duplicates were excluded. Then, full texts and abstracts were reviewed and irrelevant papers were removed.

Search strategy
To gather all relevant published studies comparing BT with pharmacological treatment or exercise for FMS, we searched the Cochrane Library, EMBASE, MEDLINE, and PubMed thoroughly from their inception to May 31st, 2019. The searching terms we used in each databases were (FMS OR fibromyal
OR musculoskeletal disease) AND "RCT" AND (BT OR spa therapy OR balneotherapy OR balneology OR thermal water). The search filter was limited to RCTs. In addition, the reference lists of relevant articles and comments were reviewed for further trials. No restriction for language was supplied.

**Data extraction and management**

Data extracted for this meta-analysis met the inclusion criteria. For all articles, two authors (KLM and MHZ) review data independently according to the requirements of this review. If necessary, existing disagreements were solved by consensus. When consensus could not be reached, the third author (FJL) would be required to extract data and discuss the paper.

**Assessment of risk of bias (ROB) in included studies**

Two authors assessed the risk of bias of each study independently according to the Cochrane Collaboration’s ROB assessment tool [12]. All disagreements were resolved by consensus. A third author was the adjudicator when no consensus was achieved. We applied the form of ROB assessment, which include the following key indicators: randomized, concealment, blinding, intention-to-treat analysis, incomplete outcome data, selective outcome reporting, interruption, and check of other bias.

**Assessment of treatment effect**

Meta-analysis was carried out using the Review Manager 5.3 software. When dichotomous variables exist, the risk ratios (RR) for each study were calculated. Standardized mean difference (SMD) was calculated using a random-effects model, when the data were continuous. And the 95% confidence intervals (CIs) were determined for all effect sizes.

**Assessment of heterogeneity**

Heterogeneity between comparable trials was analyzed using standard Cochran’s Q tests and the I² statistic before meta-analysis. A p value < 0.05 was considered as a statistically significant threshold. We intended to explain I² values according to Deeks [13], which states that an I² value of 0% to 40%, 30% to 60%, 50% to 90%, and 75% to 100% referring to 'not be important', 'moderate' heterogeneity, 'substantial' heterogeneity, and 'considerable' heterogeneity, respectively.

**Sensitivity analysis**
Sensitivity analysis were performed for high-risk and low-risk bias studies, studies with serious deficiencies in one or more key areas, and sample size for each treatment group.

Results

**Description of studies**

The literature-retrieving strategy and results are shown in Figure 1. A total of 252 relevant studies were preliminarily reviewed (PubMed search 102 citations, Cochrane search 45 citations, EMBASE search 58 citations and Medline search 47 citations). Ten RCT studies eventually satisfied the eligibility criteria and were included for this meta-analysis. Two studies were excluded given that means and standard deviation of post-test data were not provided in the articles, and could not be calculated. One study was excluded for not only bath but exercise in pool.

In total, 611 participants with FMS were treated by either BT or not, with an observational time phrase ranging from 12 to 48 weeks. A detailed list of study characteristics was shown in Table 1. Flowchart of screening process was shown in Figure 1.

**ROBs**

Only 1 of the 10 studies included had low ROBs [14]. Another 4 were designated at unspecified risk (unclear allocation and high risk publication bias: [15] and [16]; unclear outcome assessment blinding and double blind: [17]; unclear random sequence generation and high risk publication bias: [18]; unclear outcome assessment and high risk publication bias[19]). The remaining 5 studies were at high ROBs [6, 20-22], since more than two ambiguous judgments in the key areas existed.

**Effects of interventions**

1. **Primary outcomes**

   **Pain**

   Eight studies reported the comparison of pain between BT group and control group at follow up. Our meta-analysis showed that the pain scores in BT were \(-80\%\) lower than that in the control group. \([SMD= -0.80, 95\% \text{ CI} −1.28 \text{ to } −0.31, p = 0.001]\). Test statistics showed evidence of considerable heterogeneity among these studies \((I^2 = 86\%)\) and random-effects model was adopted.

   Nine studies reported the comparison of pain between BT group and control group at the end of
treatment (Figure 2). The results indicate that BT reduced the pain score by -90% (SMD= −0.90, 95% CI −1.37 to −0.42, p = 0.0002). Test statistics showed evidence of considerable heterogeneity among these studies ($i^2$=86%) and random-effects model was adopted.

**Fibromyalgia Impact Questionnaire**

Among the ten studies, there were eight studies using the Fibromyalgia Impact Questionnaire (FIQ) as outcome measures at follow up. BT improved clinical effective rate of FIQ by −89% when compared with controls (SMD= −0.89, 95% CI −1.36 to −0.42, p =0.0002). Test statistics showed evidence of considerable heterogeneity among these studies ($i^2$=85%) and random-effects model was adopted.

Nine studies reported the comparison of FIQ between BT group and control group at the end of treatment (Figure 3). Analogously, Pooled results of subgroups analysis indicated that BT improved clinical effective rate of FIQ by −81% when compared with controls at the end of treatment (SMD= −0.81, 95% CI −1.24 to −0.38, p =0.0002). Test statistics showed evidence of considerable heterogeneity among these studies ($i^2$=84%) and random-effects model was adopted.

**Tender Points Count**

There were six studies measured the Tender Points Count (TPC) as the outcome at follow up. The results of our meta-analysis showed that BT improved clinical efficacy of TPC by −84% when compared with controls group (SMD= −0.84, 95% CI −1.39 to −0.28, p=0.003). Test statistics showed evidence of considerable heterogeneity among these studies ($p <0.0001, i^2$=85%) and random-effects model was adopted.

Seven studies reported the comparison of TPC between BT group and control group at the end of treatment (Figure 4). Similarly, pooled data showed that BT improved clinical effective rate of tender points by −81% when compared with controls at the end of treatment (SMD= −0.88, 95% CI −1.63 to −0.14, p=0.02). Test statistics showed evidence of considerable heterogeneity among these studies ($p <0.00001, i^2$=91%) and random-effects model was adopted.

**Beck’s Depression Index**

There were four studies measured the Beck Depression Index (BDI) as the outcome at follow up. Test
statistics showed evidence of considerable heterogeneity among these studies ($p<0.00001$, $I^2=89\%$) and random-effects model was adopted. Pooled results of subgroups analysis indicated that there was no statistical difference effect on BDI (SMD $=−0.57$, 95% CI $−1.40$ to $0.26$, $p=0.18$).

Six studies reported the comparison of BDI between BT group and control group at the end of treatment (Figure 5). The results indicate that BT improved clinical effective rate of BDI by $−29\%$ when compared with controls at the end of treatment (SMD $=−0.29$, 95% CI $−0.53$ to $−0.05$, $p=0.02$).

Despite of no heterogeneity ($p=0.27$, $I^2=22\%$), a random-effects model was still used.

**Discussion**

There have been no guidelines or recommendations for the therapeutic management of fibromyalgia until 2017[4]. Therefore, the importance of the multidisciplinary approach is highlighted with special emphasis to non-pharmacological treatments as BT. Emerging evidence from prospective randomized trials has been reported with positive effects of BT on FMS. However, these studies have not reached conclusions with limited sample size and quality methods. Therefore, we performed an updated meta-analysis to determine the therapeutic benefits of BT in the management of FMS.

Naumann and Sadaghiani[8] performed a meta-analysis on BT and hydrotherapy in FMS treatment, covering the literature up to April 2013. Ten RCTs were included, but only six of them with 321 participants were extracted and analyzed for their meta-analysis[8]. They found moderate evidence of a medium-to-large effect on pain and TPC for BT, a medium effect on FIQ, and no significant effect on BDI.

Thereafter, there have been no latest systematic reviews regarding the topic during the past 6 years. Our search identified valuable data from emerging RCTs. Notwithstanding the somewhat overlap of interested topic, our meta-analysis provided novel evidence to the vision of FMS treatment., whereas 10 studies with a total of 611 cases were included in our study. The updated three studies greatly expanded participants, which significantly improved the reliability of the meta-analysis results.

Secondly, when we extracted and analyzed original data from included studies, we identified missing data from the previous meta-analysis [8]. For example, Fioravanti et al [22] involved the follow-up of pain outcome, which was neglected in the previous study [8]; Moreover, VAS pain data for the
endpoint follow-up were not included for pool analysis for two studies [18][22] in the previous meta-analysis[8]. Nevertheless, the two studies provided VAS pain data at 3, 6, and 12 months after treatment. Only the data of sixth months of follow-up were included in the previous study [8]. We extracted all informative data from original RCTs which may significantly improve the reliability of the meta-analysis results.

Our systematic review and meta-analysis with ten clinical trial studies, presented novel line of evidence that BT can benefit fibromyalgia syndrome with pain, FIQ, TPC at follow up. These findings are consistent with previous meta-analysis or reviews [10, 23]. However, there was no significant effect on BDI at follow up. Moderate evidence was found at the end of treatment to sustain these improvements. This outcome is contrary to the meta-analysis in 2014[8] and Evci’s RCT in 2002 [21]. However, our result is in line with Naumann’s when excluding Zijlstra’s trials [22] reporting that mental health improvement was not as obvious as physical health, and the duration is short. In their opinions, there was only limited room for improvement of their study sample because of the low baseline levels of depression. Meanwhile, they have limited time in the spa, which is not a vacation. Therefore, the improvement in symptoms seems to be independent from absence of work duties [21].

There was insufficient data on the side effects of BT, and no statistical analysis was performed. There were three included studies adopting the 100-mm Visual Analog Scale [15, 16, 18]. Remaining studies used 10-mm Visual Analog Scale. Despite the discrepancy, a significant improvement of FMS-derived pain was noted. The degrees of pain relief vary among the included studies, with different baselines. There are additional basic therapies for FMS either BT group or control group, such as exercise, health education guideline and medicine. Existing evidence has not reached consensuses on differential effects of mineral water type on reducing pain among patients with FMS. Zijlstra et al.[22] showed negative change in data indicating improvement of pain, especially at the third month of follow-up. However, it is not obvious at the end of treatment in control group. This findings was consistent with the results of Ardiç et al[20]. It is possible that the function of BT in the elimination of inflammatory factors reached an extreme in a certain period of treat time [24]. Beyond that time extreme, the pain relief from BT cannot continue. Therefore, other ways are needed to continue the
Functional capacity in daily living activities were evaluated by FIQ[25]. The results of our meta-analysis showed that BT can significantly improve the functional outcomes. Evcik et al.[21] reported a better functional scores and quality of life in the bathing treatment group than that in the control group. Interestingly, the efficacy of the BT decreased with continuing of the treatment, although it was still effective in the last follow-up (24 weeks). However, this interesting finding was not observed in the Altan’s study[26]. The possible reason for this interesting finding is that there is no subsequent treatment after the BT in Evcik’s study, which could not keep a persistent efficacy. Similarly, the current study found that TPC was significantly reduced in the bathing treatment group in comparison with the control group. This finding is also consistent with the previous studies [27, 28], which demonstrated that the BT has a significant effect on the improvement of TPC.

The efficacy of BT can be explained by heat, mineral content, and other physiologic and endocrine effects [29, 30]. Thermal stress stimulation exerts analgesic on nerve endings by increasing the pain threshold. It alleviates muscle spasms and activates pain-relieving inhibition system through the gamma fibers of muscle spindles. According to the “gate theory”, pain relief may be caused by water temperature and pressure on the skin [31, 32]. Physiologically, heat application leads to increased blood circulation, like BT and heat application to inflamed tissue induces a reduction in circulating nociceptive elements; fresh oxygen introduced after free oxygen free radicals removal enhances the repair of the inflammatory tissue [33, 34]. In different musculoskeletal diseases, the effect of BT on pain and function is significantly better and longer than that of tap water bath at the same temperature [35]. The minerals which are dissolved in the water play an important part in the mechanism of action of BT.

There is high heterogeneity (29% to 91%) for included studies. Firstly, there is clinical heterogeneity due to different in follow-up periods. It took 1 to 6 months to evaluate the results, although the average treatment intervention duration was about 2 weeks. The last follow-up time after interventional is an important factor in determining the sustained effectiveness of BT. Another relevant factor is that the composition of the mineral water is different. Also the exposure times and
temperature used for BT. In addition, the ratio of female participants was higher in all studies. The pain threshold in men and women may be different. These factors may be connected with the differences between the groups, and affect the entire effectiveness and heterogeneity of the studies. Several limitations of this meta-analysis should be recognized. Firstly, the included studies did not employ a unified evidence-based diagnostic system including mechanisms, common characteristics, comorbidities, and diagnostic criteria capable of improving the recognition of FM in clinical practice. Secondly, this meta-analysis includes ten publications, and in order to identify the factors leading to heterogeneity are still need additional studies to perform subgroup. Thirdly, each study had a different regimen, with spas in different areas.

In conclusion, our findings support the effectiveness of BT in pain control and functional improvement in FMS. The results that are gained from our study agree with the evidence of effectiveness of BT in controlling pain and improving functionality in FMS. In fact, spa therapy can be used as an effective backup of pharmacologic treatment of FMS and an effective alternative therapy for patients with drug intolerance. However, more powered randomized studies are needed to determine the results of meta-analysis.

Declarations

Conflict of Interest:
The authors declare no conflict of interest.

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Authors’ contributions:
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Prof. Hai-Qiang Wang had full access to all of the data in the study and takes responsibility for the integrity of the
data and the accuracy of the data analysis.

**Study conception and design.** Chunfeng Cao and Hai-Qiang Wang.

**Acquisition of data.** Chunfeng Cao, Kunlong Ma, Fujun Luan, Qianlu LI, Qunbo Wang and Minghua Zhang.

**Analysis and interpretation of data.** Chunfeng Cao, Kunlong Ma and Hai-Qiang.

**Data Availability Statement:**

The datasets supporting this systematic review and meta-analysis are from previously reported studies and datasets, which have been cited. The processed data are shown as Table 1, Figure 2 to Figure 10.

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**Author details:**

a Department of Orthopedics, the Yongchuan Hospital of Chongqing Medical University, 439# Xuanhua Road, Yongchuan, Chongqing, 402160, P. R. China.

b Department of Neurology, the Yongchuan Hospital of Chongqing Medical University, 439# Xuanhua Road, Yongchuan, Chongqing, 402160, P. R. China.

C Institute of Integrative Medicine, Shanxi University of Chinese Medicine, Xixian Avenue, Xixian District, Xi'an 712046, Shanxi Province, P. R. China.

1 These authors contributed equally to the article and should be considered as equal first authors.

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