Effectiveness and safety of extracorporeal shock wave treatment for low back pain:a systematic review and meta-analysis of RCTs

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Abstract

Background Extracorporeal shock wave therapy (ESWT) has been widely used in musculoskeletal disorders. This meta-analysis was designed to assess the effectiveness and safety of ESWT for patients with low back pain (LBP). Methods Multiple electronic databases including Pubmed, Embase, Cochrane's library, China National Knowledge Infrastructure (CNKI), and Wanfang Data were searched until December, 2019 to identify studies assessing the effectiveness and safety of EPSW for LBP. The prime outcome is pain intensity measured by Visual Analog Scale (VAS) or numeric rating scale (NRS). Other outcomes included functional status, quality of life, psychological outcomes measured by Oswestry Disability Index (ODI), as well as the adverse events. Mean differences were calculated for continuous outcomes, while odd ratios were calculated for binary outcomes. Revman 5.3 software was used for statistical analysis. Results Five randomized controlled trials (RCTs) were finally included in this meta-analysis. The pooled mean difference in post-treatment pain scores was −2.37 (P <0.0001), indicating that post-treatment pain scores was significantly higher by 2.37 in control group than in ESWT group. At a mean follow-up time of 4-6 weeks, the pooled mean difference in ODI scores was −14.10 (P <0.00001), indicating that the pooled mean difference of post-treatment ODI scores was 14.10 higher in control group than in ESWT group. Conclusions The use of focused ESWT is effective in alleviating pain and improving the general fuctional state for patients with LBP. However, more evidence was needed to verify its safety.

1. Introduction

As one of the most popular musculoskeletal disorders worldwide, LBP is not only the leading cause of days lost from work but also the leading indication for medical rehabilitation[1-3]. According to a survey among Saskatchewan adults, 84% of participants admitted experiencing one or more episodes of back pain lifetime[4]. In 2002, US National Health Interview Study conducted a questionnaire survey on 30000 people, the result of which showed that 26.4% of the participants had experienced at least one full day of back pain in the past three months[5]. In 2010, another research carried in Germany showed that 26% of the participants of the mandatory nationwide health insurance system have sought medical help more than once because of low back pain[6]. As a result, the social and economic burden brought by LBP is becoming more and more significant[7]. It's estimated that the direct medical costs attributed to the diagnostic and intervention of LBP are no less than $33 billion annually in America. While the total costs exceed $100 billion each year if the indirect costs of lost working time and decreased productivity were added[2]. In fact, LBP is the chief complaint in about 2.3% of all ambulatory physician visits, which means about 15 million outpatient visits each year.[5]

So far, plenty of methods have been proposed to deal with LBP, which include non-invasive interventions such as self-care, analgesics, spinal manipulation, physical therapy with or without cognitive behavioral therapy, massage, acupuncture, yoga and invasive interventions such as glucocorticoid injections and surgical procedures[3, 8]. However, pharmacological treatments inevitably involve limited efficacy, long-term dependence and, most importantly, a variety of adverse events. As a result, current guidelines for LBP mainly focus on the non-pharmacological treatments[9]. Among all the therapies mentioned above, ESWT is a physiotherapy technique that has attracted much attention in recent years, with which progress has been made in the treatment of bone and muscle diseases such as external epicondylitis of humerus, plantar fasciitis, nonunion and avascular necrosis of the femoral head[10, 11]. Introduced in Germany in 1980s, ESWT has been used for the management of urolithiasis, cholelithiasis and sialolithiasis at first. It is soon being applied in a diverse range of areas because of its usefulness, non-invasion, repeatability and safety, with no exception of the treatment of musculoskeletal system disease[12]. It was also used in the treatment of low back pain and achieved acceptable results worldwide. The ESWT equipment currently used in clinical practice is divided into radial and focused ones according to the manner by which the shock wave reaches the target. There are three methods of generating a focused-type shock wave, namely, piezoelectric, electromagnetic and electrohydraulic. While The barometric ballistic shock wave is a kind of mechanical wave produced by a metal bullet hitting the front end of the shock wave probe driven by compressed gas. The mode of wave propagation generated in this way is called radial shock wave. Although

the clear mechanisms about the impact ESWT put on the human body is still not fully understood, the surprising clinical benefits lead to a continuous increase of requests for such treatment, which has even been used in regenerative medicine recently[13].

Nevertheless, the evidence regarding the effectiveness and safety of ESWT for patients with LBP is still limited. Until now, only a study protocol of systematic review[14] and several trials about the effectiveness and safety of extracorporeal shock wave for low back pain was available. Thus this meta-analysis was therefore designed to assess the effectiveness and safety of extracorporeal shock wave therapy (ESWT) for patients with LBP so as to provide more evidence for clinical decision making.

2. Materials And Methods

This meta-analysis was carried out in accordance with the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines.

2.1 Search Strategy

The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement was used for this meta-analysis. Two investigators (Yan Yan and Jinhui Ma) independently searched multiple comprehensive databases, including Pubmed, Embase, Cochrane's library, CNKI, Wanfang Data and trial registers databases up to December, 2019 for RCTs assessing the effectiveness and safety of ESWT for LBP. The following three categories of keywords (and related synonyms) were used to build a sensitive search strategy and provide a systematical review: "extracorporeal shock wave therapy", "low back pain" and "effectiveness and safety". There were no restrictions on language, year of publication, or type of publication. Search terms were used in "all fields" item so as to expand the literature search. We tried to use MeSH words when searching in Pubmed, and combine all the synonyms relevant to keywords with Boolean command "OR" in each category. Furthermore, search terms were truncated through the use of a "*" symbol in order to find all terms beginning with a specific word. After the initial electronic search, relevant articles and their bibliographies were searched manually. Articles identified were assessed individually for inclusion.

2.2 Inclusion Criteria and Study Selection

All the studies included in this meta-analysis were independently reviewed and selected by two authors, according to predefined inclusion criteria. Titles and abstracts were read; if suitability could not be determined, the full article was evaluated. Studies were included in our meta-analysis if they met the following criteria: already published, full-text, peer-reviewed articles; RCTs with control interventions including the placebo, medications, physical exercise and so on; researches designed to assess the effectiveness and safety of EPSW for LBP; two or more of the three parameters assessing post-treatment outcome were measured: VAS, NRS and ODI; the number of patients in each group (ESWT and control), the means and standard deviations of parameters mentioned above were fully reported; adequate statistical methods were used to compare the parameters in two groups; studies with data eligible for pooling in meta-analysis. Studies were excluded according to following criteria: studies without available full text and unpublished studies; cohort studies, case-control studies, case series, reports or review;animal studies, cadaver studies, or laboratory studies; studies using the ESWT plus other therapies; the data of researches was incomplete or inconsistent or impossible to be synthesized.

The target studies was decided according to the PICO (population, intervention, control, outcome) principle as following: (1) Population: patients with LBP; (2) Intervention: ESWT; (3) Control: placebo, medications, physical exercise and so on; (4) Outcome: VAS, NRS, ODI score and adverse events or complications;

Two authors independently assessed the full study article to see if it met the inclusion criteria. Whenever there was disagreement or doubt, two authors reviewed the full article mutually. Disagreements were resolved by discussion with each other. The corresponding author was consulted in cases of unresolved disagreement.

2.3 Methodological Quality

Two reviewers (Yan Yan and Jinhui Ma) used the Cochrane Collaboration's tool for assessing risk of bias[15] to assess the quality of included RCTs separately. Each study was judged according to six items as follows: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each item of which was classified into three levels: high, unclear and low risk. The outcome was assessed with GRADE (Grading of Recommendations Assessment, Development and Evaluation) system, which was also recommended by Cochrane Collaboration. The quality of evidence was finally divided into four levels, including high, moderate, low and very low level.

2.4 Data extraction

Two authors extracted information from all the included studies independently. The following information was extracted from all eligible trials: (1) study information: author, year, country/region and number of reference; (2) study design and time of follow-up; (3) study population: population size, cohort, age, sex, body mass index (BMI), mean symptom duration; (4) intervention methods applied on the different group; (5) scoring scale used to evaluate effectiveness and safety; (6) definition of different outcome; (7) confounding factors taken into consideration such as sex, BMI, complications, intensity of pain and disability before intervention, implications from therapist or other psychosocial influencing factors.

2.5 Statistical analysis

Heterogeneity among studies was evaluated using I^2 tests. If the I^2 was no more than 50%, we would consider it a study with lower heterogeneity. And a fixed-effects model was employed. Otherwise the random-effects model was used. Mean difference and 95 % confidence intervals (CI) were calculated for continuous outcomes, while odd ratios and 95 % CI were calculated for binary outcomes. A p-value less than 0.05 was usually thought to be statistically significant. The MCIC of the rating scale was calculated and compared against the referred value to verify the efficacy of interventions[16]. All the statistical analysis was performed completely with the review manager software from the Cochrane Collaboration (Version 5.3.).

3. Result

3.1 Study inclusion

A total of 218 studies were identified through initial search (215 through electronic database, 3 through other sources). After removal of duplicate, 206 records were identified and 194 of which were excluded for no direct comparison between ESWT and control groups and the lack of uniformed measurement of outcome. The full texts of remaining 13 articles were reviewed for more details and 8 of which were excluded mainly due to reasons as following: (1) other therapies were applied in the control group in addition to placebo; (2) original data was not available for pooling. Eventually, 5 RCTs were included in this meta-analysis. The flow diagram of study selection procedure was shown in **Figure 1**.

3.2 Study characteristics and patient populations

The selected 5 studies included 116 patients in ESWT group and 106 patients in control group[17-21]. All included studies compared the pain intensity before and after intervention, among which 2 studies（Moon 2017 and Çelik 2019） used NRS as measurement while the other 3 employed VAS to determine it. ODI score was compared among 4 included studies (Yang 2015 in exception). The detailed sample size and measured parameters was shown in **Table 1**. Besides, the parameters (pulse, frequency, energy, treatment intervals and times) used in ESWT group as well as in the control group from different studies were collected in **Table 2**.

3.3 Risk of bias assessment and quality of the included studies

The judgement about each item of risk of bias for included RCTs were shown in **Figure 2**. In general, 3 studies (Çelik 2019, Walewicz 2019 and Wu 2016) were considered to have low to moderate risk of bias while the other 2 moderate to high risk. Limited to the information available in the published article, item reporting bias (selective reporting) and other bias of all the included 5 RCTs were thought to be at unclear risk, which inevitably affected the final judgement of trial quality. The random sequence generation and allocation concealment was not mentioned in 1 RCT (Yang 2015). In addition, the method of blinding was either not applied or not mentioned in 2 studies (Yang 2015 and Wu 2016). 1 study (Moon2017) was considered to be at high risk of attrition bias (incomplete outcome) for unacceptable dropping of follow-up.

Unfortunately, according to the description published in these articles, most of the participants were outpatients, which may lead to some bias (admission rate bias for example). Another issue lies in the aspect of demographic. Previous studies showed that elder women were more liable to be bothered by LBP. The participants recruited in the included studies also show remarkable imbalance in different age and gender: most of the patients were old lady, which may affect the representativeness of this meta-analysis. What's more, BMI was only available in 1 RCT (Wu 2016). Based on the analysis above, we tend to consider 3 studies (Çelik 2019, Walewicz 2019 and Wu 2016) as ones of moderate to high quality, while the rest 2 of low to moderate quality.

In **Table 3**, the GRADE evidence quality for each outcome was collected. We thought all the six items of outcome were of moderate to high quality according to GRADE criteria. Among which the pain scores for non-specific LBP and specific LBP were both judged to be associated with high quality.

3.4 Pain score

As mentioned above, the degree of pain was measured with VAS in 3 studies[17, 20, 21] and NRS in 2 studies[18, 19] respectively. Considering both scores were used to determine the intensity of pain, and they all take 0 as no pain, 10 as intolerable pain. And the final scores were both generated through participants' subjective identification (line segment for VAS and number for NRS respectively). We think it's acceptable to merge the two indicators in that they are highly correlated. Thus we generally believed that all 5 studies compared post-treatment Pain scores in the ESWT and control group after following-up for at least 3 weeks. The pooled mean difference in post-treatment Pain scores was −2.37 (95% CI −3.37 to −1.37; P＜0.0001; I^2=85%, **Figure 3**), indicating that post-treatment Pain scores was significantly higher by 2.37 in control group than in ESWT group.

3.4.1 Subgroup analysis for pain score

According to the data from included 5 studies, two types of the ESWT methods were applied to deal with specific or non-specific LBP. Coincidentally, 3studies (Çelik 2019, Walewicz 2019 and Wu 2016) concentrated on the effects of radial ESWT on patients with non-specific LBP. While Yang[20] and Moon[19] applied focused ESWT on patients with specific LBP (Condensing osteitis and Sacroiliac joint pain, respectively). So we divided the 5 studies into 2 groups based on the intervention methods and target patients to make further analysis. The pooled mean difference in post-treatment Pain

scores for non-specific LBP (radial ESWT) was −1.85 (95% CI −3.29 to −0.41; P0.0001; I²= 90 %, **Figure 4**), indicating that post-treatment Pain scores for non-specific LBP (radial ESWT) was significantly higher by 1.85 in Control group than in ESWT group. The pooled mean difference in post-treatment Pain scores for specific LBP (focused ESWT) was −3.21 (95% CI −4.65 to −1.76; P=0.06; I²=72%, **Figure 4**), indicating that post-treatment Pain scores for specific LBP (focused ESWT) was higher by 3.21 in control group than in ESWT group, although not statistically significant.

3.4.2 The change of pain score

The pooled mean difference in Pain scores between pre-and post-treatment patients was 3.53 (95% CI 2.18 to 4.89; P 0.00001; I²=91%, **Figure 5**). The mean differences for radial ESWT subgroup and focused subgroup were 2.76 (95% CI 1.73 to 3.80; P=0.01; I²=78%, **Figure 5**) and 4.90 (95% CI 0.59 to 9.21; P0.00001; I²=97%, **Figure 5**), respectively. According to the previous research by Ostelo[16], the MCIC for VAS sacle and NRS scale should at least be 20mm and 2.5 point, reapectively. So we calculated the MCIC in different subgroup to verify the efficacy of ESWT with the algorithm reported by Ostelo. In consequence, the MCIC for overall Pain score was 1.92. While the values for subgroups as radial ESWT and focused ESWT were 1.46 and 6.10, indicating that the changes brought by radial ESWT was statistically significant, but the clinical difference of which was not obvious. And the focused ESWT not only bring significant changes but also make clinically important difference.

3.5 ODI score

At a mean follow-up time of 4-6 weeks, ODI scores were assessed in a total of 4 studies[17-19, 21] except for Yang 2015 in groups of patients who underwent ESWT and ones treated with placebo. The pooled mean difference in ODI scores was −14.10 (95% CI −24.49 to −3.71; P 0.00001; I²= 98 %, **Figure 6**), indicating that the pooled mean difference of post-treatment ODI scores was 14.10 higher in control group than in ESWT group.

3.5.1 Subgroup analysis for ODI score

Among all the 4 studies with ODI score, 3 of which (Çelik 2019, Walewicz 2019 and Wu 2016) concentrated on the effects caused by radial ESWT on patients with non-specific LBP. Only Moon et al.[19] applied focused ESWT on patients with Sacroiliac joint pain. The pooled mean difference in ODI scores for radial ESWT was −17.75 (95% CI −28.69 to −6.80; P 0.00001; I²= 95 %, **Figure 7**), indicating that the pooled mean difference of post-treatment ODI scores for radial ESWT was 17.75 higher in control group than in ESWT group. While the subgroup of focused ESWT consised of only 1 study (Moon 2017) with a mean difference in ODI scores of −3.40 (95% CI −6.18 to −0.62; **Figure 7**). Moon claimed that no significant difference of post-treatment ODI scores for focused ESWT was identified[19].

3.52 The change of ODI score

We compared the ODI score before and after ESWT. The pooled mean difference in ODI scores between pre-and post-treatment patients was 17.41 (95% CI 4.66 to 30.16; P0.00001; I²=98%, **Figure** 8) with MCIC as 18.03. The mean difference for radial ESWT subgroup was 21.08 (95% CI 6.84 to 35.31; P0.00001; I²=98%, **Figure** 8) with MCIC as 20.13. Considering that only 1 study (Moon 2017) was included in the subgroup of focused ESWT, the MCIC was not available. The MCIC of ODI scale was suggested to be over 10 point to demonstrate that the smallest change possible to detect was available[16]. As a result, we could say with confidence that the ESWT, especially radial ESWT, have greater efficacy than placebo when it comes to ODI score.

3.6 adverse events and complications

Generally, Moon[19] reported that no adverse events, side effects or complications were found in ESWT group after a 4-week follow-up. Walewicz[17] and Çelik[18] simply didn't mention about any adverse events or complications associated

with ESWT. Wu[21] reported no systemic adverse reaction in all the 54 participants. However, in ESWT group 1 case quitted the trial after the treatment of non-steroidal anti-inflammatory drugs because of intolerable pain during the intervention. In the control group, there was 1 case of dizziness and headache in the control group without special inducement, related medical history or examination. 3 cases quitted after the use of non-steroidal anti-inflammatory drugs due to severe or aggravated pain. The incidence of adverse reactions in ESWT group and control group was 3.57% (1/28) and 15.38% (4/26) , respectively. Yang[20] reported no adverse events in ESWT group. However, several participants in the control group got stomachache after taking Celebrex (0.2g each time, twice a day) for two weeks.

4. Discussion

To our knowledge, there are few studies focusing on the use of extracorporeal shock waves in the treatment of LBP in the available literature (Pubmed, Embase, Cochrane's library, CNKI, and Wanfang Data). And no similar meta-analysis was previously performed to assess the effectiveness and safety of ESWT for patients with low back pain LBP according to our search result. Our main finding in this meta-analysis is that the Pain score (VAS and NRS) and ODI score were significantly higher in LBP patients treated with placebo than those with ESWT. Generally, the analysis indicated that patients with LBP experienced less pain and disability after ESWT than those underwent placebo therapy.

So far, ESWT has been used in the treatment of a variety of bone and muscle diseases, including external epicondylitis of humerus, plantar fasciitis, nonunion and avascular necrosis of the femoral head[10]. Although many researchers have made efforts in exploring the mechanism of action about extracorporeal shock wave, what is unfortunate is, the detailed pathway of action is still covered in mist.

A common sense about ESWT, also accepted by most people, is that the effect of an extracorporeal shock wave in living tissues induces characteristic changes within the cells due to the conversion of the mechanical signal into biochemical or molecular biologic signal[22, 23]. Previous researchers have demonstrated that the shock wave accelerated the procedure of neovascularization by stimulating expressions of angiogenic growth factors including vascular endothelial growth factor (VEGF), endothelial nitric oxide synthase (eNOS) and proliferating cell nuclear antigen (PCNA) in bone, tendon and the interface of them[24-26]. The new-born vessels could thus promote the healing of bone and tendon associated with increased blood supply[11]. Published studies showed that there lies a closed relationship between decreased release of P substance and relieved pain in the treatment of tendon insertion diseases[27]. ESWT can also reduce the expression of calcitonin gene-related peptide related to pain in the dorsal root ganglion, and increase the pain threshold by directly acting on peripheral sensory nerve endings[28]. What's more, some scholars also believed the alleviated pain in insertional tendinopathy was due to hyper-stimulation analgesia produced by ESWT[20]. Another hypothesis was that motor simulation of the muscles and tendons with extracorporeal shock waves may play an important role in killing pain and improving muscle strength[29]. As motion pain unquestionably lead to restricted movement, the range of joint motion will get improved once ESWT relieves low back pain and reduces the effects of interference signals on muscles and sensory organs, which result in tremendous improvement in patients' life quality.

Although it seems that ESWT can do much good to the human body, there arise doubts and concerns about its effectiveness and safety when comprehensive promotion to clinical use was made[1]. Limited to the small number of studies available and sample size of each one, we could only make a general speculation about its true value in clinical, which is also the aim of this meta-analysis. The efficacy of ESWT on dealing with LBP mainly lied in the alleviation of pain and improvement of life quality. As the change of pain intensity could be measured with VAS/NRS scores, ODI score was used to determine the severity of disability in patients with LBP by giving questions in ten aspects. However, pain intensity and disability were clinically different even though the first item of ODI was about pain. Persistent severe pain would inevitably bother our daily life and limit social activity. But, disability appeared only when intolerable pain was induced or aggravated by walking, lifting, sitting, standing, sleeping and other daily tasks, and the continence of

which was forced to interrupted. In other words, pain intensity reflected the persistent static state brought by LBP while disability concerned more about the dynamic influence. So both the pain score and the ODI score were necessary for the judgement of patients' conditions.

We synthesized the result of 5 RCTs (2 in China[20, 21], 1 in Turkey[18], 1 in Poland[17] and 1 in Korea[19] respectively), the outcome of which reminded us that ESWT was obviously superior than placebo therapy when it comes to LBP. Patients who underwent ESWT with LBP reported significantly lower VAS/NRS scores and ODI scores by 2.37 and 14.10 respectively in follow-up time ranging from three weeks in minimum to six weeks in maximum, which means that ESWT appeared especially effective in short-to-mid term. Considering that different characteristics of LBP and variable types of the extracorporeal shock wave will inevitably affect the outcomes, subgroup analysis was conducted hence. We found that 2 of the 5 studies (Moon 2017 and Yang 2015) applied focused ESWT to deal with specific LBP (Condensing osteitis and Sacroiliac joint pain) while another 3 (Çelik 2019, Walewicz 2019 and Wu 2016) concentrated on the outcomes of patients with non-specific LBP after undergoing radial ESWT. The result showed that post-treatment Pain scores for non-specific LBP (radial ESWT) and specific LBP (focused ESWT) was significantly higher by 1.47 and 1.75 respectively in Control group than in ESWT group, although the difference of the latter was not significant. And the post-treatment ODI scores were also lower in both radial ESWT group and focused ESWT group by 17.75 and 3.4 respectively when compared with control groups.

Besides, MCIC was calculated in different subgroups to verify the clinical efficacy of our interventions according to the recommended methods [16]. The MCICs for overall pain score, subgroup of radial ESWT and focused ESWT were 1.92, 1.46 and 6.10 (over 2-2.5 as reference), respectively. The changes brought by radial ESWT was statistically significant, but the clinical difference of which was not obvious. And the focused ESWT not only bring significant changes but also make clinically important difference. The MCICs for overall ODI score and subgroup of radial ESWT were 18.03 and 20.13 (over 10 as reference), which means that the ESWT, especially radial ESWT, have greater efficacy than placebo when it comes to ODI score. Generally speaking, we found that ESWT was effective in the treatment for LBP. Radial ESWT may improve the conditions of disability in patients with non-specific LBP. While for patients with specific LBP, focused ESWT was highly recommended as an effective therapy because of the clinically important change in pain intensity. However, further researches were still in meed in the future.

In addition, we collected all the adverse events and complications appeared after ESWT in the included studies. 2 studies (Moon 2017 and Yang 2015) reported no adverse events in the ESWT group while another 2 (Walewicz 2017 and Çelik 2019) just didn't mention it. Only Wu[21] reported 1 case of intolerable pain during intervention in the ESWT group (1/28). It's hard to say ESWT was totally safe to LBP patients with limited evidence like this. Even though the sum of patients undergoing ESWT in the 3 studies paying attention to adverse events was calculated, a sample of 71 participants was still far from enough to support our hypothesis. What's more, a short follow-up period (4-6 weeks) in most studies (Walewicz 2019 in exception) failed to offer convincing evidence of safety. We thought that more researches of large sample, high quality and long follow-up period were needed for further analysis.

We noticed that Walewicz performed tests at several times including before the start and after the end of the full cycle of ESWT treatment, one and three months after the end of the intervention in order to assess the immediate and long-term effect of ESWT[17]. As reported in the article, Placebo group (treated with sham ESWT) had significantly advantages over ESWT group in the immediacy after full cycle of intervention (4.4 vs. 3.1 points on the VAS; $p=0.039$). However, ESWT group achieved a more stable curative effect without sudden relapse in the long run (2.7 vs. 3.5 points, $p>0.05$, at one month after treatment and 2.0 vs. 4.4 points, $p<0.0001$, at three months after treatment). In addition, none of adverse reaction or severe complications caused by the extracorporeal shock wave were reported in all 5 studies. That's to say, we have reasons to believe that it's effective to apply ESWT on patients with LBP till now, even though the safety of which was still unsure.

Historically, the application and promotion of ESWT were associated with doubts and controversy, especially when it was firstly used in a new field[30]. The key point of these controversies lies in the uncertainty of its effectiveness and potential side effect it may cause to the human body[31, 32]. Until now, only a small number of studies assessing the effectiveness and safety of ESWT were available, while most of which offered limited sample size of no more than 30 patients in each group. Our meta-analysis synthesized all the studies meeting inclusion criteria and make a general evaluation about the efficacy of ESWT. The result reminded us that extracorporeal shock wave can be a choice for the treatment of LBP with considerable beneficial effect and probable safety.

However, there inevitably exists several limitation in our meta-analysis. First, a common limitations to all meta-analysis, ours no exception, is that some researches were omitted. To avoid this problem, we performed an extensive search with sensitive keywords and synonyms in multiple comprehensive databases, and make use of the expertise of a clinical librarian. All the references of included studies were reviewed in case of overlooking any possible inclusions. Second, we have to admitted that no study protocol of this meta-analysis was prospectively registered, which may become a source of selective reporting bias and outcome reporting bias. Third, as mentioned above, there are few studies focusing on the effectiveness and safety of ESWT, while most of which own limited sample size of less than 30 in each group. In consequence, we could only make a general speculation about it. Fourth, as we managed to included RCTs taking “standard ESWT” as intervention for observational group, the course of treatment, duration of each cycle, model of shock wave machine and the energy flux density applied on patients can’t be all the same. Differences between the intervention will undoubtedly bring bias to the synthesized result. Last, the intervention methods of the control group consisted of 3 sham ESWT[17, 19, 21], 1 placebo ESWT[18] and 1 medication therapy[20] using steroidal anti-inflammatory drugs. Although they fully meet our inclusion criteria, there inevitably exist some influence brought by the not uniformed intervention methods of the control group, which would thus affect the authenticity of our result to some degree.

5. Conclusion

Our systematic review with meta-analysis showed that patients with LBP experienced less pain and disability after ESWT than those underwent placebo therapy. It’s effective and safe to take ESWT as a option for the treatment of low back pain, but the safety of which was still unclear with limited evidence. However, due to the fact that only a small number of studies were available and most of which corresponding to poor comparability, overall study quality of the included studies was limited. In the future, more high-quality studies with large sample size and long follow-up period are needed to confirm the results of the present meta-analysis.

Abbreviations

ESWT: extracorporeal shock wave therapy

LBP: low back pain

CNKI: China National Knowledge Infrastructure

VAS: Visual Analog Scale

NRS: numeric rating scale

ODI: Oswestry Disability Index

RCTs: randomized controlled trials

GRADE: (Grading of Recommendations Assessment, Development and Evaluation

BMI: body mass index

VEGF: vascular endothelial growth factor

eNOS: endothelial nitric oxide synthase

PCNA: proliferating cell nuclear antigen

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

All the authors approved the manuscript for publication.

Availability of data and material

All data generated and analyzed during the study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no conflict of interests.

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Authors' contributions

BLW and WS conceived and designed the study. JHM and YY searched and selected relevant studies. BLW and WS extracted and interpreted data. JHM and YY analyzed the data. JHM and YY wrote the paper. BLW, WS,DBY and WGW critically reviewed and approved the final manuscript.

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Tables

acteristics of the included studies

Study (year)	Specific or non-specific LBP	Mean Symptom duration (ESWT/Control)	No. ESWT/Control	Male patients (ESWT/Control)	Mean age (ESWT/Control)	Mean BMI (ESWT/Control)	Mean follow-up time	Outcomes
Yang et al. 2015	Condensing osteitis	5.06/5.26 month	29/29	3/2	32.27/33.27	Unclear	5 week	VAS score
Wu et al. 2016	non-specific LBP	6.32/7.42 week	28/26	17/14	46.14/48.77	20.91/20.61	4 week	VAS score、ODI score
Moon et al. 2017	Sacroiliac joint pain	20.42/17.7 month	14/11	3/1	54.42/59.18	Unclear	4 week	NRS score、ODI score
Walewicz et al. 2019	non-specific LBP	9.8/9 year	20/20	6/5	51.1/55.8	Unclear	3 month	VAS score、ODI score
Çelik et al. 2019	non-specific LBP	36/33 month	25/20	15/8	40.76/40.25	Unclear	6 week	NRS score、ODI score

ESWT: extracorporeal shock wave therapy; LBP: low back pain; VAS: visual analog scale; NRS: numeric rating scale; ODI: Oswestry disability index

neters of Interventions in the included studies

Study (year)	Parameters of ESWT					control
	Radial or focused	Pulse	energy	Frequency（Hz）	Treatment interval/times	
Yang et al. 2015	Focused	1800-2500	Unclear	1.5	3-4d/6	Celebrex (0.2g each time, twice a day)
Wu et al. 2016	Radial	2000	1.8-2.5 bar	8-10	4-5d/4	Sham ESWT
Moon et al. 2017	Focused	2000	0.09-0.25 mJ/mm2	3	Single session	Sham ESWT
Walewicz et al. 2019	Radial	2000	2.5 bar	5	3-4d/10	Sham ESWT
Çelik et al. 2019	Radial	1500	0.12 mJ/mm（	2.5	3-4d/12	placebo ESWT（0.08 mJ/mm（（*

ESWT: extracorporeal shock wave therapy; *: other parameters were the same as ESWT group

ADE evidence quality for each outcome.

	No. of Included Studies	No. of patients in ESWT group	No. of patients in control group	MD (95% CI)	Heterogeneity	Quality of Evidence (GRADE)
	5	116	106	-1.61(-2.40, -0.81)	I^2=84%, P（ 0.0001	Moderate
on-specific	3	73	66	-1.47(-2.78, -0.15)	I^2=91%, P（ 0.0001	High
pecific LBP	2	43	40	-1.75(-2.27, -1.23)	I^2=0%, P=0.40	High
	4	87	77	-14.10(-24.49, -3.71)	I^2=98%, P（ 0.00001	Moderate
on-specific	3	73	66	-17.75(−28.69, -6.80)	I^2=95%, P（ 0.00001	Moderate
pecific LBP	1	14	11	-3.40(-6.18, -0.62)	Not applicable	Moderate

ain; ODI: Oswestry disability index; ESWT: extracorporeal shock wave therapy; MD: mean difference;

Figures

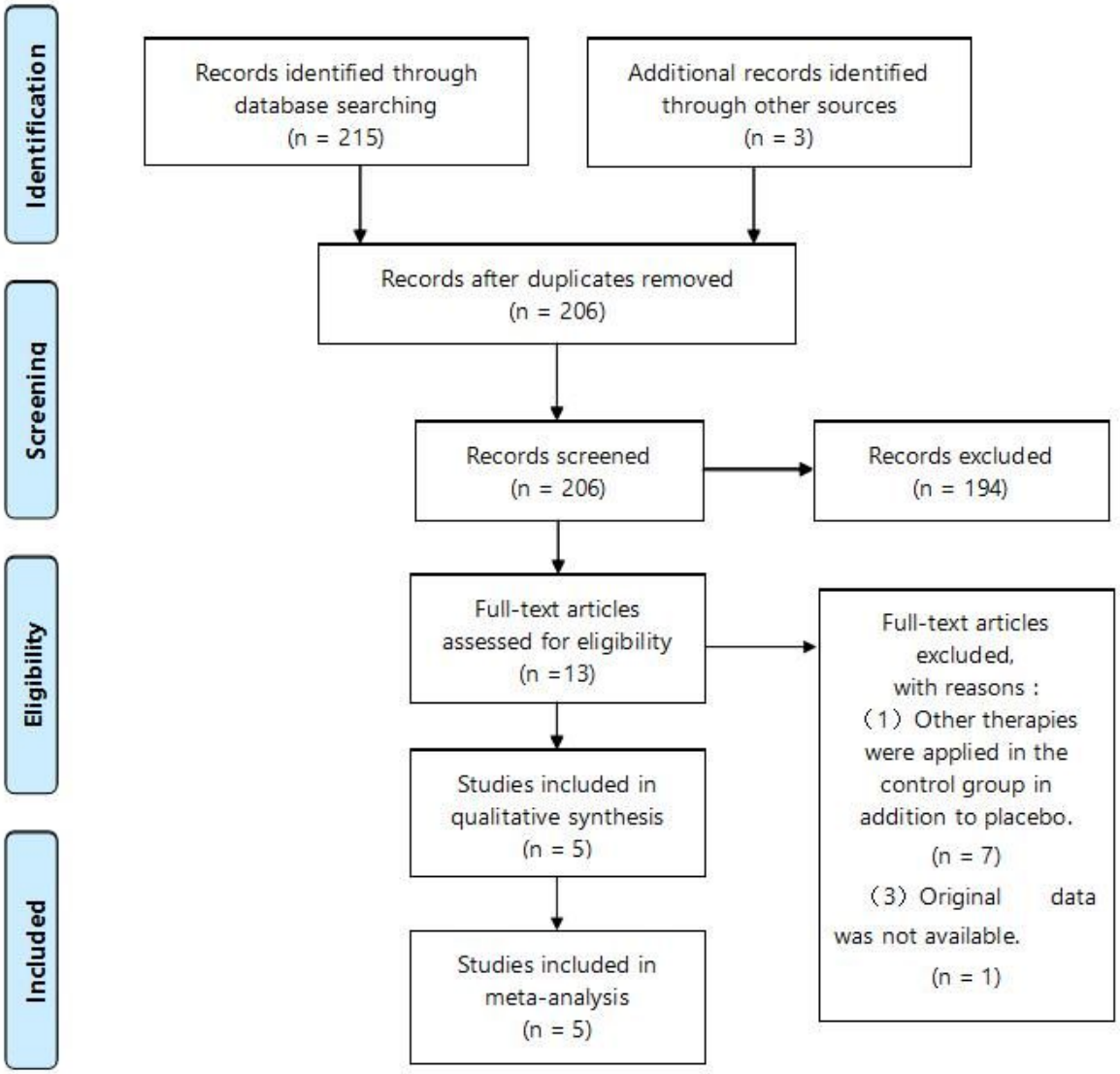

Figure 1

Flow chart of the literature search.

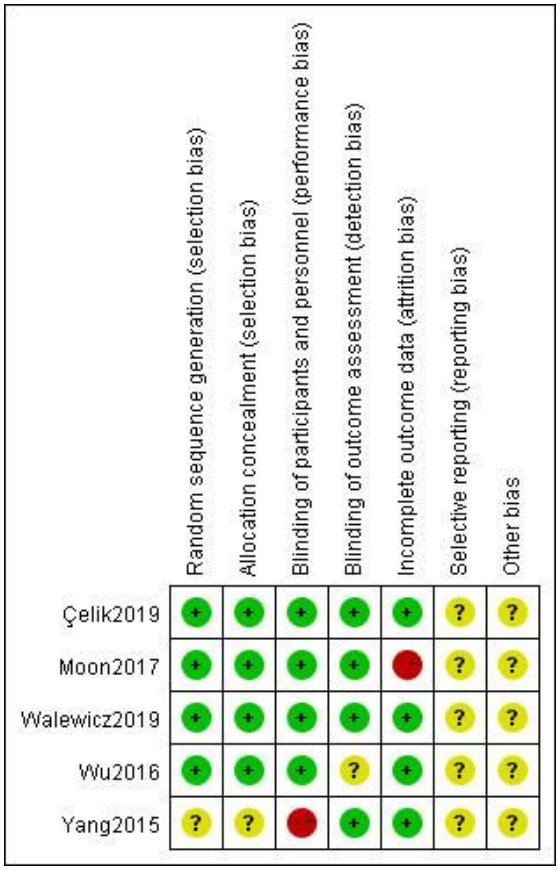

Figure 2

Risk of bias assessment of the included studies.

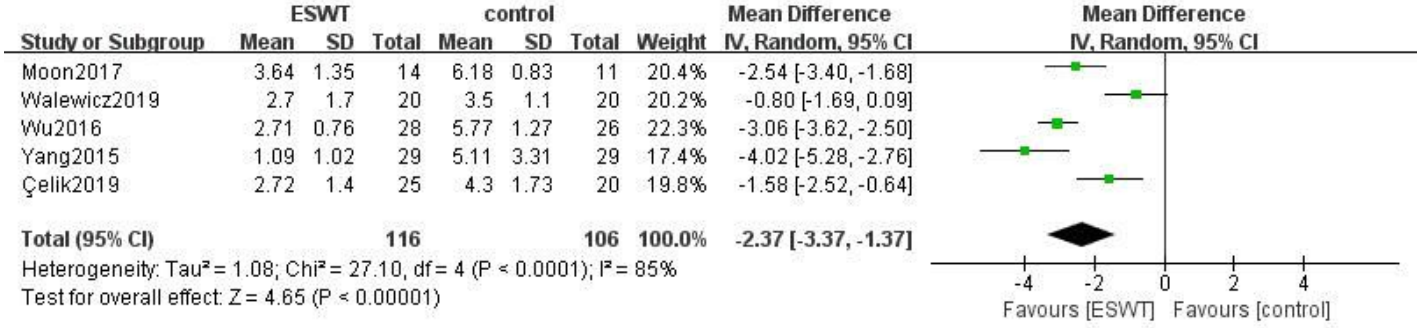

Figure 3

Forest plot analysis of Pain sores in patients with LBP after treatment between the ESWT and control group.

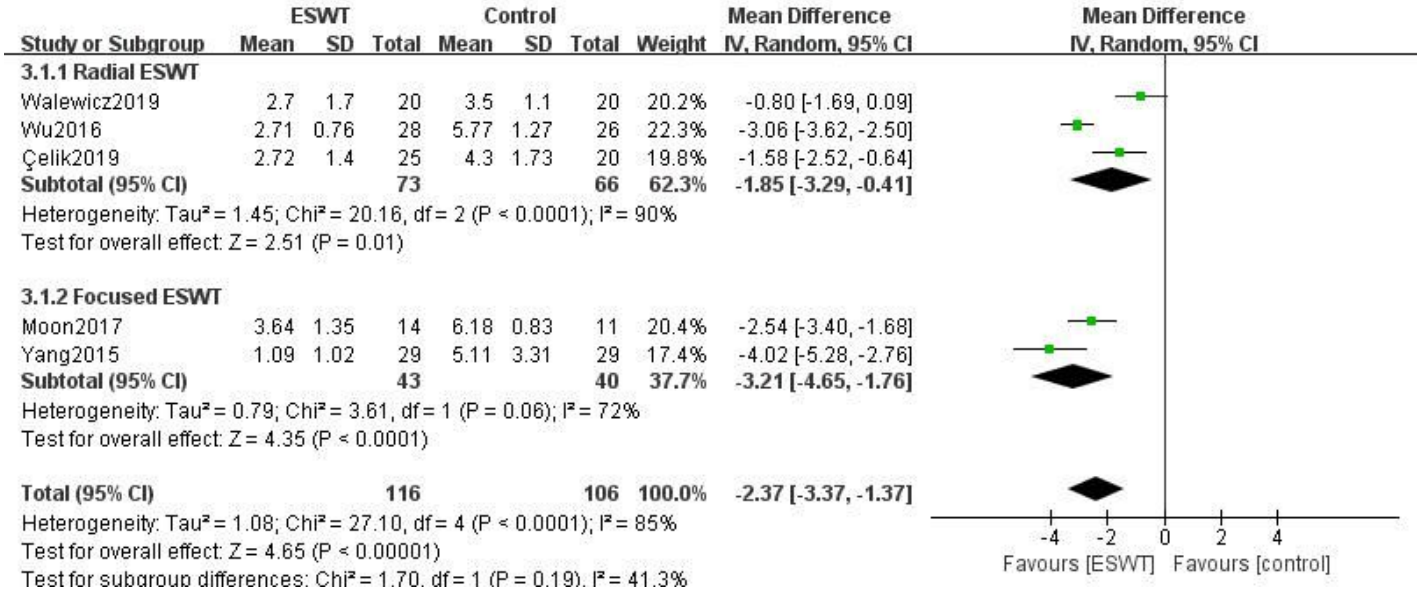

Figure 4

Forest plot analysis of Pain sores in subgroups of patients with LBP after treatment between the ESWT and control group.

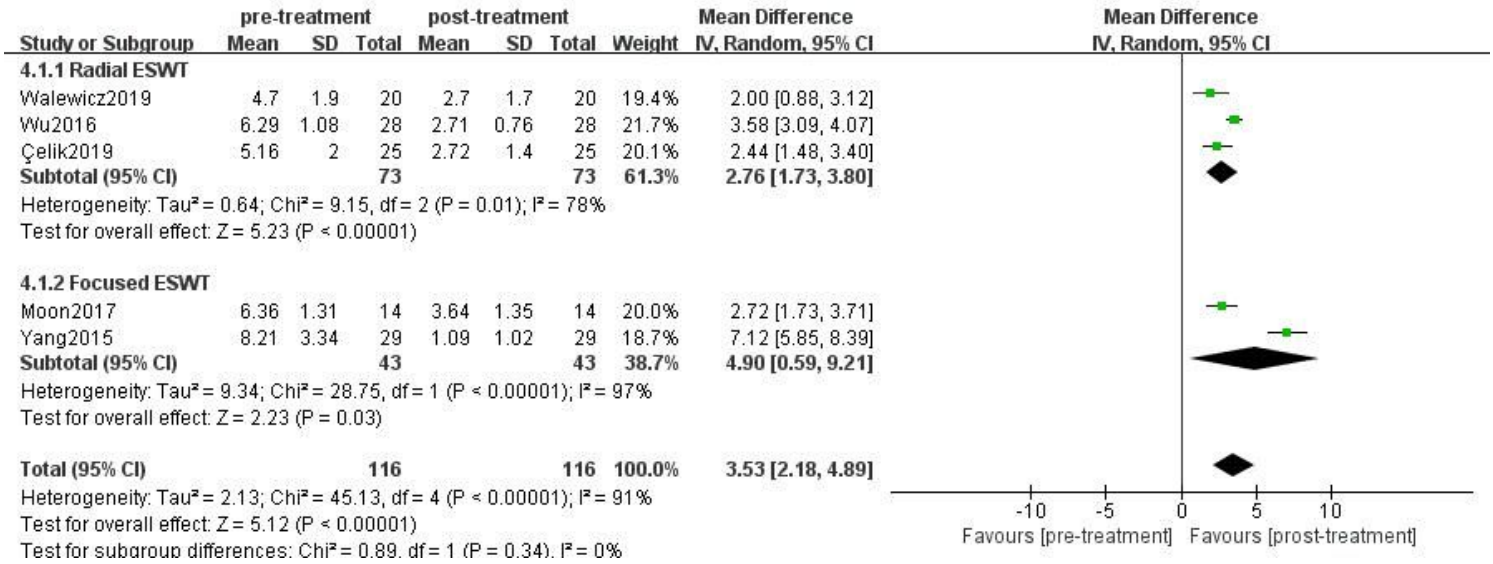

Figure 5

Forest plot analysis of Pain sores in subgroups of patients with LBP before and after the ESWT treatment.

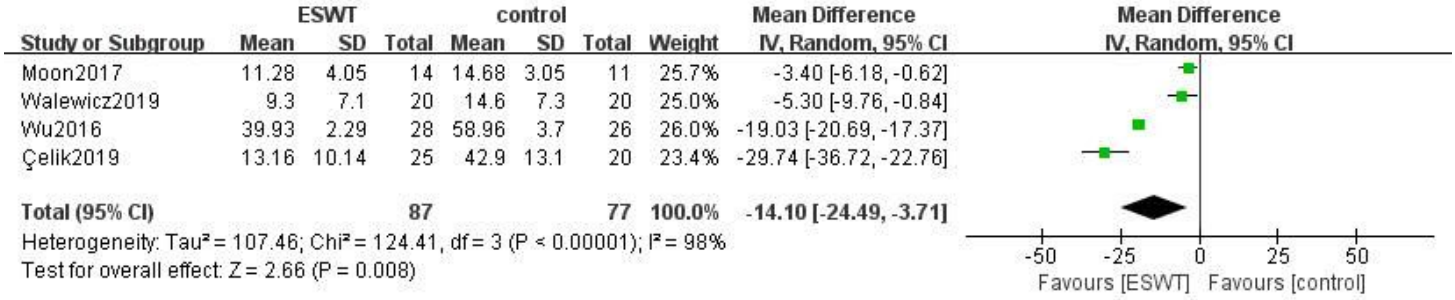

Figure 6

Forest plot analysis of ODI sores in patients with LBP after treatment between the ESWT and control group.

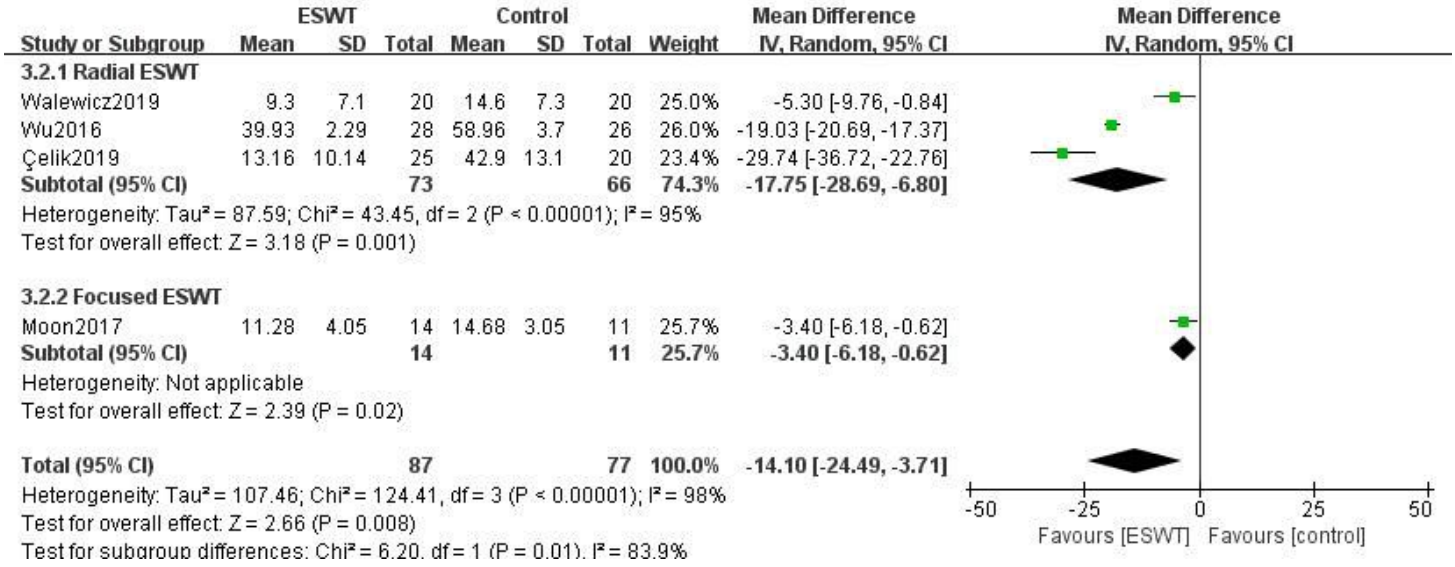

Figure 7

Forest plot analysis of ODI sores in subgroups of patients with LBP after treatment between the ESWT and control group.

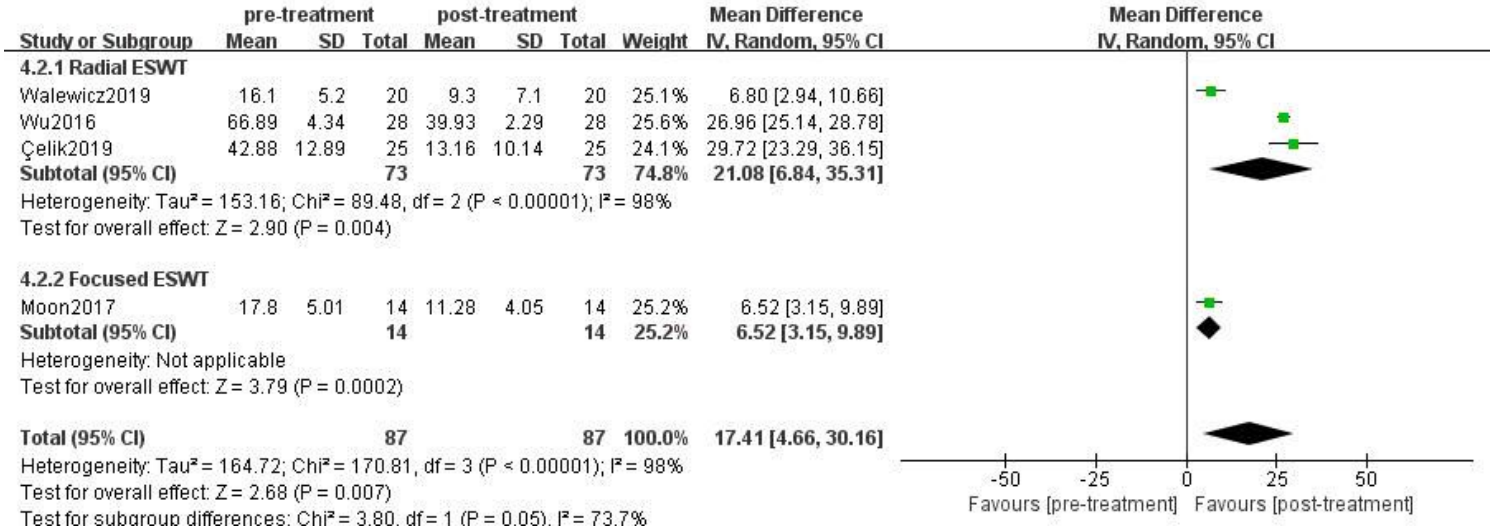

Figure 8

Forest plot analysis of ODI sores in subgroups of patients with LBP before and after the ESWT treatment.

Supplementary Files

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- PRISMA2009checklist.doc