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Intradiscal steroid injection for the treatment of chronic non-specific low back pain in patients with Modic type 1 change

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Abstract. – OBJECTIVE: The aim of this study was to evaluate and aggregate the evidence from the published studies to determine the effectiveness of intradiscal steroid injection (ISI) in patients with symptomatic Modic type I change (MCI).

MATERIALS AND METHODS: A systematic literature search was independently performed by two authors. The electronic database, including PubMed, Embase, the Cochrane Library, and Web of Science, were searched with the given search terms but without language restriction. The studies that met the inclusion criteria were included. The relevant data were extracted, and two authors independently assessed the quality of the included studies. We performed the present study using the STATA software package.

RESULTS: The present work included seven studies with 434 patients with chronic low back pain (CLBP). The risk of bias in the included randomized controlled trials (RCTs) was rated from low to unclear, and all the included observational studies were rated as high quality. The result of the meta-analysis revealed that there were significant differences in pain intensity [standardized mean difference (SMD): 3.09, 95% confidence interval (CI): 1.60-4.58; $p<0.01$] and self-assessed improvement/satisfaction [odds ratio (OR): 11.41, 95% CI: 3.39-38.41; $p=0.05$] after ISI compared to before treatment. However, no significant differences in the proportion of patients with full or part-time employment (OR: 1.03, 95% CI: 0.55-1.91; $p>0.05$), receiving additional care for CLBP (OR: 0.78, 95% CI: 0.36-1.71; $p>0.05$), and serious adverse events (OR: 1.09, 95% CI: 0.58 to 2.05; $p>0.05$) were detected between the groups.

CONCLUSIONS: Among CLBP patients with MCI, the use of ISI was significantly associated with a reduction in pain intensity in the short term.

Key Words:
Modic changes, Endplate signal changes, Intradiscal injection, Steroid.

Introduction

About 23% of the world's population suffers from chronic low back pain (CLBP), and 24-80% of them may undergo the recurrence of pain within 1-year[1]. The number of individuals with CLBP has increased dramatically from approximately 377 million in 1990 to 577 million in 2017[2]. As a leading cause of disability[4], CLBP is a major contributor to individual and societal burdens[3,4]. Therefore, understanding the pathomechanisms of CLBP and finding cost-effective therapeutic options are urgent needs.

CLBP is a complex, multidimensional symptom affecting populations of all ages rather than a disease[5]. However, it remains unclear or controversial about its etiology, pathomechanisms, and treatment strategy. Historically, the potential mechanism is strongly associated with intervertebral discs[6,7]. However, a recent study[8] has indicated that pain signals can also be transmitted from the vertebral endplates *via* the basivertebral nerve, providing new insights into the origin of CLBP.

Modic changes (MCs) are the specific signal intensity changes of the vertebral endplates and adjacent bone marrow visible *via* magnetic resonance imaging (MRI). Given the close correlations with CLBP, they have attracted widespread attention in academia. Modic et al[9,10] in 1988 reported their classifications and histological manifestations first. Current evidence[11] suggests that Modic type I change (MCI) is mostly associated with CLBP than other two types. Furthermore, the preceding studies[12,13] have shown a significantly higher level of proinflammatory cytokines in subjects with MCI than those without MCI, indicating a local inflammation. These findings provide a plausible rationale for assessing the ef-

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fectiveness of intradiscal steroid injection (ISI) targeting local inflammation.

Several studies[14,15] investigated the effectiveness of ISI for CLBP in patients with MCI. However, most of them had small sample sizes, which more likely lead to unreliable results. Therefore, we evaluated and aggregated the evidence from the published studies to determine the effectiveness of ISI in patients with symptomatic MCs.

Materials and Methods

The implementation of the present work was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[16]. The protocol of this study was registered with PROSPERO (registration number: CRD42021271207). Our institutional Ethics Committee waived ethics approval of this study. The PRISMA checklist of the present study is summarized in **Supplementary Table I**.

Search Strategy

Two authors independently performed a systematic literature search in PubMed, Embase, the Cochrane Library, and Web of Science, without language restriction. The search span was limited to the article published from 1st January 1988 to 31st July 2022 because MCs were first elaborated by Modic et al[9,10] in 1988. We used the following search terms to identify the articles reporting the effectiveness and safety of ISI for the treatment of CLBP in patients with MCI: "Modic changes", "vertebral endplate signal changes", "active discopathy", "Modic type I change", "intradiscal injection", "spinal injection", "intradiscal corticotherapy", "injection", "steroid", and "glucocorticoid". We manually searched references from related reviews and studies for additional eligible articles. The search strategy *via* PubMed database as an example is shown in **Supplementary Table II**.

Eligibility Criteria

We developed the inclusion criteria for the present work according to the principle of Participants, Interventions, Comparison, Outcome, and Study design (PICOs). The present work included studies that met the following criteria: (1) Participants: adult patients clinically diagnosed as non-specific CLBP and with evidence of MCI on MRI; (2) Intervention: intradiscal injections of different kind of steroids; (3) Comparison: placebo or no control group; (4) Outcome: any clinical outcome such as pain, disability, and adverse events; and (5) Study design: single- or double-arm observational studies, randomized controlled trials (RCTs). We only included the one with a larger sample or more accurate data if multiple articles presented overlapping outcomes from the same research team. The exclusion criteria for the present study included reviews, case reports, conference abstracts, and experimental animal studies.

Data Extraction

A standard summary form was designed before the implementation of data extraction. Two authors independently extracted the relevant data from each included study according to the established guideline and filled it into the corresponding sites of the summary form immediately. A third author was employed to resolve disagreements if unsolved after discussion between the two authors. The following data were extracted: study characteristics, selection of study population, the baseline of participants, drug and dosage, clinical outcomes, and follow-up time.

Outcomes

The outcomes for this meta-analysis were pain intensity, disability, and adverse events at the treatment endpoint or the final follow-up. Several methods used in the included studies to evaluate pain intensity and disability, including the visual analogue scale (VAS), Oswestry disability index (ODI), etc., were accepted in the present work.

Risk of Bias and Study Quality Assessment

Two authors independently evaluated the risk of bias of RCTs using the bias risk tool proposed by the Cochrane back review group[17]. They assessed the methodological quality of selected observational studies using the Newcastle-Ottawa Quality Assessment Scale (NOQAS). The disagreement was resolved by consensus or consulting a third author with more than 5-year experience in this field.

The included RCTs responded to each of the following domains with "high risk", "low risk", or "unclear" according to the Cochrane risk of bias tool: random sequence generation, allocation concealment, blinding of study participants, blinded outcomes assessment, incomplete outcome data, selective reporting, and

other biases[15]. An RCT showing a high risk of bias in two of all domains was considered as having a high risk[18].

We assessed the included cohort or case-control study following items proposed by NOQAS work group: selection of the study population, comparability among groups, and outcome evaluation. A study was considered to be high quality if the score was more than or equal to 7 points[19].

Statistical Analysis

The meta-analysis was conducted using the STATA software package, version 12.0 (StataCorp LP, College Station, TX, USA). Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for dichotomous outcomes (e.g., adverse events). For continuous outcomes (e.g., VAS and ODI), we used mean difference (MD) for the outcomes with identical scales, standardized MD for different scales, and 95% CIs to estimate the pooled effects. The random-effects model, which was reported[20] to provide better estimates with wider CIs than the fixed-effects model, was used to estimate the weighted mean. A p-value lower than or equal to 0.05 was considered to indicate a significant difference.

The quantity I^2 statistic was calculated to assess the heterogeneity across studies, with scores of more than 75%, 25-75%, and lower than 25% representing high, moderate, and low heterogeneity, respectively[21]. We would have used the subgroup or meta-regression analysis to explore possible sources of high heterogeneity if the number of the included studies was sufficient. Begg's funnel plots and Egger's tests were created to identify the potential publication bias. The sensitive analysis was carried out to detect the robustness of the pooled estimated effects by deleting the included studies one by one.

Results

Systematic Search

The flowchart of the study retrieval and selection is shown in Figure 1. We initially identified 1,075 records under the established search strategy, and 581 repetitive records were automatically eliminated after the integration of the electronic literature management software EndNote. 21 studies were eligible for inclusion after screening the titles and abstracts. Finally, 7 articles[22-28] ultimately complied with the inclusion criteria after reading the full texts.

Study Characteristics and Quality Assessment

7 studies[22-28] involving 434 patients with CLBP were included in this meta-analysis. Of which, there were 4 RCTs[24,25,27,28] with sample sizes ranging between 15 and 68, and 3 observational studies[22,23,26] with sample sizes ranging between 12 and 40. The ages of the individual included in these studies ranged between 32 and 64 years. The mean follow-up was between 6 months and 24 months. Four of these 7 studies[23,26-28] adopted intradiscal prednisolone acetate injection, while the others[22,24,25] used intradiscal betamethasone injection. Moreover, 2 studies[27,28] have compared the intradiscal steroid and non-steroid injection for MCI, 2 studies[23,26] have assessed the effectiveness of ISI in patients with or without MCI, and the remaining three studies[22,24,25] have investigated both. The characteristics of the included studies are summarized in Table I.

The risk of bias of the 4 included RCTs is presented in Figure 2. According to the evaluation criteria proposed by the Cochrane review group, the risk of bias of these RCTs was rated from low to unclear. The total quality score of each observational study was counted according to the items given by the NOQAS work group. Table II summarizes the scoring results of the 3 included observational studies[22,23,26]. All included observational studies were high quality with the quality score of more than 7 points in this meta-analysis.

Primary Outcomes

Pain intensity before and after ISI in patients with MCI

Five studies[23-26,28] published from 2007 to 2020 reported comparative results of pain intensity in patients with MCI before and after ISI. The result of the meta-analysis revealed that there was a significant difference in pain intensity after ISI compared to before treatment [standardized mean difference (SMD): 3.09, 95% CI: 1.60-4.58; $p<0.01$] (Figure 3), indicating that ISI was closely correlated with the reduction in CLBP intensity.

Self-reported satisfaction/ improvement

Several studies[22,23,26,27] included in the present work have demonstrated that the subjects with MCI receiving ISI had more remarkable self-assessed improvement compared to those in the control group. The pooled result also detected a significant difference in patients' self-reported improvement between ISI and control groups (OR: 11.41, 95% CI: 3.39- 38.41; $p=0.05$) (Figure 4).

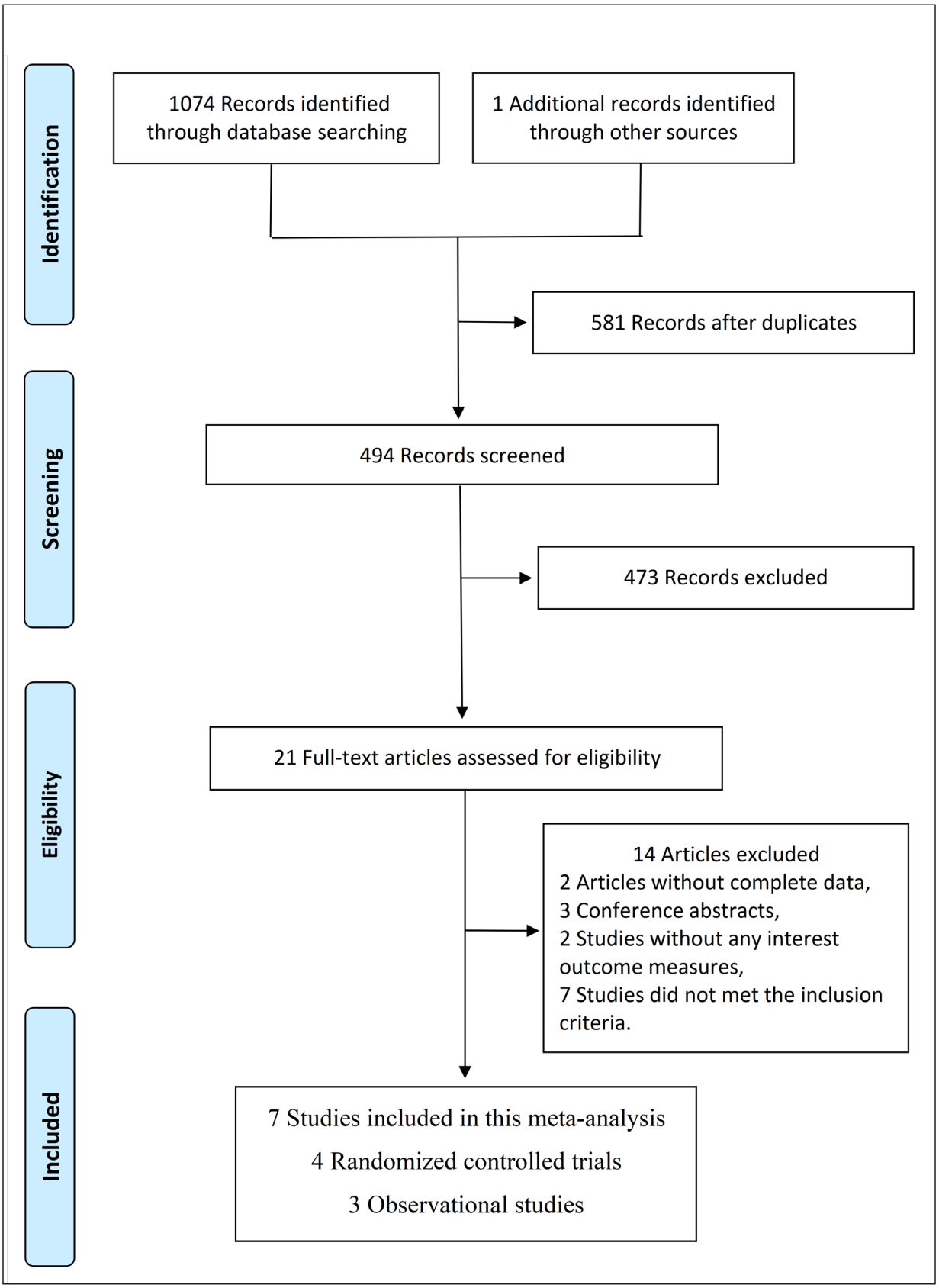

Figure 1. Flow diagram of study selection.

Table I. Characteristics of the included studies.

Author (years)	Study sites	Study design	Sample	Mean age (years)	Gender (female)	Follow-up	Study population	Interventions	Outcomes
			ISI / CG	ISI / CG	ISI / CG	ISI / CG	ISI / CG	ISI / CG	
Buttermann et al[22]	USA	PS	40/38	44/44	17/30	12-24 m	MCI/no MCI	Betamethasone (8.3 mg) / discography	②④
Fayad et al[23]	France	CS	37/12	47/53	22/7	6 m	MCI/MCII	Prednisolone acetate (25 mg)	①②⑤
Zhuang et al[24]	China	RCT	15/15	41.6	-	6 m	MCI/MCII	Betamethasone (3 ml)/saline (3 ml)	①
Cao et al[25]	China	RCT	20/20	41/42.6	7/8	6 m	MCI/MCII	Betamethasone (3 ml)/saline (3 ml)	①
Beaudreuil et al[26]	France	CS	30/30	48/46	18/12	12-14 m	MCI/no MCI	Methylprednisolone (2 ml)	①②
Nguyen et al[27]	France	RCT	67/68	46/47	38/44	12 m	MCI	Prednisolone acetate (25 mg)/discography	②③④⑤
Tavares et al[28]	France	RCT	20/22	50/50	9/14	6 m	MCI	Prednisolone acetate (50 mg)/lidocaine (40 mg)	①③④⑤

ISI: intradiscal steriod injection; CG: control group; RCT: randomized controlled trial; m: months; MCI: Modic type I change; CS: case-control study; MCII: Modic type II change; PS: perspective study.① Pain intensity before and after intradiscal steriod injection; ②Self-report satisfaction and improvement after treatments; ③ Full- or part-time employment after treatments; ④ Receiving additional cares for chronic low back pain after treatments; ⑤ Serious adverse events.

Figure 2. Risk of bias graph and summary.

Table II. Score distribution of quality assessment based on Newcastle-Ottawa Scale.

Items	Selection of study population	Comparability	Outcome evaluation	Total scores
Buttermann et al[22]	☆ ☆ ☆	☆ ☆	☆ ☆ ☆	8
Fayad et al[23]	☆ ☆ ☆	☆ ☆	☆ ☆	7
Beaudreuil et al[26]	☆ ☆ ☆	☆ ☆	☆ ☆	7

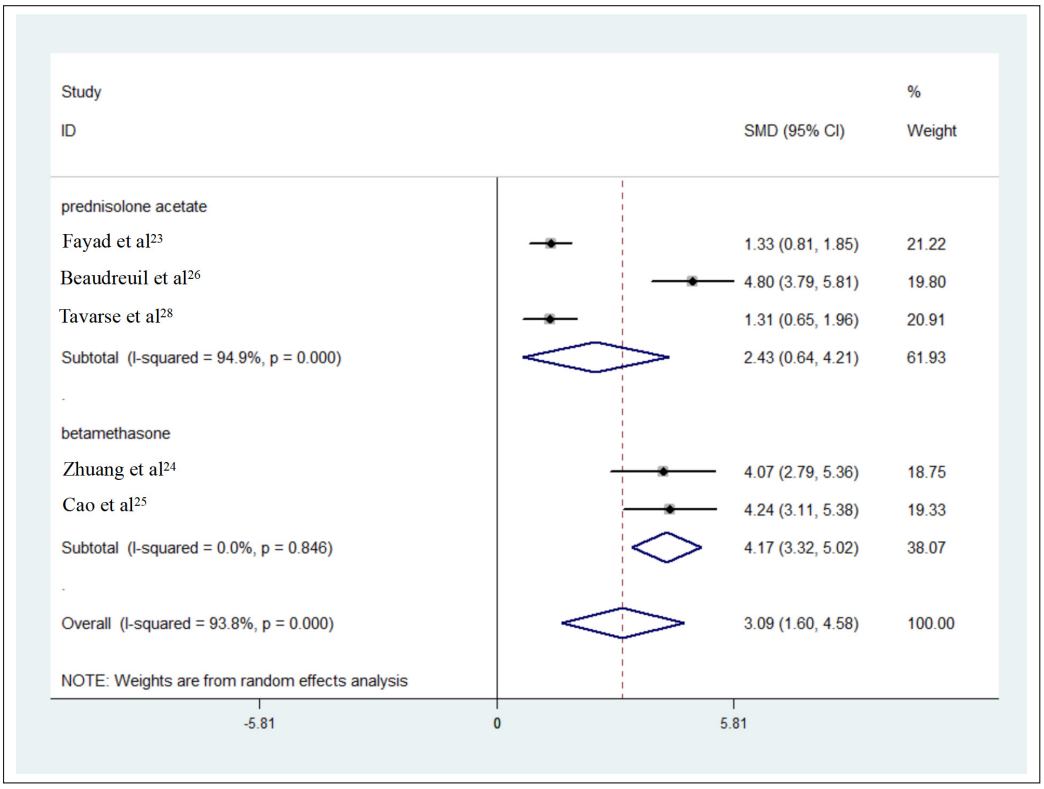

Figure 3. Forest plot of the meta-analytic estimate for pain intensity before and after intradiscal steroid injection.

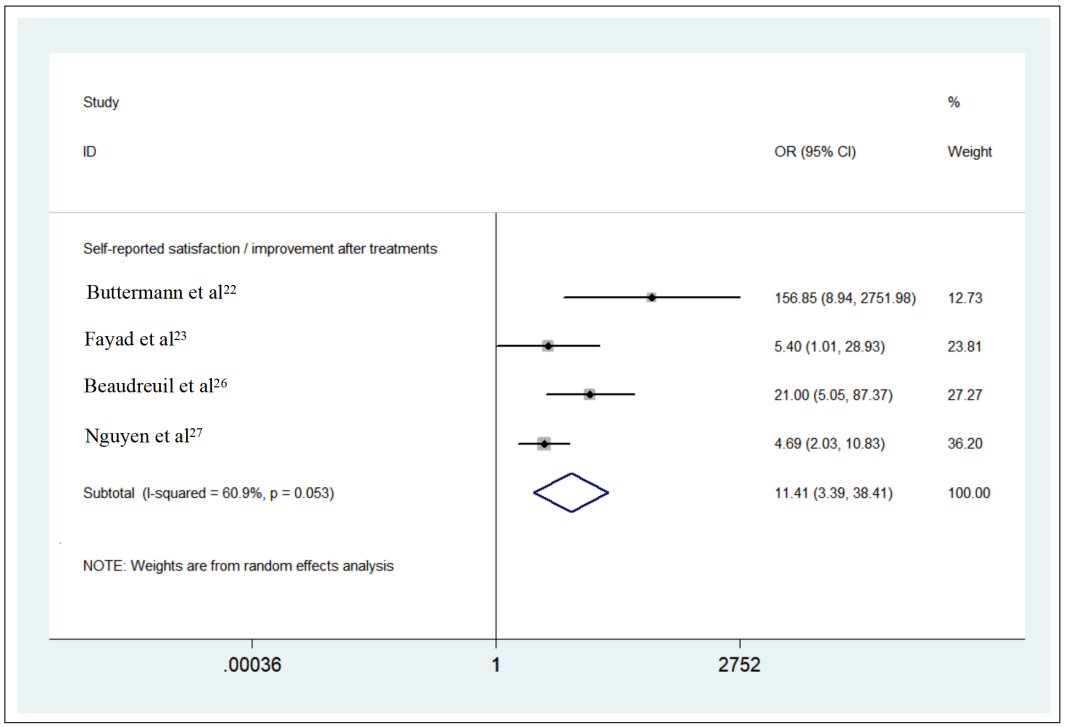

Figure 4. Forest plot of the meta-analytic estimate for self-reported satisfaction/improvement after treatments.

Secondary Outcomes

Forest plots for secondary outcomes are presented in Figure 5. The proportion of patients with full or part-time employment after treatments were not significantly different between the groups (OR: 1.03, 95% CI: 0.55-1.91; $p>0.05$). There was no significant difference in patients receiving additional care for CLBP after treatments (OR: 0.78, 95% CI: 0.36-1.71; $p>0.05$). Moreover, no significant difference in serious adverse events was detected in patients who received ISI or other interventions (OR: 1.09, 95% CI: 0.58-2.05; $p>0.05$).

Publication Bias, Heterogeneity, and Sensitive Analysis

The funnel plots and Egger's tests have waived the need because this meta-analysis, including less than ten studies, was generally underpowered to detect the potential publication bias[20]. We performed the sensitivity analysis of primary outcomes (pain intensity and self-reported satisfaction/improvement). No significant differences in these two outcomes were detected across groups using the sensitivity analysis, demonstrating that the results of primary outcomes were reliable (Figure 6).

Discussion

The treatment strategy for symptomatic MCI was mainly based on the management principles of CLBP or targeting the underlying etiopathology of MCI. It still lacks therapeutic recommendations or international guidelines on managing CLBP in a patient with MCI. To the best of our knowledge, it is the first meta-analysis to summarize the effectiveness and safety of ISI for symptomatic MCI. The present work indicated that i)

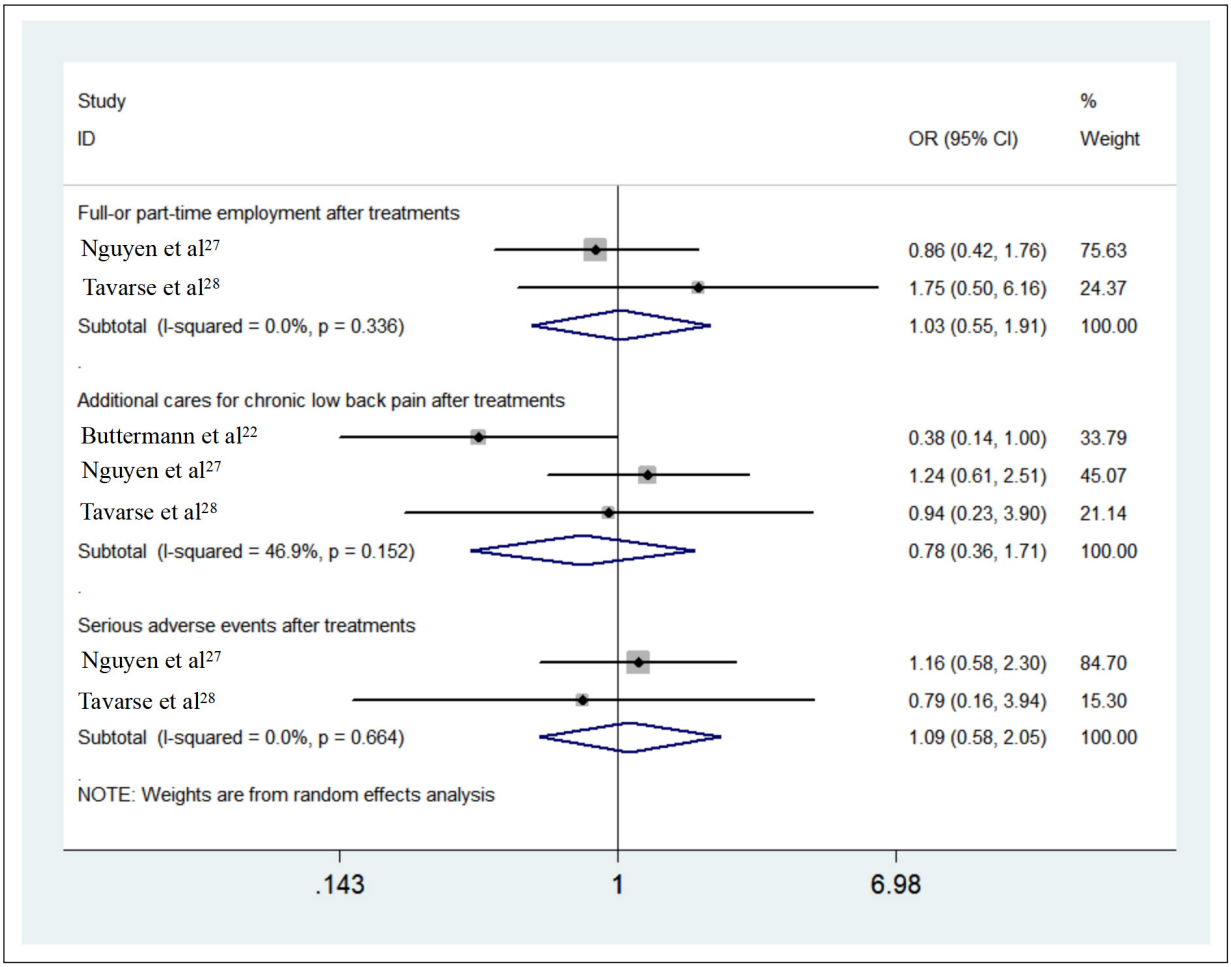

Figure 5. Forest plots of the meta-analytic estimate for full- or part-time employment, additional care for chronic low back pain, and serious adverse events after treatments.

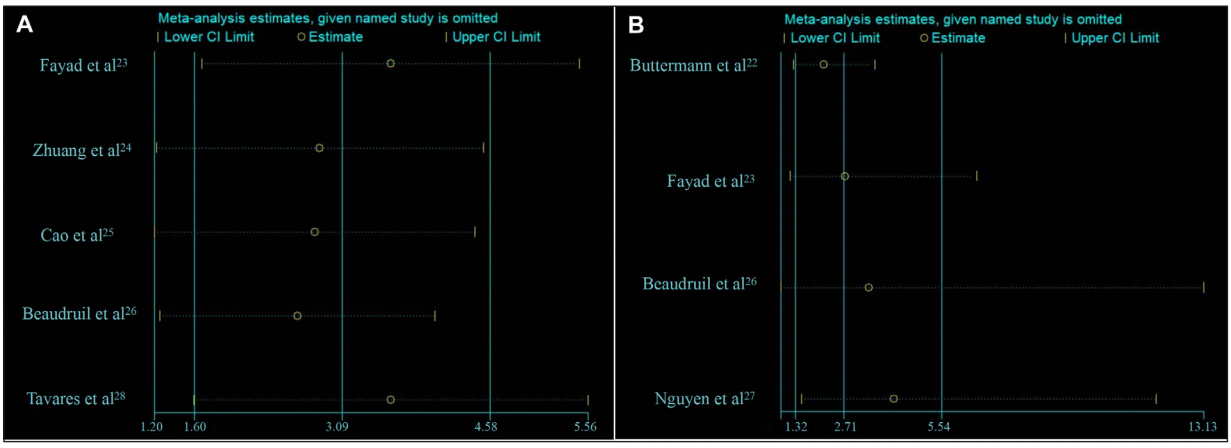

Figure 6. Sensitive analysis of pain intensity (**A**) and self-reported satisfaction/improvement (**B**).

MCI patients with CLBP had a significant short-term improvement in pain intensity after receiving ISI, and ii) Serious adverse events were not significantly higher than the other interventions in the control group.

The regimen for treating symptomatic MCI generally derived from the mechanical origins of CLBP and the potential etiopathology of MCI. A recent study[29] has defined the applicability of the custom-made rigid lumbar brace in patients with MCI. A rigid lumbar brace blocking the lumbar or lumbosacral spine worn for three months was associated with a reduction in pain for 79% of CLBP patients with MCI[29]. Moreover, a recent systematic review[8] has demonstrated that intraosseous basivertebral nerve (BVN) radiofrequency neurotomy is also effective in improving pain and disability in patients with MCI or MCII. The procedure's success is based primarily on the anatomical theory that BVN provides sensory innervation to the vertebral endplates.

However, the prevailing approach to target the potential pathogenesis of local infection or inflammation[30] in symptomatic MCI is the following two kinds of treatment: anti-infective drugs and intradiscal injection of steroids[31]. Positive bacteria cultures in disc and endplate tissues from patients with MCI provide a plausible rationale for using antibiotics[32,33]. Albert et al[34,35] in their two studies indicated the substantial effects of 90-100 days of antibiotic treatment in patients with CLBP and MCI. However, a recent RCT[36] has reported the conflict results that three months of treatment with amoxicillin did not provide a clinically meaningful benefit compared with a placebo. Therefore, the available evidence does neither support nor oppose the use of antibiotics in populations with MCI. Further studies should pay much more attention on the associations of low-toxicity bacteria with MCs.

Current studies[12,23,32] have confirmed the positive contributions of local inflammation in the development of symptomatic MCI. Therefore, using steroids against inflammatory mediators may play decisive role in killing pain. The present work including seven studies[22-28] further confirmed the above hypothesis. However, the NICE 2016 guidelines[37] does not recommend ISI for CLBP. Therefore, the place of intradiscal injection of steroids for CLBP remains to be determined, especially regarding other types of lumbar injections[38].

This study also bears several deficiencies. First, despite the meta-analysis being a powerful tool for analyzing cumulative data from individual studies, the small sample sizes of the included individual studies may have decreased the statistical power. Second, the drugs used in both groups differed, and the steroids' doses varied in studies from 8.3 mg betamethasone to 50 mg prednisolone acetate. Moreover, various interventions in the control group may have differently responded to pain intensity, leading to significantly inconsistent results. Third, language limitation and publication bias likely existed, although the present work had ethnic diversity among the study population. Fourth, the time frame for the included study follow-up varied from 6 months to 24 months, which may significantly contribute to high heterogeneity.

Conclusions

Current study has demonstrated the short-term clinical benefit of ISI in CLBP patients with MCI. However, we should cautiously interpret the findings because of a limited number of individual studies.

Conflict of Interest
The authors declare that they have no conflict of interest.

Ethics Approval
Not applicable.

Availability of Data and Materials
The datasets analyzed during the present study are available from the corresponding author on reasonable request.

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Authors' Contributions
Minke Wei and Jianxun Wei conceived and designed the study. Xiaoping Mu, Xiaohui Wei, and Shimei Chen performed the experiments. Xiaoping Mu and Yufu Ou interpreted the data. Minke Wei, Yufu Ou, and Xiaohui Wei contributed reagents, materials, analysis tools. Xiaoping Mu wrote the first draft of the manuscript.

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