Review Article

The efficacy of methylene blue for back pain: a meta-analysis of randomized controlled trials

Gang Yao1,2, Leming Xu1

1Department of Radiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Zhejiang, China; 2Department of Radiology, The Affiliated Sir Run Run Hospital of Nanjing Medical University, Nanjing, China

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Abstract: Introduction: The efficacy of methylene blue for back pain remains controversial. We conduct a systematic review and meta-analysis to explore the impact of methylene blue versus placebo on back pain. Methods: We searched PubMed, EMBase, Web of science, EBSCO, and Cochrane library databases through June 2018 for randomized controlled trials (RCTs) assessing the effect of methylene blue versus placebo on the alleviation of back pain. This meta-analysis is performed using the random-effect model. Results: Three RCTs involving 229 patients are included in the meta-analysis. Overall, compared with control group for back pain, methylene blue can remarkably decrease pain scores at 24-48 h (Std. MD = -1.69; 95% CI = -2.07 to -1.32; P < 0.00001), 2-3 month (Std. MD = -1.09; 95% CI = -1.62 to -0.56; P < 0.0001), and ODI at 2-3 month (Std. MD = -0.85; 95% CI = -1.18 to -0.52; P < 0.00001), as well as moderate-severe functional disability after 3-6 months (RR = 0.46; 95% CI = 0.24 to 0.87; P = 0.02), but has no significant impact on pain scores (Std. MD = -1.60; 95% CI = -3.50 to 0.30; P = 0.10) and ODI (Std. MD = -1.95; 95% CI = -4.34 to 0.44; P = 0.11) at 6 months. Conclusions: Methylene blue can substantially decrease pain scores and ODI within 3 months, as well as moderate-severe functional disability after 3-6 months in patients with back pain.

Keywords: Methylene blue, back pain, pain scores, randomized controlled trials, meta-analysis

Introduction

Chronic back pain has become one of the most important socioeconomic problems [1]. Although spinal surgery has obtained great progress, some patients still suffer from postoperative pain, which results in disability and loss of work productivity, prolonged hospital stays and increased health care costs [1]. In addition, discogenic low back pain is an important cause of low back pain, accounting for 28-43% of the patients with low back pain [1]. Current treatment options include medicinal anti-inflammation strategy and invasive procedures (e.g. spine fusion and spinal arthroplasty), but the back pain remains noteworthy [1].

Methylene blue is known as a low-molecular weight, partially liposoluble vital dye [2]. It has been used in various fields of clinical medicine, including destruction of free nociceptive nerve endings for the relief of pain, inhibition of nitric oxide synthesis, a neuroprotective compound, and inhibition of monoamine oxidase [1]. The local injection of methylene blue can block nerve conduction or destroy nerve endings because of neurotropic effects, and benefit to different painful ailments [1]. Several studies have reported the safety and efficacy of the low dose of methylene blue solution in systemic and epidural administration [1].

The efficacy of methylene blue on the alleviation of back pain has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [1]. With accumulating evidence, we therefore perform a systematic review and meta-analysis of RCTs to investigate the efficacy of methylene blue versus placebo for back pain.

Materials and methods

Ethical approval and patient consent are not required because this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to
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The primary outcomes are pain scores at 24-48 h, 2-3 month, and 6 month. Secondary outcomes include Oswestry Disability Index (ODI) at 2-3 month and 6 month, as well as moderate-severe functional disability after 3-6 month.

Quality assessment in individual studies

Methodological quality of the included studies is independently evaluated using the modified Jadad scale [4]. There are 3 items for Jadad scale: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [5].

Statistical analysis

We estimate the standard mean difference (Std. MD) with 95% confidence interval (CI) for continuous outcomes (pain scores at 24-48 h, 2-3 month, and 6 month, ODI at 2-3 month and 6 month) and risk ratio (RR) with 95% CIs for dichotomous outcomes (moderate-severe functional disability after 3-6 month). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and I^2 > 50% indicates significant heterogeneity [6]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity via omitting one study in turn for the meta-analysis or performing subgroup analysis. Publication bias is not evaluated because of the limited number (<10) of included studies. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in Figure 1. 391 potentially rel-
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## Table 1. Characteristics of included studies

<table>
<thead>
<tr>
<th>NO.</th>
<th>Author</th>
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<th>Control group</th>
<th>Jada scores</th>
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<td></td>
<td>Number</td>
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<tr>
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<td>34.9 ± 11.7</td>
<td>19</td>
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<td>41.6 ± 11.5</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>Peng 2010</td>
<td>36</td>
<td>42.06 ± 13.74</td>
<td>21</td>
</tr>
</tbody>
</table>
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Relevant articles are identified initially. Finally, three RCTs that meet our inclusion criteria are included in the meta-analysis [1].

The baseline characteristics of the three eligible RCTs in the meta-analysis are summarized in Table 1. The three studies are published between 2010 and 2016, and sample sizes range from 72 to 107 with a total of 229. Two RCTs report local injection of methylene blue after traumatic thoracolumbar fixation [1], and lumbar open discectomy [1]. The remaining RCT reports 1 ml of 1% methylene blue injection into discogram-proven diseased disc, followed by injection of 1 ml of 2% lidocaine hydrochloride versus normal saline and 1 ml of 2% lidocaine hydrochloride into the painful disc [7].

Among the three studies included here, two studies report pain scores at 24-48 h and 2-3 month [1], two studies report pain scores at 6 month [1], two studies report ODI at 2-3 month [1], two studies report ODI at 6 month [1], and two studies report moderate-severe functional disability after 3-6 month [1]. Jadad scores of the three included studies vary from 4 to 5, and all three studies are considered to be high-quality ones according to quality assessment.

**Primary outcomes: pain scores at 24-48 h, 2-3 month, and 6 month**

These outcome data are analyzed with the random-effects model, and the pooled estimate of the two included RCTs suggested that compared to control group for back pain, methylene blue injection is associated with substantially reduced pain scores at 24-48 h (Std. MD = -1.69; 95% CI = -2.07 to -1.32; P < 0.00001) with low heterogeneity among the studies ($I^2 = 5\%$, heterogeneity $P = 0.31$) (Figure 2), and 2-3 month (Std. MD = -1.09; 95% CI = -1.62 to -0.56; $P < 0.0001$) with significant heterogeneity among the studies ($I^2 = 53\%$, heterogeneity $P = 0.31$) (Figure 3). However, there is no significant difference of pain scores at 6 month between two groups (Std. MD = -1.60; 95% CI = -3.50 to 0.30; $P = 0.10$) with significant heterogeneity among the studies ($I^2 = 95\%$, heterogeneity $P < 0.00001$) (Figure 4).

**Sensitivity analysis**

Significant heterogeneity is observed among the included studies for the pain scores at 2-3 month and 6 month, but there are just two RCTs included in the meta-analysis. Thus, we...
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do not perform sensitivity analysis via omitting one study in turn or subgroup analysis to detect the heterogeneity.

Secondary outcomes

Methylene blue injection can remarkably reduce ODI at 2-3 month (Std. MD = -0.85; 95% CI = -1.18 to -0.52; P < 0.00001; Figure 5), but not ODI at 6 month (Std. MD = -1.95; 95% CI = -4.34 to 0.44; P = 0.11; Figure 6). Moderate-severe functional disability after 3-6 month is significantly decreased by methylene blue injection compared to control intervention for back pain (RR = 0.46; 95% CI = 0.24 to 0.87; P = 0.02; Figure 7).

Discussion

Several pharmacological and therapeutic mechanisms are provided for the clinical application of methylene blue, such as the inhibition of free-radical generation, deactivation of xanthine oxidase, inhibition of the production of nitric oxide, destruction of free nociceptive nerve endings for the relief of pain, reduction of neurotoxic structural and functional damage in brain parenchyma, anxiolytic and antidepressant activities [1]. Methylene blue is known as a potent reversible inhibitor of monoamine oxidase-A and has an influence on 5-hydroxytryptamine [5-HT, serotonin] levels. Serotonin (5-HT) is released by platelets and mast cells after tissue injury and can exert analgesic effects depending on the site of action and the receptor subtype. 5-HT has strong association with pain processing and modulation in central nervous system, and its release from brain stem structures can produce a spinal analgesic action and contribute to peripheral sensitization of nerve fibers [1].

Many patients experience pain at the surgical site in short time after surgery [1], and the most severe discomfort is caused by soft tissue injury, muscle dissection, any surgical manipulation, and surgical-site inflammation within 2 months after surgery [8]. Thus, a follow-up period of 2-3 months is important to evaluate the safety and efficacy of methylene blue for preventing postoperative pain, and 6 months is thought to be sufficient to assess the pain. In a multicenter prospective study, 40% of the patients with discogenic low back pain have at least 30% pain relief at 6 months after intradisc-
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Methylene blue has beneficial effects on pain alleviation and functional improvement in patients with back pain.

Conclusions

Discordance of conflict of interest

None.

Address correspondence to: Leming Xu, Department of Radiology, The Second Affiliated Hospital of Zhejiang University School of Medicine, No.1, Youyi Road, Zhejiang, China. Tel: 008602389342584; Fax: 008602389342584; E-mail: mdxu@zju.edu.cn

References