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Pain and functional improvement effects of methylene blue injection on the soft tissue around fusion site after traumatic thoracolumbar fixation: A double-blind, randomized placebo-controlled study

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ABSTRACT

Objective: Fractures of the thoracolumbar spine can cause pain, long-term reductions in quality of life (QOL), and neural deficits. The aim of this study was to investigate the effects of methylene blue (MB) on preventing postoperative pain and improving QOL in patients with throracolumbar fractures undergoing posterior pedicle screw fixation.

Methods: Fifty patients underwent standard posterior pedicular screw fixation for stabilization of the thoracolumbar fractures: 25 received 1 ml of MB solution at a concentration of 0.5% and 25 received normal saline on the soft tissue around fusion site. Primary outcomes were the control of pain, evaluated at 48 h, 2 and 6 months after surgery with the use of a visual analog scale (VAS), and the improvement of QOL, assessed 2 and 6 months postoperatively by means of Oswestry Disability Index (ODI) questionnaire.

Results: The mean VAS scores for pain were significantly lower in the MB group compared with the control group at 2 months (1.30 ± 0.45 vs. 2.60 ± 1.19, $P < 0.001$) and 6 months (1.17 ± 0.37 vs. 1.60 ± 0.87; $P = 0.028$) after treatment. At 2 months after the surgery, the mean ODI score was significantly lower in the MB-treated patients than the control group (20.4 ± 10.92 vs. 34.8 ± 15.11; $P = 0.001$). The ODI score in the MB-treated patients was better than the control group at 6 months after the surgery (12.2 ± 11.66 vs. 20.8 ± 11.14; $P = 0.016$).

Conclusion: A single dose of MB on the soft tissue around fusion site shows promising results in terms of safety, reduction of postoperative pain, and functional results when compared with placebo 6 months after surgery.

1. Introduction

Many people have permanent functional impairment and pain after spinal fractures. Despite progress in surgical techniques, some patients still suffer from postoperative pain [1]. This leads to a low QOL due to pain, disability and loss of work productivity, prolonged hospital stays and increased health care costs while postoperative pain relief provides benefits such as earlier mobilization, shorter hospital stay, reduced hospital costs, and morbidity reduction [2,3]. Although several methods have been introduced for postoperative pain control in spinal surgeries, this problem remains noteworthy [4–12]. In addition, outcome after surgical treatment of thoracolumbar fractures is variable, and the benefit is inconsistent [13–16].

Methylene blue (MB) is a low–molecular weight, partially liposoluble vital dye, which has been used in many different fields of clinical medicine [17]. Different theories underlie the pharmacological and therapeutic mechanisms that may be responsible for the effect of MB, including destruction of free nociceptive nerve endings for the relief of pain [18,19], inhibition of nitric oxide synthesis [17], its effectiveness as a neuroprotective compound [20], and inhibition of monoamine oxidase (MAO) [21]. Due to neurotropic effects of MB, which enables it to block nerve conduction or destroy nerve endings, the local injection of it has been used

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for many different painful ailments [18,22–24]. Based on several studies showing the safety and efficacy of the low dose of MB solution in systemic and epidural administration [25–29], we designed this study to evaluate the effect of MB on postoperative pain and QOL in patients with thoracolumbar fractures undergoing posterior pedicle screw fixation.

2. Material and methods

2.1. Study population

We performed a prospective, randomized, double-blind, placebo-controlled study in which 50 adult patients (>18 years) out of total of 58 patients, with unstable thoracic and lumbar spine traumatic fractures were eligible to participate. All the patients underwent preoperative eligibility evaluations, including MRI of the spine and examination by a neurosurgeon. The patients were enrolled from September 2012 to September 2014 to undergo standard posterior pedicular screw fixation for stabilization of the thoracolumbar fractures in Emtiaz hospital, affiliated with Shiraz University of Medical Sciences. Patients' demographic information including age, sex, body mass index (BMI), smoking, and underlying diseases were recorded before the surgery. The medical research ethics committee as well as institutional review board of Shiraz University of Medical Sciences approved the study protocol before data collection began (approval number: 91-4480). Written informed consent was obtained from all the patients before inclusion in the study. Of a total of 58 patients, 8 were excluded in accordance with the exclusion criteria, and 50 were eligible for participation. We excluded those patients who were <18 and >65 years old and had a history of previous spine surgery, epidural steroid or any other agent injections, spinal cord tumors, systemic or local infections, or dural injuries (4 patients); those patients receiving myelograms or lumbar punctures within 24 h before surgery (1 patient); those taking serotonergic psychiatric medications (1 patient); and patients who needed laminectomy for treatment or multi-stage operations and/or other surgical approaches (2 patients).

Table 1
Fracture characteristics of the patients in the two study groups.

Parameters	MB Group (n = 25)	Placebo Group (n = 25)
Mechanism of trauma		
Car accident	15 (60%)	14 (56%)
Motor vehicle accident	4 (16%)	4 (16%)
Fall	5 (20%)	5 (20%)
Others	1 (4%)	2 (8%)
Number of spinal levels involved		
2 Levels (%)	18 (72%)	17 (68%)
T4–5 & T5–6	1 (4%)	0 (0%)
T5–6 & T6–7	1 (4%)	1 (4%)
T6–7 & T7–8	1 (4%)	0 (0%)
T8–9 & T9–10	1 (4%)	0 (0%)
T11–12 & T12–L1	6 (24%)	6 (24%)
T12–L1 & L1–2	8 (32%)	8 (32%)
L1–2 & L2–3	0 (0%)	1 (4%)
L3–4 & L4–5	0 (0%)	1 (4%)
3 Levels (%)	7 (28%)	7 (28%)
T2–3, T3–4 & T4–5	0 (0%)	1 (4%)
T3–4, T4–5 & T5–6	0 (0%)	1 (4%)
T4–5, T5–6 & T6–7	1 (4%)	1 (4%)
T6–7, T7–8 & T8–9	1 (4%)	0 (0%)
T7–8, T8–9 & T9–10	0 (0%)	1 (4%)
T10–11, T11–12 & T12–L1	0 (0%)	1 (4%)
T11–12, T12–L1 & L1–2	4 (16%)	2 (8%)
L1–2, L2–3 & L3–4	1 (4%)	0 (0%)
4 Levels (%)	0 (0%)	1 (4%)
T1–2, T2–3, T3–4 & T4–5	0 (0%)	1 (4%)
AOSpine classification		
Type A: axial compression	24	22
A0	0	0
A1	3	4
A2	4	3
A3	17	15
A4	0	0
Type B: distraction	12	12
B1	6	5
B2	6	7
B3	0	0
Type C: translation	2	3
C1	2	3
C2	0	0
C3	0	0

2.2. Randomization and intervention

The eligible patients were given an admission number from 1 to 50 based on their order of referral. They were randomly assigned to the intervention and control groups using a method of sequence generation (computerized random number generators). For this purpose, we prepared 50 sheets of paper, writing on 25 sheets "I" for "Intervention: 1 ml of MB solution at a concentration of 0.5%" and on 25 "C" for "Control: 1 ml of normal saline," and put each paper sheet in an envelope. The envelopes were then sorted randomly using random allocation software. With regards to the patients' admission number and the random allocation sequences, a physician, who was the coordinator of the study group, opened the sealed envelopes that contained the word I or C and assigned each patient to the Intervention or Control group accordingly. The allocation remained concealed during the study.

The random allocation was conducted by the physician. Thus, the surgeon was not aware of the drug application and had no role in allocation. An independent statistical analyst, who was not involved in any stage of these procedures, was unaware of the study groups either, until the data were analyzed and the labels were decoded. The patients were unconscious during the surgery and thus, they knew nothing about the type of intervention they received. All the patients were followed by 2 independent assessors who were unaware of the study. A third assessor, who was likewise unaware of the study, verified the results. The assessors did not know that a study was being conducted and they were blind to group assignment. These assessors, who were not members of the anesthesia or surgical team, recorded the patients' outcome data. The surgeon, assistant surgeon, statistician, patients, and assessors were all blinded to group assignment (i.e., which patient received which treatment) throughout outcome measurement and analysis.

2.3. Drug preparation

Methylene blue was diluted by a medical staff who did not participate in the enrollment and postoperative evaluation. The MB solution was prepared by diluting 10 g of MB powder (M9140, Sigma-Aldrich) in 1 l of distilled water, and the solution was sterilized in an autoclave at a pressure of 20 lb (1.5 kg/cm^2) at 125 °C for 1 h and the sterilization process did not alter the compound. In the operation room, the physician poured the MB and normal saline into separate blue glass bottles and labeled each bottle as "I" and "C" respectively.

2.4. Surgical procedure

After general anesthesia, the patients were carefully placed prone with appropriate bolsters. Radiographic localization was used to plan the skin incision, and the site was infiltrated with 10 ml of 1% lidocaine. All the patients underwent standard pedicle screw fixation [30]. Table 1 represents the fracture characteristics