

# A randomized placebo-controlled trial of intradiscal methylene blue injection for the treatment of chronic discogenic low back pain

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## ABSTRACT

A preliminary report of clinical study revealed that chronic discogenic low back pain could be treated by intradiscal methylene blue (MB) injection. We investigated the effect of intradiscal MB injection for the treatment of chronic discogenic low back pain in a randomized placebo-controlled trial. We recruited 136 patients who were found potentially eligible after clinical examination and 72 became eligible after discography. All the patients had discogenic low back pain lasting longer than 6 months, with no comorbidity. Thirty-six were allocated to intradiscal MB injection and 36 to placebo treatment. The principal criteria to judge the effectiveness included alleviation of pain, assessed by a 101-point numerical rating scale (NRS-101), and improvement in disability, as assessed with the Oswestry Disability Index (ODI) for functional recovery. At the 24-month follow-up, both the groups differed substantially with respect to the primary outcomes. The patients in MB injection group showed a mean reduction in pain measured by NRS of 52.50, a mean reduction in Oswestry disability scores of 35.58, and satisfaction rates of 91.6%, compared with 0.70%, 1.68%, and 14.3%, respectively, in placebo treatment group ( $p < 0.001$ ,  $p < 0.001$ , and  $p < 0.001$ , respectively). No adverse effects or complications were found in the group of patients treated with intradiscal MB injection. The current clinical trial indicates that the injection of methylene blue into the painful disc is a safe, effective and minimally invasive method for the treatment of intractable and incapacitating discogenic low back pain.

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## 1. Introduction

Chronic low back pain is one of the most important socio-economic problems in the orthopaedic field [1]. Among a variety of etiologies, discogenic low back pain has been recognized as an important cause of low back pain. It has been estimated that discogenic low back pain accounts for 28–43% of the patients with low back pain [40,45]. Current treatment options range from medicinal anti-inflammation strategy to invasive procedures including spine fusion and recently spinal arthroplasty [2,3]. Unfortunately, all the current available approaches are limited to treating the symptoms of the degenerative process but not the underlying pathologic alterations of the disc. Given the prevalence of this problem and the limited treatment options, the development of any alternative treatment method should be welcome.

Discogenic back pain may be attributable to any cause that offends the sensory nerve endings of the disc. Pain is thought to be caused by mechanical and chemical mediations of nociceptors within the anulus. Recently our study found [31–33] that the pathologic features of discs obtained from the patients with discogenic low back pain were the formation of the zones of vascularized granulation tissue, with extensive innervation in fissures extending from the outer part of the annulus into the nucleus pulposus. Our study clearly demonstrated that in the zones of vascularized granulation tissue there were abundant SP-immunoreactive nerve fibres which had been thought to be nociceptive. Most likely the nociceptors within the granulation tissue could be excited by local inflammation to produce a painful response. With this assumption in mind, it is presumed that if the nerve fibres and nerve endings growing into the disc along the tear could be destroyed, discogenic pain would be alleviated or abated. Sheng et al. [41] used a mixture of procaine and methylene blue (MB) injection into the pelvic fracture site for the management of fracture pain, and found that the pain was greatly alleviated. This analgesic effect lasted about 3 weeks with a single injection. Subsequently solid bony union was observed in all cases within 4–6 weeks. Intradermal MB

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injection has been shown by electron microscopy to be able to destroy dermal nerve endings [13,15]. It led us to use intradiscal MB injection in an attempt to alleviate the discogenic pain in these patients. Recently, a minimally invasive method, intradiscal MB injection for the treatment of discogenic low back pain, has been reported [34]. Preliminary results of clinical studies are encouraging. Based on our pilot study of patients with discogenic low back pain, this study was a prospective, randomized, double-blind clinical trial to assess the efficacy of intradiscal MB injection for the treatment of discogenic low back pain.

## 2. Methods

### 2.1. Patients

From December 1, 2003 to December 1, 2004, 136 consecutive patients with chronic low back pain without radiculopathy but with evidence of lumbar disc degeneration on magnetic resonance scan were enrolled, with the preliminary diagnosis of discogenic low back pain. The age ranged from 20 to 65 years. According to their history, clinical examinations, and imaging, patients with lumbar disc herniation, spinal instability, lumbar canal stenosis, spondylolysis, spondylolisthesis (isthmic or degenerative), disc degeneration with endplate Modic changes, neurologic disease, inflammatory arthritis, tumor, and infection were excluded. The patients who had psychological problems, such as the presence of depression or taking antidepressants or anxiolytic drugs for the treatment of depression were excluded. All the patients were previously treated conservatively with physical therapy and non-steroidal anti-inflammatory drugs or opioid medications without relief of their symptoms for more than 6 months. In addition, these patients had no previous lumbar surgery, and showed a normal or slight decrease in height of the disc space on lateral plain X-ray film. Therefore, these patients were primarily considered eligible as candidates for lumbar interbody fusion. Informed signed consent was obtained from the enrolled patients before discography, and the protocol was approved by the Ethics Committees of joint hospitals. All the patients underwent routine discography. Of the 136 patients with chronic low back pain, 72 were proved to be suffering from discogenic pain. Randomization took place from the patients with discogenic low back pain who were injected with either intradiscal MB injection or a placebo treatment after discography immediately. The assignment scheme was generated from a table of random numbers. The random assignments were stratified in each study center. The study adopted a 1:1 (MB injection:placebo) randomization schedule. From the total of 72 subjects who had positive discography, 36 were randomized to MB injection and 36 to placebo.

### 2.2. Lumbar discography and intradiscal MB injection

All discography was performed under fluoroscopy, using a standard posterolateral approach and a double-needle technique [22,40]. The original plan was to conduct the discography of the discs L3–L4, L4–L5, and L5–S1 in every patient. In practice, it was not necessary to take discography of all these discs. In some patients, L2–L3 disc was punctured when the discography was negative for the three lower ones. At least two discs were studied in each patient. The discographic needles were inserted on the contralateral side of a painful area. Once the needle was accurately inserted into the center of the disc, nonionic contrast medium Isovist (Schering Ltd., Germany) was instilled slowly into the nucleus under low pressure. A positive discography was defined if the patient experienced exact reproduction of his or her usual pain response pattern, and the posterior annular disruption was shown

to extend into the outer annulus or beyond the confines of the outer annulus by the contrast medium. In addition, at least one control disc adjacent to painful disc was negative.

MB injection or placebo treatment was subsequently completed according to which treatment the patient had been allocated, which was specified in a sealed envelope to ascertain the randomization schedule. No one knows the information about the assignment of the next patient. Both patient and surgeon who were responsible for the follow-up examination were blinded to the injected material. Because MB injectate is obviously blue in colour, the surgeon who completed discography and intradiscal injection did not participate in the follow-up of the patients. One ml of 1% MB (10 mg, Sujichuan Pharmaceutical Ltd., Jiangsu, China) was injected into the discogram-proven diseased disc, followed by injection of 1 ml of 2% lidocaine hydrochloride for alleviating pain due to insertion of the discographic needle. The placebo treatment included an injection of 1 ml of isotonic saline and 1 ml of 2% lidocaine hydrochloride into the painful disc. After treatment, the patient was never in contact with anyone privy to the randomization assignment. After the treatment, all the patients were put to bed for 24 h, and asked to avoid strenuous exercise for 3 weeks. Blinding was satisfactory. Within 2 years after treatment, patients did not know what treatment they had accepted.

### 2.3. Follow-up and outcome measures

All the patients were reevaluated 6, 12, and 24 months after randomization, respectively. The data were obtained by a surgeon or investigator blinded to the both group patients to minimize investigator bias. The main objective of the study was to compare the degree of alleviation of pain and improvement in physical function between two groups. The primary outcome was chiefly assessed by the change in the degree of pain with a self assessment of pain by a 101-point numerical rating scale (NRS-101) pain scales and the Oswestry Disability Index (ODI, version 1.0, 0–100) [14]. The secondary outcomes included analysis of posttreatment patient satisfaction, medication usage, and complications induced by the treatment. Patient satisfaction was rated as follows: 1, completely satisfied (no back pain at all time and no restriction of activities); 2, satisfied (slight pain that requires no medication and mild restriction of activities); 3, unsatisfied (moderate to severe pain that requires medication and moderate to severe restriction of activities). Medication usage (nonsteroidal anti-inflammatory drugs or opioid medications) was rated as follows: 1, none; 2, occasional; 3, regular.

Any event which might potentially be life threatening, or liable to produce disability or deformity would be taken as an indication to terminate the study. The possible complications (adverse events) relevant to the discography in both groups are disc space infection and nerve root stab injury. As for MB injection-related complications, there was a possibility of neurologic defect or new radiculopathy due to leakage of MB, thus producing injury to the spinal nerve root during and after the procedure. Any patient in either of the two groups who reported back pain aggravation, fever, chill, and sweats would receive MR imaging and screening laboratory examinations including leukocyte count, erythrocyte sedimentation rate, and C reactive protein levels. Any patient in MB injection group who reported numbness, dysesthesia or radiating leg pain and weakness in lower extremity would receive a detailed neurologic examination, MR imaging, and electromyography examination.

### 2.4. Statistical analysis

The sample size was determined on the basis of previous pilot study [34], considering the expected differences, as expressed by

their mean scores on NRS three months after the treatment. The mean expected difference was 20 points (SD 20.92) for the treatment group. For a power of 90% and I level of statistical significance of 5%, the minimum sample size was estimated to be 48 patients between the randomized groups for the primary outcome. We planned to recruit 48 patients in total in 2-year time. When 48 patients were recruited, it was less than 2-year time. So, we decided to increase patients until the end time of the recruitment. The actual sample size of 72 patients at the end of the recruitment period provided much more power to detect this effect.

The data were entered and the analysis was carried out by SPSS for windows 13.0. Scores of pretreatment and posttreatment were tabulated and compared. Chi-square test, Levene's test of homogeneity of variances, Fisher's exact test, and *t* test were used to test the differences between groups. General linear model for repeated measure data was used to identify the changing trend of NRS and ODI between the two groups. Independent sample test was used to determine the efficacy of intradiscal MB injection and that of placebo treatment with different pain scores and different degrees of disability at different follow-up time points. The significance level was 0.05.

### 3. Results

Altogether 72 patients with discogenic low back pain were enrolled in the study, with 36 patients in the intradiscal MB injection group and 36 in the placebo treatment group. The baseline characteristics were similar in the two groups (Table 1). A total of 71 patients completed the three follow-up visits. One patient in the placebo treatment group failed to return because of a new serious disease (Fig. 1).

Six months after the randomization, the primary outcomes differed substantially between two groups. The mean NRS in the MB injection group was 72.33 at baseline and 24.94 at 6 months. The mean NRS in the placebo treatment group was 67.28 at baseline and 63.51 at 6 months. There was a significant difference between the MB injection group and the placebo treatment group in the NRS scores ( $P < 0.01$ ). The mean ODI in the MB injection group was 48.47 at baseline and 16.00 at 6 months. The mean ODI in the placebo treatment group was 49.37 and 48.40 at 6 months. There was a significant difference between the MB injection group and the placebo treatment group in the ODI scores ( $P < 0.01$ ) (Table 2). Of the 36 patients in the MB injection group, 7 patients (19%) claimed to have complete relief (NRS = 0–10), 10 (28%) dramatic improve-

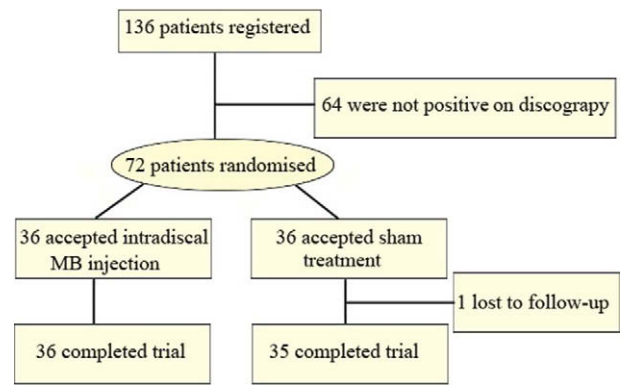


Fig. 1. Flow diagram for trial.

ment (NRS less than 20 points), and 15 (42%) with obvious improvement (a reduction in NRS of at least 20 points). As compared with the baseline values, their mean improvement in NRS was 47.39 in the MB injection group ( $P < 0.01$ ), and the ODI improved by a mean value of 32.47 ( $P < 0.01$ ) (Table 2). In contrast, when the results after treatment were compared with baseline values in the placebo treatment group, their mean improvement in NRS was 3.77 ( $P = 0.65$ ), and the ODI improved by a mean value of 0.97 ( $P = 0.99$ ). As a group, these patients showed no improvement in their pain scores and physical function (Table 2).

The results at 12 months and at 24 months were very similar to those at 6 months in both groups (Table 2). The good result was maintained in the patients in MB injection group. There were no statistically significant differences in the evaluation scores at 6, 12, and 24 months. The results indicated that the efficacy of intradiscal MB injection for the treatment of discogenic low back pain was long lasting. In the present study, 23 of 35 patients (66%) in placebo treatment group obtained pain relief and function improvement over a period of two years, but these improvements had no statistical significance. The NRS and the ODI scores at 24 months were about the same to those at baseline, as no significant difference was found in the NRS and the ODI ( $P = 0.15$  and 0.97, respectively).

Regarding patient satisfaction, 33 (91.6%) patients were completely satisfied or satisfied in MB injection group at the 24-month follow-up, but only 5 (14.3%) were satisfied in placebo treatment group (Table 3). Medication usage, including nonsteroidal

Table 1  
Baseline characteristics of 72 patients randomly assigned to undergo intradiscal MB injection or placebo treatment\*.

Characteristics	MB injection group (n = 36)		Placebo treatment group (n = 36)	
	n	%	n	%
Age (years)	42.06 ± 13.74		41.28 ± 12.84	
Male	21	58	20	56
Female	15	42	16	44
Duration of pain (years)	3.5 ± 1.6		3.2 ± 1.7	
<i>Level of painful disc</i>				
L3–L4	1	3	0	0
L4–L5	12	33	14	39
L5–S1	17	47	15	42
L3–L4, L4–L5	1	3	1	3
L3–L4, L5–S1	1	3	2	5
L4–L5, L5–S1	4	11	4	11
NRS (0–100)	72.33 ± 12.35		67.31 ± 11.62	
ODI (0–100)	48.47 ± 5.12		49.51 ± 6.72	

There were no statistically significant differences between the two groups in the demographic and clinical features (Fisher exact tests). Nor were there any significant differences in baseline values of the outcome measures (*t* test).

NRS, numerical rating scale; ODI, Oswestry Disability Index.

\* Plus-minus values are means ± SD.

**Table 2**  
Main outcomes of patients who underwent intradiscal MB injection or placebo treatment (mean ± SD).

Outcome measure	MB injection (n = 36)	Placebo treatment (n = 35)	Mean difference	95% CI	P value
<i>NRS (0–100)</i>					
Baseline	72.33 ± 12.35	67.28 ± 11.45	–5.02	–10.70 to 0.66	0.082
6 months	24.94 ± 17.38	63.51 ± 11.66	38.57	31.54–45.60	<0.001
12 months	21.58 ± 17.93	62.40 ± 12.05	40.82	33.56–48.07	<0.001
24 months	19.83 ± 16.03	60.37 ± 14.10	40.54	33.38–47.69	<0.001
<i>ODI (0–100)</i>					
Baseline	48.47 ± 5.12	49.37 ± 6.79	0.90	–1.96 to 3.76	0.532
6 months	16.00 ± 11.91	48.40 ± 7.77	32.40	27.62–37.18	<0.001
12 months	14.39 ± 12.87	49.09 ± 10.20	34.70	29.19–40.20	<0.001
24 months	12.89 ± 11.95	47.69 ± 10.92	34.80	29.37–40.22	<0.001

NRS, numerical rating scale; ODI, Oswestry Disability Index; CI, confidence interval of the difference.

Scores of baseline and posttreatment at 6, 12, 24 months were compared between two groups with Independent samples *t* test.

anti-inflammatory drugs (NSAIDs) or opioid medications, was decreased significantly compared with that of pretreatment period in MB injection group. Usually, when there was no obvious improvement these patients would take NSAIDs regularly. If pain was still not alleviated, they would take narcotics simultaneously or both opioid medications and NSAIDs. When the scores of NRS and ODI were assessed at any follow-up point, the patients who took NSAIDs or opioid medications were in the condition of not taking medication for at least 24 h. Thirty patients (83.3%) in MB injection group reported that they took no medication for their low back pain, 3 (8.3%) reported occasional use of NSAIDs or opioid medications, and 3 (8.3%) reported regular use of NSAIDs or opioid medications. Of the 35 patients in the placebo treatment group, only 2 patients (5.7%) reported that they took no medication for their low back pain, 18 (51.4%) patients took NSAIDs or opioid medications occasionally, and 15 (42.9%) took NSAIDs or opioid medications regularly (Table 4).

In all 36 patients treated with intradiscal MB injection, no patients complained of symptoms of nerve root injury or back pain aggravation after the treatment. No disc space infection and nerve root stab injury were found in both group patients during 2-year follow-up.

#### 4. Discussion

Discogenic low back pain is a common cause of disability. Its treatment has traditionally been limited to either conservative management or surgical fusion [6,25]. During recent decades, surgical fusion of the lumbar spine has been performed in increasing number on patients with chronic low back pain [12]. However, the reported results vary considerably in different studies, and the complication rate after fusion surgery in the lumbar spine is not negligible [18–20,25,28]. Consequently, artificial disc replacement has been proposed as a substitute for spinal fusion with the aim of treating back pain while preserving vertebral motion at the operated levels and protecting adjacent levels from undergoing degenerative changes, but so far, only few studies have been reported on the results of lumbar disc prosthesis [2,3]. The results with longer follow-up need to be observed further. As alternative treatments, percutaneous treatments directed at altering the internal mechanics or innervation of the disc by heat (intradiscal electrothermal annuloplasty, IDET) or radiofrequency energy have recently been

advocated [24,29,30,37,38], but data supporting their use are lacking [17]. Recent randomized trials have shown either no effect or benefit in only a small number of highly selected subjects [16,42].

In the present study, patients treated with intradiscal injections of methylene blue achieved a mean reduction in pain of 52.5, as measured by the NRS, a mean reduction in Oswestry disability scores of 35.58, and a satisfaction rate of 91.6% at 24 months after treatment. Statistically, all primary outcome measures were significantly in favour of intradiscal injection of MB, when compared with placebo treatment. The outcomes achieved were similar to, or exceeded, those obtained by fusion surgery or artificial disc replacement [2,3,18–20,23,25,28].

In any study of treatment of back pain a theoretical concern is the influence of natural history. For discogenic back pain, the literature on natural history is limited to one study [36]. That study reported that, at five years after diagnosis, 24% of patients continued to be disabled; a further 68% were said to have improved, but the magnitude of improvement was not quantified; and no patient became free of pain [36]. In the present study, having a group of patients who underwent sham treatment controlled for natural history. Their outcomes are compatible with the reported natural history of discogenic low back pain [36]. Of the 35 patients treated with placebo, 23 (66%) reported gradually decreasing scores for pain and disability in two years, but these improvements did not reach statistical significance. The low response-rate to placebo treatment is not dissonant with the low rates reported in other placebo-controlled studies of discogenic pain [16,30].

In the present study, the indication for the treatment was discogenic pain. This is not synonymous with disc degeneration. Many discs with degeneration or annular tears are not painful, either because the pathology has not affected the innervated portions of the disc, or because nerves have not reached the affected portion of the disc [33]. Therefore, medical imaging alone is not a sufficient diagnostic test for discogenic pain. Provocation discography is the only available means by which a painful disc can be identified, and for this reason discography was used to select patients for the present study. Reproduction of pain on discography correlates strongly with the presence of radial fissures that extend into the outer region of the annulus fibrosus [4,21,27,31,32,35,39]. These fissures are accompanied by granulation tissue and nerve fibres [33]. Irritation of these nerve fibres by contrast medium provides an explanation for the pain evoked by discography.

**Table 3**  
Patient satisfaction 24 months after the randomization (%).

	Completely satisfied	Satisfied	Unsatisfied
MB injection (n = 36)	7 (19.4%)	26 (72.2%)	3 (8.4%)
Placebo treatment (n = 35)	0 (0%)	5 (14.3%)	30 (85.7%)

Chi-square test,  $\chi^2 = 43.311$ ,  $P < 0.001$ .

**Table 4**  
Medication usage 24 months after the randomization (%).

	None	Occasional	Regular
MB injection group (n = 36)	30 (83.3%)	3 (8.3%)	3 (8.3%)
Placebo treatment group (n = 35)	2 (5.7%)	18 (51.4%)	15 (42.9%)

Chi-square test,  $\chi^2 = 43.209$ ,  $P < 0.001$ .

Some investigators have questioned the validity of discography as a diagnostic test [7–9], arguing that it can be positive in asymptomatic individuals and in patients with other sources of pain. Others have shown that false-positive responses can be minimized by testing control discs at adjacent segments and by keeping injection pressures low [5,10,11]. If anatomic and manometric controls are observed, the false-positive rate of discography is less than 10% [44]. Therefore, the risk that inappropriate patients were selected for the treatment in the present study is low.

Since it was first synthesised in 1876, methylene blue has been used in many different areas of medicine [43]. Among other properties, methylene blue is neurolytic, and has been used successfully to treat pruritus ani and the pain of acute fractures [13,15,26,41]. This neurolytic effect provides a rationale for its use to treat discogenic pain. This rationale is corroborated by our recent study in which lesions were induced in the anterior annulus of a rat-tail model [unpublished data]. Injection of methylene blue denervated the lesion without otherwise damaging the disc. In the present study, denervation of radial fissures would appear to be the likely mechanism of relief of pain. When injected into the nucleus pulposus, methylene blue spreads peripherally into radial fissures where it can destroy the accompanying nerve fibres. Patients who respond to treatment typically obtain relief within 24 h, which is compatible with gradual denervation of the disc. This denervation appears to be enduring, for once established, the relief persists for two years.

Intradiscal injection of methylene blue is a novel treatment for discogenic back pain. Its efficacy appears to be quite remarkable. It is imperative that others evaluate this treatment to determine if the results of the present study can be replicated and, thereby, confirmed.

## 5. Conflict of interest

All authors declare that they have no conflict of interest.

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