Retrospective Evaluation

Clinical Evaluation and Magnetic Resonance Imaging Assessment of Intradiscal Methylene Blue Injection for the Treatment of Discogenic Low Back Pain

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Background: Low back pain is a common worldwide health problem and has a significant socioeconomic impact on public health. Internal disc disruption has been considered as the most common cause of low back pain. Various therapies, including interbody fusion, disc replacement, injection therapies, and thermal annular procedures have been utilized for the treatment of discogenic low back pain. Recently, a new method of intradiscal methylene blue injection has been introduced to treat discogenic low back pain, but the clinical outcomes are controversial.

Objectives: To investigate the clinical outcomes and magnetic resonance imaging changes of intradiscal methylene blue injection for the treatment of discogenic low back pain.

Study Design: Observational study.

Setting: An interventional low back pain management practice in a university hospital.

Methods: A total of 33 patients were selected to be treated with intradiscal methylene blue injection. The clinical outcomes were evaluated by numeric rating scale and Oswestry Disability Index at pretreatment, one month, 3, 6, and 12 months after treatment. The magnetic resonance imaging changes of involved intervertebral discs were assessed by apparent diffusion coefficient and T2 values at pretreatment, 3, 6, and 12 months after treatment.

Results: All of the patients got a follow-up period up to 12 months. The mean numeric rating scale scores at pretreatment, one month, 3, 6, and 12 months after treatment were 6.54, 2.98, 3.23, 3.66, and 4.72, respectively. There was a minimum of 2 points reduction at one month, 3, and 6 months after treatment, but less than 2 points reduction at 12 months. There was at least 50% improvement on the Oswestry Disability Index at one month, 3, and 6 months after treatment, but not at 12 months. The mean apparent diffusion coefficient and T2 value were significantly higher at 6 and12 months after treatment compared to pretreatment, but there was no significant difference between pretreatment and 3 months after treatment.

Limitations: This is an observational study with a relatively small sample size and short-term follow-up.

Conclusions: The intradiscal methylene blue injection might be an effective therapy for discogenic low back pain for the short-term and could improve disc degeneration condition to some extent.

Key words: Low back pain, discogenic pain, internal disc disruption, provocation discography, methylene blue, intradiscal injection, disc degeneration, magnetic resonance, imaging

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Low back pain is a common worldwide health problem and has a significant socioeconomic impact on public health (1,2). Any pathological change of the structures in the lumbar spine region, such as intervertebral discs, ligaments, fascia, muscles, facet joints, sacroiliac joints, and nerve roots, may cause low back pain. Internal disc disruption has been considered as the most common cause of low back pain (3,4). It has been reported that pain prevalence due to internal disc disruption was up to 42% (5). What's more, the intervertebral disc has been considered as the most common source (56%) of motor vehicle collision-induced chronic low back pain (6). And the low back pain originating from the disc is happening more often among younger patients (7). The treatment of discogenic low back pain (DLBP) has been an intractable problem. Various therapies, including interbody fusion, disc replacement, injection therapies, and thermal annular procedures have been utilized for the treatment of DLBP (8-13). But there's considerable controversy over the long-term efficacy of all of these procedures. Recently, methylene blue (MB) has been used for DLBP. Peng and colleagues (14) first reported that intradiscal injection of MB was an effective and minimally invasive method for the treatment of DLBP. In another double blind and randomized control trial, Peng and colleagues (15) also demonstrated the efficacy of intradiscal MB injection for the treatment of DLBP. And Kim et al (16) found the intradiscal MB injection is a short-term effective minimally invasive treatment for DLBP in a one year prospective follow-up study. But what Gupta et al (17) found in a case series is contrary to the results reported by Peng and colleagues.

Since the outcomes are controversial, in the current study, we investigated the clinical outcome and magnetic resonance imaging change of patients after intradiscal MB injection, to further evaluate the effect of intradiscal MB injection for DLBP. In addition to the evaluation of pain relief and lumbar functional disability improvement, the apparent diffusion coefficient (ADC) and T2 map, which are 2 quantitative parameters of magnetic resonance imaging (18), were added to assess the changes of disc degeneration after treatment.

Methods

Case Information

From October 2012 to January 2014, among 51 patients with DLBP, a total of 33 consecutive patients, including 21 men and 12 women, were selected for this observational study according to the strict inclusion criteria. The mean age was 46.5 years (20 to 71) and the mean duration of low back pain was 4.3 years (0.6 to 14). The patients were recruited according to the following inclusion criteria (19-21): low back pain persisting for at least 6 months, numeric rating scale (NRS) (0 to 10) score of the pain intensity was at least 6, poor response to conservative treatment, no previous lumbar surgery, with evidence of lumbar disc degeneration (grade IHIV) on magnetic resonance image according to Pfirrmann's classification (22), and positive provocation discography. And the exclusion criteria were: lumbar disc herniation, lumbar canal stenosis, neurologic disease, tumor, infection, previous lumbar surgery, and psychiatric disease. The involved levels were L4-5: 14, L5-S1: 8, L3-4 and L4-5: 7, L4-5 and L5-S1: 4.

Discography and Intradiscal Methylene Blue Injection

The standard pressure-controlled provocative discography (23), with an opening pressure less than 50 psi and a speed less than 0.08mL/s, was performed under high-resolution C-arm fluoroscopy in all patients. As shown in Fig. 1, provocation discography was carried out by a double-needle technique and a standard posterolateral approach as described before (24). A positive discography was defined when the patient experienced exact reproduction of their usual pain over 6/10 (NRS) after an injection of contrast medium (Iohexol, JiangSu-yangtze, China) less than 3 mL/disc and a demonstrable anular fibrosus fissure or tear appeared. Once the concordant pain provoked disc was confirmed, we tried our best to suck out the residual contrast medium, then injected 1 mL of methylene blue (JiangSu-JiChuan, China) at each level of concordant disc(s) followed by 0.5 mL of 2% lidocaine. We tried to find a control disc (negative one) in all patients, but in practice, not every patient needs a control disc. Since discography may cause accelerated disc degeneration (25), if only one disc showed grade IHIV degeneration on magnetic resonance images, we didn't perform discography on other discs in case of iatrogenic disc degeneration. After the treatment, all patients were instructed to lie supine for 24 hours and avoid heavy work or strenuous exercise for 4 weeks.

Magnetic Resonance Imaging

Magnetic resonance imaging was performed on all patients with a whole-body 3.0 T clinical scanner (GE Medical Systems, USA). All magnetic resonance images in this study were obtained in the morning to minimize the diurnal variation of ADC and T2 values

in the intervertebral disc (26). The sagittal diffusion-weighted images of the lumbar spine were obtained by using a spin-echo echo-planar imaging sequence coil with the diffusion gradient applied in 3 orthogonal directions, respectively, from which the average ADC map was calculated. T2 mapping was performed by a hybrid turbo sequence with 2 effective TEs per acquisition by using a body radiofrequency coil. All data were transferred to the imaging workstation for analysis with FuncTool performance software (GE Medical Systems). ADC values from the affected discs were obtained by drawing an elliptical region of interest on the ADC map within the center of the nucleus pulposus, with no contact with the annulus fibrosus or the endplate tissue (Fig. 2). The region of interest on the ADC map was copied to the T2 map at the same level and the T2 value was measured (Fig. 3).

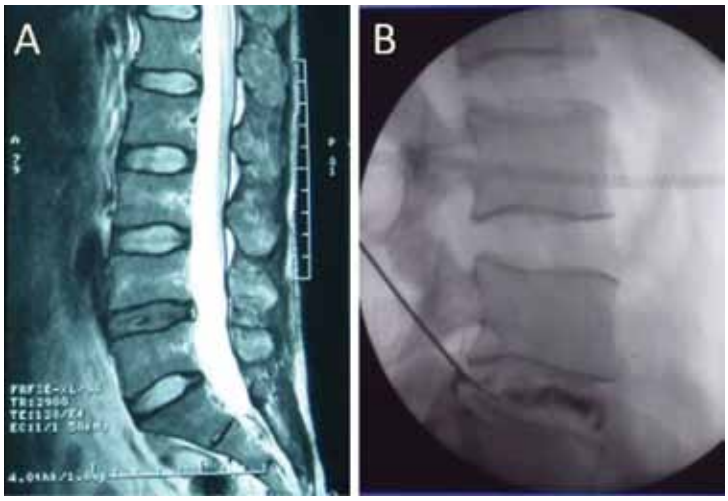

Fig.1. *A: Sagittal T2 weighted magnetic resonance image showed L4/L5 disc degeneration. B: Lateral view of provocation discography showed discrete distribution and leakage of the contrast media at L4/L5 level.*

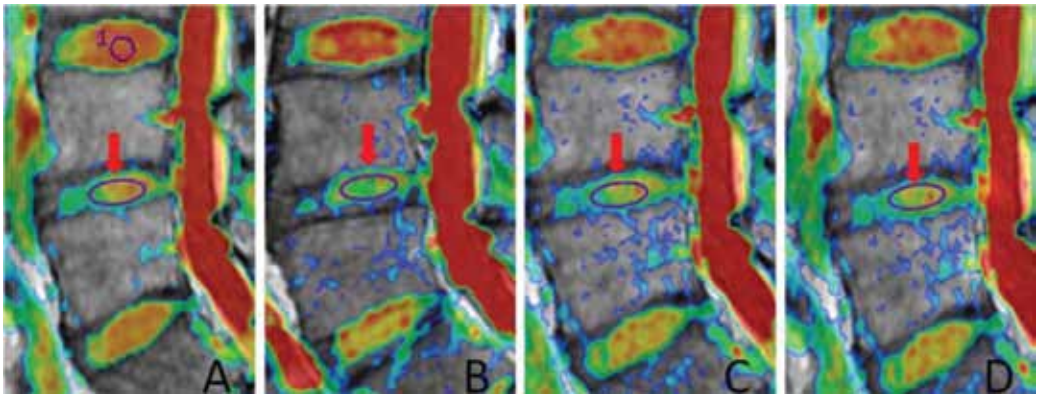

Fig. 2. *The apparent diffusion coefficient map at pre-treatment and post-treatment. (A: pre-treatment, B: 3 months after treatment, C: 6 months after treatment, D: 12 months after treatment).*

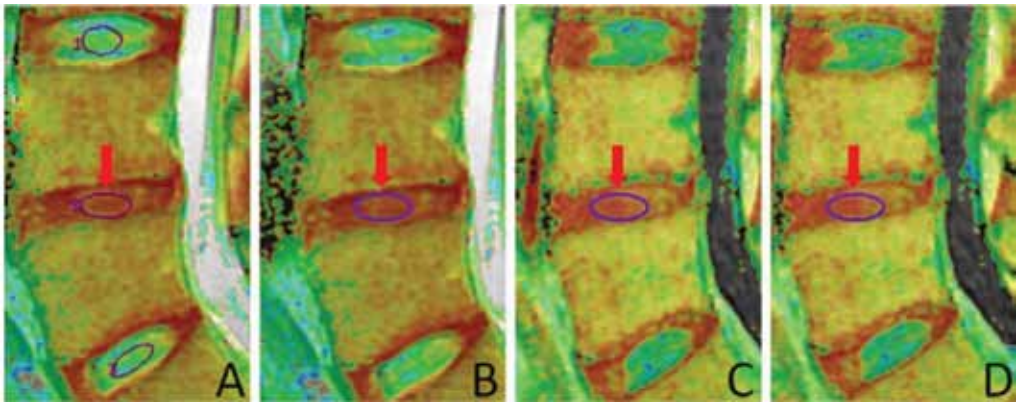

Fig. 3. *The T2 map at pre-treatment and post-treatment (A: pre-treatment, B: 3 months after treatment, C: 6 months after treatment, D: 12 months after treatment).*

Outcome Assessment

For outcome assessment, the pain intensity was assessed using 0 (no pain) to 10 (worst pain possible) on the NRS at pretreatment, one month, 3, 6, and 12 months after MB treatment. Lumbar functional disability was evaluated by Oswestry Disability Index (ODI, Version 2.0, 0 – 100) according to the Oswestry Low Back Pain Questionnaire (27). A threshold of 50% improvement on the ODI and a minimum of 2 points reduction on NRS scores were defined as a successful outcome (28,29). We also used the ADC and T2 values obtained from magnetic resonance images of the involved discs to compare the change of intervertebral disc degeneration between pretreatment and 3, 6, and 12 months after treatment.

Statistical Analysis

All data are presented as mean ± SD. Variance analysis of repeated measurement data was used to compare the statistically significant differences between pretreatment and different follow-up times after treatment. The level of statistical significance was set at $P < 0.05$.

Results

No complications such as allergic reaction to contrast medium, nerve root injury, discitis, cerebral spinal fluid leakage, retroperitoneal bleeding, blue urine, or epidural abscess occurred in any these patients. All the 33 patients treated with MB injection had a follow-up period of up to 12 months.

The NRS scores and ODI functional assessment results are shown in Table 1. The mean NRS scores at pretreatment, one month, 3, 6, and 12 months after treatment were 6.54, 2.98, 3.23, 3.66, and 4.72, respectively. There was a minimum of 2 points reduction at the time of one month, 3, and 6 months after the treatment, but less than 2 points reduction at 12 months. There was at least 50% improvement on ODI at the time of one month, 3, and 6 months after the treatment, but not at 12 months. The global clinical success rate was 81% (27 of 33), 75% (25 of 33), 63% (21 of 33), 18 of 33 (54%) at one month, 3, 6, and 12 months after treatment, respectively.

As shown in Table 2, the mean ADC and T2 value were significantly higher at 6 and 12 months after treatment compared to pretreatment, but there was no significant difference between pretreatment and 3 months after treatment.

Discussion

DLBP is a complex and multi-factorial disease. The diagnosis and treatment of DLBP is still a very difficult clinical problem. Various methods, including magnetic resonance imaging, ultrasound imaging of intervertebral disc, discography, bony vibration test, and high-sensitivity C-reactive protein have been used to help to diagnose DLBP (20). Among these methods, provocative discography has been widely used in the diagnosis of discogenic pain. Although the efficacy of lumbar discography has been questioned and the high false-positive rate of discography has been reported (30), a couple of systematic reviews found that discography is a useful imaging and pain evaluation tool for DLBP if performed according to the criteria of the International Association for the Study of Pain (19,31-33). So

Table 1. *The mean NRS and ODI score at pre-treatment, one month, 3, 6, and 12 months after treated with intradiscal MB injection.*

	Pre-treatment	Post-treatment (1 month)	Post-treatment (3 months)	Post-treatment (6 months)	Post-treatment (12 months)
NRS	6.54 ± 1.16	2.98 ± 0.83	3.23 ± 0.96	3.66 ± 0.85	4.72 ± 1.02
ODI	56.14 ± 8.06	25.26 ± 4.52	24.54 ± 4.12	27.12 ± 4.88	34.48 ± 5.35

Table 2. *The mean ADC and T2 value at pre-treatment, 3, 6, and 12 months after treated with intradiscal MB injection.*

	Pre-treatment	Post-treatment (3 months)	Post-treatment (6 months)	Post-treatment (12 months)
ADC(10-3mm2/s)	1.26 ± 0.12	1.30 ± 0.14 (P >0.05)	1.49 ± 0.15 (P <0.01)	1.53 ± 0.16 (P <0.01)
T2(ms)	58.2 ± 4.7	60.3 ± 5.2 (P >0.05)	63.6 ± 5.4 (P <0.05)	67.3 ± 6.5 (P <0.01)

the inclusion criteria we used in this study was mainly composed of positive discography, symptoms, history, and other elements.

The exact pathogenesis of DLBP is extremely complicated and poorly understood. The role of inflammatory mediators in intervertebral disc degeneration cannot be neglected (34). And glial cell-derived neurotropic factor might be a key factor in the development of intractable discogenic pain (35). And a widely accepted pathogenesis is the growth of nociceptive nerves deep into the annulus fibrosus and nucleus pulposus along the tears in the posterior part of the painful disc, which may be the most possible cause of DLBP (36,37). The oxidation and neurotropic effect of MB enables it to block nerve conduction or destroy nociceptive nerve endings. Therefore the local injection of MB might be an effective procedure for the treatment of DLBP, but the outcomes reported in previous studies are controversial (14-17,38). So we tried intradiscal MB injection for a total of 33 patients in this study and further evaluate its effect for DLBP.

The outcomes we found in the current study are encouraging for the short-term. The average pain intensity scores decreased more than 2 points and functional disability showed more than 50% improvement at one month, 3, and 6 months after the treatment. The global clinical success rate was 81% (27 of 33), 75% (25 of 33), 63% (21 of 33) at one month, 3, and 6 months after treatment, respectively. At 12 months after treatment, the mean reduction of NRS score was less than 2 points and the improvement on ODI score was less than 50%. Only 18 of 33 (54%) patients showed a successful clinical outcome at 12 months. These results indicated that the efficacy of MB injection for DLBP may not be long lasting, which is contrary to the results reported by Peng and colleagues (14,15), but similar to other studies (16,39,40).

The NRS score and ODI score are easily affected by the subjectivity of the patient, so some kind of relatively objective evaluation may be more convincing. In recent years, the ADC and T2 mappings have been used as 2 quantitative magnetic resonance imaging tools to evaluate degenerative changes of intervertebral discs (18,26,41,42). The ADC and T2 values not only directly reflect the content of water and proteoglycan in the disc, but also relate to nucleus pulposus matrix composition and integrity (43,44). In the present study we used ADC and T2 mappings to assess the changes of disc degeneration after intradiscal MB injection. And we found that the ADC and T2 values significantly increased at the time of 6 and 12 months after MB injection, especially in younger patients, but there was no significant difference between pretreatment and 3 months after MB injection. What we have found provided us some objective evidence about the efficacy of MB injection. And these findings suggested that intradiscal MB injection may improve disc degeneration condition to some extent after a certain period of time. It has been reported that nitrite oxide is involved in proteoglycan production and plays an important role in the degeneration of intervertebral discs (45-47). As one kind of redox, MB may decrease the production of nitrite oxide in the disc and then improve the disc degeneration condition. Of course, the exact mechanism needs more study to clarify. At least, we do not need to worry too much about cellular toxicity of MB to nucleus pulposus cells and potential risk og aggravating disc degeneration.

Intradiscal MB injection is a relatively safe and minimally invasive procedure. In all patients in this study, we found no severe complications such as allergic reaction to contrast medium and nerve root injury. The short-term clinical outcome of MB injection for DLBP is encouraging. For the patient who was diagnosed as DLBP and failed to conservative treatment, intradiscal MB injection may be another choice. Even if the patient showed poor response to intradiscal MB injection, we still have the chance to choose another treatment, such as interbody fusion.

Conclusion

The intradiscal MB injection might be an effective therapy for DLBP in the short-term and could improve the disc degeneration condition to some extent, but the long-term clinical outcome is not established. Before intradiscal MB injection is routinely used to treat DLBP, more studies with a larger sample size and longer follow-up period or more randomized and double-blind clinical trials will be necessary.

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