The lifetime prevalence of low back pain (LBP) is approximately 70-90%, and while it often resolves spontaneously, there is also a high rate of recurrence (1-3). Chronic pain can develop in up to 10% of patients, leading to disability and high health care costs (3,4). Low back pain, ascribed to internal disc disruption through provocation discography, has a reported prevalence of approximately 40%, but
there is an associated decline in prevalence with age (5). Over the years there have been many attempts at finding a safe, reproducible, and effective treatment for discogenic LBP (6).

Intradiscal methylene blue has been lauded as a potential “cure” for discogenic low back pain based on the results of two recent trials (7,8,9). The first, a prospective nonrandomized trial by Peng and colleagues (9), demonstrated the efficacy of a single administration of methylene blue dye in the treatment of discogenic low back pain. The second trial, a double blind, randomized control trial (DBRCT), demonstrated at the 2-year follow-up a statistical and clinically meaningful reduction in the mean numeric rating scale 101 (NRS-101) pain score of 52.5 and Oswestry function score of 35.6. Furthermore, there was a reduction in medication usage and a 91% satisfaction rate (versus a 14% satisfaction rate in the control). A decrease in the NRS 101 of at least 20 points was seen in 89% of treated patients, of which 19% reported no further pain, and 28% reported dramatic improvements in symptoms (8).

Given the scientific rigor described, these results were extremely impressive and promising. We report here our experience with this treatment in a small cohort of patients, which did not conform to the results of Peng and colleagues (8,9).

**Methods**

This is a retrospective case series of patients treated between 2010 and 2011 with methylene blue (MB) for suspected discogenic-based pain. Patients were selected for treatment based on a clinical evaluation and at the discretion of 2 treating clinicians (MR, JFA). Generally, selection was based on pain referral pattern, poor response to previous treatment, compatible imaging results, and a positive provocation discography (10). In contrast to the Peng et al study (8), patients with mental health issues and disc herniation were included in our study cohort. Care was taken to not to treat patients concurrently prescribed serotoninergic psychiatric medications to avoid any serious central nervous system reactions. We note any future elective administration of methylene blue should follow the current US Food and Drug administrations recommendations. These suggest stopping certain psychiatric medications (e.g. SSRI, SNRI, TCA, MAOI, etc) for 2-5 weeks prior to treatment, depending on the medication, and then resuming these medications 24 hours after administration of methylene blue (11).

As shown in the lateral view in Fig. 1, provocation discography, using a double-needle technique, (i.e., needle through needle) and the standard posterolateral approach was performed under fluoroscopy in all patients by one of the 3 authors (MR, JC, JFA). Upon centering of the needle within the disc, nonionic contrast medium iohexol 240 was injected under low pressure. A positive/concordant response was defined if the patient experienced exact reproduction of his or her usual pain response pattern. Discograms were performed at a control level in all cases, except for patient #5 who had reported concordant pain at all 3 levels tested. Treatment was applied for patient #5 at the level with the worst pain. Into the concordant disc(s) one mL of 1% MB was injected followed by one mL of 2% lidocaine. Unlike the previously described study, needles were not necessarily inserted in the patient’s most painful side, and patients were discharged after 2 hours of lying supine postprocedure and computed tomography (CT) imaging (Figs. 2 and 3). As defined by Peng and colleagues (8), treatment success was defined as a sustained reduction in pain scores of at least 20% with a measurable/definable improvement in function after a single injection of MB dye.
Results

Treatment was performed in 8 patients, with at least 2 months of follow-up data available that are summarized in Table 1.

Ages ranged between 36 to 77 years, with 5 women and 3 men. Pain duration varied from 1 to 7 years. All patients failed conservative treatment including physiotherapy, medication management; each had at least one interventional pain procedure prior to provocation discography.

Concordant response was achieved in all patients in at least one level. One patient (#4) had treatment at 2 levels. Substantial annular tears (i.e., greater than Grade 3) on postdiscography CT scan were present in the discs injected with methylene blue in 7 patients (8 discs). Patient #6 was treated at L4/L5, which showed a Grade 2 annular tear on postdiscography CT.

With the exception of patient #2, who experienced a good, sustained clinical pain response with an associated improvement in function, treatment was otherwise not beneficial in our patient population. Three patients failed treatment outright (i.e., #3, #6 & #7). Patient #1 had 5 months of relief with a recurrence thereafter. Patient #4 had an 80% decrease with a recurrence thereafter. Patient #5 reported a 30% decrease in pain, but no change in function was achieved. Patient #8 had complete relief, which diminished after 2 months. In our opinion, these cases represent a failure of treatment.

No adverse events were reported, but patient #4 reported blue urine for one week, which could have an effect on the blinding of patients in clinical trials. Treatment was not repeated in any case.

Discussion

The postulated mechanism of methylene blue is denervation of small nociceptive fibers that grow into the annulus fibrosis, which are implicated in discogenic pain (8). Our case series revealed one clinical success in a cohort of 8 patients treated with a single injection of methylene blue for discogenic pain, which is contrary to the results reported by Peng and colleagues (8).

Peng and colleagues (8,9) showed an 89% success rate in their DBRCT and 87% success rate in their cohort study. In comparison, our results revealed a success rate of only 13%. The 5 months of 100% relief achieved by Patient #1 was considered a failure because, unlike epidural treatment for radicular pain or medial branch thermo-radiofrequency for facet joint pain, there is
currently no clinical precedent for repeat treatment (1,2). In addition, Peng and colleagues (9) also considered a time-limited response a clinical failure in their initial publication.

Differences in outcome for our patients with discogenic pain (i.e., positive provocation discography) could exist because of the small sample of patients in our cohort, the fact they were not kept supine for 24 hours postprocedure (which we did for practical reasons), and the presence of psychiatric comorbidity/medico-legal influences for some of our patients. While our treatment was not investigated in a controlled manner, the significant differences in outcomes should encourage closer inspection of methylene blue treatment for discogenic pain, in a nonresearch-based setting, where a complex interaction of factors are relevant to the pain experience.

Various treatments have previously been reported

Table 1. Patients treated with intradiscal methylene blue for presumed discogenic pain.

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Pain Duration</th>
<th>Previous Treatment</th>
<th>Pretreatment MRI/CT</th>
<th>Painful Levels/Treated Levels</th>
<th>Post-CT Discogram Results</th>
<th>Pain Reduction and Duration</th>
<th>Functional Change</th>
<th>Follow-up Time Frame</th>
<th>Adverse Events</th>
<th>Significant Co-morbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1-66F</td>
<td>4 years</td>
<td>Epidural, SI, MBB</td>
<td>AT-L4/L5 &amp; L5/S1</td>
<td>L5/S1</td>
<td>AT - L5/S1 (Grade 4)</td>
<td>100% x 5 months</td>
<td>Not sustained</td>
<td>&gt; 1 year</td>
<td>None</td>
<td>Diabetes, hypothyroid, dyslipidemia, Raynaud's</td>
</tr>
<tr>
<td>#2-70M</td>
<td>7 years</td>
<td>Epidural, TRF, SI</td>
<td>DB – L4/L5</td>
<td>L5/S1</td>
<td>AT - L4/ L5 (Grade 4) &amp; L5/S1 (Grade 4)</td>
<td>100% reduction – ongoing</td>
<td>Good</td>
<td>One year</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>#3-77F</td>
<td>4 years</td>
<td>Epidural, TRF</td>
<td>CT Scan – DDD &amp; Z- Joint OA, stable L2</td>
<td>L5/S1</td>
<td>AT- L4/L5 &amp; L5/S1 (Grade 4)</td>
<td>None</td>
<td>None</td>
<td>&gt; One year</td>
<td>None</td>
<td>Depression, osteoporosis, hypertension dyslipidemia</td>
</tr>
<tr>
<td>#4-44M</td>
<td>4 years</td>
<td>Epidural</td>
<td>DH L4/L5</td>
<td>L4/L5 &amp; L5/S1</td>
<td>AT – L3/ L4 (Grade 3) L4/L5 (Grade 4) &amp; L5/S1 (Grade 4)</td>
<td>80% x 6 weeks</td>
<td>Not sustained</td>
<td>&gt; 1 year</td>
<td>Blue urine for one week</td>
<td>None</td>
</tr>
<tr>
<td>#5-46F</td>
<td>1 year</td>
<td>Epidural</td>
<td>AT- L4/L5 &amp; L5/S1</td>
<td>L5/S1</td>
<td>AT- L3/ L4 (Grade 3) L4/L5 (Grade 3) &amp; L5/S1 (Grade 4)</td>
<td>30%</td>
<td>None</td>
<td>6 months</td>
<td>None</td>
<td>Depression, work-related injury.</td>
</tr>
<tr>
<td>#6-36M</td>
<td>&gt;2 years</td>
<td>Epidural, facet blocks</td>
<td>AT- L2/L3 DE- L4/L5 DB-L5/S1</td>
<td>L4/L5</td>
<td>AT- L4/L5 (Grade 2) &amp; L5/S1 (Grade 4)</td>
<td>None</td>
<td>None</td>
<td>2 months</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>#7-58F</td>
<td>6 years</td>
<td>Facet blocks</td>
<td>DB-L4/L5</td>
<td>L5/S1</td>
<td>AT L4/L5 (Grade 4) &amp; L5/S1 (Grade 4)</td>
<td>None</td>
<td>None</td>
<td>1 year</td>
<td>None</td>
<td>Depression, gastritis, hysterectomy.</td>
</tr>
<tr>
<td>#8 46F</td>
<td>&gt; 5 years</td>
<td>Epidural, MBB, facet TRF</td>
<td>Disc osteophyte L3/L4 and post-op changes</td>
<td>L3/L4</td>
<td>AT L3/L4 (Grade 4)</td>
<td>100% x 2 weeks</td>
<td>Not sustained</td>
<td>6 months</td>
<td>None</td>
<td>Hysterectomy, T10-L1 anterior fusion.</td>
</tr>
</tbody>
</table>

SI = Sacroilliac joint Injection, MBB = Lumbar Medial Branch/Dorsal Ramus Blocks from L3-L5, TRF = Lumbar Medial Branch/Dorsal Ramus Thermal Radiofrequency, VB = Vertebroplasty, AT = Annular Tear, DE = Disc Extrusion, DB = Disc Bulge, DH = Disc Herniation

NB : Grading of Annular Tear According to Modified Dallas Discogram Classification (10)
Methylene Blue in the Treatment of Discogenic Low Back Pain

for discogenic pain with differing quality of studies and success rates. Intradiscal electrothermal therapy (IDET) has a reported clinical success rate (i.e., pain and function) in some uncontrolled cohort studies of between 75-79% of patients, with improved success correlated with discographic concordance, high intensity zones, Pfirrmann grade, and the percentage of annulus coverage (3,4). Pauza et al (5) reported on a blinded randomized controlled trial (RCT) showing an improvement in function for treated patients and that 40% of treated patients achieved at least 50% pain relief, while 33% of patients in the placebo group achieved the same. Other studies, including one larger case series (6) and a blinded, randomized placebo control trial (7) showed little to no benefit at follow-up.

Intradiscal steroids may be beneficial for patients with end plate change and disc pain, but when not controlling for Modic changes, 2 RCTs showed no differences compared to placebo. (6,8-9). In case series reports, intraforaminal and/or intradiscal ozone treatment has been reported successful in small case series, but no controlled trials have been published (12,13).

Intradiscal radiofrequency thermo-coagulation has been shown ineffective in 2 RCTs (14, 15). The value of rami communicans radiofrequency thermo-coagulation remains to be seen. Despite its efficacy, the use of the enzyme chymopapain has been stopped due to complications, supply, and dosing issues (6). Finally, lumbar transpedicular fusion is not more beneficial at long-term follow-up than exercise and cognitive intervention in patients with nonspecific low back pain and disc degeneration as seen on magnetic resonance imaging (16).

Based on our results and review of the literature, discogenic low back pain continues to be an elusive, difficult-to-treat entity. We have reserved further treatment with methylene blue until further studies can elucidate more clearly which patients, if any, can reliably benefit.

Acknowledgments

The authors gratefully acknowledge the unrestricted funding support provided for Dr. Gaurav Gupta’s fellowship training by the Louise and Alan Edwards Foundation and Pfizer Canada.

References


www.painphysicianjournal.com


