Relation of inflammatory modic changes to intradiscal steroid injection outcome in chronic low back pain

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Abstract The purpose of this study was to analyze the association between the severity of inflammatory endplate changes (Modic) on MRI and the clinical response to intradiscal injection of corticosteroids (IDIC) in chronic low back pain (LBP). A total of 74 patients with LBP and inflammatory Modic changes who showed no response to 3-month conservative treatment received lumbar IDIC. Two spine specialists and a radiologist assessed independently the endplate marrow changes of the injected discs. We classified patients with a pure edema endplate changes on MRI as Modic type I ($n = 37$); those with a mixture of Modic type I and type II changes but predominantly edema changes as Modic I-2 ($n = 25$) and those with predominantly fatty changes as Modic II-1 ($n = 12$). The primary outcome was the change in LBP intensity between baseline and 1 month after IDIC, as measured on a visual analog scale (range 0–100 mm). At 1 month, reduction in pain score was significantly higher in the Modic I and Modic I-2 groups than in the Modic II-1 group (30.2 ± 26.6 and 29.4 ± 21.5 vs 5.3 ± 25.5 ; $P = 0.009$ and $P = 0.017$, respectively). At 3 and 6 months, IDIC tended to be more effective in the

Modic I and Modic I-2 groups but not significantly. No complications such as infection or hematoma were reported. IDIC could be a short-term efficient treatment for patients with chronic LBP and predominantly inflammatory endplate changes when conservative treatments have failed.

Keywords Low back pain · Modic changes · Magnetic resonance imaging (MRI) · Intradiscal injection · Corticosteroids

Introduction

Low back pain (LBP) is common condition; 6–10% of cases may become chronic and result in major disability, high medical expenses, and lost productivity [1, 2, 13, 15, 28]. LBP may originate from many spinal structures, but degenerative processes in the intervertebral discs seem to be among the most common causes [12]. Because of its ability to detect disc and subchondral bone marrow signal changes, magnetic resonance imaging (MRI) has emerged as the imaging study of choice for LBP and has significantly advanced the evaluation of degenerative disc disease [18, 26]. Signal intensity changes in the vertebral bone marrow adjacent to the endplates are common MR imaging observation. These changes have been classified into three general types that have been associated with degenerative disease in the adjacent disc [11, 23]. Modic type I changes (low signal in T1-weighted sequences and high signal in T2) were associated with fissuring of the cartilaginous endplate and increased vascularity within the subchondral bone on histologic examination [23], and correspond to vertebral body

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edema. Modic type II changes (high signal in T1-weighted sequences and either high or intermediate signal in T2) reflect fatty replacement of the adjacent marrow [23]. Type III lesions (low signal in T1 and low signal in T2) are observed in vertebral bodies with sclerotic changes.

Several studies showed a strong association between Modic I changes and LBP [20, 27]. Furthermore, type I changes in asymptomatic subjects are uncommon [29]. Type I changes may represent various stages of an inflammatory process in the endplate. A recent study showed a significantly higher level of proinflammatory mediator in disc tissue from patients undergoing anterior fusion for discogenic LBP than in tissue from patients undergoing discectomy for sciatica [6]. Type I changes, representing more active inflammation, seem to be mediated by proinflammatory cytokines [24], whereas type II and III changes could be more quiescent stages of the process.

This hypothesis of a local inflammatory reaction in the subchondral bone marrow adjacent to the endplate provides a rationale for local injections of corticosteroids. Few studies have reported variable results on the efficacy of intradiscal injections of corticosteroids (IDIC) in chronic discogenic LBP [14, 17, 19, 25]. However, these studies did not select patients with inflammatory endplate changes. Recently, Buttermann [7] reported that IDIC might be effective in improving clinical symptoms in patients with inflammatory endplate changes on MRI. Therefore, IDIC could be an alternative treatment with an interesting benefit-to-risk ratio in patients with chronic LBP and Modic I changes whose pain did not respond to conservative therapy.

Since MRI of the lumbar spine can show a mixture of inflammatory and fatty changes in the vertebral subchondral bone marrow [22, 30], we hypothesized that patients with predominantly inflammatory changes were more likely to have better response to IDIC than those with predominantly fatty changes. The purpose of this pilot study was to analyze the association between the severity of inflammatory endplate changes on MRI and the clinical response to IDIC.

Materials and methods

Patient selection

Two of the authors (FF, NQ) reviewed the standardized medical records of 74 patients (30 men, 44 women; age range 32–70 years; mean age 47.9 years) who underwent lumbar IDIC at our institution from 1998 to

2004. All patients had disabling chronic LBP with Modic changes on MRI of the lumbar spine and had not responded to at least 3 months of conservative treatment. The retrospective research protocol did not require the local ethics committee approval.

Injection procedure

Discography was performed under fluoroscopic control and strict aseptic conditions by radiologists highly experienced in performing spinal interventions. Patients were not sedated during the procedure. Injections involved a posterolateral approach with use of a coaxial device (3.50 in., 18 G spinal needle and 7.80 in., 22-gauge disc needle). During incremental advancement of the needle, the location of the needle tip and the orientation of the needle in the sagittal and coronal planes were assessed by sequential fluoroscopic imaging. Needle-tip placement into the center of the disc was confirmed in the anteroposterior and lateral views before intradiscal injection of 1–2 ml of iodixanol (Visipaque 320 TM, Amersham Health SA, France). The similarity between the pain provoked upon disc injection and that of usual patient's clinical symptoms was recorded. One milliliter (25 mg) of acetate of prednisolone (Hydrocortancyl 2.5% TM, Aventis Laboratories, France) was then injected, and the patient wore a stiff lumbar corset for 2 weeks. As observed in knee synovitis, post-injection rest following intra-articular steroid therapy may result in a prolonged duration of clinical response and reduce the need for frequent steroid injections and the risk of complications [8]. Thus, we tried to optimize the chance of a better response to intradiscal injection of steroids by prescribing a stiff lumbar corset to the patients.

Clinical parameters recorded

The policy of our department was to record clinical parameters for all patients who underwent spinal injections at baseline and at 1, 3 and 6 months after treatment. All data were collected by an independent reviewer (AN). The following parameters were recorded at baseline: age, sex, duration of symptoms, LBP intensity on a visual analogue scale (VAS 100 mm length), Quebec disability score (20 items, scored from 0, no disability, to 5, impossible to do; range of final scores 0–100) for self-rated disability [21], waking because of LBP, morning stiffness, and lumbar flexibility (modified Schöber test and fingertip-to-floor test).

Outcome measurement

The primary outcome was change in LBP intensity from baseline to 1 month after IDIC, as measured on a visual analog scale (range, 0–100 mm). The change in LBP intensity recorded at 3 and 6 months after treatment and change in disability score at 1-, 3- and 6-month follow-up were secondary outcomes. Other secondary outcomes included the proportion of responders with at least 50% reduction of pain intensity at 1 month and the patient's global assessment (PGA) of treatment efficacy at 1 month (excellent, good, moderate, poor, and nil).

Analysis of MRI

The lumbar spine MR images were assessed independently by a panel of 2 spine specialists (MR, MMLC) and a radiologist (JLD), each with at least 10 years' experience in MRI of the spine. The reviewers graded the endplate marrow changes of the injected discs. Patients with a pure edema endplate changes were classified as Modic type I and those with a pure fatty endplate changes were classified as Modic type II. Patients with a mixture of type I and II changes but predominantly edema were classified as having Modic I-2 changes (Fig. 1a), and those with a mixture of type I and Modic II changes but predominantly fatty changes were classified as having Modic II-1 changes (Fig. 1b). Intraobserver and interobserver reliability was good to excellent, with weighted Cohen's kappa correlation coefficients of 0.85 and 0.74, respectively (unpublished data). The final diagnosis was based on diagnostic concordance by at least 2 of the 3 panelists. Consequently, Modic I changes were seen in 37 patients, Modic I-2 and Modic II-1 changes in 25 and 12 patients, respectively, and Modic II changes in no patients.

Data analysis

Data analysis involved use of Systat 9 software. Quantitative variables were described with means,

standard deviations (SD), and ranges. Qualitative variables were described with proportions and percentages. We compared the baseline parameters and the average change in pain and disability scores during follow-up between the Modic I, Modic I-2, and Modic II-1 groups using nonparametric kruskal-Wallis and Kolmogorov-Smirnov tests. A Fisher's exact test was used when appropriate. A $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics for the three groups are shown in Table 1. Patients were primarily female, with a minimum symptom duration of 13 months. The three groups were comparable with respect to gender, age, pain and level of disability. The mean delay between MRI imaging and intradiscal injection of steroids was 2.9 ± 2.3 months (range, 0.1–9 months) which is largely below the time of 24–36 months needed for the process of natural conversion of type I to type II [21, 22]. Injected discs in each group and the number of patients in whom discography provoked similar lumbar pain are shown in Table 2. The injected discs were L4–L5 and L5–S1 in most cases. Usual lumbar pain was more frequently provoked by discography in patients with Modic I and Modic I-2 changes than in those with Modic II-1 changes but not significantly ($P = 0.36$).

All patients were evaluated at least once after baseline assessment. Forty-two patients were assessed at each follow-up visit, 27 patients twice and the remaining 5 patients only once. Therefore, data were available for 69 (93.2%) patients at 1 month: 33 of 37 in the Modic I group, 25 of 25 in the Modic I-2 group and 11 of 12 in the Modic II-1 group. At 3 and 6 months, follow-up data were available for 81.1 and 75.7% of the patients, respectively (Fig. 2).

The pain intensity decreased from baseline to 1 month by a mean of 30.2 ± 26.6 mm in the Modic I group, 29.4 ± 21.5 mm in the Modic I-2 group, and 5.3 ± 25.5 mm in the Modic II-1 group (Table 3). The

Fig. 1 **a** Modic I-2 changes of L5–S1 on MRI of the lumbar spine. MRI shows a mixture of edema and fatty changes on L5–S1, but edema changes are predominant. **b** Modic II-1 changes of L4–L5 on MRI of the lumbar spine. MRI shows a mixture of edema and fatty changes on L4–L5, but fatty changes are predominant

Table 1 Baseline characteristics of patients with low back pain receiving intradiscal injection of corticosteroids, by Modic type

Variable	All patients (<i>n</i> = 74)	Modic I (<i>n</i> = 37)	Modic I-2 (<i>n</i> = 25)	Modic II-1 (<i>n</i> = 12)
Sex, female, <i>n</i> (%)	44 (59.5)	22 (59.5)	15 (60.0)	7 (58.3)
Age (year), median (min–max)	48 (32–70)	47 (32–64)	48 (35–62)	53 (39–70)
Duration of symptoms (month), median (min–max)	53 (13–240)	52 (13–240)	41 (17–183)	72.5 (15–228)
Pain, mean (SD)	62.6 (16.8)	60.1 (18.1)	66.9 (13.7)	60.9 (17.9)
Quebec disability score, mean (SD)	50.1 (15.9)	47.1 (14.1)	51.2 (16.2)	56.7 (19.2)
Wakening because of LBP and/or morning stiffness, <i>n</i> (%)	69 (93.2)	33 (89.2)	25 (100)	11 (91.7)
Modified Schöber test (cm), mean (SD)	19.2 (1.6)	19.3 (1.6)	19.4 (1.5)	18.7 (1.8)
Fingertip-to-floor test (cm), mean (SD)	27.4 (17.2)	22.2 (16.5)	31.2 (17.7)	35.5 (13.5)

LBP low back pain

Modic I-2 mixture of Modic type I and type II changes but predominantly edema changes

Modic II-1 predominantly fatty changes

Table 2 Lumbar discography findings of patients with low back pain receiving IDIC, by Modic type

Variable	Modic I (<i>n</i> = 37)	Modic I-2 (<i>n</i> = 25)	Modic II-1 (<i>n</i> = 12)
Disc injected			
L5-S1	17	11	5
L4-L5	13	11	6
L3-L4	4	1	0
L2-L3	3	2	1
Pain reproduction at discography, <i>n</i> (%)	21 (56.8)	13 (52.0)	5 (41.7)

Modic I-2 mixture of Modic type I and type II changes but predominantly edema changes

Modic II-1 predominantly fatty changes

reduction was significantly higher in the Modic I and Modic I-2 groups than in the Modic II-1 group ($P = 0.009$ and 0.017 , respectively), with no significant difference between Modic I and Modic I-2 groups. The proportion of responders with at least 50% reduction in pain at 1 month was 54.5% in the Modic I, 52% in the Modic I-2 and 8.3% in the Modic II-1 groups ($P = 0.02$). In addition, patient's global assessment of treatment efficacy was rated excellent or good in 18 (54.5%) patients from the Modic I group as compared with 8 (32%) from the Modic I-2 group and 2 (18.2%) from the Modic II-1 group. The reduction in disability score was greater in the Modic I and Modic I-2 groups than in the Modic II-1 group but not significantly (Table 3).

At 3 and 6 months, results of IDIC in the Modic I and Modic I-2 groups tended to be better than in the Modic II-1 group for all outcome measures. However, there were no significant differences between the groups (Table 4; Fig. 2). Finally, no complications such as infection or hematoma were reported.

Discussion

Main findings

The present study showed that IDIC was more effective in patients with Modic I and Modic I-2 changes than in those with Modic II-1 changes. Most outcome variables tended to be better when the inflammation process in the bone marrow endplates was predominant. Our results agree with those of Buttermann who suggested that IDIC was more effective in patients with MRI findings of discogenic inflammatory endplate changes [7].

All our patients had chronic LBP with a particularly disabling episode of inflammatory pain, characterized

Sample Size	Mod I	37	33	31	27
	Mod I-2	25	25	21	19
	Mod II-1	12	11	8	10

Fig. 2 Mean $\pm$ SE development of low back pain intensity in the three groups. *Mod I* Modic I changes, *Mod I-2* Modic I-2 changes, and *Mod II-1*, Modic II-1 changes

Table 3 Assessment of efficacy of IDIC at 1 month in patients with low back pain, by Modic type

Variable	Modic I (n = 33)	Modic I-2 (n = 25)	Modic II-1 (n = 11)	P value
Primary outcome				
Difference in LBP intensity between baseline and 1 month (VAS), mean $\pm$ SD	30.2 $\pm$ 26.6	29.4 $\pm$ 21.5	5.3 $\pm$ 25.5	< 0.02
Secondary outcomes				
Difference in quebec disability score between baseline and 1 month, mean $\pm$ SD	13.0 $\pm$ 19.1	10.9 $\pm$ 15.3	2.5 $\pm$ 20.2	NS
Pain improvement $\geq$ 50%	18 (54.5)	13 (52.0)	1 (9.1)	0.02
PGA of IDIC efficacy: excellent or good	18 (54.5)	8 (32.0)	2 (18.2)	0.07

VAS Visual analog scale, PGA patient's global assessment of treatment efficacy, IDIC intradiscal injection of corticosteroids. Data are number (percent) unless otherwise indicated

Modic I-2 mixture of Modic type I and type II changes but predominantly edema changes

Modic II-1 predominantly fatty changes

Table 4 Comparison of mean pain and disability score changes at 3 and 6 months in patients with low back pain receiving IDIC, by Modic type

Variables	Modic I	Modic I-2	Modic II-1
Mean pain intensity change (VAS), (SD)			
3 months	13.7 (33.3)	22.1 (15.0)	5.3 (29.5)
6 months	10.6 (36.1)	18.1 (16.9)	10.2 (22.5)
Mean quebec disability score change (SD)			
3 months	7.3 (19.1)	10.7 (18.9)	-0.4 (21.5)
6 months	8.1 (23.5)	6.7 (19.3)	4.1 (14.7)

VAS Visual analog scale

Modic I-2 mixture of Modic type I and type II changes but predominantly edema changes

Modic II-1 predominantly fatty changes

by an awakening because of pain and/or lumbar morning stiffness (>93% of cases). In addition, no patients showed improvement with at least 3-month conservative treatment. MRI revealed inflammatory endplate changes in all cases. However, the severity of changes differed among subjects. The response to IDIC was, as hypothesized, better in patients with predominantly inflammatory changes.

As observed in peripheral joints [3], the benefit of local corticosteroid injection may decline over time. Although outcome measures did not differ significantly between Modic I, Modic I-2, and Modic II-1 groups at 3- and 6-month follow-up, the results of IDIC seem to be better in patients with predominantly inflammatory endplate changes. This observation may explain the discrepancy between our results and those of Khot et al. [19], who showed, in a randomized controlled trial the absence at 12-month follow-up of a significant difference in therapeutic effect between intradiscal steroid injection and saline placebo injection in patients with chronic discogenic LBP. Another possible explanation for the absence of significant effect of intradiscal steroid injection in

the study of Khot et al. [19] could be the lack of selection of patients with inflammatory endplate changes.

The relation of endplate changes to symptoms has been studied both clinically [20, 27, 29] and in comparison to discography performed at the affected levels [4, 30]. Toyone et al. [27] reviewed the MR images of 500 patients with LBP and leg pain and found significant LBP in 73% of patients with Modic I changes but only 11% of patients with Modic II changes, whereas the incidence of leg pain was the same between the two groups. Kjaer et al. [20] reported in a cross-sectional cohort study of a general population (412 40-year-old individuals) that the strongest association with LBP during the previous year were Modic changes and anterolisthesis. When Modic I changes were analyzed separately, the strength of association was increased in terms of LBP during the previous month and during the previous year [20]. By contrast, type I changes were seen in only one disc space by only 1 reader in 60 asymptomatic volunteers and 300 intervertebral discs [29]. Finally, Modic changes have been identified as being predictive of reproducing pain on discography [4, 30].

Many studies have identified elevated levels of inflammatory mediators [6] and enzymes capable of degrading protein within the disc, such as matrix metalloproteinase [16], in degenerated disc specimens. Specifically, higher levels of interleukin-6, interleukin-8 and prostaglandin E2 were found in disc tissue from patients undergoing anterior fusion for discogenic LBP than in those from patients undergoing discectomy for sciatica [6]. Modic I changes, representing more active inflammation, seem to be mediated by proinflammatory cytokines such as tumor necrosis factor alpha (TNF- α) [24], whereas type II and III changes could be more quiescent stages of the process. In addition, repeated trauma to the intervertebral disc may result in production of inflammatory substances within the

nucleus pulposus. Diffusion of such toxic chemicals through vertebral endplates could result in a local inflammatory reaction, giving rise to back pain [10]. One author has proposed type I change being related to instability [27], and one not [5]. However, better results of anterior fusion for LBP patients with degenerative disc disease were observed in patients with Modic I changes [9]. All of the above findings have led to the use of intradiscal corticosteroid treatment for patients with chronic LBP and inflammatory endplate changes.

Usual lumbar pain was more frequently provoked by discography in patients with Modic I (21/37, 56.8%) and Modic I-2 (13/25, 52%) changes than in those with Modic II-1 (5/12, 41.7%) changes but not significantly ($P = 0.36$). The lack of significant difference between these groups could be explained by the small number of patients in each group and particularly in the Modic II-1 group. Furthermore, the aim of the injection of contrast agent was not to obtain an optimal pressure into the disc, but only to be sure that the needle tip was into the disc before the injection of steroids. Indeed, in the study of Weishaupt et al. [30], the authors stated that “the nonionic contrast agent (iopamidol) was injected with a 5-mL syringe until firm resistance to the injection was felt, until severe pain was provoked, or until contrast medium was seen out the disk into the spinal canal”. Consequently, the amount of contrast agent injected ranged from 0.8 to 4 mL, whereas this amount was <2 mL of iodixanol in the current study.

Limitations

Several limitations of our study relate to its retrospective design, although collection of data for patients undergoing spinal injection in our institution was standardized for demographic and clinical parameters before treatment and at each follow-up visit. In addition, the MR images were prospectively assessed and independently graded by three panelists. A second limitation is the small sample size of the Modic II-1 group and the lack of control group. Thus, randomized controlled trials with a large population of patients are needed to confirm our results.

Conclusion

Intradiscal injection of corticosteroids could be a short-term efficient treatment for patients with chronic LBP and predominantly inflammatory endplate changes on

MRI when conservative approaches to pain reduction have failed.

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