

Clinical efficacy of calcitonin compared to diclofenac sodium in chronic nonspecific low back pain with type I Modic changes: a retrospective study

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Background: The objective of this study was to compare the efficacy of calcitonin with diclofenac sodium in the treatment of patients with nonspecific low back pain (LBP) and type I Modic changes (MC1).

Patients and methods: The study was a retrospective observational study with 109 patients who had nonspecific LBP and MC1 that appeared as bone marrow lesions on magnetic resonance imaging (MRI). Between October 2013 and March 2016, 62 patients were injected intramuscularly with calcitonin 50 IU once daily and 47 patients were treated with diclofenac 75 mg once per day for 4 weeks for the treatment of LBP associated with MC1 on MRI. Visual analog scale (VAS) (0–10) and Oswestry Disability Index (ODI) (0–100) questionnaires were acquired from clinical records to evaluate LBP perception and degree of disability. Imaging data were also collected before and after treatment.

Results: Significant improvements were found in VAS and ODI at posttreatment compared with baseline in both groups ($P < 0.05$). Meanwhile, there was a significant difference between calcitonin group and diclofenac group at both 4 weeks and 3 months of follow-up (4 weeks: VAS 4.46 ± 1.58 vs 5.08 ± 1.50 , ODI 20.32 ± 9.64 vs 24.35 ± 7.95 ; 3 months: VAS 3.70 ± 1.74 vs 4.51 ± 1.67 , ODI 16.67 ± 9.04 vs 21.18 ± 9.56 ; $P < 0.05$ for all). Moreover, the proportion of patients with a significant change in LBP scales was higher in the calcitonin group (4 weeks: VAS 50.00% vs 23.40%, ODI 54.83% vs 25.53%; 3 months: VAS 58.06% vs 38.29%, ODI 59.67% vs 38.29%; $P < 0.05$ for all). According to MRI, 43.54% patients in the calcitonin group showed improvement compared with 21.27% patients in the diclofenac group ($P < 0.05$).

Conclusion: There was greater short-term efficacy of calcitonin compared with diclofenac in patients with LBP and MC1 on MRI.

Keywords: calcitonin, diclofenac sodium, Modic changes, bone marrow lesions, low back pain

Introduction

Low back pain (LBP) is the world's most disabling condition with enormous impact on population health and social economy.¹ It is estimated that LBP in less than 15% of individuals could be attributed to a specific cause.² Hence, the vast majority of LBP patients are categorized as having nonspecific LBP.³ Many therapeutic options have been used for LBP.⁴ Nonsteroidal anti-inflammatory drugs (NSAIDs), especially diclofenac sodium, are widely prescribed by physicians in treating nonspecific LBP.

Although LBP may originate from many spinal structures, there is a positive association between Modic changes (MC) presented as vertebral bone marrow lesions (BMLs)

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on magnetic resonance imaging (MRI) and LBP.⁵ Three types of MC have been described according to their appearance on T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Type I Modic changes (MC1; hypointensity on T1WI and hyperintensity on T2WI) represent disrupted and fissured endplates and vascular granulation tissue adjacent to the endplates, which correspond to vertebral body lesions; type II MC (MC2; hyperintensity on both T1WI and T2WI) indicate fatty replacements of the red bone marrow; and type III MC (MC3; hypointensity on both T1WI and T2WI) are thought to represent subchondral bone sclerosis.^{6–8} Generally, MC1 have been mostly reported as being associated with LBP than other MC types. Besides, the existence of the MC1 manifestation is related to persistence of symptoms.^{9–12} A recent histomorphometric analysis of biopsies showed that MC1 had a highest bone turnover, whereas MC2 manifested as a reduced remodeling state and MC3 tended to be a stable sclerotic phase, revealing the characteristics of three MC types through microarchitecture.¹³

Calcitonin is an effective inhibitor of osteoclastic bone resorption and has been approved for the treatment of osteoporosis and other conditions involving accelerated bone turnover.^{14,15} A few studies have demonstrated that calcitonin could reduce duration and shorten mean clinical recovery of hip BMLs,^{16–18} but calcitonin in the treatment of MC1, which presented as vertebral BMLs on MRI, has not been reported. Because of the antiresorptive effects of calcitonin and the state of high turnover in MC1, we treated patients with nonspecific LBP coupled with MC1 by using calcitonin in recent years. If calcitonin could take effect for patients with nonspecific LBP and MC1, it may be demonstrated by LBP scales and imaging data. This retrospective observational study was conducted to examine the effect of calcitonin in the treatment of LBP and MC1 on MRI compared with diclofenac sodium.

Patients and methods

Patients

A total of 133 consecutive patients who were diagnosed with chronic nonspecific LBP and MC1 between October 2013 and March 2016 in our hospital were reviewed retrospectively. The definition of LBP is pain and discomfort, localized below the costal margin and above the inferior gluteal folds, with or without leg pain.⁴

Patients with the following characteristics were included: 1) suffered from LBP more than 3 months and 2) MC1 confirmed by lumbar MRI. Patients with the following characteristics were excluded: 1) osteoporosis, fracture, tumor, infection, structural deformity or compression of the nerve

root (n = 7); 2) rheumatic or rheumatoid arthritis disease or other serious systemic diseases (n = 1); 3) prior surgery of lumbar spine (n = 1); and 4) lack of adequate follow-up data (n = 15). Finally, 109 patients were included in this study.

Approval and consent

The study was approved by the Medical Ethics Committee of Tianjin Medical University General Hospital and conducted in accordance with the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from each subject. Owing to off-label drug use in patients, patients treated by calcitonin provided additional written informed consent for off-label use of calcitonin. Individuals who refused calcitonin were treated with diclofenac sodium.

Treatment

We conducted a retrospective study for these 109 patients. A total of 62 patients received calcitonin (Miacalcic®; Novartis Pharma Schweiz AG, Rotkreuz, Switzerland), and 47 patients who refused off-label drug received diclofenac sodium (Votalin®; Novartis Pharma Schweiz AG). All patients' baseline information, including age, sex, smoking, body mass index (BMI), imaging data, as well as intensity and duration of LBP, was gathered from chart review. Patients' data for each follow-up were also collected.

Calcitonin (50 IU) was injected intramuscularly once daily, whereas diclofenac (75 mg) was orally administered once daily for 4 weeks for the treatment of LBP associated with MC1 on MRI. None of patients received calcium or vitamin D supplements. At the end of treatment, patients were followed up and asked about adverse effects. Meanwhile, patients were asked to do a lumbar MRI at 3 months of follow-up. Because of the correlation between MC1 and LBP, non-MC1 was considered as an obvious improvement according to MRI.

Assessment of low back pain

A visual analog scale (VAS) ranging from 0 to 10 was used to estimate LBP perception.¹⁹ 0 indicates no pain at all and 10 indicates the most severe pain (intolerable pain). Oswestry Disability Index (ODI) ranging from 0 to 100 is a self-report questionnaire consisting of 10 domains, namely pain intensity, personal care, lifting, walking, sitting, standing, sleeping, sex life, social life, and traveling. The sum of the section scores (0–5 for each section) was divided by the total score (50 if all sections were completed), and the resulting total was multiplied by 100 to yield a percentage score. It was used to evaluate the degree of disability before and after the therapy.²⁰ VAS and ODI questionnaires were

also acquired from clinical records. At least 30% reduction in LBP scale scores (VAS and ODI) was considered as a remarkable improvement.²¹

Analysis of imaging data

All of the imaging data were collected and reviewed by two orthopedic surgeons (YX and JZ). Regular meetings and discussions were held to guarantee data reliability. According to the criteria presented by Modic et al, MC1 (low signal on T1WI and high signal on T2WI) were identified. Patients with a specific cause as noted earlier would be excluded in order to make sure to conform to the nature of nonspecific LBP. A patient with MC1 is illustrated in Figure 1A and B. In addition, routine dual-energy X-ray absorptiometry scan (SONOST-3000; OsteoSys Co Ltd, Seoul, Korea) was used to evaluate bone marrow density (BMD) at L2–L4 before treatment for excluding osteoporosis.

Sample size

Based on previous study and preexperiment, we assumed a normal distribution and a VAS SD of 2.5. With a two-sided $\alpha=0.05$, a sample size of 44 patients in each group would give us a power of 0.8 to detect a mean difference of 1.5 in VAS.

Statistical analysis

Baseline characteristics were presented as mean values (with SD), frequencies (with proportions), or median values (with interquartile range). Differences between groups were assessed by the chi-squared test for categorical variables and by the independent sample *t*-test for continuous variables, whereas a paired *t*-test was performed to analyze intragroup

differences. Treatment effects at 4 weeks and 3 months were also analyzed by comparing the change in the outcomes of the two groups through using independent sample *t*-test. Statistical significance was accepted for a *P*-value < 0.05. Analyses were performed using SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, NY, USA).

Results

Characteristics of the study population

A total of 109 patients were included in the study (60 men and 49 women) with a mean \pm SD age of 52.88 ± 6.26 years. Baseline comparison of calcitonin and diclofenac groups showed that age, sex distribution, smoking, BMI, BMD, duration of LBP, as well as the scales of VAS and ODI were similar between the treatment groups (*P* > 0.05) (Table 1).

Treatment effect on study parameters

At 4 weeks and 3 months of follow-up, significant improvements were found in VAS and ODI compared with baseline in both groups. When we compared variables between the treatment groups, calcitonin group showed a significant difference in VAS and ODI (*P* < 0.05). Meanwhile, between-group differences in change of the outcome demonstrated that calcitonin had significant improvements in VAS and ODI compared with diclofenac sodium (Table 2). Besides, the proportion of individuals with a significant change (30% reduction compared to baseline) in LBP scales was higher significantly among calcitonin users than among subjects treated with diclofenac: 4 weeks: VAS 31/62 vs 11/47, ODI 34/62 vs 12/47; 3 months: VAS 36/62 vs 18/47, ODI 37/62 vs 18/47, *P* < 0.05 for all (Table 3).

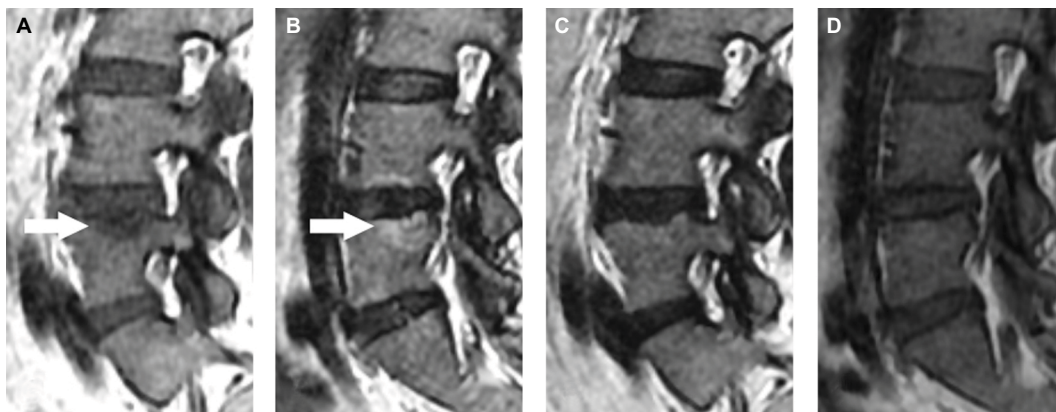


Figure 1 A patient with MC1 (arrows) on MRI: low intensity on T1-weighted image (A) and high intensity on T2-weighted image (B). After calcitonin treatment, no abnormal signal intensity was found on T1- and T2-weighted images (C, D).

Abbreviations: MC1, type I Modic changes; MRI, magnetic resonance imaging.

Table 1 Baseline characteristics of patients

Characteristics	Calcitonin (n = 62)	Diclofenac (n = 47)	P-value
Age, mean (years) (SD)	53.53 (5.89)	52.04 (6.68)	0.220
Sex, n (male) (%)	32 (51.61)	28 (59.57)	0.408
Smokers, n (%)	13 (20.96)	12 (25.53)	0.575
BMI, mean (kg/m ²) (SD)	24.82 (2.09)	24.11 (2.29)	0.095
BMD, mean (g/cm ²) (SD)	1.08 (0.13)	1.06 (0.09)	0.388
Duration, mean (days) (IQR)	342 (180,360)	301 (150,360)	0.396
VAS, mean (SD)	6.25 (1.47)	6.34 (1.35)	0.765
ODI, mean (SD)	30.49 (11.09)	29.74 (8.73)	0.703

Abbreviations: BMI, body mass index; BMD, bone mineral density; IQR, interquartile range; VAS, visual analog scale; ODI, Oswestry Disability Index.

Table 2 VAS and ODI changes in the study population

Scales	Original values			Changes		
	Calcitonin (n = 62)	Diclofenac (n = 47)	P-value	Calcitonin (n = 62)	Diclofenac (n = 47)	P-value
VAS, mean (SD)						
Baseline	6.25 (1.47)	6.34 (1.35)	0.765			
4 weeks	4.46 (1.58)*	5.08 (1.50)*	0.042	1.79 (1.46)	1.25 (1.20)	0.044
3 months	3.70 (1.74)*	4.51 (1.67)*	0.018	2.54 (1.78)	1.82 (1.44)	0.023
ODI, mean (SD)						
Baseline	30.49 (11.09)	29.74 (8.73)	0.703			
4 weeks	20.32 (9.64)*	24.35 (7.95)*	0.022	10.17 (10.04)	5.39 (7.89)	0.008
3 months	16.67 (9.04)*	21.18 (9.56)*	0.013	13.82 (11.75)	8.56 (9.26)	0.010

Note: *P < 0.05 vs baseline

Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index.

Table 3 Percentage of patients with 30% reduction in low back pain scales at each follow-up compared with baseline

	Calcitonin (n = 62)	Diclofenac (n = 47)	P-value
VAS			
4 weeks	50.00%	23.40%	0.005
3 months	58.06%	38.29%	0.041
ODI			
4 weeks	54.83%	25.53%	0.002
3 months	59.67%	38.29%	0.027

Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index.

Treatment effect on imaging data

At 3 months of follow-up, all patients received a lumbar MRI in our hospital. In the calcitonin group, 11 patients demonstrated no MC (Figure 1), 16 patients demonstrated MC2 (Figure 2), and 35 patients demonstrated MC1 on MRI. Whereas in the diclofenac group, 4 patients did not demonstrate MC, 6 patients demonstrated MC2, and 37 patients demonstrated MC1 on MRI. No MC3 was found in all these patients. Briefly, the proportion of patients with non-MC1, a significant improvement on MRI, was 43.54% and 21.27% in the calcitonin group and diclofenac group, respectively, ($P = 0.015$).

Adverse events

Adverse events occurred in 17/62 patients in the calcitonin group (27.41%) and 7/47 (14.89%) in the diclofenac group, a difference that was not significant ($P = 0.118$). Adverse effects in the calcitonin group were nausea (3; 4.83%), abdominal pain (5; 8.06%), diarrhea (3; 4.83%), hypodynamia (4; 6.45%), headache (2; 3.22%), hot flushes (4; 6.45%), dizziness (2; 3.22%), and hypocalcemia (1; 1.61%). Adverse effects in the diclofenac group were nausea (1; 2.12%), abdominal pain (2; 4.25%), diarrhea (2; 4.25%), constipation (1; 2.12%), hypodynamia (1; 2.12%), headache (1; 2.12%), and dizziness (2; 2.12%).

Discussion

In this retrospective study, we observed that calcitonin 50 IU injected intramuscularly once daily was associated with superior improvement in patients suffering from LBP and MC1 on MRI compared with diclofenac 75 mg once per day. Patients treated with calcitonin for 4 weeks showed a more obvious reduction in pain scores as well as disability index, as shown in VAS and ODI, compared with the patients administered with diclofenac. In addition to the numerical change, the proportion of cases who achieved the clinically

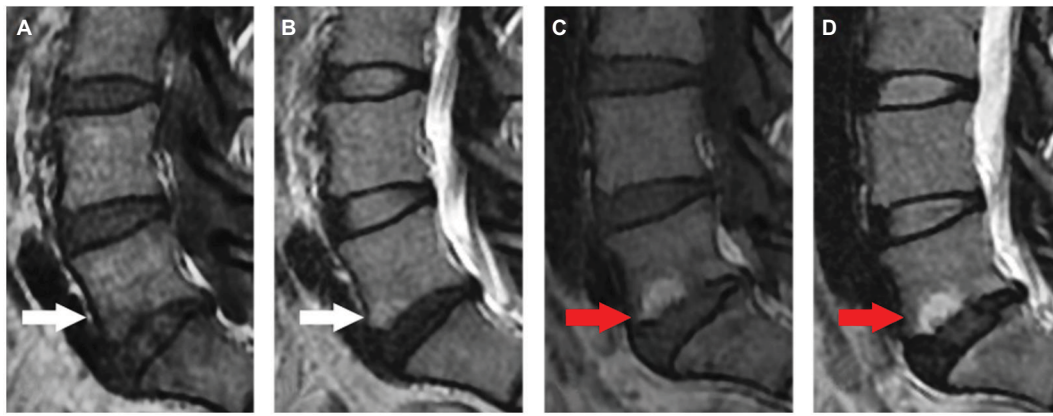


Figure 2 A patient with MC1 (white arrows) on MRI: low intensity on T1-weighted image (A) and high intensity on T2-weighted image (B). After calcitonin treatment, MC1 converted to MC2 (high signal intensity on T1- and T2-weighted images) (red arrows) (C, D).

Abbreviations: MC1, type I Modic changes; MRI, magnetic resonance imaging; MC2, type II Modic changes.

meaningful improvement (30% reduction compared with baseline) in VAS and ODI was also greater in the group of patients treated with calcitonin. Besides, the proportion of patients with significant improvement on MRI was greater in the calcitonin group than in the diclofenac group.

LBP is the major cause of disability-adjusted life years both in developed and developing countries with considerable socioeconomic impact.^{1,22,23} Although there is little scientific evidence on the prevalence of chronic nonspecific LBP, best estimation suggests that the prevalence is 23% or so.²⁴ A few therapies are recommended for the management of chronic nonspecific LBP, such as exercise therapy, behavioral treatment, brief educational interventions, and pharmacological approaches including but not limited to NSAIDs and weak opioids. Although an increasing number of studies have focused on LBP with MC, few therapeutic options have been evaluated for it.

Calcitonin is a naturally occurring peptide that inhibits osteoclast function potently through specific receptors.²⁵ Following its discovery in 1962,²⁶ an injectable form of calcitonin was introduced in the European market in 1973. The antiresorptive action of calcitonin has led to its widespread application in treating metabolic bone diseases characterized by high turnover, such as postmenopausal osteoporosis and Paget's disease of the bone. It was also applied to treat hip BMLs by a few scholars.^{16–18} A localized high turnover in BMLs has been verified,^{27,28} which may explain the positive effects of antiresorptive drugs like calcitonin on the condition extension and symptoms associated with the lesion.²⁹ Recently, a quantitative histomorphometric study on bone biopsies found that MC1 presented the highest bone turnover.¹³ In a similar way, the role of calcitonin in inhibiting

bone turnover may explain our result that calcitonin could provide a better effect in patients with LBP and MC1.

The microfractures and fissures in the endplates were identified as a major source of MC through the biomechanical mechanism. As mentioned earlier, MC1 are disruption and fissuring of the endplates.³⁰ If microfractures have taken place recently, phenomenon that decreases signal intensity on T1WI and increased signal intensity on T2WI will be found, which is equivalent to MC1.³¹ Therefore, this appearance might reflect edema and inflammatory response following accumulated lesions. Moreover, the high turnover state in MC1 may be caused by the microfractures in endplates under the condition of persistent inflammatory stimulus.³² Calcitonin has been found to promote the cartilaginous phase of fracture healing in animal studies. These studies concluded that calcitonin facilitates early endochondral ossification, leading to enhanced chondrification and earlier maturation of callus. In a randomized controlled trial on calcitonin in elderly patients with hip fracture, no significant difference was found in functional recovery, length of hospital stay, or complications between calcitonin group and placebo group. However, a higher rate of fracture fusion and a tendency of diminishing bone loss and pain were observed in calcitonin group.³³ Accordingly, the microfractures in MC1 may gain an accelerated healing from calcitonin. Besides, the pharmacologic effect of calcitonin in maintaining subchondral and trabecular microstructure has been reported both in animal experiments and clinical trials,^{34–37} which could contribute to improving the biomechanical characteristics of the healing bone, such as fracture load and stiffness.

In addition to inhibition of bone turnover, acceleration of bone healing, and protection of bone microstructure,

calcitonin has been shown to have a direct positive effect on pain reduction, and thus is clinically useful in several diseases that involve bone pain, such as pain owing to bone metastasis. The mechanism for the analgesic effect of calcitonin is yet to be studied in details. In humans, similarities were found between calcitonin- and morphine-induced analgesia,^{38,39} and elevation of plasma β -endorphin level following administration of calcitonin was reported,^{40–42} suggesting that endogenous opiate system may be involved in the mediation of analgesic role triggered by calcitonin. Besides, there is sufficient evidence that calcitonin has a direct effect on the central nervous system (CNS). Specific calcitonin receptors have been found in areas of the CNS involved in pain perception as well as transmission and modulation of sensory stimuli.^{43,44}

Since MC1 have been more frequently reported as being associated with LBP and it correlates to persistence of LBP symptoms,^{9–12} we defined non-MC1 which indicating improved significantly on MRI. In our study, the proportions of patients with non-MC1 after treatment were 43.54% and 21.27% in the two groups, showing an obvious improvement in calcitonin group in the light of MRI.

As an anti-osteoporosis drug, calcitonin could relieve pain originating from osteoporotic vertebral compression fracture.⁴⁵ In this retrospective study, patients underwent dual-energy X-ray absorptiometry scan before treatment for excluding osteoporosis, showing its effective role in patients with nonspecific LBP and MC1. Koivisto et al reported that zoledronic acid had a positive efficacy in the treatment of LBP with MC, with mild to moderate side effects.⁴⁶ But due to the risk of developing kidney failure, renal function must be monitored during zoledronic acid treatment. Hence, we think that calcitonin may be more secure in treating LBP with MC1. Besides, calcitonin has the analgesic effect that is lacking in other anti-osteoporosis drugs.

NSAIDs are the most frequently prescribed medications around the world and are recommended for short-term use in patients with chronic LBP in order to relieve pain.²⁴ In our study, we found that calcitonin could offer more effects compared with diclofenac in the treatment of chronic nonspecific LBP with MC1 on MRI, which manifested as more obvious reduction in VAS and ODI, as well as a much higher proportion of significantly improved patients. Meanwhile, side effect was not significantly different in the calcitonin group compared with the diclofenac group, although the incidence was higher in the calcitonin group.

This study has some limitations that must be pointed out. The current study was a single-center retrospective observational study that lacked randomization, which may

induce a potential bias. In addition, many factors could take part in the development and prognosis of LBP due to its multidimensional nature. The potential influence of physical exercise, education, and psychosocial factors was not taken into account in our study. Lack of long-term follow-up was also a limitation in our study. Further multi-center randomized control trial with long-term follow-up is needed to evaluate the therapeutic use of calcitonin for the treatment of LBP accompanied by MC1.

Conclusion

In this retrospective comparative study, patients with LBP associated with MC1 on MRI who were treated with calcitonin showed statistically significant improvements compared to the diclofenac group in all measured parameters. As far as we know, this is first study to evaluate the effect of calcitonin on LBP with MC1. Although there is still a controversy regarding association between MC and LBP, our findings in this study could make a recommendation that calcitonin is a treatment protocol for patients with nonspecific LBP and MC1 when all other treatment approaches have failed.

Author contributions

All the authors contributed toward data analysis, drafting, and critically revising the paper; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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