ORIGINAL ARTICLE

Bisphosphonates and Antibiotics Combination Therapy for Chronic Low Back Pain Associated with Modic Change: A Quasi-Experimental Study

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Abstract

Background: Although effective treatments are still lacking for chronic low back pain (CLBP) associated with Modic changes (MC), in recent years, the efficacy of bisphosphonate and antibiotic treatment has been tested separately with variable success. This study aimed to compare the effectiveness of combined therapy of bisphosphonate and antibiotics versus single-drug therapy in CLBP patients with MC.

Methods: This quasi-experimental study was carried out from October 2019 to September 2020 according to 1964 Helsinki declaration among 60 adult CLBP patients with MC (confirmed by magnetic resonant imaging) and randomly allocated in Group-A (n=20): Zoledronic acid (ZA) only, Group-B (n=20): amoxicillin-clavulanate only, and Group-C (n=20): both ZA and amoxicillin-clavulanate. The primary outcomes were measured by the visual analog scale (VAS) and Roland Morris disability questionnaire (RMDQ) at follow-ups after 1 month, 100 days, and 6 months. Per-protocol analysis was performed using SPSS 24.

Results: Out of the 60 patients, 43 patients (72%) completed all three follow-ups. The VAS score gradually decreased in all groups after treatment, wherein Group-C patients had the significantly lowest score at the 2nd and 3rd follow-ups (2.87±0.80 and 1.68±0.70, respectively) compared to Group-A (3.40±0.63 and 2.20±0.67, respectively) and Group-B (3.50±0.52 and 2.41±0.66, respectively). In addition, RMDQ also decreased significantly after 1 month compared to pretreatment ($p<0.05$) in all 3 groups, and this gradual decrement was continued until 6 months of treatment. However, it was reduced more in Group-C (6.26±0.70) than in group-A (6.69±1.40) and Group-B (7.75±1.21) at the end of the 3rd follow-up. Moreover, Group-C patients had the highest satisfaction level and lowest number of days with absence from work score compared to A and B ($p<0.05$). However, adverse effects were relatively higher in Group-C than A and B ($p>0.05$).

Conclusion: Bisphosphonates and antibiotics combination therapy is more effective than single-drug therapy for CLBP associated with MC.

Keywords: CLBP, Modic change, Bisphosphonate, Antibiotic, VAS, RMDQ

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Introduction

Low back pain (LBP) is an extremely common symptom experienced by people of all ages[1]. It is the leading cause of activity limitation throughout the world, imposing a high economic burden on individuals, families, communities, and governments[2]. Although no specific pathologies are present in majority cases (>85%), a subset of patients has one particular type of pathology named Modic change (MC), which is strongly associated with nonspecific LBP. Modic changes are vertebral end plate and subchondral bone marrow changes that are most readily demonstrated in lumbar spine magnetic resonance imaging (MRI). Studies have attributed Modic type 1 vertebral endplate changes to mechanical stress or traumatic injury to the vertebral endplate[3,4,5], localized action of proinflammatory mediators such as interleukin 6 (IL-6) and prostaglandin E2 (PGE2) [6,7,8] or, more recently, low-virulence anaerobic bacterial infection such as Propionibacterium acnes[9,10]. However, these processes are inter-linked and are not mutually exclusive[11].

Multiple modalities of treatment have been tried previously for LBP associated with MC[12-15]. Treatment options included nonsteroidal anti-inflammatory drugs (NSAIDs)[16] and local treatments ranging from intradiscal cortisone injections[17] to arthrodesis[18,19]. The results are, however, ineffective or controversial[20]. These invasive procedures expose the patient to a risk of infection for intradiscal injections and operating complications for arthrodesis[18]. In recent years, Koivisto et al. conducted two separate studies to determine the efficacy of Zoledronic acid (ZA) in LBP patients and found that ZA was effective in reducing the intensity of LBP in the short term and in reducing the use of NSAIDs[21] and in the conversion of MC1-dominant to MC2-dominant Modic changes (MCs)[22]. In addition, growing evidence shows that as well as affecting osteoclasts, bisphosphonates also exert effects on osteoblasts, osteocytes, and adipocytes[23,24], which might explain the positive effects of ZA in these studies. In addition, amoxicillin- clavulanate is known to be able to penetrate intervertebral discs[25] and has an inhibitory effect on IL-1, IL-5 and IL-8, not TNF-α, which is present in Modic changes[26,27]. Albert et al. observed that antibiotics (amoxicillin- clavulanate) were significantly more effective than placebo in patients with chronic LBP and vertebral bone edema (Modic type 1 changes)[10].

However, as there is no conclusive way to identify the underlying mechanisms causing Modic changes aided by MRI only, it is very difficult to choose the best treatment option suitable for these patients. Therefore, this study compared the effectiveness of a combination of antibiotics (amoxicillin-clavulanate) and bisphosphonate (Zoledronic acid) with individual treatments for reducing pain and functional limitations in chronic LBP associated with Modic changes.

Methods

Study design, population and settings

This study was conducted at the pain medicine unit outpatient department, under the Department of Anesthesia, Analgesia, and Intensive Care Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, from October 2019 to September 2020. A total of 60 adult patients aged in between 30 to 60 years of either sex were interviewed. After informed written consent was obtained, clinical, functional, and radiological assessments were performed for all patients at the first visit. The severity of pain was assessed by a visual analog scale (VAS), and disability was assessed by a disease-specific Roland Morris disability questionnaire (RMDQ).

The selection criteria were having chronic LBP with documented Modic change in MRI. Chronic LBP was defined as pain in the area between the lower costal margin and the gluteal folds lasting for ≥12 weeks regardless of accompanying radiating pain that was not merely associated with febrile illness, menstrual periods or pregnancy[28]. Modic changes were determined on MRI as alterations in signal intensity of the bone marrow adjacent to a degenerated disc[29].

The exclusion criteria were as follows: specific pathological entities, such as metastasis and osteoporosis, known allergy to penicillin or cephalosporin antibiotics or Zoledronic acid or other bisphosphonates or ingredients of the infusion product,

renal impairment with reduced creatinine clearance defined as an estimated glomerular filtration rate (eGFR) below 40 ml/min, hypocalcaemia, the presence of red flags, nerve root entrapment and premenopausal women of childbearing potential.

Drug allocation

The subjects were randomly assigned into three groups through a computer generated master randomization list containing three treatment modalities in random order: Group A (n=20): single intravenous infusion of 5 mg Zoledronic acid (ZA); Group B (n=20): amoxicillin- clavulanate 625 mg (500 mg/125 mg) tablets three times daily for 100 consecutive days; Group C (n=20): amoxicillin-clavulanate 625 mg (500 mg/125 mg) tablets three times daily for 100 consecutive days along with a single intravenous infusion of 5 mg ZA. All patients were given oral paracetamol 665 mg three times a day after a meal as a primary analgesic to reduce LBP. Before initiation of treatment and in subsequent follow-ups, liver function test, serum creatinine, eGFR, and serum. calcium estimation were performed in all patients. Before the administration of the ZA infusion, patients received oral paracetamol 665 mg to prevent acute phase reactions and calcium carbonate 1000 mg and vitamin D supplementation 40,000 IU to prevent hypocalcemia. Patients who developed diarrhea after antibiotic treatment were treated with probiotics (each capsule contained Lactobacillus acidophilus (2 billion), Bifidobacterium bifidum (1 billion) and fructo-oligosaccharides (100 mg)). Patients were recommended not to seek any other treatment for chronic LBP during the 6-month follow-up period except mild analgesic (oral paracetamol, 665 mg three times a day after a meal).

Follow up and outcome measurement

All patients underwent follow-up examination after -1 month, 100 days (at the end of antibiotic treatment) and 6 months (at the end of the study) at the pain clinic or over the phone. Patient compliance was measured by empty blisters of medicine. The primary outcome was the measurement of pain by VAS score and disability by RMDQ[30]. Patient satisfaction with treatment was assessed by a 5-point Likert scale[31], and the number of days with absence from work (average in a month) was the secondary outcome.

Adverse events

Adverse events such as diarrhea, fever, nausea, anorexia, jaundice, and hypersensitivity were observed during the infusion and inquired about at each of the follow-up visits. If hypersensitivity to any tested drugs was manifested, he was supposed to be excluded from this study. However, none of the study patients had developed any hypersensitivity to any allocated drugs.

Data collection methods

Data were collected from patients by principal investigator himself through direct interviews by a semi-structured questionnaire containing: i) Demographic profile, ii) Baseline and follow up assessment of VAS score, RMDQ score, patient satisfaction by Likert scale and number of days with absence from work and iii) Any adverse events. All the data were recorded in separate case record form.

Ethical statement and consent procedure

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institution (BSMMU) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. In all cases, informed written consent was ensured before participation. Ethical measures were taken throughout the study period to maintain a high standard of confidentiality and anonymity of the participants.

Statistical analysis

The collected data were analyzed using SPSS (Statistical Package for Social Sciences) for Windows, version 24.0 (SPSS Inc., Chicago, Illinois, USA). Qualitative variables were expressed as percentages. Quantitative variables are expressed as the mean ± standard deviation. In determining the differences between the three groups, one-way ANOVA was used for continuous variables, and the chi-square test was used for categorical variables. A p value of <0.05 was considered significant.

Results

Patients were randomly enrolled into three groups: Group A: zoledronic acid (ZA), Group B: antibiotics, and Group C: both ZA and antibiotics. Out of 60 patients, 17 (28%) dropped out from the study as

follows: 14 patients did not complete all 3 follow-ups (23.33%), 02 patients developed adverse effects of the drug (3.33%), and 01 patients were shown to use opioid analgesia (5%). Finally, 15 patients were included in Group A, 12 were included in Group B, and 16 were included in Group C according to per-protocol analysis.

The demographic characteristics of the studied groups are shown in **(Table I).**

Table I: Demographic characteristics of the studied groups

Variables	Group A (n=15)	Group B (n=12)	Group C (n=16)	p value
Age (Years)	52.50±6.22	49.50±8.18	50.06±9.32	
Sex				
Male	8(53.3%)	7(58.3%)	9(56.2%)	0.539**
Female	7(46.7%)	5(41.7%)	7(43.8%)	0.966*
BMI (kg/m^2)	25.4±1.26	25.15±2.33	24.70±1.06	0.70**

Values are expressed as the mean±SD, and within parentheses are percentages over column total. The p value was determined by the chi-square test* and one-way ANOVA**

The pretreatment VAS score was statistically similar between the groups (p>0.05). The VAS score gradually decreased in all 3 groups after treatment, wherein Group C patients had the significantly lowest VAS score at the 2nd and 3rd follow-ups (2.87±0.80 and 1.68±0.70, respectively) compared to Group A (3.40±0.63 and 2.20±0.67, respectively) and Group B (3.50±0.52 and 2.41±0.66, respectively). However, after the 1st follow-up, no significant difference was observed in the VAS score between the groups (p>0.05) **(Table II)**.

Table II: Pain evaluated by VAS at different time intervals among the studied groups

Time points	Group-A (n=15) Mean±SD	Group B (n=12) n (%)	Group C (n=16) n (%)	p value
Pretreatment	5.80±0.67	5.75±0.96	5.81±0.65	0.975
Post-treatment follow ups				
1st follow up (1 month)	4.53±0.51	4.41±0.66	4.0±0.73	0.066
2nd follow up (100 days)	3.40±0.63	3.50±0.52	2.87±0.80	0.036^s
3rd follow up (6 months)	2.20±0.67	2.41±0.66	1.68±0.70	0.020^s

p value was determined by one-way ANOVA. s=significant

RMDQ decreased significantly after 1 month of treatment compared to pretreatment (p<0.05) in all 3 groups, and this gradual decrement was continued until 6 months of treatment. However, it was reduced more in group C (6.26±0.70) than in group A (6.69±1.40) and group B (7.75±1.21) at the end of the 3rd follow-up **(Fig. 1)**.

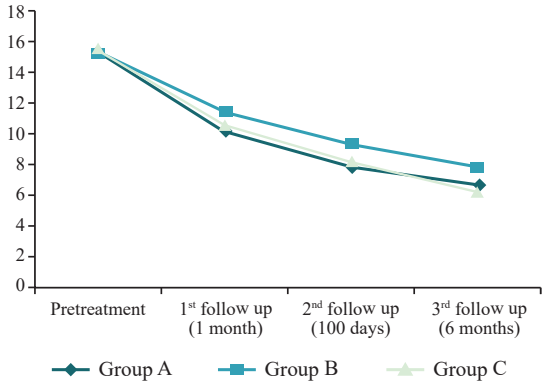

Fig. 1: RMDQ among the studied groups

Patient satisfaction measured by the Likert scale improved in all 3 studied groups but was statistically insignificant between groups after the 1st and 2nd follow-ups (p>0.05). At the end of the 3rd follow-up, Group C patients had the highest satisfaction level compared to Groups A and B (p<0.05) **(Table III)**.

Table III: Patient satisfaction evaluated by the Likert scale at different time intervals among the studied groups

Time points	Group A (n=15) Mean±SD	Group B (n=12) Mean±SD	Group C (n=16) Mean±SD	p value
Pretreatment	18.80±1.47	17.66±2.05	18.43±2.50	0.368
Post-treatment follow ups				
1st follow up (1 month)	17.46±1.88	17.36±1.58	17.30±2.16	0.888
2nd follow up (100 days)	17.36±1.88	17.33±3.65	17.23±1.54	0.362
3rd follow up (6 months)	16.80±1.65	17.06±1.03	15.56±1.36	0.031^s

p value was determined by one-way ANOVA.
s=significant

Improvement in patient pain and disability evaluated by the number of days with absence from work decreased in all studied groups after intervention. No significant difference was observed between groups

after the 1st follow-up, whereas from the 2nd follow-up to the end of 6 months, they were statistically significant ($p<0.05$). The number of days without work scores decreased more in group C than in groups A and B ($p<0.05$) **(Fig.2)**.

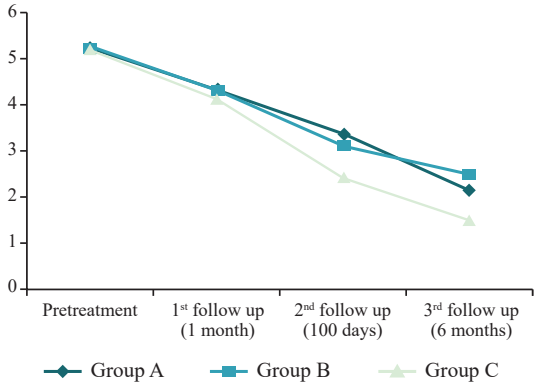

Fig. 2: Number of days with absence from work among the studied groups

Adverse effects were relatively higher in Group C than in Groups A and B, without any significant differences ($P>0.05$). The frequency of adverse effects is summarized in **Table IV.**

Table IV: Frequency of adverse effects

Adverse effects	Group A (n=15) n (%)	Group B (n=12) n (%)	Group C (n=16) n (%)	p value
Diarrhea	0(00)	2(16.7%)	3(18.7)	0.769
Fever	4(26.6%)	0(00)	3(18.7%)	0.352
Nausea	2(13.3%)	2(16.7%)	4(25%)	0.136
Anorexia	2(13.3%)	2(16.7%)	3(18.7%)	0.397
Jaundice	0(00)	1(8.3%)	1(6.25%)	0.462

p value was determined by chi-square test

Discussion

Chronic low back pain (LBP) is a common and disabling problem that has been treated with multiple treatment options. Although no specific pathologies are present, Modic changes are independent risk factors for chronic LBP, suggesting that it is an independent treatment target[32]. This study was a prospective quasi-experimental study to evaluate the effectiveness of antibiotic (amoxicillin- clavulanic acid) and bisphosphonate (Zoledronic acid, ZA) treatment in combination compared with their individual use in patients with chronic LBP associated with MRI-supported Modic changes. In this trial, the demographic characteristics of patients in all treatment groups were statistically similar in the context of age, sex and BMI ($p>0.05$). In addition, the pretreatment visual analog scale (VAS) score, disease-specific disability status by RMDQ, and number of days with absence from work were also statistically similar between groups ($p>0.05$).

The current study demonstrates that the VAS score gradually decreased in all groups after treatment, wherein the combined treatment group had the significantly lowest VAS score at the 2nd and 3rd follow-ups compared to the individual treatment groups. A previous study conducted by Cai et al. compared the effect of ZA, denosumab, and placebo and found no significant difference in the reduction of VAS among the three groups but observed statistically significant improvement in the LBP Rating Scale (RS) after 6 months of follow-up[32].

In addition, this study revealed that RMDQ decreased significantly after 1 month of treatment compared to pretreatment ($p<0.05$) in all groups, and this gradual decrement was continued until 6 months of treatment. However, it was reduced more in the combined group than in the individual groups at the end of the 3rd follow-up. Comparable to these findings, Albert HB et al. also found significant improvement in disability status after antibiotic treatment even after the end of 1 year[10]. This gradual and continuous improvement in pain relief and disability status after the end of combined treatment could be due to reduced compression of the nerve roots that occurred as a result of edema and inflammatory changes in the vertebral end plate that appeared during the process of developing Modic change. Hence, it can be assumed that the reduction in pain intensity might be because of the diminution of infectious products from the disc capable of irritating the nerve roots.

In this research project, improvement in patient pain and disability evaluated by the number of days was observed in all studied groups after intervention. However, the number of days with absence from work score was decreased more in the combined group than in the individual groups, which might have also led to the highest satisfaction level in the combined group.

Adverse effects (diarrhea, fever, nausea, anorexia and jaundice) were observed in all treatment groups but slightly more in the combined group, although without statistical significance ($p>0.05$). A similar study by Braten et al. reported fifty patients (56%) in the amoxicillin group compared with 31 (34%) in the placebo group who experienced at least one drug-related adverse event[33]. However, all of the adverse events of our study participants were managed with appropriate drugs without further deterioration. Diarrhea was treated with probiotics, and patients improved uneventfully.

The limitation is that the sample size was inadequate to demonstrate clinically relevant changes in the outcomes. However, despite the small sample size, a favorable trend in the combined treatment group was observed in reducing pain and disability in patients with chronic LBP associated with Modic change.

Conclusion

Treatment with Zoledronic acid and amoxicillin-clavulanate in combination is more effective than their individual use in reducing pain and disability in patients with chronic LBP associated with Modic change. Considering the adverse effects, it is better to use a combined treatment protocol only for patients with severe disabling LBP due to confirmatory Modic change and when symptoms are not adequately controlled with analgesics and physiotherapy. However, further larger multicenter studies are recommended to corroborate our research findings.

Declaration

Ethics approval:
Ethical approval was taken from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University.

Author contributions:
Conception and development of the idea
KD, MSI, AKMA
Data collection: *KD, MMK*
Data analysis *KD, MSI*
Writing - Original Draft Preparation *KD, MSI, MMK, DKB*
Writing – Review & Editing *KD, MMK, AKMA*

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Conflict of interests: None

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