Antibiotic Treatment in Patients with Chronic Low Back Pain and Vertebral Bone Edema (Modic Type I Changes): A Randomized Clinical Controlled Trial of Efficacy

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ABSTRACT:

BACKGROUND:

Modic type I changes/bone edema in the vertebrae are present in 6 % of the general population and 35–40 % of the low back pain population. It is strongly associated with low back pain. Chronic Low back pain (CLBP) is a leading cause of disability. It occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations.A new method of treatment included the use of antibiotic in management of CLBP with Modic type I changes has proved to be effective in some cases.

OBJECTIVE:

The aim was to test the efficacy of antibiotic treatment in patients with chronic low back pain (>6 months) and Modic type I changes (bone edema).

PATIENTS AND METHODS:

The study was a randomized clinical trial(RCT) with 71 patients whose only known illness was chronic LBP of greater than 6 months duration occurring after a previous disc herniation and who also had bone edema demonstrated as Modic type I changes in the vertebrae adjacent to the previous herniation. Patients were randomized to either 100 days of antibiotic treatment or placebo and were evaluated at baseline, and end of treatment.

Outcome measures: are the disease-specific disability Questionnaire, which is Roland Morris Disability Questionnaire (RMDQ) and lumbar pain.

RESULTS:

43 of the 71 original patients were evaluated at baseline and at end of treatment follow-up. The two groups were similar at baseline. The antibiotic group had better improvement on the outcome measures and improvement continued after end of treatment. At baseline, 100 days follow-up the means of the disease specific disability-RMDQ changed: antibiotic 15.5, 12; placebo: 15, 14.8. For Lumbar pain: antibiotics 6.4, 4.8; placebo 6.1, 6.0.

CONCLUSION:

The antibiotic protocol in this study was more effective for this group of patients (CLBP associated with Modic changes type I) than placebo in the outcomes.

KEYWORDS: modic changes, antibiotics, chronic low back pain, end plate changes.

INTRODUCTION:

Low back pain is a leading cause of disability. It occurs in similar proportions in all cultures, interferes with quality of life and work performance. [1]

Diagnosing patients with low back pain (LBP) is a challenge for clinicians[2]. It is frequently stated that only a small proportion (approximately 20%) of patients with LBP can with certainty be diagnosed based on a patho-anatomical entity [2].

The most commonly used classification, ‘‘non-specific LBP’’ (80%), is not satisfactory for the LBP patient or the clinician. Therefore, the identification and diagnosis of relevant subgroups of patients with persistent LBP, preferably with a sound patho-anatomical basis, is strongly needed [3].

In the majority of cases the backache is associated with degeneration of the intervertebral discs in the lower lumbar spine. Disc herniation is considered a complication of disc degeneration in the dysfunction and instability stages.

Bone marrow changes as a result of vertebral end plate changes have been associated with degenerative intervertebral disk disease. These changes have been classified into three types on the basis of chronicity of the degeneration (Modic changes)[4] (fig.1).

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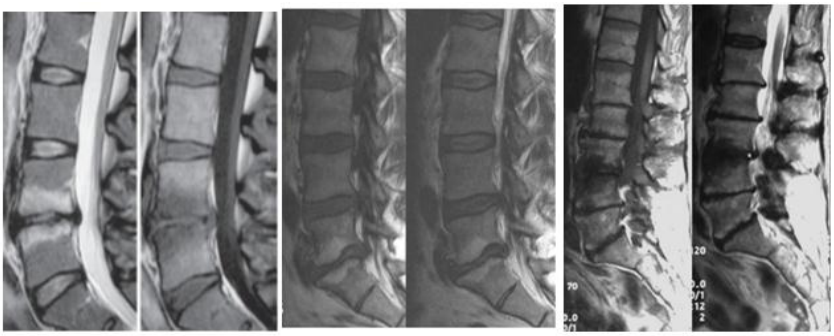

Fig 1: Modic changes.

Type I is seen on T2-weighted MRI as areas of increased signal intensity and on T1- weighted MRI as low signal intensity extending from the vertebral endplates. Type II is observed as increased signal intensity on both T1- and T2-weighted images, portraying disruption of the end plates with increased reactive bone and granulation tissue. The hematopoetic elements in the vertebrae are replaced by abundant fat (yellow marrow) [(5)]. Modic changes type III are presumably bone sclerosis and are visualized on MRI as decreased signal intensity on both T1 and T2-weighted images [(5)].

Several studies on nuclear tissue from herniated discs have demonstrated the presence of low virulent anaerobic microorganisms, predominantly Propionibacterium acnes, in 7–53 % of patients. [(6-10)]

When an intervertebral disc is degenerated or herniated, nuclear material extrudes into the spinal canal. Within a short time, neocapillarisation begins in and around the extruded nucleus material [(11)] and inflammation occurs with an increased presence of macrophages. As the avascular anaerobic disc provides an ideal environment for anaerobic bacteria, it is plausible that these low virulent anaerobic bacteria may enter the disc and give rise to a slowly developing infection.

So, Infection is one of the hypothetical causes of the bone edema underlying Modic type I changes [(12)].

Two recent published studies confirm that the antibiotic protocol {Modic antibiotic spine therapy (MAST)} was significantly more effective for those group of patients (CLBP associated with Modic I) than placebo in all the primary and secondary outcomes [(13, 14)].

PATIENTS AND METHODS:

This study involved a randomized clinical controlled trail of patients having CLBP and vertebral bone edema (Modic changes type I), and was conducted at orthopedic department of the medical city of Baghdad and the participants were recruited from the orthopedic consultation clinic. The inclusion criteria were : age between 18 and 65 years, MRI confirmed Modic changes type I adjacent to the previously disc herniation at L2/L3, L3/L4, L4/L5 or L5/S1 within the preceding 6–24 months, lower back pain of more than 6 months duration.

Patients also had to have LBP in the area from L1 to L5 with a Numerical Pain Rating Scale score of 5 or more after adding the current LBP (0–10); the mean LBP during the last 2 weeks (0–10) and worst LBP during the last 2 weeks (0–10) and then dividing by three. The exclusion criteria were: allergy to antibiotics, current pregnancy or lactation, or planned to be pregnant, any kidney disease, and radiculopathy. We started collecting patients and randomization was performed into the antibiotic treated group (MAST protocol) and placebo group.

Placebo tablets were Calcium Carbonate tab. (Calcid tab.500mg), and for the antibiotic group, the antibiotic of choice was amoxicillin–clavulanate. This drug is known to be able to penetrate into the discs [(15)].Therefore; treatment consisted of amoxicillin–clavulanate (500 mg/125 mg) (Gloclav) tablets two times a day, for 100 days. There was a trend towards a dose–response relationship, with double dose antibiotics being more efficacious. During their 3-month participation in this trial patients were not provided with any other treatment except mild analgesics (paracetamol), if required. At

both baseline and at end of treatment follow-up each participant underwent a physical examination and completed self-reported questionnaires. Also, MRI and blood samples were also taken (complete blood picture and ESR) at baseline.

The participants were 71 patients; randomization was performed into two groups. Forty two patients were participated in antibiotic group and 29 patients in placebo group.

All patients were followed up at orthopedic consultation clinic of Baghdad medical city on regularly weekly visits at their first two weeks of treatment and then monthly visits. During each visit, the patients checked up for taking medicine, any side effects of medicine, routine physical examination of the back, and any improvement reported by the patient.

Outcome measures: The outcome measures were disease-specific disability Roland Morris Questionnaire [16] (RMDQ) and lumbar pain [17] (LBP Rating Scale).A clinically important change was defined as a 30 % reduction of the individual's baseline score and 2 LBP rating scale points [17].

All patients were instructed to use the medicine regularly and instructed to mention any concomitant administration of drugs other than the prescribed drug whether by their own or have been prescribed by other doctors. All data were analysed using SPSS. V. 20 statistical program. The study flow chart is shown in (Fig.2).

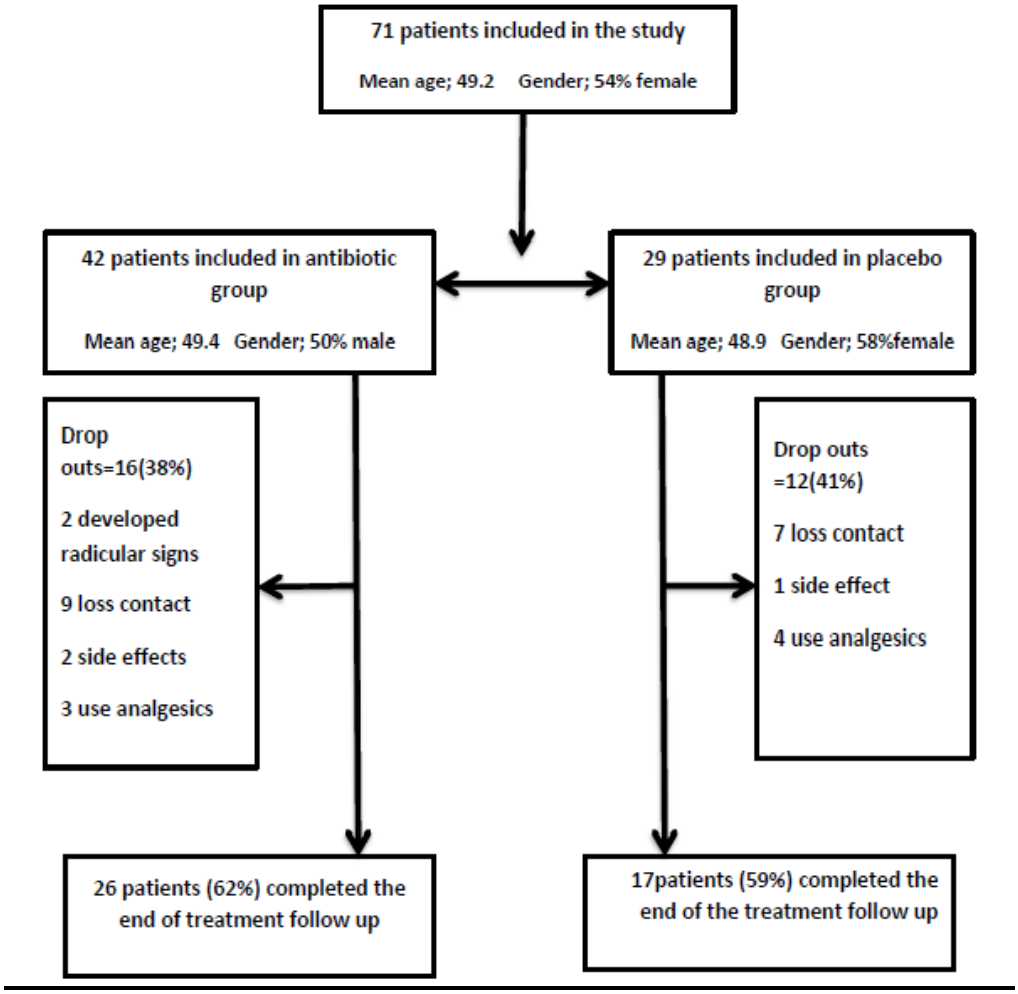

Fig.2: The study flow chart.

RESULTS:

All baseline variables were equally distributed in the placebo and antibiotic groups. There were no significant differences in age and gender between the participants and those lost to follow-up; however, there were significantly more young employees amongst those lost to follow-up.

Of the 71 patients that entered the study, 43patients (60%) completed the end of treatment questionnaires.

The antibiotic treated group: 42 patients were included, 16 patients of them were drop out as follow:

- 9 patients not show on follow up or end of treatment (21%).
- 2 patients developed adverse effects of the drug (4%).
- 2 patient developed radicular signs (4%).
- 3 patients shown to use strong additive analgesia (7%).

The placebo group: 29 patients were included, 12 patients of them were drop out as follow:

- 7 patients not show on follow up and end of treatment (24%).
- 4 patients shown to use strong additive analgesia (13%).
- 1 patient adverse effect (3%).

Mean age of the participants was 49.2 year and females were 54% of them. There were no significant differences in age and gender between the two groups.

The antibiotic group improved on all outcome measures. In comparison to the placebo group, the improvement was both statistically different on all outcome measures and clinically important in terms of the relative magnitude of improvement. There were no differences between the groups in the blood tests at baseline or follow-up.

Patients reported that pain relief and improvement in disability commenced gradually, for most patients 6–8 weeks after start of the antibiotic tablets and for some at the end of the treatment period and most patients reported continuing improvement after end of treatment.

From the 26 patients treated with MAST, 10 patients (approximately 38% of patients) had more than 30% improvement, and 2 score reduction in LBP rating scale. The other 16(approximately 62%) patients had shown between 12%to30% improvements in ROMQ, and 1 to 2 score reduction in LBP rating scale.

Patients received placebo treatment experienced no or minimal improvement. From the 17 patients with placebo treatment, 4 patients (approximately 23% of patients) have got 6% to13 % improvements on RMDQ, 3 patients have got 6% worsening. Two (11%) patients have got 1 score reduction in LBP rating score. Other patients reported no any improvement.

Results are summarized in **(tables 1- 4),** and **(figures 3** and **4)**.

The overall improvement in antibiotic group patients was about 22% on RMDQ, and 1.57 reductions in LBP numerical pain score.

The clinically and statically significant improvement occurred in 10 patients (38%) of the 26 patients in antibiotic group, (*P value=0.001*).

While in placebo group, there was neither clinically nor statically significant improvement, the only4 patients who got improvement, their improvement ranges from 6%-13% only! (*P value =0.5*).

Table1: Outcome Measures at Baseline and end of Treatment (AB=Antibiotic Group, Q=RMDQ, P=Numerical Pain Rating Score, C=Control Group, Post=Post Treatment).

Group		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	BaselineABQ	15.5000	26	1.65529	.32463
	post AB. Q	12.0385	26	1.92833	.37818
Pair 2	BaselineAB.P	6.4231	26	.90213	.17692
	post AB .P	4.8462	26	.83390	.16354
Pair 3	Baseline C.Q	15.0000	17	1.69558	.41124
	post C.Q	14.8235	17	1.46779	.35599
Pair 4	Baseline C.P	6.1176	17	.85749	.20797
	post C.P	6.0000	17	.79057	.19174

Groups	variables

Table2: Differences in

		Mean	Std. Deviation
Pair 1	Baseline AB .Q – post AB. Q	3.46154	1.44861
Pair 2	Baseline AB.P – post AB .P	1.57692	.57779
Pair 3	Baseline C.Q – post C.Q	.17647	.88284
Pair 4	Baseline C.P – post C.P	.11765	.33211

Improvement between the Two Groups at Baseline and End of Treatment (AB=antibiotic group, Q=RMDQ, P=numerical pain rating score, C=control group, post=post treatment).

Table3: Descriptive Data of RMDQ in the Two Groups at Both Baseline and End of Treatment (AB=antibiotic group, Q=RMDQ, C=control group, post=post treatment).

Descriptive Statistics					
group	N	Minimum	Maximum	Mean	Std. Deviation
baselineAB.Q	26	12.00	18.00	15.5000	1.65529
postAB.Q	26	8.00	15.00	12.0385	1.92833
baselineC.Q	17	12.00	18.00	15.0000	1.69558

Table4: Descriptive Data of LBP in the Two Groups at Both Baseline and End of Treatment

Descriptive Statistics					
group	N	Minimum	Maximum	Mean	Std. Deviation
BaselineAB.P	26	5.00	8.00	6.4231	.90213
PostAB.P	26	3.00	7.00	4.8462	.83390
BaselineC.P	17	5.00	8.00	6.1176	.85749
Post placebo.P	17	5.00	7.00	6.0000	.79057

(AB=antibiotic group, P=LBP score, C=control group, post=post treatment)

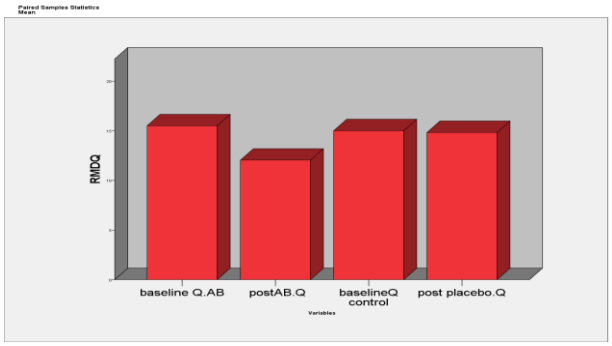

Fig.3: RMDQ Score Distribution in Antibiotic and Placebo Groups at Baseline and End of Treatment. (Q=RMDQ, AB=antibiotic group).

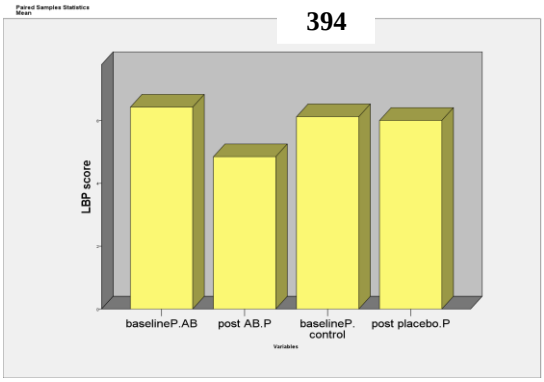

Fig.4: LBP Rate Score Distribution in Antibiotic and Placebo Groups at Baseline and End of Treatment. (P=numerical pain rating score, AB=antibiotic group).

Unintended effects: Adverse events were more common in the antibiotic group (60 % of participants) compared to the placebo group (6%). These were mainly low-grade gastroenterological complaints such as loose bowel movements, increased flatus or infrequent attacks of abdominal colic. Considerable side effects in 4 and 3 %, respectively.

DISCUSSION:

Most LBP episodes are diagnostically classified as 'non-specific LBP' and this remains a source of frustration for patients [18] trying to understand their problem and uncertainty for clinicians developing treatment plans. A positive association between MC (bone oedema) and non-specific LBP was found in 70 % of studies with odds ratios ranging from 2.0 to 19.9 [(19)].

Several recent studies supporting the theory that the occurrence of MCs Type I in the vertebrae adjacent to a previously herniated disc might be due to oedema surrounding an infected disc. The sole microorganism identified to cause this infection was the bacterium P. acnes) [(6)].

This RCT investigating the efficacy of Modic antibiotic spine therapy (MAST) for CLBP patients with Modic type I changes in the adjacent vertebral endplates, demonstrated statistically and clinically significant improvements in the outcome measures in about 38%of patients while patients receiving placebo treatment experienced no or minimal improvement. Perhaps most encouraging for further work in this area has been the finding that the improvements obtained with the current MAST protocol, in this group of traditionally resistant chronic low back pain patients, has been substantially greater than those described with all other established conservative treatments [(20)].

Factors which may contribute to the outcome results like; life style, smoking, chronic diseases (DM, renal failure, etc.) and body built, should be studied and this will further clarify this subgroup of patients of CLBP and actually we think that these factors may contribute to the variation of improvement in antibiotic group, and also in the placebo group.

As most patients reported that pain relief and improvement in disability commenced gradually and continuing improvement after end of treatment, this could be interpreted as reflecting a biological healing process that starts only when and after the bacteria have been killed.

The predominance of P. acnes might reflect the unusual environment in the disc where the lack of vascularity results in a very low oxygen tension and a low pH which provides ideal conditions for low virulent anaerobic bacteria to grow. Proprionibacterium acnes bacteria secrete propionic acid, which has the capacity to dissolve fatty bone marrow and bone. Diffusion of propionic acid from the disc into the vertebrae may cause the Modic changes. Similarly, as

increased TNF-alfa and the growth of PGP-5 unmyelinated nerve fibers have been reported in Type I Modic changes [21], with the inherent slowness of these pathological processes perhaps explaining the delayed onset of improvement observed in this study. Explanations for this pain reduction include: an amelioration of somatic pain referred from the disc or a diminution of infectious by products from the disc capable of irritating the nerve endings.

The placebo group demonstrated minimal or no improvement on the outcome measures in this trial. This reinforces the clinical impression, gained from years of working with CLBP patients with Modic changes that 'Modic pain' is difficult to treat effectively with conservative treatment methods not including the antibiotics [22].

With wide range of antibiotic susceptibility of P.acne, many antibiotics have an anti-inflammatory effect, via TNFa-inhibition. However, amoxicillin–clavulanate has been shown to have a very small anti-inflammatory effect comparable to other antibiotics[23,24] and only an inhibitory effect on IL-1 and IL-8, not TNFa which is present in the Modic changes. This was an additional reason for the selection of amoxicillin–clavulanate (Gloclav) in this study. Normally, anti-inflammatory effects are rapid quite fast-acting, whereas in this study the effect took 6–8 weeks to manifest, more consistent with the clinical course of resolving infection in poorly vascularized infected tissue, i.e., an antibiotic effect.

At our three months follow-up, 26% of the patients in the antibiotic group had consulted a doctor for back pain compared to53 % in the placebo group. This likely indicates that the placebo group was less satisfied with their result and therefore sought additional help, in addition ,13%(4patients) from placebo group(29patients) were shown to use strong additive analgesics compared to 7%(3patients) in the antibiotic group(42patients).

For practical reasons, the patients should not have MRI shortly before 1-year follow-up. This is because that the time span taken for Modic changes to develop, although uncertain, is in years. So, we did not do follow –up MRI as nothing was expected to change at three months after the treatment. Ideally follow-up MRI evaluation should be carried out at a much later date (after one year).

Although we did not include those patients with radicular signs or those being surgical candidate, the original studies reported its efficacy in patients following lumbar disc herniation, with and without surgery. More confirmatory work in other populations, for example, Modic type 2 changes, is needed.

CONCLUSION:

Antibiotics could be considered as a treatment option for this special subgroup of patients with CLBP and Modic type I changes after a lumbar disc herniation when all other treatment options have failed. As 38% of the patients in the antibiotic group obtained statistically significant improvements compared to the placebo group; this actually may need further study and evaluation for refinement this subgroup of patients, to define further criteria of those patients who may get benefit of this protocol, this may include the diagnostic tests for presence of bacteria, radiological finding and even the history and clinical examination.

We will continue following up our patients as some patients reported continuing improvement after the end of treatment and this will include MRI studies also to evaluate their Modic course of changes as well as their clinical improvement.

Recommendations:

We recommend that the study need to be expanded to include those patients whose are surgical candidate to investigate the presence and prevalence of infected herniated nucleus material in lumbar disc herniations with Modic changes type I, by collecting biopsies from them to confirm our results and to move into new era in diagnosis and treatment of those subgroup of CLBP patients.

Also we recommend including larger number of patients and following up them for longer than one year clinically and radiographically by MRI for Moding course of changes and studying other variables like life style, history of smoking, and history of chronic diseases for their effects in outcome results.

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