Antibiotic treatment in patients with low-back pain associated with Modic changes Type 1 (bone oedema): a pilot study

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ABSTRACT

Objective: The aim of this study was to assess the clinical effect of antibiotic treatment in a cohort of patients with low-back pain (LBP) and Modic changes Type 1 (bone oedema) following a lumbar herniated disc.

Design: This was a prospective uncontrolled trial of 32 LBP patients who had Modic changes and were treated with Amoxicillin-clavulanate (500 mg/125 mg) 3 × day for 90 days. All patients had previously participated in a randomised controlled trial (RCT) that investigated active conservative treatment for a lumbar herniated disc (n = 166). All patients in that RCT who had Modic changes and LBP at 14 months follow-up (n = 37) were invited to participate in this subsequent antibiotic trial but five did not meet the inclusion criteria.

Results: 29 patients completed the treatment, as three patients dropped out due to severe diarrhoea. At the end of treatment and at long-term follow-up (mean 10.8 months) there was both clinically important and statistically significant (p < 0.001) improvement in all outcome measures: LBP intensity, number of days with pain, disease-specific and patient-specific function, and global perceived effect.

Conclusions: In this uncontrolled trial, the clinical effect of antibiotic treatment was large in a group of patients with Modic changes suffering from persistent LBP. These results provide tentative support for a hypothesis that bacterial infection may play a role in LBP with Modic changes and indicate the need for randomised controlled trials to test this hypothesis.

Modic changes (bone oedema) in vertebrae are an imaging finding recently identified as a prevalent pathoanatomical finding that is commonly associated with low-back pain (LBP).1 2 Modic changes are only visible on magnetic resonance images (MRI)3 and three subtypes have been identified (Types 1 to 3). From histological studies of material harvested during surgery, Modic changes Type 1 involve disruption and fissuring of the endplate with regions of degeneration, regeneration, reactive bone formation, endplate oedema and vascular granulation tissue.3 4 Type 1 are 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.

There is an association between Modic changes and LBP.1 2 A recent systematic review of Modic changes and LBP identified 77 study samples from the general, working, and clinical populations. The median prevalence rate for any type of Modic change was 46% in patients with non-specific LBP and 6% in non-clinical populations. A positive association between Modic changes and non-specific LBP was found in 70% of studies with odds ratios ranging from 2.0 to 19.9.5

Infection is one hypothetical cause of Modic changes Type 1.6 Both Van Goethem et al7 and Modic et al8 showed that vertebral endplate signal changes resembling Modic changes Type 1 were a sensitive indicator for spondylodiscitis or disc space infection. Caragea9 observed that about one-third of patients with pyogenic vertebral osteomyelitis were infected with low-virulent bacteria. When antibiotics were given, the majority recovered and became pain- and symptom-free. Similarly, in nuclear tissue removed under sterile conditions during surgery for lumbar herniated discs, 53% of patients were found to be infected with low-virulent anaerobic organisms (Propionibacterium acnes and Corynebacterium propionicum) in contrast to no patients who were operated on for other spinal disorders.10 Stirling et al10 11 therefore, hypothesised that patients with sciatica sustain a breach in the mechanical integrity of the spinal disc, possibly from minor trauma, which allows access by low-virulent microorganisms.10

The aim of this pilot study was to test antibiotic treatment in a group of patients with Modic changes Type 1 and LBP following herniation of a lumbar disc.

MATERIALS AND METHODS

This was a prospective uncontrolled trial of LBP patients who had Modic changes Type 1 (bone oedema). All patients had previously participated in a randomised controlled trial (RCT) comparing two types of active conservative treatment for a lumbar herniated disc (n = 166).12 All patients in the RCT received a MRI scan at the 14 month follow-up. Patients were invited to participate in the current trial if their follow-up MRI displayed Modic changes Type 1 in a vertebra adjacent to their previous herniated disc and they had LBP at the time of this follow-up examination. Patients were excluded if they had an allergy to antibiotics, had a current infection or declined participation in the antibiotic trial.

Treatment consisted of Amoxicillin-clavulanate (500 mg/125 mg) (Spektramox) three times a day, at 8 hour intervals, for 90 days. Three independent experts in infectious diseases were presented with the bacterial culture results in Stirling’s10 study and requested to suggest the ideal antibiotic. All experts recommended Amoxicillin-clavulanate. Treatment was for 90 days as this is the usual duration of antibiotic treatment for...
postoperative discitis. During the treatment and follow-up period of this antibiotic trial, the patients received no other treatment except optional mild analgesics.

Outcome measures
All patients had a clinical examination and filled in questionnaires at baseline, at end of treatment and at a follow-up approximately 11 months later. Serum analysis was performed at baseline and at the end of treatment.

The outcome measures were: Global perceived effect, Roland Morris Questionnaire (RMQ),\(^2\) the Self-Perceived Function Scale, days with LBP, the LBP Rating Scale\(^7\) and serum analysis (table 1).

Statistics
To test for differences between baseline, end of treatment and the long-term follow-up measures, Wilcoxon signed-rank tests were performed (p<0.05) using SPSS version 13.0 (SPSS, Chicago, Illinois, USA).

Ethics
The study was approved by The Danish Medicine Agency and The Regional Scientific Ethical Committee no. VE20030212, and written informed consent was obtained from all participants prior to participation.

RESULTS
Of the 166 patients in the previous RCT, 87 met the inclusion criteria for the current antibiotic trial (a further six patients had Modic changes but no LBP at 14 months review). The distribution of patients from the two treatment groups in the previous RCT was similar (16% and 18%). Five patients were excluded from the current antibiotic trial, due to: not wanting to take antibiotics for such a long period (n = 3), spontaneous recovery in the waiting period before the study started (n = 1), and loss of contact (n = 1). Therefore, 32 patients enrolled in the study but three dropped out due to severe diarrhoea, leaving 29 patients who completed the antibiotic treatment regime.

Of the 29 patients who completed the antibiotic treatment, 10 (34%) were female, mean age 45.7 (SD 11.1) years and 19 (66%) were male, mean age 47.7 (8.2) years. The original disc lesions were as follows: four (14%) patients had a bulge, 12 (41%) a focal protrusion, five (17%) a broad-based protrusion, seven (24%) an extrusion, and one (3%) a sequestrated disc, according to the Fardon and Milette nomenclature.\(^1\)

The outcome measures at baseline, at end of treatment, and at follow-up are described in table 2.

All outcome measures (disease-specific function, patient-specific function, global perceived health, and LBP) showed statistically significant improvements both at the end of the treatment period and at the long-term follow-up. Using the measure of global perceived health, at the end of treatment, 15 (52%) of the patients reported that they were much better or cured, seven (24%) were moderately better, and seven (24%) reported they were unchanged. None experienced a worsening of symptoms.

The patients’ improvement of disease-specific function was measured using the Roland Morris Questionnaire (RMQ). A reduction in RMQ score is regarded as clinically important if it exceeds 30% of the patient’s original score.\(^1\) In our cohort, approximately two-thirds of the patients reduced their RMQ scores more than 30% (table 3). Furthermore, a 30% reduction in the average baseline RMQ score of this cohort would have been 2.6 RMQ points and the observed average reduction of 3.1 RMQ points exceeded that estimate.

Table 1  Outcome measures

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline</th>
<th>End of treatment</th>
<th>Follow-up</th>
<th>Significant difference between baseline and long-term follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient-specific function scale (n = 28)</td>
<td>14</td>
<td>21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scale 0–30 (30 is best)</td>
<td>10.5–18.5</td>
<td>17.5–24.5</td>
<td>13–25</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Days with low-back pain during the last 100 days (n = 27)</td>
<td>100</td>
<td>35</td>
<td>20</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Scale 0–100 (0 is best)</td>
<td>25–100</td>
<td>7–35</td>
<td>10–84</td>
<td></td>
</tr>
<tr>
<td>low-back pain (n = 29)</td>
<td>9</td>
<td>5</td>
<td>5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Scale 0–30 (0 is best)</td>
<td>6–15</td>
<td>1.5–9.5</td>
<td>2.5–12</td>
<td></td>
</tr>
<tr>
<td>Roland Morris Questionnaire (n = 29)</td>
<td>8</td>
<td>4</td>
<td>5</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Scale 0–23 (0 is best)</td>
<td>4.5–13.5</td>
<td>0.5–9</td>
<td>1–10</td>
<td></td>
</tr>
</tbody>
</table>

The median scores at baseline, at end of treatment, and at long-term follow-up on average 10.8 months after end of treatment are presented (median and 25th and 75th percentiles).

Table 2  The scores of the outcome measures; level of LPB, days with LBP, and physical function

<table>
<thead>
<tr>
<th>Variable</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinically improved</td>
<td>Unchanged</td>
<td>Clinically worse</td>
<td></td>
</tr>
<tr>
<td>on RMQ, or a value of 0</td>
<td>Between 30% improvement and 30% worsening on RMQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>After end of treatment</td>
<td>18 (62%)</td>
<td>10 (34.5%)</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td>Long-term follow-up</td>
<td>18 (62%)</td>
<td>9 (31%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

Table 3  The percentage of patients whose Roland Morris Questionnaire (RMQ) scores were clinically improved, unchanged or worse

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The clinical importance of this improvement in function is reinforced by the observation that, prior to commencement of antibiotic treatment, the RMQ scores of people in this cohort were worsening over time. Modic changes were first observed in participants when they were reviewed at the 14 month follow-up of the previous RCT. At this time the patients had a mean RMQ of 5.3. Patients then waited for varying time periods for the commencement of the current antibiotic study. The mean waiting period was 9 months and during this period the average functional level measured on this scale worsened from a mean of 5.3 to 8.9. However, the mean functional level at the end of the antibiotic treatment and at long-term follow-up showed both clinically important and statistically significant improvement (fig 1).

The serum analysis revealed that only a few patients exceeded the reference values, indicating that no aggressive infection was present. There were only modest changes from baseline to the end of treatment. Unfortunately, during the study period the laboratory changed the methods of analysis for lactate dehydrogenase and also alkaline phosphatase; therefore values of the first method are presented for the respective number of patients, likewise with the second method (table 4).

Table 4 The serum analyses at baseline and end of treatment

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference values</th>
<th>Mean baseline value</th>
<th>No. of patients exceeding reference values (total n = 29)</th>
<th>Mean values at end of treatment</th>
<th>No. of patients exceeding reference values (total n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin</td>
<td>8.0–11.0 mmol/l</td>
<td>9.4</td>
<td>0</td>
<td>9.1</td>
<td>2</td>
</tr>
<tr>
<td>Leucocytes</td>
<td>3.0–10.0 x 10^9/l</td>
<td>6.7</td>
<td>1</td>
<td>7.1</td>
<td>3</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.5–7.5 x 10^9/l</td>
<td>4.1</td>
<td>0</td>
<td>4.2</td>
<td>1</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.04–0.5 x 10^9/l</td>
<td>0.2</td>
<td>0</td>
<td>0.22</td>
<td>1</td>
</tr>
<tr>
<td>Basophils</td>
<td>&lt;0.2 x 10^9/l</td>
<td>0.03</td>
<td>0</td>
<td>0.03</td>
<td>1</td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.0–3.5 x 10^9/l</td>
<td>2.0</td>
<td>0</td>
<td>2.22</td>
<td>2</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.2–0.8 x 10^9/l</td>
<td>0.6</td>
<td>3</td>
<td>0.59</td>
<td>1</td>
</tr>
<tr>
<td>P/S Creatininium</td>
<td>62–134 μmol/l</td>
<td>90</td>
<td>0</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>Lactate dehydrogenase, original 'method (n = 13)</td>
<td>150–500 U/l</td>
<td>372</td>
<td>0</td>
<td>393</td>
<td>0</td>
</tr>
<tr>
<td>Lactate dehydrogenase, new method (n = 16)</td>
<td>105–205 U/l</td>
<td>214</td>
<td>7</td>
<td>227</td>
<td>8</td>
</tr>
<tr>
<td>Alkaline phosphatase, original method (n = 13)</td>
<td>80–275 U/l</td>
<td>194</td>
<td>0</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>Alkaline phosphatase, new method (n = 16)</td>
<td>35–105 U/l</td>
<td>82</td>
<td>3</td>
<td>73</td>
<td>2</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>&lt;10 mg/l</td>
<td></td>
<td>5</td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

DISCUSSION

Modic changes (bone oedema) observed on MRI are associated with LBP, but the pathogenesis of Modic changes remains unclear. Both mechanical stress and infection secondary to disc herniation have been hypothesised as pathological pathways. In this pilot study of the infection hypothesis, antibiotic treatment appeared to be effective in patients with LBP and Modic changes Type 1. We included patients whose only known illness was a previous disc herniation with present Modic changes and LBP. Patients’ health status improved on all outcome measures: global perceived health, disease-specific and patient-specific disability, pain in the lumbar area and number of days with pain.

It is often reported that LBP fluctuates, and, by nature, patients normally seek medical assistance when the pain is at its worst. Therefore, the positive results observed in many cohort studies may be due to spontaneous recovery and/or regression towards the mean. In order to minimise this, we only recruited patients at a prescheduled follow-up examination 14 months after experiencing a herniated lumbar disc. No patients were recruited when seeking medical assistance for an acute episode of LBP.
where they do not present any health risks due to the aerobic 
the circulatory system (for example during tooth brushing),
other spinal disorders. These bacteria are found in all individuals
contrast to none of those patients who underwent surgery for
Propionibacterium acnes
(7) outcomes observed in this study.
end plates.8 They were treated with antibiotics for 4 weeks and
1984 with suspected infection in the disc and in the vertebral
scarce. A few longitudinal studies241 71 9 describe over a period
improvement after antibiotic treatment would suggest sponta-
native recovery. Furthermore, the observation that, on
average, patients experienced a worsening of their condition
during the 9 months observation period but demonstrated
exacerbation of their condition, and all patients were observed
example, in individuals with a prosthetic device.
Modic changes may result from a low-
virulent bacterial infection.6 Modic identified five patients in
1984 with suspected infection in the disc and in the vertebral
plates.5 They were treated with antibiotics for 4 weeks and
rescanned. A change in the signal in the central area within the
disc was observed suggesting healing and degeneration. Stirling
et al19 cultured nuclear tissue removed under sterile conditions
during surgery for lumbar herniated discs. Of these, 55% were
infected with low-virulent anaerobic organisms (Propionibacterium acnes and Corynebacterium propinquum) in
contrast to none of those patients who underwent surgery for
other spinal disorders. These bacteria are found in all individuals
on their skin and in their oral cavities. They frequently invade
the circulatory system (for example during tooth brushing),
where they do not present any health risks due to the aerobic
environment in the bloodstream.20–23 They can, however, impose
a health risk in patients with a special environment, for
example, in individuals with a prosthetic device.
In a herniated disc, nuclear material may migrate into the
spinal canal. Within a short time, new capillarisation takes place
and around the extruded nuclear material24–27 and inflamma-
ton occurs with an increased presence of macrophages.26–29 In
this particular environment we hypothesise that anaerobic bacteria may enter the disc, resulting in a low-virulent and
slowly developing infection. As intervertebral discs are avascu-
lar, they are an ideal environment for the growth of anaerobic
bacteria and local inflammation in adjacent bone may result due
production of cytokines. Due to the low virulence of these
bacteria, tissue reactions are slow and therefore poorly
illuminated on MRI. Also, the infection will not spread to
aerobic tissues, which may explain why Modic changes are
usually observed in close proximity to the site of a disc
herniation. Adding credibility to this pathoanatomical model is
the observation that patients with a normal disc contour do not
develop Modic changes and that larger disc lesions result in
more frequent Modic changes.5

Many antibiotics, especially tetracycline derivatives, have an
anti-inflammatory effect, via TNFα inhibition, and are therefore
able to reduce pain. The positive effect observed in the current
trial could be attributed to the anti-inflammatory effect rather
than to an antibiotic effect. However, Amoxicillin-clavulunate
(Spektramox) was chosen in part due to its extremely low anti-
inflammatory effect29 30 and therefore we believe that the
antibiotic effect is more likely to be responsible for the positive
outcomes observed in this study.

We acknowledge that bacteria may not be the only cause
of Modic changes, and that Modic changes may be the end stage of
a number of pathological pathways. For example, in some cases
there may be a biomechanical aspect, where a degenerated disc
with diminished resistance to shear forces may result in Modic
changes. However, the results of the current study tentatively
suggest that antibiotic treatment could benefit some patients
suffering from LBP and Modic changes. Clearly, this study is an
observation of a highly selected patient group, and these results
need to be tested in randomised controlled trials using
antibiotics and placebo treatment. Further insight could be
 gained from biopsy studies of discs to identify any bacteria
associated with Modic changes and provide greater precision in
determining ideal antibiotic treatment.

Competing interests: None.

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