COMPARATIVE EFFICACY AND SAFETY OF METHOCARBAMOL AND THIOCOLCHICOSIDE IN ACUTE LOW BACK PAIN.

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ABSTRACT

Purpose To evaluate the efficacy and safety of either oral methocarbamol or thiocolchicoside in combination with paracetamol in acute low back pain associated with muscle spasm. Methods: Study Design: Prospective, randomized, single blind, single centre comparative study. 201 patients were randomized to receive either a methocarbamol 500 mg p.o. thrice daily (group M) or a thiocolchicoside 8 mg p.o. twice daily (group T) with paracetamol 650 mg p.o. twice daily for 7 days. Outcome was evaluated primarily by visual analogue scale (VAS) and secondarily by hand-to-floor distance, visual and palpable muscle spasm and Oswestry disability index (ODI) at baseline visit, day 3, and 7 and based on patients’ global evaluation. Adverse effects were monitored. Results: The pain intensity, as measured by VAS, showed significant reduction of pain in both groups on day 3, and 7 but improvement was better in group M as compared to group T (p<0.0001). Hand-to-floor distance and muscle spasm decreased significantly (p<0.005 for HFD, p<0.006 for visible and p<0.0001 for palpable spasm) on day 7 in group M as compared to group T. Mean % ODI scores improved significantly on both day 3 and 7 (p<0.0001) in group M as compared to group T. Patients’ global evaluation showed 80% of patients in group M evaluated the treatment as very good. Both treatments were well tolerated and group T had more adverse effects, the most common being diarrhea. Conclusion: It is concluded that either methocarbamol or thiocolchicoside in combination with paracetamol are effective in acute LBP with spasm. Methocarbamol is...
superior in efficacy as well as safety. **Running Title:** Methocarbamol / Thiocolchicoside in acute LBP

**Key words:** Acute / Low back pain / Muscle spasm / Muscle relaxant / Methocarbamol / Thiocolchicoside.

**INTRODUCTION**

Low Back Pain (LBP) is one of the common presenting complaints in general, orthopedic and Spine outpatient centers. Its prevalence ranges from 8% to 37% with peak prevalence between 45 to 60 years [1, 2]. Epidemiologic studies indicate that 60-80% of the population in industrialized countries will experience LBP at some stage in their lives and this is with the most common cause of absenteeism [2, 3]. Muscle spasm is a typical feature of LBP due to the/a reflex phenomenon which originates from the irritated deep structures like muscles, ligaments, tendons, disc protrusion and/or nerve irritation. It disturbs normal function and thereby physical mobility [4, 5, 6].

Acute back pain occurs with or without radiation to the legs. The most common causes of LBP vary from Lumbar Strain, Trauma, Degenerative spondylitis, Lysis/ Listhesis, Prolapsed disc, Osteoporosis, Osteomalacia, Infection/ Tumors, Ankylosing, Spondylosis etc.[7]. Most episodes of back pain and spasm are self limiting and 90% recover within one month[8]. Returning to normal ADL (activities of daily living) as soon as possible and maintaining the psychometric performance during the recovery period is important in terms of quality of life and economical aspects of the problem [4, 5, 9].

The most commonly used medications for the treatment of LBP include analgesics paracetamol, acetyl salicylic acid, and other NSAIDs [10]. Muscle relaxants are also effective in limiting the ensuing disability [11]. The most commonly used muscle relaxants have sedative like effects [9]. However, Thiocolchicoside [6, 9] and methocarbamol [12] are effective muscle relaxants with no or little sedative effect.

Thiocolchicoside, a semi-synthetic derivative of colchicoside derived from a naturally occurring glycoside present in the plant *Gloriosa superba*. Animal studies show strong affinity for the inhibitory GABA A and strychnine sensitive glycine receptor and it produces muscle relaxation without any subjective and objective sedative side-effects. The
experimental models also found that thiocolchicoside possesses analgesic and anti-inflammatory activities [13, 14].

Pharmacological studies conducted on methocarbamol demonstrated its main locus of action to be at the internuncial neurons of the spinal cord and that it exerted muscle relaxation by depression of the multisynaptic pathways in the spinal cord [15].

There is sufficient evidence to suggest the efficacy of only paracetamol in acute LBP [16]. Our hypothesis is that, combining low dose paracetamol (analgesic) with either methocarbamol or thiocolchicoside (muscle relaxant) may act synergistically via a different mode of action to improve LBP with spasm with lesser side effects. The purpose of the study was to evaluate the efficacy and safety of our hypothesis.

MATERIALS AND METHODS

Study design

This was a prospective, randomized, single blind, single centre comparative study designed to assess the efficacy and safety of oral methocarbamol as compared to oral thiocolchicoside. The protocol was approved by the institutional Human ethical committee.

Inclusion criteria: (1) Age ≥ 18 and less than 65. (2) Patients of LBP associated with muscle spasm. (3) Patients with signs and symptoms of muscle spasm of the lumbar region. (4) The existence of LBP equal to or greater than 5 mm on VAS.

Exclusion criteria: (1) Pregnant and nursing women. (2) Patient/s with inadequate follow-up. (4) Presence of any psychiatric or mental disorder which may prevent the patient from following the study protocol. (5) Patients with severe gastrointestinal disorders. (6) Patients with a history of Alcohol or substance abuse.

Study drug (Treatment protocol).

Patients were randomized into two treatment groups. Patients in group M are given methocarbamol 500 mg thrice daily and paracetamol 650 mg thrice daily for 7 days. Patients in group T are given thiocolchicoside 8 mg twice daily and Paracetamol 650 mg thrice daily for 7 days. All the patients were seen as outpatients. After the baseline evaluation, those patients fulfilling all the criteria were sent for the laboratory investigation (CBC, SGPT and serum creatinine) on the same day.
Outcome measures
Three follow-ups were done during the study period: at the beginning, on day 3 and on day 7. The primary outcome measure was the degree of improvement in the intensity of LBP between days 0 and 3 and between days 3 and 7 as measured by primary outcome measure based on VAS [17]. Secondary outcome measures were functional disability using ODI [18], hand-to-floor distance, muscle spasm, and patient’s global evaluation [9, 19].

VAS: is a 0-10 cm scale, stretching from “no pain” to “pain as bad as it could be” and is commonly used tool in research and clinical practice. Its reliability and validity in pain assessment has been clearly demonstrated.

Hand-to-floor distance: Also called mobility assessment in which the patient was asked to bend forward with unflexed knee and try to touch the floor with his/her fingers; the remaining distance was evaluated by a simple cm graduated bar (0 value at floor).

Muscle spasm: Evaluated using two semi-quantitative scales (visual and palpation assessment) in increasing order of intensity. Visual assessment includes 1= no visual signs of muscle spasm; 2= visible spasm of muscle without fixed antalgic gait; 3= visible spasm of muscle with fixed antalgic gait. The palpation scale includes 0= absence of spasm; 1= mild spasm without evoked pain during palpation; 2= moderate spasm; 3= severe spasm of muscle spasm with evoked pain during palpation.

Functional disability (ODI): Evaluated by information on how back pain affects ability to manage patients ADL (activities of daily living). ODI contains 10 sections. The sections are: pain intensity, personal care (washing/dressing), lifting, walking, sitting, standing, sleeping, sex life (if applicable), social life and travelling. For each section the total possible score is 5: if the first statement is marked the section score is 0, if the last statement is marked it = 5. The total score of all sections as a percentage of the total achievable score is the ODI score.

Patient’s global efficacy: Evaluation was recorded at the end of the treatment by the patients as 0= ineffective, 1= minimal effective, 2= moderately effective, 3= good, 4= very good.

Safety: Patients were monitored for laboratory and clinical adverse events based on the baseline and final visits.

Statistical analysis: Statistical analysis was done with Statistical software’s SPSS and PRISM. Descriptive statistics
used for the quantitative parameters were mean and standard deviation. \( p \) values <0.05 were considered statistically significant with a confidence interval of 0.95.

RESULTS

A total of 201 patients (105 male and 96 female) with LBP associated with muscle spasm participated in a prospective randomized and comparative study on the basis of the clinical symptoms as well as inclusion and exclusion criteria. All of them completed the study (27 patients were excluded beforehand due to loss of follow up). There was no significant difference regarding gender, age, and the baseline values of the outcome measures between the two groups.

Pain assessed by VAS showed significant improvement on day 3 and 7 within the groups in both groups. Pain intensity reduced significantly in M group as compared to T group \( (p<0.0001 \text{ for both day 3 and 7}) \). The intensity of pain reduced from 100% to 42.84% in M group whereas it reduced to 66.18% in T group (Table 1).

A statistically significant improvement was observed in hand-to-floor distance in both groups \( (p<0.0001) \). This improvement was observed in both groups beginning from the second visit. But, a marked improvement \( (p<0.0001) \) was observed in M group as compared to T group (Table 2).

The muscle spasm assessed by the visual and palpation scale was significantly and progressively decreased in group M as compared to group T on day 7 \( (p<0.006 \text{ for visible and } p<0.0001 \text{ for palpable spasm}) \) (Table 3).

The mean percent Oswestry Disability Index scores significantly improved within the groups on day 3 and 7, \( (p<0.0001 \text{ for all comparisons}) \). But, M group showed a marked improvement in LBP related disability as compared to T group on day 7 \( (p<0.0001) \) (Table 4).

The patients’ opinion regarding the treatment in terms of pain evaluated as good and very good were 53% and 36% for M group and 30% and 4% for T group. There were no significant changes observed in safety laboratory parameters among the treatment group during the study period. Common spontaneous adverse events reported in M group were fever, constipation and in T group diarrhea was the most frequent (Table 5).
Table 1: Effect of methocarbamol and thiocolchicoside on pain intensity.

<table>
<thead>
<tr>
<th>Assessment Day</th>
<th>Group M (n = 100)</th>
<th>Group T (n = 101)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>701.6 (100%)</td>
<td>736.5 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>476.9 (67.77%)*†</td>
<td>614.2 (83.4%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 7</td>
<td>302.4 (42.84%)*†</td>
<td>487.4 (66.18%)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Statistically significant compare to baseline (paired t test)
†Statistically significant in compare with group T (unpaired t test).

p < 0.05 – statistically significant.
NS- Not Significant (group M v/s group T)

Table 2: Effect of methocarbamol and thiocolchicoside on Mobility Assessment (Hand-to-floor Distance)

<table>
<thead>
<tr>
<th>Assessment Day</th>
<th>Group M (n = 100)</th>
<th>Group T (n = 101)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>30.25 cm (100%)</td>
<td>25.91 cm (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>19.0 cm (67.77%)*†</td>
<td>21.30 cm (82.20%)*</td>
<td>NS</td>
</tr>
<tr>
<td>Day 7</td>
<td>10.62 cm (42.84%)*†</td>
<td>16.80 cm (64.82%)*</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

*Statistically significant compare to baseline (paired t test)
†Statistically significant in compare with group T (unpaired t test).

p < 0.05 – statistically significant.
NS- Not Significant (group M v/s group T)

Table 3: Effect of methocarbamol and thiocolchicoside to decrease in muscle spasm (Visual and palpation)

<table>
<thead>
<tr>
<th>Assessment Day</th>
<th>Group M (n = 100)</th>
<th>Group T (n = 101)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>246.0 (100%)</td>
<td>156.0 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>183.0 (63.49%)*†</td>
<td>133.0 (96.89%)*</td>
<td>&lt;0.0004</td>
</tr>
<tr>
<td>Day 7</td>
<td>302.4 (55.19%)*†</td>
<td>103.0 (78.11%)*</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Palpation Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>269.0 (100%)</td>
<td>174 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>160.0 (57.79%)*†</td>
<td>142 (86.39%)*</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 7</td>
<td>65.0 (27.38%)*†</td>
<td>106 (61.04%)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Statistically significant compare to baseline (paired t test)
†Statistically significant in compare with group T (unpaired t test).

p < 0.05 – statistically significant.
NS- Not Significant (group M v/s group T)
Table 4: Effect of methocarbamol and thiocolchicoside on Decrease in Disability (ODI)

<table>
<thead>
<tr>
<th>Assessment Day</th>
<th>Group M (n = 100)</th>
<th>Group T (n = 101)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>90.14(100%)</td>
<td>96.63 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Day 3</td>
<td>65.62 (72.26%)*†</td>
<td>80.63 (83.49 %)*</td>
<td>=0.0003</td>
</tr>
<tr>
<td>Day 7</td>
<td>40.12 (49.69%)*†</td>
<td>64.38 (66.46 %)*</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Statistically significant compare to baseline (paired t test)  
†Statistically significant in compare with group T (unpaired t test).  

Table 5: Effect of methocarbamol and thiocolchicoside on incidence of adverse events

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Group M (n = 100)</th>
<th>Group T (n = 101)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>1(0.99%)</td>
<td>1</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>0</td>
<td>1(0.99%)</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>1 (1%)</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>4 (3.96%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>5 (4.95%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>15 (14.85%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (1%)</td>
<td>0</td>
<td>0.5</td>
</tr>
</tbody>
</table>

p value is based on Fisher’s Exact test.  
p value <0.05 is significant

DISCUSSION

The immediate goal in the treatment of patients with low back pain is to relieve the accompanying pain and muscle spasm with analgesics and/or muscle relaxants. The agency for Health Care Policy and Research (AHCPR) back pain guidelines, released in 1994, suggest that paracetamol is the safest and most effective medication for acute LBP. They also suggest that non-steroidal anti-inflammatory drugs (NSAIDs), although effective, should be used sparingly since they can cause gastrointestinal irritation, ulceration, renal or allergic problems [16].

There is conflicting Level 3 evidence that NSAIDs are more effective than paracetamol for acute low back pain and furthermore, when used in combination with muscle relaxant they associated with frequent incidence of adverse events [20]. A review of clinical practice guidelines from around the world found that almost all the guidelines recommended paracetamol as part of the first line drugs for patients with LBP [21]. Subsequent clinical practice guidelines for acute LBP, published in Australia [22], New Zealand [23] and Europe
[24] have also recommended paracetamol. Paracetamol used as a rescue analgesic (dose up to 4 gm a day) [19] has strong potential for acute hepatotoxicity. In the current study, only a low dose of paracetamol was allowed in combination with the respective study medication.

Muscle relaxants offer additional benefits for patients with acute LBP [6, 9, 11,], when used alone or in combination with an analgesic / anti-inflammatory agent within 7 days of onset of symptoms [25]. Commonly used muscle relaxants are central nervous system depressants with effects like mild to moderate drowsiness, dizziness, impairment of voluntary motor function, diarrhea, dry mouth and nausea [9].

Methocarbamol (1500mg 4 divided doses) was found to be effective in approximately 60% of patients compared with 30% of patients in painful muscle spasm receiving placebo for 7 days. [26]. In another placebo controlled study the effect of methocarbamol was excellent in several patients. In others, it gave no relief and represented a total of approximately 78% beneficial effect [27].

In our study, the results of group M were dramatic in most patients (94%), where as it gave no relief in a total of 6% patients. The mild side effects, in the form of fever and constipation, were found in only two patients.

Thiocolchicoside alone with rescue medicine paracetamol is effective with common side effects like headache, diarrhea, dizziness/drowsiness, and dyspepsia [6,9]. Multicenter, double blind, placebo-controlled studies with thiocolchicoside in LBP have shown significantly improved principal outcome criteria as compared to placebo [28, 29].

In our study, the results of group T were excellent in 93.07% patients, where as it gave no relief in a total of 6.93% patients. The side effects which were in the form of moderate diarrhea were found in 15 patients; however this never forced a halt in the treatment. The diarrhea stopped within the day following the 7th day. The results of this study showed that both group M and T showed progressive improvement based on VAS, hand-to-floor distance, muscle spasm, and disability by day 3 and 7. But, marked improvements have been shown in group M as compared to group T. Though both groups had tolerable adverse events Methocarbamol had a better tolerability than thiocolchicoside.

The cost of the therapy per day with thiocolchicoside was 34.8 INR, whereas the same with methocarbamol was 5.6 INR. Thus, the treatment with group T was almost 2.5 times more
costly than group M, rendering group M economically favorable. We recommend the use of methocarbamol and paracetamol in acute LBP patients for our economically poor patients.

Though our study was prospective and randomized it has many limitations. No control was done. The patients who did not respond to a (group (not sure of meaning) should have been switched to the other group to prove its comparative efficacy with a crossover study design.

CONCLUSION
According to the results of this prospective randomized study, we conclude that methocarbamol or thiocolchicoside in combination with paracetamol are both effective in acute LBP with spasm. Methocarbamol is superior in efficacy and safety with cost effectiveness. Further multicenter, randomized, double blind controlled studies with crossover designs are required before it can be recommended as a standard primary protocol in treating the patients with acute Low Back Pain.

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REFERENCES


