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RESEARCH ARTICLE

Comparing efficacy and tolerability of eperisone with thiocolchicoside in the management of non-specific low back pain

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ABSTRACT

Background: Low back pain (LBP) afflicts 60–80% of the people worldwide at some point in their lifetime. Association of spinal muscle spasm justifies centrally acting muscle relaxants in the treatment. Controversial superiority of eperisone vis-a-vis thiocolchicoside was instrumental to inception of this research. **Aims and Objectives:** This study aims to compare the efficacy and safety of eperisone with thiocolchicoside in treatment of non-specific LBP. **Materials and Methods:** This follow-up study was done in C. R. G. Hospital, Ujjain (India). Eligible 215 patients, of either sex, between 18 and 60 years from the outpatient orthopedic department were included and dysfunctional status was quantified by modified Oswestry Disability Index. The patients were given eperisone hydrochloride 100 mg 3 times daily or thiocolchicoside 8 mg twice daily. The analgesic activity and adverse drug reactions were evaluated on the follow-up visit after 7 days of treatment against the baseline. **Results:** Of 196 patients who completed the study, females were more (119; 60.71%) than the male (77; 39.28%). "Mean score ± standard deviation" of disability decreased from 26.13 ± 8.28 at baseline to 11.47 ± 4.86 in eperisone group and from 24.78 ± 7.24 at baseline to 9.92 ± 3.63 in thiocolchicoside group. Change in the score against the baseline was statistically significant ($P < 0.05$) in both the groups but insignificant across the groups. Adverse events experienced were less with eperisone. **Conclusion:** Compared to thiocolchicoside, eperisone hydrochloride is equipotent but better tolerated option in LBP.

KEY WORDS: Low Back Pain; Modified Oswestry Scale; Skeletal Muscle Relaxant; Thiocolchicoside; Eperisone

INTRODUCTION

Low back pain (LBP), or lumbago, is an ailment which 60–80% of the people around the world experiences at some point in their lifetime.[1] As the most frequent reason for visiting a physician, LBP is the second only to the common cold. At the same time, it is the most common chronic pain syndrome as an individual concern.[2] LBP is correlated to disability and work absence and accounts for high economical costs in Western societies.[3] In about 90% of people presenting with acute LBP, the cause is non-specific while serious manifestation exclusively due to LBP is rare.[4]

LBP involves a self-perpetuating cycle of pain and spasm.[5,6] Muscle spasm is a sustained and painful involuntary contraction as a reflex response to the pain and may induce further pain in turn.[7] LBP may be attributed to muscle sprains with spasms, mechanical strain on the dorsolumbar muscles, poor posture, or any fatigue otherwise, herniated lumbar intervertebral disc, spondylosis deformans, and various other degenerative changes of the vertebrae.[8]

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Skeletal muscle relaxants may exert their pharmacological effects at the level of spinal cord, brainstem, cerebrum, and muscle fiber. Their centrally mediated mechanism of action can exert a clinically significant peripheral therapeutic effect.[9] There is a strong evidence that the skeletal muscle relaxants relieve spasm and break the spasm-pain-spasm cycle significantly more than placebo. However, side effects such as drowsiness and gastric irritation limit the use of these useful agents.[10,11]

Musculoskeletal diseases associated with painful muscle spasm, particularly LBP, also have a high prevalence.[12] However, LBP, as such, is mostly a self-limiting symptomatology, i.e., many attack of LBP resolve quickly due to ensuing immobility and rest. In general, the symptoms of most of the uncomplicated LBP are managed with short-term use of nonsteroidal inflammatory drugs.[13]

However, some patients proceed to severe, long-term disability.[12] The involvement of reflex muscle spasms in such cases leads to the frequent use of muscle relaxants either alone or in combination with analgesics. Eperisone hydrochloride is a centrally acting skeletal muscle relaxant acting which, through poly- and mono-synaptic reflexes in the spinal cord, exhibits vasodilator effect, increases blood flow, and inhibits the pain reflex pathway.[14] An oral dose of 150 mg/day in three divided doses has been shown to be effective for the treatment of various myotonic conditions.

Thiocolchicoside is an another skeletal muscle relaxant with anti-inflammatory and analgesic effects.[10,15-17] It acts equipotent as a competitive gamma-aminobutyric acid/glycine receptor antagonist and a nicotinic acetylcholine receptors antagonist to a much lesser extent.[18,19] Thiocolchicoside has a proven clinical efficacy and tolerability in many recent clinical trials.[10,19,20-22] The maximum recommended oral dose is 8 mg every 12 h for no more than 7 consecutive days. The maximum intramuscular dose should be 4 mg every 12 h, for up to 5 days.[23]

The modified Oswestry score used for the evaluation of pain during the follow-up is used to measure a patient's functional disability which is a direct indication of how much pain is relieved. Many other studies have compared the outcome using finger floor distance, Lasegue's sign, visual analog scale, etc. We have chosen Oswestry Disability Index scale because this is quite extensive and covers all the day-to-day movements, in which back pain can be experienced. That is why Oswestry Disability Index (also known as the Oswestry LBP disability questionnaire) is considered the "gold standard" of low back functional outcome tools.[24]

The previous studies found one or the other drugs superior due to unequal distribution of the underlying pathology which might have induced a lurking Berksonian bias in favor or against a group. Moreover, these contradictory outcomes necessitated the present study.

The objective of this study was to compare the efficacy and safety of eperisone with thiocolchicoside in the treatment of non-specific LBP.

MATERIALS AND METHODS

Study Population

It was a follow-up study done in C. R. G. Hospital, Ujjain. A total of 215 eligible patients of either sex between 18 and 60 years of age attending the outpatient setting of the orthopedic department were screened and assessed according to the specified inclusion and exclusion criteria. Those willing to take medications as directed and come for the follow-up were included in the study after obtaining written informed consent.

Patients with other associated unrelated spasm conditions such as muscle sprains with spasms of hip or knee or ankle, traumatic pain with spasms, cervical spondylitis, and pain and spasm associated with fractured bone were excluded from the study. Patients with a history of severe infection, trauma or major surgery, severe metabolic, endocrine or electrolyte disturbances, seizure during the preceding 8 weeks, severe hepatic or renal insufficiency, uncontrolled diabetes mellitus, and severe cardiac dysfunction were also not enrolled.

Furthermore, those who had received an investigational new drug in the preceding 4 weeks or any form of muscle relaxants in the previous 7 days, with known hypersensitivity to any of the ingredients of the formulations understudy, pregnant and lactating females, women of child-bearing potential (not practicing adequate contraceptive measures), and patients unwilling or unable to comply with study procedures were excluded from the study.

After the patients' consent to take part into the study, they were evaluated by the investigator for the intensity of pain and functional status.

Primary Outcome Measure

The primary outcome measured for this study was dysfunctional status quantified by modified Oswestry Disability Index at the baseline and after 7 days.[25]

Ethics Approval

The study protocol was approved by the Institutional Ethics Committee of Ruxmaniben Deepchand Gardi Medical College, Ujjain, with approval number 344/2013.

Study Procedure

The prescriptions of patients were screened for the following information:

1. Age, sex, and weight
2. Diagnosis of the condition, comorbidity (diabetes mellitus, hypertension, arthritis, etc.)
3. Information on drugs already in use (i.e., name, number, dose, route, duration, etc.)
4. Any reported/suspected adverse drug reaction (ADR).

Patients were stratified as per different underlying pathology [Table 2] and divided in the two (nearly equal) halves by blind randomization. In the two groups, eperisone hydrochloride 100 mg 3 times daily (n = 97) or thiocolchicoside 8 mg twice daily (n = 99) was given and patients were assessed on the 1st day (baseline) and followed up after 7 days.

The modified Oswestry Disability Questionnaire is designed to assess the extent to which patient's back pain had affected their everyday activities Annexure. It consists of 10 sections. For each section, the total maximum score is 5 for choosing the 5th (and the last) option and minimum score is 0 for choosing the 1st option. Once, all the 10 sections get completed, the score is calculated as follows:

Example: (16 [patient's total score]/50 [total maximum score of 10 sections]) × 100 = 32%.

Missed section was totally excluded from the calculation. During the study, antacids, H_2 blockers, or proton-pump inhibitors were planned to be prescribed, if required. No medicines other than these were allowed. The details of adverse events that occurred during this period, if any, were also recorded pro forma.

Interpretation of scores	
0–20%: Minimal disability	The patient can cope with most living activities. Usually, no treatment is indicated apart from advice on lifting, sitting, and exercise.
21–40%: Moderate disability	The patient experiences more pain and difficulty with sitting, lifting, and standing. Travel and social life are more difficult and they may be disabled from work. Personal care, sexual activity, and sleeping are not grossly affected and the patient can usually be managed by conservative means.
41–60%: Severe disability	Pain remains the main problem in this group but activities of daily living are affected. These patients require a detailed investigation.
61–80%: Crippled	Back pain impinges on all aspects of the patient's life. Positive intervention is required.
81–100%	These patients are either bedbound or exaggerating their symptoms.

RESULTS

We enrolled 215 patients with LBP satisfying the inclusion criteria after obtaining written informed consent. There were 19 dropouts – remaining 196 patients completed the study. Of these 196 patients, female patients were more (119; 60.71%) compared to male (77; 39.28%). A maximum of 60 patients (30.61%) were in the age group of 49–58, while a minimum of 15 (7.65 %) were in the age group of 19–28 [Table 1].

Stratification based on the underlying pathology is shown in Table 2. Both treatment groups were comparable with respect to demographic baseline characteristics – even the disability score difference was statistically insignificant. Mean change in modified Oswestry scores from the baseline to that after the follow-up visit on day 7 in eperisone and thiocolchicoside group (within group) was statistically significant. Table 3 shows the respective scores in both the groups. Across the group, the score difference was always statistically insignificant (at the baseline as well as follow-up).

As per Table 4, only 8 patients of 99 suffered from side effects in eperisone group compared to 14 patients of 97 in thiocolchicoside group. All adverse events were of mild-to-moderate intensity on the Hartwig scale of severity of ADR

Table 1: Gender-wise distribution of low back pain

Age (in years)	Male	Female	Total
19–28	06	09	15
29–38	12	22	34
39–48	19	32	51
49–58	23	37	60
≥59	17	19	36
Grand total (%)	77 (39.28)	119 (60.71)	196 (100)

Table 2: Distribution of low back pain as per basic pathology

Disease	Male	Female
Prolapsed intervertebral disc	16	35
Muscle spasm	31	38
Arthrosis	19	24
Others	11	22

Table 3: Drug wise outcome

Variables	Eperisone	Thiocolchicoside
Baseline Oswestry score	26.13±8.28	24.78±7.24
Score on day 7	11.47±4.86	9.92±3.63

Table 4: Adverse events reported by patient during the study period

Adverse events	Eperisone	Thiocolchicoside
Nausea	2	2
Abdominal pain	2	1
Diarrhea	1	5
Headache	1	1
Giddiness	1	4
Itching	1	0

and resolved without any intervention. They were reported on day 2–3 and resolved by day 7 of the study. Adverse events experienced were significantly less with eperisone as compared to thiocolchicoside and were mostly of mild-to-moderate intensity.

DISCUSSION

In this study, of 196 patients, females were more (119; 60.71%) than the male (77; 39.28%). "Mean score ± standard deviation" of disability decreased from 26.13 ± 8.28 at baseline to 11.47 ± 4.86 in eperisone group and from 24.78 ± 7.24 at baseline to 9.92 ± 3.63 in thiocolchicoside group. Change in the score against the baseline was statistically significant ($P < 0.05$) in both the groups but insignificant across the groups. Eight patients of 99 suffered from side effects in eperisone group compared to 14 patients of 97 in thiocolchicoside group.

A study by Cabitza and Randelli had shown to relieve pain more in eperisone group after 7 days of treatment.[13] Maaz *et al*.[26] and Rani *et al*.[27] have also supported the results of Cabitza *et al*. Since the deep tissue pain can, at least in part, be attributed to reduce muscle blood flow, which comprises the metabolic demand during muscle work,[26] it has been suggested that in some cases, one factor leading to LBP might be various degrees of ischemia of the extensor muscles in the lumbar spine.[27]

In these conditions, due to its effects of improving local blood flow, eperisone could be a better and appropriate alternative to thiocolchicoside in the treatment of LBP. However, thiocolchicoside is reported as a better drug in comparison to eperisone in studies done by Rao *et al*.[28] and Soonawalla and Joshi.[16]

In above studies, non-randomization of the underlying pathology might have induced a Berksonian bias in favor or against a group. We have nullified the Berksonian bias by stratified randomization of patient population. As we removed this bias, our study showed the differences down to insignificance.

Yet, in this study, adverse events experienced were significantly less with eperisone as compared to thiocolchicoside and were mostly of mild-to-moderate intensity. Thus, eperisone had a better tolerability than thiocolchicoside. This could be because, unlike other centrally acting skeletal muscle relaxants, it has no substantial affinity to adrenergic, cholinergic, dopaminergic, or serotonergic receptors in the central nervous system. The study by Cabitza *et al*.[9] also states that eperisone was better tolerated by patients.

Strength and Limitation

This study successfully resolved the conflict of opinion favoring one drug or the other. Both drugs being nearly equally benefit in outcome, the choice now depends mainly on ADR profile.

As it was a convenience sampling without exact representation of catchment population or randomization thereafter, the outcomes may not be fit for generalization for policy-making. A meta-analysis of large-scale randomized trials on the same line can be more conclusive.

CONCLUSION

Change in score with eperisone and thiocolchicoside was statistically significant on day 7 ($P < 0.05$) from the baseline (within group), but mutually, the two groups were not significantly different in disability reduction outcome (across the group, baseline as well as follow-up). The apparently opposite preference in the various prior studies might be due to unequal distribution of basic pathologies, leading to the LBP symptoms. This Berksonian bias has been annulled by our stratified randomization of patient population.

Of course, there was a significant difference between ADRs of eperisone and thiocolchicoside at 5% level of significance. Hence, we conclude that our results indicate eperisone as an equally effective muscle relaxant agent with better safety profile than thiocolchicoside.

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ANNEXURE

This questionnaire has been designed to give your therapist information as to how your back pain has affected your ability to manage in everyday life. Please answer every question by placing a mark in the **one** box that best describes your condition today. We realize you may feel that 2 of the statements may describe your condition, but **please mark only the box that most closely describes your current condition.**

Pain Intensity
- I can tolerate the pain I have without having to use pain medication.
- The pain is bad, but I can manage without having to take pain medication.
- Pain medication provides me with complete relief from pain.
- Pain medication provides me with moderate relief from pain.
- Pain medication provides me with little relief from pain.
- Pain medication has no effect on my pain.

Personal Care (eg, Washing, Dressing)
- I can take care of myself normally without causing increased pain.
- I can take care of myself normally, but it increases my pain.
- It is painful to take care of myself, and I am slow and careful.
- I need help, but I am able to manage most of my personal care.
- I need help every day in most aspects of my care.
- I do not get dressed, wash with difficulty, and stay in bed.

Lifting
- I can lift heavy weights without increased pain.
- I can lift heavy weights, but it causes increased pain.
- Pain prevents me from lifting heavy weights off the floor, but I can manage if the weights are conveniently positioned (eg, on a table).
- Pain prevents me from lifting heavy weights, but I can manage light to medium weights if they are conveniently positioned.
- I can lift only very light weights.
- I cannot lift or carry anything at all.

Walking
- Pain does not prevent me from walking any distance.
- Pain prevents me from walking more than 1 mile.[b]
- Pain prevents me from walking more than ½ mile.
- Pain prevents me from walking more than ¼ mile.
- I can only walk with crutches or a cane.
- I am in bed most of the time and have to crawl to the toilet.

Sitting
- I can sit in any chair as long as I like.
- I can only sit in my favorite chair as long as I like.
- Pain prevents me from sitting for more than 1 hour.
- Pain prevents me from sitting for more than ½ hour.
- Pain prevents me from sitting for more than 10 minutes.
- Pain prevents me from sitting at all.

Standing
- I can stand as long as I want without increased pain.
- I can stand as long as I want, but it increases my pain.
- Pain prevents me from standing more than 1 hour.
- Pain prevents me from standing more than ½ hour.
- Pain prevents me from standing more than 10 minutes.
- Pain prevents me from standing at all.

Sleeping
- Pain does not prevent me from sleeping well.
- I can sleep well only by using pain medication.
- Even when I take pain medication, I sleep less than 6 hours.
- Even when I take pain medication, I sleep less than 4 hours.
- Even when I take pain medication, I sleep less than 2 hours.
- Pain prevents me from sleeping at all.

Social Life
- My social life is normal and does not increase my pain.
- My social life is normal, but it increases my level of pain.
- Pain prevents me from participating in more energetic activities (eg, sports, dancing)
- Pain prevents me from going out very often.
- Pain has restricted my social life to my home.
- I have hardly any social life because of my pain.

Traveling
- I can travel anywhere without increased pain.
- I can travel anywhere, but it increases my pain.
- My pain restricts my travel over 2 hours.
- My pain restricts my travel over 1 hour.
- My pain restricts my travel to short necessary journeys under ½ hour.
- My pain prevents all travel except for visits to the physician/therapist or hospital.

Employment/Homemaking
- My normal homemaking/job activities do not cause pain.
- My normal homemaking/job activities increase my pain, but I can still perform all that is required of me.
- I can perform most of my homemaking/job duties, but pain prevents me from performing more physically stressful activities (eg, lifting, vacuuming).
- Pain prevents me from doing anything but light duties.
- Pain prevents me from doing even light duties.
- Pain prevents me from performing any job or homemaking chores.

[a] Modified by permission of The Chartered Society of Physiotherapy from Fairbanks JCT, Couper J, Davies JB, et al. The Oswestry Low Back Pain Disability Questionnaire. *Physiotherapy*. 1980;66:271-273.
[b] 1 mile=1.6 km.