Original Article

Effectiveness of Tolperisone Hydrochloride with Aceclofenac as Combined Therapy in Acute Low Back Pain.

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Abstract

Objective: An open label, non-randomised, prospective study was conducted to evaluate the effectiveness of tolperisone hydrochloride 150mg thrice daily with aceclofenac 100mg twice daily compared to aceclofenac 100mg twice daily alone for the treatment of acute low back pain (LBP) for 14 days. total (n=242) patients recruited for the study were divided into two treatment groups. One of the group (n=124) received oral tolperisone plus aceclofenac and the other (n=118) Aceclofenac alone. The pain intensity was assessed by visual analogue scale. Patients were informed to report any adverse effect encountered during the study period. The overall effect of the drug (global assessment of the study medication) on pain and adverse effects were assessed by the patients at the end of the trial on a categorical scale. There was significant reduction in pain score in the tolperisone group than aceclofenac group with insignificant adverse effects which didn't require discontinuation of the study. Tolperisone when added with aceclofenac can be more effective than aceclofenac alone for relief of acute LBP with minimum adverse effects.

Key Words: **Low back pain, tolperisone, aceclofenac, visual analogue scale**

Introduction:

Low back pain (LBP) is one of the common causes of disability in patients under 45years of age. Sustained muscle spasms associated with LBP due to involuntary contraction are usually very painful and cannot be completely relieved by voluntary effort[1]. LBP is the most common cause of disability for work population leading to increased sickness absenteeism [2]. Some common causes of LBP are bad sitting posture, lumbar spine arthritis, spondylolisthesis, herniated disc etc. Compression fracture from osteoporosis is common cause of LBP among women.

Non-steroidal anti-inflammatory drugs (NSAIDs), opioids, analgesics and muscle relaxants are commonly used for the treatment of this disorder. Most of the centrally acting muscle relaxants have considerable side-effects such as sedation, dizziness, impairment of coordination, mental confusion, weakness, withdrawal phenomenon or anti-cholinergic adverse events.[3] Traditional NSAIDs are associated with several adverse effects like gastritis, gastrointestinal bleeding, nausea, constipation with long term effects like renal dysfunction. On the other hand natural opioids and their synthetic congeners are the alternative ways of managing LBP, though it has its own drawbacks in the form of nausea, vomiting, ileus and respiratory depression etc.

Aceclofenac is a non-steroidal anti-inflammatory agent which acts by blocking cyclooxygenase enzyme thereby inhibiting PGE_2 synthesis. It also inhibits interleukin-1â-induced prostaglandin E_2 production by human rheumatoid synovial cells [4, 5]. Aceclofenac is also converted into diclofenac and 42 -hydroxy diclofenac by human polymorphonuclear leuk ocytes and monocytes. 42 -hydroxy diclofenac suppressed prostaglandin E_2 production specifically by blocking cyclooxygenase-2 activity[6].

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Cite as:
B.Bhattacharjya, S.Mohammad Naser, A.Biswas, F. Kamal, K. Banerjee. Effectiveness of Tolperisone Hydrochloride with Aceclofenac as Combined Therapy in Acute Low Back Pain.IJPMR Jun 2012; Vol 23(2): 74-8.

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Received on 16/07/2011,Revised on 28.03.2012, Accepted on 16/05/2012

Tolperisone is a centrally-acting muscle relaxant that has been in therapeutic use for more than three decades in the western world for the symptomatic treatment of spasticity and muscle spasm[7, 8]. It differs from other myotonolytic agents in its pharmacological properties, which mediate muscle relaxation without concomitant sedation or withdrawal phenomena [9]. It also blocks mono and polysynaptic reflexes by inhibiting presynaptic neurotransmitters from the primary afferent endings in a dose dependent manner at the spinal level via a combined action on voltage-gated sodium and calcium channels [9, 10].

Tolperisone increases the blood supply to skeletal muscles; this action is noteworthy since muscle contracture may compress the small blood vessels and induce ischaemia leading to release of pain stimulating compounds[11]. It causes preferential antinociceptive activity against thermal stimulation that is likely to be attributed to its local anesthetic action [12]. Besides being an effective antispastic agent, tolperisone also has analgesic activity in rodents and human by the inhibition of the action potential propagation on both the A and C fibres [13, 14].

Earlier studies [7, 9] done abroad concluded a better efficacy and safety of tolperisone when compared with placebo or pridinol mesylate.

Therefore it was felt necessary to conduct this study in our institute for understanding the effect of tolperisone with the following objectives: i)To compare the oral analgesic and antispastic effect of tolperisone hydrochloride with aceclofenac for treatment of acute low back pain ii) Safety evaluation: Incidences of adverse effects during the study period.

Materials and Methods:

An open label, non-randomised, prospective study was conducted at Calcutta National Medical College and Hospital, Kolkata in collaborations with the Department of Orthopaedic Surgery, Physical Medicine & Rehabilitation and Pharmacology. The total duration of the study was one year (July 2010 to June 2011). After prior approval from Institutional Ethics Committee, patient aged 20 to 60 years of both genders suffering from acute or acute exacerbation of chronic LBP were included according to inclusion/ exclusion criteria. Patient with history of major trauma or fracture, associated with other medical conditions like uncontrolled diabetes mellitus, hypertension, hepatic or renal disease etc. as well as pregnant and lactating women were excluded from the study. A sample size of (n=255) patients were calculated on the basis of Raosoft® software (www.raosoft.com © 1996-2011 by Raosoft, Inc.) with 90% confidence interval and 5% margin of error.

Patients included in the study were thoroughly counselled and explained about visual analogue scale (VAS) for pain where 0 cm denoted no/minimum imaginable pain and 10cm denoted maximum imaginable pain.

The patients were divided into two groups receiving either Tab Myotop® (tolperisone Hydrochloride -150mg, Zuventus) thrice daily plus tab. Hifenac® (aceclofenac -100mg, Intas) twice daily (n=124) or Tab. Hifenac® (Aceclofenac - 100mg) alone twice daily (n=118) for 14 days. On initial visit the patients were examined clinically and the intensity of pain was assessed by visual analogue scale (VAS) as follows: 0 – no pain, 1 to 3 – mild pains, 4 to 6 – moderate pain, 7 to 8 – severe pain, 9 to10 – very severe pain. Further changes in the intensity of pain were noted by VAS score of patients on 8th (2nd visit) and 14th day (3rd visit) of the study. The adverse effects of study drugs were also noted during these visits. Biochemical tests (Hb%, TC, DC, ESR, uric acid, creatinine, sugar, bilirubin , SGPT, SGOT and urine for routine examination were done during screening and at the end of the trial (day 14) to assess any change in parameters.

Global assessment for effectiveness and tolerability was assessed separately by the patient at the end of therapy on day 15 on a 5-point scale of excellent, good, satisfactory, poor and very poor [15]. A Student's unpaired 't' test was used to compare the pain intensity (VAS) between the two treatment groups. Serial changes within the two study groups were assessed by repeated measure ANOVA. The p values below 0.05 were considered to be statistically significant.

Results:

Out of 255 patients enrolled, 242 patients completed the study. Total 13 patients of which (n=5) belonging to tolperisone group and (n =8) of aceclofenac group were dropped from the study due to discontinuation of the trial. Patients who have been dropped from the study had similar age (mean= 45.72 yrs) and weight (mean = 62.43 kg) as compared to those completed the study. There was a predominance of male subjects (77.27%) among the dropouts. Since these patients (n=13) were excluded from the study at a very early stage, they were not included in final statistical analysis.

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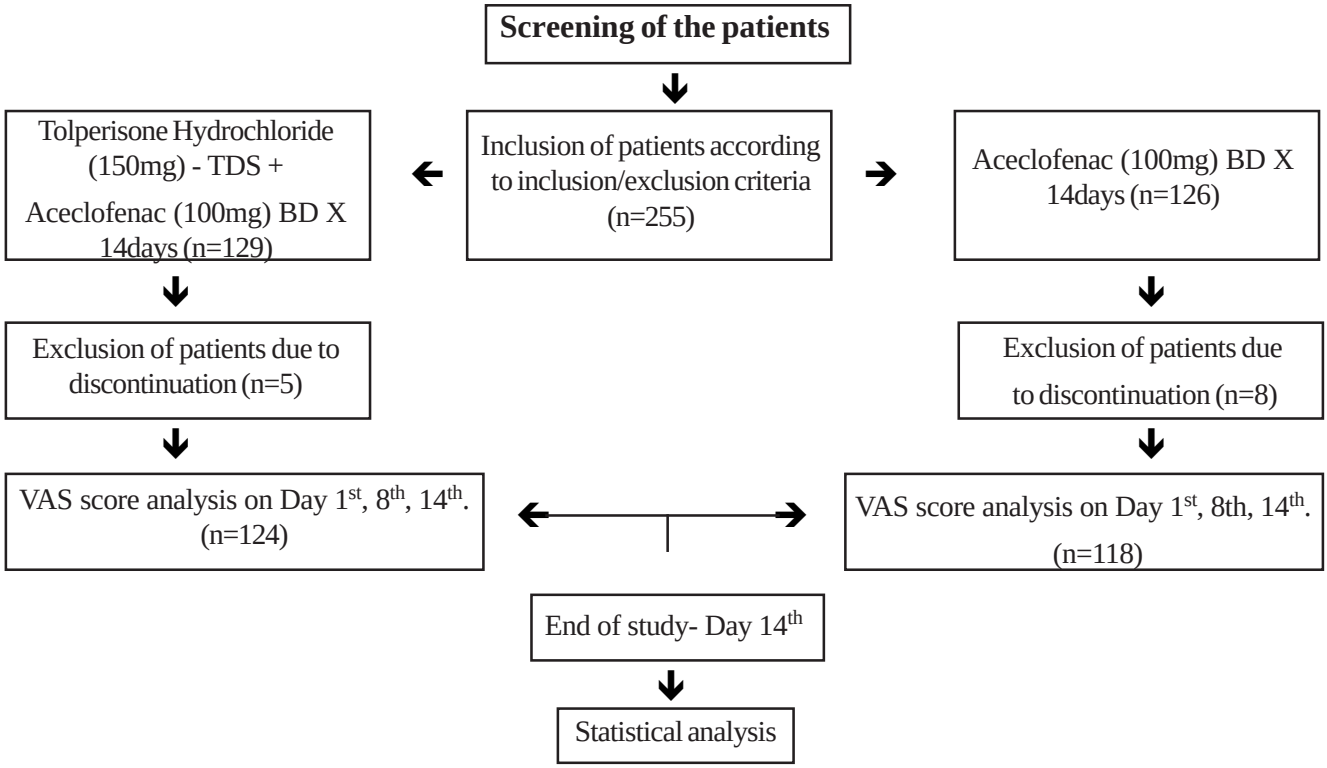


The baseline demographic characteristics were similar between the groups. Overall 59.10% (143 / 242) of patients were female (Table: 1).

Table: 1 – *Demographic Characteristics of Subjects*

Characteristics	Tolperisone Hydrochloride + Aceclofenac (n=124)	Aceclofenac (n=118)
Sex (n) Female	72	71
Male	52	47
Age, Yr (mean ± SD)	42.53 (4.5)	44.04 (5.2)*
Weight, Kg (mean ± SD)	63.52 (5.8)	64.11 (6.4)*

**Difference of age & weight statistically not significant*

The primary effectiveness measure was pain intensity. The overall analgesic effect of the study drugs over the period of day 0, day 8 and day 14 were measured by reduction in pain intensity using visual analogue scale.

There was significant reduction in pain score ($p < 0.001$) [Table: 2] when compared within the Tolperisone plus Aceclofenac groups between day 0, day 8 and day 14. The reduction in pain intensity score at day 8 as well as day 14 was significant ($p < 0.001$) in tolperisone plus aceclofenac group in comparison to Aceclofenac group ($p= 0.004$). Ten patients experienced adverse effects such as nausea, vomiting, dizziness, epigastric pain etc. [Table: 3]. However

Table: 2 – *Mean score of vas from the baseline (n=242)*

Assessment	Tolperisone Hydrochloride + Aceclofenac (n=124) (mean ± SD)	Aceclofenac (n=118) (mean ± SD)
Day 0	9.86 ± 0.50	9.73 ± 0.61
Day 8	1.86 ± 1.02*	4.84 ± 1.24*,[a]
Day 15	0.18 ± 0.69*	4.11 ± 1.11**,[a]

**p< 0.001 when compared between Day 0 & Day 8, Day 8 & Day 14 of respective group*
*** p= 0.004 when compared between day 8 & Day 14 of aceclofenac group*
[a]p<0.001 when compared between Day 8 & Day 14 of both groups

Table: 3 – *Adverse event profile of study drugs*

Adverse Events	Tolperisone Hydrochloride + Aceclofenac (n=124)	Aceclofenac (n=118)
Nausea, Vomiting	3	2
Dizziness	1	0
Epigastric Pain	2	2
Total No. of Adverse Events	6 (4.8%)	4 (3.3%)

Total No. of adverse reaction - 10(4.1%)

none of the patients had to discontinue the drugs due to these adverse effects. No serious adverse event was reported among patients in all treatment groups. Patients of both the groups suffered similar kind of adverse effects [tolperisone plus aceclofenac = 4.83% (6/124) aceclofenac 3.38% (4/118)] which was statistically insignificant.

There was no significant change in biochemical parameters both before and after the administration of study drugs.

The overall effect (global assessment of the study medication) of the combined drug therapy on the patients was assessed as 'excellent' (78.14%) of the tolperisone plus aceclofenac group where 66.42% of the patients assessed 'good' for aceclofenac alone regarding control of pain and adverse effects at the end of the trial (day 15) on a categorical scale [Fig 2, 3].

Treatment compliance was comparable in both the treatment groups.

Discussion:

From the result in terms of effectiveness, it was concluded that there was highly significant reduction in pain score in the tolperisone plus aceclofenac group ($p < 0.001$) when prescribed for 2 weeks in patients of acute or acute

Fig -1: Effect of combined drug therapy

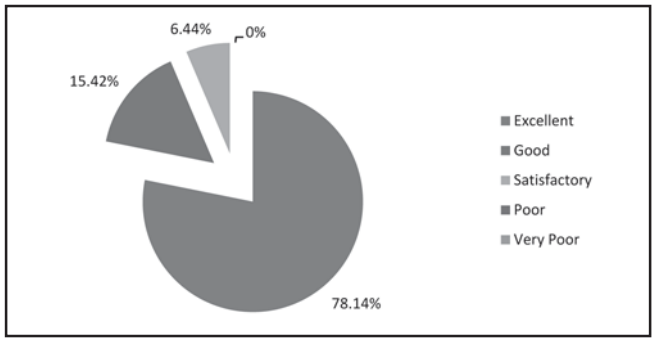
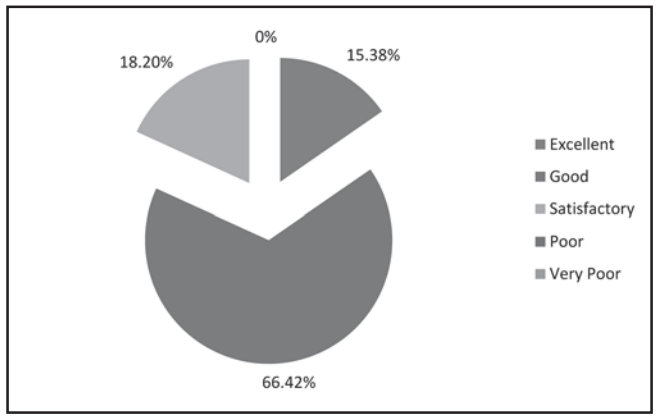
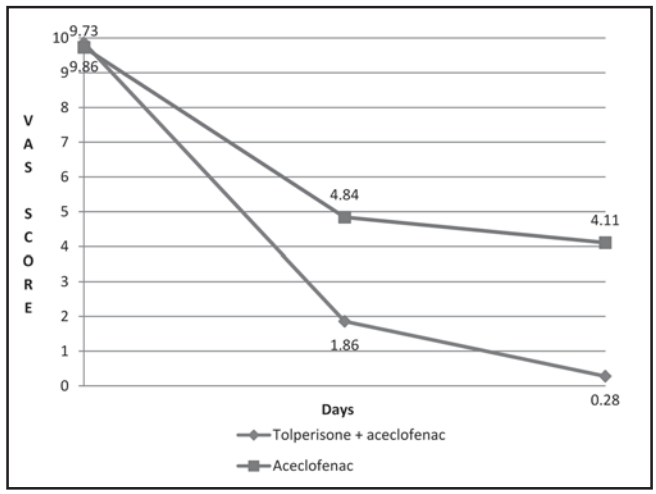


Fig -2: Effect of aceclofenac alone



exacerbation of chronic low back pain due to various degenerative and inflammatory conditions when compared to Aceclofenac alone group [Fig 1]. This finding is comparable with the earlier results of other studies[9, 16] done abroad . The added advantage of combination group may be due to tolperisone induced increase in flow of blood which prevents the release of pain producing compounds due to ischaemia precipitated by contracture of skeletal muscles. The local anaesthetic action of tolperisone might have also contributed for better effectiveness. The other conclusion drawn from this study was fewer side-effects of the study drugs.

Fig -3: Drug effect on categorical scale.



In the present study tolperisone was well tolerated with no sedation reported by any patient during the study period. The lack of sedative side-effects in the present study also correlates well with the results of another study done earlier which has concluded that tolperisone has no sedative action and does not impair reaction time [17].

Thus it appears that addition of tolperisone with aceclofenac does not aggravate the chances of any extra adverse effects.

On the contrary the combination therapy proved to be more effective than the comparator group. The present study however limited by the fact that, it was neither truly randomised nor blinded and conducted on patients of similar ethnic group. It is proposed that further multicentric studies will be helpful to generate more data.

Conclusion:

Tolperisone hydrochloride is a muscle relaxant that can be safely prescribed along with analgesics for getting additive effect for the symptomatic treatment of acute LBP.

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