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Research article

COMPARISON OF EFFECTIVENESS AND SAFETY OF THIOCOLCHICOSIDE AND TOLPERISONE IN PATIENTS WITH CERVICOBRACHIALGIA - A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Aims: study has been conducted to compare the effectiveness and safety of Thiocolchicoside (TCC) versus Tolperisone (TOL) in the treatment of cervicobrachialgia.Settings and Design: Prospective observational study was conducted in Physical Medicine and Rehabilitation Department of Tertiary care Teaching Hospital in Kerala for a duration of 6 months. Methods and Material: 170 patients, 85 in each group with M:F ratio-1:2.9, having cervicobrachialgia were included and were assigned to receive 150 mg of Tolperisone thrice daily or 8 mg of Thiocolchicoside twice daily for 14 days. Patients were assessed on their initial visit and followed up after 7 and 14 days.Pain status and disability level due to neck pain were determined using, visual analogue scale (VAS) and neck pain disability index questionnaire (NPDIQ) respectively. Adverse events during this period were also recorded.
Statistical analysis used: Analysis was done with nonparametric tests like Wilcoxon Signed Ranks Test and Mann Whitney U Test using SPSS16Results: Even though both groups showed statistically and clinically significant reduction in VAS(TCC p-<0.001,TOL p-<0.001) and NPDIQ (TCC p-<0.001, TOL p-<0.001) scores, there was no significant difference between the groups in the reduction of mean scores(VAS-P =0.512;NPDIQ-P-0.621). Safety analysis showed a statistically significant higher incidence of gastrointestinal adverse drug reactions with Thiocolchicoside than Tolperisone group (P= 0.005).Conclusions: Skeletal muscle relaxants, Thiocolchicoside and Tolperisone are equally effective in the treatment of cervicobrachialgia, but the safety index is better for Tolperisone and hence is a safer alternative.

Key-words: Skeletal muscle relaxant, Cervicobrachialgia, Thiocolchicoside, Tolperisone

INTRODUCTION

Neck pain (or cervicobrachialgia) is a common problem, with two-thirds of the population having neck pain at some point in their lives. Neck pain, although felt in the neck, can be caused by numerous other spinal problems. Joint disruption in the neck and upper back creates muscular tightness. Neck pain may arise due to muscular tightness in both the neck and upper back. [1] In several studies conducted so far it is observed that neck pain is not a self-limiting problem, and many patients will have long-term symptoms which may be moderately disabling. [2] Hence it has to be given due importance and treated properly. Centrally acting skeletal muscle relaxants combined with analgesics are commonly used for the treatment of cervicobrachialgia. [3-4]

Skeletal muscle relaxants are a heterogeneous group of medications commonly used to treat spasticity from upper motor neuron syndromes and muscular pain or spasms from peripheral musculoskeletal conditions. Thiocolchicoside (TCC) and Tolperisone (TOL) are centrally acting skeletal muscle relaxants which reduce skeletal muscle tone by selective action in the cerebrospinal axis by modulating stretch reflex arc, without altering consciousness. [5]

Objectives

1)To compare the effectiveness of Thiocolchicoside with that of Tolperisone.

2)To compare the safety of Thiocolchicoside with that of Tolperisone.

SUBJECTS AND METHODS:

This was a prospective observational study conducted in the outpatient Department of Physical Medicine and Rehabilitation, in a tertiary care hospital during the period of October 2010 to March 2011. A total of 170 patients were included in the study with 85 in each group after satisfying the inclusion criteria which consisted of Patients complaining of pain anytime within the last 7 days, age between 18-65 years. Those who not willing to participate in the study, pregnant and lactating women, those with history of epilepsy, and those with cognitive deficit were excluded from the study. Structured performa validated by the statistician was used for collecting data.

STUDY PROCEDURE

Research committee and Ethics committee approval were obtained. Patients satisfying the entry criteria were enrolled in the study. A written informed consent was obtained from the patient. Study comprehended three visits- an initial visit and two follow up visits. First follow up was done after 7 days and second follow up was done after 14 days.

In the first visit information regarding patient demographics, past history, concomitant diseases and medications he/she were on, was obtained from the patient / care giver. All the information collected from each patient was recorded in the pre-prepared proforma. Data regarding the symptoms of the disease and clinical diagnosis were also recorded. Drug prescribed to each patient included in the study, that is either Thiocolchicoside or Tolperisone was also noted. Clinician's opinion about patient's X-ray of cervical spine and the data regarding baseline investigations like routine blood examination and fasting blood sugar were also recorded in the proforma.

Tools selected for comparing the effectiveness of drugs were: Visual Analogue Scale for pain (VAS) and Neck Pain Disability Index Questionnaire (NPDIQ).

At first patient's pain status was determined using, VAS for pain. VAS is usually a horizontal line, 10 centimetres in length, anchored by word descriptors at each end like 0 represents no pain, 10 represent maximum pain. The patient was asked to mark on the line, the point that he/she feel represents the pain perception at that time. The VAS score was determined by measuring in centimeters from the left hand end of the line to the point marked by the patient.

After taking VAS score the disability level of the patient due to neck pain was found out using NPDIQ. This questionnaire is designed to assess the extent to which patient's neck pain

had affected their everyday activities. It consists of 10 sections each containing 5 set of questions. Patient was asked to answer each section by circling his/her choice among the 5 questions in each section.

SCORING TECHNIQUE FOR NECK DISABILITY INDEX: Each of the 10 sections is scored separately and then added up. Maximum score in each section is 5. So maximum total obtained would be 50.

- If all 10 sections are completed, simply double the patient's total score.
- If a section is omitted, use the following formula for calculating % disability

FORMULA:

$$\frac{\text{Patient's total score of completed sections} \times 100}{\text{Number of sections completed} \times 5} = \_\_\_\_\_ \% \text{ disability}$$

Baseline assessments were done by these tools. Patients were followed up after 7 days and 14 days.

First follow up visit (after 7 days): Pain status and disability level of the patient were assessed using VAS and NPDIQ in a similar way as in the initial visit. The details of adverse events, if any that occurred during this period were also recorded in the proforma. The data regarding the presence or absence of subjective side effects like dizziness, tremor, paresthesia, somnolence, seizure, sweating, pruritus, abdominal pain, nausea, vomiting etc were obtained by questioning the patients or the accompanying person. Data regarding objective side effects like erythema, rash, tachycardia, hypotension etc were obtained from the clinician examining the patient.

Second follow up visit (after 14 days): The same procedure was repeated in the second follow up also and all the findings were recorded.

Data analysis was done with the help of excel 2007 and SPSS 16 statistical software. As the outcome measurement was a pain score which would not follow the Gaussian distribution, Wilcoxon Signed Ranks Test was applied to analyze the reduction of pain score with in each treatment group and Mann Whitney U Test was applied to compare the reduction of pain score between the two treatment groups. Descriptive statistics was used to describe the various types of adverse drug reactions.

RESULTS:

In this study, assessment of effectiveness and safety of Thiocolchicoside and Tolperisone in the treatment of cervicobrachialgia was done. A total of patients with diagnosis of cervicobrachialgia who were prescribed either Thiocolchicoside or Tolperisone were selected for the study. The age range of patients included in the study was between 20 and 65 with a mean age of 47.41 ± 9.76years. The median age was 49 in TCC and 47 in TOL group. The maximum number of patients falls in the age interval of 40-49 years in both groups i.e.TCC (36.5%) and TOL (41.2%)**.** 74.1% of the patients included in the study are females in both groups. Majority of patients are labourers (63.5% in Thiocolchicoside treated group and 60% in Tolperisone treated

group). 84.7% in Thiocolchicoside treated group and 87.1% in Tolperisone treated group, are diagnosed to have cervical spondylosis.

ASSESSMENT OF EFFECTIVENESS OF TREATMENT

Assessment of effectiveness using VAS

The effectiveness of TCC and TOL in cervicobrachialgia is assessed separately using Visual Analogue Scale. On day 0 the mean VAS score of patients in TCC treated group was 7.88. It is reduced to 3.93 on day 14 of treatment. The reduction in mean VAS score between day 0 and day 14 is found to be statistically significant (p value-<0.001).On day 0 the mean VAS score of patients in TOL treated group was 7.76. It is reduced to 3.76 on day 14 of treatment. On statistical analysis, the reduction of pain score from day 0 to day 14 is observed to be significant (p value-<0.001).

The difference in mean VAS score between two groups is used for comparing the effectiveness of Thiocolchicoside and Tolperisone. On day 7 the mean VAS score in TCC group was 5.48 and that in TOL group was 5.18. On statistical analysis the difference in mean VAS scores between the two groups is not significant (p value-0.171). On day 14 the mean VAS score in TCC group was 3.93 and that in TOL group was 3.76. On statistical analysis the difference between mean scores is not significant (p value-0.512).

Table: 1 Assessment of effectiveness using VAS

Pain assessment using VAS	Thiocolchicoside			Tolperisone		
	Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
Mean ±SD	7.88 ±1.1	5.48 ±1.39	3.93 ±1.80	7.76 ±1.09	5.18 ±1.37	3.76 ±1.7
Median	8.00	5.00	4.00	8.00	5.00	3.00
Range	5-10	3-8	1-8	4-10	2-8	1-8

Assessment of effectiveness using Neck Pain Disability Index Questionnaire (NPDIQ)

The effectiveness of TCC and TOL was also assessed by using NPDIQ which can reveal the extent of disability due to cervicobrachialgia. On day 0 the mean NPDIQ score of patients in TCC treated group was 69.92. It is reduced to 35.27 on day 14 of treatment. The reduction in mean NPDIQ score between day 0 and day 14 is found to be statistically significant (p value-<0.001). On day 0 the mean NPDIQ score of patients in TOL treated group was 69.24. It is reduced to 34.08 on day 14 of treatment. On statistical analysis the reduction of pain score from day 0 to day 14 is observed to be significant (p value-<0.001).

The difference in mean NPDIQ score between two groups is used for comparing the effectiveness of Thiocolchicoside and Tolperisone. On day 7 the mean NPDIQ score in TCC group was 47.85 and that in TOL group was 45.81. On statistical analysis the difference between mean scores is not significant (p value-0.313). On day 14 the mean NPDIQ score in TCC group

was 35.27 and that in TOL group was 34.08. On statistical analysis the difference between mean scores is not significant (p value-0.621).

Table: 2 Assessment of effectiveness using NPDIQ

Disability assessment using NPDIQ	Thiocolchicoside			Tolperisone		
	Day 0	Day 7	Day 14	Day 0	Day 7	Day 14
Mean ±SD	69.92±13.2	47.85±15.3	35.27±5.9	69.24±13.5	45.81±6.6	34.08±16.2
Median	68.00	50.00	31.00	68.00	42.00	28.00
Min-maximum	35-97	20-80	10-75	37-95	20-89	13-84

Safety assessment

In the first follow up, system wise distribution of ADR shows highest incidence in gastrointestinal system in both groups (38.8% of patients in TCC group and 18.8% of patients in TOL group). On statistical analysis the difference in incidence of gastrointestinal ADRs between the two groups is found to be significant (p value 0.004).

Table: 3 System wise distributions of ADRs (first follow up)

ADR	Thiocolchicoside		Tolperisone		TCC vs TOL P-value
	Number	%	Number	%	
CNS	7	8.2	3	3.5	0.192
CVS	3	3.5	1	1.2	0.621
GIT	**33**	**38.8**	**16**	**18.8**	**0.004**
SKIN	2	2.4	3	3.5	1.000
OTHER	1	1.2	4	4.7	0.368

Adverse drug reactions in CNS, CVS, Dermatological and other systems were also observed in both treatment groups. On statistical analysis the difference in incidence of ADR between two treatment groups is found to be not significant. On comparing the individual ADRs, the incidence of nausea in TCC group(10) is found to be significantly high compared to that in TOL group(3) on statistical analysis (P value-0.043).

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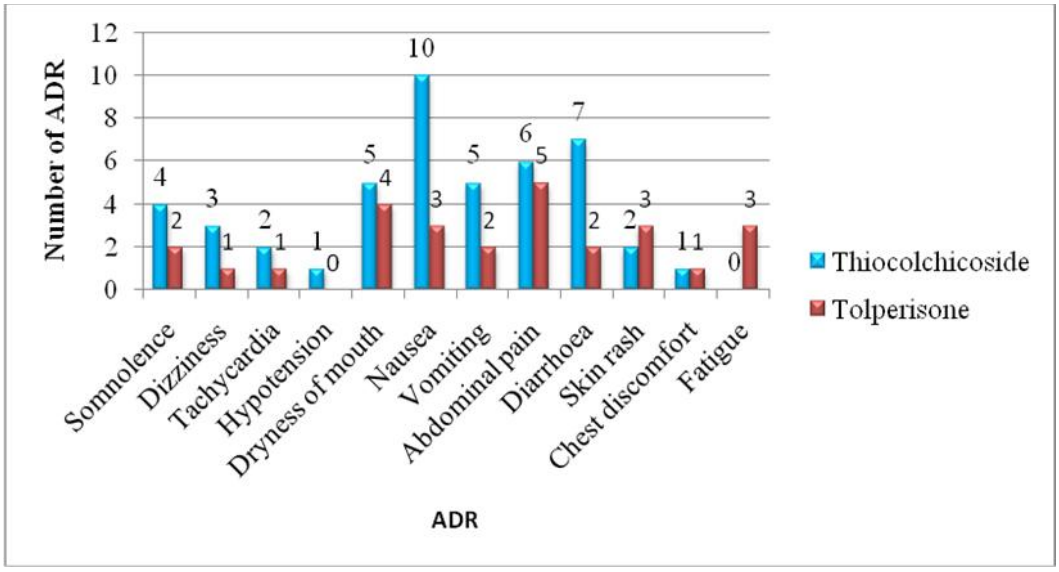

Figure 1: Distribution of individual ADR (first follow up)

In the second follow up also, system wise distribution of ADR showed highest incidence in gastrointestinal system in the both groups (41.2% of patients in TCC treated group and 21.2% of patients in TOL treated group). On statistical analysis the difference in incidence of gastrointestinal ADRs between the two groups is found to be significant (p value 0.005). Difference in distribution of adverse drug reactions in CNS, CVS, Dermatological and other systems is also evaluated in the two treatment groups in the second follow up. It is seen that there is no statistically significant difference.

Table: 4 System wise distributions of ADRs (second follow up)

ADR	Thiocolchicoside		Tolperisone		TCC vs TOL P value
	Number	%	Number	%	
CNS	11	12.9	4	4.7	0.058
CVS	5	5.9	1	1.2	0.210
GIT	**35**	**41.2**	**18**	**21.2**	**0.005**
SKIN	0	0	4	4.7	0.121
OTHER	2	2.4	3	3.5	1.000

On comparing the individual ADRs, the incidence of nausea (12) in TCC group is found to be significantly high compared to that in TOL group (3) on statistical analysis(p value-0.015).

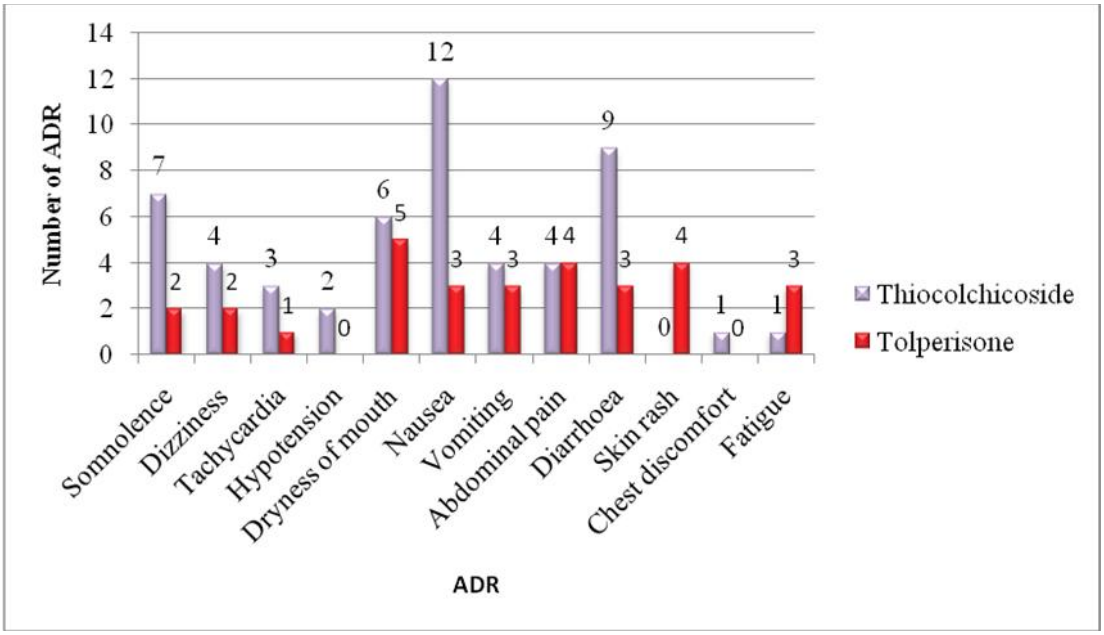

Figure: 2 Distribution of individual ADR (second follow up)

DISCUSSION

Neck pain remains as public health problem and a challenge to clinicians, rheumatologists and orthopedicians. Neck pain, a high prevalent condition among middle aged population, is usually associated with 'muscle spasm' that is responsible for pain. Therefore centrally acting skeletal muscle relaxants are commonly used for its treatment. The objective of this study is to assess the efficacy and safety of Thiocolchicoside (TCC) versus Tolperisone (TOL) in patients visiting Physical Medicine and Rehabilitation outpatient Department and diagnosed to be suffering from cervicobrachialgia

Earlier studies show that maximum prevalence of cervicobrachialgia was seen in middle aged and elderly patients as the degenerative changes of cervical spine increases with age.[6] In the present study also majority of patients belong to the age group of 40-49 years and mean age of patients in this study is 47.41 years. Majority of patients in this study were females (74.1%) in both treatment groups. Considering the socioeconomic status, in the present study, majority of the patients were manual labourers in both treatment groups (61.8%). The results agreed with observations in previous studies which had shown that mentally and physically stressful job is a major risk factor for cervicobracialgia. .[6] In the present study majority of patients (85.9%) were diagnosed to have cervical spondylosis. According to many previous studies in this context, cervical spondylosis is the commonest cause of cervicobrachialgia and age is the major predisposing factor for developing Cervical spondylosis.[6]

Efficacy analysis was done using tools Visual analogue scale (VAS) and Neck Pain Disability Index Questionnaire (NPDIQ).

Mean VAS score in the initial visit is found to be 7.9 in Thiocolchicoside treated group and 7.8 in Tolperisone treated group. This was reduced to 3.9 and 3.8 respectively in each group in the second follow up after 2 weeks. Thus assessment of pain based on Visual analogue scale (VAS) has shown a statistically significant reduction in the two treatment groups. But, there was no significant difference in the reduction of mean VAS scores between the two groups. This shows that both drugs are equally efficacious in reducing pain. A previous study also showed significant reduction in VAS score in TCC and TOL treated groups but there was no statistically significant difference in mean score between the two treatment groups.[7]

The disability due to pain was assessed using the NPDIQ. In the Thiocolchicoside group, mean score of patients was reduced from the initial score of 69.9 to 35.3, and in the Tolperisone group a reduction from 69.2 to 34.8 was observed. The two treatment groups demonstrated significant reductions from baseline scores, after 7 and 14 days of therapy. But there was no significant difference in the reduction of mean score between the two groups, after 7 days of therapy or after 14 days of therapy. This was supported by the results obtained from the previous study done by in patients with acute neck pain. [8]

The safety analysis was performed in all patients. As per the present study system wise distribution of ADR showed high incidence of ADRs in gastrointestinal system in both treatment groups. But a statistically significant higher incidence is found in Thiocolchicoside treated group compared to Tolperisone treated group both in first and second follow ups. In the first follow up 38.8 % of patients in Thiocolchicoside group and 18.8% of patients in Tolperisone group developed ADR in gastrointestinal system which was increased to 41.2% in Thiocolchicoside group and 21.2% in Tolperisone group during second follow up. In a similar study [7] 21.5% of Thiocolchicoside treated patients showed gastrointestinal side effects, while the incidence of the same in Tolperisone treated group was 5%. The incidence of gastrointestinal side effects in TCC group was significantly high. Hence this study supports the results obtained in the present study. But the incidence of gastrointestinal side effects is higher in the two treatment groups in the present study. This could be due to the differences in genetic constitution, tolerability to drugs or food habits of the two populations.

In the present study, on comparing the individual ADRs, the incidence of nausea (14.1%) in TCC group is found to be significantly high compared to that in TOL group (3.5%). The results correlates with the findings obtained from previous studies [9-10] in which nausea was one of the main side effects of TCC. The incidence of diarrhoea is also high in TCC treated group(8.2% in first follow up and 10.6% in second follow up) compared to TOL treated group (2.3% in first follow up 3.5% in the second follow up) .This is supported by the another study[6] in which TCC treated patients developed diarrhoea of moderate intensity.

Limitations of the study

Pain assessment was done using VAS and the pain score obtained for each patient is subjective which dependent on his/her approach to pain. Disability status of the patient was assessed using NPDIQ which is a disease non-specific scale. For complete assessment of adverse drug reactions, patients had to be followed up over a longer time.

CONCLUSION

This study compares the effectiveness and safety of TCC and TOL in cervicobrachialgia and it was done in South Indian population. Even though both groups showed statistically and clinically significant reduction in VAs and NPDIQ scores, there was no significant difference between the groups in the reduction of mean scores. Safety analysis showed a statistically significant higher incidence of gastrointestinal adverse drug reactions with Thiocolchicoside than Tolperisone group. Skeletal muscle relaxants, Thiocolchicoside and Tolperisone are equally effective in the treatment of cervicobrachialgia, but the safety index is better for Tolperisone and hence is a safer alternative.

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