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Original Article

A multi-center, double-blind, randomized parallel-group Phase IV study comparing the efficacy and safety of thiocolchicoside ointment versus placebo in patients with chronic mechanical low back pain and an acute muscle spasm

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ABSTRACT

Objectives: This study aims to evaluate the efficacy and safety of thiocolchicoside (TCC) ointment treatment compared to placebo in patients with chronic mechanical low back pain (LBP) accompanied by acute muscle spasms.

Patients and methods: A total of 292 adult patients (106 males, 186 females; mean age: 38.5±11.2 years; range, 18 to 64 years) were randomized to TCC group (n=147) and placebo group (n=145) in 12 centers between March 2020 and March 2021. Eight patients from each group were excluded from the analysis. The primary endpoint was pressure pain threshold (PPT) on Day 3, which was measured using a pressure algometer. Secondary endpoints were PPT on Day 7, patient, and physician Visual Analog Scales-pain (VAS-pain) on Days 3 and 7, and safety.

Results: The PPT values on Day 3 was not significantly different between the treatment groups (p=0.701). Similarly, TCC and placebo group had similar VAS-pain scores over trial period (p=0.577 or higher for comparisons). Significantly higher PPT values and lower VAS-pain scores on Days 3 and 7 were observed in both groups (p<0.001 for all). In patients with a PPT value of ≥3.87, TCC arm had higher PPT on Day 3 compared to placebo (p=0.029). Three patients (two in the TCC arm and one in the placebo arm) discontinued the trial due to an adverse event.

Conclusion: Topical TCC can be an appropriate option in a subset of patients with mild chronic LBP accompanied by muscle spasms. In a subset of patients with milder pain intensity, topical TCC may improve pain earlier. The results of this trial are compatible with the treatment approaches used in daily practice.

Keywords: Chronic low back pain; placebo; pressure pain threshold, thiocolchicoside.

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Low back pain (LBP) is an important, common public health problem that affects individuals of all ages and causes social and economic losses. It has been the leading cause of years lived with disability in 126 of the 195 countries and territories, with an increase of 57.5% since 1990.[1] Some estimates of point prevalence of LBP range from 12 to 33%, the one-year prevalence ranges from 22 to 65%, and lifetime prevalence ranges from 11 to 84%.[2]

The prevalence ranges across the age groups, which is higher in adults aged between 40 and 69 years.[3] Low back pain is also a recurrent problem; the recurrence rate within 12 months was found to range between 66 to 84%.[4] Several factors play a role in the development of back pain including age, educational status, psychosocial factors, job satisfaction, occupational factors, and obesity.[5] Several studies have reported that severity of pain decreases rapidly for acute LBP and most patients are able to return to work and normal activities within the first month. Further improvements in pain occur up to three months, after which pain and disability levels remain almost constant for 12 months.[4]

There are several treatment options for LBP. Treatment of an acute episode of back pain includes relative rest, activity modification, physical therapy, patient education, and limited medications. Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, muscle relaxants, antidepressants, and opioids are frequently used in the treatment of both acute and chronic back pain.[5]

Thiocolchicoside (TCC) is a semi-synthetic derivative of colchicoside, which shows an affinity for the inhibitory glycine and gamma-aminobutyric acid type A (GABA-A) receptors. Thiocolchicoside induces muscle relaxation without any subjective or objective sedative side effects.[6] In experimental models, TCC was also found to possess analgesic and anti-inflammatory activities.[7]

Guidelines usually suggest consideration of muscle relaxants for short periods in patients with severe, frequent muscle spasms accompanying LBP, although there is insufficient evidence for their use in chronic LBP.[8,9] In the present study, we aimed to evaluate the efficacy and safety of external TCC treatment compared to placebo in patients with chronic mechanical LBP accompanied by acute muscle spasms.

PATIENTS AND METHODS

This national, multi-center, double-blind, parallel-group, placebo-controlled randomized Phase IV study was conducted in 12 centers located in six different geographical regions of Türkiye between March 2020 and March 2021. Inclusion criteria were being between 18 and 65 years, diagnosis of mechanical LBP lasting more than six weeks, detection of an acute muscle spasm on physical examination, and planned initiation of outpatient treatment. Patients who underwent a major spinal injury or who were using alternative medicine methods or herbal products were excluded. Of a total of 301 patients, 292 (106 males, 186 females; mean age: 38.5±11.2 years; range, 18 to 64 years) were included (Figure 1).

The primary endpoint was to assess the efficacy of TCC on Day 3 using the results in pressure pain threshold (PPT) via a pressure algometer (PA). Secondary endpoints were the efficacy of TCC on Day 7 with PPT and on Days 3 and 7 with patient and physician Visual Analog Scale-pain (VAS-pain), safety profile of TCC over time, and the use of paracetamol as a rescue drug. Timepoints were chosen according to a previous study that evaluate the efficacy of topical TCC in the treatment of acute cervical myofascial pain syndrome.[10] As a moderate response to placebo was observed across chronic LBP studies employing VAS, PPT was considered to be a more objective tool and chosen as the primary outcome measure.[11] Patients were randomized into two groups at a ratio of 1:1 electronically through an automated system that was uploaded to the electronic case report form. The first group (TCC group) received 0.25% TCC ointment, while the second group received matching placebo ointment. The patients and the physicians were blinded to the treatment. Topical applications were applied on the painful area in the lumbar region, on lesion-free/intact skin, three times a day for seven days. Data were obtained for demographics, PA measurements and VAS-pain scores, concomitant rescue drug treatment, and adverse events. The PA is used for pain assessment in daily practice; however, an application video was prepared, and the physicians were trained with an online meeting to eliminate the differences between the centers. The PA was applied on the muscle groups with the most intense pain and the intensity that the patient expressed that he/she felt pain was recorded in kg/cm^2 unit at baseline, on Days 3 and 7. A total of three consecutive measurements were made at each visit and the arithmetic mean of these measurements was recorded as algometric

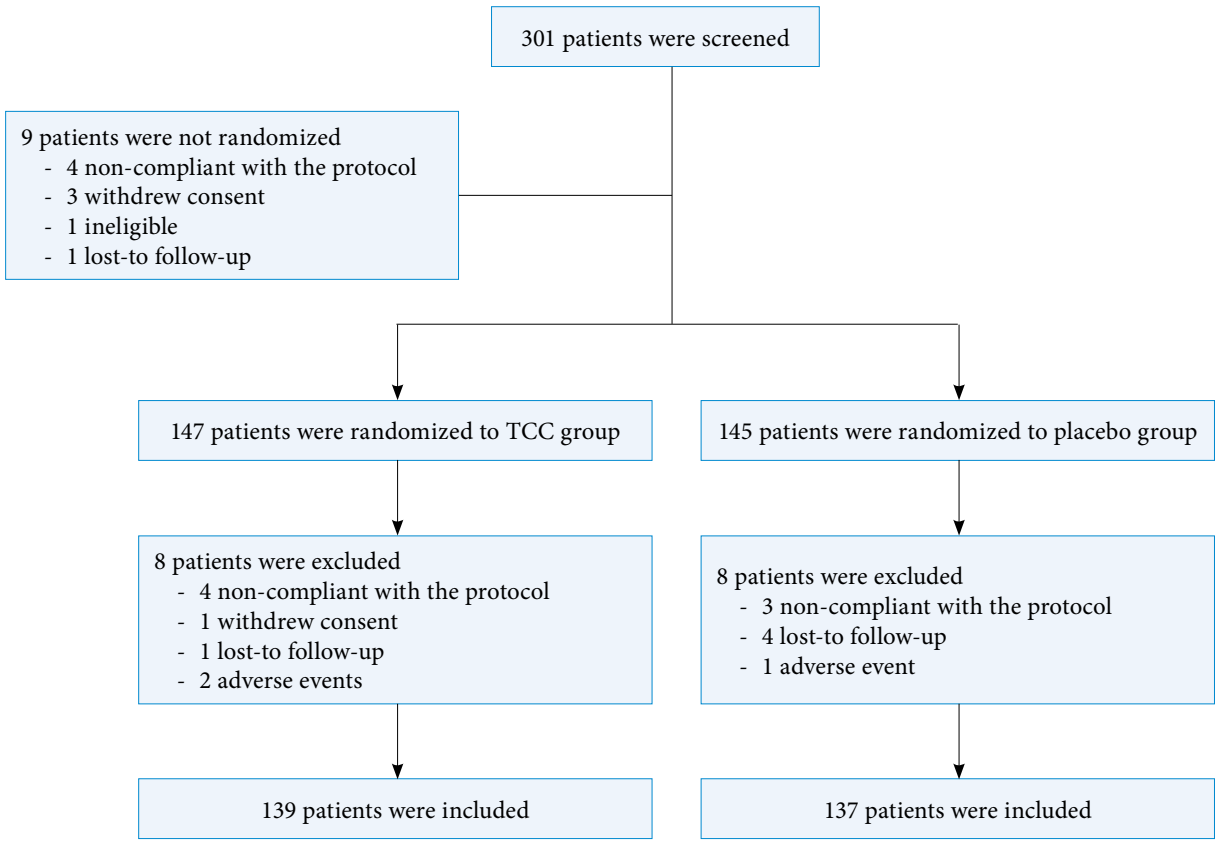

Figure 1. Patient flow chart.
TCC: Thiocolchicoside.

data. The VAS was a self-reported scale consisting of a vertical line of 10 cm referring as 0 was the best status of pain, while 10 was the worst status. The physicians had a standardization training for VAS use. The physician estimate of pain intensity was recorded on physician VAS-pain subjectively after patient's examination and expression of pain status, and the palpation of muscle spasm. If required, a rescue drug (paracetamol, 500 mg tablets with a maximum of 6 tablets/24 h) was used.

Since the study was planned as a superiority study, de Oliveira et al.[12] was taken as an example. Improvements between 1.86 and 6.73 N were defined in the examination of pressure-related pain threshold determined by algometer in kg with three to seven days of treatments. An improvement of at least +4.32 in the TCC group and +2.86 in the placebo group was predicted for superiority which must be confirmed. The common standard deviation was taken as 3.65. It would be sufficient to include 135 patients in each group with alpha 0.10 and a statistical power of 95%.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean ± standard deviation (SD) or median (min-max and the first and third quartiles [Q1-Q3]), while categorical variables were expressed in number and frequency. The normality of the variables was tested using the Shapiro-Wilk test. As the Shapiro-Wilk test suggested normality, independent samples t-test were used to compare parametric values between groups. Repeated measure comparisons of PPT values and VAS scores within group over time were measured with the repeated measures analysis of variance (rANOVA), and in case of significance, Bonferroni test was used for post-hoc analysis. A p value of <0.10 was considered statistically significant.

RESULTS

Randomized patient distribution according to geographical regions was as follows: Marmara,

90 (30.8%); Aegean, 80 (27.4%); Mediterranean, 38 (13.0%); Black Sea, 34 (11.6%); Eastern Anatolia, 30 (10.3%); and Central Anatolia, 20 (6.9%). Of these, 276 patients were included in the final analysis. The mean body mass index (BMI) was 26.4±4.5 kg/m². All the patients attended the third and seventh-day visits. There were 139 patients in the TCC group. Both treatment groups were similar regarding age, sex, and BMI. Baseline demographic and clinical characteristics of the patients are shown in Table 1.

The median (Q1-Q3) PPT value was 3.87 (range, 2.93 to 5.27) for the TCC group and 3.87 (range, 3.15 to 5.29) for the placebo group at baseline. The PPT values significantly improved in both treatment groups over time (p<0.001 for all pairwise comparisons); however, they did not differ between treatment groups (p>0.05 for each visit, Table 2). As both treatment groups had an equal baseline median PPT value, the groups were divided into two according to the median value to compare the patients with milder pain intensity with the patients with more severe pain. Both PPT subgroups were similar regarding age and sex at baseline. In the group with a median PPT value of ≥3.87, the TCC group showed significantly better results than the placebo group on Day 3 (p=0.029); however, it did not significantly differ on Day 7 (p=0.743, Table 3). All treatment subgroups based on median PPT values had significant differences over time (p<0.001 for all subgroups, Table 3). Post-hoc analysis revealed a significant difference of mean PPT values on Days 3 (p=0.004) and 7 (p=0.001) compared to baseline in TCC group with a median PPT value of ≥3.87; however, there was no significant difference between the third and seventh days (p=0.243). In the subgroup with a median PPT value of <3.87, both treatment groups had a difference over time (p<0.001, Table 3), and there was significant difference between all timepoints with the post-hoc analysis (p<0.001 for all comparisons).

The median (Q1-Q3) physician and patient VAS-pain scores were similar for both treatment groups at baseline (Table 4). Both physician and patient VAS-pain scores significantly improved in both treatment groups over time (p<0.001). Post-hoc analysis also revealed a difference for all pairwise comparisons (p<0.001 for all). However, both physician and patient VAS-pain scores did not significantly differ between TCC and placebo groups (p>0.05 for each visit) (Table 4).

During the study, 20.7% (n=57) of the patients used rescue drugs to reduce their pain. Of them, 25 (43.9%) patients were in the TCC group. A total of 15 adverse events were reported by 13 patients during the study (Table 5). A total of 80% of the adverse events were classified as mild in both groups. In the TCC group, two adverse events of two patients were found to be related to the study medication which were pain and

TABLE 1
Baseline demographic and clinical characteristics of patients according to groups

According to treatment groups

	TCC group			Placebo group			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			38.3±11.3			38.6±11.2	0.796
Sex							0.622*
Female	87	62.6		81	59.1		
BMI (kg/m²)			26.2±4.5			26.6±4.5	0.313

According to median PPT value subgroups

	PPT value <3.87							PPT value ≥3.87						
	TCC group			Placebo group				TCC group			Placebo group			
Characteristics	n	%	Mean±SD	n	%	Mean±SD	*p*	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			38.9±11.9			38.7±11.1	0.922			37.7±10.7			38.5±11.3	0.652
Sex														
Female	46	66.7		39	58.2		0.376*	41	58.6		42	60.0		1.000*
BMI (kg/m²)			25.6±4.6			27.2±4.8	0.061			26.5±4.5			26.1±4.1	0.574

TCC: Thiocolchicoside; SD: Standard deviation; BMI: Body mass index; PPT: Pressure pain threshold; * Chi-square test.

TABLE 2
Pressure algometer results of the treatment groups in all visits

Algometric measurements (PPT)													
	Baseline				3rd day				7th day				
Treatment	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	*p*
TCC group (n=139)	4.2±1.6	1.13-9.07	3.87	2.93-5.27	4.6±1.8	1.10-9.50	4.20	3.23-5.90	4.9±1.9	1.10-10.00	4.53	3.47-6.33	<0.001
Placebo group (n=137)	4.2±1.4	1.07-7.53	3.87	3.15-5.29	4.5±1.5	1.07-8.67	4.37	3.40-5.54	5.1±1.9	1.07-14.00	5.13	3.65-6.20	<0.001
P value (TCC *vs.* placebo)			0.906				0.701				0.411		

PPT: Pressure pain threshold; SD: Standard deviation; Q1: First quartile; Q3: Third quartile; TCC: Thiocolchicoside; * Repeated measures analysis of variance (rANOVA).

TABLE 3
Pressure algometer results of subgroups in all visits

		Algometric measurements (PPT)												
		Baseline				3rd day				7th day				
	Treatment	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	*p*
PPT value <3.87 group	TCC group (n=69)	2.9±0.6	1.13-3.83	2.93	2.45-3.44	3.3±1.0	1.10-6.40	3.27	2.60-3.69	3.6±1.3	1.10-7.13	3.57	2.67-4.47	<0.001
	Placebo group (n=67)	3.0±0.6	1.07-3.80	3.13	2.67-3.43	3.6±1.1	1.07-5.93	3.43	2.87-4.37	4.1±1.3	1.07-6.67	4.13	3.13-5.20	<0.001
	P value (TCC *vs.* placebo)			0.355				0.076				0.040		
PPT value ≥3.87 group	TCC group (n=70)	5.4±1.3	3.87-9.07	5.27	4.27-6.34	5.9±1.5	2.17-9.50	5.83	5.02-6.63	6.1±1.6	2.23-10.00	6.19	4.79-7.16	<0.001
	Placebo group (n=70)	5.3±1.0	3.87-7.53	5.25	4.36-6.00	5.4±1.3	2.90-8.67	5.33	4.32-6.30	6.0±1.9	2.50-14.00	5.95	4.92-7.01	<0.001
	P value (TCC *vs.* placebo)			0.408				0.029				0.743		

PPT: Pressure pain threshold; SD: Standard deviation; Q1: First quartile; Q3: Third quartile; TCC: Thiocolchicoside; * Repeated measures analysis of variance (rANOVA)

TABLE 4
Physician and patient Visual Analog Scale scores of treatment groups

Treatment groups	Baseline				3rd day				7th day				p*
	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	Mean±SD	Min-Max	Median	Q1-Q3	
Physician VAS pain scores													
TCC group (n=139)	5.8±1.4	2-10	6	5-7	4.5±1.7	0-10	4	3-6	3.5±2.0	0-9	3	2-5	<0.001
Placebo group (n=137)	5.7±1.3	2-9	6	5-7	4.6±1.6	0-9	5	3-6	3.6±2.2	0-8	4	2-5	
P value (TCC *vs.* placebo)	0.577				0.828				0.770				
Patient VAS pain scores													
TCC group (n=139)	6.2±1.5	3-10	6	5-7	4.8±1.7	0-10	5	4-6	3.8±2.1	0-10	3	2-5	<0.001
Placebo group (n=137)	6.3±1.5	3-10	6	5-7	4.9±1.8	1-9	5	4-6	3.9±2.3	0-9	4	2-5	
P value (TCC *vs.* placebo)	0.673				0.846				0.604				

VAS: Visual analog scale; PPT: Pressure pain threshold; SD: Standard deviation; Q1: First quartile; Q3: Third quartile; TCC: Thiocolchicoside; * Repeated measures analysis of variance (rANOVA).

TABLE 5
Proportions of patients with adverse events

	TCC group		Placebo group	
	n	%	n	%
Abdominal pain	0	0	1	0.73
Nausea	0	0	1	0.73
Pain (application region)*	1	0.72	1	0.73
Hypersensitivity (application region)*	1	0.72	0	0
Hyperhidrosis	1	0.72	0	0
Peripheral edema	1	0.72	0	0
Arthralgia	0	0	1	0.73
Lumbar pain	2	1.44	0	0
Headache	2	1.44	0	0
Dyspnea	1	0.72	0	0
Paraesthesia	0	0	1	0.73
Chelation therapy (planned)	1	0.72	0	0
Total	10	7.20	5	3.65

TCC: Thiocolchicoside; * Related to the study medication.

hypersensitivity of the application region. One patient in the placebo group had a serious adverse event of hospitalization due to chest pain which did not lead to any complications.

DISCUSSION

The aim of this study was to assess the efficacy and safety of external TCC treatment versus placebo in patients with mechanical LBP. Our study results showed that there was no significant difference between the groups for the primary endpoint of assessing the efficacy of TCC on Day 3 as evidenced by the PPT results. Subgroup analysis revealed an improvement of pain intensity for TCC in the group of patients with higher PPT values. The safety profile of TCC ointment was found to be similar to the placebo group.

There are several studies of systemic TCC treatment reporting significant improvement in back pain. Tüzün et al.[13] revealed that intramuscular injection of TCC showed a significant improvement for acute LBP compared to placebo by changes of VAS scores. Similarly, it was found that pain at rest improved significantly in the oral TCC group, compared to tizanidine group for acute LBP.[14] An open, randomized-controlled trial[15] and an observational study[16] evaluated the efficacy of TCC when added to standard NSAID therapy compared to NSAID monotherapy. Both studies revealed decrease in

pain and improvement in functional status with combination therapy according to VAS assessment. In a previous study, the ointment form of TCC had similar results with intramuscular injection and concluded that the ointment form may be a good alternative, particularly in patients who cannot receive injections.[10]

In our study, the PPT and VAS-pain results were similar at all visits between TCC and placebo groups. These results were not in line with some previous studies. In a recent study, TCC was identified as the only variable able to affect muscle parameters in the professional cyclists.[17] It was shown that in the group of athletes that used topical TCC treatment with massage therapy, the increase in tone, stiffness, and soreness was significantly lower than in the group receiving only massage therapy. Similarly, Altan et al.[18] showed superior improvement in the patients with acute LBP that used phonophoresis with the combination of diclofenac + TCC gel compared to routine ultrasound treatment with non-therapeutic gel by several parameters. However, in our study, pain intensity ranged widely regarding the PPT values and, therefore, a subgroup analysis was done according to the baseline median PPT value. Earlier studies showed lower PPT values in chronic pain patients which are compatible with the PPT values in our study.[19-21] Our subgroup analysis revealed that TCC had a better improvement of pain compared to placebo in patients with higher PPT values on Day 3. Therefore, TCC can be a good topical option for patients with milder LBP.

Although the European Medicines Agency (EMA) recommended restricting use of systemic TCC due to adverse events since 2014, topical forms of the medication were found to be safe.[22] In our study, TCC ointment was also found to be safe, and no new safety signal was observed.

There are several strengths of this study. First, the PA was used as an objective measure of pain sensation. Also, patients' results were distributed homogenously in a multi-center study, and the patient recruitment and study procedures were completed during the anxious and unusual environment of the novel coronavirus disease-2019 (COVID-19) pandemic period. In Türkiye, the close evaluation and follow-up of the patients by professors in each center is also another strength; however, this may have created an increased placebo effect. The main limitations are inability to recruit patients with severe muscle spasms due to the outpatient nature of the study and failure to demonstrate the efficacy in patients with obesity due to the use of a topical treatment for chronic LBP.

In conclusion, LBP is a leading cause of activity limitation and work absence, resulting in an economic burden.[23] There are several studies concerning the economic burden of back pain contributed with productivity losses due to disability and increased indirect costs due to absenteeism.[24-26] In a study of over 28,000 workers in the United States, it was shown that headaches and back pain were dominant causes of lost productive time and missed days of work.[27] Returning to daily life activities as soon as possible is important in terms of both quality and economical aspects of the problem. However, sedation, which is the most important side effect of muscle relaxants, limits the use of these medications regularly. Therefore, topical TCC can be an appropriate option in a subset of patients with mild chronic LBP accompanied by muscle spasms, in terms of decreasing the number of days with pain and allowing an earlier functional recovery. The results of this study are compatible with the treatment approaches used in daily practice. Further comprehensive studies are needed on the use of muscle relaxants for spasms of various back muscle groups.

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Ethics Committee Approval: The study protocol was approved by the Clinical Research Ethics Committee of Istanbul University (date: 10.01.2020, no: 2011-KAEK-57-94). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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