A RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL, COMPARING THE COMBINATION OF CAFFEINE, CARISOPRODOL, SODIUM DICLOFENAC AND PARACETAMOL VERSUS CYCLOBENZAPRINE, TO EVALUATE EFFICACY AND SAFETY IN THE TREATMENT OF PATIENTS WITH ACUTE LOW BACK PAIN AND LUMBOISCHIALGIA

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SUMMARY

Objective: To evaluate the efficacy and safety of the combination of diclofenac, paracetamol, carisoprodol, and caffeine in the treatment of acute low back pain and lumboischialgia, compared to the efficacy and safety of cyclobenzaprine. **Study design:** Single-center, comparative, randomized, double-blind clinical trial. **Method:** Drugs were administered t.i.d. for a period of 7 days. **Study population:** 108 patients with a diagnosis of acute low back pain and lumboischialgia in the last 7 days were randomized, being included 54 patients in each group. **Endpoints:** The primary efficacy endpoints selected for the study were the pain visual analog scale and the Roland-Morris questionnaire, the results of which were compared before and after treatment. The secondary endpoints were the patient's and the investigator's overall assessment of the treatment, as well as the use of the analgesic rescue medication. The safety criteria were the tolerability analysis, the medication discontinuation due to adverse events, and laboratory tests. **Results:** There were no statistically significant differences among the groups regarding efficacy in any of the endpoints examined. Both medications have been shown to be safe and tolerable in the treatment of acute low back pain and lumboischialgia. The thorough statistical analysis revealed a difference between the two groups only concerning adverse events, which were more frequent in the group treated with cyclobenzaprine.

Keywords: Diclofenac; Carisoprodol; Caffeine; Acetaminophen; Clinical trial; Randomized controlled trials; Double-blind method; Low back pain.

INTRODUCTION

The terms acute low back pain and mechanical-postural acute lumboischialgia, idiopathic or on-specific, are frequently employed to describe a clinical condition for which, at least in 85% of the cases, is impossible to establish a specific diagnosis. The matter gained attention at least 20 years ago but still remains as one of the most controversial topics in medicine. An article recently published on Archives of Internal Medicine journal questions if this entity really exists (low back pain) and wonders if there is any well-designed and qualified study to answer this question[1].

The difficulties of studying and addressing low back pain are due to many factors, such as: inexistence of a true relationship between clinical findings and imaging findings; the segment being innervated by a diffuse and interlaced nervous meshwork, making difficult to precisely determine the original site of pain, except in radiculomedullary affections; by the fact that muscles contractions, frequent and painful, are not accompanied by an demonstrable histological injury, and; for being rarely surgical, there are scarce and inadequate information about anatomical and histological findings of potentially compromised structures, which makes difficult to interpret the painful phenomenon[2].

Low back pain constitutes a frequent cause of morbidity and impairment, only surpassed by headache on the scale of painful disorders affecting the human being. All over the world, 60% - 80% of people shall develop low back pain during the course of life, and 2% - 5% shall present it in any given moment. In the United States, low back pain is one of the most common problems that lead people to seek for healthcare, and this is the most common cause of disability in individuals younger than 45 years old. Annual costs with healthcare and the productivity loss in that country are approximately 100 million dollars. However, only 10% of the patients account for 90% of the costs, regarding this disease treatment as one of the primary health concerns[3]. There are no Brazilian statistics regarding this.

The definition of low back pain and acute lumboischialgia is the intolerance to activity caused by low back pain and, sometimes, reflecting on the legs, lasting less than 3 months. Mechanical causes of acute low back pain include musculoskeletal and ligament structures dysfunction. Pain may be originated at intervertebral discs and joints, ligaments, and muscles. Usually, it presents a good prognosis, if not related to secondary causes, which are much less frequent[4].

Study conducted at the Department of Orthopaedics and Traumatology of the Federal University of São Paulo – Paulista Medical School

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Most of patients improve just with a symptomatic treatment for pain. Indeed, about 60% of the low back pain patients refer pain relief within 7 days only with conservative treatment, and the majority improves within up to a month. First-choice drug therapy consists of ordinary analgesics, such as paracetamol and dipirone, and non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin and diclofenac. Myorrelaxants are an option, although they have not shown to be superior to NSAIDs in numerous clinical assays[5].

There are no large, placebo-controlled and well-designed clinical trials determining the best treatment for acute low back pain and acute lumboischialgia. But there are many smaller controlled studies with a wide range of treatment approaches, from the most conservative treatment, that is, where no drug intervention or rest exists, to aggressive treatments, such as surgery. We can find clinical assays with any of those interventions[5].

- Pharmacologic treatment with ordinary analgesics, NSAIDs, myorrelaxant agents, opioid analgesics, colchicine and antidepressant agents;
- Physical treatments, such as spinal manipulation, physical agents application and their modalities, transcutaneous neural electric stimulation, use of inner soles on shoes, use of lumbar support corsets, tractions, biofeedback, intra-articular injections, epidural steroid, lidocaine and opioids injections, and acupuncture;
- Change of activity, such as recommendations to avoid some kinds of exercises for a period of time, bedtime rest and the practice of corrective exercises.

However, no treatment has been proven to be the elected one, nor any of them has been adopted by scientific community as the first-choice one. One of the reasons for this is that clinical cases presentation in emergency services happens quite heterogeneously: each case is a different case, and the doctor must pay attention to patient's history, his/ her signs and symptoms, and his/ her physical examination in the search for suspect traces of more severe diseases, especially cancer.

One of the most remarkable issues regarding the use of drug therapy to control pain in acute low back pain and acute lumboischialgia was if myorrelaxant agents were indeed efficient; and if so, which was the best one. In 1983, Glassman and Soyka[6] tried to answer this question by conducting a double-blind study involving 78 patients: half receiving cyclobenzaprine 40 mg/ day, and the other half receiving carisoprodol 1400 mg/ day. The authors concluded that there was no statistically significant difference between both groups, determining that both myorrelaxant agents were similar in terms of efficacy.

Here another question emerges: is it better to associate NSAID and myorrelaxant agents or to use it alone? Borenstein e col.[7] performed an open, randomized clinical trial comparing naproxen alone and combined to cyclobenzaprine in patients diagnosed with acute low back pain and muscular spasm. They concluded that the combination of naxopren and cyclobenzaprine was more efficient for pain relief than naxopren alone, showing a statistically significant difference.

More recently, the role of anti-inflammatories selectively inhibiting the COX-2 enzyme[8] and of opioids for moderate to severe cases – whether combined to ordinary analgesics or not[9,10] - have been studied, always comparing them with the drug therapy mostly used: the NSAID.

Caffeine is a methylxanthine structurally related to theophylline. It seems to be an efficient adjuvant analgesic and is frequently used as a stimulant. It is a powerful competitive inhibitor of phosphodiesterase, the enzyme responsible for AMPc inactivation. Increased intracellular levels of AMPc in vitro act as mediators in cell activities, such as for relaxing muscular layer and inhibiting histamine release by mast cells. In addition, caffeine increases permeability to calcium at the sarcoplasmic reticulum and competitively blocks adenosine receptors[11]. Caffeine is approved by FDA for analgesic indications, because it was proved that caffeine reduced the need of analgesics by 40%[12].

Carisoprodol is a musculoskeletal relaxant chemically related to meprobamato. It is an efficient adjuvant agent in acute musculoskeletal disorders treatment. Its mechanism of action remains unclear, as well as of other myorrelaxants, although it is already known that, at high doses, a depression of polysynaptic and even monosynaptic reflexes occurs. Carisoprodol is FDA-approved as an adjuvant therapy for painful acute musculoskeletal processes[13].

Diclofenac is a NSAID, with analgesic, anti-inflammatory and anti-pyretic activities. Chemically, this is a byproduct of phenylacetic acid. In clinical practice, it is indicated for many processes - whether inflammatory or not – such as rheumatoid arthritis, osteoarthrosis, ankylosing spondylitis, nephrocolic, minor surgeries, trauma and dysmenorrhea. It has been used in 94 countries for treating 115 million people a month. In the last 12 years, it was tested in 18.000 research subjects in controlled clinical trials and in 85.000 in open trials, in 12 countries. Diclofenac is a powerful inhibitor of the cyclooxigenase activity, causing a great reduction on the formation of prostaglandins, prostacyclin and thromboxane, all of them mediators of the inflammatory response[14].

Paracetamol is an analgesic and anti-pyretic agent. The mechanism of action is not clearly described, but it seems to be related to the inhibition of the enzyme prostaglandin synthetase, on central level. The fact that paracetamol does not inhibit platelet aggregation and does not cause adverse reactions on the gastrointestinal tract, makes it an excellent option for controlling pain and fever in patients formally contraindicated to use anti-inflammatory agents, such as the acetylsalicylic acid[15].

Cyclobenzaprine is a musculoskeletal rexalant, indicated in muscular spasms of musculoskeletal ethiology, accompanied by acute pain, such as low back pain, wrynecks, fibrositis, scapulohumeral periarthritis, cervicobrachialgias. Its efficacy is comparable to carisoprodol. It is structurally related to tricyclic antidepressants and present similar pharmacological effects, acting on central nervous system, precisely on brain stem[16].

The combination of caffeine 30mg, carisoprodol 125mg, sodium diclofenac 50mg, and paracetamol 300mg is registered at the Ministry of Health under the name Tandrilax since October 1979.

In this clinical trial, efficacy and safety of the combination of caffeine 30mg, carisoprodol125mg, sodium diclofenac 50mg and paracetamol 300mg have been tested in acute low back pain and lumboischialgia, compared to the efficiency and safety of cyclobenzaprine.

CASE SERIES AND METHODS

This randomized, double-blind clinical trial was conducted at the Orthopaedic Emergency Care, Hospital São Paulo - UNIFESP-EPM, according to the Good Clinical Practices as defined by the International Conference on Harmonization (ICH) and by the Declaration of Helsinki. Clinical protocol was approved by the Committee on Ethics at UNIFESP and all patients included in the study signed an informed consent prior to screening.

Patients from both genders, ages ranging from 18 to 45 years old, complaining of low back pain or lumboischialgia in the last 7 days, presenting normal laboratory tests and lumbar spine X-ray images have been assessed. Patients with any concomitant arthropathy, history of trauma of any nature, strong pain at minor efforts, and history of cancer or significant weight loss in the last 3 months have been excluded from assessment. Additionally, patients with history of spine surgery, chronic-degenerative diseases, transplanted, neurological changes at examination, epigastralgia, or history of gastritis and peptic ulcer, allergy to any of study drugs components, or those under treatment for low back pain have also been excluded.

Clinical phase comprehended 3 visits. In the first visit, the patient was submitted to clinical investigation and laboratory tests (hemogram, creatinine, glucose, TGO, TGP, and prothrombin activity) and X-ray images of the lumbosacral spine were requested. The patients who delivered screening tests within normal parameters were randomized in the second visit. These were performed at the AFIP Laboratory, of the Psychobiology Institute, UNIFESP, with checked laboratory certificates. Randomization was made with blocks exchange with 6 patients each (3 in each therapy). Treatment duration was 7 days, after which the patients were assessed again and submitted to the same clinical tests for safety.

Primary efficacy criteria selected for the study were the analogical visual scale for pain and the Roland Morris' questionnaire, of which previous and subsequent results were compared. Secondary criteria included global assessment of treatment by the patient and by the investigator and the use of analgesic rescue medication (paracetamol). Safety criteria included tolerability analysis, drug withdrawal due to adverse reaction and the laboratory tests mentioned. Data on adverse reactions were collected during the third visit and from patients' diaries, which also provided information regarding the use of analgesic rescue medication.

A primary statistical analysis was performed based on the principles of intention to treat including patients who discontinued treatment. This analysis was used to categorize patients as respondent or non-respondent. The chi-square test was applied with the intention of seeking for differences among therapies studied.

The secondary analysis was limited to patients who completed the treatment or to those withdrawn from treatment due to inefficiency, concomitant disease or due to adverse events.

The outcomes were assessed by the software Statistica version 5.0 (StatSoft, Inc - Tulsa - USA) by adopting a significance level of 0.05 ($a = 5\%$) and adjusting it whenever necessary. The assessment comprehended a description of the study population, and subjective and objective clinical analyses. Biodemographic and clinical data were investigated and checked for eligibility of all patients. Deviations from normality and homogeneity were recorded and appropriate changes for statistical comparisons were made. Qualitative variables (nominal) are represented by absolute frequency (n) and relative frequency (%). Quantitative variables (ordinals) are represented by average, standard deviation, median, minimum and maximum values.

By applying the Roland-Morris' quality-of-life questionnaire, 24 domains are created – functional capacity, physical aspects limitation, pain, overall health status, vitality, social aspects, emotional aspects and mental health. The evolution analysis for those 24 aspects was performed by means of the Variance Analysis (ANOVA) for repeated measures in one factor, when normality (Kolmogorov-Smirnov's test with Lilliefors' adaptation) and data homogeneity (Levene's test) were confirmed. Wilcoxon's and Mann-Withney's non-parametric tests were applied, after the adjustment of the significance level (a), in case the conditions for ANOVA use had not been satisfied, even after data transforming technique.

For pain assessment by the Analogical Visual Scale (AVS) ANOVA was used for repeated measurements of one factor, after variances normality and homogeneity were verified. In case variances homogeneity has not been observed, Wilcoxon's and Mann-Withney's non-parametric tests were applied and the significance level (a) was adjusted. The effective change between the first and the last visit was compared by using non-parametric tests for the following variables: disease severity (investigator's assessment) and overall assessment by the patient – global improvement, work, social and domestic lives.

ANOVA was used to determine whether differences among treatments existed or not regarding global assessment according to investigator's opinion and patient's opinion, measured by the Analogical Visual Scale.

After determining the frequency of patients requiring paracetamol as rescue medication, the chi-squared/ Fisher's test was applied. Variables of physical examination, including vital signs, were analyzed by ANOVA.

All patients receiving at least one dose of the medications foreseen on protocol shall be included in the tolerability analysis. Tolerability was studied by the frequency of adverse events and their relationship with the drug. All adverse events reported were analyzed for frequency, intensity and cause-relationship.

RESULTS

One hundred and eight patients with acute low back pain or acute lumboischialgia were randomized for trial, being 54 from the combination group (T), and 54 from the cyclobenzaprine group (C). From the 108 patients included, 98 were included in the efficacy analysis. Drop out causes were: adverse events (6), lost follow-up (5), patient's decision (2), protocol violation (2), lack of efficacy (1) and one patient was disregarded due to administrative reasons. All patients above mentioned received at least one dose of the study drugs and, therefore, were included in the tolerability analysis (108 patients).

There was no statistically significant difference between both treatment groups regarding biodemographic characteristics (Table 1). Vital signs and physical examination at baseline did not show significant differences between both groups as well.

EFFICACY ANALYSIS

The assessment of pain observed by AVS has shown a statistically significant evolution for both treatments ($F = 220.52 – p<0.000001$), but without differences between them
($F = 1.17$ – ns) (Table 2 – Figure 1).

Pain was also assessed by the Roland-Morris' Questionnaire. In the combination group, patients achieved a resulting score of 6.1 in average (from the original 15.5) for the questionnaire, and, in the cyclobenzaprine group, we saw a reduction from 15.4 to 7.3. Evolution was significant for both treatment groups ($F = 171.57 – p<0.000001$), although not establishing a difference between them ($F = 0.36$-ns) (Table 3- Figure 2).

Global assessment of treatments in the opinion of the physicians and patients was not different between both treatments (Physician:

U = 1066.5 – ns / Patient: U = 1127.5 – ns) (Figure 3). Few patients referred taking the rescue medication the day before last visit (Table 4).

The evolution of vital signs and endpoint physical examination did not show changes and differences between treatments. The only exception to this was the heart rate, which demonstrated a significant increase (F = 4.85 – p<0.05), especially in the group receiving cyclobenzaprine (F = 4.93 – p<0.05) (Table 5).

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol	CYCLOBENZAPRINE	Test
AGE (years)	N = 50	N = 48	Student's t-test, non-paired
• Average ± Standard Deviation	37.,5 ± 9.3	36.5 ± 9.4	
• Median	38.5	35.0	t = 0.52 - ns
• Minimum – Maximum	19 – 54	18 – 54	
GENDER	N = 50	N = 48	
• Male	22 (44.0)	21 (43.8)	χ^2_1 = 0.03 - ns
• Female	28 (56.0)	27 (56.2)	
RACE	N = 50	N = 48	Caucasians vs others
• Caucasian	35 (70.0)	36 (75.0)	
• Yellow	2 (4.0)	-	
• Black	6 (12.0)	2 (4.2)	χ^2_1 = 1.46 - ns
• Mulatto	7 (14.0)	10 (20.8)	

Table 1 - *Biodemographic Data*

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol		CYCLOBENZAPRINE	
	DAY 0	DAY 7	DAY 0	DAY 7
PAIN ASSESSMENT	N = 50	N = 50	N = 48	N = 48
• Average ± Standard Deviation	7.9 ± 1.9	2.9 ± 3.0	8.1 ± 1.6	3.6 ± 3.2
• Median	8.0	2.0	8.0	4.0
• Minimum – Maximum	0 – 10	0 – 10	5 – 10	0 – 10

ANOVA: Drugs' effect: F = 1.17 - ns — Treatment Time effect: F = 220.52 – p<0.000001

Table 2 - *Pain Assessment - AVS*

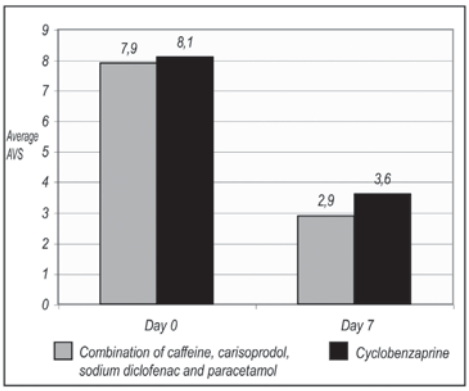

Figure 1 - *Pain Assessment - AVS*

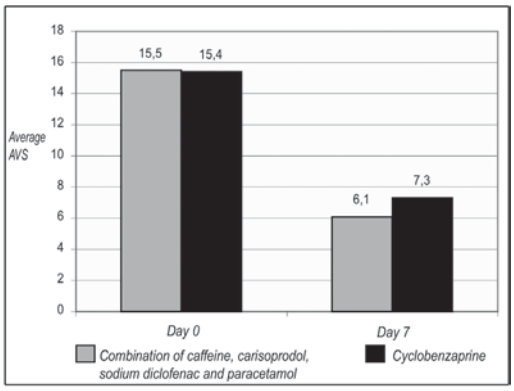

Figure 2 - *Pain Assessment – Roland Morris' Questionnaire*

Tolerability Analysis

The tolerability analysis was performed in all patients (108). The investigator considered that 77.7% of patients receiving *Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol presented excellent or good tolerability. In the group receiving cyclo-benzaprine, this rate was 75.8% - with no differences between treatments (Table 6). Despite this doctor's evaluation, we saw that a higher and significant number of patients in the cyclobenzaprine group referred at least one adverse event (p<0.05).

Considering only the adverse events related to medication, this factor is also observed, with 57.7% of the patients in the cyclobenzaprine group referring an adverse event against 33.3% of the patients in the combination group (p<0.05) (Tables 7 and 8). Although 34 events have been referred with the combination, and 71 with cyclobenzaprine, most of those were mild (Table 9 – Figure 4).

A statistically higher number of patients referring dry mouth (P = 0.0018), somnolence (P = 0.0002) and dizziness (P = 0.0014) was observed in the cyclobenzaprine group.

The results of hemogram and biochemical tests did not show significant changes.

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol		CYCLOBENZAPRINE	
	DAY 0	DAY 7	DAY 0	DAY 7
PAIN ASSESSMENT	N = 50	N = 50	N = 48	N = 48
• Average ± Standard Deviation	15.5 ± 4.8	6.1 ± 5.7	15.4 ± 4.9	7.3 ± 6.9
• Median	16.5	4.5	16.5	5.0
• Minimum – Maximum	5 – 23	0 – 18	4 – 22	0 – 23

ANOVA: Drugs´effect: F = 0,36 - ns — Treatment time effect: F = 171,57 - p< 0,000001

Table 3 - *Pain Assessment –Roland Morris' Questionnaire*

DISCUSSION

Low back pain and lumboischialgia remain as a public health problem and a challenge in clinicians, rheumatologists and orthopedists offices. Various medications are indicated as therapy, but there is no consensus about it yet.

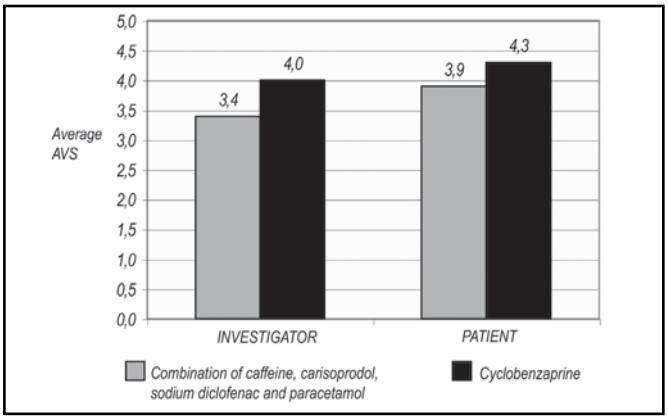

Figure 3 - *Overall Treatment Assessment*

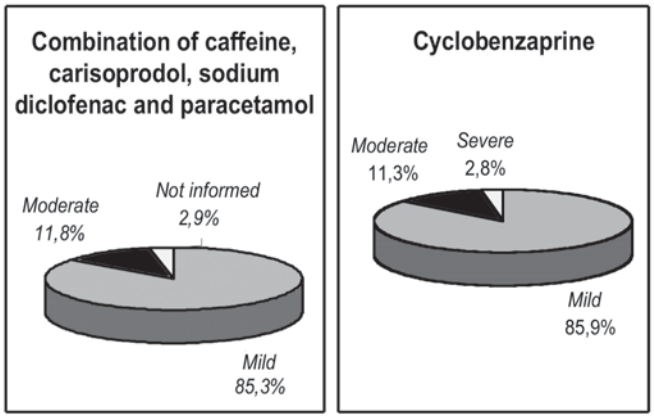

Figure 4 - *Intensity of adverse events*

In the attempt of analyzing the efficiency of an anti-inflammatory agent combined to a myorrelaxant and an analgesic, we designed a comparative study for checking the effects produced by each of the drugs on patients' symptoms, as well as for assessing tolerability towards drugs.

In the study design, we tried to minimize the variables involved in the low back pain and to analyze just the signs and symptoms that could be statistically compared targeting the comparison between both drugs.

The absence of identifiable anatomical causes in imaging tests that could be considered as causative of low back pain is also a factor making studies difficult. Today, with magnetic resonance, we have been able to find, in a higher frequency, anatomical changes that could explain some low back pain cases. However, magnetic resonance is not a test indicated for patients presenting with an acute low back pain picture, especially when we are faced with an infrequent complaint, with no apparent cause and usually as an isolated episode.

A patient with acute low back pain presents as an important feature an improvement within few days, since appropriately prescribed. Our objective is to find the clinical therapy that could reduce symptoms as fast as possible and more efficiently, allowing the patient to return to his/her daily activities.

In the past years, the most used treatment is the combination of an analgesic and a non-steroidal anti-inflammatory agent with a myorrelaxant. Nevertheless, a question remains unanswered regarding the use of a combination of myorrelaxant and anti-inflammatory agent or the use of an anti-inflammatory agent alone.

We conducted the double-blind, comparative study between two products: the combination of caffeine, carisoprodol, sodium diclofenac and paracetamol, and cyclobenzaprine. This clinical trial studied the efficiency of drugs, as well as the safety of both products. We also performed the comparative study between groups in an attempt to compare drugs groups to each other.

We began the study with 108 patients, but six (5.5%) were excluded due to adverse effects, and ten (9.2%) due to variable administrative causes. The six patients who experienced adverse effects received only one dose of the drug and were analyzed only for tolerability. Symptoms disappear with drug withdrawal, not requiring additional therapies.

Both studied groups didn't show differences regarding biodemographic data, which is expected in a double-blind study performed in a general hospital's emergency service. Both groups were homogenous and enable an adequate comparison.

At physical examination, overall appearance, skin, respiratory system, heart, ends and other signs and symptoms in general have been assessed. There was no difference between pre and post-treatment and there were no differences between both treatment groups.

When we assessed vital signs, we found similar behaviors for both groups regarding blood pressure, respiratory rate, temperature and body weight. However, when we analyze heart rate, we noticed a significant raise for both groups. In the group receiving cyclobenzaprine, this rise was higher, but with an insignificant difference when compared to the increased heart rate in the group receiving the combination of caffeine, carisoprodol, sodium diclofenac and paracetamol.

By analyzing tolerability in each group, we included all patients, even those who discontinued the study, but previously received at least one dose of the drug. Tolerability was considered as excellent or good in 77.7% of patients receiving the Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol, and in 75.8% of the patients receiving cyclobenzaprine. There was no significant difference among groups.

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol	CYCLOBENZAPRINE	Fisher's Test
Did the patient use paracetamol in the last 24 hours before endpoint visit?	N = 50	N = 48	
• Yes	3 (6.0)	6 (12.5)	P = 0.22 - ns
• No	47 (94.0)	42 (87.5)	

Table 4 - *Rescue Medication Use*

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol		CYCLOBENZAPRINE	
	DAY 0	DAY 7	DAY 0	DAY 7
SYSTOLIC BP (mmHg)	N = 50	N = 50	N = 47	N = 48
• Average ± Standard Deviation	123.3 ± 10.3	124.7 ± 13.4	123.9 ± 10.9	121.1 ± 12.2
• Median	120.0	125.0	125.0	120.0
• Minimum – Maximum	100 – 143	100 – 160	97 – 145	92 – 147
DIASTOLIC BP (mmHg)	N = 50	N = 50	N = 47	N = 48
• Average ± Standard Deviation	81.9 ± 9.3	81.5 ± 10.7	81.6 ± 10.4	78.7 ± 9.9
• Median	80.0	80.0	80.0	80.0
• Minimum – Maximum	50 – 100	60 – 116	59 – 100	60 – 100
HEART RATE (beats/min)	N = 50	N = 50	N = 47	N = 48
• Average ± Standard Deviation	75.9 ± 12.4	78.0 ± 15.3	78.8 ± 10.4	85.9 ± 14.6
• Median	74.5	73.0	76.0	82.5
• Minimum – Maximum	55 – 120	56 – 147	62 – 109	68 – 128
RESPIRATORY RATE (breath/min)	N = 50	N = 50	N = 47	N = 48
• Average ± Standard Deviation	18.6 ± 3.3	19.0 ± 2.9	19.0 ± 3.2	18.5 ± 3.2
• Median	20.0	20.0	20.0	20.0
• Minimum – Maximum	10 – 24	12 – 24	11 – 24	12 – 24
TEMPERATURE (°C)	N = 50	N = 50	N = 47	N = 48
• Average ± Standard Deviation	36.4 ± 0.5	36.4 ± 0.4	36.3 ± 0.5	36.5 ± 0.5
• Median	36.4	36.4	36.4	36.5
• Minimum – Maximum	35 – 37.2	35 – 37.4	34.9 – 37.2	35.4 – 37.2
WEIGHT (kg)	**BASELINE** - N = 50	N = 50	**BASELINE** - N = 48	N = 48
• Average ± Standard Deviation	68.2 ± 14.0	68.7 ± 13.7	70.5 ± 13.5	70.9 ± 13.0
• Median	67.0	67.5	68.5	69.5
• Minimum – Maximum	40 – 98	44 – 98	49 – 114	49 – 114

Table 5 - *Vital Signs*

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol	CYCLOBENZAPRINE	Test
• Excellent	26 (48.1)	26 (48.1)	Excellent vs Good vs Fair + Bad
• Good	16 (29.6)	15 (27.8)	
• Fair	7 (13.0)	6 (11.1)	
• Bad	3 (5.6)	4 (7.4)	$\chi^2_2 = 0.02$ - ns
• Not assessed	2 (3.7)	3 (5.6)	
TOTAL	54	54	

Table 6 - *Global Tolerability Assessment – Investigator's Opinion*

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol	CYCLOBENZAPRINE	Test
• No	31 (57.4)	17 (31.5)	Yes vs No
• Yes	21 (38.9)	34 (63.0)	$\chi^2_1 = 6.13$
• Unknown	2 (3.7)	3 (5.6)	p<0.05
TOTAL	54	54	

Table 7 - *Number of patients with at least one adverse event*

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol	CYCLOBENZAPRINE	Test
• No	33 (61.1)	20 (37.0)	Yes vs No
• Yes	18 (33.3)	31 (57.4)	$\chi^2_1 = 5.66$
• Unknown	3 (5.6)	3 (5.6)	p<0.05
TOTAL	54	54	

Table 8 - *Number of patients with at least one adverse event related*

If we analyze the number of patients presenting at least one adverse event, we find the group receiving cyclobenzaprine with a significant higher number of adverse events than the group receiving the Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol. There was also a significant difference when both groups are compared regarding drug-related adverse events. Nevertheless, we highlight that those effects were mild, but were seen by patients and analyzed by us. Among those events reported in the groups receiving cyclobenzaprine we find complaints of dry mouth, somnolence and dizziness as the most commonly reported.

Laboratory tests did not show changes worthy to note due to treatment in any of the groups.

	Combination of caffeine, carisoprodol, sodium diclofenac and paracetamol				CYCLOBENZAPRINE			
Adverse events	**Mild**	**Moderate**	**Severe**	**Not Informed**	**Mild**	**Moderate**	**Severe**	**Not Informed**
Allergy	-	1 (2.9)	-	-	-	-	-	-
Change on body sensitiveness	-	-	-	-	1 (1.4)	-	-	-
Heartburn	-	-	-	-	1 (1.4)	-	-	-
Swollen belly	1 (2.9)	-	-	-	-	-	-	-
Bitter mouth	-	-	-	-	2 (2.8)	-	-	-
Dry mouth	2 (5.9)	1 (2.9)	-	-	14 (19.7)	1 (1.4)	-	-
Headache	-	-	-	1 (2.9)	3 (4.2)	1 (1.4)	-	-
Colic	-	-	-	-	1 (1.4)	-	-	-
Constipation	-	-	-	-	1 (1.4)	-	-	-
Diarrhea	1 (2.9)	-	-	-	-	-	-	-
Pain in the belly	1 (2.9)	-	-	-	-	-	-	-
Stomachache	3 (8.8)	-	-	-	2 (2.8)	-	-	-
Epigastralgia	4 (11.8)	1 (2.9)	-	-	1 (1.4)	1 (1.4)	-	-
Epistaxis	-	-	-	-	1 (1.4)	-	-	-
Ecchymosis	1 (2.9)	-	-	-	-	-	-	-
Gastralgia	2 (5.9)	-	-	-	-	-	-	-
Insomnia	1 (2.9)	-	-	-	-	-	-	-
Myalgia	-	-	-	-	1 (1.4)	-	-	-
Weakness	-	-	-	-	1 (1.4)	-	-	-
Nausea	3 (8.8)	-	-	-	4 (5.6)	-	-	-
Intestinal obstipation	1 (2.9)	-	-	-	-	-	-	-
Burning sensation	3 (8.8)	1 (2.9)	-	-	1 (1.4)	-	-	-
Thirst	-	-	-	-	1 (1.4)	-	-	-
Somnolence	4 (11.8)	-	-	-	16 (22.5)	3 (4.2)	1 (1.4)	-
Tachycardia	-	-	-	-	1 (1.4)	1 (1.4)	-	-
Dizziness	-	-	-	-	7 (9.9)	1 (1.4)	1 (1.4)	-
Shivering	-	-	-	-	1 (1.4)	-	-	-
Vertigo	-	-	-	-	1 (1.4)	-	-	-
Vomiting	2 (5.9)	-	-	-	-	-	-	-
TOTAL	29 (85.3)	4 (11.8)	-	1 (2.9)	61 (85.9)	8 (11.3)	2 (2.8)	-

Mi: Mild **Mo:** Moderate **S:** Severe **NI:** Not Informed

Table 9 - *Intensity of Adverse Events (total % of events)*

Therefore, we concluded that the detailed statistical analysis showed differences between groups only regarding adverse events, being more common in the group treated with cyclobenzaprine. Both drugs were efficient in controlling patients' complaints and were well tolerated, with no significant changes at physical examination or at laboratory tests.

CONCLUSION

We noted that both drugs promoted a significant reduction of the low back pain, triggering some adverse events, but, in the vast majority, fully tolerable. Medications involved in the research were shown to be safe, because they caused few clinically significant changes on laboratory tests.

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