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Treatment of Acute, Non-traumatic Pain Using a Combination of Diclofenac-cholestyramine, Uridine Triphosphate, Cytidine Monophosphate, and Hydroxycobalamin

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Abstract

This randomized, controlled, double-blind clinical study in parallel groups evaluated the safety and efficacy of an oral combination diclofenac-cholestyramine, nucleotides (uridine and cytidine) and vitamin B_{12} versus the oral combination of nucleotides and vitamin B_{12} in the treatment of acute, non-traumatic pain. Subjects received twice-daily, 10-day oral administration of diclofenac-cholestyramine + uridine + cytidine + vitamin B12 (Group DN, n= 40) or uridine + cytidine + vitamin B_{12} (Group NB, n= 41). The primary study endpoint was the number of subjects with VAS reduction of >30mm after 10 days of treatment. Secondary endpoints included the number of patients with improvement >5 points in the Patient Functionality Questionnaire after 10 days of treatment, and the number of subjects presenting adverse events. Treatment with the combination of diclofenac-cholestyramine, nucleotides and Vitamin B_{12} resulted in a higher number of subjects with VAS score reductions >30mm after 10 days of treatment (87.5% subjects) than in the control group administered nucleotides and Vitamin B_{12} (51.23% of subjects), ($p>0.0006$). A significantly higher number of subjects in the DN group (80%) had a score reduction of >5 points in the Patient Functionality Questionnaire at after 10 days of treatment compared to Group NB (29.3%), ($p<0.001$). The number of subjects presenting AEs did not vary significantly between treatment groups ($p=0.587$). The combination of diclofenac-cholestyramine with uridine, cytidine and vitamin B_{12} was well-tolerated over a 10-day treatment period. The combination reduced pain and improved functionality among subjects presenting acute, non-traumatic pain in the lower back, hips, and neck.

Introduction

The impact of pain on the quality of life can be noted by its interference with patient's ability to carry out normal activities of daily living. The amount of time and resources spent on medical treatments and other healthcare considerations, along with the sense of loss of independence, loss of capacity to work and frustration with pain make them important medical considerations among all ages and walks of life [1].

Although hip pain may occur at any age, its prevalence is higher in individuals over 60 years of age [2]. The etiology of hip pain can generally be determined with a detailed medical history and a physical examination, since different underlying factors lead to different pain patterns [3]. Whereas increased pain upon use and improvement with rest is strongly suggestive of a joint problem, constant pain in contrast points to infectious, inflammatory or neoplastic processes [3].

Neck pain of various origins affects roughly 15% of the global adult population, and is more prevalent in women than men. The incidence of neck pain tends to increase with age, and is also common among those who perform physically demanding or static work [4]. Among the most common underlying causes of neck pain is trauma (e.g., “whiplash”), but it can also represent a local manifestation of systemic disease or a primary disorder of the cervicobrachial region [4]. A conclusive diagnosis of the underlying cause of neck pain is rarely made due to the multifaceted nature of the condition [5].

Acute low back pain presents as pain and muscle stiffness or tension located below the costal margin and above the anterior gluteal fold [6]. An extremely common complaint, it is the second most common symptom-related reason for physician visits in the United States, and affects up to 80% of the worldwide adult population at some point. In contrast to hip and neck pain, low back pain is rarely indicative of additional illness such as infection, systemic disease or malignancy, and the majority of cases are classified as nonspecific low back pain [7].

Management of acute pain affecting the lower back, neck and hips is to recommend first or second-line treatment with a simple analgesic or a non-steroidal anti-inflammatory agent (NSAID) [8,9]. NSAIDS are among the most widely used and commonly prescribed drugs for the symptomatic relief of painful and/or inflammatory clinical conditions, combining an analgesic effect with anti-inflammatory activity [10]. Diclofenac, like other prototypical NSAIDs, exerts its effects by inhibition of prostaglandin synthesis in body tissue by inhibiting cyclooxygenases (COX), specifically COX-1 and COX-2, which act as catalysts in prostaglandin formation in the arachidonic acid pathway. While diclofenac does inhibit both COX-1 and 2, it shows a mild preference towards COX-2 inhibition [11,12]. The diclofenac-cholestyramine complex forms an ion exchange resin, whose administration as compared to diclofenac alone, potentially minimizes toxicity while improving bioavailability, allowing for rapid plasma levels and facilitated drug transfer to tissue sites where the desired drug activity takes place [13,14].

Numerous preclinical investigations have been carried out on the role of the pyrimidine nucleotides uridine and cytidine in peripheral neuropathies of various origins. They have been shown to have beneficial effects in animal studies of nerve and muscle regeneration, where accelerated nerve and muscle fiber regeneration following experimentally-induced crush injury have been reported [15-17]. Other preclinical findings include increased nerve conduction velocity, increased axon myelin surface area and thickness, along with increased levels of neuritic protein neurofilaments and neuronal cell membrane phospholipids (phosphatidylcholine and phosphatidylethanolamine) [18]. Administration of cytidine and uridine has also been evaluated in the clinical setting, in painful conditions such as lumbar and cervical pain, diabetic neuropathy, and traumatic-compressive lesions and neuralgias. These clinical findings indicate a reduction in pain intensity following nucleotide administration [18-23].

Vitamin B_{12} is essential to a variety of processes in the human body, including the maintenance of normal erythropoiesis, cell reproduction and growth, as well as synthesis of nucleoproteins and myelin. In tissues, vitamin B_{12} is converted to coenzyme B_{12}, making it essential in the conversion of methylmalonate to succinate and the synthesis of methionine from homocysteine (a reaction that also requires folate) [24]. It is important to nerve metabolism *via* the remethylation of homocysteine to methionine for *de novo* synthesis of s-adenosylmethionine. Vitamin B_{12} may also play a role in fat and carbohydrate metabolism as well as protein synthesis, *via* the maintenance of sulfhydryl groups in the reduced form required by many sulfhydryl-activated enzyme systems [25,26]. In deficiency states, neurological damage is caused by a disruption of myelin formation that is thought to result from alterations in s-adenosylmethionine requiring reactions [24,26].

Study Objectives. The primary study objective was to evaluate the safety and efficacy of an oral combination of diclofenac-cholestyramine, nucleotides (uridine triphosphate and cytidine monophosphate) and vitamin B_{12} versus the oral combination of, nucleotides (uridine triphosphate and cytidine monophosphate) and vitamin B_{12} in the treatment of acute, non-traumatic pain. The primary study endpoint was the number of subjects with Visual Analog Pain Scale (VAS) reduction of >30mm after 10 days of treatment. Secondary endpoints included the number of patients with improvement >5 points in the Patient Functionality Questionnaire after 10 days of treatment, and the number of subjects presenting adverse events.

Methods

Patients. The study was a double-blind, randomized controlled study performed at Hospital Universitario Constantino Otaviano – a UNIFESO university hospital in Rio de Janeiro, Brazil. The study was submitted to and approved by the UNIFESO ethical committee.

Study Population: After written informed consent and screening, a total of 81 subjects were randomized to treatment on an ambulatory basis. Eligible subjects were between 18 and 65 years of age, with a clinical presentation of acute, non-traumatic pain in the lower back, hips, or neck. A urine pregnancy test was performed on all premenopausal female subjects, who were also required to maintain adequate birth control throughout the treatment period. Exclusion criteria included acute disc damage (evidenced by physical examination, imaging tests or medical history), need for surgical treatment, use of other analgesics or NSAIDs, gastric or intestinal ulcers, and any laboratory exams performed at pretreatment out of reference range.

Study Procedures. Subjects were randomized in order of arrival to the study center, and were assigned a three-digit sequential randomization code that was also used to identify each subject. The randomization codes were

generated using Random Allocation Software (Version 1.0.0) in equal size blocks of 10. Aside from the statistician who generated the study randomization sequence, all other study assessors and personnel were blinded to the randomization sequence until the final patient had completed treatment.

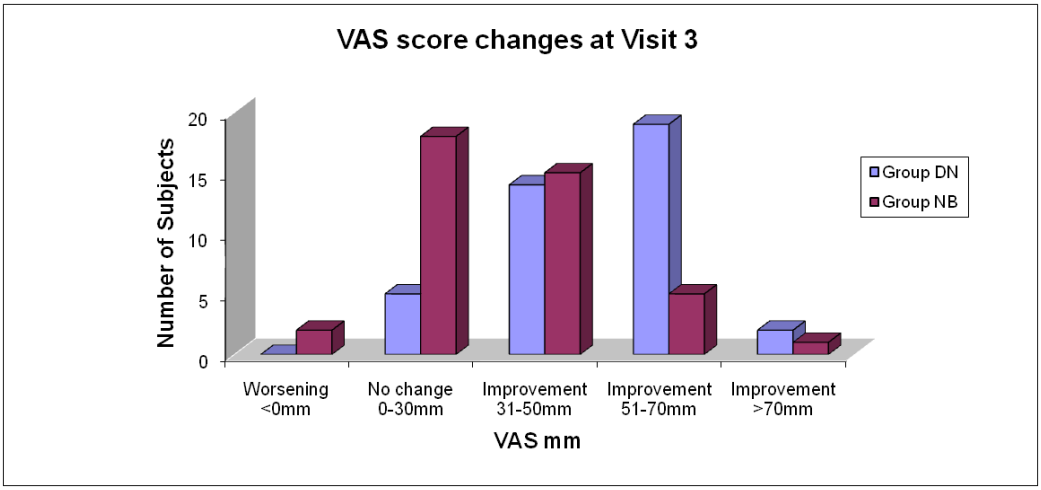

Figure 1. VAS score changes from baseline to Visit 3

Study subjects participated in three visits to the study center: Visit 1 which included screening, randomization, and baseline evaluations, Visit 2 following 5 days of treatment, and Visit 3 after 10 days of treatment. The subjects were divided in two groups: Group DN and Group NB. At pretreatment, each subject received two boxes of study medication (Boxes A and B, respectively). Group DN received Box A containing capsules of 70 mg diclofenac cholestyramine (140 mg of the diclofenac-cholestyramine complex, equivalent to 70 mg of diclofenac), while Box B contained blisters of capsules with 1.5 mg uridine triphosphate, 2.5 mg cytidine monophosphate and 1 mg hydroxocobalamin.

Group NB received Box A containing dummy capsules identical to those of Group DN, while Box B contained the corresponding number of capsules and concentrations as those of Group DN. The study dosing regimen was carefully described to each subject, who was instructed to take one capsule from Box A at breakfast and dinner and two capsules from Box B at breakfast, lunch and at dinner.

The total daily dose of study medication for Group DN was 140 mg diclofenac-cholestyramine; 15 mg cytidine monophosphate; 9 mg uridine triphosphate; 6 mg hydroxocobalamin, while Group NB received: 15 mg cytidine monophosphate; 9 mg uridine triphosphate; 6 mg hydroxocobalamin. After the first 5 days of treatment, the subjects returned to the study center for follow-up evaluations (Visit 2) and were given study medication for the next 5 days of treatment. At each study visit, subjects were asked to return all study medication blisters and packaging for drug compliance evaluation.

Efficacy & Tolerability Evaluations. At pretreatment, a medical history was taken and a complete physical examination was performed. The following information was registered in the clinical research form for each subject during baseline evaluations: date of birth, gender, ethnicity, height, weight, vital signs, pain location, general nutrition status, alcohol consumption, smoking, manual labor and sports activities.

Subjects were submitted to laboratory tests at each study visit, including a complete blood count, fasting blood sugar, partial thromboplastin time, international normalized ratio (INR), creatinine, creatinine kinase, glycosylated hemoglobin A, alanine aminostransferase, aspartate aminotransferase, uric acid, blood urea nitrogen, and blood sedimentation rate.

The efficacy evaluations performed at each study visit were the Visual Analog Pain Scale (VAS), Patient Functionality Questionnaire (PFQ) and an overall efficacy evaluation by the investigating physician. For the VAS, the investigator asked the subject to place a vertical mark along a 100 mm line on the data collection form, from 0 mm (no pain) on the left side to 100 mm (most severe pain) on the right side. The distance from the left side of the scale (0 mm) to the subject's mark was recorded as the VAS score in mm.

For the PFQ, the subjects answered yes or no to the following questions, and one point was scored for each 'yes' answer:

Due to the pain in my (lower back/hips/neck):

1. I do not sleep well
2. I have to lie down more often
3. It is difficult for me to get up from my bed or a chair
4. I can stand only for a short while
5. I can walk up stairs only slowly
6. It is difficult for me to wash or dry off my whole body
7. It is difficult for me to put on my clothes
8. I can only walk short distances
9. I try to avoid picking things up from the floor
10. I have to change my posture more often
11. I cannot carry heavy things
12. I have to ask other people for assistance

At the end of the study treatment period, the investigating physician was asked to evaluate the overall efficacy of the study medication, as "Very Good", "Good", "Fair" or "Poor".

Adverse event monitoring took place at throughout the study treatment period. Any alterations in laboratory tests from baseline at Visit 2 or Visit 3 at were recorded as adverse events. At the end of the study treatment period, the investigating physician was asked to evaluate the overall tolerability of the study medication, using the same scale of "Very Good", "Good", "Fair" or "Poor" as was used for the final efficacy assessment.

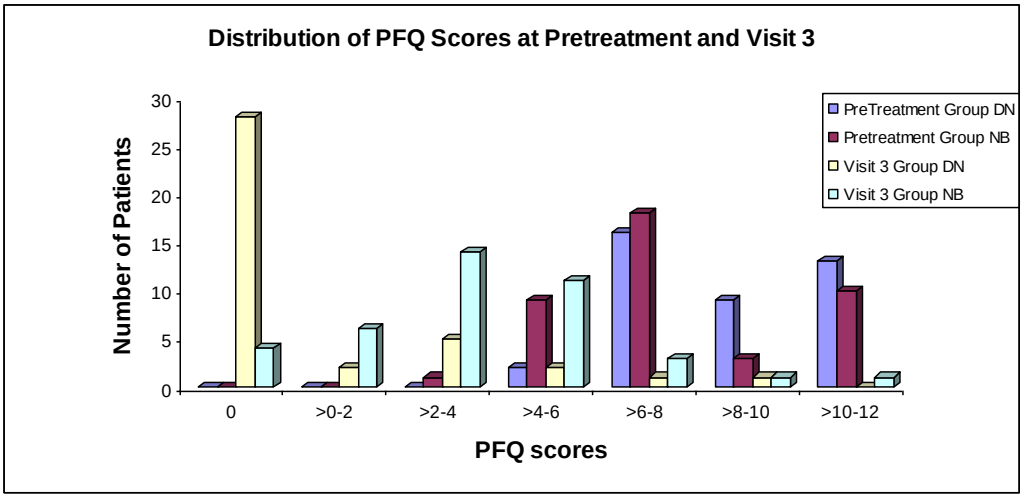

Figure 2. Patient Functionality Scores at Pretreatment and Visit 3

Statistical Analysis: The statistical data analysis followed a pre-established protocol for the intent-to-treat population, including all subjects randomized to treatment who had received at least one dose of the study medication. Data analysis was performed using the software GraphPad Prism, version 5.0. Statistical significance was defined with a two-tailed p value of less than 0.05 with a confidence interval of 95%. Results were compared within and between treatment groups using the χ^2 or Fisher's exact test for categorical variables and the Student's-T test or ANOVA for continuous variables.

Results

Demographic Data and Pretreatment Evaluations. A total of 81 subjects was randomized to treatment, with 40 subjects in Group DN (diclofenac cholestyramine + nucleotides + vitamin B_{12}) and 41 subjects in Group NB (nucleotides + vitamin B_{12}). Table 1 summarizes the subject's demographic data. The mean age of the patients in group NB was higher than that of group DN ($p<0.05$). The remaining pretreatment evaluations did not vary significantly between treatment groups. At pretreatment, manual labor and physical exercise were also evaluated. Of the total subjects, 19 (7 in Group DN and 12 in Group NB) reported heavy manual labor, while 24 subjects (12 in each group) exercised at least one time per week.

Randomized subjects reported pain in the neck, hip, or lower back. The distribution of the pain locations was homogenous between the two treatment groups (χ^2=0.17; DF=2; p=0.918). The mean VAS scores at baseline were 59.03mm (±1.707) and 59.44mm (±1.941)

for Group DN and Group NB, respectively. The median pretreatment PFQ score was 9 points in Group DN and 7 points in Group NB.

Efficacy Evaluations. Improvements in VAS scores observed from baseline to Visit 3 as presented in Fig. 1. Treatment with the combination of diclofenac cholestyramine, nucleotides and Vitamin B_{12} resulted in a higher number of subjects with VAS score reductions >30mm after 10 days of treatment (87.5% subjects) than in the control group administered nucleotides and Vitamin B_{12} (51.23% of subjects) ($p>0.0006$). A reduction in mean VAS scores was observed from baseline in both treatment groups, individually**.** The mean VAS scores for Group DN at Visit 2 and Visit 3 were 26.9 ($\pm$15.49) and 9.41 ($\pm$10.47) ($p<0.0001$ from pretreatment) while those of Group NB at Visit 2 and Visit 3 were 42.41 ($\pm$17.66), and 30.35 ($\pm$17.51) ($p<0.0001$), respectively.

Table 1. Demographic data collected at Pretreatment

Demographic data	Group DN	Group NB
Gender (n)		
Female	19	17
Male	21	24
Ethnicity (n)		
Asian	1	0
Black	18	16
Caucasian	7	8
Mulatto	14	17
Age (years; $\bar{x}\pm$SD)	43.23 $\pm$1.026	46.29 $\pm$0.908*
Height (cm; $\bar{x}\pm$SD)	170.9 $\pm$1.506	170.2 $\pm$1.261
Weight (kg; $\bar{x}\pm$SD)	73.10 $\pm$2.07	74.95 $\pm$1.715
BP (mmHg; $\bar{x}\pm$SD)		
Systolic	122.6 $\pm$1.029	123.2 $\pm$0.99
Diastolic	77.43 $\pm$1.315	79.9 $\pm$1.294
Heart rate (bpm; $\bar{x}\pm$SD)	68.85 $\pm$0.857	70.27 $\pm$0.849
Pain location (n)		
Knee	10	9
Hip	4	5
Lower back	26	27

*defines difference as $p<0.05$; $\bar{x}$ = mean

The median PFQ scores at Visit 2 were reduced to 3.5 for Group DN and 6 for Group NB. Further score reductions were seen at Visit 3, with the Group DN PFQ score median of 0, while that of Group NB was 4. Figure 2 summarizes the PFQ score reductions seen in both groups from Pretreatment to Visit 3. A significantly higher number of subjects ($p<0.0001$) had a score reduction of >5 points in the PFQ at Visit 3 in the DN group, with 80% of subjects showing a score reduction of >5 points, compared to Group NB with 29.3% of subjects showing the same score decrease. It may be concluded that at Visit 3 the functionality of the subjects in Group DN shows a greater improvement than in Group NB.

At Visit 3, the investigating physician assessed overall efficacy of the study drug for each subject. The following results were collected for Group DN/Group NB, respectively: "Very Good": 21/4; Good": 11/11; "Fair": 6/16; "Poor": 2/10. Comparing the number of responses in the "Very Good" and "Good" categories (32 for Group DN, 15 for Group NB) with those of the "Fair" and "Poor" response categories for each treatment group (8 for Group DN, 21 for Group NB) yielded a statistically significant difference in favor of Group DN ($p=0.0009$).

Safety-Adverse Events. Adverse events (AEs) were recorded at Visits 2 and 3. The distribution of AEs is summarized in Table 2. Some subjects experienced multiple AEs. One subject in Group DN was withdrawn from treatment due to GI adverse events (nausea, vomiting and abdominal pain). The number of subjects presenting AEs did not vary significantly from one treatment group to the other ($p=0.587$).

There were no significant differences between the groups in vital signs throughout the study. In both groups, mean laboratory values remained within reference range at each study visit. There were no statistical differences in laboratory values between the groups at each visit in relation to pretreatment values.

During the final assessment of overall tolerability performed by the investigating physician, the following results were collected for Group DN/Group NB, respectively: "Very Good": 22/12; Good": 12/23; "Fair": 5/5; "Poor": 1/1. Comparing the number of responses in the "Very Good" and "Good" categories with those of the "Fair" and "Poor" response categories for each treatment group**,** it did not yield statistically significant difference ($p=1.00$).

Discussion:

During the treatment period, we observed clinical improvements in the study subjects as evidenced by the VAS and PFQ assessments performed at each study visit. In terms of pain reduction, while there were significant reductions in VAS scores for both treatment groups, we did observe a greater reduction in reported pain intensity among the subjects who received the combination of diclofenac cholestyramine, nucleotides, and vitamin B_{12}.

NSAIDs such as diclofenac are thought to reduce pain by inhibition of prostaglandin synthesis, through inhibition of isoenzymes COX-1 and COX-2, both of which are known catalysts of prostaglandin formation in the arachidonic acid pathway. Diclofenac and other NSAIDs exert analgesic, anti-inflammatory, and antipyretic action as a consequence of competitive inhibition of COX-2 active sites. COX-1 and COX-2 generate prostanoids by catalyzing the conversion of free arachidonic acid to prostaglandin G2 and then to prostaglandin H2 [27]. The prostanoids – including prostaglandins, prostacyclins, and thromboxane – are bioactive lipids which play important roles in a wide variety of cellular responses and pathophysiological processes through interactions with specific G-protein-coupled receptors [28].

Table 2. Adverse events (AEs) during treatment

	Total no. of subjects with AEs			
	Visit 2 Groups		Visit 3 Groups	
	DN	NB	DN	NB
Abdominal pain	2		2	
Constipation				1
Dyspepsia	1		1	
Flatulence	1		1	
Headache			1	1
Increased BSR		1		2
Increased creatinine		1		1
Increased CPK				1
Increased GOT/GPT			1	
Increased uric acid		1		1
Insomnia			1	
Nausea	2	1		3
Rhinitis			1	
Vertigo			1	
Vomiting	1			1
Total AEs	7	4	9	11

CPK = creatinine phosphokinase

As with other NSAIDs, one of the primary concerns related to diclofenac administration is the possibility of adverse effects, among the most common of which are gastrointestinal side effects arising from disruption of the protective effects of the prostaglandins on the gastric mucosa [11]. The analgesic and anti-inflammatory properties of diclofenac are exerted at specific anatomical sites, or effect compartments, which include injured tissues and the central nervous system. In order to achieve a therapeutic effect, diclofenac must reach a sufficiently high concentration within the respective effect compartments, which are independent of plasma concentrations [29].

One approach to the issue of diclofenac-induced GI adverse effects is the combination of diclofenac with other compounds in order to decrease toxicity or increase bioavailability. Cholestyramine is an ion exchange resin that forms a complex with diclofenac and reduces mucosal damage by direct contact in the gastric lumen [13, 14]. The diclofenac-cholestyramine complex is commercially available in Latin America (Brazil, Chile, Mexico, and Venezuela) [11]. Kurowski et al (1994) reported a faster absorption rate and subsequent lower plasma peak concentration of diclofenac-cholestyramine as compared to diclofenac alone [14]; this observation was also reported by al-Balla et al. (1994) [13]. The combination of a diclofenac-cholestyramine complex has been shown to be beneficial in reducing the number and length of gastric lesions as compared to isolated diclofenac administration in rats [30]. This combination was also found to offer a fast onset and long duration of analgesic effect in patients with rheumatoid arthritis [31]. While the half-life of the diclofenac-cholestyramine complex is short (around 2 hours), the complex remains in effect compartments such as synovial fluid for a longer period of time and continues to exert a therapeutic effect [13, 14].

Although the pain reduction observed in the treatment group receiving the combination of diclofenac cholestyramine, nucleotides and vitamin B_{12} was superior to the group receiving only nucleotides and vitamin B_{12}, we did nonetheless observe pain reduction in this treatment group, suggesting therapeutic efficacy of these compounds. Indeed, vitamin B_{12} and other B vitamins have been confirmed to possess antinociceptive effects that are independent of vitamin deficiency, in both animal models and in clinical trials [32, 33]. On the other hand, B_{12} deficiency may lead to neurological alterations, the most common of which are sub-acute degeneration of the dorsal and lateral spinal column, which arise as a result of alterations in myelin formation [25].

Vitamin B_{12} has been shown to experimentally inhibit thermal hyperalgesia whether administered alone or in combination with vitamins B_1 and B_6. Administration of vitamin B_{12} resulted in a dose-dependent reduction of tactile allodynia induced by spinal nerve ligation in the rat [33]. Patients with mechanical or irritative lumbago and who did not exhibit nutritional deficiency were

treated with vitamin B_{12}, resulting in significant improvement in pain and related disability, along with a reduction in paracetamol consumption. This effect has been attributed to the effect of vitamin B_{12} on axonal conduction [33].

The nucleotides may also have played a role in the pain reduction experienced in both treatment groups. Although the nucleotides do not exert any direct analgesic or anti-inflammatory action, they may contribute to symptomatic improvement in conditions in which peripheral nerves are affected. The neuroregenerative capacity of the pyrimidine nucleotides has been demonstrated in animal models of nerve damage, revealing that both axons and myelin sheaths of regenerating nerve and muscle fibers are favorably impacted by nucleotide administration, with improvements in nerve fiber conduction velocity [15, 16, 17]. Clinical benefits of nucleotide administration have been demonstrated in cases of diabetic neuropathy and polyneuropathy as well as neuropathic pain syndrome [19, 20, 34].

The combination of uridine, cytidine, and vitamin B_{12} has been employed with favorable results in the clinical trial setting in the treatment of a variety of pain syndromes of neural origin, including chronic neuropathic lumbar pain [22], pain following neurological surgical procedures [23], neural compression-induced neuralgias [35], peripheral neuropathies [21], as well as pain and paresthesia in anemic patients [36]. This combination is commercially available in Brazil as well as in Spain [11].

The combination of NSAIDs such as diclofenac with other compounds that could potentiate the anti-inflammatory and analgesic effect of this drug has also been extensively tested in clinical trials. In particular, the combination of vitamins B_1, B_6 and B_{12} together with diclofenac, have resulted in achievement of more rapid onset of pain reduction and restoration of functionality [37, 38, 39]. The results of this study may indicate that there may also be a therapeutic benefit with the addition of nucleotides uridine and cytidine to diclofenac therapy for painful conditions. Additional studies are warranted in order to further explore this possibility.

Conclusion:

The combination of diclofenac cholestyramine with uridine triphosphate, cytidine monophosphate and vitamin B_{12} was well-tolerated over a 10-day treatment period. The combination reduced pain and improved functionality among subjects presenting acute, non-traumatic pain in the lower back, hips, and neck.

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