ARTIGO ORIGINAL

Neural compression-induced neuralgias: clinical evaluation of the effect of nucleotides associated with vitamin B_{12}

Neuralgias decorrentes de compressão neural: avaliação clínica da ação de nucleotídeos associados à vitamina B_{12}

Uniterms: uridine, cytidine, hydroxocobalamin, neuralgia.
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SUMMARY

The use of a combination of uridine triphosphate (UTP), cytidine monophosphate (CMP), and hydroxocobalamin was evaluated in a double-blind, randomized study in the treatment of neuralgia due to degenerative orthopedic alterations with neural compression. Following informed consent, 80 patients were randomized to a 30 day treatment period. The subjects received a thrice-daily oral treatment regimen of either the combination treatment (Group A: total daily dose of 9mg UTP, 15mg CMP, 6 mg hydroxocobalamin) or vitamin B_{12} alone (Group B: total daily dose of 6 mg hydroxocobalamin). Efficacy measures evaluated global patient condition from the perspective of the subject and the investigating physician; pain – measured by a visual-analog scale; and functionality, using a patient-response questionnaire. The safety evaluation took into account physical evaluations and laboratory tests performed at each visit to the study center as well as the incidence and severity of adverse events. At the end of the 30-day treatment period, there were reductions in the pain scale scores in both groups, however there was a significantly larger reduction in the scores of the Group A patients. The Patient Global Evaluation scores improved in both groups but showed greater improvement in Group A, while the Physician Global Evaluation improved significantly only in Group A. A similar finding was observed in the scores of the Patient Functionality Questionnaire. Based on the findings of this clinical trial, we conclude that the combination of UTP, CMP, and vitamin B_{12} has a positive effect on pain and functionality improvement in the treatment of degenerative orthopedic alterations with neural compression, in the study population evaluated.

INTRODUCTION

Biological molecules are divided into four major classes: proteins, lipids, carbohydrates, and nucleic acids. The precursors or monomeric units of the nucleic acids are known as nucleotides, which play a vital role in many cellular processes, contributing as activated intermediates in many biosynthetic pathways with structural, energetic, metabolic, and regulatory functions[1,2]. The basic structure of a nucleotide consists of three components: a nitrogenous base, a pentose sugar, and a phosphate group, while a nucleoside presents both the pentose sugar and base, but lacks the phosphate group. Nucleotides occur in mono-, di- or triphosphate forms[1,2].

Among the many biochemical roles of the nucleotides and their derivatives is the replication of the genome and transcription of genetic information into RNA. Probably the most widely known nucleotides and their functions are adenosine triphosphate (ATP), an adenine nucleotide that is the universal currency of energy, and guanosine triphosphate or GTP, a guanine nucleotide that also serves as an energy source for various biological functions,

specifically the energizing of macromolecule movements in processes such as the activation of signal-coupling proteins[3,4]. UDP-glucose and other nucleotide derivatives participate as activated intermediates in biosynthetic processes such as glycogen formation. Nucleotides also function as essential components of both intra- and extra-cellular signal transduction pathways, as well as in neurotransmission and in the transfer of biochemical radicals of the intermediate metabolism. Coenzymes NAD, FAD and CoA are nucleotide derivatives[1,4].

Nucleotide biosynthesis may occur by two pathways. In salvage pathways, preformed bases formed during cellular metabolism and normal digestion are recovered and reconnected to a ribose unit, while in *de novo* pathways, both purines and pyrimidines are assembled from simpler precursors[1,5]. Both pathways consist of elementary reactions that are repeated with minor differences, which leads to the formation of the various nucleotides[6,7]. Both uridine and cytidine are pyrimidine nucleotides that, following oral administration are thought to be broken down into nucleosides and nitrogenous bases in the digestive tract, then absorbed by the intestinal epithelium[8,9]. Plasma levels are increased following oral administration, while concentrations in the brain fluctuate with the plasma concentrations following both oral and systemic administration[10].

There have been several preclinical investigations in the role of these nucleotides in peripheral neuropathies of various origins. The preclinical findings include increased nerve conduction velocity, increased axonal myelin surface area and thickness, along with increased levels of neuritic protein neurofilaments and neuronal cell membrane phospholipids (phosphatidylcholine and phosphatidylethanolamine)[11-14]. Clinical efficacy in painful conditions such as diabetic neuropathy, lumbar and cervical pain, as well as traumato-compressive alterations has also been established, with reports of reduction of pain intensity following uridine and cytidine administration[15-19].

Vitamin B_{12} is actively absorbed from the gastrointestinal tract as a result of binding to intrinsic factor (a glycoprotein secreted by the gastric mucosa)[20,21]. Vitamin B_{12} is essential in humans for maintenance or normal erythropoeisis, cell reproduction and growth, as well as for the synthesis of nucleoproteins and myelin[22]. It is important to nerve metabolism as a result of its role in the remethylation of homocysteine to methionine for *de novo* synthesis of S-adenosylmethionine[23]. The importance of this vitamin in the nervous system is highlighted by the neurological damage due to disruption of myelin formation that occurs in deficiency states, thought to result from disruption of reactions beginning with S-adenosylmethionine[24,25,26].

In this study, we evaluated the use of a combination of uridine, cytidine, and vitamin B_{12} in patients presenting neuralgias caused by degenerative orthopedic alterations with neural compression.

MATERIAL & METHODS

Following informed consent, 80 patients were randomized to a 30 day treatment period. The subjects received a thrice-daily oral treatment regimen of either the combination treatment (Group A: total daily dose of 9mg uridine, 15mg cytidine, 6mg hydroxocobalamin) or vitamin B_{12} alone (Group B: total daily dose of 6mg hydroxocobalamin). The capsules of study medication were visually identical and both the subjects and the clinical trial staff were blinded to treatment allocation. The study protocol, informed consent documents and clinical research forms received ethical committee approval prior to study startup (approval no. 23/2004). The study was carried out in accordance with Resolução 196/96 of the Conselho Nacional de Saúde. Data analysis was performed in accordance with the plan established in the trial protocol, using GraphPad Prism 5.0. Results were compared within and between treatment groups using the chi-squared or Fisher's exact test for categorical variables and the Student's t-test or ANOVA for continuous variables. Statistical significance was defined as $p<0.05$ with a 95% confidence interval.

Study subjects participated in three visits to the study center: Visit 1 for pretreatment evaluations, Visit 2 following 15 days of treatment, and Visit 3 after 30 days of treatment. Eligibility criteria included patients over 18 years of age with a clinical presentation of a degenerative orthopedic alteration with neural compression. Female subjects were not to be pregnant or nursing, and used appropriate birth control methods throughout the study period, if not post-menopausal. Subjects were excluded in cases of any intolerance to the study drug or need for surgical treatment, as well as use of other analgesics. Other exclusion criteria included dyshematopoesis, any active bleeding (gastrointestinal, cardiovascular etc.), significant alterations to laboratory tests, acute asthma or rhinitis, and any other condition that in the opinion of the investigating physician should have excluded the subject from the trial.

The tolerability parameters recorded at each study visit included a complete physical examination, recording weight and vital signs as well as adverse event monitoring and clinical laboratory evaluations. Concomitant medication use was also recorded at each study visit. At the end of each subject's treatment period, the investigator evaluated overall drug tolerability based on the above parameters, on a four-tiered scale of: "Very Good", "Good", "Fair", or "Poor" (Overall Tolerability Evaluation).

Each subject was submitted to four efficacy assessments at each study visit:

1) Patient's Global Evaluation: A 10-point scale evaluating the subject's overall condition from 1 point (worst score) to 10 points (best possible score);
2) Physician's Global Evaluation: using the 10-point scale with the same range as above; this evaluation was completed by the investigating physician;
3) Visual-Analog Pain Scale (VAS): Using a 100 mm line, each subject placed a vertical mark at a point from 0mm on the left side to 100 mm on the right side of the line, indicating the severity of their pain from 0mm or "no pain" to 100 mm or "most severe pain". The distance between "0" and the patient's

mark was recorded in millimeters;

4) Patient Functionality Questionnaire: This evaluation consisted of 12 questions answered with true or false by the subject, with one point awarded for each "true" answer. The following questions were responded by the each patient:
   - Because of my pain:
   - I don't sleep well;
   - I have to lie down more often;
   - It is difficult for me to get up from my bed;
   - I can stand only for a short while;
   - I can walk up stairs only slowly;
   - It is difficult for me to wash my body;
   - It is difficult for me to put on my clothes;
   - I can only walk short distances;
   - I try to avoid picking things up from the floor;
   - I have to change my posture more often;
   - I cannot carry heavy things;
   - I have to ask other people for assistance;

Additionally, the investigating physician evaluated overall drug efficacy upon completion of each subject's treatment using a 4-tiered scale of: "Very Good", "Good", "Fair" or "Poor" (Overall Efficacy Evaluation).

RESULTS

A total of 80 subjects was randomized to treatment, with 40 subjects in each treatment arm (Group A combination therapy; Group B – vitamin monotherapy). The pretreatment and demographic characteristics of the randomized subjects are summarized in Table 1. There were no statistically significant differences in any of the pretreatment evaluations between the two groups. At pretreatment, manual labor and physical exercise were also evaluated. Of the total patients, 28 (13 in Group A and 15 in Group B) reported heavy manual labor, while 16 subjects exercised at least once a week (7 in Group A and 9 in Group B).

The results of the safety evaluations are summarized in Table 2. There were no significant alterations in systolic blood pressure (Group A: p=0.576; Group B: p=0.446), diastolic blood pressure (Group A: p=0.789; Group B: p=0.889) and weight (p=0.966 for Group A and p=0.947 for Group B) in either group throughout the study treatment period. A total of 12 subjects presented adverse events (AEs) during the treatment period. Of these, 11 belonged to Group A and 1 to Group B. The most frequent AE observed was nausea (n=5), followed by constipation and epigastralgia (n=3), flatulence and laboratory alteration (n=2; elevated blood sedimentation rate in one subject in Group A and uric acid elevation in one subject in Group B). Other reported AEs included anxiety, increased appetite, headache and pyrosis. All AEs were considered mild to moderate and

Table 1 - Demographic & pretreatment data

Assessment/study visit	Group A	Group B	Change from PT*
Gender			p=0.654
Male	20	23	
Female	20	17	
Ethnicity			p=0.384
Afro-descendant	23	25	
Asian	0	2	
Caucasian	17	12	
Age (years)	46.65 (±1.36)	45.68 (±1.642)	p=0.6487
Height (cm)	169.2 (±1.318)	170.4 (±1.222)	p= 0.4975
Pain location			p=0.591
Hip	5	13	
Spine	35	27	
Previous pain episode			p= 1.000
No	30	30	
Yes	10	10	

*Data are represented as n or mean (± SD). *PT= Pretreatment.*

Table 2 - Safety evaluations

Assessment/study Visit	Group A	Group B	Change from PT*
Weight (kg)			p= 0.932
Pretreatment	78.83 (±2.22)	77.73 (±2.13)	
Visit 2	79.66 (±2.25)	77.43 (±2.14)	
Visit 3	79.26 (±2.27)	76.72 (±2.26)	
Pulse (bpm)			p= 0.4380
Pretreatment	70.48 (±0.77)	69.40 (±0.710)	
Visit 2	69.21 (±0.72)	68.58 (±0.89)	
Visit 3	70.05 (±0.81)	68.67 (±0.69)	
Systolic blood pressure (mmHg)	p=0.708		
Pretreatment	125.2 (±0.88)	125.3 (±1.02)	
Visit 2	124.4 (±0.96)	123.3 (±1.25)	
Visit 3	123.9 (±0.89)	124.1 (±1.02)	
Diastolic blood pressure (mmHg)	p=0.937		
Pretreatment	80.63 (±1.24)	79.60 (±1.43)	
Visit 2	79.97 (±1.36)	78.63 (±1.50)	
Visit 3	79.34 (±1.37)	79.14 (±1.4)	

*Data are represented as n or mean (± SD). *PT= Pretreatment*

Table 3 - Efficacy evaluations

Assessment/study visit	Group A	Group B	Between-group difference
VAS			
Pretreatment	59.25 (±2.09)	59.10 (±2.75)	p=0.966
Visit 2	34.34 (±2.98)	53.85 (±3.63)	p< 0.0001
Visit 3	21.11 (±3.47)	41.75 (±3.36)	p< 0.0001
Patient global evaluation			
Pretreatment	4	4	p=0.70001
Visit 2	6	4	p=0.0016
Visit 3	10	6	p=0.0071
Physician global evaluation			
Pretreatment	4	4	p= 0.6763
Visit 2	7	3	p= 0.0006
Visit 3	10	4	p= 0.0025
PFQ			
Pretreatment	12	12	p= 0.85
Visit 2	5	12	p= 0.076
Visit 3	0	8	p= 0.023
Overall efficacy evaluation			p< 0.0001
Very good	14 (36.8%)	3 (7.5%)	
Good	10 (26.3%)	1 (2.5%)	
Fair	10 (26.3%)	19 (47.5%)	
Poor	4 (10.5%)	17 (42.5%)	

*Data are means (±SD), mode, or n (%). *PT= Pretreatment*

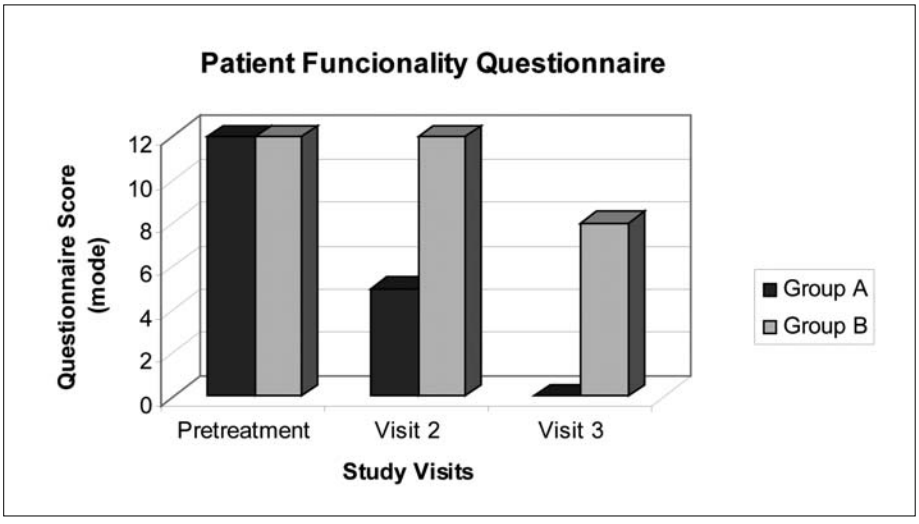

Figure 1 - Patient Functionality Questionnaire Scores.

all but 3 were resolved within the treatment period (laboratory alterations and constipation continuing after Visit 3). At the final Overall Tolerability Evaluation, the following results were collected for Group A/Group B, respectively: "Very Good": 12/4; "Good": 13/31; "Fair": 9/5; "Poor": 4/0. The between-group difference was statistically significant, in favor of Group B (p=0.0009).

Table 3 summarizes the results of the efficacy evaluations. There were reductions in VAS scores in both treatment groups during the treatment period (p<0.0001 for Group A and p=0.0011 for Group B). However, there was a greater score reduction observed among the subjects in Group A (see Table 3). The scores of the Patient's Global Evaluation among the patients in Group A improved significantly from pretreatment to Visit 3 (χ^2=81.05; DF=18; p<0.0001), as did those of the subjects in Group B (χ^2=44.59; DF=18; p=0.0005). There was a statistically significant between-group difference in the scores, in favor of Group A (χ^2=161.3; DF=45; p<0.0001).

The scores of the Physician's Global Evaluation improved significantly during the treatment period in the patients from Group A (χ^2=79.24; DF=16; p<0.0001), but no significant change in scores was noted in the Group B subjects (χ^2=27.44; DF=18; p=0.071). The between-group score difference was also statistically significant, in favor of Group A (χ^2=167.2; DF=45; p<0.0001). From Pretreatment to Visit 3, there was a statistically significant score reduction in the Patient Functionality Questionnaire from among the Group A subjects (χ^2=65.65; DF=24; p<0.0001). However, no significant change in scores was seen throughout the treatment period in the Group B patients (χ^2=24.76; DF=24; p=0.419). Comparing the two treatment groups, the scores of the Group A subjects showed a much greater reduction throughout the treatment period in relation to Group B, a difference that was also statistically significant (χ^2=264.4; DF=195; p=0.0007), (Figure 1).

The final Overall Efficacy Evaluation results are shown in Figure 2. There was a statistically significant difference between the two treatment groups (χ^2=25.29; DF=3; p<0.0001), with 24 (63.2%) subjects in Group A receiving efficacy evaluations of "Very Good" or "Good", as compared to 4 (10%) of the subjects in Group B who received the same assessment.

DISCUSSION

The results of this study confirm the findings in the literature in terms of pain improvement with nucleotide therapy in neuropathic pain conditions[11-19]. Nociceptive and neuropathic pains differ in neurophysiologic etiologies and conse-

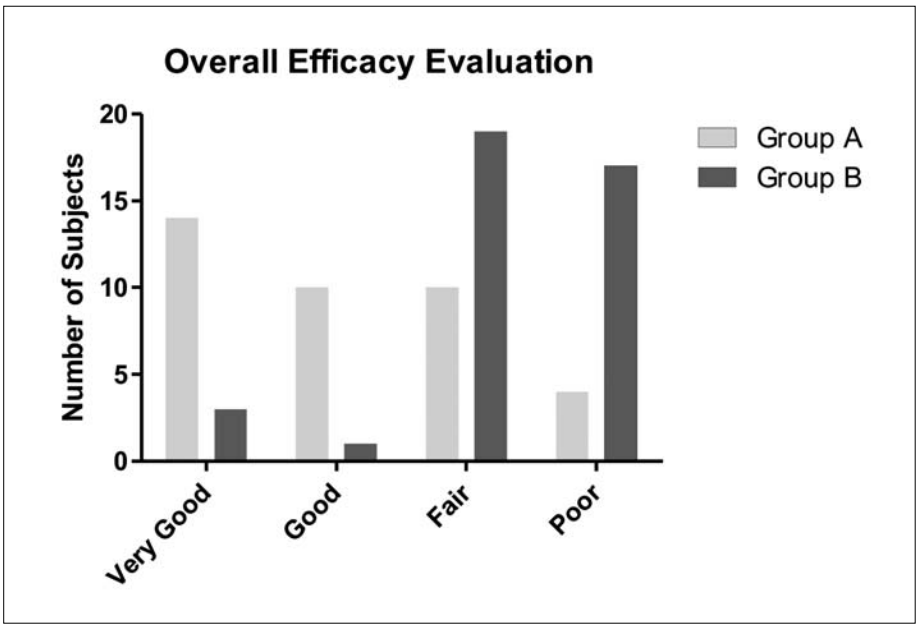

Figure 2 - Overall efficacy assessment performed by the investigating physician at the end of the treatment period.

quently tend to respond to different treatment modalities. While nociceptive pain is mediated by receptors on A-delta and C-fibers, neuropathic pain is the result of damage or pathological changes in the nervous system at the peripheral and/or central level, which lead to allodynia and hyperalgesia[27]. Conventional drug alternatives are often met with limited success, requiring combination therapy with tricyclic antidepressants, anti-convulsants and systemic local anesthetics, while severe cases may call for chronic opioid therapy[28,29].

The subjects treated with the combination of uridine, cytidine and vitamin B_{12} showed significant reduction in pain severity during the course of therapy. Additionally, there was a clear improvement in quality of life evaluations, specifically in terms of functionality, indicating that the pain reduction enabled greater independence and ability to carry out normal daily activities.

One interesting finding was the improvement in pain evaluations among the patients treated only with Vitamin B_{12}. This finding is in agreement with the literature, not only confirming the use of vitamin B_{12} in pain conditions but also may help to explain the excellent results observed among the patients who were administered the combination treatment. An analgesic action of vitamin B_{12} has been confirmed in both animal pain models and in clinical trials with non-deficient patients. In addition, numerous studies indicate that when used in conjunction with analgesic or anti-inflammatory agents, vitamin B_{12} appears to potentiate the action of these drugs[30]. Mauro et al. (2000) reported significant improvement in patients with low back pain and no signs of B_{12} deficiency following parenteral vitamin B_{12} administration. In addition, a reduction in paracetamol consumption was reported[31]. The exact mechanism underlying the analgesic effect of vitamin B_{12} is unknown but may be due, in part, to the effect of vitamin B_{12} on axonal conduction[30].

Both back and hip pain are common complaints with many possible causes. Back pain may vary in severity, ranging from mild discomfort to a severe, debilitating pain. Pathologies affecting the spinal cord vary considerably, the most common etiology of which is trauma. Other common causes may be linked to autoimmunity, infections, neoplasms, vascular disorders, and hereditary degenerative disease[32]. The incidence of back pain also depends on the clinical setting, but is an extremely common occurrence, for instance, it is estimated that up to 84% of the adult American population has experienced at least one episode of low back pain at some point during adulthood[33]. Some of the most common underlying causes of hip pain are bursitis, osteoarthritis, and femur fractures. While less common than back pain, hip pain represents a significant source of discomfort and impairment of mobility, which significantly impacts quality of life[34,35].

Although adverse events were observed during the treatment period, no severe or serious AEs were reported and all patients recovered quickly and without sequelae. The tolerability profile of vitamin B_{12} is considered excellent, with no reports of serious adverse events attributed to the vitamin, even at high doses. Uridine and cytidine are naturally present in the human organism, consequently the adverse effects related to supplementation at therapeutic levels are expected to be mild. Few adverse reactions have reported in previous clinical evaluations, which included moderate diarrhea, fever and chills. The tolerability of this combination, taken together with its efficacy in pain reduction presents an advantage as a therapeutic alternative with a relatively low AE profile that can be used for an extended period of time without the concerns regarding long term use of other commonly used analgesics for these conditions, including NSAIDs, corticosteroids or opioid narcotics.

CONCLUSION

Based on the findings of this clinical trial, we conclude that the combination of uridine, cytidine and vitamin B_{12} has a positive effect in the treatment of degenerative orthopedic alterations with neural compression, in the study population evaluated.

RESUMO

O uso de uma combinação de uridina trifosfato (UTP), citidina monofosfato (CMP) e hidroxocobalamina foi avaliado em um estudo duplo-cego e randomizado no tratamento de neuralgias decor-

rentes de alterações ortopédicas degenerativas com compressão neural. Após a assinatura do termo de consentimento informado, 80 pacientes foram randomizados para um período de tratamento de 30 dias. Os pacientes receberam um regime de tratamento oral da combinação (Grupo A: posologia diária total de 9mg UTP, 15mg CMP, 6mg hydroxocobalamina) ou vitamina B_{12} isoladamente (Grupo B: posologia diária total de 6mg hidroxocobalamina). As medidas de eficácia avaliaram a condição global do paciente da perspectiva do paciente e do médico investigador; a dor foi mesurada por uma escala visual de dor; e a funcionalidade foi avaliada utilizando um questionário respondido pelo paciente. A avaliação de segurança levou em conta as avaliações físicas e exames laboratoriais realizados em cada visita ao centro de estudo bem como a incidência e severidade de eventos adversos. Ao final do período de tratamento de 30 dias, houve reduções na pontuação da escala de dor em ambos os grupos de tratamento. Entretanto houve uma redução significativamente maior na pontuação dos pacientes do Grupo A. Houve melhora na pontuação da Avaliação Global do Paciente em ambos os grupos, sendo observada uma melhora mais acentuada no Grupo A, enquanto a pontuação da Avaliação Global do Médico melhorou de forma significativa apenas no Grupo A. Um achado semelhante foi observado na pontuação do questionário de funcionalidade realizado pelo paciente. Com base nos achados desta pesquisa clínica, concluímos que a combinação da UTP, CMP e vitamina B_{12} apresenta um efeito positivo nos parâmetros de dor e funcionalidade no tratamento de alterações ortopédicas degenerativas com compressão neural, na população avaliada.

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