

A double-blind, randomized, comparative study of the use of a combination of uridine triphosphate trisodium, cytidine monophosphate disodium, and hydroxocobalamin, versus isolated treatment with hydroxocobalamin, in patients presenting with compressive neuralgias

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Context: This paper reports on the results of treatment of compressive neuralgia using a combination of nucleotides (uridine triphosphate trisodium [UTP] and cytidine monophosphate disodium [CMP]) and vitamin B₁₂.

Objectives: To assess the safety and efficacy of the combination of nucleotides (UTP and CMP) and vitamin B₁₂ in patients presenting with neuralgia arising from neural compression associated with degenerative orthopedic alterations and trauma, and to compare these effects with isolated administration of vitamin B₁₂.

Methods: A randomized, double-blind, controlled trial, consisting of a 30-day oral treatment period: Group A (n=200) receiving nucleotides + vitamin B₁₂, and Group B (n=200) receiving vitamin B₁₂ alone. The primary study endpoint was the percentage of subjects presenting pain visual analog scale (VAS) scores ≤20 at end of study treatment period. Secondary study endpoints included the percentage of subjects presenting improvement ≥5 points on the patient functionality questionnaire (PFQ); percentage of subjects presenting pain reduction (reduction in VAS scores at study end in relation to pretreatment); and number of subjects presenting adverse events.

Results: The results of this study showed a more expressive improvement in efficacy evaluations among subjects treated with the combination of nucleotides + vitamin B₁₂, with a statistically significant superiority of the combination in pain reduction (evidenced by VAS scores). There were adverse events in both treatment groups, but these were transitory and no severe adverse event was recorded during the study period. Safety parameters were maintained throughout the study in both treatment groups.

Conclusion: The combination of uridine, cytidine, and vitamin B₁₂ was safe and effective in the treatment of neuralgias arising from neural compression associated with degenerative orthopedic alterations and trauma.

Keywords: uridine triphosphate trisodium, cytidine monophosphate disodium, hydroxocobalamin, compressive neuralgia

Introduction

Uridine and cytidine are substances belonging to the pyrimidine nucleotide family, which in turn comprises one of four main classes of biological molecules (along

with carbohydrates, lipids, and proteins) that play several fundamental roles in cellular metabolism. Aside from being components of DNA and participating in genome transcription and translation, functions of these nucleotides include energy transfer for chemical bonding, intracellular signaling, neurotransmission, and transfer of biochemical radicals from intermediate metabolism.¹

Vitamin B₁₂ is essential in the human body for growth and maintenance of a variety of processes, including cell reproduction and synthesis of myelin and nucleoproteins, and must be supplied from an exogenous source.² Adequate vitamin B₁₂ levels in the body depend on adequate ingestion and absorption (requiring an acid-pepsin complex in the stomach that releases cobalamin from its binding proteins, pancreatic proteins that release cobalamin from the R factor bond, secretion of intrinsic factor by gastric parietal cells in order to bind cobalamin, and the presence of cobalamin and intrinsic factor receptors in the ileum).^{3,4} Vitamin B₁₂ is important to nerve metabolism via the remethylation of homocysteine to methionine for de novo synthesis of s-Adenosyl methionine.⁵ Vitamin B₁₂ deficiency can be caused by numerous factors, usually some combination of inadequate ingestion and absorption.⁶ Deficiency can lead to megaloblastic anemia and neurological alterations, the latter likely linked to the absence of s-Adenosyl methionine formation.^{7,8}

This trial assessed treatment outcomes following administration of a combination of uridine triphosphate trisodium (UTP), cytidine monophosphate disodium (CMP), and vitamin B₁₂ in the treatment of patients with compressive neuralgias. There is a body of clinical and preclinical evidence in the literature, supporting use of CMP and UTP in neuropathic pain, with potential symptomatic benefits.⁹⁻²²

Several preclinical studies of peripheral neuropathies of varying etiologies have indicated beneficial effects of UTP and CMP administration in situations such as experimentally induced crush injury. Reported preclinical observations include accelerated nerve and muscle fiber regeneration, increased nerve conduction velocity, increased levels of neuritic protein neurofilaments, increased axon myelin surface area and thickness, and increased levels of neuronal cell membrane phospholipids phosphatidylcholine and phosphatidylethanolamine following nucleotide administration.¹⁹⁻²² In the clinical setting, the combination of UTP and CMP with vitamin B₁₂ has been investigated in several painful conditions with

favorable results, among which are diabetic neuropathy, acute non-traumatic pain, lumbar pain, cervical pain, and traumatic-compressive lesions.^{10-13, 18}

Objectives

The objectives of this study were to assess the safety and efficacy of the combination of nucleotides (UTP and CMP) and vitamin B₁₂ in patients presenting with neuralgia arising from neural compression associated with degenerative orthopedic alterations and trauma, and to compare these effects with isolated administration of vitamin B₁₂.

Materials and methods

This was a randomized, double-blind, comparative, controlled trial performed at UNIFESO Medical School facilities and hospital. The study was registered with the Brazilian National Database GGMED/GESF-ANVISA under the following numbers: NOTIFICAÇÃO EM PESQUISA CLÍNICA Nº 61/2014 Expediente do CE: 0331070141. After study approval by the UNIFESO ethical committee (approval no 509.682) and written informed consent of all participants, subjects meeting inclusion criteria were randomized to a 30-day oral treatment period. Inclusion criteria included patients of both genders, ≥18 years of age, with a clinical presentation of degenerative orthopedic alteration with neural compression. Female patients performed a urine pregnancy test prior to inclusion and were required to maintain adequate birth control throughout the study period. Exclusion criteria included need for surgical treatment and need for other analgesics.

Enrolled subjects were randomized by order of arrival to the study center into two treatment groups: Group A received the combination of nucleotides and vitamin B₁₂, while subjects in Group B received vitamin B₁₂ monotherapy. The study drug and treatment regimen was two capsules, three times per day for Group A. Each capsule contained: CMP 2.5 mg; UTP 1.5 mg; and hydroxocobalamin 1.0 mg. Study treatment regimen for subjects in Group B was two capsules, three times per day, each capsule contained hydroxocobalamin 1.0 mg. There was no visible difference between the study drugs, in accordance with blinding procedures for double-blind trials. Subjects were instructed to swallow the capsules whole at breakfast, lunch, and dinner.

The study hypothesis was that the combination of nucleotides and vitamin B₁₂ would show superior efficacy in relation to B₁₂ monotherapy. The study protocol outlined three patient visits to the study center: pretreatment for screening,

randomization, and study drug distribution; visit two took place after 15 days of treatment; and visit three occurred at the end of the 30-day treatment period. At each of these study visits, subjects underwent a series of efficacy and tolerability assessments.

Efficacy assessments included a 100 visual analog pain scale (VAS), and the Patient Functionality Questionnaire (PFQ), a 12-item yes or no questionnaire about management of daily needs. The assessment included sleep quality, need to rest, ability to get up, standing and climbing stairs, washing, drying, and dressing, picking up things from the floor, changing posture, carrying weight, and need for assistance from other people. At each assessment, the patient and the investigating physician also evaluated the patient's overall condition on a scale of 1-10 points. Safety assessments took into account vital signs at each assessment and occurrence, severity, and duration of any adverse effects, including changes in laboratory tests.

The primary study endpoint was the percentage of subjects presenting VAS ≤ 20 mm at end of study treatment period. Secondary study endpoints included the percentage of subjects presenting improvement ≥ 5 points on the PFQ; percentage of subjects presenting pain reduction (reduction in VAS scores at study end in relation to pretreatment); and number of subjects presenting adverse events.

Study sample size took into account the results of a previous study,¹⁰ evaluating 80 subjects (40 per treatment group), in which mean VAS scores at end of treatment were 21.11 in the combination group versus 41.75 in the B₁₂ monotherapy group. Thus, a study sample size of 400 was determined, taking into account the mean between group difference of 20.6mm and standard deviation of 10.3mm, from the previous study, with a standard error of 1.03. The 95% confidence interval was 18.58–22.62, with a power of 1.0 and a two-tailed alpha of 0.05. Data were statistically analyzed using the software GraphPad Prism 5.0. Overall clinical efficacy and tolerability were analyzed via comparison of the results of each assessment in relation to pretreatment values, within and between treatment groups. For categorical variables, we used the χ^2 or Fisher's test, while continuous variables were analyzed using the repeated measures ANOVA or Student's *t*-test.

Results

A total of 400 subjects were randomized to treatment, with 200 subjects per treatment group. Figure 1 shows the flow of subjects through the trial. No significant between-group

differences were noted at pretreatment in the demographic data and pretreatment characteristics of the study population, as summarized in Table 1.

The safety measures monitored during the study are summarized in Table 2. Pretreatment safety measures did not vary significantly between Groups A and B: weight ($p=0.148$), body mass index (BMI) ($p=0.532$), blood pressure ($p=1.0$ for systolic blood pressure and $p=0.849$ for diastolic blood pressure), and heart rate ($p=0.413$). Throughout the treatment period within the treatment groups, with the exception of systolic blood pressure in both groups and diastolic blood pressure in Group B, there was no statistically significant change in weight (Group A, $p=0.855$; Group B, $p=0.0603$), BMI (Group A, $p=0.6$; Group B, $p=0.257$), blood pressure (Group A, $p=0.0013$ for systolic blood pressure and $p=0.133$ for diastolic blood pressure; Group B, $p=0.0046$ for systolic blood pressure and $p=0.0032$ for diastolic blood pressure), and pulse (Group A, $p=0.541$; Group B, $p=0.337$).

Pretreatment PFQ scores were significantly lower among patients in Group B (median for Group A, 9.0; median for Group B, 8.0; $p=0.0036$). Median PFQ scores were 5.0 at visit two in both treatment groups and 0.0 at visit three in both treatment groups. Both groups showed statistically significant improvement at the end of the study in relation to pretreatment PFQ scores ($p<0.0001$ for both treatment groups). In relation to the secondary study endpoint, there was no between-group difference in the percentage of subjects presenting improvement ≥ 5 points on the PFQ ($p=0.135$).

Pretreatment patient overall assessment scores were homogenous between treatment groups ($p=0.29$). At visits two and three, the scores of this assessment improved within each treatment group, but Group A patients showed a greater improvement in scores at both visit two ($p=0.014$) and visit three ($p=0.0024$) in comparison to Group B scores (Figure 2). Physician overall assessment scores were also homogenous between treatment groups at pretreatment ($p=0.717$), but at visits two and three scores were significantly lower in Group A as compared to Group B ($p=0.0029$ for visit two and $p=0.006$ for visit three) (Figure 3).

At pretreatment, mean VAS scores among the patients in Group A was 51.26mm (± 12.38) while in Group B mean pretreatment VAS score was 51.06 (± 11.72) ($p=0.87$). Visit two VAS scores for Group A and Group B were 29.86 mm (± 12.94) and 33.88 mm (± 11.86) ($p=0.0014$); At visit three, mean Group A VAS scores were 16.06 mm (± 12.03) and 20.40 mm (± 11.42) for Group B ($p=0.0003$). The percentage of subjects presenting VAS scores ≤ 20 mm (primary study endpoint) at

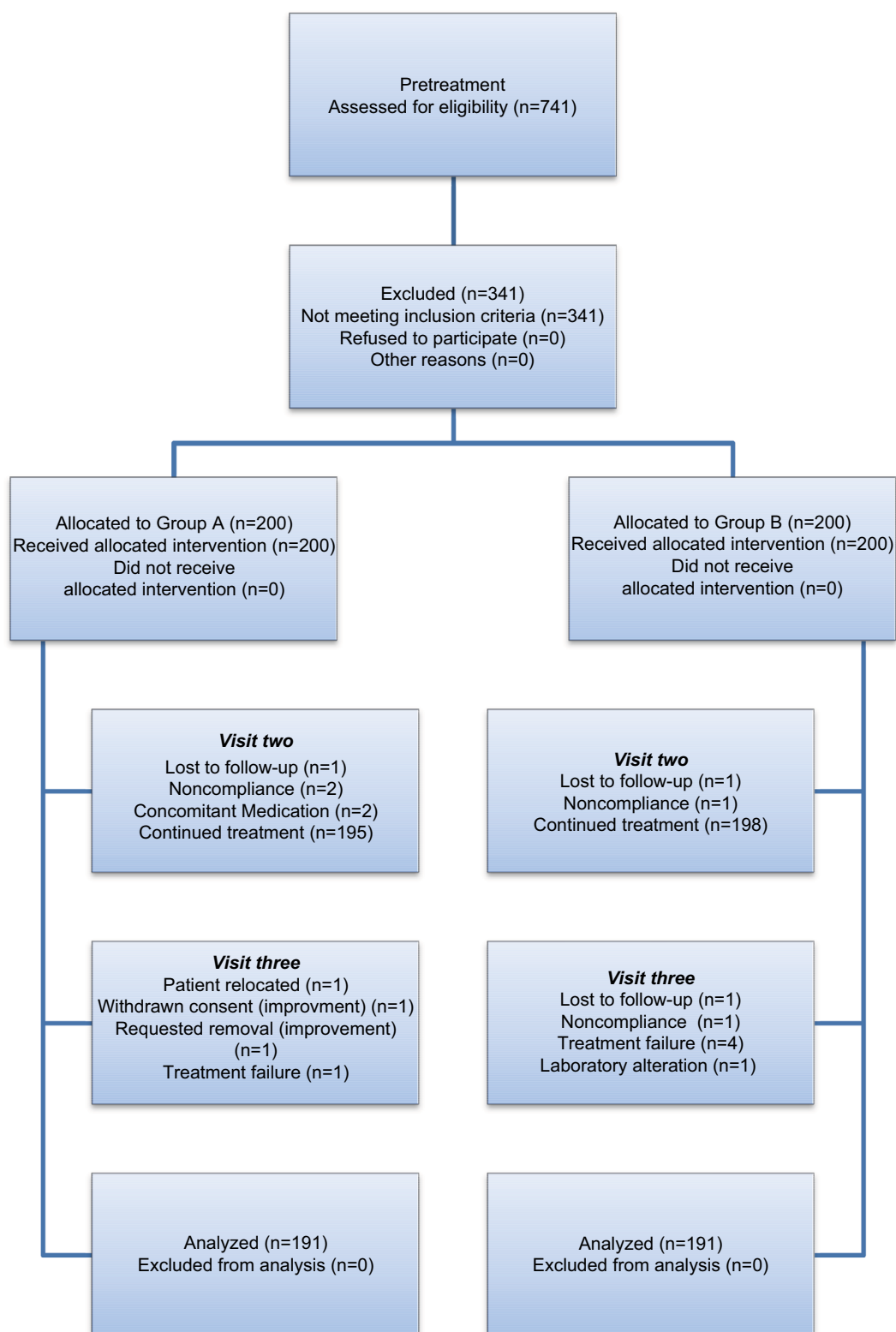


Figure 1 Flowchart of subjects through the study

visit three was significantly higher in Group A as compared to Group B ($p=0.0425$). Within the treatment groups, VAS score reduction was statistically significant for both Group A and Group B ($p<0.0001$ for both groups) (Figure 4).

Adverse events were recorded in both treatment groups, though for the most part these were not serious and were transient. Table 3 summarizes the adverse events determined by the investigating physician to be related to the study drug.

Table 1 Pretreatment and demographic data

Variable	Results		
	Group A	Group B	Between-group difference
Gender			$p=0.6998$
Male	98	114	
Female	102	86	
Age (years)	43.74 (± 9.73)	44.12 (± 10.22)	$p=0.133$
Height (cm)	166.91 (± 9.23)	168.49 (± 8.86)	$p=0.0824$
Ethnicity			$p=0.314$
Asian	2	0	
Black	71	83	
Caucasian	90	86	
Mulatto	37	31	
Pain location			$p=0.5112$
Back pain	125	127	
Hip pain	45	37	
Carpal tunnel syndrome	30	36	
Overall diet			$p=0.415$
Good	72	61	
Moderate	87	99	
Poor	41	40	
Alcohol consumption			$p=0.57$
None	63	72	
≤ 2 drinks/day	82	73	
> 2 drinks/day	55	55	
Cigarette smoking			$p=0.102$
Non-smoker	91	78	
< 10 cigarettes/day	54	47	
≥ 10 cigarettes/day	55	75	
Manual labor			$p=0.309$
Light	57	68	
Moderate	69	56	
Heavy	74	76	
Physical exercise			$p=0.415$
Regular (at least 1x/week)	49	41	
Irregular	81	77	
None	70	82	

Notes: Data are n, or mean ($\pm$ standard deviation). Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.

Table 2 Safety assessments

Parameters	Results	
	Group A	Group B
Weight (kg)		
Pretreatment	72.27 (± 12.29)	74.05 (± 12.27)
Visit two	72.35 (± 12.28)	73.87 (± 12.29)
Visit three	72.42 (± 12.31)	74.04 (± 12.39)
BMI		
Pretreatment	25.80 (± 3.03)	25.99 (± 3.05)
Visit two	25.80 (± 3.013)	25.96 (± 3.099)
Visit three	25.82 (± 3.009)	26.02 (± 3.121)
Systolic blood pressure (mmHg)		
Pretreatment	123.7 (± 8.541)	123.7 (± 7.285)
Visit two	122.4 (± 7.376)	122.7 (± 8.124)
Visit three	122.4 (± 7.813)	123.0 (± 7.644)
Diastolic blood pressure (mmHg)		
Pretreatment	80.29 (± 7.42)	80.14 (± 8.269)
Visit two	79.67 (± 7.755)	79.43 (± 8.655)
Visit three	80.04 (± 7.576)	79.38 (± 8.672)
Pulse (bpm)		
Pretreatment	68.54 (± 4.644)	68.92 (± 4.503)
Visit two	68.17 (± 5.165)	68.47 (± 5.647)
Visit three	68.30 (± 4.789)	68.57 (± 4.648)

Notes: Data are n, or mean ($\pm$ standard deviation). Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.

Abbreviations: BMI, body mass index; bpm, beats per minute.

There was no between-group difference in the percentage of subjects presenting adverse events during the treatment period ($p=0.6009$).

Discussion

We report the results of a clinical trial using the combination of uridine, cytidine, and vitamin B₁₂ in the treatment of neuralgias caused by degenerative orthopedic alterations with neural compression. This combination is commercially available in Brazil under the brand name Etna®. The combination of the nucleotides with vitamin B₁₂ yielded a more significant pain

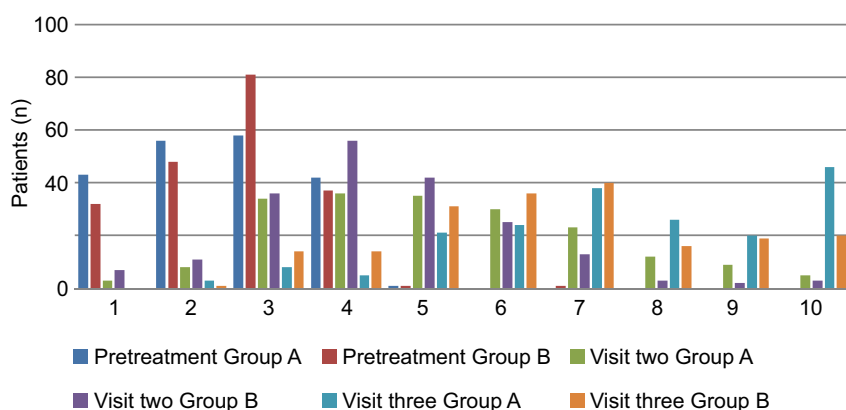


Figure 2 Patient overall assessment: graded on a 10 point scale from 1 (worst assessment of overall condition) to 10 (best assessment of overall condition) for treatment groups A and B at each study visit.

Note: Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.

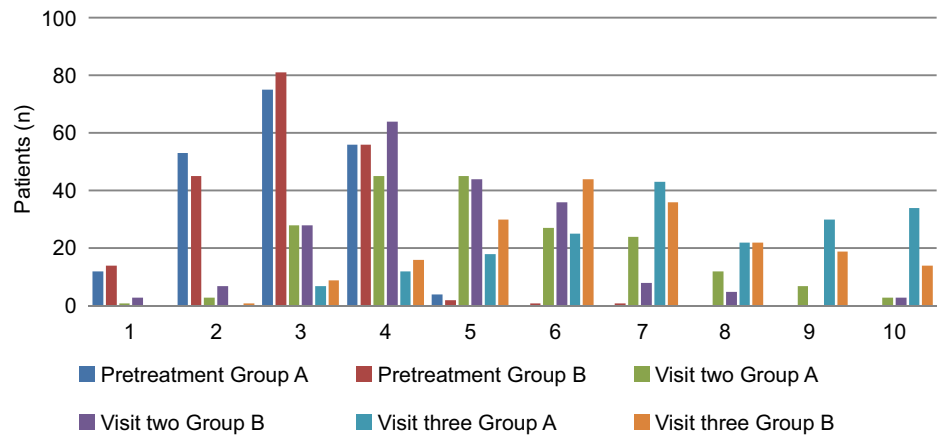


Figure 3 Physician overall assessment: graded on a 10 point scale from 1 (worst assessment of overall condition) to 10 (best assessment of overall condition) for treatment groups A and B at each study visit.
Note: Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.

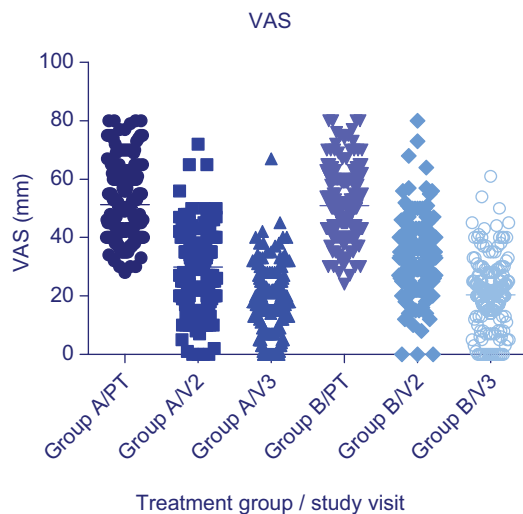


Figure 4 Visual analog scale scores for pain, for treatment groups A and B.
Note: Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.
Abbreviations: PT, pretreatment; VAS, visual analog scale; V2, visit two (after 15 days of treatment); V3, visit three (after 30 days of treatment).

reduction as measured by the VAS. Assessments performed by both the patients and the investigating physician had higher scores after 15 and 30 days of treatment among subjects treated with the combination. Treatment with the combination and with the control of vitamin B₁₂ monotherapy resulted in significant improvement in patient functionality throughout the treatment period, as measured by the patient functionality questionnaire.

The findings of this study are in agreement with those previously described in the literature. A previous study performed by Goldberg et al (2009) assessed the use of this combination in the treatment of back pain and hip pain, reporting significant reduction in pain assessments as well as functionality.¹⁰ As with the study of Goldberg and also another recent study in alcoholic polyneuropathy in which the authors compared the use of the combination of UTP + CMP + vitamin B₁₂ with the use of vitamin B₁₂ monotherapy,¹⁷ there

Table 3 Adverse events considered to be associated with study drug administration

Adverse event	Severity	Number of affected subjects
Group A		
Abdominal colic	Mild	1
Abdominal discomfort	Moderate	1
Abdominal distension	Moderate	2
Abdominal distension	Mild	1
Abdominal disturbance	Moderate	1
Feeling of bloating	Moderate	1
Flatulence	Moderate	1
Increased appetite	Mild	1
Nausea	Moderate	1
Nausea	Mild	3
Group B		
Abdominal discomfort	Mild	1
Abdominal distension	Moderate	1
Abdominal distension	Mild	1
Constipation	Moderate	1
Constipation	Mild	1
Elevated uric acid	Mild	2
Epigastralgia	Mild	2
Epigastralgia	Moderate	1
Flatulence	Mild	1
Nausea	Moderate	1
Nausea	Mild	1

Note: Group A: subjects treated with uridine, cytidine, and vitamin B12. Group B: subjects treated with vitamin B12 alone.

was a significant improvement over the treatment period in pain manifestations as compared to the monotherapy group, although the patients within the monotherapy group also displayed significant improvement throughout the treatment as compared to pretreatment status. This finding and that of our study highlights the importance the vitamin B₁₂ component in the treatment of these painful conditions.

A limitation of this study was the inclusion of three distinct pain locations: lower back, hip, and carpal tunnel

syndrome which ultimately reduced the number of subjects in each pain subcategory. Future studies should focus on a single pain location in order to achieve more specific results. Nevertheless, we believe the results of this study are in concordance with findings in the literature and serve to contribute to the growing body of evidence indicating the therapeutic value of the combination of UTP, CMP and vitamin B₁₂ for the treatment of peripheral neuropathies. It is also important to point out that unlike vitamin B₁₂ (which has been confirmed to exhibit antinociceptive effects in both animal and human studies) the nucleotides do not have any direct role in anti-inflammation or analgesia and thus the symptomatic improvements observed in our study and in previous studies are suggestive of structural neuroregeneration by the nucleotides as a mechanism of action.^{10, 11, 14, 15} Indeed, previous studies on animal models give credence to this notion, with previous observations of the nucleotides playing a positive role in axon and myelin sheaths of nerve and muscle fibers during regeneration following experimentally-induced damage, in addition to improved nerve fiber conduction velocity.¹⁹⁻²¹

A combination of uridine, folic acid, and vitamin B₁₂ was recently reported to be effective in the treatment of carpal tunnel syndrome. Although in a small scale exploratory trial of 48 subjects, authors reported reduced pain scores and improvement in symptom intensity following 60 days of treatment with the combination therapy.²³ An important limiting factor in our study with regards to carpal tunnel syndrome is the relatively small sample size in relation to the total patient population, as mentioned in the preceding paragraph. However, these findings together with the results of our study warrant further investigation into the use of the nucleotides and vitamin B₁₂ in the treatment of this very common ailment.

Clinical trials of painful conditions attributable to neuropathic pain (pain following neurological surgical procedures, neural compression-induced neuralgias, chronic neuropathic lumbar pain, peripheral neuropathies, and pain and paresthesia related to B₁₂ deficiency anemia) have consistently yielded encouraging results with use of the combination of uridine, cytidine, and vitamin B₁₂, and further studies may reveal additional indications where this combination or others like it may be of use, while also expanding our understanding of the interaction between the nucleotides and vitamin B₁₂ in painful conditions.⁹⁻²¹ For instance, the combination of uridine, folic acid, and vitamin B₁₂ was also reported to be effective in neuropathic pain of peripheral neuropathies, with a reduction in pain intensity and also allowing for reduction in concomitant medication use.^{23,24} These types of study are important to explore new alternatives for addressing neuropathic pain

– with the aim of providing treatment options that reduce pain, decreased need for other drugs with more unwanted side effects, and improve patient care and quality of life.

Conclusion

The results of this study showed a more expressive improvement in efficacy evaluations among subjects treated with the combination of nucleotides + vitamin B₁₂, with a statistically significant superiority of the combination in pain reduction (evidenced by VAS scores). There were adverse events in both treatment groups, but these were transitory and no severe adverse event was recorded during the study period. Safety parameters were maintained throughout the study in both treatment groups. The combination of uridine, cytidine, and vitamin B₁₂ was safe and effective in the treatment of neuralgias arising from neural compression associated with degenerative orthopedic alterations and trauma. Considering these results, a prospective, multi-center randomized controlled clinical trial, comparing the activity of vitamin B₁₂ alone to the activity of vitamin B₁₂ in combination with nucleotides in pain reduction, is warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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