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Research Article

Evaluation of the Efficacy of an Association of Uridine Monophosphate, Folic Acid and Vitamin B12 in the Treatment of Pain in Patients with Diabetic Peripheral Neuropathy

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Abstract

Background: Diabetes mellitus is the most common cause of peripheral neuropathy (PN). About half of diabetic patients are affected by this condition, and up to 15 - 25% of them suffer from neuropathic pain. Pyrimidine nucleotides, like cytidine and uridine, have proven efficacious in the treatment of peripheral nerve lesions, palliate the pain and enhancing the neuroregenerative effect.

Aim and Method: An open-label, exploratory, multicentre study was conducted in Portugal to evaluate the effectiveness and safety of a food supplement as Keltican® in patients with painful diabetic peripheral neuropathy (PDPN) in primary care. Patients were treated with 2 capsules of Keltican® (uridine monophosphate (UMP, 50 mg), folic acid (400 µg) and vitamin B12 (3 µg)) per day for the first two weeks, and one capsule per day in the remaining 6 weeks. Decrease of the intense pain felt in the 24 hours before visits was evaluated by Visual Analogic Scale of pain (VAS). Additional qualitative aspects of pain and its evolution were assessed using the Short-form McGill Pain Questionnaire (SF-MPQ), the Present Pain Intensity (PPI) Scale, the Clinical Global Impression-Severity Scale (CGI-S) and the Karolinska Sleepiness Scale (KSS).

Results: 42 patients were included. There was a reduction of the VAS score from 5,4 ± 1,6 to 3,4 ± 1,7 after 60 days of the treatment administration ($p < 0,0001$ [-2,5; -1,5]). An 83,3% (35/42) of the patients reported a reduction of the VAS score after 60 days of treatment administration. A significant improvement was also observed in secondary variables of pain (PPI, KKS and CGI-S) between baseline and final values. A statistically significant improvement was registered in the sensorial dimension of pain (SF-MPQ), specially dysesthesia, needle pain and continuous pain, being 0,7, 0,6 and 0,5, respectively.

Discussion: Patients treated with a combination of uridine nucleotides with folic acid and vitamin B12 could relief the pain associated to peripheral diabetic neuropathy as well as decreasing the necessity of concomitant pain killers, without major safety concerns. A randomised placebo-controlled trial with electromyographic evaluation should be performed in order to corroborate the results presented.

Keywords: *Diabetic Peripheral Neuropathy; Nucleotides; Neuropathic Pain; Primary Care*

Abbreviations

DM: Diabetes Mellitus; DPN: Diabetic Peripheral Neuropathy; PDPN: Painful Diabetic Peripheral Neuropathy; VAS: Visual Analogic Scale of Pain

Introduction

The estimated prevalence of diabetes mellitus (DM, type 1 and type 2 combined) in 2019 was 463 million people worldwide and will affect 578 million people by 2030 and 700 million by 2045 [1]. DM is the most common cause of peripheral neuropathy and about half of

diabetic patients are affected by this condition (diabetic peripheral neuropathy, DPN), that includes diverse clinical disorders [2]. Neuropathic pain, which occurs in 15 - 25% of all patients with DM [3], can be a disabling symptom with significant interference in the patients' quality of life [4]. The majority of guidelines stablish pregabalin, duloxetine, amitriptyline and gabapentin as first-line therapy for painful diabetic peripheral neuropathy (PDPN) and noted venlafaxine, valproate, tramadol, tapentadol, capsaicin, and opioids as second-line therapies [2]. However, the available treatment for PDPN is far from being fully effective and some of the most common prescribed drugs have side-effects that reduce their potential therapeutic effect [2,5]. Moreover, that drugs are solely aimed at symptomatic pain relief, without effect in the progression of the neuropathic process [2].

Pyrimidine nucleotides, such as cytidine and uridine, have proven efficacious in the treatment of peripheral nerve lesions affecting the myelin sheath produced by the Schwann cells [6]. Pharmacologic studies have shown that these nucleotides in isolation or in different combinations, even with other agents, such us vitamins, speed up and reinforce structural and physiologic recovery in animals with experimental lesions of the sciatic nerve [7,8]. These effects have been confirmed in different clinical studies in patients with different neuropathies, demonstrating that the administration of nucleotides have a positive effect not only in pain but also in EMG measures, suggesting a neuro-regenerative effect [9-25].

Keltican® is a food supplement composed of a combination of uridine at high doses (50 mg), folic acid and vitamin B12 that demonstrated effectiveness in the treatment of different types of peripheral neuropathies without safety concerns [9,13,15,17] although the information of its effects in neuropathic pain associated a DPN is still scarce [15,23].

Objective of the Study

The objective of our study was to evaluate the effectiveness and safety of Keltican® in patients with PDPN.

Patients and Methods

It was an open-label, exploratory multicentre study done in patients from 9 Primary Care areas located in the Minho district (northwestern Portugal). Inclusion criteria were type 2 diabetes mellitus with a HbA1c < 10%, symptoms of painful peripheral neuropathy of more than two months of duration (pain, paraesthesia, dysesthesia and abnormal sweating in the feet) and a score of > 30 mm in the visual analogic scale of pain (VAS).

After the signed informed consent, patients received two capsules of Keltican® (uridine monophosphate (UMP, 50 mg), folic acid (400 µg) and vitamin B12 (3 µg)) per day for the first 2 weeks, and one capsule per day in the remaining 6 weeks. Patients were free to keep their usual medication for the whole study.

The inclusion period was set at 13 months (January 2018 - January 2019). A first clinical assessment was made prior the administration of treatment and the final assessment was performed 60 days after.

The main variable of the study was the decrease of the more intense pain felt in the 24 hours before the visits, measured by VAS, between the first and final visit, considering a 20% reduction in this measure as sensitive. The sensorial dimension of pain, measured by the first eleven parameters of the Short-form McGill Pain Questionnaire (SF-MPQ), the affective dimension of pain (measured by the 12 - 15 parameters of the SF-MPQ), the actual intensity of pain using the Present Pain Intensity (PPI) Scale, the evolution of the severity of pain using the Clinical Global Impression-Severity Scale (CGI-S) and the degree of interference of pain experience in the quality of sleep according to the Karolinska Sleepiness Scale (KSS), were also evaluated.

Finally, any reduction or interruption in the medication taken for pain, sleep or anxiety, and adverse effects were also collected.

The study was approved by the Portuguese Data Protection Agency and performed in accordance with the International Conference on Harmonization and Good Clinical Practice, the Declaration of Helsinki, and Portuguese legislation.

Taking into consideration the exploratory nature of the study, no sample size was calculated.

Statistical analysis

A non-parametric Wilcoxon test was used to compare both primary (VAS scores) and secondary (SF-MPQ, PPI, CGI-S, KSS) variables at baseline and after 60 days of administration. Confidence interval to 95% was also used.

A descriptive analysis was applied to evaluate the possible reduction of concomitant medications and the adverse events reported.

Results

Forty-two patients were included, 25 being of the female gender. The mean age was 69.9 ± 9,2 years, with the mean weight and height being 76,6 ± 11,0 kg and 1,61 ± 0,09 m, respectively. The mean time of diabetes duration until inclusion was 11,1 ± 5,6 years and the median levels of HB A1c were 7,1 ± 0,9%.

Concerning the main goal, the variation in the degree of the more intense pain felt in the 24 hours before the visits, there was a reduction of the VAS score from 5,4 ± 1,6 at baseline to 3,4 ± 1,7 after 60 days of the treatment administration ($p < 0,0001$ [-2,5; -1,5]) (Figure 1). A VAS score reduction was present in 83.3% (35/42) of the patients. Considering as "responders" those patients in which the reduction in the VAS score was, at least, 20% between the two visits, an 81% (34/42) of the patients were "responders" regarding the prescribed treatment.

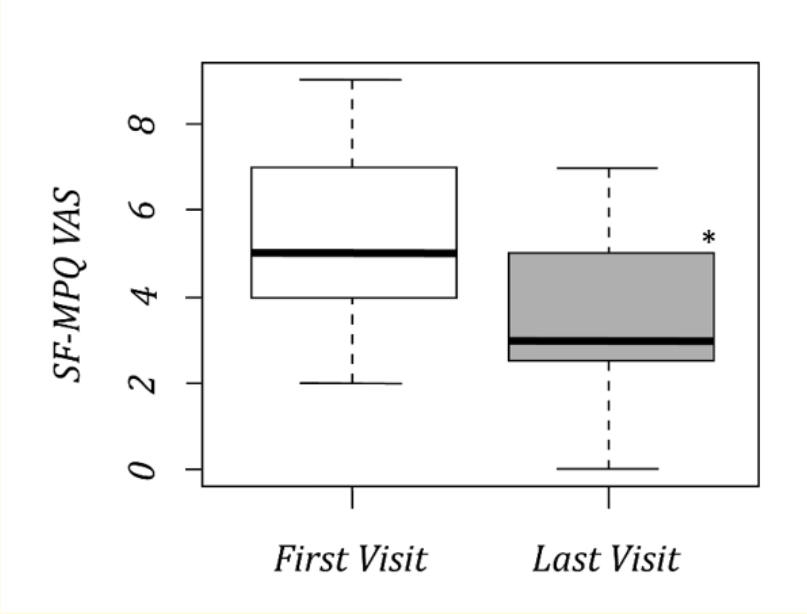

Figure 1: *Reduction in the degree of the more intense pain felt in the 24 hours before the visits (VAS).*
** = Statistically significant (Wilcoxon Test): p-value < 0,0001.*

A significant improvement was also observed in the secondary variables of pain (PPI, KSS and CGI-S) between baseline and final values (Table 1).

Parameter	First Visit	Last visit	Difference between visits	Statistically significance (Wilcoxon Test) [interval confidence 95%]
Actual intensity of pain (PPI Score)	2,5 ± 0,8	1,3 ± 0,8	-1,1 ± 0,9	p < 0,0001 [-1,5; -1,0]
Sleep disturbance in the night before the visits (KSS)	4,0 ± 2,7	2,1 ± 1,9	-1,9 ± 2,1	p < 0,0001[-2,5; -1,5]
Severity scale of pain (CGI-S)	3,8 ± 1,0	2,9 ± 1,0	-0,8 ± 1,7	p < 0,01 [-2,0; -0,5]

Table 1: *Evolution of the actual pain intensity, sleep disturbance and subjective appreciation of the severity of pain, between the visits.*
PPI: Present Pain Intensity; KSS: Karolinska Sleepiness Scale; CGI-S: Clinical Global Impression-Severity Scale.

Regarding the change in the sensorial dimension of pain according to SF-MPQ between the visits, there was a statistically significant improvement in most of the parameters evaluated. The parameters dysesthesia, needle pain and continuous pain registered the greatest improvement of 0,7, 0,6 and 0,5, respectively. In some cases, as for parameters tight pain and stinging pain, basal values were so small that invalidated an effective evaluation (Table 2).

	None		Mild		Severe		No anwser		
Parameter	**FV**	**LV**	**FV**	**LV**	**FV**	**LV**	**FV**	**LV**	**Statistically significance**
Continuous pain	9 (21,4%)	12 (28,6%)	12 (28,6%)	22 (52,4%)	18 (42,9%)	4 (9,5%)	3 (7,1%)	4 (9,5%)	p < 0.001
Lancinating pain	22 (52,4%)	26 (61,9%)	5 (11,9%)	7 (16,7%)	9 (21,4%)	2 (4,8%)	6 (14,3)	7 (16,7%)	p < 0.05
Local acute pain	21 (50,0%)	26 (61,9%)	9 (21,4%)	5 (11,9%)	4 (9,5%)	1 (2,4%)	8 (19,0%)	10 (23,8%)	p < 0.05a
Electric shock	22 (52,4%)	29 (69,0%)	9 (21,4)	4 (9,5%)	2 (4,8%)	0	9 (21,4)	9 (21,4)	p < 0.05a
Needle pain	15 (35,7%)	27 (64,3%)	7 (16,7%)	6 (14,3%)	11 (26,2%)	1 (2,4%)	9 (21,4%)	8 (19,0%)	p < 0.001
Tight pain	28 (66,7%)	29 (69,0%)	3 (7,1%)	2 (4,8%)	2 (4,8%)	1 (2,4%)	9 (21,4%)	10 (23,8%)	b
Stinging pain	24 (57,1%)	26 (61,9%)	6(14,3%)	5 (11,9%)	2 (4,8%)	1 (2,4%)	10 (23,8%)	10 (23,8%)	b
Burning pain	11 (26,2%)	17 (40,5%)	9 (21,4%)	15 (35,7%)	16 (38,1%)	6(14,3%)	6 (14,3%)	4 (9,5%)	p < 0.01
Dysesthesia	5 (11,9%)	10(23,8%)	7 (16,7%)	18 (42,9%)	30 (71,4%)	12 (28,6%)	0	2 (4,8%)	p < 0.0001
Heavy pain	21 (50,0%)	27 (64,3%)	6 (14,3%)	6 (14,3%)	7 (16,7%)	2 (4,8%)	7 (16,7%)	6 (14,3%)	p < 0.05a
Sensitive pain	17 (40,5%)	24 (57,1%)	8 (19,0%)	8 (19,0%)	9 (21,4%)	4 (9,5%)	8 (19,0%)	6 (14,3%)	p < 0.01

Table 2: *Evolution of the sensorial dimension of pain between the visits. Number of patients and percentage by each category.*
a= Inferiority Test; b = Cannot Compute Confidence Interval and p-value when all observations are tied; FV= First Visit; LV= Last Visit.

Finally, a significant reduction in the continuous pain within the affective dimension of SF-MPQ was shown when the baseline values were compared to those obtained at the end of treatment (Table 3). It was not possible to evaluate the other affective parameters of pain (suffocating pain, frightening pain and terrifying pain) because of their very low incidence at the basal visit.

	None		Mild		Severe		No anwser		
Parameter	**FV**	**LV**	**FV**	**LV**	**FV**	**LV**	**FV**	**LV**	**Statistically significance**
Continuous pain	4 (9,5%)	8 (19,0%)	13 (31,0%)	25 (59,5%)	25 (59,5%)	8 (19,0%)	0	1 (2,4%)	P < 0.001
Lancinating pain	26 (61,9%)	30 (71,4%)	2 (4,8%)	2 (4,8%)	5 (11,9%)	1 (2,4%)	9 (21,4%)	9 (21,4%)	a
Local acute pain	27 (64,3%)	29 (69,0%)	1 (2,4%)	3 (7,1%)	4 (9,5%)	0	10 (23,8%)	10 (23,8%)	a
Electric shock	28 (66,7%)	32 (76,2%)	2 (4,8%)	0	1 (2,4%)	0	11 (26,2%)	10 (23,8%)	a

Table 3: *Evolution of the affective dimension of pain between visits. Number of patients and percentage by each category. a = Cannot compute confidence interval and p-value when all observations are tied; FV= First Visit; LV= Last Visit.*

Regarding the number of patients with pain medication, it was confirmed a reduction in the number of patients taking nonsteroidal anti-inflammatory drugs (NSAID) (Table 4).

Type of medication	First Visit	Last Visit
NSAID	11	5
COXibs	5	5
Paracetamol	16	14
Metamizole	0	0
Tramadol	5	6
Others	1	1

Table 4: *Number of patients taking different types of pain medication.*

Only two patients (4,8%) presented secondary effects: one diarrhoea and the other feeling sick and epigastric pain. They were both considered related to medication and of mild intensity.

Discussion

Our results showed that a food supplement with uridine nucleotides as main component could relief the pain associated to diabetic peripheral neuropathy, decreasing the necessity of concomitant pain killers, without major safety concerns. These results agree with the still scarce studies published with Keltican® in this type of peripheral neuropathies.

The positive effect of uridine in nerve injury has been evidenced in several basic studies. In this way, it has been demonstrated that pyrimidine nucleotides play a major role in human cellular metabolism, particularly in neuronal tissue, stimulating the synthesis of phospho- and glyco- (or sphingo-) lipids, as well as glycoproteins, essential structural elements of neuronal membranes [6]. Moreover, uridine nucleotides act as cell-to-cell signalling in the nervous system and activate specific P2Y receptor subtypes [6], such as UTP-activated receptors P2Y2 and P2Y4, that are coupled to G-protein and are involved mainly in differentiation, neurite outgrowth, and cell survival or death [26]. Extracellular UTP interacts with Schwann cell nucleotide receptors and activates the molecular apparatus that induces changes in the cytoskeleton of altered glial cells in neuropathic models [27], contributes to the increase of the excitatory communication with axons and increases N-cadherin expression, an adhesion protein that accelerate myelination and axonal regeneration [28].

On the other hand, uridine tri and di-phosphate seem to modulate the spinal transmission of pain. Okada., *et al*. [29], for example, in a neuropathic pain model, in which the sciatic nerves of rats were partially ligated, demonstrated that uridine 5'-triphosphate (30 and 100 nmol/rat) and uridine 5'-diphosphate (30 and 100 nmol/rat) produced significant antiallodynic effects. These effects were reaffirmed in a neuropathic pain model, showing that UTP significantly alleviated mechanical allodynia in relation to its agonism at P2Y1 inotropic receptors [30].

For a long time, several clinical trials used nucleotides in patients with peripheral neuropathic pain of different aetiologies [9-25], some of them showing an improvement not only in pain but also in neurophysiologic parameters, in agreement with the mechanism of action of uridine. Gallai., *et al*. [23], for example, published a double-blind neurophysiologic study done in 40 diabetic patients with peripheral neuropathy, demonstrating that the administration of 300 mg of uridine once a day improved several neurophysiologic EMG parameters after 120 days of administration and persisted 90 days after of discontinuation of the treatment. On the other hand, Müller., *et al*. [21], in an observational study carried out with 40 patients with painful diabetic neuropathy showed that a combination of nucleotides (CMP and UTP) taken for 3 months produced an improvement of pain and in the conduction velocity of the external saphenous nerve at the end of treatment, suggesting a positive effect in the neuro-regenerative process. Additionally, in an open-label, controlled study, 42 patients with diabetic polyneuropathy received an intramuscular injection containing CMP and UMP (16 mg) once daily for 10 days, followed by 16 mg/day orally for 14 days, while 10 patients in the control group received standard treatment [16]. The treatment resulted in an improvement in all the sensitivity thresholds and the function of the peripheral nerves. Finally, Seck., *et al*. [14] evaluated the efficacy of an oral combination of CMP and UMP (24 mg/day) in 75 patients with painful diabetic neuropathy for 3 months. The medication improved sensory disturbances and pain intensity, and there was also a significant increase in sensory conduction velocity in the right median nerve and left sciatic nerve during electromyographic testing.

In our study, no EMG was performed given its observational nature and scope, the primary care. However, the effects of the treatment observed in sensorial dimensions of pain, such as dysesthesias, needle pain and sensitive pain would reinforce the idea that the effects of nucleotides in painful neuropathies are beyond the symptomatic pain relieve. It is highly recommendable, then, to perform a neurophysiologic study to this kind of patients in order to confirm this effect.

Another important finding observed in our study was the decrease in the use of analgesic medication, as NSAIDs. It is important, because at least 25% of patients with PDNP are undertreated due to the adverse effects related to the different drugs used in this pathology (mainly anticonvulsants and antidepressants) [31]. This decrement has been observed in previous studies done with nucleotides and in different painful neuropathies [13,15,22].

On the other hand, the patients also reported a significant improvement in their quality of sleep at the end of the study. Among people with chronic pain, insomnia is highly prevalent, closely related to the mechanism of central sensitization, characterized by low-grade neuroinflammation, and commonly associated with stress or anxiety; in addition, it often does not respond effectively to drug treatments [32]. Moreover, research findings show that sleep disturbances may have a bidirectional relationship with chronic pain [33]. Therefore,

the positive effects observed with Keltican® on sleep pain-related disturbances could have an impact on the global management of patients with PDPN, not only in pain but also in some other main symptoms, such as sleep disturbances.

Finally, it is important to remark that Keltican® is considered a food supplement, that is, a balanced complement of micronutrients to diet, uridine monophosphate, vitamin B12 and folic acid, with specific effect in painful neuropathies. In favour of combined administration of these nutrients are not only the effects on endogenous nerve regeneration but also the mutually supportive effects, taken into account the often simultaneous occurrence of nerve damage and insufficient B vitamin status [34,35]. These findings confirm that nutritional factors play a, not previously recognized, important role in the neuro-regenerative process than was previously assumed.

Our study has several limitations as an exploratory uncontrolled study: patients maintained their usual medication depending on the decision of their physician and, accordingly, no pharmacological intervention could be performed, and no comparison made. In addition, it is difficult to confirm the neuro-regenerative effect of Keltican® without performing an EMG test. However, the food supplement was evaluated under clinical practice conditions and its positive effect in several sensorial dimensions of pain suggests that this neuroprotector effect could exist.

Conclusion

In summary, our study provides more evidence about the efficacy of a combination of uridine nucleotide, vitamin B12 and folic acid in improving the intensity of pain experience in patients with DPN, in the sensorial and affective dimensions of pain and in improving the quality of sleep. There was a very small number of patients with side-effects that were short-lived and mild in severity and it was possible to reduce previous analgesic medication (NSAID) at the end of the study.

These promising results should encourage in the future a double-blind, placebo-controlled study about the efficacy of pyrimidine nucleotides in PDPN.

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Conflict of Interest

No financial interest or conflict interest to declare.

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