Use of ascorbic acid (vitamin C) and alpha tocopherol (vitamin E) as adjuvants in the treatment of neuropathic pain

Uso do ácido ascórbico (vitamina C) e alfa-tocoferol (vitamina E) como adjuvantes no tratamento da dor neuropática

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ABSTRACT

BACKGROUND AND OBJECTIVES: High concentrations of free radicals can damage nucleic acids, proteins and lipids and their accumulation may be involved in hypersensitivity to pain. The objective of this study was to evaluate the effect of vitamins C and E as adjuvants in the treatment of neuropathic pain.
METHODS: This study included 98 patients with neuropathic pain, classified by the Douleur Neuropathique 4 Questions (DN4), randomized into two groups: control and intervention. The control group received 150 mg of pregabalin and the intervention group 150 mg of pregabalin combined with 500 mg of vitamin C and 400 mg of vitamin E. Treatment and follow-up of the participants lasted 12 weeks. At the initial assessment, the patients answered the Quick Disabilities of the Arm, Shoulder and Hand (Quick-DASH) to assess upper limb functionality; quality of life was described using the World Health Organization Quality of Life-Bref (WHOQOL-bref) and pain assessment was measured using the visual analogue scale (VAS). After 12 weeks of treatment, the patients responded to the same instruments.
RESULTS: 86 patients completed treatment. Losses of participation in the sample were due to abandonment of treatment (n=7) or adverse effects to pregabalin (n=5). The intervention group presented superior results compared to the control group. Multiple comparisons between groups and moments for the evaluated scores demonstrated a mean difference from pre-treatment to post-treatment only in the intervention group ($p < 0.05$), with a mean reduction in Quick-DASH and VAS and a mean increase from WHOQOL.
CONCLUSION: It was observed that the use of vitamin C and E in combination with pregabalin had a greater analgesic effect than the use of pregabalin alone.
Keywords: Ascorbic acid, Chronic pain, Pregabalin, Vitamin E.

RESUMO

JUSTIFICATIVA E OBJETIVOS: Altas concentrações de radicais livres podem danificar ácidos nucleicos, proteínas e lipídios e o seu acúmulo pode estar envolvido na hipersensibilidade à dor. O objetivo deste estudo foi avaliar o efeito das vitaminas C e E como adjuvantes no tratamento da dor neuropática.
MÉTODOS: Foram incluídos 98 pacientes com dor neuropática, classificados pelo *Douleur Neuropathique 4 Questions* (DN4), randomizados em dois grupos, controle e intervenção. O grupo controle recebeu 150 mg de pregabalina e o grupo intervenção150 mg de pregabalina associada a 500mg de vitamina C e 400mg de vitamina E. O tratamento e acompanhamento dos participantes foi de 12 semanas. Na avaliação inicial, os pacientes responderam ao *Quick Disabilities of the Arm, Shoulder and Hand* (Quick-DASH) para avaliar a funcionalidade dos membros superiores; a qualidade de vida foi descrita utilizado o *World Health Organization Quality of Life-Bref* (WHOQOL-bref) e a avaliação da dor foi mensurada através da escala analógica visual (EAV). Após 12 semanas de tratamento, os pacientes responderam aos mesmos instrumentos.
RESULTADOS: Oitenta e seis pacientes concluíram o tratamento. As perdas de participação na amostra foram por abandono do tratamento (n=7) ou por efeito adverso à pregabalina (n=5). O grupo intervenção apresentou resultados superiores em comparação com o grupo de controle. As comparações múltiplas en-

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HIGHLIGHTS
- The antioxidants vitamins C and E attenuate mechanical allodynia induced by neuropathic injury.
- The use of vitamins C and E in combination with gabapentinoids can potentiate the effect of these drugs.
- The combination of vitamins C and E with pregabalin shows superior analgesic results when compared to the use of pregabalin alone.

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tre grupos e momentos para os escores avaliados demonstraram uma diferença média do pré-tratamento para o pós-tratamento somente no grupo intervenção (p<0,05), com redução média no Quick-DASH e na EAV e um aumento médio no WHOQOL.
CONCLUSÃO: Observou-se que o uso da vitamina C e E, em associação com a pregabalina, apresentou um efeito analgésico maior quando comparado ao uso isolado da pregabalina.
Descritores: Ácido ascórbico, Dor crônica, Pregabalina, Vitamina E.

INTRODUCTION

Chronic neuropathic pain (CNP) is caused by a lesion or disease of the somatosensory nervous system and can be spontaneous, evoked as an increased response to a painful stimulus (hyperalgesia) or arising from a non-painful stimulus (allodynia). The diagnosis of CNP requires a history of injury or disease of the nervous system and a neuroanatomically plausible distribution of pain. CNP can present negative symptoms, such as decreased or loss of sensation, or positive symptoms, such as allodynia or hyperalgesia, indicating the involvement of the somatosensory nervous system, which must be compatible with the innervation territory of the nerve structure[1].

Despite significant advances in the understanding of pathophysiological mechanisms in recent years and an increase in the number of treatments, neuropathic pain (NP) remains a difficult condition to treat, given that underlying mechanisms generally respond poorly to traditional analgesics and anti-inflammatory agents[2].

High concentrations of free radicals, such as superoxides, hydrogen peroxides and hydroxyl radicals, can damage nucleic acids, proteins and lipids, and their accumulation is involved in the development of hypersensitivity to pain[3]. Substances known for their antioxidant properties, vitamins C and E, neutralize free radicals, reducing oxidative stress that can damage neurons[4,5], as well as having anti-inflammatory properties that inhibit the production of pro-inflammatory cytokines, other mediators and the expression of cell adhesion molecules, helping to reduce inflammation in nerve and peripheral tissues, relieving pain[6,7]. In addition to their antioxidant and anti-inflammatory functions, vitamins C and E have other specific mechanisms that can influence pain control.

Vitamin C is crucial for the synthesis of neurotransmitters such as norepinephrine and serotonin, which are involved in pain modulation and general well-being. Adequate levels can help reduce the perception of pain[8] and modulate the function of the immune system, helping to regulate the inflammatory response and promoting tissue repair, being particularly important in conditions where inflammation contributes to chronic pain[9].

Vitamin E acts in neural protection by preventing the oxidation of polyunsaturated fatty acids in neuronal membranes, maintaining the structural and functional integrity of neurons. This is particularly relevant in NP conditions, in which nerve degeneration is a key factor[10]. In addition, vitamin E can influence the expression of genes related to oxidative stress and inflammation, modulating signaling pathways that are involved in the perception and transmission of pain[11].

A study carried out on animal models found that the combination of vitamins C and E was more effective in treating NP induced by chronic compression of the sciatic nerve than when used alone; the antinociceptive effect was greater when vitamins C and E were co-administered with gabapentin than when they were administered alone[12].

Pharmacological treatment with gabapentin or pregabalin, combined with ascorbic acid, can provide greater relief from NP symptoms[13]. The same can be observed with the use of pregabalin and vitamin E, which result in analgesic effects when administered alone or in combination, as well as having neuroprotective properties[14,15].

The aim of this study was to evaluate the efficacy of vitamin C and vitamin E as adjuvants in the treatment of NP.

METHODS

A randomized clinical study was carried out on patients with compressive syndrome in the upper limb who had secondary NP, to evaluate the effect of vitamins C and E as adjuvants in the treatment.

The sample included patients admitted to the hand surgery outpatient clinic of a tertiary hospital between November 2022 and January 2024, diagnosed with NP according to the Douleur Neuropathique 4 Questions (DN4) questionnaire, and aged over 18 years. The following were excluded from the study: pediatric patients; those with chronic renal failure; those with a history of kidney stones; those taking vitamins C, E or multivitamins; those with a history of glucose-6-phosphate dehydrogenase deficiency and hyperoxuria; those allergic to vitamin C or E; and those who did not agree to take part in the research protocol.

NP was defined using the DN4 questionnaire, translated and validated for Portuguese, which consists of seven items referring to symptoms and another three related to the physical examination. Each item scores 1 if the answer is positive, and zero if it is negative, leading to a minimum value of zero and a maximum of 10. A sum of points greater than or equal to 4 suggests NP[16].

The sample consisted of 98 patients; the participants were randomized into two groups using online software (https://www.randomizer.org/), with 51 patients in the intervention group (IG) and 47 patients in the control group (CG). The sample was calculated using the formula for a finite population, with the sample size being adjusted for the population of people with NP in Brazil, with a 95% confidence level, a 5% margin of error and an estimate of 7% of the affected population.

The intervention lasted 12 weeks, with the CG receiving 150 mg of pregabalin and the IG 150 mg of pregabalin combined with 500mg of vitamin C17 and 400mg of vitamin E[18]. The drug was prescribed by a member of staff without the knowledge of the principal investigator, who was responsible for the reassessment. The initial dose of pregabalin in both groups was 75mg/day for 4 weeks, after which the dose was increased to 150mg/day for a further 8 weeks. All groups were followed up with physiotherapy at the same rehabilitation service, with analgesic measures, transcutaneous electrical nerve stimulation and laser therapy, as well as an individualized kinesiotherapy program.

At the initial consultation, the patients answered the Quick Disabilities of the Arm, Shoulder and Hand (Quick-DASH)[19] and World Health Organization Quality of Life-Bref (WHOQOL--bref) questionnaires and their pain was recorded on a visual analog scale (VAS).

Upper limb functionality was determined using the Quick--DASH questionnaire, made up of 11 questions that assess physical function in the last week. The score for each item ranges from zero to five and the final score ranges from zero to 100. The final classification of the result found was: <20 points, excellent; 20 to 39, good; 40 – 60, fair; and >60 points poor, with this result defining severe functional incapacity.

The WHOQOL-bref, a simplified psychometric instrument created by the World Health Organization (WHO), was used to assess quality of life (QOL). This instrument highlights individual perception, making it possible to assess QoL in various groups and situations, regardless of level of education. The WHOQOL--bref consists of 26 questions relating to four domains: physical, psychological, social relationships and environment. The instrument has satisfactory psychometric properties and requires little time to administer, allowing it to describe an individual's subjective perception of their physical and psychological health, social relationships and the environment in which they live[20].

Patients were asked to rate the intensity of their current pain using the VAS, a one-dimensional instrument consisting of a line with the ends numbered 0-10, meaning "no pain" and "worst pain imaginable", respectively.

At the end of the 12 weeks of treatment, the patients underwent a new clinical assessment, answering identical instruments (Quick-DASH, DN4 and WHOQOL-bref), and their pain was quantified using VAS.

This study was evaluated and approved by the Human Research Ethics Committee of Santo Antônio Hospital/Irmã Dulce Social Works (Opinion number 5.800.624, 2022).

Statistical analysis

The data collected was stored using Microsoft Excel 2013 software; IBM-SPSS for Windows, version 22.0, was used to carry out the analysis. The tests were carried out at a 5% significance level.

The qualitative characteristics assessed were described according to the groups using absolute and relative frequencies; the association was verified using the Chi-square test and the quantitative characteristics were described using summary measures (mean, standard deviation, median and quartiles) and then compared between the groups using the unpaired Student's *t*-test. The questionnaire scores were described according to groups and times of assessment, using summary measures and compared between groups and times using Generalized Estimating Equations (GEE), with normal distribution and identity link function, assuming the matrix of 1st order autoregressive correlations (AR(1)) between the times of assessment of the same patient. The results were followed by Bonferroni multiple comparisons to assess which groups and moments were different.

RESULTS

Eighty-six patients completed the 12-week study, 45 in the IG and 41 in the CG. Losses from the sample were due to treatment abandonment in the CP (n=2) and the IG (n=5), and adverse effects to pregabalin with reports of dizziness and drowsiness in the IG (n=3) and the CG (n=2).

The sample consisted of 73 women (84.9%) and 13 men (15.1%), with an average age of 53.7 years; 47.7% of the participants reported comorbidities; isolated systemic arterial hypertension (SAH) was identified in 26.8% of the CG and 28.9% of the IG; diabetes mellitus (DM) was present in 14.7% of the CG and 17.8% of the IG, either in isolation or in association with SAH. The characteristics of each group are detailed in table 1.

Table 1. Description of personal characteristics according to groups and results of statistical tests

Variables	Groups		Total	p-value
	Control (n=41)	Intervention (n=45)	(n=86)	
Age (years)				0.225**
Mean ± SD	52.2 ± 11.7	55.2 ± 10.8	53.7 ± 11.3	
Median (p25; p75)	55 (43.5; 57)	54 (48.5; 60.5)	54.5 (47; 60)	
Gender. n (%)				0.905
Female	35 (85.4)	38 (84.4)	73 (84.9)	
Male	6 (14.6)	7 (15.6)	13 (15.1)	
Comorbidity. n (%)				0.504
No	23 (56.1)	22 (48.9)	45 (52.3)	
Yes	18 (43.9)	23 (51.1)	41 (47.7)	
Sistemic arterial hypertension (SAH)	11 (26.8)	13 (28.9)	24 (27.9)	
Diabetes Mellitus (DM)	4 (9.8)	4 (8.9)	8 (9.3)	
SAH + DM	2 (4.9)	4 (8.9)	6 (6.9)	
Anxiety		1 (2.2)	1 (1.2)	
Neoplasia		1 (2.2)	1 (1.2)	
Rheumatoid arthritis	1 (2.4)		1 (1.2)	

Chi-square test; **Unpaired Student's *t*-test

Analysis of the results of each research instrument showed that the IG had better results than CG. The average behavior of the Quick-DASH, WHOQOL and VAS scores was statistically different across the evaluation moments (p Interaction <0.05). Regarding the DN4, this instrument only showed a difference between the assessment moments, regardless of the group (p_{Moment} <0.001), i.e. its score decreased, on average, with treatment (Table 2).

After analyzing the multiple comparisons between groups and times for the scores evaluated (Table 3), it was found that only the IG showed a mean difference from pre- to post-treatment (p<0.05), with a reduction in Quick-Dash and VAS, and a mean increase in WHOQOL. Only VAS showed a difference between groups after treatment (p<0.001), being lower in the intervention group. Although both groups had reduced DN4 (Table 2), in the detailed comparison, only the

Table 2. Description of the scores evaluated according to groups, evaluation times and results of the statistical analysis

Variables	Control		Intervention		p_{Group}	p_{Moment}	$p_{Interaction}$
	Pre-treatment	Post-treatment	Pre-treatment	Post-treatment			
DN4					0.207	< 0.001	0.138
Mean ± SD	7 ± 1.9	6.3 ± 2.6	6.9 ± 1.5	5.4 ± 2.5			
Median (p25; p75)	7 (6; 8.5)	7 (5; 8)	7 (6; 8)	6 (4; 7.5)			
Quick-DASH					0.349	< 0.001	< 0.001
Mean ± SD	66.1 ± 21	61.4 ± 27.7	70.6 ± 15.6	48.8 ± 25			
Median (p25; p75)	73 (59; 82)	73 (48; 82)	73 (59; 84)	52 (30.5; 66)			
WHOQOL					0.171	0.014	0.005
Mean ± SD	3.2 ± 0.5	3.2 ± 0.5	3.2 ± 0.3	3.4 ± 0.6			
Median (p25; p75)	3 (2.8; 3.6)	3.3 (2.7; 3.6)	3.2 (2.9; 3.4)	3.4 (3.1; 3.8)			
VAS					< 0.001	< 0.001	< 0.001
Mean ± SD	7.9 ± 1.5	7.1 ± 2.4	8.1 ± 1.3	3.5 ± 2.4			
Median (p25; p75)	8 (7; 10)	7 (6; 9.5)	8 (7;9)	3 (2;5)			

Quick-DASH = Quick Disabilities of the Arm, Shoulder and Hand; WHOQOL = World Health Organization Quality of Life-Bref; DN4 = Douleur neuropathique 4 questions; GEE with normal distribution and identity link function, assuming AR(1) correlation matrix between moments.

Table 3. Results of the multiple comparisons between groups and times for the evaluated scores

Variables	Comparison	Mean difference	Standard error	p-value	CI (95%)	
					Lower	Higher
DN4	Pre-control - post-control	0.76	0.36	0.207	-0.19	1.70
	Pre-control - pre-intervention	0.14	0.47	>0.999	-1.10	1.37
	Pre-control – post-intervention	1.62	0.47	0.003	0.39	2.86
	Post-control – pre-intervention	-0.62	0.47	>0.999	-1.86	0.61
	Post-control – post-intervention	0.87	0.47	0.382	-0.37	2.10
	Pre-intervention – post-intervention	1.49	0.34	<0.001	0.59	2.39
Quick-DASH	Pre-control - post-control	4.71	3.27	0.899	-3.91	13.33
	Pre-control - pre-intervention	-4.48	4.90	>0.999	-17.41	8.45
	Pre-control – post-intervention	17.34	4.90	0.002	4.41	30.28
	Post-control – pre-intervention	-9.19	4.90	0.366	-22.12	3.75
	Post-control – post-intervention	12.63	4.90	0.060	-0.30	25.57
	Pre-intervention – post-intervention	21.82	3.12	<0.001	13.59	30.05
WHOQOL	Pre-control - post-control	0.02	0.07	>0.999	-0.17	0.20
	Pre-control - pre-Intervention	0.01	0.10	>0.999	-0.26	0.28
	Pre-control – post-intervention	-0.24	0.10	0.113	-0.52	0.03
	Post-control – pre-intervention	-0.01	0.10	>0.999	-0.28	0.27
	Post-control – post-intervention	-0.26	0.10	0.070	-0.54	0.01
	Pre-intervention – post-intervention	-0.25	0.07	0.001	-0.43	-0.08
VAS	Pre-control - post-control	0.78	0.41	0.327	-0.29	1.85
	Pre-control - pre-intervention	-0.26	0.43	>0.999	-1.38	0.87
	Pre-control – post-intervention	4.39	0.43	<0.001	3.26	5.52
	Post-control – pre-intervention	-1.04	0.43	0.093	-2.17	0.09
	Post-control – post-intervention	3.61	0.43	<0.001	2.48	4.74
	Pre-intervention – post-intervention	4.64	0.39	<0.001	3.62	5.67

Quick-DASH = Quick Disabilities of the Arm, Shoulder and Hand; WHOQOL = World Health Organization Quality of Life-Bref; DN4 = Douleur neuropathique 4 questions; VAS = visual analog scale; Bonferroni Multiple Comparisons.

IG showed a marked decrease, considered statistically significant ($p<0.001$).

DISCUSSION

This study showed that the use of vitamins C and E (both antioxidants) in combination with pregabalin had a greater analgesic effect than pregabalin alone.

Free radicals are critically involved in the generation of pain in various conditions, including neuropathic and inflammatory pain[3]. The antioxidants, vitamins C and E, attenuate mechanical allodynia induced by injury and their association has a greater antiallodynic effect, which may be involved in inhibiting the modulation and processing of NP in the spinal cord[21].

Ascorbic acid (vitamin C) is a water-soluble antioxidant with a high concentration in the central nervous system, exceeding the serum concentration by 10 times[2,22]. It is a powerful antioxidant and anti-inflammatory agent and is a cofactor in adrenal steroidogenesis and catecholamine biosynthesis. Vitamin C participates in serotonin synthesis and modulates synaptic dopamine and glutamate, the main excitatory amino acid neurotransmitter in cortical and hippocampal neurons, playing a significant role in the process of nociceptive behavior[2]. Vitamin C can also increase the synthesis of endomorphins[23] and acts as a cofactor for the biosynthesis of amidated opioid peptides[24] .

Preliminary evaluations show that vitamin C can act as a neuromodulator, facilitating the release of neurotransmitters and inhibiting their binding to receptors, including dopamine, N-methyl-D-aspartate (NMDA) and calcium channels[2,25,27].

NMDA receptors are one of the types of ionotropic glutaminergic receptors and are widely implicated in the development of hypersensitivity to pain. Thus, it is assumed that treatment with NMDA receptor antagonists produces a positive effect in NP conditions[2].

Ascorbic acid has been shown to protect cortical neurons from the toxic effects of N-methyl-D-aspartate, an effect mediated through NMDA receptors[2]. Ascorbic acid levels in the brain are associated with NMDA receptor activity and increasing its concentration may be beneficial for patients at risk of neurological complications[2,28,29].

A study investigating the efficacy of acute administration of different doses of vitamin C and the involvement of NMDA receptors in antinociceptive action was carried out in a rat model of NP. The study showed that systemic administration of ascorbic acid produces a significant inhibition of the response caused by chronic compression of the sciatic nerve. This effect is dose-dependent, as small doses do not reverse the mechanical and thermal limits[2].

It is well established that vitamin C participates in peptide amidation, acting as a cofactor for peptidylglycine α-amidating monooxygenase, which is the only enzyme known to amidate the carboxy-terminal residue of neuropeptides and peptide hormones[24].

It is believed that the nociceptive response of ascorbic acid is largely mediated by NMDA receptors, more specifically through interaction with ionotropic glutaminergic receptors. There is good evidence revealing the involvement of NMDA receptors in pain modulation, compounds that reduce transmission and exert an antinociceptive action[2,30-32].

Vitamin E (alpha-tocopherol), a fat-soluble vitamin, is the main chain-breaking antioxidant in the body's tissues, being the first line of defense against lipid peroxidation, protecting cell membranes from free radical attacks[15].

Sensitized spinal dorsal horn neurons become normalized after treatment with vitamin E. After spinal nerve injury, excessive oxidizing agents accumulate in the spinal cord, causing oxidative stress that sensitizes the posterior horn of the spinal cord. By removing the excessive oxidizing agents with vitamin E, the normal physiological condition is restored, thus relieving the pain[33]. The analgesic effect of vitamin E occurs through a spinal mechanism, reducing central sensitization, as demonstrated by the decrease in pNR1 levels in the dorsal horn after its administration[15].

A study investigating the efficacy and mechanisms of vitamin E in analgesia in a rat model of NP produced by spinal nerve ligation showed that a single daily systemic injection of high or low doses of vitamin E significantly reduced NP behaviors. Vitamin E has been shown to be effective in producing analgesia by subarachnoid injection, suggesting the importance of spinal mechanisms. In spinal dorsal horn neurons, vitamin E reduced evoked responses to mechanical stimuli, as well as the size of receptive fields. In addition, NDMA receptor levels in neuropathic rats were also reduced by vitamin E injection. These data suggest an analgesic effect mediated by a reduction in central sensitization[33].

A research carried out in an animal model found that treatment with a combination of vitamin C associated with vitamin E was more effective for NP induced by chronic compression of the sciatic nerve than when used alone, and the antinociceptive effect was greater with coadministration of vitamins C and E with gabapentin, than when it was administered alone[12]. In a clinical study, vitamin E supplementation as an antioxidant reduced the pain score, generating an improvement in the QoL of patients with diabetic neuropathy more than with the use of pregabalin alone3[3], with the same result being observed in the present study, showing the beneficial effect on patients with diabetes.

Although vitamin E is located in membranes and vitamin C is present in aqueous phases, vitamin C acts to regenerate vitamin E from its radical form, providing an explanation for the synergy of antioxidant effects if administered in combination. Vitamin C increases the ability of vitamin E to inhibit nociceptive behavior, with the antioxidant process being the main mechanism underlying antinociception mediated by the combination of this vitamins[15].

The use of antioxidants in association with gabapentinoids may act to enhance the effects of these drugs. In this sense, some researches have indicated that the dose of gabapentin can be reduced if combined with an antioxidant, as these seem to enhance its analgesic effect. Some studies have found that antioxidants in combination with gabapentin would provide a synergistic effect in suppressing thermal hypersensitivity in a rat model of NP[33,34].

Other authors described that vitamin C can increase the analgesic effect of gabapentin and the mechanism may be related

to antioxidant responses that were more obvious in peripheral blood than in neurons[35].

The association of vitamin C and E with pregabalin presents better analgesic results than those resulting from the administration of pregabalin alone. Considering that the administration of vitamins C and E is associated with little or no adverse effects, they are relatively low cost and have been shown in the literature to improve NP, their administration may be a beneficial adjuvant therapy[33,35].

A limitation of this study was the use of drugs or other substances by participants that were not reported or were intentionally omitted, which may have introduced bias in the results. For example, an unreported drug may have synergistic or antagonistic effects with the studied treatment, altering the observed efficacy or safety. Another limitation, the omission of the use of complementary or alternative therapies, which may have made it difficult to identify and control confounding variables, which are uncontrolled factors that can influence both exposure and outcome. In summary, the omission of this information by participants can be a significant limitation, impacting the accuracy, interpretation and applicability of the results.

Further studies should be carried out with a larger number of participants associated with the use of placebo in the CG, in order to avoid situations identified as limiting factors of the present study.

CONCLUSION

Vitamins C and E can be used as adjuvants in the pharmacological treatment of NP. Their association with pregabalin showed superior analgesic results when compared to the isolated use of pregabalin.

AUTHORS' CONTRIBUTIONS

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