Research Article

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Comparative Clinical Trial of Safety and Tolerability of Gabapentin Plus Vitamin B1/B12 versus Pregabalin in the Treatment of Painful Peripheral Diabetic Neuropathy

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Abstract

Introduction: The B complex vitamins (B1 and B12) have been shown to have antiallodynic, antihyperalgesic and antinociceptive effect. Neuromodulators as gabapentin (GBP) and pregabalin (PGB) are effective in the treatment of painful peripheral diabetic neuropathy, but are related to occurrence of adverse events at high doses (sleepiness, vertigo and dizziness). The aim of this study was to evaluate the efficacy and safety on pain intensity reduces of GBP + B1/B12 versus PGB in patients with painful diabetic peripheral neuropathy of moderate to severe intensity.

Methodology: Multicenter, randomized, single-blind study. 336 patients were evaluated, 181 with GBP + B1/B12 and 165 with PGB, with an intensity average of 7/10 on the numerical pain scale; 5 visits (12 weeks) were set. The visual analog scale (VAS), the numerical pain scale (END), the clinical global impression (IGC) and patient's global impression of change (IGCP) were used for the efficacy analysis. Reported adverse events were analyzed to assess safety.

Outcomes: Both drugs showed reduction in pain intensity, with no statistically significant difference (P= 0.900) between the two treatment groups, although the reduction in group GBP/B1/B12 was associated with doses of 300 - 1800 mg/d, compared with 300-600 mg/d of PGB. Regarding the IGC and IGCP, both drugs improved the perception of improvement, with no statistically significant difference observed between the two treatment groups between basal and final visit (P= 0.586 and P= 0.429) and (P= 0.893 and P= 0.276) respectively. Higher frequency of dizziness (P = 0.012), and vertigo (P= 0.006) were observed in the group using PGB.

Conclusions: This study shows that GBP + B1/B12 equally reduces pain intensity as PGB, although this reduction was obtained with lower doses (300 - 1800 mg) to those reported in clinical trial with GBP as monotherapy; likewise, a reduced occurrence of dizziness, vertigo and somnolence was also observed. These results are showing that the combination of vitamins B plus gabapentin is as effective as pregabalin in the painful diabetic neuropathy treatment; however, the combination improves the safety profile.

Keywords: Neuropathic pain; Neuropathy; Gabapentin; Pregabalin B Complex; Dizziness; Vertigo

Introduction

The most common cause of neuropathy worldwide is diabetes mellitus [1]. Prevalence of neuropathy in patients with diabetes is 30% and it is estimated that more than 50% may develop during the course of the disease [2]. Treatment of painful diabetic neuropathy (NDD) comprises the use of various types of drugs such as antidepressants, anticonvulsants, calcium channel ligands and opiates, among other drugs. One of the main problems with the use of these drugs is the adverse events (AEs), which sometimes limits the possibility of using the recommended dose in clinical trials. The B complex vitamins, specifically thiamine (B1) and cyanocobalamin (B12) have demonstrated utility in some painful conditions by having effects on the central nervous system, in the synthesis and secretion of serotonin in several brain areas [3], by blocking three metabolic pathways related to oxidative stress [4] and also its effects on nitric oxide-GMPc path [5], among other mechanisms. The synergism these vitamins produce with other drugs, for example gabapentin, would reduce the recommended dose as monotherapy achieving a greater effect in reducing pain intensity with reduced occurrence of AEs [6].

Pregabalin (PGB), a ligand of the calcium channel, has shown benefit in the treatment of neuropathic pain, but the greatest benefit is related to high doses, which obviously relate to onset of AEs such as dizziness, somnolence, peripheral edema, among other [7]. Gabapentin (GBP), other calcium channel ligand has shown benefit in the treatment of NDD with effective results in the dosage range of 1800-3600 mg per day, although these doses are associated with AEs between 20 to 50%, such as nausea, vomiting, dizziness and sleepiness [8].

The aim of this study was to determine the safety and tolerability of gabapentin + vitamin B1 and B12 versus pregabalin for the treatment of painful diabetic neuropathy during 12 weeks of follow-up.

Material and Methodology

Multicenter, phase IV, randomized, open, parallel groups trial. This protocol was submitted and approved by an Independent Ethics Committee in Mexico City; complied with the ethical standards of the 1975 Declaration of Helsinki of the World Medical Association, (ethical principles for medical research involving human subjects) and its 2000 revision. All patients included in the study signed an informed consent to participate in the study. 459 subjects from 18 to 65 years of age with diabetes mellitus type 1 or 2 and documented diagnosis of sensitive

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motor NDD from moderate to severe were studied using LANSS [9] scale that met the following criteria : neuropathic pain present at least one year before the study, with a score > 40 mm on the visual analog scale (VAS) [10] (at the selection visit and basal visit), receiving stable hypoglycemic treatment for at least 6 weeks prior to randomization, with HBA 1c < 8.5 % in selection visit without analgesics or with stable analgesic medication for at least 4 weeks, but not acceptable pain relief.

Sample size calculation

The primary efficacy variable was the change in the mean score of the NPI (Numeric Pain Intensity Scale). Two groups of treatment were compared. The design was done to detect differences of 0.1 points, with a type I error of 0.05 and a power of 0.90, considering a standard deviation (SD) of 26 mm. It was calculated that 286 patients were needed. In order to consider a dropout rate of 25%, a recruitment of 360 patients was considered, 180 on each group.

Subject disposition in safety population

A total of 353 patients were screened and randomized in two groups: Group A, 176 patients treated with gabapentin/B1/B12 and Group B, 177 patients treated with Pregabalin. Five patients did not take their medication and were withdrawn from the study (2 and 3, respectively), remaining 348 to safety population.

Intervention

Test product, dose and mode of administration:

Gabapentin 300 mg/thiamine 100 mg/ cyanocobalamin 0.20 mg tablets, oral administration of 300 mg/day (day 1), followed by 900 mg/day at visit 1, 1800 mg/day at visit 2 , 2700 mg/day at visit 3 and 3600 mg/day at visit 4 and 5, each divided into 3 daily doses.

Reference therapy, dose and mode of administration:

Pregabalin capsules: Oral administration. 75 mg/day every 12 hrs, followed by 300 mg/day every 12 h at visit 2, followed by 600 mg/day in visits 3, 4 and 5. If the patient did not tolerate increased dose at the corresponding visit, it remained with the previous dose tolerated for the rest of the study.

To assess improvement in pain, Clinical Global Impression scale (IGC) [11] and patient's global clinical impression of change (PGIC) [12] at baseline and the end of study was used. 5 visits were established,

Figure 1: Trial Design.

the total study duration was 15 weeks (1 pre-selection, 1 selection and 12 weeks of randomized treatment) (Figure 1).

Safety and Tolerability Measures

All adverse events (AE) related and unrelated, as well as changes in physical examination including weight and height, laboratory tests (including glycosylated hemoglobin) were measured. Information on the subjects sleeping hours during the night as well as the answers to questions 4 and 6 of the sleep questionnaire (Sleep Questionnaire in the Mexican population) [13] consisting of 10 questions, was obtained, evaluating daytime sleepiness by EPWORTH scale [14] was also obtained.

For statistical analysis, the homogeneity between groups was assessed using chi-square for categorical variables and student t for continuous variables. Student t for paired test was used for analysis of basal-post-basal changes between visits and Mantel-Haenszel test for security measures between visits. All statistical tests were performed with a significance level of 0.05 and confidence intervals of 95% (CI). SPSS software for Windows® (SPSS Inc., version of Chicago, IL, 18.0) was used.

Outcomes

459 subjects were selected, of whom 353 were randomized and 348 patients comprised the safety population in two parallel groups: Group A: 174 patients treated with GBP + B1/B12 and Group B: 174 patients treated with PGB. Two patients were withdrawn from the study because they did not have the information recorded after their initial visit (one from each group), leaving 346 (intention to treat population, ITTP). 76 patients were withdrawn from the study for various reasons, leaving 270 patients as per protocol population (PPP). 68% in the GBP/B1-B12 group and 62% in the PGB group were women; the average age in both groups was 54 (+/-9 years), with no statistically significant differences between groups regarding comorbidity, body mass index (BMI) and glycosylated hemoglobin levels, Table 1. The years of the DM duration, the NDD and the treatment used for disease control, are shown in Table 2.

Effectiveness

Pain intensity at visit 1 was 7 points (SD +/- 1.6) as measured by the visual analog scale (VAS), with a reduction of over 30% at visit 3 (2.5 points on the VAS) with 1800mg/day of GBP + B complex and (3 points on the VAS) for PGB with 150mg, with no statistically significant difference (p = 0.900). The greatest reduction of 50% was observed at doses of 2700 mg of GBP/B complex.

Regarding the perception of improvement, there was no statistically significant difference between the two treatment groups: the Global Impression of Clinical Change (GICC) between visit 1 (p = 0.586) and at visit 5 (p = 0.429), and Patient's Global Impression of Change (PGIC) between visit 1 (p = 0.893) and visit 5 (p = 0.276), Tables 3 and 4.

While evaluating isolated IGCC questions: At the end of the study, how do you consider our health? 88% reported excellent or good self-rated health in the GB + B1/B12 group vs. 83% of subjects in the PGB group, with no statistically significant difference (p = 0.410). In the PGIC question: Compared to your health before the test, how do you currently feel? 86% responded much better with PGB and 94% with GBP + B1/B12, showing a statistically significant difference in favor of GBP + B1/B12 (p = 0.022).

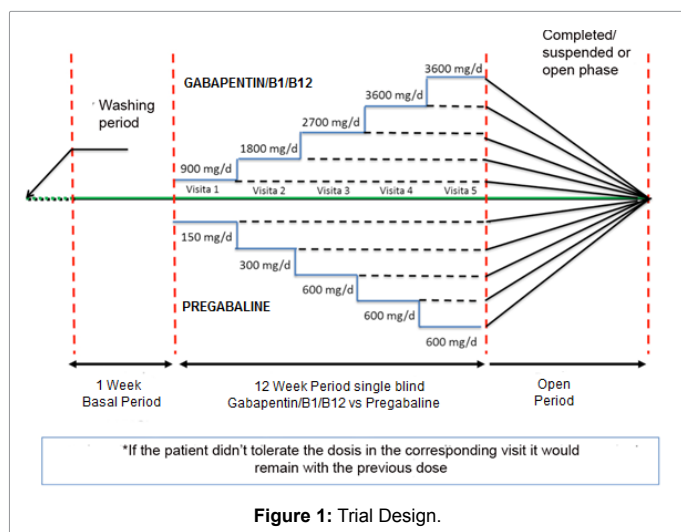When looking for establishing a link between patients who had an

		Pregabalin		Combined Gabapentin		P-Value
		n=174	%	n=174	%	
Gender	Female	109	62.6	119	68.4	0.260
	Male	65	37.4	55	31.6	
Age (years)	Average	54.3		53.2		0.326
	Standard Deviation	9.4		10.5		
	Minimum – Maximum	23.0-71.0		19.4-70.6		
Risk Factors						
Smoking	Yes	14	8.1	20	11.6	0.279
Hypertension	Antecedent	63	36.2	67	38.5	0.658
Hypothyroidim	Antecedent	1	0.6	1	0.6	1.000
Cholesterol	Average	198.7		195.9		0.542
(Basal Measurement)	Standard Deviation	47.1		38.4		
	Minimum – Maximum	101.0-542.0		71.0-366.0		
Tryglycerides	Average	200.8		197.0		0.806
(Basal Measurement)	Standard Deviation	159.3		126.0		
	Minimum – Maximum	53.0-1390.0		63.0-952.0		
BMI	Average	28.6		28.2		0.371
	Standard Deviation	4.4		4.2		
	Minimum – Maximum	18.4-39.6		17.4-39.4		
Glycated Haemogoblin	Average	7.4		7.4		0.86
	Standard Deviation	1.3		1.4		
	Minimum – Maximum	5.2-10.2		4.9-10.0		

Table 1: Demographic and basal characteristics by treatment group.

		Pregabalin		Combined Gabapentin		P-Value
		n=174	%	n=174	%	
Years with Diabetes	Average	10.1		9.6		0.361
Mellitus	Standard Deviation	6.2		6.6		
	Minimum – Maximum	1.5-32.6		1.4-32.0		
Years with Neuropathic	Average	2.7		2.7		0.868
Diabetes	Standard Deviation	1.1		1.1		
	Minimum – Maximum	0.6-5.9		0.8-6.6		
Diabetes treatment	Oral	139	79.9	135	77.6	0.681
	Insulin	4	2.3	6	3.4	
	Both	31	17.8	33	19.0	

Table 2: NDD Characteristics by treatment group.

		Pregabalin		Combined Gabapentin		Total		
		N	%	N	%	N	%	P-value*
Visit 1	Has improved much or very much	65	37.6%	60	34.9%	125	36.2%	0.893
	Improved a bit, it hasn't changed or is worst.	108	62.4%	112	65.1%	220	63.8%	
	Total	173	100.0%	172	100.0%	345	100.0%	
Visit 5	Has improved much or very much	140	91.5%	150	93.8%	290	92.7%	0.276
	Improved a bit, it hasn't changed or is worst.	13	8.5%	10	6.3%	23	7.3%	
	Total	153	100.0%	160	100.0%	313	100.0%	

Table 3: Overall Results of Patient's Global Clinical Impression in visits 1 to 5 (Since the beginning of the study my health….).

adverse event and the PGIC, no association between treatment and the level of response at visit 5 was found.

Safety

Adverse Events: Adverse events (AEs) occurred in 53% of patients on pregabalin and 43% in the gabapentin group. With PGB, the most frequent AEs were nausea (30%), somnolence (30%), headache (7.5%) and vertigo (5.7%); for GBP + B1/B12 group were: sleepiness (27%), dizziness (24.1%), headache (7.5%), and vertigo (3.2%). As shown in Table 5 and Figure 2. Dizziness and vertigo was less frequent in the group of GBP + B1/B12, with statistically significant difference (p = 0.012) and (0.006) respectively.

Sleep and daytime sleepiness: In relation to the hours of sleep at basal visit were 6.3 (SD +/- 1.2) hours for GBP + B1/B12 and 6.5 hours (SD +/- 1.3) for to PGB (p = 0.185). At the end of the study, the average of sleeping hours were 7.0 hours (SD +/- 1.3) for GBP/B1/B12 versus 7.1 hours (+/- 1.3) for PGB, with no statistically significant difference (P = 0.636).

Regarding the question of the Sleep Questionnaire, Have you slept enough to feel rested at wake up time in the morning? It was found that there was improvement in groups between basal visit and the final study visit (GBP + B1/B12), p < 0.001) and (PGB, p < 0.023). Daytime sleepiness was similar in both treatment groups, with a mean score at basal visit of the sleepiness scale of 8.8 (SD +/- 5.2) points to PGB versus 8.5 (SD +/- 5.5) for GBP/ B1/B12 (p = 0.568) at the final visit it was a mean of 6.9 (SD +/- 5.7) points to PGB and an average of 7.4 (SD +/-

		Pregabalin		Combined Gabapentin		Total	
		N	%	N	%	N	%
Visit 1: How mentally ill is the patient at this time? (p-value = 0.586)	Normal, not sick at all	139	80.3%	142	82.6%	281	81.4%
	In the edge between health and sick, or sick (mild or more)	34	19.7%	30	17.4%	64	18.6%
	Total	173	100.0%	172	100.0%	345	100.0%
Visit 5: How mentally ill is the patient at this time? (p-value = 0.429)	Normal, not sick at all	135	88.2%	145	90.6%	280	89.5%
	In the edge between health and sick, or sick (mild or more)	18	11.8%	15	9.4%	33	10.5%
	Total	153	100.0%	160	100.0%	313	100.0%
Visit 1: Compared to the status of the patient at the beginning of the study, how much has changed? (p-value =0 .787)	Improved much or very much	46	26.6%	43	25.0%	89	25.8%
	Improved a little, or didn't change or is worst	127	73.4%	129	75.0%	256	74.2%
	Total	173	100.0%	172	100.0%	345	100.0%
Visit 5: Compared to the status of the patient at the beginning of the study, how much has changed? (p-value = 0.755)	Improved much or very much	142	92.8%	149	93.1%	291	93.0%
	Improved a little, or didn't change or is worst	11	7.2%	11	6.9%	22	7.0%
	Total	153	100.0%	160	100.0%	313	100.0%

Table 4: Overall result of global impression of clinical change in visits 1 y 5 (final).

	Pregabalin		Combined Gabapentin		Total		P-VALUE
Event description	N=174	%	N=174	%	N	%	
With adverse event	93	53.4	80	46.0	173	49.7	0.164
Headache	13	7.5	14	8.0	26	7.5	0.841
Dizziness	52	29.9	32	18.4	84	24.1	0.012*
Somnolence	52	29.9	41	23.6	93	26.7	0.183
Vertigo	10	5.7	1	0.6	11	3.2	0.006*

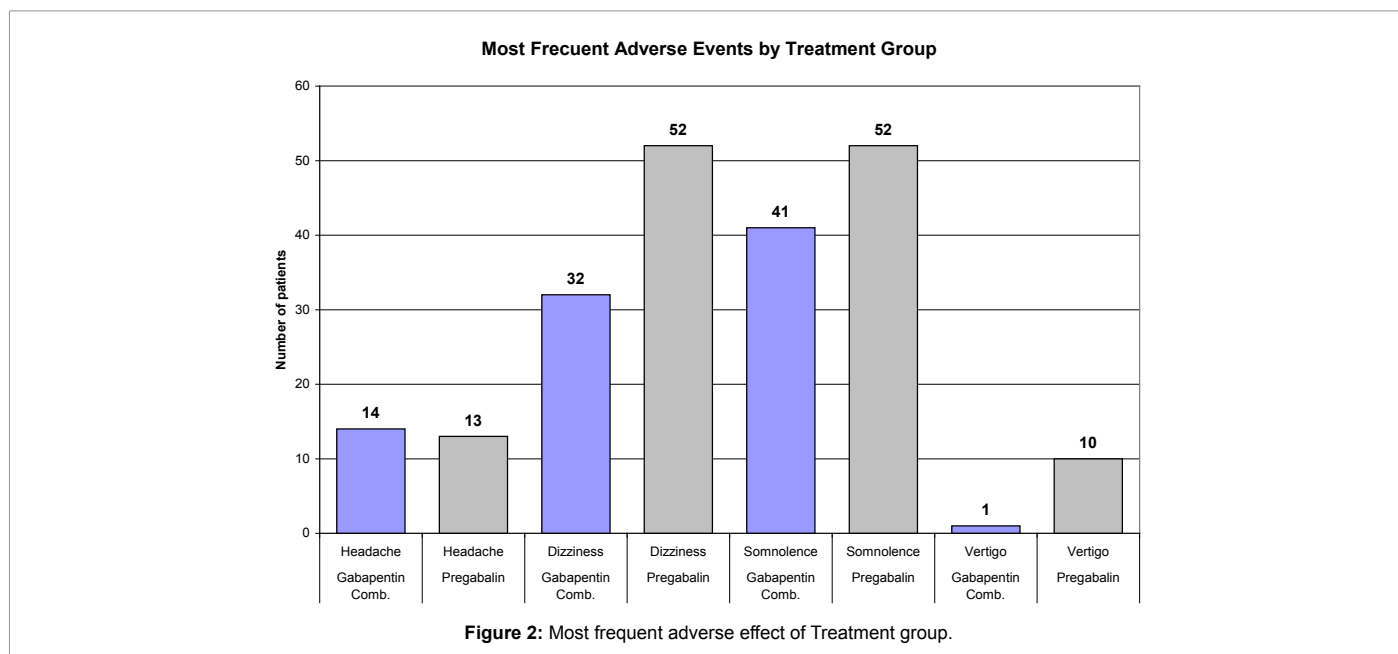**Table 5:** Most frequent adverse event by treatment group.

Figure 2: Most frequent adverse effect of Treatment group.

6.4) in the GBP/B1/B12 group (P = 0.763). A comparison between basal visits and final visit in each treatment regarding daytime sleepiness (P < 0.001) to PGB and (P < 0.015) for GBP/B1/B12 was established.

The suspension rate for adverse event (RAE) was in 4 patients (2.3%) in both groups. Three PGB patients discontinued treatment due to the presence of dizziness, vertigo or somnolence and two patients with GBP + B1/B12 suspended by somnolence and dizziness.

Discussion

This is the first multicenter, randomized, open, parallel group study that seeks to demonstrate the synergistic effect of vitamin B1 and B12 with gabapentin in the treatment of NDD for 12 weeks when compared to standard treatment.

The use of the complex B in the treatment of diabetic neuropathy has been controversial. Ang CD et al. in a meta-analysis reported that there was insufficient evidence to recommend for or disqualify the use

of B complex vitamins in the treatment of diabetic neuropathy, due to the heterogeneity of the studies [15].

Gorson K et al. in a crossover study showed that the GBP daily dose of 900 mg was ineffective or marginally effective in the treatment of NDD [16]. Gómez Pérez et al. in a parallel group trial, concluded that gabapentin doses higher than 1200 mg produced pain reduction of more than 50% [17] and Backonja M et al. reported in a systematic review that GBP doses of 1800-3600 mg /d, were effective and well tolerated in the treatment of neuropathic pain [18]. The results of our study show that in 94% of patients receiving GBP/B1/B12 improved in the Global Clinical Impression and Patient's Global Impression of Change with 50% fewer doses of GBP (1800 mg/d) [each tablet contains GBP 300 mg/B1 (100 mg)/B12 (.20 mg)] in relation to the reduction obtained with PGB, but with higher doses of these (600 mg). Reyes Garcia et al. showed the synergistic effect of GBP with thiamine (B1), and cyanocobalamin (B12) [7] as a result of many effects of these vitamins at a metabolic level. These effects can be divided into two groups: those that decrease the effect of damage to the nerve fiber and antihyperalgesic and antinociceptive effects. B1 reduces the formation of end products in protein glycosylation, which is a powerful free radical generator that ultimately produces oxidative stress [19]. Another effect is through the inhibition of the dialcilglicerol pathway (DAG), which has the effect of reducing the activation of protein kinase C (PKC) and with this an antiallodynic effect [20]. Likewise, it also reduces the activity by the hexosamine pathway, and through alternate paths thereof, improving metabolism through the pentose phosphate pathway. B1 (thiamine diphosphate) functions as a coenzyme for the erythrocyte transketolasa, a critical enzyme in carbohydrate metabolism. There is evidence that between 17 to 79% of diabetic type 1 and 2 has thiamine deficiency, as part of the metabolism of carbohydrates, this phenomenon occurs in euglycemic or hyperglycemic environment [19]. All these effects decrease the damage to the nerve fiber, which undoubtedly contributes to the development of painful diabetic neuropathy.

The B complex vitamins act directly on pain control, as they have antiallodynic, antihyperalgesic and antinociceptive effects3 all this through: 1 - the route of nitric oxide-cyclic GMP, which enhances the soluble guanylyl cyclase, this produces cyclic GMP, which has the effect of activating a protein kinase type G (PKG), which produces hyperpolarization of the potassium channel in the nociceptor [21]. Also increases afferent inhibitory control of nociceptive neurons of spinal cord, and reduces the thalamic neurons response to nociceptive stimulation [22]. Another effect that explains its antihyperalgesic action is through increasing the synthesis of serotonin and GABA and decreasing glutamate levels in several brain areas [23]. Therefore, it is the sum of all effects on carbohydrate metabolism and pain pathways that explains its efficacy in the treatment of painful diabetic neuropathy.

Using a neuromodulator is related to occurrence of adverse events, particularly dizziness, vertigo and somnolence, sometimes limiting the use of higher doses and sometimes leading to treatment discontinuation. Freeman et al. reported in a meta-analysis adverse events related to the use of pregabalin were related to dose, dizziness being the most frequent AE (28%) with 600 mg/d, peripheral edema (16%) and somnolence (13%) [5]. The most frequently reported AE with the use of GBP are dizziness (24%), somnolence (23%) and headache (11%) [6]. Our study showed lower dizziness and vertigo with GBP + B1/B12 (GBP: doses of 300 to 1800 mg, B1: 100 to 600 mg and B12: .20 mg to 120 mg daily) compared to PGB (75- 600 mg daily), associated with this lower dose of GBP used in the study added to the synergistic effect of vitamin B1 and B12, allowing optimization of the GBP doses needed to reduce the intensity of pain with a greater margin of safety and tolerability.

The rate of adverse events (RAE) was much lower (2.3%) than that reported in clinical trials of GBP + B1/B12 (8%) [6]. As already mentioned, it is likely that this lower SREA is related to the lower dose of GBP + B1/B12 used to achieve a reduction in pain intensity.

Sleep disorders are usually present in 50-70% of patients with chronic pain. Insomnia may be a cause or effect of the painful process. GBP + B1/B12 effect on sleep improvement is related to the reduction of pain, but also related to the modulation of neurotransmitter synthesis. Backonja M et al. showed that doses of 1800 mg/d improved measures on sleep interference scales [6]. Our study demonstrates that GBP enhances sleep hours and the perception of improvement of the same, as with PGB, although with lower dose of the former. A study of Lo HS et al. showed that GBP increases slow-wave sleep in patients with primary insomnia, improving sleep quality by improving its efficiency and decreasing spontaneous awakenings [22]. It is also worth mentioning that this improved sleep is not related to the presence of daytime sleepiness, as evidenced by the results of our study.

Our study has some limitations, as is the fact that not all patients reached the maximum dose, and other outcomes related to chronic pain also were not measured, as is the impact on quality of life.

Conclusions

This study shows that the combination of gabapentin B complex is as effective as pregabalin, but a doses of 300-1800 mg /day, (50% less than the required dose as a monotherapy), which produces a lower onset of AE (dizziness, vertigo) with combination of gabapentin + B1 / B12 compared to pregabalin. Both drugs improve sleep without causing daytime sleepiness. However, to test the absolute benefit and potential of this combination, it is necessary to corroborate the role of vitamins in isolation and in combination.

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