# EVALUATION OF THE EFFECT OF NIMODIPINE OD VS. TID NIMODIPINE IN THE TREATMENT OF PERIPHERAL VERTIGO

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## SUMMARY

The vertigo has a negative Impact on quality of life, it is important to therefore find an effective and convenient therapy allows the patient to that join the everyday tasks as possible and as quickly with the best quality of life.

**Methods:** We assessed the effectiveness in the treatment of vertigo of peripheral origin of two Formulations; nimodipine three times daily (Nimotop ®) 30 mg versus nimodipine of once daily (Tropocer ®) 90 mg AP, im a prospective, randomized, double-blind, double dummy, multicenter and parallel-group study, Included patients with peripheral vertigo defined as a score ≥7 on the Vertigo-Dizziness Differential Diagnosis Score .

The patients were evaluated by: scale of vertigo severity index and index of vestibular disability.

**Results**: In the nimodipine group AP (NAP) decreased vertigo severity index by 50%: in 24% of patients at 14 days, 41% at 4 weeks and 89% at 8 weeks. The vestibular disability index decreased by 50%: at 15 days in 24% of patients, in 83% at 4 weeks and in 92% patients at 8 weeks.

In the nimodipine group conventional (NC) decreased rate of vertigo severity by 50%: in 17% of patients at 14 days, 41% of patients at 4 weeks and 90% at 8 weeks. The vestibular disability index by 50% decreased: at 15 days in 17%

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of patients, in 53% at 4 weeks and in 64% at 8 weeks, without difference between groups.

**Conclusions:** both products were effective and well tolerate in the treatment of peripheral vertigo.

**Keywords: Nimodipine, extended release, dizziness.**

## INTRODUCTION

Vertigo is defined as an illusion of movement, rotation of the body or the environment, is a common and debilitating complaint in patients with peripheral or central vestibular disorders. It reflects a distortion of spatial orientation [1] covers pre sensations of syncope, dizziness and imbalance, [2] and is very common in primary care. Vertigo is diagnosed as: benign paroxysmal positional vertigo (BPPV), acute vestibular neuritis or Meniere's disease. BPPV is characterized by sudden, brief episodes of severe vertigo associated with a change in the position of the head, often while turning in bed. Meniere's disease by sudden attacks of vertigo accompanied by tinnitus, hearing loss associated with aural fullness, and vestibular neuritis is a sudden onset of severe vertigo associated with nausea and / or vomiting which usually lasts a few days followed by a period of a week of gradual and progressive improvement [1, 2].

Vestibular disorders can result in reduced postural control during gait instability and during the transition activities, like going from lying to sitting, sitting to standing or from lying to standing. Dizziness, imbalance and instability experienced by patients are associated with an increased incidence of falls, psychological and psychiatric disorders, panic disorders and cognitive impairment, especially among the elderly [1, 2]. The evidence is thus clear that the problems associated with vertigo and vestibular disorder can dramatically affect quality of life of patients and even totally incapacitate a person.

Blockers of calcium channels can have different effects on central and peripheral vestibular system. From a pharmacological point of view, the involvement of calcium channels in neurotransmitter release at synaptic

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terminals is the main therapeutic target of calcium antagonists, although the flow of calcium-activated potassium can also be an important objective that helps action of these drugs. Neurotransmitter release in hair cells is mediated by calcium channel high voltage (CaV1.3) that can be blocked by dihydropyridines [2-10].

The expression of L-type calcium channels, N, P and Q have been shown in primary afferent neurons vestibular system. All these channels identified in the basis of their biophysical and pharmacological features are involved in the generation of action potential e and control the excitability of afferent neurons by activation of potassium current activated by calcium.

Calcium currents that occur in the afferent neurons also involved in the release of neurotransmitters in the vestibular nucleus [2-10]. The vestibular nuclei neurons express high thresholds for L-type calcium channels and N, and low threshold T-type [11, 12]. Therefore, blockers of calcium channels affect the input and output information from the vestibular nuclei. Depending on the functional role of the subtypes of channels in each synapse, the effect of some blockers could be larger than others, leading to selectivity [9]. In the central nervous system synapses, the calcium channels involved in neurotransmitter release are N or P / Q-type. These channels are not blocked by dihydropyridines. In contrast, in the hair cells afferent neuronal synapses, which are L-type channels are sensitive to dihidropiridines.

The Calcium channel blockers used most commonly for the treatment of vestibular disorders are nimodipine, nitrendipine (a dihydropyridine with a long lasting effect) and verapamil. Other long-term dihydropyridines such as amlodipine, felodipine, nicardipine and nifedipine are rarely used [13, 14, 15]. Of dihydropyridines nimodipine and nitrendipine are a typical channel blockers L-type calcium and exercise their effect on calcium currents in the hair cells by inhibiting the release of neurotransmitters [13, 14].

In a multicenter, double-blind study, which compared the effectiveness of cinnarizine (150 mg per day) with that of nimodipine (30 mg three times daily) after 12 weeks of treatment in patients with vertigo, nimodipine reduced

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incidence of attacks of moderate vertigo in 79%, and severe in 85%, whereas cinnarizine reduced in 66% of moderate vertigo and in 90% in severe vertigo [15].

Nimodipine is also a highly lipophilic originally indicated for reducing the severity of neurological deficits resulting from vasospasm after subarachnoid hemorrhage. Its pharmacokinetic characteristics of rapid absorption, low bioavailability and short half-life require the administration of 3 or 4 doses per day in order to maintain serum levels and sustained effect on calcium channels.

In Venezuelan has developed a formulation of modified-release nimodipine 90 and 120 mg, which allows a release schedule, with a rapid initial uptake followed by a sustained release in the gastrointestinal tract. Nimodipine administration once a day helps the degree of therapy compliance, especially in older groups [16, 17].

This study evaluated the effectiveness in the treatment of vertigo of peripheral origin of two formulations of nimodipine, nimodipine traditional three times daily administration (Nimotop ®) 30 mg nimodipine administration versus 1 time per day (Tropocer ®) 90 mg AP.

## MATERIALS AND METHODS:

We performed a prospective, randomized, double-blind, double dummy (double dummy), national multicenter parallel-group clinical study , which included patients of both sexes, aged between 20 and 80 years, with vertigo of peripheral origin, defined as a score greater than or equal to 7 on the Vertigo-Dizziness Differential Diagnosis Score (VDDDS).

The protocol was approved by an Institutional Ethics Committee and all patients were informed of the details of the study, endorsing his signature, consent to participate in this clinical study.

Not allowed the admission of patients with: probable central origin vertigo, migraine, epilepsy, medication with ototoxic drugs, systemic etiology vertigo (uremia, diabetes mellitus decompensated liver disease), benign paroxysmal

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positional vertigo, fistula perilymph, trauma, acoustic neuroma, or infections, known intolerance to dihydropyridines.

Nor was allowed those patients those two weeks before the study had been treated with antihistamines, phenothiazines, barbiturates and benzodiazepines, vasodilators (clonidine, reserpine, methyldopa), anticholinergics, or Gingko biloba.

Patients were evaluated using the severity index scale of vertigo and vestibular disability index (DHI). The DHI questionnaire comprises 25 questions covering three domains, defined by the authors as emotional, physical and functional. To each question the patient answers "Yes", "No" or "Sometimes." It gets the value "total" (DHIt) of the sum of all responses to assign to each a numerical value "Yes" = 4, "sometimes" = 2, "No" = 0. The emotional subscales (DHIe) and functional (DHIf) are each consisting of 9 questions that are preceded by the letter "E" and "F" respectively, while the physical subscale (DHIfs) consists of 7 questions are preceded by the letters "FS". The maximum score in each of these subscales is in DHIf DHIe and 36 and in DHIfs 28.

It was considered as "treatment success" rate decreased severity between weeks 0-8, and the vestibular disability inventory by 50%.

Tolerability was assessed by routine laboratory tests and direct examination of adverse effects.

The variables: patients with 50% decrease in the index, were statistically analyzed using chi-square test with Yates correction and the values of the indices were evaluated by nonparametric Wilcoxon test for intragroup changes between week 0 and week 8, and by Mann Whitney test between groups at the same times.

Variables: age, weight, blood pressure and laboratory tests were evaluated by analysis of variance.

**RESULTS:**

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We evaluated a total of 67 patients, 51 entered by intention to treat analysis, i.e. patients who had at least one post-treatment evaluation. Were admitted 26 patients in the nimodipine group AP (NAP) and 25 in the conventional nimodipine group (NC).

**Tabla N° 1: Principal diagnosis**

| PRINCIPAL DIAGNOSIS | **NAP** | **NC** |
|---|---|---|
| Peripheral vestibular syndrome | 50% | 40% |
| Labyrinthitis | 23 % | --- |
| Meniére disease | 8% | 12% |
| Endolymphatic hypertension | 8% | 12% |
| Hyporeflexia vestibular | 12% | 4% |
| Vestibular Neuronitis | --- | 16% |

**Table N° 2: Description of the population**

| | **NAP** | **NC** | **P** |
|---|---|---|---|
| VDDS | 11.43 ± 3.12 | 10.89 ±2.00 | 0.52 |
| Sex (F/M) | 20/6 | 18/7 | |
| Age year | 46.73 ± 13.06 | 46.17 ±13.36 | 0.88 |
| Weight Kg. | 70.55 ±15.67 | 66.52 ± 10.97 | 0.30 |
| Height m | 1.62 ± 0.09 | 1.61 ± 0.08 | 0.79 |
| IMC | 26.45 ±4.39 | 25.49 ±2.96 | 0.38 |
| SBP mmHG | 119.62 ±10.38 | 117.39 ±11.65 | 0.48 |
| DBP mmHg | 78.65 ±9.55 | 80.36 ± 7.15 | 0.47 |
| Rate l/min | 76.64 ±7.13 | 75.99 ±7.31 | 0.75 |

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**Table N° 3: Changes in the vertigo severity index**

| **Nimodipine AP** | **0** | **14 Días** | **4 Semanas** | **8 Semanas** |
|---|---|---|---|---|
| Severity Index | 16.75±10.46 | 12.91±9.77 | 8.55±6.56 | 4.67±5.00 |
| Decrease ≥ 50% | | 24% | 41% | 89% |
| **Nimodipine TID** | | | | |
| Severity Index | 16.36±10.64 | 13.64±9.38 | 8.64±7.66 | 4.08±5.51 |
| Decrease ≥ 50% | | 17% | 41% | 90% |
| ≥ 50%<br>Chi cuadrado<br>(Yates correction) | | 0.58 | 0.76 | 0.81 |

**Table 4: Table of disability vestibular**

| **AP Nimodipine** | **0** | **Day 14** | **Week 4** | **Week 8** |
|---|---|---|---|---|
| Index | 58.57±20.49 | 36.50±22.15 | 21.00±16.55 | 11.73±17.92 |
| Decrease ≥ 50% | | 5/21 (24%) | 15/18 (83%) | 12/13 (92%) |
| P intra | | 0.000 | 0.07 | 0.08 |
| **Conventional Nimodipine** | | | | |
| Index | 48.44±19.37 | 37.33±20.26 | 22.25± 15.35 | 13.00±14.27 |
| Decrease ≥ 50% | | 3/18 (17%) | 8/15 (53%) | 9/14 (64%) |
| P intra | | 0.024 | 0.003 | 0.01 |
| ≥ 50%<br>Chi square (corrección Yates) | | 0.88 | 0.14 | 0.20 |

At the end of the study only one patient in each group had failed to lower the severity of their dizziness in 50%.

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**Table N° 5: Evolution of the other symptoms**

| | NAP | | | NC | | |
|---|---|---|---|---|---|---|
| week | 0 | 4 | 8 | 0 | 4 | 8 |
| Hearing Loss | 6/26 23% | 1/23 4.34% | 0/18 0 % | 13/25 52% | 0/22 0% | 1/21 5% |
| Tinnitus | 16/26 62% | 6/25 24% | 1/18 6% | 21/25 84% | 7/22 32% | 3/21 14% |
| Earful | 6/26* (23%) | 0/25 0% | 0/23 0% | 7/17 (40%) | 0/15 0% | 0/14 0% |

The early symptoms were more severe in the NC group and fewer patients in the NAP group, associated symptoms persisted at the end of 8 weeks of treatment.

**TABLE 6: Evolution of the subscales vestibular disability index**

| | **AP Nimodipine** | | | | **Conventional Nimodipina** | | | |
|---|---|---|---|---|---|---|---|---|
| **DHLe Emotional** | | | | | | | | |
| DHLe | Inicio | 15 Días | 4 Sem. | 8 Sem. | Inicio | 15 Días | 4 Sem. | 8 Sem. |
| Media | 17.40 | 10.14 | 5.47 | 2.67 | 11.67 | 7.89 | 5.33 | 1.71 |
| SD | 13.25 | 7.15 | 4.88 | 4.88 | 7.40 | 6.42 | 4.88 | 2.70 |
| **DHLf** Functional | | | | | | | | |
| Media | 22.19 | 12.70 | 6.95 | 4.80 | 17.22 | 12.447.60 | 7.60 | 5.14 |
| SD | 17.39 | 7.59 | 6.27 | 6.75 | 8.00 | 8.96 | 7.10 | 5.70 |
| **DHLs** Physical | | | | | | | | |
| Media | 22.19 | 14.90 | 9.26 | 5.73 | 21.67 | 15.44 | 9.60 | 6.14 |
| SD | 7.17 | 8.32 | 6.67 | 7.32 | 7.17 | 9.20 | 7.83 | 6.99 |

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**Adverse effects:**

In the NAP group, two patients had adverse effects, a case with drowsiness and anther with moderate increase in blood pressure. In the NC group three patients had adverse effects, a case of drowsiness with syncope, a case of allergy and headache and a patient who presented with tachycardia, none of these effects resulted in the suspension of treatment. There were no laboratory abnormalities in the group receiving nimodipine AP, there was a moderate increase of transaminases in a patient in the conventional nimodipine.

**DISCUSSION:**

Nimodipine is a logical choice for use in the treatment of vertigo of peripheral origin, including Meniere's disease and migraine associated vertigo. Authors such as Lassen (1996) in a pilot study for the prophylaxis of Meniere's syndrome demonstrated the efficacy of nimodipine. [13] Virtually no exist monotherapy for the treatment of vertigo, because it must meet three different objectives: Treat underlying etiology (if possible), to promote adaptation and compensation through the stabilization of the peripheral and central vestibular function , and treat dystonia autonomic nervous system. Nimodipine has vasodilator (vascular etiologies), sedative vestibular and moderate anticholinergic effect, which in many cases of vertigo of peripheral origin partially unbalanced has a potential therapeutic role in the etiology, functional and autonomic.

On the other hand, the studies agree that adherence to treatment worsens as the number of times daily. However, the effectiveness of this strategy also reduces the duration of treatment. A meta-analysis showed that the average rate of compliance with antihypertensive drugs was significantly higher when using a single daily dose than when using multiple (91.4% vs. 83.2%) p

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<0.001) [19]. For many interventions to improve compliance with treatment is difficult to draw any real conclusions, due to the shortcomings of the included studies. However, reducing the number of daily doses appears to be effective, to increase compliance with medication and should be tried as a first line strategy [19,20].

The aim of this paper is to demonstrate that the drug studied is as effective as the reference with a clinical trial known as' equivalence 'or' non-inferiority. [21].

This study was conducted based on these premises, in order to perform a therapeutic equivalence study, evidence type, A, prospective, randomized, double-blind, double false, considering the advantage of the dosing regimen of a single administration once a day.

In the results we observed an improvement of over 50% in the severity of vertigo in both groups, only one patient in each group had not dropped the index at the end of 8 weeks of treatment. There was also an improvement in associated symptoms such as hearing loss, tinnitus and ear feeling full.

Being able to administer nimodipine once a day instead of three times a day, resulting in better compliance with treatment and comfort in it.

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