Using Pyridoxine to Treat Carpal Tunnel Syndrome

Randomized control trial

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SUMMARY

In this study, we examined prospectively the effect of pyridoxine on idiopathic carpal tunnel syndrome. Thirty-two patients with the disease were randomized to receive treatment or placebo. No differences in outcome were found in electrophysiologic signs, clinical signs, or significant symptoms. Our findings do not support the use of pyridoxine for treating carpal tunnel syndrome.

RÉSUMÉ

Cette étude prospective a permis d'examiner l'effet de la pyridoxine sur le syndrome du canal carpien d'origine idiopathique. Trente-deux patients affectés par cette maladie furent assignés par randomisation à recevoir soit un traitement actif, soit un placebo. Les résultats ne révèlent aucune différence au niveau des signes électrophysiologiques, cliniques ou symptômes significatifs. Notre conclusion ne supporte pas la recommandation d'utiliser la pyridoxine pour traiter le syndrome du canal carpien.

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CARPAL TUNNEL SYNDROME (CTS), first described by Marie and Foix in 1913,[1] is probably the most frequently encountered peripheral nerve lesion; most family physicians can expect to see at least two cases yearly.[2] The walls of the carpal tunnel are the carpi and the transverse flexor retinaculum; the contents are the flexor tendons and their sheaths, and the softer median nerve.

Any condition that reduces the cross-sectional area of the carpal tunnel or that increases the volume of its contents will compress the median nerve against the flexor retinaculum, causing distal sensory and motor dysfunction. While many different types of disorders are known to reduce the size of the carpal tunnel or to cause its structures to swell, the common form of CTS is idiopathic.

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Most patients with idiopathic CTS are women, usually older than 40 years. In The Netherlands, researchers estimate that 9% of adult women will develop the condition, but less than 1% of men will.[3] The increase in incidence among perimenopausal women suggests that hormonal factors have a role in idiopathic CTS, although the mechanism is unknown.[4]

As a biochemical explanation of CTS, researchers have postulated for many years that the condition is primarily the result of a deficiency of pyridoxine.[5,6] Pyridoxine, when administered for 10 to 12 weeks[7-8,9] at a dose of 100 to 300 mg daily,[6] is claimed to bring about a resolution of the symptoms and the electrophysiologic signs of the disease.[10,11]

While it is accepted that a deficiency of pyridoxine (as well as other B vitamins) correlates with peripheral neuropathy, many authorities dispute the contention that pyridoxine deficiency leads to pure CTS.[12] Some believe that the positive responses reported among patients with CTS taking supplemental pyridoxine are related to an unrecognized peripheral neuropathy.[13]

To assess the claim that CTS can be virtually cured,[14] or at least greatly ameliorated with pyridoxine, we conducted a randomized, double-blind, placebo-controlled trial of pyridoxine (200 mg daily for 12 weeks) among 32 patients with CTS.

METHODS

Patients

Subjects entered into the study were recruited over 1 year from patients who regularly received their primary health care at the ambulatory clinic of the Department of Family Medicine, University of Saskatchewan, or from patients who had been referred to the Division of Neurology, University of Saskatchewan, by their family physicians in Saskatoon for nerve conduction studies as part of a workup for the diagnosis of CTS.

A total of 35 patients, 22 female and 13 male, met the inclusion criteria. The mean age was 42.5 years (range 18 to 76 years). Each patient entered the study when two of the investigators made a clinical diagnosis of CTS and when testing revealed electrophysiologic evidence of an abnormal median palmar distal latency in the affected hand. Median palmar distal latency, which establishes whether conduction defects are due to compression by the flexor retinaculum or to disease in the terminal nerve segment, is very sensitive for the electrophysiologic diagnosis of carpal nerve entrapment.[15]

Clinical diagnosis was established by the presence of at least one provocative sign – either Phalen's or Tinel's – and two or more of the following symptoms:

- tingling or discomfort in one or both hands during the night;
- fingers often feeling swollen;
- tingling or discomfort in the hand follows repetitive movements, such as knitting, hammering, wringing out a cloth, or driving;
- difficulty with coordinated movements, such as sewing, buttoning clothes, or attaching an earring.

Both tests for provocative signs have shown variation in measurements of their performance,[16-17,18,19] but they still remain standards of clinical examination. Phalen's sign, which has the best negative predictive value (0.74; 95% confidence interval [CI], 0.62 to 0.84)[18] is performed by having the patient actively place the affected wrist in complete flexion. In a positive test, numbness or tingling are produced in the median nerve distribution within 60 seconds. Tinel's sign, which has the best positive predictive value (0.55; 95% CI, 0.45 to 0.65)[18] is performed by percussion with a Queen Square hammer at the distal wrist crease with the wrist held in hyperextension.[19] When the test is positive, paresthesias or pain are produced in at least one finger in the median nerve distribution.

Of the symptoms assessed, the constellation with the most clinical significance is nocturnal pain, paresthesia, and numbness in the distribution of the median nerve that often causes the patient to awaken. This discomfort in women has a positive predictive value of 0.45 (95% CI, 0.31 to 0.60) and in men a positive predictive value of 0.08 (95% CI, 0.02 to 0.36).[3]

Conventional median nerve conduction studies were performed recording from the thenar muscles with surface disk electrodes and stimulating the nerve at the wrist and elbow. In our laboratory the normal median motor amplitude is 4.0 mV or higher, the median motor distal latency is 4.0 milliseconds or less, and the median motor conduction velocity is 50 m/s or higher.

Median palmar distal latency was determined by stimulating the median nerve in the palm and recording the nerve action potential at the wrist with a distance between stimulation and recording sites of 8 cm. The normal value in our laboratory is 2.2 milliseconds or less.

Compliance

To measure patient compliance, the activity of erythrocyte aspartate aminotransferase (AST) was measured with and without exogenous pyridoxal 5'-phosphate (PLP). Pyridoxal 5'-phosphate is the most important plasma transport form of pyridoxine. Individuals with normal or low levels of pyridoxine are expected to show a large increase in the activity of AST with the addition of PLP, whereas those with high plasma levels of pyridoxine (ie, those taking supplemental pyridoxine) are expected to show a small PLP effect because the available binding sites on AST have already been occupied. With increasing saturation by PLP, enzyme

activity increases more slowly when pyridoxine is added.[20]

Although alanine aminotransferase is a more sensitive indicator of pyridoxine status in humans, its basal activity is difficult to measure and it is less stable in vitro than AST. For this reason we chose to use AST as our index aminotransferase.[20]

Table 1. **Mean effect of PLP**

TIME OF MEASUREMENT	TREATMENT % CHANGE IN AST (SD)	CONTROL % CHANGE IN AST (SD)
Entrance	73 (36)	74 (31)
After 6 weeks	17* (16)	69 (18)
After 12 weeks	20* (15)	65 (23)

*$P < 0.001$.

Selection

Patients were excluded from the trial if they were pregnant or had a history of alcoholism, significant trauma to the forearm, diabetes mellitus, hypothyroidism, or rheumatoid arthritis, all of which are known to be associated with CTS.

On entrance, all patients were screened for serum thyroxine, fasting blood sugar, and rheumatoid factor levels. In addition, the peroneal nerve conduction velocity was measured in order to exclude patients whose CTS was part of a polyneuropathy.

Protocol

Each patient was assessed at the time of entrance into the trial, at 6 weeks, and at 12 weeks (exit) by a physician who was blinded to the patient's treatment allocation. Each assessment included the patient's completing a five-point scale questionnaire about symptom severity (0 = none; 4 = a great deal), sampling of blood for the estimation of AST activity, and physical examination by one of the authors (G.R.S.). At entrance and at 12 weeks, electrophysiologic studies were done. These consisted of the measurement in both hands of median palmar distal latency, median motor distal latency, median motor amplitude, and median motor conduction velocity.

After informed consent was obtained, each patient was randomized into either the treatment group or the control group using a random number table. The treatment group received 200 mg of pyridoxine in capsule form once daily. The control group received identical capsules containing placebo. The type of medication was known only to the dispensing pharmacist.

Aspartate aminotransferase activity was measured on hemolysates prepared and frozen within 1 hour of when blood was drawn at the time of each assessment.

Statistical methods

The change in patient scores over the 12 week period was assessed by using the paired *t* test and the Wilcoxon signed rank test. The difference in the degree of change between treatment and control groups was assessed using the independent *t* test and the Wilcoxon rank sum test. Differences were considered significant at the $P < 0.05$ level.

RESULTS

Thirty-five patients were eligible for the study; 18 were randomized to the treatment group and 17 were randomized to the placebo group. Two members of the treatment group dropped out before completion, but to our knowledge neither had any drug side effects, and neither had a median nerve entrapment release procedure carried out subsequently. One member of the control group dropped out shortly after entering the trial to have a median nerve entrapment release done.

Thirteen of the 16 patients remaining in the control group and nine of the 16 patients remaining in the treatment group were female. The mean age of the placebo group (42.5 years) was not significantly different from that of the treatment group (42.3 years).

In the treatment group, the mean PLP effect on AST showed a significant ($P < 0.001$) and sustained reduction at 6 weeks and at 12 weeks, whereas the control group showed no change in PLP effect during the trial period (*Table 1*). One member of the control group showed a low PLP effect (29%)

Table 2. **Changes in incidence of patient symptoms, signs, and electrophysiologic studies in treatment and control groups**

PATIENT CHARACTERISTICS	TREATMENT GROUP (N = 16)			CONTROL GROUP (N = 16)		
	ENTRANCE	12 WK	MEAN CHANGE	ENTRANCE	12 WK	MEAN CHANGE
SYMPTOMS*: MEAN SCORE (SD)						
Night discomfort	2.4 (1.4)	1.9 (1.2)	-0.5	2.6 (1.3)	2.4 (1.3)	-0.2
Swelling	2.1 (1.6)	1.3 (1.4)	-0.8†	2.6 (1.3)	2.3 (1.2)	-0.3
Movement discomfort	3.1 (1.2)	1.7 (1.4)	-1.4‡	3.1 (1.3)	2.7 (1.3)	-0.4
Poor coordination	1.6 (1.8)	1.2 (1.4)	-0.4	1.9 (1.5)	1.8 (1.4)	-0.1
SIGNS (% positive)						
Phalen's	88	69	-19%	100	75	-25%
Tinel's	44	25	-19%	56	50	-6%
ELECTROPHYSIOLOGIC STUDIES: MEAN (SD)						
Median palmar distal latency (ms)	2.5 (0.6)	2.6 (0.4)	0.1	2.8 (0.6)	2.7 (0.4)	0.1
Median motor distal latency (ms)	4.6 (0.9)	4.5 (0.8)	-0.1	5.0 (1.1)	4.9 (1.1)	0.0
Median motor amplitude (mV)	8.3 (3.0)	9.5 (2.8)	-1.3	8.3 (2.6)	9.3 (2.9)	-1.0
Median motor conduction velocity (m/s)	49.6 (4.6)	51.0 (5.3)	-1.5	51.3 (4.6)	52.9 (3.7)	-1.6

**Scale: 0 - 4;* †$P < 0.05$; ‡$P < 0.001$.*

and one member of the treatment group showed a high PLP effect (65%). This suggests that the member of the control group was taking pyridoxine, while the member of the treatment group could have discontinued therapy before completion of the trial. Our conclusion is that compliance throughout the trial was excellent for 15 of the 16 patients in the treatment group.

Over the 12-week study period, participants in the treatment group showed a statistically significant reduction in the symptoms of swollen fingers and of tingling or discomfort in the hand after repetitive movements (*Table 2*), whereas there was no change in the control group. There were, however, no significant differences between the treatment group and the control group with respect to nocturnal pain, numbness, and tingling, nor with respect to any of the provocative signs or electrophysiologic measurements.

DISCUSSION

Our study is one of the larger randomized, controlled trials on the use of pyridoxine in CTS. It has a power of 77% to detect a 0.4-millisecond or greater change in median palmar distal latency in the treatment group (α 0.05, β 0.1). A change of a lesser magnitude, however, would not have been detectable (type II error).

The study would have been stronger if it had a cross-over design. We decided against this design because of our uncertainty over what the washout period of pyridoxine would be in the treated group.

The AST data strongly suggest that the treatment group complied with taking pyridoxine and that the control group was not exposed to pharmacologic doses of the drug.

We agree with those studies claiming that pyridoxine in pharmacologic dosage has no electrophysiologic effect on the median nerve,[12,21] and we are satisfied that

it does not alter important clinical signs of CTS. Patients treated with pyridoxine showed a statistically significant improvement in two of the symptoms assessed. In a study of painful diabetic neuropathies,[22] the results were similar to ours: patients given pyridoxine noted a reduction in pain, but electrophysiologic values were unaffected, suggesting that diabetic neuropathy is not dependent on pyridoxine, but that pyridoxine can influence pain thresholds.

On the basis of animal studies, two possible mechanisms have been postulated for the mild antinociceptive properties of pyridoxine.[23] The first is that pyridoxine could inhibit the presynaptic release of neurotransmitters from afferent pain fibres at the level of both the spinal dorsal horn and the thalamus. The second is that pyridoxine enhances the synthesis of serotonin and γ-aminobutyric acid, which contribute to the inhibition of pain-related information in the spinal cord and brain.

The question arises whether primary care patients with CTS should be given a trial of pyridoxine for control of symptoms before considering referral for surgical division of the flexor retinaculum. Although there are proponents of this approach,[11] and of the use of pyridoxine as an adjunct to surgery,[24] we urge caution.

First, pyridoxine should not be assumed to be innocuous. Most cases of pyridoxine-induced neuropathy occurred at very high dosages (2 to 6 g daily from 2 to 40 months),[25,26] but in one case, serious neuronal damage developed at a dose of 500 mg over 2 years.[27] In none of the studies using 100 to 300 mg daily over 12 weeks were side effects reported; nevertheless, the toxic range of pyridoxine is unknown and its indefinite use at 200 mg daily would not be prudent.

Second, in terms of symptom control, pyridoxine alleviates irritating dysesthesias and paresthesias from repetitive movement, but in our trial it had no effect on nocturnal symptoms, which most patients consider the most distressing of CTS and which are the usual reason for seeking a physician's help.

Third, in patients with significant symptoms of CTS, surgery not only offers immediate relief of discomfort but prevents further nerve damage and functional deterioration and allows for repair of already damaged nerve fibres.[28,29]

In view of the uncertainty of the safety of pharmacologic doses of pyridoxine over a long period, its failure to control significant symptoms, and its lack of effect on nerve conduction, we do not recommend its use for treating CTS. ■

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