Pyridoxine Hydrochloride Treatment of Carpal Tunnel Syndrome: A Review

Elaine Aufiero, M.D., Todd P. Stitik, M.D., Patrick M. Foye, M.D., and Boqiang Chen, M.D., Ph.D.

It has been hypothesized that idiopathic carpal tunnel syndrome (CTS) is a manifestation of vitamin B₆ deficiency. Some claim that B₆ supplementation can alleviate symptoms. Others argue that pain relief occurs because of vitamin B₆’s anti-nociceptive properties or because B₆ supplementation addresses an unrecognized peripheral neuropathy. Few studies on CTS and B₆ employed electrodiagnostic techniques in diagnosis, and few showed a correlation between symptoms and improved electrodiagnostic parameters with supplementation. Other studies failed to measure or estimate B₆ levels. Nevertheless, it appears reasonable to recommend vitamin B₆ supplementation to people with CTS. Some patients will improve symptomatically with low risks of toxicity in recommended doses.

Key words: Carpal tunnel syndrome, electrodiagnosis, median nerve, pyridoxine, vitamin B₆

© 2004 International Life Sciences Institute

Introduction

Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment (a.k.a. entrapment neuropathy). Physicians will inevitably encounter many patients with this condition, given its incidence of 3.46 cases per 1000 person-years and the fact that up to 9% of adult women develop it.¹ ² Physicians who are involved in the management of injured workers will also find it to be a potentially significant economic problem, particularly in certain professions.³ ⁴ CTS is very rarely found in the adolescent population with activity-related risk factors, although it does seem to result from some motor vehicle accidents.⁵ ⁶ Treatment often includes an initial attempt at conservative measures followed by carpal release surgery if conservative measures fail. Of the commonly recommended conservative treatment measures, perhaps the most controversial is the administration of pyridoxine (vitamin B₆). This article will examine the hypothesis that vitamin B₆ deficiency leads to CTS and that treatment of these patients with vitamin B₆, in the form of pyridoxine hydrochloride, will therefore result in resolution of symptoms. This article will summarize the evidence for and against the use of pyridoxine in CTS and will make practical recommendations regarding it.

CTS Etiology

CTS is generally believed to be caused by relative compression of the median nerve as it passes through the carpal tunnel. This compression can be due to a disorder in any of the tissues that pass through or comprise the floor or roof of the carpal tunnel. For example, tenosynovitis of the finger flexor tendons can occur with repetitive activities involving the wrists. Post-traumatic osteoarthritis of the carpal bones can lead to osteophytic compression of the median nerve. Volume overload can occur within the tunnel, as in anasarca, nephrotic syndrome, or pregnancy. The median nerve itself can also be directly affected as part of a systemic disease such as rheumatoid arthritis, lupus, diabetes mellitus, and peripheral neuropathies of varying etiologies.⁷ ⁸ In some cases, there is no obvious precipitating factor or underlying medical condition to explain the development of CTS.

CTS Presentation and Diagnosis

Because the sensory division of the median nerve seems to be more susceptible to pathology, patients often present to their physician complaining of paresthesias, hyperalgesia, or hypoesthesia in the distribution of the median nerve (i.e., all or part of the palmar and distal dorsal surfaces of the first, second, third, and half of the fourth digits of the hand) or involving the entire hand. Many patients will complain of discomfort that is often most severe at night and can lead to nocturnal awakening.⁹ Classically patients also describe the flick maneuver.
ver after nocturnal awakening in which rigorous shaking of the affected hand(s) helps with symptom resolution. As the disease progresses and there is involvement of the motor division of the median nerve, patients might report complaints related to diminution of thumb function.

In addition to testing peripheral sensation and hand strength, an attempt is frequently made to replicate the symptoms by the use of provocative maneuvers that apply a stressor to the median nerve as it enters the carpal tunnel in the wrist. Sensitivities and specificities of these maneuvers have been summarized elsewhere and range widely, in part due to test performance variability.9,10

Although diagnosis is often made based on history and physical exam, the physician may choose to refer the patient for electrodiagnostic studies (i.e., nerve conduction studies with or without needle electromyography) as this is generally considered to be the diagnostic “gold standard” short of assessing the patient’s response to carpal ligament release surgery. Relative sensitivities and specificities of the various electrodiagnostic tests have been reviewed.11–13 The American Association of Electrodiagnostic Medicine (AAEM) Quality Assurance Committee concluded after a literature review, that median sensory and motor nerve conduction studies confirm a clinical diagnosis of CTS with a high degree of sensitivity and specificity.12 One shortcoming of electrodiagnostic testing, however, is that it is very operator dependent.11,14,15

**CTS Treatment Overview**

The treatment of CTS is in part dependent upon its etiology. For example, modifying or ceasing to perform a causative occupational or advocational activity can usually obtain essentially complete relief. Unfortunately, the etiology often cannot be determined, and general conservative management is begun in an attempt to alleviate symptoms. Initial treatment of CTS usually includes relative rest through activity modification and wrist splinting, oral anti-inflammatory agents, occupational therapy, and corticosteroid injections. If the above conservative management strategy fails or if the disease is advanced, surgical decompression is indicated. It is estimated that 50% of patients diagnosed with CTS will ultimately require surgery. Surgery, however, can be costly and is associated with potential risks as well as time lost from work in the postoperative period. Given the incidence of the disease and the fact that surgery is often the only option after other conservative management fails, one can appreciate the value of uncovering another effective nonsurgical pharmacologic treatment. One of these is the administration of pyridoxine.

**Vitamin B₆**

Vitamin B₆ is a critical cofactor needed for neuronal protein synthesis.16 Although the exact mechanism of action of B₆ on peripheral nerves is unclear, it is known that vitamin B₆ is involved in numerous pathways of neural function, including neurotransmitter synthesis, amino acid metabolism, and sphingolipid biosynthesis and degradation.17 It has been theorized that a deficiency in vitamin B₆, with its proposed role in peripheral nerve metabolism, may in part contribute to the development of CTS. Although clinically significant pyridoxine deficiency presents as a constellation of signs and symptoms reflective of diminished protein synthesis in various organ systems, exactly how B₆ deficiency can cause CTS is not completely understood. One theory comes from Ellis et al., who reported that a vitamin B₆–deficient patient with CTS was found to have subendothelial layers of synovium that were edematous and proliferated with fibrous tissue.18 The authors felt that perhaps this was a result of B₆ deficiency and was the likely mechanism of vitamin B₆ deficiency leading to CTS. Additionally, they believed that chronic B₆ deficiency could result in tissue damage that is irreversible even with subsequent surgery.

By contrast to the possible benefits of pyridoxine supplementation, pyridoxine toxicity can cause seborrheic dermatitis, stomatitis, glossitis, cheilosis, depression, and irritability, which paradoxically lead to peripheral neuropathy. Supplementation with vitamin B₆ is therefore not without potential problems. For example, Schaumburg et al. reported the development of a sensory neuropathy in seven patients who had been taking between 2 and 7 g pyridoxine/day for several months for various reasons.19 All seven patients developed ataxia and severe sensory nervous system dysfunction and became severely disabled. Although all improved after withdrawal, some had residual nerve damage. In addition, Parry et al. described 16 patients with neuropathy associated with pyridoxine abuse who subsequently improved following pyridoxine discontinuation.20 Because vitamin B₆ is available over the counter and is classified as a vitamin, patients may be more likely to use it in excessive doses.

Although patients with low serum B₆ concentrations are perhaps more susceptible to the effects of median nerve compression and hence CTS, it is unclear as to whether vitamin B₆ is generally found in lower concentration in patients with CTS.

**Assessment of Vitamin B₆ Levels**

There are different approaches to assessing B₆ status. Serum or urinary vitamin B₆ or vitamin B₆ derivatives can be directly measured or can be estimated by measuring the rate of enzymatic reactions that utilize vitamin
and what is the underlying pathophysiology. Specification helps to alleviate the signs and symptoms of CTS, patients were found to be vitamin \( B_6 \) deficient.24 Using the EGOT assay, all 10 patients showed clinical improvement and the one patient who had undergone electrodiagnostic testing also showed electrodiagnostic improvement after treatment. This particular study, however, does not pertain exclusively to CTS patients. The author clearly stated in the title of the paper that the study group comprised patients with \( B_6 \) deficiency and a clinical syndrome that included CTS. Therefore, this particular study did not exclusively examine vitamin \( B_6 \)-deficient CTS patients (of the 10 study patients, 6 had classic signs and symptoms of CTS, whereas the other 4 did not).

In a second prospective controlled study, Ellis et al. examined the effects of pyridoxine on 11 patients diagnosed with CTS by the same clinical signs and symptoms as in their first study.27 Only 1 out of 11 pretreatment electromyographic studies (EMGs) were diagnostic of CTS. Four patients were treated with pyridoxine for 4 to 6 weeks. Three patients received treatment for 11 weeks and four patients served as controls. Electrodiagnostic testing was repeated in the treatment group at 6 weeks. Pre- and post-treatment assessments included symptomatology, second-digit function (flexion and strength), \( B_6 \) levels as indicated by serum SA, and electrodiagnostic parameters. Treated patients improved symptomatically after 6 weeks \((0.01 < P < 0.02)\); treatment was more significant \((P < 0.001)\) in those patients receiving 11 weeks of pyridoxine supplementation. There was no statistical difference between pre- and post-treatment range of motion but there was a statistically significant improvement in strength \((0.001 < P < 0.01)\). All of the patients were found to be vitamin \( B_6 \) deficient by the EGOT assay prior to therapy. SA in the treatment group increased throughout the study, as indicated by SA measurements done at 6 and 11 weeks, supporting the authors’ earlier claim that more enzyme is synthesized with continued \( B_6 \) therapy. The follow-up EMGs were “inconclusive” with respect to improvement. Based on clinical signs and symptoms, however, patients were felt to have improved to a greater degree after 11 weeks of pyridoxine therapy compared with after only 6 weeks of therapy.

In a subsequent paper, Ellis et al. reported on a crossover study involving one CTS patient (diagnosed via electrodiagnostic testing) from a previous study.22 The patient received varying doses of pyridoxine (including the recommended dietary allowance [RDA] of 2 mg/day and the supplemental dose of 100 mg/day) and placebo over approximately 11 weeks. EGOT assays revealed that \( B_6 \) levels fluctuated depending upon the level of \( B_6 \) supplementation. Similarly, symptoms, physical exam maneuvers, and functional measurements changed in proportion to \( B_6 \) supplementation. The electrodiagnostic study parameters also improved, albeit

\( B_6 \) as a coenzyme. This latter and more commonly used method frequently employs an assay developed by Kishi et al.21 In this assay (further referred to as the EGOT assay), the specific activity (SA) of the enzyme glutamic-oxalacetic transaminase (AST) in erythrocytes is measured in the absence of and then in the presence of vitamin \( B_6 \), the coenzyme utilized in the reaction. An increase in the SA in the presence of vitamin \( B_6 \) is thought to represent a deficient state. Whereas the direct assay method quantifies a specific \( B_6 \) concentration, many believe that the indirect assay method is superior because it is more reflective of vitamin activity.

The measurement of vitamin \( B_6 \) levels, either directly or indirectly, is not generally performed in the diagnosis or management of patients with CTS because it remains unclear as to whether there is a relationship between \( B_6 \) status and CTS. Although Ellis et al. found that CTS patients frequently present with an SA less than 0.2—0.25 and that the value increased to a level greater than 0.7 in response to pyridoxine supplementation, other investigators report no relationship between CTS and pyridoxine status.22–26

**Methods**

A literature search was conducted to help clarify whether CTS is related to \( B_6 \) deficiency, whether \( B_6 \) supplementation helps to alleviate the signs and symptoms of CTS, and what is the underlying pathophysiology. Specifically, Pub Med was queried using the key words carpal tunnel syndrome and vitamin \( B_6 \). Original articles were then pulled so that the details of the studies could be uncovered. Studies were then grouped based upon whether or not they concluded that pyridoxine supplementation was useful in CTS. Three categories of articles were formed: those that were supportive, those that were inconclusive, and those that were not supportive.

**Results**

**Literature in Support of Pyridoxine Supplementation in CTS**

Ellis et al. first explored the use of pyridoxine to treat CTS in depth in the 1970s. Their first paper, published in 1976, examined the subjective effects of 4 weeks of pyridoxine therapy on 10 patients with signs and symptoms of CTS.24 (Table 1). Using the EGOT assay, all 10 patients were found to be vitamin \( B_6 \) deficient.21 This deficiency resolved after 2 weeks of 300 mg pyridoxine/day as determined by an increase in SA. Interestingly, after 4 weeks of therapy, an even greater increase in SA was seen. These results led the authors to conclude that after 2 weeks of pyridoxine replacement improvement could be seen, but that if patients were treated for longer, more enzyme would be synthesized leading to an even greater increase in SA. All 10 patients showed clinical improvement and the one patient who had undergone electrodiagnostic testing also showed electrodiagnostic improvement after treatment. This particular study, however, does not pertain exclusively to CTS patients. The author clearly stated in the title of the paper that the study group comprised patients with \( B_6 \) deficiency and a clinical syndrome that included CTS. Therefore, this particular study did not exclusively examine vitamin \( B_6 \)-deficient CTS patients (of the 10 study patients, 6 had classic signs and symptoms of CTS, whereas the other 4 did not).

In a second prospective controlled study, Ellis et al. examined the effects of pyridoxine on 11 patients diagnosed with CTS by the same clinical signs and symptoms as in their first study.27 Only 1 out of 11 pretreatment electromyographic studies (EMGs) were diagnostic of CTS. Four patients were treated with pyridoxine for 4 to 6 weeks. Three patients received treatment for 11 weeks and four patients served as controls. Electrodiagnostic testing was repeated in the treatment group at 6 weeks. Pre- and post-treatment assessments included symptomatology, second-digit function (flexion and strength), \( B_6 \) levels as indicated by serum SA, and electrodiagnostic parameters. Treated patients improved symptomatically after 6 weeks \((0.01 < P < 0.02)\); treatment was more significant \((P < 0.001)\) in those patients receiving 11 weeks of pyridoxine supplementation. There was no statistical difference between pre- and post-treatment range of motion but there was a statistically significant improvement in strength \((0.001 < P < 0.01)\). All of the patients were found to be vitamin \( B_6 \) deficient by the EGOT assay prior to therapy. SA in the treatment group increased throughout the study, as indicated by SA measurements done at 6 and 11 weeks, supporting the authors’ earlier claim that more enzyme is synthesized with continued \( B_6 \) therapy. The follow-up EMGs were “inconclusive” with respect to improvement. Based on clinical signs and symptoms, however, patients were felt to have improved to a greater degree after 11 weeks of pyridoxine therapy compared with after only 6 weeks of therapy.

In a subsequent paper, Ellis et al. reported on a crossover study involving one CTS patient (diagnosed via electrodiagnostic testing) from a previous study.22 The patient received varying doses of pyridoxine (including the recommended dietary allowance [RDA] of 2 mg/day and the supplemental dose of 100 mg/day) and placebo over approximately 11 weeks. EGOT assays revealed that \( B_6 \) levels fluctuated depending upon the level of \( B_6 \) supplementation. Similarly, symptoms, physical exam maneuvers, and functional measurements changed in proportion to \( B_6 \) supplementation. The electrodiagnostic study parameters also improved, albeit...
<table>
<thead>
<tr>
<th>Study Type</th>
<th>Authors</th>
<th>Year</th>
<th>n</th>
<th>Main Conclusion(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive</td>
<td>Ellis et al.</td>
<td>1976</td>
<td>10</td>
<td>Patients with a severe CTS have vitamin B₆ deficiency</td>
</tr>
<tr>
<td>Prospective</td>
<td></td>
<td></td>
<td></td>
<td>B₆ deficiency and CTS symptoms are relieved with pyridoxine supplementation</td>
</tr>
<tr>
<td>Prospective, control</td>
<td>Ellis et al.</td>
<td>1977</td>
<td>11</td>
<td>CTS symptoms are improved more with a greater duration of pyridoxine therapy (11 weeks vs. 6 weeks)</td>
</tr>
<tr>
<td>Crossover, clinical</td>
<td>Ellis et al.</td>
<td>1979</td>
<td>1</td>
<td>There is a causal relationship between B₆ deficiency and CTS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CTS symptoms improved more with 100 mg pyridoxine vs. the RDA (2 mg/day)</td>
</tr>
<tr>
<td>Double-blind, crossover</td>
<td>Ellis et al.</td>
<td>1982</td>
<td>7</td>
<td>CTS is a primary deficiency of vitamin B₆ rather than one of a dependency state; clinical improvement of CTS with pyridoxine therapy may frequently obviate hand surgery</td>
</tr>
<tr>
<td>Double-blind, control</td>
<td>Wolaniuk et al.</td>
<td>1983</td>
<td>6</td>
<td>B₆ deficient CTS patients improve pathophysiologically with pyridoxine supplementation</td>
</tr>
<tr>
<td>Retrospective, review</td>
<td>Kasdan et al.</td>
<td>1987</td>
<td>494</td>
<td>The addition of vitamin B₆ to other forms of conservative treatment may be helpful in treating many cases of CTS</td>
</tr>
<tr>
<td>Prospective, control</td>
<td>Laso Guzman et al.</td>
<td>1989</td>
<td>12</td>
<td>Although vitamin B₆ deficiency is not common in CTS patients, pyridoxine supplementation can be recommended as adjuvant treatment</td>
</tr>
<tr>
<td>Prospective</td>
<td>Bernstein et al.</td>
<td>1993</td>
<td>16</td>
<td>Vitamin B₆ deficiency may not be a cause of carpal tunnel syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Significant symptom improvement is due to primary analgesic effect of B₆</td>
</tr>
<tr>
<td>Unclear</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>Amadio et al.</td>
<td>1985</td>
<td>19</td>
<td>Pyridoxine supplementation can be used as an adjunctive treatment for mild CTS</td>
</tr>
<tr>
<td>Not supportive</td>
<td>Byers et al.</td>
<td>1984</td>
<td>33</td>
<td>No correlation between pyridoxine metabolic activity and CTS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Symptomatic improvement after pyridoxine supplementation is due to replenishing B₆ deficiencies in patients with underlying peripheral neuropathy</td>
</tr>
<tr>
<td>Prospective</td>
<td>Smith et al.</td>
<td>1984</td>
<td>6</td>
<td>No consistent improvement in clinical findings or electrodiagnostic measurements following pyridoxine treatment</td>
</tr>
<tr>
<td>Prospective, double-blind, randomized, Control</td>
<td>Stransky et al.</td>
<td>1989</td>
<td>15</td>
<td>No advantage of B₆ vs. other conservative therapy</td>
</tr>
<tr>
<td>Prospective, double-blind, randomized, control</td>
<td>Spooner et al.</td>
<td>1993</td>
<td>32</td>
<td>No statistically significant difference in electrophysiologic signs or symptoms in CTS treated with pyridoxine for 12 weeks</td>
</tr>
<tr>
<td>Prospective, randomized</td>
<td>Franzblau et al.</td>
<td>1996</td>
<td>125</td>
<td>Vitamin B₆ status is unrelated to CTS among industrial workers</td>
</tr>
</tbody>
</table>
minimally, with treatment. The authors concluded that the above study strongly suggested a causal relationship between B₆ deficiency and CTS, and that supplementation doses need to be significantly greater than RDA doses in order to achieve maximal benefit.

In their next study, Ellis et al. performed a double-blind clinical trial on seven CTS patients (4 placebo, 3 treatment) who were diagnosed by clinical criteria and electrodiagnostic testing and who were also vitamin B₆ deficient per EGOT assay. Treatment consisted of 12 weeks of pyridoxine therapy. The four placebo patients were later treated with pyridoxine. Pre- and post-treatment assessments were made for SA, function (range of motion and strength), and signs and symptoms of CTS. All of the above parameters improved in the initial treatment group and in the placebo group after they later received pyridoxine. From the SA measurements, the authors concluded that an SA of 0.20–0.25 in the EGOT assay is diagnostic of severe B₆ deficiency and correlates with severe CTS, and that clinical improvement is observed after 12 weeks of pyridoxine therapy.

Wolnaniuk et al. evaluated 6 patients in a double-blind controlled study (3 control, 3 treatment). All patients were initially found to be B₆ deficient by the EGOT assay and underwent pre-treatment electrodiagnostic studies. Patients in the treatment group subsequently received pyridoxine treatment for 12 weeks, whereas control patients received placebo. The authors reported that there was no statistically significant change in post-treatment electrodiagnostic studies in the placebo group. By contrast, two patients in the treatment group showed a significant change in these parameters after therapy. The authors attribute the lack of change in the third patient who did receive pyridoxine to poor compliance with the treatment regimen as reflected in the EGOT assay. This study implies that there is pathophysiologic improvement in vitamin B₆–deficient CTS patients receiving pyridoxine supplementation and that this improvement is reflected both clinically and electrodiagnostically.

A retrospective review of 994 charts of patients with CTS by Kasdan et al. found a 14.3% rate of satisfactory symptom alleviation in 500 patients treated conservatively with one or a combination of the following: splinting, anti-inflammatory agents, job or activity change, and corticosteroid injections. By contrast, a symptom alleviation rate of 68% was noted in those 494 patients whose conservative treatment also included vitamin B₆ (100 mg bid). Although this appears to be strong evidence for B₆ supplementation, the findings must be interpreted within the context of shortcomings typical of retrospective reviews. In addition, laboratory assessment of B₆ status was not performed and there was no mention of the percentage of patients who underwent electrodiagnostic testing to make the diagnosis of CTS.

Laso Guzman et al. studied clinical and electrodiagnostic changes in 12 CTS patients after treatment with pyridoxine (150 mg/day) for 12 weeks. Although none were previously found to be B₆ deficient based on the EAST assay (a pyridoxine-dependent enzyme assay), all patients showed increased enzyme activity in response to pyridoxine supplementation. After treatment, patients were divided into two groups based on whether or not they clinically improved. Those six patients who clinically improved also showed a significant improvement in electrodiagnostic parameters. This study therefore implies that B₆ supplementation can lead to clinical and pathophysiologic improvement in some patients.

Lastly, Bernstein et al. studied 20 patients (16 completed the study) diagnosed clinically and via EMGs with CTS. Although vitamin B₆ levels were not directly measured, the patients were screened for B₆ deficiency by electroencephalograms (EEGs), which are abnormal in vitamin B₆–deficient states. Bernstein et al. thus hypothesized that EEGs might be considered a potential marker for B₆ deficiency and a predictor of response to therapeutic doses of vitamin B₆. However, all patients had normal baseline and post-treatment EEGs, thus implying that they were not B₆ deficient. After 3 months of pyridoxine therapy, patients were reassessed clinically (through a pain visual analogue score and a pain questionnaire) and by EMGs. Pain scores significantly improved, but only the median sensory latency (the EMG parameter for CTS that is generally regarded as the most sensitive) showed statistically significant improvement after treatment. The authors concluded that because pain scores improved out of proportion to the EMG data, pyridoxine’s success in alleviating pain from CTS may actually be due to its known ability to alter pain thresholds per se without actually improving the underlying pathophysiology. Furthermore, the authors inferred that because vitamin B₆ deficiency has been associated with abnormal EEGs and because the patients in this study had normal EEGs both before and after treatment, vitamin B₆ deficiency may not be a cause of CTS.

**Literature Unclear with Respect to Pyridoxine Supplementation in CTS**

In a study by Amadio, 19 patients with CTS were diagnosed by history and by having at least one typical physical exam finding or positive electrodiagnostic study findings (Table 1). The patients were divided into three groups according to the severity of symptoms: mild (n = 4), moderate (n = 12), and severe (n = 3). Vitamin B₆ status was evaluated by physical exam directed at looking for signs of B₆ deficiency, including the presence or absence of glossitis, stomatitis, seborrheic dermatitis, and generalized peripheral neuropathy. Al-
though none were felt to be $B_6$ deficient, all received pyridoxine supplementation, and some were also treated with a variety of other conservative treatment modalities. All patients reported on symptoms throughout the study. Of the four patients with mild symptoms, two improved while taking $B_6$. Of the 12 patients with moderate symptoms and 3 with severe symptoms, none improved on $B_6$ therapy alone. One-third noted some relief when other conservative therapies were added. Because surgery was subsequently recommended to 2/3 of the patients with moderate or severe symptoms despite 3 months of pyridoxine supplementation and other conservative treatment, the authors concluded that vitamin $B_6$ might have a role as an adjunct only in cases of mild CTS.

**Literature Not in Support of Using Pyridoxine in CTS**

In 1984, Byers et al. assessed pyridoxine status in patients with electrodiagnostic evidence of CTS and/or peripheral neuropathy in an attempt to determine if vitamin $B_6$ deficiency was associated with CTS or an underlying peripheral neuropathy (PN). Thirty-three patients were divided into four groups based on electrodiagnosis: group 1 contained patients with CTS only; group 2 contained patients with PN only; group 3 contained patients with both CTS and PN; and group 4 contained patients with neither condition. Pyridoxine levels were estimated using the EGOT assay method of measuring vitamin $B_6$ metabolic activity (PMA). A statistically significant difference in PMA was found only for patients with peripheral neuropathy (i.e., groups 2 and 3) but did not correlate with the presence or absence of neuropathy. This suggests that earlier studies supporting the causal role of vitamin $B_6$ in CTS were flawed if electrodiagnostic testing was not used to exclude an underlying peripheral neuropathy. The results also imply that success with pyridoxine in treating CTS seen in earlier studies was due to improvement in an unrecognized underlying peripheral neuropathy.

Smith et al. used electrodiagnostic studies to diagnose idiopathic CTS in six patients whose vitamin $B_6$ status was assessed using direct and indirect measurements and who were subsequently treated with pyridoxine. The direct measurements varied but the $B_6$ status was normal in all subjects via the indirect assay method. Although four patients reported symptomatic improvement after at least 9 weeks of pyridoxine supplementation, none of the patients had any significant post-treatment changes in the assay or electrodiagnostic parameters. The authors concluded that there is no relationship between $B_6$ status and idiopathic CTS. They suggested that the four patients who had symptomatic improvement did so because of selection artifact. Specifically, they felt that this improvement represented spontaneous waning of disease activity as sometimes occurs after symptoms worsen to the point where patients visit physicians.

A randomized, double-blind, placebo-controlled study investigating the therapeutic effect of vitamin $B_6$ on CTS was conducted by Stransky et al. Fifteen patients diagnosed with CTS electrodiagnostically were randomly assigned to a control ($n = 4$), placebo treatment ($n = 5$), or pyridoxine treatment group ($n = 6$). After 10 weeks, repeat electrodiagnostic studies and questioning regarding symptoms revealed no significant changes among the groups. Based on this data, the authors concluded that there is no advantage to using vitamin $B_6$ over other forms of conservative treatment. They felt that given the natural history of the disease, in which symptoms can diminish with time, most patients would improve in a clinical trial almost regardless of the intervention.

In a randomized, double-blind controlled study, Spooner et al. examined the effects of pyridoxine on patients diagnosed clinically and electrodiagnostically with CTS. The treatment group consisted of 16 patients who received 200 mg of pyridoxine for 12 weeks, whereas the control group comprised 15 patients who received placebo. Compliance was measured using the EAST assay at entrance, 6 weeks, and 12 weeks, and was found to be excellent throughout the trial. After 12 weeks, a statistically significant reduction was seen in tingling and discomfort in the hand after repetitive movements in the treatment group only. By contrast, there was no difference observed between groups with regards to nocturnal symptoms of pain, numbness, and tingling, nor was there any difference in physical exam provocative maneuvers or follow-up electrodiagnostic testing. The authors suggested that perhaps the two symptoms that improved did so because of pyridoxine’s known influence on increasing pain threshold without actually affecting the underlying disease process. They emphasized that pyridoxine did not alleviate nocturnal symptoms, which they felt are the most distressing to the patient. In view of these results, they felt that pyridoxine is not useful as a treatment for CTS.

In one of the larger investigations conducted thus far, Franzblau et al. studied 125 randomly selected workers in an attempt to determine if their was a relationship between $B_6$ status and CTS. Those patients who reported symptoms of CTS in a questionnaire underwent a physical exam, had electrodiagnostic testing done to confirm the diagnosis, and had $B_6$ levels measured using the EAST assay and by measuring pyridoxal-5-phosphate (PLP) directly. Of these, 31 had electrodiagnostic evidence of CTS, but only 11 subjects had abnormal lab values suggestive of $B_6$ deficiency. By statistical analysis, they concluded that there was no relationship between $B_6$ status and electrodiagnostic parameters or be-
tween B_6 status and reported symptoms of CTS, and therefore no relationship between B_6 status and CTS in industrial workers.

**Discussion**

The literature investigating the relationship between vitamin B_6 and CTS is somewhat imperfect with respect to study design. For example, there are very few prospective studies that have addressed this question. In fact, most of the literature in support of using vitamin B_6 supplementation in CTS involves only case studies and case reports. Another problem was the lack of patient randomization in those studies that were actually controlled. In fact, only two of the studies that support the use of vitamin B_6 in CTS were controlled and it is unclear if the patients were randomly assigned to control or treatment groups. None of the supportive studies, and only two of the non-supportive studies, was a double-blind, randomized, controlled study of a large patient population.

In addition to the variation in basic study set-up, there was large variation among the studies in the method of diagnosing CTS. Diagnostic methods ranged from history and physical exam without provocative maneuvers to history, physical exam including provocative maneuvers, and electrodiagnostic testing. Even though electrodiagnostic testing is considered to be the diagnostic gold standard, pretreatment electrodiagnostic testing was not used in the majority of cases.

Study results are at times conflicting. For example, although most studies do support the notion that vitamin B_6 supplementation results in pain relief in CTS patients, what is unclear is whether the analgesia is due to an alteration of underlying pathophysiology or via primary anti-nociceptive effects. Some of the above studies found that patients can report symptomatic improvement from pyridoxine despite the absence of a significant improvement in electrodiagnostic study parameters. Two mechanisms have been postulated to explain this. Sharma found that a sustained analgesic effect of pyridoxine was accompanied by a partial attenuation of thalamic-evoked nociceptive burst discharge activity measured in rats. The results suggested that B_6 may increase the pain threshold by enhancing synthesis of serotonin and GABA, neurotransmitters that play a role in the inhibitory control of pain-related impulses in the spinal cord and brain. In another study, Zimmerman proposed that B_6 may work by inhibiting presynaptic release of neurotransmitters from nociceptive afferent fibers. Spooner pointed out that if B_6 is in fact working to increase pain thresholds and therefore ultimately delaying surgery, than compression of the median nerve will continue and result in greater nerve damage. By contrast, two other studies found electrodiagnostic improvement in those CTS patients who also reported symptomatic improvement.

Studies have also varied as to whether they measured B_6 levels. Failure to do so makes it difficult to test the hypothesis that a vitamin B_6 deficiency state leads to CTS and thereby correction of this deficiency leads to symptom resolution. Even for those studies that did measure B_6 levels, another area of controversy is whether the current assays actually reflect true B_6 deficiency. Fuhr et al. measured vitamin B_6 levels in patients with idiopathic CTS and compared them with controls. They concluded that although the difference in vitamin B_6 levels between the two groups was statistically significant, not all patients presenting with CTS have detectable vitamin B_6 deficiency. Smith et al. found no B_6 deficiency in six patients with electrodiagnostically-proven CTS. Franzblau et al. found that only 11 of 31 patients diagnosed with CTS had abnormal lab values suggestive of B_6 deficiency. Furthermore, Byers et al. only found B_6 deficiencies in peripheral neuropathy patients. Azuma et al. actually used the EGOT assay to study vitamin B_6 levels in an asymptomatic population and found that more than 50% of the population had increased rates of stimulation when pyridoxine was added to their samples. Azuma et al. interpreted this data to indicate a mild deficiency state in the general population. However, others believe that this does not represent an abnormality. They in fact believe that supplementing B_6 to the level at which there is no increase in SA (approximately 11 weeks according to Ellis) actually represents a hypervitaminosis state, which can be potentially dangerous according to several reports on vitamin B_6 toxicity.

Given the shortcomings of current research on this topic, it is clear that additional randomized, controlled, double-blind studies need to be conducted in which larger CTS populations undergo pre- and post-treatment clinical evaluation, electrodiagnostic testing, and vitamin B_6 level determinations. Until such a time, so as not to deny CTS patients this potentially beneficial and relatively safe conservative treatment, the following recommendations for B_6 supplementation seem to be reasonable. Consider recommending this supplement, particularly if there is an underlying peripheral neuropathy.

In most studies that reported improvement of CTS symptoms, pyridoxine was administered in doses ranging from 50 to 300 mg daily for 12 weeks. Although most side effects have been reported with ingestion of 500 to 2000 mg daily, there are some reports of side effects in patients taking as little as 200 mg daily. Based on these clinical studies and toxicity reports, a therapeutic trial with pyridoxine should probably not exceed 200 mg daily for 12 weeks. It is also important to note that the
Institute of Medicine established an upper tolerable limit of 100 mg per day for adults.\textsuperscript{41}

Supplementation beyond multivitamins will be required because most multivitamins only contain the RDA (2.0 mg for men and 1.6 mg for women of vitamin B\textsubscript{6}). Patients should be monitored for signs and symptoms of pyridoxine toxicity including seborrheic dermatitis, stomatitis, glossitis, cheilosis, depression, irritability, and peripheral neuropathy.

Laboratory determination of the vitamin B\textsubscript{6} status may be useful in making decisions relative to surgery. Theoretically, the patients who are not deficient in vitamin B\textsubscript{6} have an etiology that is less correctable via the addition of vitamin B\textsubscript{6} and thus might have a greater need for carpal ligament release.\textsuperscript{42} Consider stopping the pyridoxine if there has been no apparent response to it after 12 weeks.

**Acknowledgements**

Lisa Schoenherr and Michael McNulty, D.C., assisted with the review of the manuscript.
