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RESEARCH ARTICLE

ORAL GLYCINE REDUCES PAIN PERCEPTION AND IMPROVES CONDUCTION VELOCITY IN CARPAL TUNNEL SYNDROME

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ABSTRACT

Objective: Several studies on the use of glycine consumption have demonstrated its anti-inflammatory properties, but not in persons with Carpal Tunnel Syndrome. We conducted a study with glycine consumption in CTS to prevent pain and improve Median Nerve function. **Material and Methods:** Nineteen patients diagnosed with bilateral CTS were selected and administrated glycine 1 g daily for 2 months. Pain level was assessed using the Wong scale and the electrophysiological study was performed to check MN function.
Results: Nerve Conduction Velocity was lower than normal at baseline studies and increased to normal values per treatment month, decreasing pain perception of pain after 1 month and 2 months of treatment.
Conclusions: The findings of this study suggest that consumption of glycine may reduce pain perception and improve motor nerve conduction in electrophysiological studies.

INTRODUCTION

Carpal Tunnel Syndrome (CTS) is the most frequent form of MN entrapment and accounts for 90% of all entrapment neuropathies (Ghasemi-Rad, 2014). CTS is a neuropathy caused by entrapment of the Median Nerve (MN) at the level of the carpal tunnel (Alfonso, 2010) by increased pressure within the carpal tunnel and traction of the MN, thus decreased MN function at that level (Alfonso, 2010; Burns, 2005; Ibrahim, 2012; Aboonq, 2015). Treatment of CTS can be classified as surgical and non-surgical. Surgical treatments include standard open carpal tunnel release, endoscopic carpal tunnel release, open carpal tunnel release combined with procedures, and open carpal tunnel release using various incision techniques (Shi and MacDermid, 2011). Non-surgical treatments comprise a wider range of options, such as splinting, cortical steroid injections, Non-Steroidal Anti-Inflammatory Drugs (NSAID), B6 vitamin, diuretics, UltraSound (US) therapy, ergonomic positioning, manual therapy intervention, lidocaine patches, and acupuncture (Kumnerddee and Kaewtong, 2010; Nalamachu, 2014). Glycine is an amino acid with a simple structure, and it displays important biological activities by acting as a modulator of the systemic inflammatory cascade, improving microcirculation and assisting in the inhibition of Tumor Necrosis Factor alpha (TNF-α) and InterLeukin 1beta (IL-1β) (Hartog, 2007; Figueiredo, 2009). Many studies have proposed glycine as a useful treatment for many types of inflammatory processes (Carmans, 2010; Wheeler, 1999; Wang, 2013). Inclusion of 5% glycine in the diet has shown to exert an important effect on the treatment of inflammatory processes and tumors (Wheeler, 1999; Wang 2013; Vieira, 2015). Recently, treatment with glycine in the diet was found to lead to improvements in biomechanical properties, organization of collagen bundles, and synthesis of ExtraCellular Matrix (ECM) molecules in tendonitis induced in rats (Vieira, 2015). Dietary or intravenous (i.v.) application of glycine has been demonstrated to prevent inflammatory complications in several experimental models, such as ischemia/reperfusion, transplantation, shock, endotoxemia, and diabetes (Wheeler, 2000). The main objective of this study was to evaluate glycine supplementation as a viable alternative in treatment for Carpal Tunnel Syndrome.

MATERIALS AND METHODS

This research is an auto-controlled study that was approved by the Ethical Committee of the National Institute of Rehabilitation (INRehab), Secretaría de Salud (SS), Mexico City. All of the participants included in this study provided their written informed consent after receiving a clear explanation of the procedures and potential risks of the study.

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Nineteen patients diagnosed with CTS were carefully selected from the Department of Plastic and Reconstructive Surgery of the General Hospital of Mexico during 2 years. Patients were aged 18–70 years, 73.7% were women and 26.3% were men, and both hands of the study participants were affected by classic CTS symptoms according to the diagnostic criteria in the Katz hand diagram (Eulenburg et al., 2005).

Each patient had symptom duration of at least 2 months, nerve conduction tests showing the presence of anormal nerve conduction; the patients were also diagnosed clinically and had physician office studies, as in patients with bilateral CTS caused by occupational factors leading to excessive use of their hands. All patients proved to be candidates for surgical treatment. We performed a clinical history on each patient that included age, gender, dominant hand, CTS symptoms timeline (in months), predisposing factors (occupational or pathological), and symptomatology. All patients reported initial symptoms that included numbness, hyperesthesia and/or hypoesthesia, paresthesia, and pain (type, location, and path). Likewise, the delayed symptoms reported were weakness (abduction, flexion, and thumb opposition) and atrophy (thenar eminence). Neurological examination of both hands consisted of inspection and palpation of muscle mass, areas of strength, myotatic reflexes, sensitivity, and Tinel (Stewart and Eisen, 1978) and Phalen (Seror, 1988) clinical assessments.

Glycine administration

All patients were administered 1 g/day of glycine orally for 2 months. Prior to administration of glycine, patients were assessed for Motor Conduction Velocity (MCV) of the MN. They were subsequently assessed after months 1 and 2 of treatment. Exclusion criteria comprised previous steroid injection for CTS in the same wrist, severe sensory loss (two-point discrimination exceeding 8 mm), thenar atrophy, inflammatory joint disease, diabetes mellitus, vibration-induced neuropathy, polyneuropathy, pregnancy, trauma to the affected hand in the previous year, severe medical illness, and known drug or alcohol abuse.

Neurophysiological evaluation

A Cadwell 5200-A was conducted of recording electrodes and bipolar skin stimulators and was used for neurophysiological assessment. Skin temperature was set at 32°C for these assessments. The study of the Nerve Conduction Velocity (NCV) of the MN was performed, with the recording electrode at the midpoint of the abductor muscle pollicis brevis, and the reference electrode was placed on insertion of the abductor muscle pollicis brevis on the thumb's metacarpophalangeal joint. The ground electrode was placed on the back of the hand. The first stimulus was applied 8 cm from the recording electrode, and the second stimulus was applied 13 cm from the recording electrode (Kimura, 1981). Nerve conduction results were reviewed by a Neurologist from the National Institute of Rehabilitation (INRehab) to ascertain which nerves had normal or abnormal response values.

Measurement on pain scale

Pain level was assessed utilizing the Wong scale (Whalen, 1995), which ranges from 0–10 and where 0 is no pain, 1–2 is mild pain, 3–4 uncomfortable pain, 5–6 moderate pain, 7–8 intense pain, and 9–10, intolerable pain.

Statistical analysis

We calculated medians and Standard Deviations (SD), frequencies and percentages, and Kolmogorov–Smirnov, Student *t* with the Welch correction, Mann–Whitney *U*, Student *t,* and Analysis Of VAriance (ANOVA) tests were applied.

Data analysis was performed using the GraphPad Prism ver. 5 statistical software program. We employed a $p < 0.05$ value for statistical significance.

RESULTS

We studied 19 patients diagnosed with Carpal Tunnel Syndrome (CTS) who were treated at the General Hospital of Mexico. The average age of these patients was 49.89 ± 13.46 years, with a 25–75-year age range. We observed that the majority of patients were women (73.3%). No differences were found ($p > 0.05$) in average age between males and females; however, the median was less for females (48.29 ± 10.81 vs. 54.4 ± 19.06 years). With respect to the baseline conduction velocity of female patients with CTS in our study, these were lower on average than that reported in the literature as normal Conduction Velocity (CV) for the MN ($p < 0.05$; 44.43 ± 2.73 m/s vs. 56.30 ± 2.39 m/s, according to that reported by Owolabi et al. (2016). To patients with CTS, we administered 1 gr of glycine orally daily for 2 months. Measurements were performed at treatment months 1 and 2. The results are presented in Figure 1 An increase was observed in Motor-Nerve Conduction Velocity (MNCV) at month 1 (54.16 ± 3.32 m/sec; $p = 0.02$) and at month 2 (58.04 ± 10.9 m/sec; $p = 0.0006$) with respect to the baseline average.

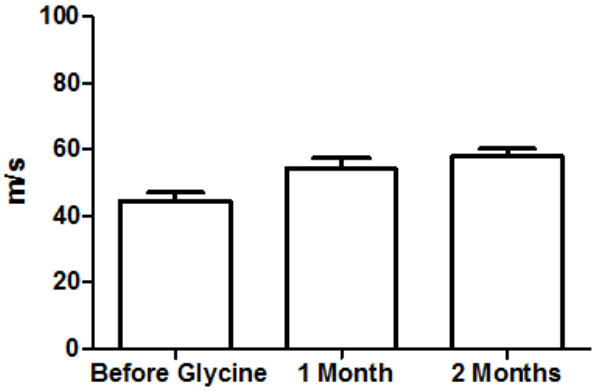

Figure 1. Means of (NCV) in Mexican patients with (CTS) before glycine treatment and after treatment at 1 month (p = 0.02) and 2 months (p= 0.006)

Pain was determined by applying the Wong scale. We observed that patients with CTS initiated on average with a score of 4.89 ± 2.02, this diminishing at 1 month of treatment with glycine (3.6 ± 1.83; $p = 0.004$) and at 2 months (1.96 ± 1.42; $p = 0.0001$) (Figure 2). In Table 1, the averages of MCV and pain are depicted in relation to analysis of age groups evaluated before and after treatment with glycine. The 42–58-years of age group exhibited a greater increase in MCV (19.5 m/s) and greater diminution of pain (3.33 points), followed by the group aged 59–76 years (9.35 m/s), and last, by the youngest group (7.15 m/s), taking into account initiation vs. end, emphasizing that these fell outside the parameters without a statistical difference in MCV and pain ($p > 0.05$). In Table 2, we may observe the averages of MCV and of pain in relation to

gender evaluated before and after treatment with glycine; women increased their MCV by 11.37 m/s and diminished pain by 3.14 points, while males increased their MCV by 31.93 m/s and diminished pain by 2.25 points, considering the measurement prior to the treatment vs. that taken at 2 months.

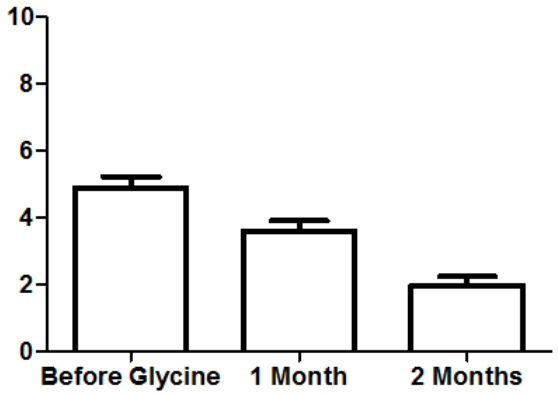

Figure 2 Means of pain in Mexican patients with (CTS) with glycine treatment at 1 month (p = 0.004) and 2 months after treatment (p = 0.0001)

Averages of baseline MCV and pain between men and women were different without a significant difference (p >0.05).

investigators found that CV diminishes with age, but the correlation between these results is not very clear (Owolabi, 2016). Study limits are defined by establishing a normal function for the nerve. Results falling out-of-range suggest the presence of some type of neuropathy. Our results at 1 month of treatment with glycine revealed that the MNCV increased the normal levels (taking as standard the parameters reported by Hennessey (1994) (62.5 m/s), Kimura (2001)(57.7 m/s), and Mishra & Kalita (1999)(58.52 m/s). In the pain-scale results, there was a significant difference between pain perception before and after treatment with glycine at both cut-off points (at month 1, 3.53 ± 1.83, and at month 2, 1.94 ± 1.42). With regard to CV, there was diminution from the beginning of the study. On comparing our baseline measurements with the normal values found in the Nigerian population evaluated by Owolabi et al. (2016), in the first age group (25–41 years), there was a diminution in CV of 30%; in the second age group (42–58 years), we found a diminution of 39%, while in the third age group (59–76 years), there was a diminution of 17% in NCV. These velocities were raised during the study (see Table 1); thus, it is considered that glycine improves the NCV of the MN in the case of patients with CTS. Similarly, glycine has been utilized in the diet, demonstrating immense benefits, improving microcirculation (Rosse, 1989; Shechter, 1999; Zhong, 1996), inhibiting inflammation (Stachlewitz, 2000), stimulating the synthesis of hydroxyproline, glycosaminoglycans, and non-collagen

Table 1. NCV and Pain means in CTS before and after glycine treatment
Age groups

Age group (year)	Basal		1 Month		2 Months	
	NCV (m/s)	Pain	NCV (m/s)	Pain	NCV (m/s)	Pain
25- 41	45.51±14.02	4.25±2.9	51.81±13-02	3.25±2.5	52.66±13.37	1.5±1.8
42-58	38.06±20.2	5.33±1.5	44.51±18.37	3.67±1.4	57.49±13.07	2±1.11
59-76	50.63±13.4	4±2.19	58.83±24.6	3.8±2.56	59.98±12.94	2.5±1.91

Table 2. NCV and Pain means in CTS before and after glycine treatment by sex

Sex	Basal		1 Month		2 Months	
	NCV (m/s)	Pain	NCV (m/s)	Pain	NCV (m/s)	Pain
Woman	44.06±16.1	5±1.99	54.5±12.9	3.64±1.8	55.37±14.8	1.86±1.4
Men	31.44±19.83	4.5±2.17	35.56±13.4	3.5±2	63.37±11.2	2.25±1.4

DISCUSSION

In our results, the average age of patients with CTS was around 50 years, these patients were in their majority women, which is in agreement with that reported, given that women are at greater risk of having CTS than men (Kanaan and Sawaya, 2001) and that age is associated with hormonal changes taking place during menopause (Harris-Adamson, 2013; Fernández-de-Las-Peñas, 2013). The patients were selected with bilateral CTS, the majority of these women, similar to the works of Padua (1998) and Yucel (2015). In this work, we did not find significant differences in Motor-Nerve Conduction Velocity (MNCV) of the between the genders, which was 48.32 ± 19.92 m/s for females and 42.34 ± 30.77 m/s for males, very similar to that found by Atroshi and colleagues (2003)[29] in patients with CTS. In that Conduction Velocities (CV) aid us in evaluating the relative state of the nerve-under-study, some disorder that affects the MN can be reflected by an alteration of the MNCV in the patient (Owolabi, 2016). Likewise, we found that MNCV exhibits a reduction as age increase, and other proteins, and maintaining the organization of collagen molecules. Glycine induces rapid tissue remodeling. All of this taken together suggests that supplementation of glycine in the diet can comprise a good adjuvant treatment for individuals with tendon lesions and other types of connective tissue damage and inflammatory events (Vieira, 2015). It is noteworthy that our patients did not stop carrying out their normal activities during any study stage, in that they refused to do this due to that their daily work was 100% manual. According to our results, we are able to consider that supplementing glycine in the diet contributes in reducing our perception of pain and in improving Motor-Nerve Conduction Velocity (MNCV) in patients with CTS in a safe manner, due to that it modulates the genesis, development, and the perception of pain at the central level (Pellicer, 2010; Coffeen, 2012). Glycine inhibits the excitatory effect of the thick-caliber neurons of the modulatory center of posterior-horn nociceptive messages at the encephalic leve (Baños-Diez, 1996). In conclusion, the absence of associated effects and the fact that

glycine is a component of the human diet makes it an attractive therapeutic agent, in that, in our study, a reduction of pain and in increase of Motor-Nerve Conduction Velocity (MVCV), reaching normal levels in patients with carpal tunnel syndrome.

REFERENCES

Aboonq, M.S. 2015. Pathophysiology of carpal tunnel syndrome. *Neurosciences (Riyadh).*;20:4-9. Review.

Alfonso, C., Jann, S., Massa, R. et al. 2010. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. *Neurol Sci*., 31:243-52.

American Academy of Orthopaedic Surgeons Work Group Panel. Clinical guidelines on diagnosis of carpal tunnel syndrome, 2007

Atroshi, I., Gummesson, C., Johnsson, R. et al. 2003. Diagnostic properties of nerve conduction tests in population-based carpal tunnel syndrome. *BMC Musculoskelet Disord*. 4:9.

Baños-Diez, J.E., Navarro Acebes, X. 1996. Aspectos actuales de la transmisión nociceptiva: mecanismos periféricos y modulación espinal. *Rev. Neurología* 24: 769 - 778.

Burns, T.M. 2005. Mechanisms of acute and chronic compression neuropathy. In: Dyck PJ, Thomas PK, editors. Peripheral neuropathy. 4th ed. Amsterdam: Elsevier; pp. 1391-402.

Carmans, S., Hendriks, J.J., Thewissen, K. et al. 2010. The inhibitory neurotransmitter glycine modulates macrophage activity by activation of neutral amino acid transporters. *J Neurosci Res.* 88:2420-30.

Coffeen, U., Simón, K., Mercado, F. et al. 2012. Procesamiento central del dolor neuropático: una aproximación integrativa. *Salud Ment*. 35: 367-374.

Eulenburg, V., Armsen, W., Betz, H. et al. 2005. Glycine transporters: essential regulators of neurotransmission. *Trends Biochem Sci*., 30:325-33.

Fernández-de-Las-Peñas, C., Cleland, J.A., Plaza-Manzano, G., et al. 2013. Clinical, physical, and neurophysiological impairments associated with decreased function in women with carpal tunnel syndrome. *J Orthop Sports Phys Ther*.43:641-9.

Figueiredo, J.A., Petroianu, A., Correia, M.I. et al. 2009. Effect of the nutritional supplementation with glicine and glutamine, oral feeding, in the colonic cicatrization in rabbits. *Rev Col Bras Cir*. 36:148-51.

Ghasemi-Rad, M., Nosair, E., Vegh, A. et al. 2014. A handy review of carpal tunnel syndrome: From anatomy to diagnosis and treatment. *World J Radiol*. 6:284-300.

Harris-Adamson, C., Eisen, E.A., Dale, A.M. et al. 2013. Personal and workplace psychosocial risk factors for carpal tunnel syndrome: a pooled study cohort. *Occupational and environmental medicine*.70:529-537.

Hartog, A., Leenders, I., van der Kraan, P.M. et al. 2007. Anti-inflammatory effects of orally ingested lactoferrin and glycine in different zymosan-induced inflammation models: evidence for synergistic activity. *Int Immunopharmacol*. 15:1784-92.

Hennessey, W.J., Falco, F.J., Goldberg, G. et al.1994. Gender and arm length: influence on nerve conduction parameters in the upper limb. *Arch Phys Med Rehabil*. 75:265-9.

Ibrahim, I., Khan, W. S., Goddard, N., & Smitham, P. Suppl 1: Carpal Tunnel Syndrome: A Review of the Recent Literature. *The open orthopaedics journal*. 2012;*6:* 69-76.

Kanaan, N., Sawaya, R.A. 2001. Carpal tunnel syndrome: modern diagnostic and management techniques. *Br J Gen Pract*. 51:311-4.

Kimura, J. 2001. Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice. 3rd ed. Philadelphia: Davis; pp. 131–68. 180, 412-3.

Kumnerddee, W., Kaewtong, A. 2010. Efficacy of acupuncture versus night splinting for carpal tunnel syndrome: a randomized clinical trial. *J Med Assoc Thai*. 93:1463-9.

Misra, U.K., Kalita, J. 1999. Clinical Neurophysiology, B.I.Churchill Livingstone Pvt Ltd (New Delhi). *ISBN:81-7042-147-0. pp*. 24-9.

Nalamachu, S., Nalamasu, R., Jenkins, J. et al. 2014. An Open-Label Pilot Study Evaluating the Effectiveness of the Heated Lidocaine/Tetracaine Patch for the Treatment of Pain Associated with Carpal Tunnel Syndrome. *Pain Pract*. 14:607-12.

Owolabi, L.F., Adebisi, S.S., Danborno, B.S. et al. 2016. Median Nerve Conduction in Healthy Nigerians: Normative Data. *Ann Med Health Sci Res*., 6:85-9.

Padua, L., Padua, R., Nazzaro, M. et al. 1998. Incidence of bilateral symptoms in carpal tunnel syndrome. *J Hand Surg Br*., 23:603-6.

Pellicer, F., Ortega-Legaspi, J.M., López-Avila, A. et al. 2010. Dopamine pathways and receptors in nociception and pain. Pharmacology Pain: IASP Press.

Rosse, R.B., Theut, S.K., Banay-Schwartz, M. et al. 1989. Glycine adjuvant therapy to conventional neuroleptic treatment in schizophrenia: an open-label, pilot study. *Clin Neuropharmacol*. 1989;12:416-24.

Seror, P. 1988. Phalen's test in the diagnosis of carpal tunnel syndrome. *J Hand Surg Br*., 13: 383-5.

Shechter, M., Merz, C.N., Paul-Labrador, M. et al. 1999. Oral magnesium supplementation inhibits platelet-dependent thrombosis in patients with coronary artery disease. *Am J Cardiol*. 84:152-6.

Shi, Q., MacDermid, J.C. 2011. Is surgical intervention more effective than non-surgical treatment for carpal tunnel syndrome? A systematic review. *J Orthop Surg Res*., 11:17.

Stachlewitz, R.F., Li, X., Smith, S. et al. 2000. Glycine inhibits growth of T lymphocytes by an IL-2-independent mechanism. *J Immunol*.164:176-82.

Stewart, J.D, Eisen A. Tinel's sign and the carpal tunnel syndrome. *British Medical Journal.* 1978;2:1125-1126.

Vieira CP, Guerra Fda R, de Oliveira LP, et al. Green tea and glycine aid in the recovery of tendinitis of the Achilles tendon of rats. *Connect Tissue Res*. 2015;56:50-8.

Vieira, C.P., De Oliveira, L.P., Da Ré Guerra, F. et al. 2015. Glycine improves biochemical and biomechanical properties following inflammation of the achilles tendon. *Anat Rec (Hoboken).*;298:538-45.

Wang W, Wu Z, Dai Z, et al. Glycine metabolism in animals and humans: implications for nutrition and health. *Amino Acids*. 2013;45:463-77.

Whalen L. Wong D. Baker faces pain rating scale. In: Clinical Manual of Pediatric Nursing Clinical Manual of Pediatric Nursing (L. Whaley & D.Wong. ed.) Nursing care of pain Mosby, St. Louis, 1995. 161 -167.

Wheeler MD, Ikejema K, Enomoto N, et al. Glycine: a new anti-inflammatory immunonutrient. *Cell Mol Life Sci*. 1999;56:843-56. Review.

Wheeler MD, Rose ML, Yamashima S, et al. Dietary glycine blunts lung inflammatory cell influx following acute

endotoxin. *Am J Physiol Lung Cell Mol Physiol*. 2000; 279:L390-8

Wheeler MD, Thurman RG. Production of superoxide and TNF-alpha from alveolar macrophages is blunted by glycine. *Am J Physiol*. 1999; 277:L952-9.

Yucel H. Factors affecting symptoms and functionality of patients with carpal tunnel syndrome: a retrospective study. *J Phys Ther Sci*. 2015;27:1097-101.

Zhong Z, Jones S, Thurman RG. Glycine minimizes reperfusion injury in a low-flow, reflow liver perfusion model in the rat. *Am J Physiol*. 1996;270:G332-8.

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