# Analytical, longitudinal, and self-controlled trial of glycine in carpal tunnel syndrome pain

## *Glycine in carpal tunnel syndrome pain*

**Cortes-Altamirano JL[1,2], Alfaro-Rodríguez A[1], Reyes-Long S[1,3], Morraz-Varela A[1,3], Bonilla-Jaime Herlinda[4], González-Maciel A[5], Herrera-Lopez ME[2], Bandala C[1,3*]**

[1] Coordinación de Neurociencias Básicas, Instituto Nacional de Rehabilitación "Luis Guillermo Ibarra Ibarra" (INRLGII), CDMX, México.

[2] Departamento de Quiropráctica, Universidad Estatal del Valle de Ecatepec (UNEVE), Edo. De México, México.

[3] Escuela Superior de Medicina., Instituto Politécnico Nacional (IPN), CDMX, México.

[4] Departamento de Biología de La Reproducción. Universidad Autónoma Metropolitana-Iztapalapa (UAM-I), CDMX, México.

[5] Laboratorio Morfología Celular y Tisular. Instituto Nacional de Pediatría (INP), CDMX, México.

*Corresponding auhtor

***Abstract*— Glycine is a non-essential amino acid and an anti-inflammatory agent that protects against pathological states in animal models. Pain in carpal tunnel syndrome is secondary to ischemia rather than direct physical damage of the nerve. A patient has a nerve compression that begins with symptoms such as pain, dysesthesia and paresthesia. Plausibly, acute compression causes inflammatory changes and development of neural irritation. Nerve injury due to acute compression increases intra-carpal canal pressure and causes changes in the microcirculation that leads to total ischemia. In the present study, we tested in patients with bilateral carpal tunnel syndrome, whether glycine administration could ameliorate the pain intensity, carrying nerve conduction velocity at normal levels. Nineteen patients were administered glycine (1 g) daily for two months. Glycine significantly diminished pain in patients with carpal tunnel syndrome, and it had no significant effects on nerve conduction velocity but normalized values of this. This study provides further insight into glycine; administered orally could be a potential therapeutic in carpal tunnel syndrome.**

***Keywords:** Glycine, Pain, Nerve, Conduction, Velocity, Carpal Tunnel Syndrome.*

### I.- INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy [1] and is caused by compression of the median nerve as it passes through the carpal tunnel [2,3]. It is more common in women, with rates of 57% to 80% and a 7:1 ratio in relation to men. CTS occur mainly between the fifth and sixth decades of life [4,5]. Pain is determined by nociception and illness progression [6]. The Tinel's sign is positive in 63% of patients and Phalen at 66%, electromyography is positive in 100% of patients, but the final surgical decision is made based on symptomatology [7-9]. Nerve injury due to acute compression increases intra-carpal canal pressure and causes changes in the microcirculation up to complete ischemia. Thus, pain may occur by mechanical irritation of the nerve [10].

Glycine is a non-essential amino acid; it has the simplest molecular structure of all. Is calculated that human synthetize daily approximately 45 g of endogenous glycine, and 3 – 5 g of glycine is taken up from the diet. Endogenously synthesized glycine functions as an inhibitory neurotransmitter in the central nervous system via the glycine receptors (GlyRs). In contrast, glycine also acts as a co-agonist for the channel opening of the N-methyl-D-aspartate subtype of ionotropic glutamate receptors (NMDARs) [11].

### II.- MATERIAL AND METHODS

This research was approved by the Ethical Committee of the National Institute of Rehabilitation LGII. Mexico City. All the participants included in this study provided their written informed consent after receiving a clear explanation of the study procedure and the potential risks of the study.

An analytical, longitudinal and self-controlled study was carried out with nineteen patients diagnosed with carpal tunnel syndrome, they were carefully selected from the department of plastic and reconstructive surgery of the General Hospital of Mexico (Mexico City, Mexico) during the past two years; with age ranging from 18 to 70 years; either gender, with both hands affected, symptoms of classic CTS according to the diagnostic criteria in the Katz hand diagram [12], symptom duration of at least two months, nerve conduction tests showing median neuropathy at the wrist and no other abnormalities or, in the presence of normal nerve conduction test results, they were also diagnosed clinically and had desk studies as patients with bilateral carpal tunnel syndrome caused by occupational factors that lead to excessive use of their hands, all of them candidates for surgical treatment. We performed a detailed clinical history including age, sex, dominant hand, and time evolution of the symptoms (in months), predisposing factors (occupational or pathological) and symptomatology. All patients reported as initial symptoms numbness, hyperesthesia and/or hypoesthesia, paresthesia, pain (type, location and path), relief or not, with movement.

Likewise, the reported delayed symptoms were weakness (abduction, flexion and opposition the thumb) and atrophy (thenar eminence).

The neurological examination of both hands consisted of inspection and palpation of muscle mass, areas of strength, myotatic reflexes, sensitivity and clinical signs of Tinnel [13] and Phalen [14].

All patients were administered glycine (Sigma) orally 1 g/day during the two months of treatment. Prior to the administration of glycine, patients were assessed for motor conduction velocity of the median nerve as well as during the first- and second-month post treatment. The trial was a prospective randomized with 1 gr glycine oral in the carpal tunnel in patients with moderately severe idiopathic CTS not previously treated with steroid injection. The exclusion criteria were: 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, previous surgery for CTS in the affected hand, surgery for CTS in the contralateral hand within the past 2 months, inability to respond to questionnaires (e.g., because of language difficulty or cognitive impairment), severe medical illness, and known abuse of drugs or alcohol.

**Neurophysiological evaluation.**

The Cadwell 5200-A was used as a tool using contact recording electrodes and bipolar skin stimulators; for the neurophysiological assessment, the skin temperature was 32°C. The study of nerve conduction velocity (NCV) of median nerve was performed, with the recording electrode at the midpoint of abductor muscle *pollicis brevis,* and the reference electrode placed on the insertion of the abductor muscle *pollicis brevis* on the joint metacarpophalangeal of the thumb. The ground electrode was placed in the back of the hand. The first stimulus was applied at 8 cm from the recording electrode, and the second stimulus was applied at 13 cm from the recording electrode [15]. Nerve conduction data was reviewed by a neurologist from the National Institute of Rehabilitation to ascertain which nerves had normal/abnormal response values.

**Measurement on Pain Scale.**

The pain level was assessed using the Whaley & Wong scale [16] which goes from 0 to 10 where 0 is no pain, 1 to 2 is mild pain, 3 to 4 uncomfortable pain, 5 to 6 moderate pain, 7 to 8 intense pain, and 9 to 10 intolerable pain. This assessment took place while neuropsychological evaluations were being conducted to observe if there was improvement in pain levels of patients secondary to treatment with glycine.

**Ethics.**

This study was performed according to the ethical principles stated in Helsinki Declaration of 1975

**Statistical analysis.**

SPSS ver. 19.0 was used for statistical analysis. Means were reported with their associated standard deviations (SDs). The data was analyzed with repeated measures of ANOVA with adjustment for multiple comparisons: Bonferroni. Pearson Correlation was performed. Statistical significance was set at $p < 0.05$ with a 95% of confidence interval.

## III.- RESULTS

38 hands of 19 patients diagnosed with carpal tunnel syndrome were included in this study, 73.7% subjects were women and 26.3% were men. The age mean was 49.89 ± 3.46 (mean ± SD); the age range for these patients was 25 – 75 years, there was no difference in the mean age according to sex (F=5. 77, p=0. 22).

The average onset of median nerve conduction velocity (MNCV) was 48.32 ± 19.92 for women and 42.34 ± 30.77 for men, we found no differences among them. There was a significant correlation between basal median nerve conduction velocity and age (r= -0.37, p= 0.02, Figure 1A) and basal median nerve conduction velocity and pain perception (r=0.35, p= 0.03, Figure 1B), but they were not associated with sex.

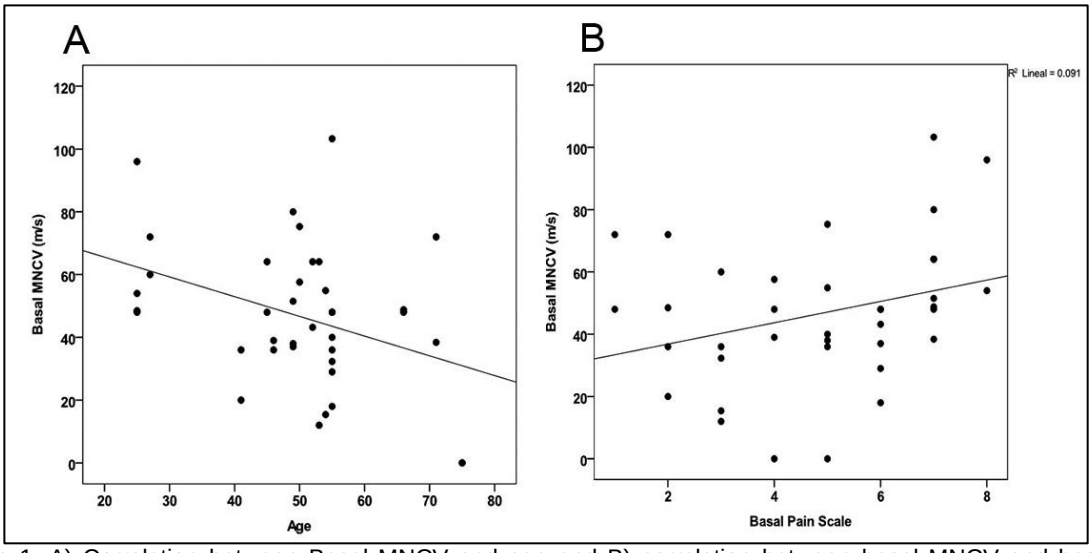


Figure 1. A) Correlation between Basal MNCV and age and B) correlation between basal MNCV and basal pain measurement, both in patients with carpal tunnel syndrome. MNCV = median nerve conduction velocity.

Basal mean MNCV (46.74 ± 22.96) did not have statistical difference with first (52.99 ± 22.89) and second (74 ± 108.73) measures after treatment with glycine (p= 0.22); despite this result, we could see that MNCV increased after 2 months of treatment with glycine (Figure 2A).

Related to basal pain perception, we did not find statistical differences between women and men (5.04 ± 1.99, 4.50 ± 2.17 respective averages). Regarding age and pain perception we could see that patients with >50 years had increased pain perception (5.27 ± 1.5) than younger ones (4.38 ± 2.5), but these differences had not statistical significance. Interestingly, there was a statistical difference (p= 0.001, figure 2B) between pain perception before treatment with glycine (4.72 ± 2.02) and after treatment with glycine in both measurements (First month = 3.53 ± 1.83, second month = 1.94 ± 1.42). We also found interesting results about pain perception related to sex and age of patients studied in this research (Table 1A, 1B and figure 3).

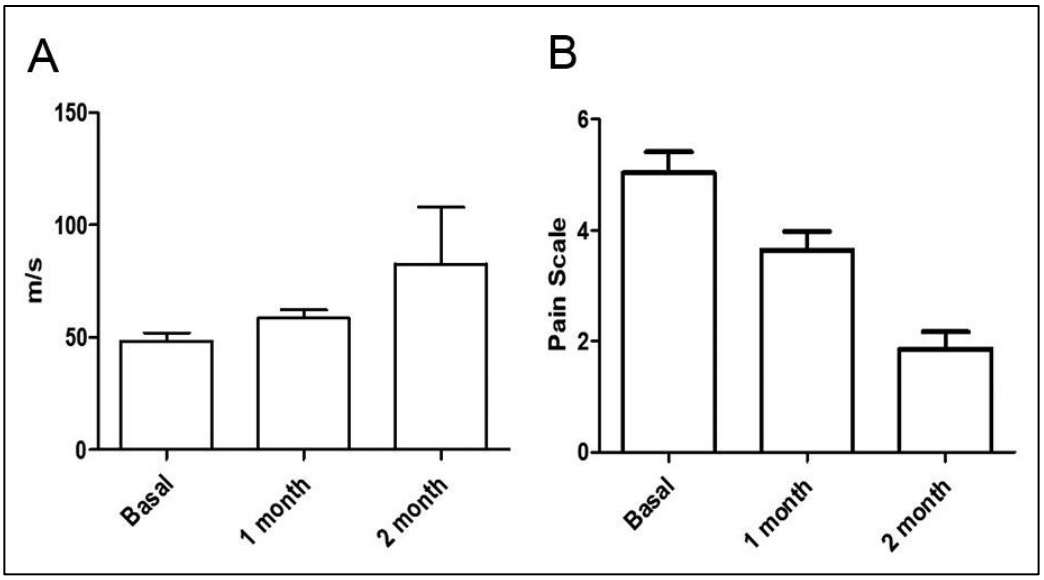


Figure 2. A) MNCV in basal measurement and 1 and 2 months after treatment with glycine. B) Pain perception in basal measurement and 1 and 2 months after treatment with glycine.

Table 1A. Mean of pain perception measurements related to age and sex.

| | | | | | IC+ 95% | |
|---|---|---|---|---|---|---|
| Age | Sex | Pain measurement | Mean | SE | Lower limit | Upper limit |
| <50 years | Women | Basal | 3.50 | 0.72 | 2.01 | 4.98 |
| | | 1 month | 3.00 | 0.72 | 1.50 | 4.49 |
| | | 2 months | 1.25 | 0.50 | 0.21 | 2.28 |
| | Men | Basal | 5.00 | 1.42 | 2.03 | 7.96 |
| | | 1 month | 3.00 | 1.45 | 0.01 | 5.98 |
| | | 2 months | 2.00 | 1.01 | - 0.07 | 4.07 |
| >50 years | Women | Basal | 5.71 | 0.54 | 4.59 | 6.83 |
| | | 1 month | 4.14 | 0.54 | 3.01 | 5.27 |
| | | 2 months | 2.21 | 0.38 | 1.42 | 3.00 |
| | Men | Basal | 4.66 | 0.83 | 2.95 | 6.37 |
| | | 1 month | 4.00 | 0.83 | 2.27 | 5.72 |
| | | 2 months | 2.33 | 0.58 | 1.13 | 3.53 |

IC+: Confidence interval; SE: Standard Error

Table1B. Statistical analysis of pain perception measurements related to age and sex in patients with carpal tunnel syndrome.

| Sex | Age | Pain measurements | | Differences between means | SE | P value[a] | CI 95% for differences[a] | |
|---|---|---|---|---|---|---|---|---|
| Women | < 50 years | Basal | 1 month | 0.50 | 0.34 | 0.47 | - 0.38 | 1.38 |
| | | Basal | 2 months | 2.25 * | 0.55 | 0.001 | 0.82 | 3.67 |
| | > 50 years | Basal | 1 month | 1.57 * | 0.26 | 0.0001* | 0.90 | 2.23 |
| | | Basal | 2 months | 3.50 * | 0.42 | 0.0001* | 2.42 | 4.57 |
| Men | < 50 years | Basal | 1 month | 2.00 * | 0.69 | 0.02 * | 0.23 | 3.76 |
| | | Basal | 2 months | 3.00 * | 1.12 | 0.03 * | 0.15 | 5.84 |
| | > 50 years | Basal | 1 month | 0.66 | 0.39 | 0.31 | - 0.35 | 1.68 |
| | | Basal | 2 months | 2.33 * | 0.64 | 0.004 * | 0.69 | 3.97 |

Based on estimated marginal means. [a] Adjustment for multiple comparisons: Bonferroni.*

The mean difference is significant at $p < 0.05$.

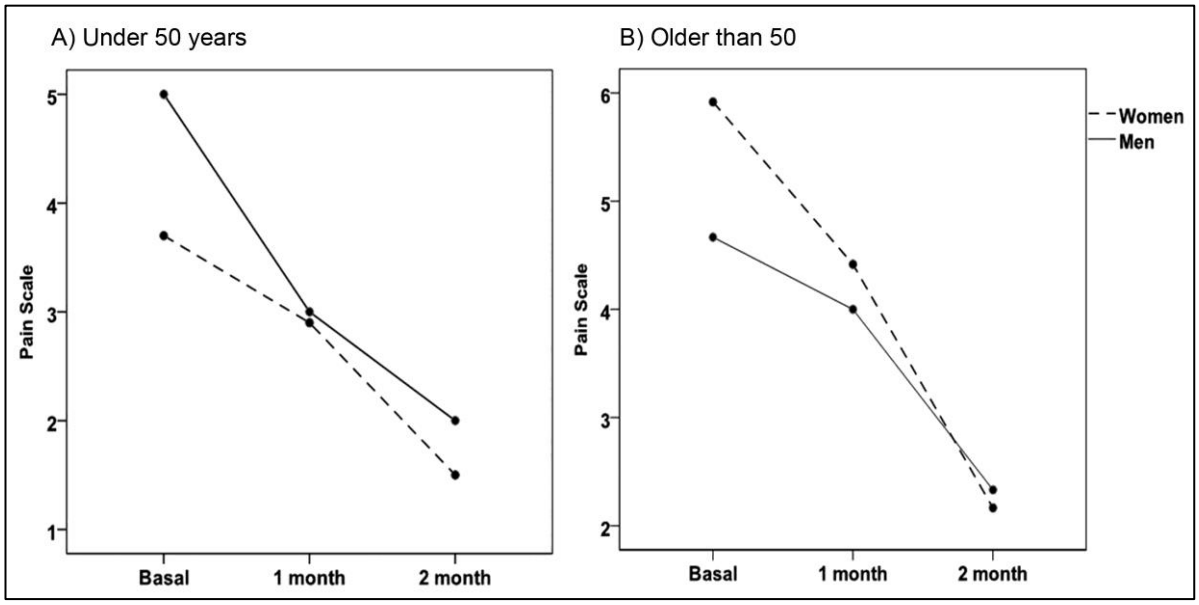


Figure 3. A) Pain perception in patients under 50 years and B) older than 50 years segregated by sex in basal measurement and 1 and 2 months after treatment with glycine

## IV.- DISCUSSION

The present study provides evidence that oral administration of glycine administered daily for two months ameliorated pain in patients with carpal tunnel syndrome. Glycine has been reported to exhibit many biological and pharmacological activities (sometimes at very low doses) including protection to the liver, small intestine, lung, skeletal muscle and potentially the heart against injury mediated by ischemia–reperfusion *in vivo* and it also increases survival following hemorrhagic shock and resuscitation. A wide variety of cells involved in inflammation (Kupffer cells, alveolar macrophages, and neutrophils) have also been shown to contain glycine-sensitive chlorine channels. Glycine causes less sensitivity to inflammatory stimuli such as endotoxins and possibly a wide variety of growth factors through hyperpolarization of the plasma membrane of leukocytes [17,18]. At the central nervous system level it has been reported that in lamina I neurons of the spinal cord dorsal horn, synaptic inhibition is almost exclusively mediated by glycine [19, 20].

Petrat and coworkers were the first to suggest that glycine protects from ischemia–reperfusion injury by inhibiting the activation of macrophages and other cells of the immune system and thus the inflammatory response [21]. Glycine has anti-inflammatory effects during ischemia, injury, and transplantation [22]. These improvements in pain were observed in the two consecutive months of treatment. Additionally, our performance, which was evaluated by electrophysiology vigilance test was also improved at this period of time. Thus, glycine improved subjective pain parameters.

Median nerve injuries that cause the CTS to occur as a result of the anatomical conditions of the region, the fibro-osseous tunnel, are susceptible to narrowing by compression factors, affecting the structures inside. Individuals, who by their occupation undergo more compression and continue with the injury, reach ischemia and epineural edema, blocking axonal transport, leading to an injury that interferes with nerve function by altering the ionic environment of axons and decreased capillary flow. If these levels of compression continue or increase, besides the pain, eventually they could produce complete ischemia and, finally, demyelization and axonal degeneration [23-25]. These changes correlate with the clinical symptoms in some patients with CTS; just as in our study subjects, some patients show evidence of paresthesia, attributed to excessive discharge of neurons in the median nerve related, like pain, with the ischemia [26]. Weakness or atrophy does not appear until later stages where there are greater demyelization and axonal degeneration with damage to several nerve fibers [27]. At this stage, sensitivity loss is permanent. The neurophysiologic diagnosis of CTS is made by demonstrating, through the area of entrapment, the decrease in conduction velocity due to the process of demyelization / remyelination, which is the primary fact, in the CTS, being the NCS a more sensitive parameter then the motor [28]. Moreover, conduction study values are more preserved in the early stage when compression or ischemia occurs in the carpal tunnel [29].

We took into consideration the standardized normal values for the median nerve, ranging from 50 to 67 m/s as established by Kimura, as normal nerve conduction velocity in utilizing the Cadwell equipment. It is noteworthy that sensory abnormalities usually occur before the motor. In other words, sensory latencies are slowed down before the motor. This fact is not surprising since 94% of the axons of the median nerve

at the wrist are sensory. Sensory axons are more susceptible to compression than motor [29], making it the reason we decided to assess the effect of glycine on motor fibers, to find the true effect of glycine at this level and correlate it with a degree of pain.

The results obtained in this study demonstrate the effects of glycine in the electrophysiological responses, thus measurements at the second month shows how the records of the patients in the study tend to normally. The absence of side effects and the fact that glycine is a natural component of the human diet becomes an attractive therapeutic agent, reducing inflammation, pain and therefore damage to the median nerve in CTS cases. Furthermore, the effect of glycine seems to be acceptable during the first two months of treatment.

## V.- CONCLUSION

These results suggest that in patients diagnosed with carpal tunnel syndrome treated with glycine, had a significant reduction in pain after two months of oral administration although normal electrophysiological recording in the median nerve. This could allow us to propose Glycine as a co-adjuvant in pain treatment in this

## VI.- ETHICAL RESPONSIBILITIES

**Protection of people.** The authors declare that the procedures followed were in accordance with the ethical standards of the responsible human experimentation committee and in accordance with the World Medical Association and the Declaration of Helsinki.

**Confidentiality of the data.** The authors declare that no patient data appear in this article.

**Right to privacy and informed consent.** The authors declare that no patient data appear in this article.

**Acknowledgments**

We thank the National Institute of Rehabilitation LGII or the facilities to carry out this research and to Drs Rebeca Uribe-Escamilla and Juan Bernardo Baltazar-Rendón for the recruitment of patients from the department of plastic and reconstructive surgery of the General Hospital of Mexico.

**Conflict of interest:** The authors declare that there is no conflict of interest.

## VII.- REFERENCES

[1]. Azmy RM, Labib AA, Elkholy SH. Axonal degeneration of the ulnar nerve secondary to carpal tunnel syndrome: fact or fiction? Neural Regen Res 2013; 8(15):1418–1422.

[2]. Tavee J. Nerve conduction studies: Basic concepts. Handb Clin Neurol 2019; 160:217–224. doi:10.1016/B978-0-444-64032-1.00014-X

[3]. Urits I, Gress K, Charipova K, Orhurhu V, Kaye AD, Viswanath O. Recent Advances in the Understanding and Management of Carpal Tunnel Syndrome: a Comprehensive Review. Curr Pain Headache Rep 2019; 23(10):70.

[4]. Amo C, Fernández-Gil S, Pérez-Fernández S. Carpal tunnel syndrome: clinical and neurophysiological correlation: review of 100 cases. (in Spanish). Rev Neurol 1988; 27:490-3.

[5]. Schols AMR, Beekman R, Cals JWL, van Alfen N, Ottenheijm RPG. Carpale tunnelsyndroom, een klinische diagnose [Carpal tunnel syndrome: a clinical diagnosis]. Ned Tijdschr Geneeskd 2018 162:D2862.

[6]. Doughty CT, Bowley MP. Entrapment Neuropathies of the Upper Extremity. Med Clin North Am 2019; 103(2):357–370.

[7]. Mc Carthy. Cirugía Plástica. Interamericana, Buenos Aires; 1995

[8]. Lied L, Borchgrevink GE, Finsen V. Wide Awake Hand Surgery. J Hand Surg Asian Pac Vol 2017; 22(3):292–296.

[9]. Cheah AE, Etcheson J, Yao J. Radial Nerve Tendon Transfers. Hand Clin 2016; 32(3):323–338.

[10]. Vanti C, Bonfiglioli R, Calabrese M, Marinelli F, Guccione A, Violante FS, et al. Upper limb neurodynamic test 1 and symptoms reproduction in carpal tunnel syndrome. A validity study. Manual Therapy 2011; 16: 258-263.

[11]. Bannai M, Kawai N. New Therapeutic Strategy for Amino Acid Medicine: Glycine Improves the Quality of Sleep. J Pharmacol Sci 2012; 118: 145 – 148.

[12]. Eulenburg V, Armsen W, Betz H, Gomeza J. Glycine transporters: essential regulators of neurotransmission. Trends Biochem Sci 2005; 30: 325–333.

[13]. Stewart JD, Eisen A. Tinel's sing and the carpal tunnel syndrome. Br Med J 1978; 2: 112-56.

[14]. Seror P. Phalen's test in the diagnosis of carpal tunnel syndrome. J Hand Surg 1988; 13: 383-5.

[15]. Kimura J. Electrodiagnosis in diseases of nerves and muscle: principles and practice. F. A. Davis Company, Philadelphia; 1989.

[16]. Whaley L, Wong D. 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; pp 161 -167.

[17]. Stachlewitz RF, Ikejima K, Thurman RG. Increases in intracellular calcium in neutrophils (PMNs) due to formyl-methionine-leucine-phenylalanine (FMLP) and endotoxin are blocked completely by glycine. Hepatology 1995; 22:1105.

[18]. Ikejima K, Qu W, Stachlewitz RF, Thurman RG. Kupffer cells contain a glycine-gated chloride channel. Am J Physiol 1997; 272:G1581-G1586.

[19]. Chery N, de Koninck Y. Junctional versus extrajunctional glycine and GABA(A) receptor-mediated IPSCs in identified lamina I neurons of the adult rat spinal cord. The Journal of Neuroscience 1999; 19:7342–7355.

[20]. Lynch JW, Zhang Y, Talwar S, Estrada-Mondragon A. (2017) Glycine receptor drug discovery. In Advances in Pharmacology 2017; 79;225-253.

[21]. Petrat F, Boengler K, Schulz R, Groot H. Glycine, a simple physiological compound protecting by yet puzzling mechanism(s) against ischaemia–reperfusion injury: current knowledge. British Journal of Pharmacology 2011; 165:2059–2072.

[22]. Zhong Z, Li X, Froh M, Schemmer P, Yin M, Bunzen-daul H, et al. L-Glycine: a novel anti inflammatory, immunomodulatory, and cytoprotective agent. Curr. Opin Clin Nutr Metab Care 2003; 6: 229–240.

[23]. Sunderland S. The nerve lesion in the carpal tunnel syndrome. J Neurol Neurosurg Psychiatry 1976; 39:615-26.

[24]. Ballestero-Pérez R, Plaza-Manzano G, Urraca-Gesto A, Romo-Romo F, Atin-Arratibel MA, Pecos-Martin D, et al. Effectiveness of Nerve Gliding Exercises on Carpal Tunnel Syndrome: A Systematic Review. J Manipulative Physiol Ther 2017; 40(1):50–59.

[25]. Kim DH, Kam AC, Chandika P, Tiel RL, Kline DG. Surgical management and outcomes in patients with median nerve lesions. J Neurosurg 2001; 95(4):584–594.

[26]. Campero M, Serra J, Marchettini P, Ochoa JL. Ectopic impulse generation and autoexcitation in single myelinated afferent fibers in patients with peripheral neuropathy and positive sensory symptoms. Muscle Nerve 1998; 21:1661-7.

[27]. Lo SL, Raskin K, Lester H, Lester B. Carpal tunnel syndrome: a historical perspective. Hand Clin 2002; 18(2):211–v.

[28]. Slutsky DJ. Nerve Conduction Studies in Hand Surgery. J Am Soc Surg Hand 2003 3:152-169.

[29]. Mackenzie SP, Stone OD, Jenkins PJ, Clement ND, Murray LR, Duckworth AD, et al. Carpal tunnel decompression in patients with normal nerve conduction studies. J Hand Surg Eur Vol 2020; 45(3):260–264.