New role for insulin injection in the treatment of idiopathic carpal tunnel syndrome

Soha Eldessouki Ibrahim, Azza Hussein

Assisstant professor of physical medicine rheumatology and rehabilitation, Faculty of Medicine, Ain Shams University, Cairo, Egypt. Consultant Rheumatology, BSUH NHS Trust, UK.

Correspondence to Soha Eldessouki Ibrahim, MD, Rheumatology and Rehabilitation, Assistant Professor Ain Shams University, Cairo, Egypt.
Tel: 01223331609;
e-mail: soha_eldessouki@yahoo.com

Received 30 April 2016
Accepted 18 May 2016

Egyptian Rheumatology & Rehabilitation
2016, 43:157–162

Objective
Local insulin injection for the median nerve was administered in patients with mild to moderate idiopathic carpal tunnel syndrome (CTS) to evaluate its effectiveness on the median nerve regeneration as it has been suggested that insulin has an effect on nerve regeneration, similar to that of nerve growth factor.

Patients and methods
This study included 82 patients (130 hands) with clinical and electrophysiologic evidence of mild to moderate idiopathic CTS (grade 3 or less according to Bland's classification). The 130 hands were randomly assigned to two groups: group I received insulin injection of 10 IU Neutral Protamine Hagedorn known as humulin N (NPH) insulin locally into the affected carpal tunnel at the first visit and a similar dose of insulin after 2 weeks; and group II received a single injection of 40 mg triamcinolone acetonide injection into the carpal tunnel. Clinical and electrophysiologic evaluations were carried out at the start of the study and at 1 month after treatment. Patients were evaluated on the basis of the mean score on the Symptom Severity Scale and Functional Status Scale of the Boston Carpal Tunnel Questionnaire.

Results
All patients showed a symptomatic and functional improvement. Distal motor latency and distal sensory latency were decreased for both groups (4.84±0.74 vs. 4.61±0.72 and 2.88±0.27 vs. 2.55±0.19, respectively), with a significant decrease in the mean of Functional Status Scale score and Symptom Severity Scale score for patients treated with the insulin injection (2.5±0.6 vs. 2.07±0.55 and 3.13±0.47 vs. 2.23±0.5, respectively).

Conclusion
Local insulin injection effectively reduced the symptoms of CTS and improved electrophysiological findings in the present study. Our findings suggest that local insulin injection may be of great benefit in improving nerve functions in patients with mild to moderate idiopathic CTS. Further controlled studies are needed to confirm our preliminary findings and to compare local insulin injection with conventional approaches for the treatment of CTS.

Keywords:
carpal tunnel syndrome, insulin injection, steroid injection

Egypt Rheumatol Rehabil 43:157–162

1110-161X

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremity. The prevalence of CTS in the general population has been estimated to be 1–5% [1]. NSAIDs, diuretics, vitamin B_6 injections, ultrasound therapy, laser therapy, acupuncture, magnetic therapy, bracing, and local steroid injections have been used in closed treatment [2].

The pathophysiological mechanism of idiopathic CTS is the increased pressure within the carpal tunnel, which results from an increase in the volume of canal's contents, particularly of the flexor tenosynovium [3]. Chronic nerve compression produces focal demyelination and in more severe cases there is an axonal degeneration of the nerve fibers [4].

The symptoms include pain, paresthesia, and numbness in the hand area supplied by the median nerve. The pain may radiate proximally and may be more severe at night. Patients may develop motor symptoms such as difficulty in gripping, leading to objects falling out of the hand.

The treatment of CTS includes nonsurgical modalities such as splinting, analgesics, oral steroids, local steroids, and surgical decompression for severe disease. The use of local steroid injections has been

 DOI: 10.4103/1110-161X.192256

mentioned in the literature as early as 1980 [5]. A Cochrane review by Marshall et al. [6] concluded that the local corticosteroid injection for severe CTS provided symptomatic benefit after 1 month compared with placebo.

It has been reported that peripheral nerves carry abundant receptors for nerve growth factor (NGF), a member of the insulin-like growth factor-1(IGF-1) family, and insulin [7]. Both of these are thought to promote neuronal growth and regeneration, and could be important in restoring nerve function following metabolic or vascular damage. In their study, Singhal *et al.* [8] found out that near-nerve local insulin injection prevented conduction slowing in experimental diabetes.

Some studies have assessed the effect of local insulin injection in diabetic patients with CTS, suggesting that local insulin injection may be of great potential benefit in the improvement of nerve functions in noninsulin-dependent diabetes mellitus with mild to moderate CTS.

Therefore, we conducted this study to evaluate the effectiveness of local insulin injection on median nerve regeneration for the treatment of mild to moderate idiopathic CTS in nondiabetics patients compared with local steroid injection to assess its role as a new treatment for CTS.

Patients and methods

This study was carried out on 130 hands of 80 adult patients, diagnosed to have mild to moderate CTS according to Bland's classification [9]. Patients were recruited from the Department of Physical Medicine, Rheumatology, and Rehabilitation, Ain Shams University Hospitals. The study was approved by the Ethical Committee of Ain Shams University. Written informed consent was obtained from each patient from the two studied groups.

Exclusion criteria included thenar atrophy, previous carpal tunnel release surgery, previous local injection, pregnancy, diabetes mellitus, hypothyroidism, inflammatory arthropathy, polyneuropathy, or simultaneous affection of the ulnar nerve in neurophysiological testing.

All patients were subjected to the following:

(1) Full medical history taking with particular attention to disease duration, paresthesia or hypoesthesia in the thumb, index and middle fingers, nocturnal paresthesia in the affected digits, hand pain especially nocturnal pain, and wasting in the thenar muscles.
(2) Thorough clinical examination including sensory and motor examination of the hand, and special tests for CTS (Tinel's sign, Phalen test, and reverse Phalen test).
(3) Assessment of the clinical severity of CTS: Symptom severity was assessed by using the Symptom Severity Scale (SSS) and functional disability by using the Functional Status Scale (FSS), which are both part of the Boston Carpal Tunnel Questionnaire (BCTQ). The BCTQ is a patient-reported outcome measure for CTS and has been tested for validity, reliability, and responsiveness. Psychometric properties of the BCTQ have been described extensively elsewhere [10]. The SSS has 11 questions, the FSS eight questions, and both use a five-point scale. Each scale generates a final score (sum of individual item scores divided by the number of items) that ranges from 1 to 5. Higher SSS and FSS scores correlate with more severe symptoms and functional impairment, respectively.
(4) Electrophysiological assessment: It was performed in a quiet room with a constant temperature of 27°C set using thermostat of an air conditioner. The electromyographic apparatus used was EMG/NCV unit (EMG/NCV/EP System Topas 230/240V; Schwarzer GmbH, Dantec, Germany). The bipolar surface-recording electrodes were used in the nerve conduction study (NCS).

Motor nerve conduction study of the median nerve

The active electrode was placed on the motor point of the abductor pollicis brevis (APB) muscle, about two-thirds proximally on the line from the metacarpophalangeal joint to the carpometacarpal joint of the first finger. The reference electrode was put on the metacarpophalangeal joint of the thumb. Stimulating sites were at the wrist and at the elbow in the antecubital fossa. Stimulus intensity was increased up to the maximal compound muscle action potential amplitude, reflecting stimulation of the whole of the motor nerve fibers. The conduction velocity was calculated by dividing the distance between proximal and distal stimulation by the difference between the proximal and distal latencies.

Sensory antidromic nerve conduction of the median nerve

The active and reference electrodes (ring electrodes) were placed 4 cm apart, with an active electrode placed proximally, at the base of the second digit (index).

Stimulation was carried out 14 cm proximal from the active electrode.

Motor nerve conduction study of the ulnar nerve

The active surface electrode was placed over the abductor digiti minimi muscle and the reference over the proximal phalanx of the fifth digit. The ulnar nerve was stimulated supramaximally with the elbow extended and forearm supinated. The stimulation at wrist was carried out 8 cm proximal to the active electrode at the distal wrist crease, just lateral to the tendon of flexor carpi ulnaris, whereas the stimulation at elbow was posterior to the medial epicondyle of the humerus.

Sensory antidromic nerve conduction of the ulnar nerve

The active electrode was located on the fifth digit just distal to the metacarpophalangeal joint. Stimulation was carried out 14 cm proximal from the active electrode. The reference electrode was placed distal on the fifth digit. The peak latency was measured at the midpoint of the first negative peak.

F-wave of the median and ulnar nerves

They were obtained by recording from the APB and abductor digiti minimi muscles, respectively. F-wave minimal and maximal latencies were obtained using 10 stimulations, at a rate of once every 2 s. F-wave chronodispersion was also measured, which basically refers to the difference of maximal and minimal latencies in a series of F-waves. F-wave was measured to exclude proximal root affection.

Electrophysiological diagnostic criteria

Patients with CTS were classified according to electrodiagnostic grading into the following:

Grade 0: Normal (normal standard and comparative tests).

Grade 1: Very mild CTS (normal standard tests and abnormal comparative tests).

Grade 2: Mild CTS [abnormal sensory and a normal motor response – i.e. prolonged antidromic distal sensory latency (DSL)>2.9 ms to the second digit].

Grade 3: Moderate CTS [abnormal median sensory and motor response – i.e. prolonged distal motor latency (DML) to APB>4.2 ms but <6.5 ms and prolonged antidromic DSL with decreased amplitude sensory nerve action potential].

Grade 4: Severe CTS (absence of sensory response, abnormal DML to APB but still <6.5 ms with decreased amplitude of compound muscle action potential, and abnormal EMG activity in APB).

Grade 5: Very severe CTS (terminal latency to APB>6.5 ms).

Grade 6: Extremely severe CTS [absence of median motor and sensory responses (surface motor potential from APB<0.2 mV amplitude)] [9].

The patients were randomly divided into two groups:

(1) Group I (the insulin injection group), in which the participants received 10 U of Neutral Protamine Hagedorn known as humulin N. (NPH) insulin locally into the affected carpal tunnel at the first visit and a similar dose of insulin after 2 weeks [11]
(2) Group II (the corticosteroid injection group) received 40 mg of triamcinolone acetonide injected into the carpal tunnel.

The site of the injection was at the proximal crease of the wrist, just medial to the palmaris longus tendon, with the needle angled at 45° toward the palm and directed slightly medially for both groups [12].

One month after the injection the patients were reviewed [11]. During this period, patients were not permitted to use any other form of therapy like splints or drugs.

Electrophysiology studies were repeated and the previously mentioned parameters were recorded.

Statistical analysis

Analysis of data were performed with an IBM compatible computer using stastistical package for social sciences (SPSS 10 for Windows). Statistical analysis was performed using the paired t-test to look for a significant difference in the electrophysiological values of each parameter at baseline, which were compared with those at 1 month after a local injection. A *P*-value of less than 0.05 was considered statistically significant and a *P*-value of less than 0.001 was considered highly statistically significant.

Results

Our study included 82 patients (130 hands) with mild to moderate idiopathic CTS. Their age ranged from 30 to 48 years, with a mean of 39.6±4.8 years. The disease duration ranged from 2 to 15 months, with a mean of 7.58±3.3 months.

Group I (the insulin injection group) included 43 patients (65 hands) with mild to moderate CTS.

There were 38 (88.3%) women and five (11.6%) men; their ages ranged from 32 to 48 years with a mean of 40.05±4.89 years. The duration of CTS ranged from 2 to 13 months, with a mean of 8.48±2.98 months. Twenty-two (51.1%) of the patients had bilateral CTS and the other 21 (48.8%) patients had unilateral CTS. As regards severity of CTS, 37 (56.9%) hands were considered as mild CTS and 28 (43.08%) hands as moderate CTS. FSS score was 2.5 ±0.6 and SSS score was 3.13±0.47 for patients before insulin injection.

Group II (the steroid injection group) included 39 patients (65 hands) with mild to moderate CTS. There were 35 (89.7%) women and four (10.2%) men, with an age range of 30–46 years and a mean of 39.08±4.61 years. The duration of CTS ranged from 2 to 15 months with a mean of 6.69±3.29 months. Twenty-six (66.6%) of these patients had bilateral CTS and the other 13 (33.3%) had unilateral CTS. As regards severity of CTS, 39 (60%) hands were considered as mild CTS and 26 (40%) hands considered as moderate CTS. FSS score was 2.54 ±0.63 and SSS score was 3.10±0.5 for CTS patients before steroid injection.

There was a statistically significant reduction (improvement) as regards mean value of DML, DSL of median nerve, FSS score, and SSS score 1 month after the treatment in the steroid injection group ($P<0.01$). A more significant improvement in the mean DML, DSL, FSS score, and SSS score was observed in the insulin group. The results of electrophysiological studies for both groups are presented in Tables 1 and 2.

Discussion

CTS is the most commonly diagnosed and treated entrapment neuropathy and is a significant cause of morbidity. The syndrome is characterized by pain, paresthesia, and weakness in the median nerve distribution of the hand, which occurs following entrapment of the median nerve within the carpal tunnel [13].

CTS can be treated with oral analgesics, splinting, and injections with corticosteroids or surgery. A Cochrane review investigating local corticosteroid injection for CTS showed that steroid injection provides greater improvement in symptoms 1 month after injection but significant symptom relief from steroid injection beyond 1 month could not be demonstrated [6]. The risk for adverse events for steroid injection therapy for CTS has been estimated to be less than 0.1% [14]. Another Cochrane review comparing surgical to nonsurgical treatment concluded that surgical treatment of CTS relieves symptoms significantly better [15].

Steroid injections are known to be a safe and effective treatment for relieving symptoms associated with CTS. It can lead to significant improvement of both NCSs and clinical parameters. Steroids are effective at reducing swelling on account of their anti-inflammatory action. Therefore, the use of local steroid injections, which have anti-inflammatory effect, has been the cornerstone of conservative management in CTS [16].

Our study provides an evaluation comparing the use of local insulin injection as a new method of treatment versus steroid injection as a traditional method for treating idiopathic CTS.

It is believed that the most important factor in nerve compression injury is the effect of local pressure. Many studies have found changes in the microvascular structure of the nerve in the early stages of the disease [17]. It appears that increased pressure may induce a slowing of venular blood flow at the epineural level of a nerve. At higher levels of nerve compression, circulatory arrest may occur in the nerve [18]. It has been also shown that external compression of nerves may induce a deep block of axonal transport. Any condition that increases the volume of the carpal tunnel contents will compress the median nerve

Table 1 Electrophysiological studies of carpal tunnel syndrome patients before and after insulin injection

Insulin	Mean±SD		*t*-Test	
	Before	After	*t*	*P*-value
DML (ms)	4.84±0.74	4.61±0.72	2.784	<0.05
MCV (m/s)	53.57±2.14	54.04±2.26	0.542	0.537
DSL (ms)	2.88±0.27	2.55±0.19	10.866	<0.001
SSS score	3.13±0.47	2.23±0.53	20.169	<0.001
FSS score	2.50±0.60	2.07±0.55	7.635	<0.001

DML, distal motor latency; DSL, distal sensory latency; FSS score, Functional Severity Scale score; MCV, motor conduction velocity; SSS score, Symptom Severity Scale score.

Table 2 Electrophysiological studies of carpal tunnel syndrome patients before and after steroid injection

Steroids	Mean±SD		*t*-Test	
	Before	After	*t*	*P*-value
DML (ms)	5.21±0.69	5.00±0.74	2.762	<0.05
MCV (m/s)	53.57±2.12	53.60±1.96	0.179	0.858
DSL (ms)	2.78±0.25	2.70±0.20	3.115	<0.05
SSS score	3.10±0.51	2.77±0.53	6.690	<0.001
FSS score	2.54±0.63	2.51±0.70	0.450	0.654

DML, distal motor latency; DSL, distal sensory latency; FSS score, Functional Severity Scale score; MCV, motor conduction velocity; SSS score, Symptom Severity Scale score.

against the flexor retinaculum and result in distal motor and sensory dysfunction. In addition, any medication that reduces the swelling of the structures within the carpal tunnel may be effective in the treatment of CTS.

To our knowledge, no other studies have evaluated the effects of insulin injection in the treatment of CTS in nondiabetic patients. The choice of insulin injections was based on the previous published studies in treating CTS in diabetic patients [11] and on the known mechanism of action of insulin. Our study demonstrated that insulin injections produced a more significant improvement in NCV and FSS than did steroid injections. Our results were in agreement with those obtained in the study conducted by Ashraf *et al*. [11], who found a decrement in DML of the median nerves and an increment in the sensory nerve conduction velocity of the median nerve after local insulin administration in patients with type 2 diabetes mellitus and mild to moderate CTS. In addition, there was a decrease in pain, paresthesia, numbness, weakness/clumsiness, and nocturnal awaking [12].

It has been reported that peripheral nerves carry abundant receptors for insulin, NGF, and a member of the IGF-1 family [7]. It has been suggested that insulin has an effect on nerve regeneration, similar to that of NGF. All of these are thought to promote neuronal growth and regeneration, and could be important in restoring nerve function following vascular damage [8,11]. In their study, Apel *et al*. [19] found that IGF-1 improved nerve regeneration by acting on the axons and Schwann cells, and secondarily on the neuromuscular junctions.

The present study was a trial to promote median nerve regeneration by local insulin injection. The favorable findings of insulin injections in CTS suggest a role of this novel treatment for this common entrapment neuropathy even in nondiabetic patients, as insulin injections produced a more significant improvement in NCS and FSS and SSS than did steroid injection.

Recommendations

Extended follow-up of our cases treated with local insulin injection is advised to show the long-term effect of this novel treatment in nondiabetic patients. Furthermore, future short-term and long-term follow-up studies comparing insulin injection with platelets rich plasma (PRP), which also has been claimed to have nerve generation effects, are recommended to see which of them is a better treatment modality.

Conflicts of interest

There are no conflicts of interest.

References

1 Shiri R, Miranda H, Heliövaara M, Viikari-Juntura E. Physical work load factors and carpal tunnel syndrome: a population-based study. Occup Environ Med 2009; 66:368–373.

2 Huisstede BM, Randsdorp MS, Coert JH, Glerum S, van Middelkoop M, Koes BW. Carpal tunnel syndrome. Part II: effectiveness of surgical treatments – a systematic review. Arch Phys Med Rehabil 2010; 91:1005–1024.

3 Gelberman RH, Hergenroeder PT, Hargens AR, Lundborg GN, Akeson WH. The carpal tunnel syndrome. A study of carpal canal pressures. J Bone Joint Surg Am 1981; 63:380–383.

4 You H, Simmons Z, Freivalds A, Kothari MJ, Naidu SH. Relationships between clinical symptom severity scales and nerve conduction measures in carpal tunnel syndrome. Muscle Nerve 1999; 22:497–501.

5 Van Rossum J, Kamphuisen HA, Wintzen AR. Management in the carpal tunnel syndrome: clinical and electromyographical follow-up in 62 patients. Clin Neurol Neurosurg 1980; 82:169–176.

6 Marshall S, Tardif G, Ashworth N. Local corticosteroid injection for carpal tunnel syndrome. Cochrane Database Syst Rev 2007; 2: CD001554.

7 Ward JD, Tesfaye S. Pathogenesis of diabetic neuropathy. In: Pickup JC, Williams G, editors. *Textbook of diabetes*. 2nd ed. Malden, MA: Blackwell Science; 1997. 2.49.1–49. 19.

8 Singhal A, Cheng C, Sun H, Zochodne DW. Near nerve local insulin prevent conduction slowing in experimental diabetes. Brain Res 1997; 763:209–214.

9 Bland JD. A neurophysiological grading scale for carpal tunnel syndrome. Muscle Nerve 2000; 23:1280–1283.

10 Leite JC, Jerosch-Herold C, Song F. A systematic review of the psychometric properties of the Boston Carpal Tunnel Questionnaire. BMC Musculoskelet Disord 2006; 7:78.

11 Ashraf A, Yazdani AH, Mirshams S. Evaluation of the effectiveness of local insulin injection in type 2 diabetic patients with carpal tunnel syndrome. Int J Endocrinol Metab 2008; 2:95–103.

12 Gupta S, Tewari AK, Nair V, Gupta A. Reliability of motor parameters for follow-up after local steroid injection in carpal tunnel syndrome. J Neurosci Rural Pract 2013; 4:392–396.

13 Katz JN, Simmons BP. Clinical practice. Carpal tunnel syndrome. N Engl J Med 2002; 346:1807–1812.

14 Bland JD. Treatment of carpal tunnel syndrome. Muscle Nerve 2007; 36:167–171.

15 Verdugo RJ, Salinas RA, Castillo JL, Cea JG. Surgical versus non-surgical treatment for carpal tunnel syndrome. Cochrane Database Syst Rev 2008; 4:CD001552.

16 Hagebeuk EE, de Weerd AW. Clinical and electrophysiological follow-up after local steroid injection in the carpal tunnel syndrome. Clin Neurophysiol 2004; 115:1464–1468.

17 Dahlin LB, Lundborg G. The neurone and its response to peripheral nerve compression. J Hand Surg Br 1990; 15:5–10.

18 Akelman E, Weiss AP. Carpal tunnel syndrome. Etiology and endoscopic treatment. Orthop Clin North Am 1995; 26:769–778.

19 Apel PJ, Ma J, Callahan M, Northam CN, Alton TB, Sonntag WE, Li Z. Effect of locally delivered IGF-1 on nerve regeneration during aging: an experimental study in rats. Muscle Nerve 2010; 41:335–341.