

Randomized Trial

Efficacy of Hyalase Hydrodissection in the Treatment of Carpal Tunnel Syndrome: A Randomized, Double-Blind, Controlled, Clinical Trial

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Background: Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, which results from median nerve compression. A lot of nonsurgical modalities are available for the management of mild to moderate situations. Local Hyalase hydrodissection (HD) of the entrapped median nerve could offer a desirable sustained symptom alleviation.

Objectives: To evaluate the clinical efficacy of Hyalase/saline solution carpal tunnel HD on pain, functional status, and nerve conduction in patients with CTS.

Study Design: A randomized, double-blinded trial.

Setting: Anesthesia, pain, and rheumatology clinics in a university hospital.

Methods: Patients: 60 patients with CTS (> 6 months' duration). Intervention: patients were allocated equally into either group 1 (HD with Hyalase + 10 mL saline solution injection), or group 2 (HD with 10 mL saline solution only). Measurements: assessment of pain using Visual Analog Scale (VAS), functional disability (FD) score, and nerve conduction studies before injection, and over 6 months after injection. Nerve conduction parameters before injection and postinjection by the end of 3 and 6 months were evaluated as well.

Results: Statistically significant lower postinjection values of VAS (1 ± 1.8 , 2 ± 1.1 , 2 ± 1.2 , 2 ± 1.1) in group 1 versus (2 ± 1.2 , 3 ± 1.7 , 4 ± 1.5 , 5 ± 2.6) in group 2 by the end of the first week, and the first, third, and sixth months, and significantly lower FD scores (15.3 ± 1.2 , 13 ± 1.3 , 10.2 ± 1.3 , 10.2 ± 1.3) in group 1 versus (17.5 ± 1.8 , 16.6 ± 2.8 , 19.4 ± 3.2 , 21.2 ± 2.5) in group 2 during the same time intervals. Nerve conduction study parameters have shown significantly higher velocity and lower latency in the Hyalase group than in the saline solution group by the 3 and 6 month follow-up.

Limitation: We suggest a longer period could be reasonable.

Conclusions: Carpal tunnel HD with Hyalase with saline solution is considered as an efficient technique offering a rapid onset of pain relief and functional improvements, and better median nerve conduction in patients with CTS over 6 months follow-up duration.

Key words: Carpal tunnel syndrome, Hyalase, median nerve hydrodissection

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Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy, which results from median nerve compression (1). The recent American Academy of Orthopaedic Surgeons Clinical Guidelines defines CTS as a symptomatic compression neuropathy, which is characterized by decreased median nerve function at the level of the wrist because of increased pressure within the carpal tunnel (2). The incidence of CTS has been estimated to be 1 to 3 per 100 cases per year in the United States (3). CTS is associated with a significant socioeconomic burden because of its impact on productivity, function, quality of life, and significant costs associated with its management (4).

Guidelines endorsed by professional associations have suggested a trial of nonsurgical interventions for the patients with mild or moderate CTS symptoms; however, surgery could be the treatment of choice when symptoms are severe, prolonged, or unresponsive to conservative management (2). Mild to moderate CTS (5,6) can be treated by conservative interventions, such as functional braces and local infiltrations in the carpal tunnel mainly with corticosteroids (7). Despite the evident beneficial effects of local steroid injection, the side effects are not avoidable, for example atrophy of the median nerve, subcutaneous fat, and systematic complications, such as hair loss (8). However, the beneficial effects of local steroid on pain is not long enough, particularly with nonsignificant improvement of the nerve conduction (9-12). Local Hyalase hydrodissection (HD) could offer a desirable sustained effect.

Hyaluronidases are enzymes (endoglycosidases) that carry the ability to depolymerize hyaluronic acid (HA) leading to its degradation. They are licensed in the United Kingdom for enhancing permeation of subcutaneous or intramuscular injections. Their subcutaneous infusion can promote resorption of excess fluids and blood (13,14). Accordingly, we have built the hypotheses of the current study to evaluate the impact of carpal tunnel ultrasonography-guided Hyalase HD on the disability and pain produced by median nerve entrapment in patients with CTS over a period of 6 months.

The primary goal was to assess pain alleviation through the Visual Analog Scale (VAS). The secondary goals included the changes in the functional disability (FD) score, and nerve conduction studies in response to the intervention.

METHODS

This is a randomized, controlled trial. It was conducted in university hospitals and approved by the local

research ethics committee of the Faculty of Medicine, then registered at ClinicalTrials.gov (NCT03675295). It was conducted in accordance with the Declaration of Helsinki in the pain clinic and rheumatology and rehabilitation departments (electrodiagnosis unit).

The patients were recruited from an outpatient rheumatology clinic. They were complaining of CTS of at least 6 months' duration and were nonresponsive to the conservative treatment, which included vitamin B complex, nonsteroidal antiinflammatory drugs, oral steroids, and/or night splint. The patient's initial examination was based on the American Academy of Orthopaedic Surgeons Clinical Practice Guideline recommendations prior to their inclusion and confirmed by nerve conduction studies (15,16). Exclusion criteria included patients with severe CTS (distal latency to abductor pollicis brevis muscle > 6.5 ms or with absent motor or sensory potentials of the median nerve by electrophysiological study, cross-sectional area [CSA] of median nerve > 15.0 mm² by ultrasonography) according to the Karadag classification (17), previous carpal tunnel surgery, CTS due to underlying systemic causes (pregnancy, thyroid disease, diabetes mellitus, or acromegaly), or other conditions, for example, rheumatoid arthritis, osteoarthritis, gout, or psoriatic arthritis. Patients with a history of allergy to bee or wasp venom or concurrent use of antihistaminic, cortisone, or salicylates were excluded as well.

After the declaration of the research benefits and suspected side effects to the patients, the informed written consent was obtained. Randomization of the patients was done through a web-based randomizer (www.randomizer.org), in which they were equally assigned to 1 of the 2 study groups as follows: group 1 (carpal tunnel HD with Hyalase + 10 mL saline solution injection), and group 2 (carpal tunnel HD with 10 mL saline solution only). We used Hyaluronidase Injection IP (Ovine) (C-Hynidase, IndiaMART InterMESH Ltd, Uttar Pradesh, India), 1,500 IU (C-Hynidase) vial, and its powder was dissolved in 10 mL saline solution. All patients and outcome-assessing physician were kept blinded to treatment assignment during the whole study period.

Patient Assessment

At the first visit, demographic, baseline clinical and laboratory information were collected. In regard to CTS, the following data were obtained; duration, laterality, and symptoms of CTS, such as pain and its radiation, paresthesia or numbness, weakness or clumsiness

of the hand, and nocturnal awakening because of pain or tingling.

Assessment questionnaires, the Arabic version of the modified Boston Carpal Tunnel Questionnaire (FD score), was used for the evaluation of FD of the patients (18,19), in addition to VAS scale for pain grading. The severity of CTS (mild or moderate) was assessed electrophysiologically (grades 1-3) according to the Bland classification (20). The most affected side was subjected to injection in the case of bilateral involvement. Electrophysiological studies had ruled out conditions that mimic CTS mentioned in the exclusion criteria according to the report of the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation (21) using the unit 4 channels NIHON KOHDEN (Nihon Kohden America, Inc, Irvine, CA) Neuropak M1, MEB-9200EMG. The median nerve was stimulated at the wrist between the palmaris longus and flexor carpi radialis, as well as at the antecubital fossa over the area covering the brachial artery. The electrode that recorded the response was placed over the abductor pollicis brevis (motor evaluation). For sensory component evaluation, the median nerve was stimulated at the wrist (the same previous landmark), whereas the recording electrode was placed on the index finger (22).

Ultrasound-Guided HD Injection Technique

The patient was seated facing the examiner with the forearm supinated and semiflexed at 90°, and the wrist placed on the examination couch with semiextended fingers. We used MyLab 7 (Esaote, Europe BV, Maastricht, Netherlands) 10 to 19 MHz high frequency linear transducer, and a dedicated preprogrammed protocol for optimization of the parameters (depth, focal zone, frequency), and color Doppler settings for low-flow vessels. At first, the carpal tunnel was scanned to identify its contents, as well as structural abnormalities (e.g., volar ganglion cysts, flexor tendon tenosynovitis, and/or tumors) and anatomic variations (e.g., bifid median nerve, a persistent median artery, and/or anomalous muscles) that may affect the procedure. The full course of the median nerve within the carpal tunnel was evaluated in both the transverse and longitudinal scans, and with just the weight of probe and plenty of sonographic gel, gentle scanning was done without additional pressure to avoid deformation of the nerve (23).

The CSA of the median nerve was measured by tracing the inner margin of the epineurium of it at the

tunnel inlet. The severity of CTS was graded according to the CSA of median nerve as follows: 10 to 12.9 mm² as mild, 13.0 to 15 mm² as moderate, and >15 mm² as severe grade (19,20). The blood flow in the median nerve sheath was then detected 2 cm proximal to the carpal tunnel using power Doppler ultrasonography to detect nerve vascularity as one of the diagnostic tools for CTS (24,25)

Skin allergy test for Hyalase was done earlier. The injection for HD was done under complete sterile conditions. A 26-gauge needle was introduced from the lateral side toward the midline, using the in-plane approach to target the median nerve in the carpal tunnel using the ulnar approach (26). The freehand one-man technique was used by the physician who simultaneously held the syringe with one hand and the ultrasonography probe with the other hand. Ultrasonographic visualization of the needle tip was continuous, the injection was done gradually, and the needle was advanced dissecting the flexor retinaculum away from the median nerve via gradual drug infiltration (Fig. 1). Patients were observed for 10 minutes after injection for the possibility of paresthesia or bleeding. They were instructed to maintain their daily activities as usual and monitored for worsening of the paresthesia or pain during the follow-up period. Oral ibuprofen in a dose of 400 mg/day was allowed whenever the VAS score was ≥ 4 .

Data Collection

Pain and disability through the VAS, symptom severity (SS) score, and FD score at 5-time points (before injection, postinjection by the end of the first week, and the first, third, and sixth months) were assessed. Pain assessment through the VAS was explained to the patient (through selection of the number that represents his/her pain with 0 = no pain, and 10 = worst pain). Ultrasound evaluation (CSA and power Doppler) and nerve conduction parameters before injection and postinjection by the end of the third and sixth months were done as well.

Statistical Analyses

The power analysis of this study suggested has that 60 patients would be sufficient to demonstrate a relevant difference between the 2 groups in respect to the postinterventional VAS scale (to decrease at least by 20%), with 80% power, and 5% probability of type 1 error. Statistical analysis was performed through IBM SPSS Statistics version 22.0 (IBM Corporation, Armonk,

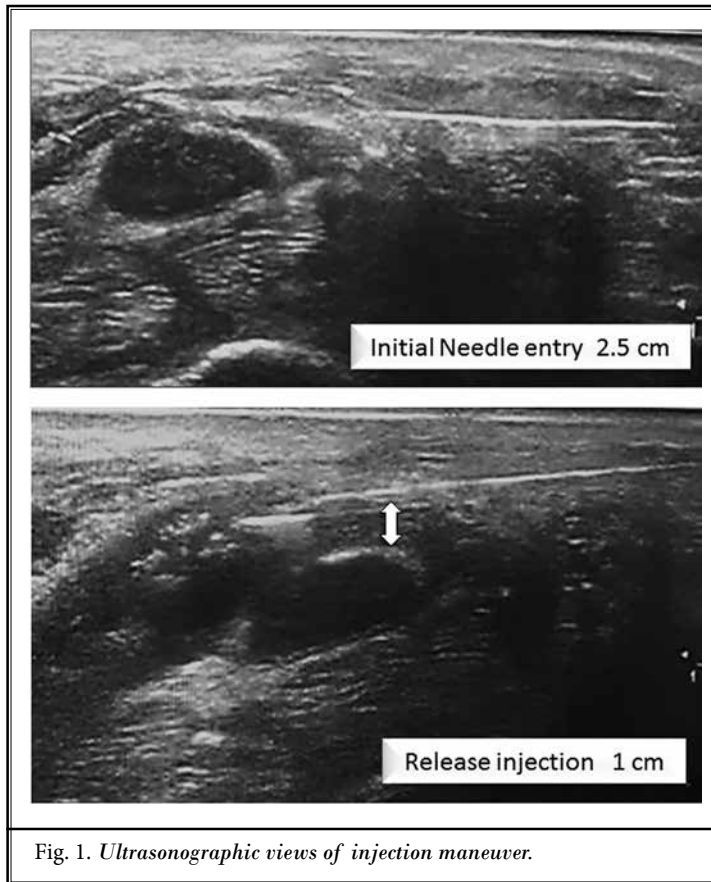


Fig. 1. Ultrasonographic views of injection maneuver.

NY). The Shapiro–Wilk test was used to assess the normality of the data distribution. Data are presented as mean \pm standard deviation, median (range) as appropriate. Continuous parametric data was compared by unpaired t test (between groups), and paired samples t test (within the group), nonparametric data compared by the Mann–Whitney U test (between groups), and by the Wilcoxon rank-sum test (within the group). Categorical data were presented as numbers (%) and compared through the chi-square test or the Fisher exact test as appropriate. A 2-tailed $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-two patients were included in this study and equally randomized into the 2 groups as shown in the CONSORT flow chart (Fig. 2). The 2 groups were comparable in regard to their demographic and clinical data, with insignificant differences in-between (Table 1).

The pain VAS scores were significantly decreased by the first week after injection in both groups; however, the VAS score was significantly lower in the Hyalase group than in the

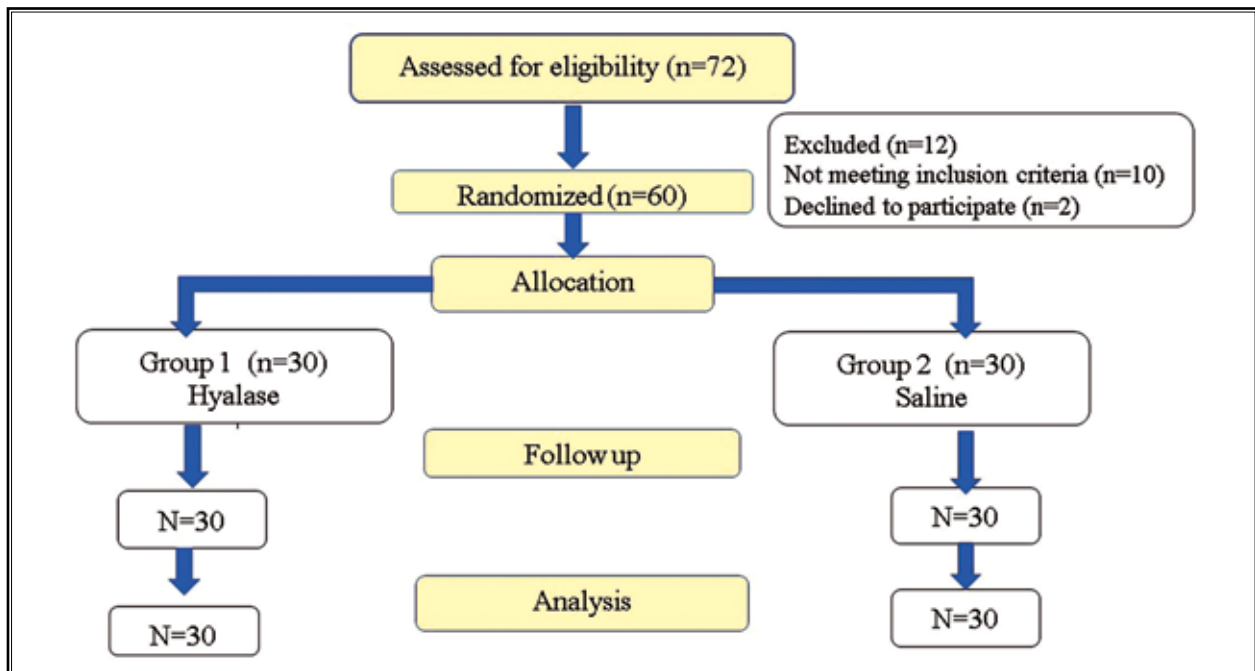


Fig. 2. CONSORT flow chart of the patients.

Table 1. Demographic and clinical characteristics of the patients.

Variables	Group 1 (Hyalase) n = 30	Group 2 (saline solution) n = 30	P value
Age (years)	40.7 ± 6.5	38.3 ± 5.4	0.1
Gender (female/male)	17/13	17/13	0.7
Duration of CTS (months)	8.5 ± 2.6	8.5 ± 2.1	0.9
Clinical characteristics			
Paresthesia	30 (100%)	30 (100%)	1
Weakness	17 (56.6%)	18 (60%)	0.79
Night awakening	27 (90%)	27 (90%)	1
Tingling and numbness	29 (96.6%)	29 (96.6%)	1
Forearm pain	24 (80%)	24 (80%)	1
Hypoesthesia	15 (50%)	17 (56.6%)	0.6
Hyperesthesia	11 (36.7%)	11 (36.6%)	1
Positive Tinel sign	20 (66.7%)	18 (60%)	0.59
Positive Phalen test	22 (73.3%)	26 (86.6%)	0.19
Positive reversed Phalen	19 (63.3%)	19 (63.3%)	1

Data are presented as mean ± standard deviation, ratio, or numbers (percentage). *P* < 0.05 is considered statistically significant.

saline solution only group during the whole follow-up period up to 6 months. VAS score has also demonstrated significant decreases in comparison to its basal value in each group over the 6 months (Table 2).

The severity of symptoms and functional status revealed significant differences between both groups during the follow-up period, with significantly lower values in the Hyalase group than in the saline solution only group. There was significant improvement within each group in comparison to the preinjection value in regard to the severity of symptoms and functional status up to the 3 months. The values of SS and FD scores continued to decrease (improve) significantly in the Hyalase group only up to 6 months. The severity of symptoms and functional status of the Boston assessment questionnaire started to increase again by 6 months in the saline solution group to show values with insignificant differences with their basal values (Table 2).

In regard to nerve conduction studies (distal motor latency, peak sensory latency, and sensory nerve conduction velocity), all have demonstrated significantly higher velocity and lower latency in the Hyalase group than in the saline solution group by the 3 and 6 month follow-up. Nerve conduction study values have revealed significant improvement in comparison to the preinjection values within each group, except the third month distal motor latency in the Hyalase group (Table 3).

The median nerve CSA in the Hyalase group showed a

Table 2. Baseline and follow-up of pain VAS and clinical scores.

Variables	Group 1 (Hyalase) n = 30	Group 2 (saline solution) n = 30	P value
VAS score			
Before injection	7 (5-10) 7 ± 1.5	7 (5-10) 7 ± 2	0.7
Week 1	1 (0-4)* 1 ± 1.8	2 (0-6)* 2 ± 1.2	0.05
Month 1	2 (0-4)* 2 ± 1.1	3 (1-6)* 3 ± 1.7	0.05
Month 3	2 (0-5)* 2 ± 1.2	4 (1-7)* 4 ± 1.5	0.001
Month 6	2 (0-5)* 2 ± 1.1	5 (3-7)* 5 ± 2.6	0.001
SS score			
Before injection	31 (17-38) 28.8 ± 5.2	32 (18-37) 29.9 ± 4.5	0.1
Week 1	20 (13-27)* 19.8 ± 3.5	22 (15-30)* 22.4 ± 3.8	0.05
Month 1	20 (12-27)* 19.2 ± 3.8	24 (16-30)* 23.5 ± 3.2	0.001
Month 3	18 (11-28)* 15.9 ± 3.5	26 (15-32)* 26.4 ± 3.1	0.001
Month 6	15 (11-28)* 14.9 ± 3.3	29 (16-35) 29.6 ± 3.5	0.001
FD score			
Before injection	20 (17-25) 20.3 ± 2.3	20 (16-24) 19.8 ± 2.2	0.7
Week 1	15 (14-18)* 15.3 ± 1.2	18 (14-20)* 17.5 ± 1.8	0.01
Month 1	13 (11-16)* 13 ± 1.3	16 (12-22)* 16.6 ± 2.8	0.05
Month 3	10 (8-14)* 10.2 ± 1.3	17 (15-25)* 19.4 ± 3.2	0.001
Month 6	10 (8-14)* 10.2 ± 1.3	20 (15-25) 21.2 ± 2.5	0.001

Data are presented as median and range, mean ± standard deviation. (*) significant difference in comparison to basal value within the same group. *P* < 0.05 is considered statistically significant.

significant decrease in comparison to the saline solution group by the end of 3 and 6 month follow-up. It has also demonstrated significant decrease in comparison to the pretreatment CSA in Hyalase group only (Fig. 3).

The number of patients who showed a positive power Doppler effect significantly decreased in each group (completely disappeared in Hy-

alase group). There was a significant difference between the groups in regard to the number of patients by the sixth month, in which the number of patients who revealed positive power Doppler had increased up to 6 patients in the saline solution group (Table 3).

In regard to analgesia consumption, the saline solution group showed that 15 patients required ibuprofen versus 2 patients in the Hyalase group ($P < 0.001$) in the third month, and 20 patients in the saline solution group versus 3 in the Hyalase group in the sixth month ($P < 0.001$).

DISCUSSION

In this study, carpal tunnel HD was done using Hyalase/saline solution or saline solution only in patients with mild to moderate CTS. To our knowledge, this is the first prospective trial to explore the efficacy of HD using Hyalase injection for such group of patients. The results have demonstrated that Hyalase HD has more significantly reduced pain severity and disability, in conjunction with improved nerve conduction parameters and CSA of the median nerve, when compared with saline solution only HD.

We found considerable improvement in VAS score, the severity of symptoms, and functional status of the Boston questionnaire and electrodiagnostic parameters in the Hyalase group after 3 months of treatment and up to 6 months. In the saline solution HD group, clear changes in VAS score and symptoms severity of the Boston questionnaire were seen during the early 3 months; however, the pain and disability symptoms started to increase again after the third month to figures lower than preinjection val-

ues. This can reveal the valuable effect of nerve liberation through HD even with saline solution only.

Considering the SS score based on the Boston questionnaire, which is a self-administered and well-recognized validated outcome instrument specific for CTS (18,19), the improvement was observed early. The improvement in the FD was sustained up to 6 months in the Hyalase group only.

The pathophysiology of CTS has not been completely elucidated. Increased pressure within the carpal tunnel is a proposed mechanism, which could be due to fibrosis of connective tissue and subsynovial area of the median nerve, increased volume inside the carpal tunnel, as well as flexor tendon synovial connective tissue adhesion around the median nerve. Hydro dissection itself may release the adhesions; hence liberating the nerve from the surrounding tissues (27,28).

The term hydrodissection has become common in the descriptions of ultrasound-guided carpal tunnel injections and described recently as being a useful technique for disrupting adhesions, especially when combined with multiple needle fenestration of the transverse carpal ligament in an attempt to weaken it (29). Evers et al (30) demonstrated that infiltration of saline solution only into the carpal tunnel can reduce the resistance to longitudinal sliding of the median nerve, and this can explain the improvement in pain, SS, and functional status we found in the saline solution group. Smith et al (26) described ultrasound-guided HD of the carpal tunnel to be a familiar procedure of CTS corticosteroid injection. They mentioned that

Table 3. Baseline and follow-up of nerve conduction study, and positive power Doppler in both groups.

Variables	Group 1 (Hyalase) n = 30	Group 2 (saline solution) n = 30	P
Distal motor latency (m/s)			
Before injection	4.7 ± 0.7	4.8 ± 0.6	0.2
month 3	4.4 ± 0.66*	4.8 ± 0.93	0.05
month 6	4.1 ± 0.52*	5.1 ± 0.64*	0.001
Peak sensory latency (m/s)			
Before injection	4.1 ± 0.7	4.2 ± 0.7	0.6
Month 3	3.68 ± 0.4*	3.8 ± 1.0*	0.05
Month 6	3.42 ± 0.3*	3.9 ± 2.1*	0.05
Sensory nerve conduction velocity (m/s)			
Before injection	37.3 ± 6.5	36.5 ± 5.3	0.9
Month 3	44.3 ± 5.5*	40.0 ± 1.1*	0.001
Month 6	44.9 ± 6.3*	39.3 ± 2.3*	0.001
Positive power Doppler			
Before injection	12 (40%)	11 (36.6%)	0.8
After month 3	0 (0.0%)*	4 (13.3%)*	0.1
After month 6	0 (0%)*	6 (20%)*	0.05

Data are presented as mean ± standard deviation or number (percentage). (*) significant change in comparison to the basal value within the same group. $P < 0.05$ is considered statistically significant

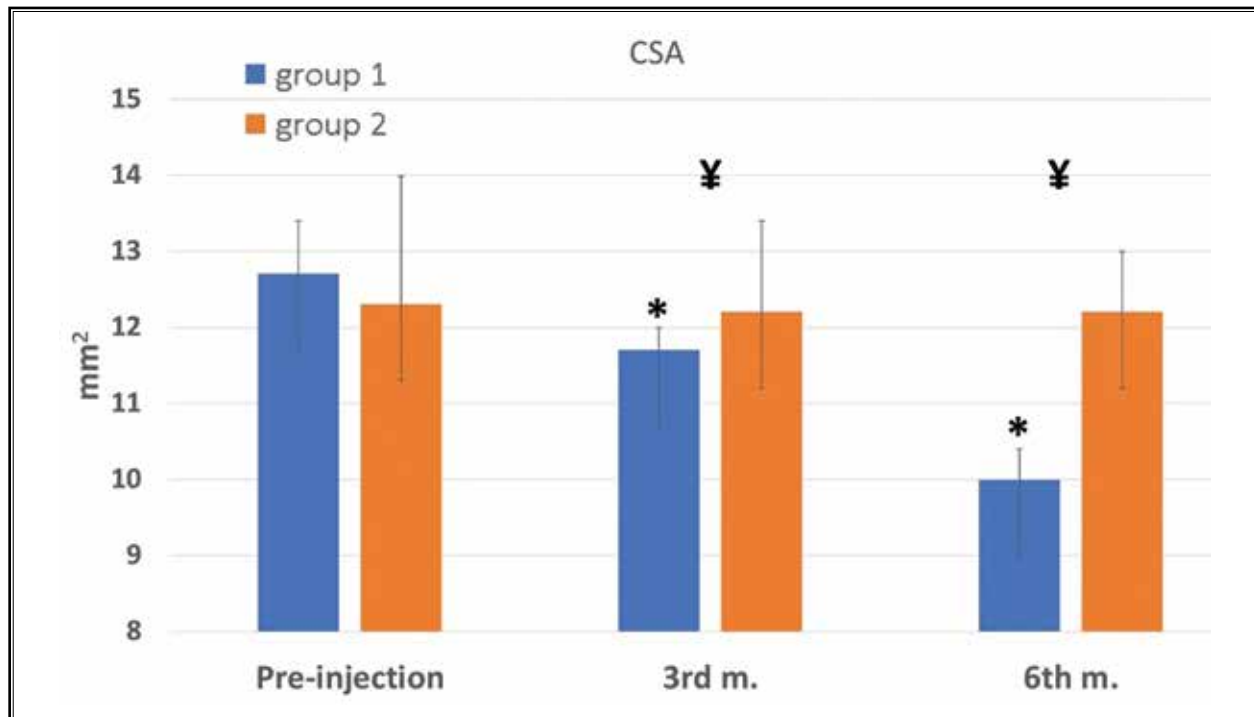


Fig. 3. CSA changes of the median nerve during the study period. Data are plotted as mean \pm standard deviation. (*) significant change in comparison to baseline value, (¥) significant difference between the groups. $P < 0.05$ is considered statistically significant.

the needle can be inserted from the ulnar border of the wrist transversely into the carpal tunnel. The authors speculated that the infiltration of injectate between the median nerve and transverse carpal ligament, as well as the underlying tendons, may disrupt adhesions. The Salman Roghani et al (31) study noted that HD of the carpal tunnel in elderly patients with CTS using saline solution and lidocaine has shown significant improvement in such group of patients, and is as effective as a low- or high-dose local steroid injection. The effect was evaluated through the pain VAS, Boston Carpal Tunnel Questionnaire, median nerve motor and sensory nerve conduction, and its sonographic inlet CSA, and our results agree with this in regard to the saline solution HD group (31). Hwang et al (32) published a case study in which both longitudinal and transverse (in correlation to the median nerve) needle insertions to create fenestrations has been done and revealed early symptom relief by the second week, and 50% improvement with sustained effect up to 3 months.

HA is anchored to the extracellular surface and acts as a scaffold to maintain molecules and proteins, and this supports the cellular viability in close proximity to

the surface (33). HA can influence the neurotransmission and signaling; thus manipulation of HA might have consequences for neuronal viability (34). However, multiple signals within the microenvironments of demyelinating lesions contribute to the failure of oligodendrocyte progenitor cell (OPC) maturation and remyelination. It has been previously found that high molecular weight (HMW) forms of the glycosaminoglycan hyaluronan (HA) are among these signals. Glycosaminoglycan hyaluronan is synthesized by transmembrane synthases and is composed of multiple disaccharide units of glucuronic acid and N-acetylglucosamine (35,36). Previous animal studies reported that HMW HA can accumulate in the demyelinating lesions, and this can prevent OPC maturation and remyelination; indeed HA and HA receptors, including CD44 and TLR2, are elevated coincidentally with astrogliosis following a variety of central nervous system insults, including demyelinating lesions in patients with multiple sclerosis (37,38).

We suggested that the strategy of using hyaluronidases can promote remyelination within the demyelinating lesions through the degradation of accumulated HA. Jiang et al (39) mentioned that during

inflammatory responses outside the central nervous system, activated fibroblasts or other cells, which secrete hyaluronidases that degrade HA, can be considered as immune regulators.

We believe that the improvement in symptoms and nerve CSA, as well as nerve conduction studies, which were noticed in our results could not be limited to the well-known benefits of HD only, but to the evident beneficial effects of Hyalase on the perineural matrix through adhesiolysis, as well as nerve remyelination enhancement.

Electrodiagnostic studies of the median nerve can provide a reliable measure to document neuropathy at the wrist, and therefore contribute to the diagnosis and follow-up treatment of CTS (40). Doppler ultrasound is also a well-established diagnostic test for the presence of hyperemia in the perineural area of the median nerve and can be correlated with the severity of CTS (41). El Miedany et al (42) noted that ultrasonographic

Doppler signal that reflects the neural vasculature is inversely correlated with severity of the CTS. Our results agree with such facts, in which improvement of power Doppler signal and the median nerve CSA after HD in both groups were noticed.

Limitations

The follow-up period was only 6 months, and we suggest a longer period up to 12 months could be reasonable. It would be useful to compare hyaluronidase versus cross-linked HA products in further studies.

CONCLUSIONS

Carpal tunnel HD technique using Hyalase with saline solution can be considered as an effective option offering rapid response and sustained duration of pain relief in patients with CTS. Local Hyalase injection has offered improvements in the functions, and nerve conduction studies.

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