Randomized Trial

Intra-Carpal Injection of Ozone versus Methylprednisolone in Carpal Tunnel Syndrome of Systemic Sclerosis Patients: A Randomized Single-Blind Clinical Trial

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Background: Carpal tunnel syndrome (CTS) is the most entrapment syndrome in general and is the most frequent peripheral nervous system involvement in systemic sclerosis (SSc). Local injection of steroid hydrodissection or ozone-oxygen showed favourable outcome in CTS in general.

Objectives: To compare the clinical efficacy of ozone versus methylprednisolone intracarpal injection upon pain, functional status, and nerve conduction in patients with CTS due to SSc.

Study Design: A randomized single-blinded trial.

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

Methods: Fifty CTS patients with > 3 months duration of SSc were equally randomized into either group O (injection of ozone/oxygen 25 µg/mL in 20 mL) or group M (methylprednisolone acetate 40mg, and 40 mg lidocaine in 20 mL). Visual analog scale (VAS) was measured pre-injection, then re-evaluated post-injection at 4 time points (1 week, 1 month, 3 months , and 6 months); Cochin Hand Function Scale (CHFS); and a median nerve electrophysiologic study was done before injection, then by the end of 3 months and 6 months.

Results: VAS was significantly lower in group M after 1 week (P = 0.01). Group O showed significantly lower VAS after 3 and 6 month (P < 0.001). Additionally, there was a significant decrease in the VAS during the whole study period within each group, in comparison to its baseline value. CHFS was significantly lower in the ozone group after 6 months (P < 0.001). The sixth month's sensory conduction was significantly higher in group O (P = 0.002). The motor distal latency was significantly lower in the ozone group after 3 and 6 months (P < 0.001).

Limitations: Follow-up period could be furtherly extended.

Conclusion: Both intracarpal ozone or methylprednisolone afford favorable effects upon CTS in patients with SSc. However, ozone alleviates pain much more, enhances the hand functional status, and improves median nerve conduction in study with over six months duration.

Key words: Carpal Tunnel Syndrome, systemic sclerosis, methylprednisolone, ozone

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Systemic sclerosis (SSc) is an immune-mediated, rheumatic disease that is characterized by fibrosis of the skin and internal organs and vasculopathy (1). Carpal tunnel syndrome (CTS) is the most entrapment syndrome in general, and the most frequent peripheral nervous system involvement in SSc (2). There are many additional risk factors for the development of CTS, including: forceful hand exertion, family history, hypothyroidism, diabetes mellitus, pregnancy, obesity, and other connective tissue diseases (3).

Over 80% of persons suffering from CTS have a positive response to conservative treatments, which include splinting, therapeutic ultrasound, yoga, and oral corticosteroids. However, there is a high incidence of symptoms recurrence within 1 year. Surgical intervention is considered when there is minimal response or deterioration despite conservative therapies (3-5)

One of the novel modalities is the local injection of ozone in some patients complaining of CTS (6). Ozone is well known to have anti-inflammatory and analgesic effects through the inhibition of pro-inflammatory mediators, as well as stimulation of anti-inflammatory mediators' release (7).

The comparison between local ozone versus methylprednisolone in CTS patients due to SSc was our rationale for this study.

The primary goal was a comparison of pain visual analog scale (VAS) between the 2 groups of patients over 6 months duration.

Secondary goals included the difference of Cochin Hand Function Scale (CHFS) (8), the change of ulcer size, and Raynaud's attacks between 2 groups.

Methods

This is a prospective randomized clinical trial study. It was evaluated and approved by our institutional ethical review board (IRB17300356) and registered in clinicaltrials.gov under the number of (NCT03742466 masked). The study was run with adherence to the Declaration Helsinki (9).

Fifty adult patients with CTS (confirmed by electrophysiologic study) due to scleroderma over more than 3 months duration aged 20-60 years old were enrolled from outpatient rheumatology and anesthesia and pain clinics. We obtained informed consent from all patients, who were then randomized through a computer-based randomization table into 2 groups in a ratio of 1:1 (Ozone group O, and steroid group M). In the case of bilateral affection, we selected the side which was more affected regarding the complaint.

SSc diagnosis was confirmed through the clinical picture and autoantibodies markers (Subsets of SSc) (10). The participants were complaining of CTS and non-responders to the conservative treatment e.g., nonsteroidal anti-inflammatory drugs, oral steroids, and/or night splint. The examination for CTS was established and based upon the American Academy of Orthopaedic Surgeons Clinical Practice Guideline recommendations before enrollment and confirmed by an electrodiagnostic study by an experienced physiatrist (11,12). The modified Rodnan skin score (MRSS) was also included (13)

Exclusion criteria included previous surgery for CTS or recent injection on the side of the study, coagulopathy, uncontrolled diabetes during the last 3 months, polyneuropathy, sever CTS (distal latency to abductor policies breves muscle > 6.5 milliseconds or with absent motor or sensory potentials of the median nerve by electrophysiological study, cross-sectional area (CSA) of median nerve > 15.0 mm^2 by ultrasonography), CTS due to pregnancy, acromegaly, thyroid dysfunction, or another systemic disease such as rheumatoid arthritis, gout, psoriatic arthritis, etc. Presence of any contraindication for ozone injection eg pregnancy, glucose-6 phosphate dehydrogenase deficiency, thyroid dysfunction, thrombocytopenia, unstable cardiovascular disease with the uptake of angiotensin-converting enzyme inhibitors (14) excluded the patient as well.

The patients were seated and the area of injection was prepared with antiseptic. Maintenance of ultrasonography probe sterility was also guaranteed using a sterile barrier. The forearm was kept supinated and the wrist in a palm-up position. Under sonographic guidance, the flexor retinaculum was visualized as hyperechoic structure across the scaphoid and pisiform bones. The median nerve was visualized just under the flexor retinaculum. The injection was done through the ulnar approach using a 23-G needle. The entry from the ulnar side begins from skin to subcutaneous layer superficially to ulnar artery (identified by Doppler) and ulnar nerve. The needle then pierced the flexor retinaculum until its tip reached just beyond the median nerve, (15,16) then injection was done. Ozone group (O): Intracarpal injection of ozone/oxygen mixture (20 mL, 25µg/mL) was performed. Steroid Group (M): Intracarpal injection of methylprednisolone acetate 40 mg, and 40 mg lidocaine (20 mL total volume). Patients were allowed to administer acetaminophen, in the case of possible post-injection discomfort or pain during the first 48 hours.

Data collection was done by a physician who was

blinded to the grouping. The initial pain visual analog scale (VAS) pre-injection, then re-evaluated post-injection at 4-time points (1 week, 1 month, 3 months, and 6 months). Raynaud's attack frequency and duration, ulcer size and its VAS pain, CHFS, and median nerve electrophysiologic study were assessed before injection, then by the end of 3 months and 6 months.

Statistical Analysis

Sample size calculation was guided by previous studies (6,17). We enrolled 50 patients for compensation of any drop out of patients during the study period. Data are presented as mean ± standard deviation, standard error or median (interquartile range), and or number (percentage) as appropriate. Data were firstly tested by the Shapiro-Wilk test for parametricity. Parametric data were compared by the unpaired t-test, whereas nonparametric data by the Mann Whiney U-test. Comparison of data changes regarding their baseline values within the group was done by Wilcoxon rank test for nonparametric data and paired t-test for parametric data. $P < 0.05$ is considered statistically significant. Data were analyzed through the computer program IBM, Statistical Package for Social Sciences, (SPSS) Version 22, 2015.

Results

Both groups were comparable regarding their demographic data, subsets of SSc, and its autoantibodies markers with insignificant differences between the 2 groups (Fig.1, Table1).

The primary outcome (hand VAS scale) was significantly lower in Group M after the 1 week than Group O. Group O showed significantly lower VAS after the 3 months and 6 months. Additionally, there was significant improvement (decrease) of the VAS, during the whole study period, within each group in comparison to its baseline value (Table 2).

CHFS was significantly lower in the ozone group after 6 months; otherwise, both groups showed significant improvement during the follow-up period (Table 2).

Raynaud's attacks frequency and duration were significantly lower in the ozone group after 3 months

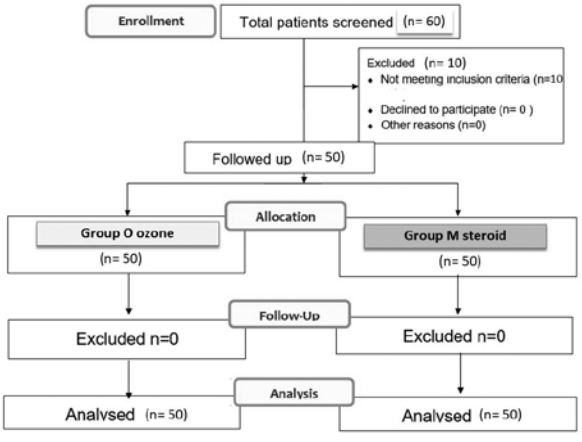

Fig. 1. *CONSORT flow chart of the participants*

Table 1. *Demographic and clinical data in the studied groups*

Variables	Group O Ozone (n = 25)	Group M Steroid (n = 25)	*P* value
Age years	41.4 ± 12.7	38 ± 12.5	0.36
Onset in years of 1st Raynaud's (years) 1st non-Raynaud's phenomenon (years)	 7.7 ± 1.2 6 ± 1.2	 8.3 ± 1 6.4 ± 1	 0.51 0.78
MRSS (modified Rodnan skin score)	13(5.5)	13(5.5)	0.25
Subsets of SSc according to Le Roy Diffuse Limited	 12 (48%) 13 (52%)	 8 (32%) 17 (68%)	0.38
SSc marker autoantibodies ana aca ana/scl 70 scl70 all	 4 (16%) 7 (28%) 7 (28%) 7 (28%) 0(0%)	 4(16%) 3 (12%) 7 (28%) 9 (36%) 2 (8%)	0.43

Data are presented as mean ± standard deviation or standard error, median (interquartile range), or number (percentage%). SSc systemic sclerosis. $P < 0.05$ is considered statistically significant.

Table 2. *Hand VAS pain and Cochin function scale in the studied groups*

Variables	Group O Ozone (n = 25)	Group M Steroid (n = 25)	*P* value
VAS of hand pain			
Pre-injection	80(11)	77(8)	0.06
After 1 week	60(12.5) ¥	55(10) ¥	0.01
After 1 month	50(12.5) ¥	50(20) ¥	0.38
After 3 months	42(12) ¥	60(20) ¥	< 0.001
After 6 months	35(12) ¥	60(20) ¥	< 0.001
Cochin Hand Function Scale (CHFS)			
Pre-injection	55(38)	55(27)	0.86
After 3 months	40(30) ¥	44(29) ¥	0.34
After 6 months	30(25) ¥	50(17.5) ¥	< 0.001

Data are presented as median (interquartile range). (¥) significant change from the baseline value. $P < 0.05$ is considered statistically significant.

and 6 months. The ulcer size and its VAS pain scale were significantly lower in the ozone group than the steroid group after 3 months and 6 months (Table 3).

Median nerve cross-sectional area was significantly smaller and the sensory conduction was significantly higher in the ozone group at 6 months. Motor conduction showed insignificant differences between both groups; however, the motor distal latency was significantly lower in the ozone group after 3 months and 6 months. All the nerve study data showed significant improvement in comparison to the baseline value in each group except for the motor distal latency in the steroid group.

Discussion

In this study, CTS in systemic SSc patients was treated with a local intracarpal injection of ozone or methylprednisolone. According to our knowledge, this is the first trial to compare the efficacy of both interventions in such a group of patients.

We found significant improvement in VAS pain of CTS, improvement of the CHFS, Raynaud's frequency and duration, and ulcer size and pain VAS score in patients treated with ozone after 3 months of treatment continuing up to 6 months. Improvement with the ozone group was more significant than the steroid group. However, both groups showed significant improvement of the previously mentioned data, in comparison to the baseline value.

The CHFS was chosen for the present study because of its validity and reliability, which have already been established in the international literature (8). We also choose the CHFS because the questions in it are shorter and required less time to complete (18,19).

Our findings were matched with Bahrami, et al, who enrolled 40 patients with CTS into 2 groups. The patients were equally randomized either to receive local ozone injection in one group, versus wrist splinting in the other group (6). The severity of symptoms and functional status as well as nerve conduction showed more statistically significant improvement in the ozone injection patients.

Our study results are also in agreement with Zambello, et al, study where they estimated the efficacy of ozone injection in 112 CTS patients, who received a local injection of an oxygen-ozone mixture (2–3 mL with 10 ug/mL concentration) twice per week for 5 conse-

Table 3. *Raynaud's attacks and ulcer clinical data in the studied groups*

Variables	Group O Ozone (n = 25)	Group M Steroid (n = 25)	*P* value
Raynaud's frequency / day			
Pre-injection	3 (2)	3(2)	0.70
After 3 months	2(1)¥	2(1) ¥	0.002
After 6 months	1(1.5) ¥	2 (1) ¥	< 0.001
Raynaud's duration treatment (minutes)			
Pre-injection	11±0.8	12±0.76	0.21
After 3 months	5±0.58¥	9.8±0.74¥	< 0.001
After 6 months	3.8±0.43¥	9.8±0.73¥	< 0.001
VAS of ulcer pain			
Pre-injection	70(10)	70(10)	0.37
After 3 months	41(12) ¥	72(15) ¥	< 0.001
After 6 months	20(30) ¥	72(15) ¥	< 0.001
Ulcer size in mm			
Pre-injection	3.7 ± 0.18	5 ± 0.88	0.01
After 3 months	0.76 ± 0.07¥	2.5 ± 0.18¥	< 0.001
After 6 months	0.44 ± 0.09¥	2.46 ± 0.18¥	< 0.001

Data are presented as median (interquartile range) or mean± standard error. (¥) significant change from the baseline value. $P < 0.05$ is considered statistically significant.

Table 4. *Median nerve study in the studied groups*

Variables	Group O Ozone (n = 25)	Group M Steroid (n = 25)	*P* value
Cross-sectional area			
Pre-injection	15.6 ± 3.2	16.7 ± 3	0.26
After 3 months	11.4 ± 1¥	11.5 ± 0.2¥	0.92
After 6 months	11.4 ± 1¥	12.6 ± 1.4¥	0.002
Sensory conduction velocity			
Pre-injection	30 ± 9	29.8 ± 9.7	0.28
After 3 months	36 ± 6.3¥	37.3 ± 6.7¥	0.49
After 6 months	41.2 ± 3.9¥	36 ± 5.8¥	0.002
Motor conduction velocity			
Pre-injection	47.7±7.6	49±6.7	0.46
After 3 months	52.3±5.9¥	49.7±4.6¥	0.09
After 6 months	51.4±6¥	48.3±4.6¥	0.45
Motor distal latency			
Pre-injection	4 ± 1	4.4 ± 1	0.28
After 3 months	3.2 ± 1¥	4.2 ± 0.96	0.001
After 6 months	3.2 ± 1¥	4.2 ± 0.93	0.001
Latency of sympathetic skin response			
re-injection	1736 ± 77	1728 ± 66	0.7
After 3 months	1539 ± 72¥	1716 ± 71¥	< 0.001
After 6 months	1538 ± 73¥	1716 ± 71¥	< 0.001

Data are presented as mean± standard deviation. (¥) significant change from the baseline value. $P < 0.05$ is considered statistically significant.

quent weeks, then 2 more injections at a 2 week interval. The outcome was patient-reported, and consisted of 4 qualitative grades: "excellent, good, satisfactory, and absent". There were remarkable short-term results in the form of pain reduction at the level of excellent/good (90% immediately post-injection), and this result was almost maintained at long-term follow-up after 1 year (87%). However, 6% of patients showed absent efficacy and underwent surgical release (20).

We assume that the noticeable improvement of pain VAS, as well as Raynaud's frequency and duration, is based upon the well-evidenced favourable ozone molecule biological properties. Ozone molecule has as anti-inflammatory, analgesic, anti-oxidant, immune-modulatory effect, and increases blood supply (20). Ozone therapy induces tissue hyperoxygenation and has become an effective treatment tool for musculoskeletal disorders (21). Local injection of ozone is already used as a therapeutic choice in musculoskeletal conditions. Ozone therapy has been used in the management of patients with knee osteoarthritis, back pain, myofascial pain syndrome tendinitis, and tendon injuries (22-26).

Additionally, local ozone treatment acts by 3 mechanisms that are participated in the treatment of spinal disc herniation. Firstly, ozone increases oxygenation trans and intra-tissue and reduces hypoxia and lymphatic stasis, leading to indirect vessel-mediated decompression of the nerve roots. Second, by increasing immunosuppressive cytokines and proteinase through macrophages, leading to inhibition of release of polymorphonucleates through action on the cell-mediated inflammatory. Finally, ozone inhibits the release of pro-inflammatory bradykinins and prostaglandins (27).

On the other hand, the role of local steroid injection in the form of a single shot was revealed in a study done by Evers and coworkers. Follow-up period reached 7.4 years and 32% of patients did not require any further intervention (28). Another study, done by Delea and colleagues, showed that hydrodissection of the carpal tunnel followed by corticosteroid significantly reduced pain scores by 67% in CTS associated with scleroderma ($P < 0.001$) (29).

We have kept an eye upon median nerve conduction because it is well established that the diagnosis of CTS mainly depends on clinical symptoms and diagnostic tests. Electrodiagnostic studies and ultrasonography are used to confirm the diagnosis and determine the extent of involvement (30). According to the American Academy of Orthopaedic Surgeons 2016, nerve conduction study can contribute to diagnosis and treatment follow-up in of CTS (2). Follow-up of median nerve sensory conduction velocity in this study showed significant improvement at 6 month follow-up in patients injected with ozone, compared to those injected with the corticosteroid. Moreover, motor distal latency and latency of sympathetic skin response evaluation after 3 and 6 months were significantly more favorable in the ozone group, while there was no significant difference in motor conduction velocity between both.

The nature and extent of peripheral neuropathy in SSc are not clear. Systemic sclerosis has been shown to affect the conduction of median nerve; however, patients' symptoms may not improve after surgical intervention, and this suggests that symptoms may occur owing to compression of the nerve itself or nerve fascicles (caused by connective tissue proliferation of peri- and endoneurium) or vas nervorum microangiopathy (31-33).

In regard to effects of local ozone injection upon the median nerve conduction, Rascaroli, et al, included 35 patients with idiopathic CTS. They received a local injection of an oxygen-ozone mixture (4 mL with 10 ug/mL concentration) twice per week, for a total of 8 sessions. They found a slight statistical improvement in sensory and motor parameters after treating patients of CTS with ozone treatment (34). Bahrami, et al, study showed significant improvement of sensory nerve action potential and median sensory nerve action potential latency, compared to the pre-treatment level in both groups (one group treated with wrist volar splint alone, the other group treated with ozone injection and splint) (6).

Limitations

Follow-up period could be extended. Analgesic consumption was not recorded.

Conclusion

Both intracarpal ozone or methylprednisolone afforded favorable effects upon symptoms of CTS in patients with SSC; however, ozone alleviates pain, enhances the hand functional status, decreases the duration and frequency of Raynaud's attacks, declines the size of ulceration, and improves median nerve conduction study over 6 month duration.

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