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Original Article

Local ozone injection compared to local glucocorticoid injection in carpal tunnel syndrome: A randomized controlled trial

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ABSTRACT

Objectives: This study aimed to compare the effectiveness of local ozone (O_3) injection versus corticosteroid injection in the treatment of mild to moderate carpal tunnel syndrome (CTS).

Patients and methods: This double-blind randomized controlled trial was performed on 42 patients (9 males, 33 females; mean age: 46.7±2.1 years; range, 18 to 70 years) with mild to moderate CTS between May 2021 and June 2021. The corticosteroid group (n=21) was injected with 40 mg triamcinolone, and in the O_3 group B (n=21), 4 mL of a 10 mcg/mL oxygen (O_2)-O_3 mixture was injected. Symptom severity and functional impairments were assessed using a Visual Analog Scale and Boston Carpal Tunnel Questionnaire. Electrodiagnostic and ultrasonographic parameters were obtained at baseline and eight weeks after the procedure.

Results: The O_2-O_3 solution improved pain and Boston Carpal Tunnel Questionnaire score after eight weeks ($p<0.001$); however, the change was nonsignificant compared to the corticosteroid group ($p>0.05$). Sensory nerve and compound muscle action potential latencies were not significantly changed eight weeks after O_2-O_3 injection ($p>0.05$), while both were significantly decreased in the steroid injection group ($p<0.001$). Volar bulging and median nerve cross-section surface area were not improved after O_2-O_3 injection, while the improvement was significant in the corticosteroid arm ($p=0.02$).

Conclusion: Symptoms in patients with mild to moderate CTS may be alleviated by local O_2-O_3 injection; however, electrodiagnostic and ultrasonographic indices may be unchanged. Corticosteroid local injection may alleviate patient symptoms along with electrodiagnostic and ultrasonographic parameters.

Keywords: Carpal tunnel syndrome, corticosteroid, ozone.

Carpal tunnel syndrome (CTS), the most common entrapment neuropathy, is a condition that causes pain, numbness, and tingling in the hand and arm.[1] The carpal tunnel is a small space in the wrist that houses the median nerve and tendons within the flexor retinaculum. This nerve provides feeling to its distribution, mainly in the thumb and the second, third, and radial sides of the fourth finger. Symptoms occur as the nerve travels through the wrist. There are risk factors associated with this condition, namely pregnancy, obesity, monotonous wrist activities, and rheumatoid inflammation.[2] Carpal tunnel syndrome occurs when the median nerve is compressed. This compression usually happens due to inflammation or swelling.[2] The carpal tunnel is a narrow space, and therefore, even a small amount of tissue swelling can cause the median nerve to be compressed.[3]

This condition occurs in females at a rate of 5.8%, while males are less involved (0.6%).[3] Annually, one to three per 100 individuals are diagnosed with CTS. Carpal tunnel syndrome is often caused by repetitive wrist and hand motion. This repeated motion can be from activities such as typing, knitting, painting, or using hand tools. Other causes include pregnancy, arthritis, and diabetes.[2,4-6] Smoking remains a controversial risk factor, as there are paradoxical reports. However, recent meta-analyses do not support this relationship.[5,7,8]

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Symptoms of CTS include pain, numbness, and tingling in the hand and fingers. These symptoms typically start gradually and worsen over time. They are often worse at night. Symptoms may also be worse when the wrist is bent for a long time, such as when driving or using a phone. Carpal tunnel syndrome diagnosis is typically based on symptoms and a physical examination. A nerve conduction study may also be done to confirm the diagnosis. This test measures how well electrical signals are conducted through the median nerve. Furthermore, if the patient is a candidate for surgery, an accurate diagnosis of CTS is necessary.[9]

Although the surgical release of the flexor retinaculum remains the first choice in advanced stages of median nerve entrapment, there is no consensus on the best approach in mild to moderate scenarios. Nonsteroidal anti-inflammatory drugs, pyridoxine, splinting, or physical modalities such as laser are common choices.[10,11] Local injections have shown to be beneficial in mild to moderate cases, and there are promising results with corticosteroids (CS), progesterone, and platelet-rich plasma.[12] Local injection of CS is usually preferred in mild to moderate cases refractory to other modalities. There is often a rapid and significant improvement; however, it may not last in the long term. Steroids act by reducing the local inflammation triggered by mechanical, immunological, or chemical factors.[13] Corticosteroids inhibit phospholipase A2, deactivating a proinflammatory cascade.[10] In addition, it has been reported that local CS may block type-C sensory nerve fibers.[13-15]

One of the novel modalities is local ozone (O_3) injection, which is available in oxygen (O_2)-O_3 solutions. Ozone could be effective due to its biochemical behavior.[16] It induces cellular antioxidant mechanisms, rapidly reacts with polyunsaturated fatty acids, and triggers subsequent anti-inflammatory and analgesic signaling pathways.[17,18] However, the downregulation of proinflammatory cytokines (interleukin-6, tumor necrosis factor-alpha), suppression of prostaglandin synthesis, and bradykinin release are presumed to be the main mechanisms.[19-22] In fact, O_3 as a prodrug-in nontoxic doses-could activate secondary messengers to moderate biological pathways.[16,23] Locally it may cause vasodilation, muscle relaxation, and decreased tissue edema and acidosis, which synergistically could alleviate pain.[24] It has been reported to be effective in the management of other musculoskeletal conditions, namely, myofascial pain syndrome and knee osteoarthritis.[25-27] Recent studies have shown promising yet inconclusive results on implementing O_2-O_3 in the management of CTS.[1,22,28]

This study aimed to evaluate the effectiveness of O_3 injection compared to CS injection in patients with mild to moderate CTS. Subjective data, including the perceived pain and Boston Carpal Tunnel Syndrome Questionnaire (BCTQ), along with neurophysiological parameters and ultrasonographic indices, were assessed during the study.

PATIENTS AND METHODS

This double-blind randomized controlled study was conducted with 42 patients (9 males, 33 females; mean age: 46.7±2.1 years; range, 18 to 70 years) who had persistent symptoms for three months and objectively confirmed mild to moderate CTS referring to the rehabilitation clinic of the Shahid Sadoughi University Hospital between May 2021 and June 2021. Patients with comorbid conditions (e.g., diabetes mellitus, rheumatoid arthritis, and thyroid disorders), prior trauma/release surgery, thenar atrophy, cervical radiculopathy, polyneuropathies, infertility, thrombocytopenia, glucose-6-phosphate dehydrogenase deficiency, patients on angiotensin-converting enzyme inhibitors, and history of steroid injection within six months were excluded. The severity of the disease (mild, moderate, or severe) was established using clinical symptoms and electrodiagnostic study results. Patients were randomly allocated into two groups (CS and O_3 groups) in a one-to-one ratio using a simple random allocation method. A preset table (www.random.org/integers) was used for generating random numbers. Each patient was assigned a code in an envelope by a researcher not aware of the intervention.

The determination of the required sample size to achieve a significant statistical and clinical difference between the two groups (2-point change in VAS) was guided by a statistical power of 80% (β=0.2), a level of statistical confidence at 95% (α=0.05), and standard deviation of 2.2, according to the results of a previous similar article.[29] The following formula was used to determine the sample size. Considering a drop rate of 10%, the required sample size was 21 participants for each group, with a total of 42 individuals. Since the follow-up period in the study was not long, there were no loss of

participants. The Bonferroni correction was used for pairwise comparisons.

$$n=\frac{(Z_2^{\alpha}-+Z\beta)^2\times 2S^2}{(\chi_2-\chi_2)^2}$$

The patients were placed in a supine position, with the forearm supinated and the wrist positioned over a pillow in 25° to 35° dorsiflexion. The ultrasound-guided CTS injection with a high-frequency linear transducer was performed using a proximal to distal in-plane longitudinal approach.[30] Patients either received single-dose injections of CS or O_2-O_3 as treatment. The CS group was administered 40 mg triamcinolone acetonide (Triamhexal; Hexal AG, Holzkirchen, Germany), while the O3 group was administered 4 mL of a 10 mcg/mL O_2-O_3 solution. Both groups received 1 mL of 1% lidocaine, and a 25-gauge needle was used to deliver the medication. Both groups were prescribed to use plastic volar splints (5° carpal extension) for eight weeks during the night and most working hours. Patients were allowed to take acetaminophen in the first 48 h after the procedure if necessary. The quantity and dosage of the pills taken were recorded.

Secondary to random allocation, perceived pain was retrieved using a Visual Analog Scale (VAS; 0 to 10, with 10 being the worst pain experienced) and the Persian version of the BCTQ to assess function impairment (11 items) and symptom severity (eight items) on a 5-point Likert scale, with 5 being the worst experience.

Alpinion E-CUBE8 ultrasound device (Alpinion Medical Systems Co., Ltd, Gangseo-gu, Seoul, Republic of Korea) with a 5-18 Hz linear array transducer was used for the ultrasonographic study. With the patient in a supine position, the boundary of the median nerve, excluding the perineurium, was traced. The proximal cross-sectional surface area (CSA) of the median nerve (excluding the hyperechoic epineurium; mm^2) and volar bulging (the longest distance between the distal imaginary line, tangential to trapezium, and hamate bones on the distal side and flexor retinaculum; mm) were measured.

Electrodiagnostic studies were also applied to patients using Nicolet EDX EMG/NCS/EP/IOM system (Natus Medica Inc., Middleton, WI, USA). The nerve conduction study included median nerve antidromic sensory nerve action potential (SNAP) assessment according to the 2002 American Association of Neuromuscular and Electrodiagnostic Medicine guideline. In addition, compound muscle action potential (CMAP) latency of the median nerve was studied using the abductor pollicis brevis muscle with standard techniques.

Clinical, ultrasonographic, and electrodiagnostic data were collected at baseline and eight weeks after the procedure. Each ultrasonographic and electrodiagnostic study was done by different operators unaware of previous examinations.

Statistical analysis

Data were analyzed using IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test, along with inspection of shape parameters, such as skewness and kurtosis coefficients, were used for testing normality of data. The repeated-measure analysis of variance was used for the comparison of differences across different time points within groups and between groups. Considering the small sample size, comparisons were made using the generalized estimating equation model for the nonnormally distributed outcomes. Multiple comparison tests were performed by the Bonferroni adjustment method. The statistical significance level was determined at $p<0.05$.

TABLE 1
Demographic and clinical data in study groups

	Corticosteroid group (n=21)			Ozone (O_2-O_3) group (n=21)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			48.8±10.1			44.4±6.2	0.09
Sex							0.454[a]
Female	18.3	85.7		15.6	71.4		
Male	3	14.3		6	28.6		
Body mass index (kg/m^2)			25.4±1.8			24.4±1.8	0.09

SD: Standard deviation; a: *P*-value is resulted from Fisher-exact test.

TABLE 2
Pain VAS, SS and FSS in study groups at baseline and eight weeks after injection

		Time					
		Baseline	After eight weeks	Intragroup analysis		Time	Group* time
Outcome	Group	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
VAS	Ozone (O_2-O_3)	5.95±1.42	1.86±0.8	4.10±0.8	<0.001[a*]	<0.001*	0.026*
	Corticosteroid	6.57±1.46	1.86±0.77	4.71±0.92	<0.001[a*]		
Intergroup analysis		−0.62±2.06	0.00±1.1				
p value		0.166[a]	1.00[a]				
FSS	Ozone (O_2-O_3)	2.62±0.64	1.50±0.18	-	-	<0.001*	0.524
	Corticosteroid	2.40±0.6	1.38±0.23	-	-		
Intergroup analysis		-	-				
p value		-	0.057				
SS	Ozone (O_2-O_3)	2.65±0.41	1.52±0.18	-	-	<0.001*	0.532
	Corticosteroid	2.60±0.47	1.40±0.92	-	-		
Intergroup analysis		-	-				
p value		-	0.016*				

VAS: Visual Analog Scale; SD: Standard deviation; * *P*-value < 0.05 was considered as statistically significant. P-values are resulted from generalized estimating equation model; a: Adjustment method for multiple comparisons was Bonferroni. SS: Symptom severity; FSS: Functional scale status

RESULTS

There was no significant difference between O_2-O_3 and CS groups in age, body mass index, and sex (p>0.05, Table 1). As shown in Table 2, a significant improvement was observed in VAS scores in both groups at eight weeks after injection (p<0.001). Furthermore, symptom severity and functional status scale were significantly improved in the two groups at eight weeks after injection (p<0.001, Table 2). The interaction effect of time and group on the VAS score was statistically significant. This finding implies that the improvement in VAS scores in the two groups was different. Indeed, in the CS group, the VAS score decreased more sharply compared to the O3 group eight weeks after injection (Table 2). Symptom severity showed

TABLE 3
Electro-diagnostic findings in study groups at baseline and eight weeks after injection

		Time					
		Baseline	After eight weeks	Intragroup analysis		Time	Group* time
Outcome	Group	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
SNAP	Ozone (O_2-O_3)	4.81±0.55	4.71±0.46	0.095±0.18	0.035[a*]	<0.001*	<0.001*
	Corticosteroid	4.59±0.46	3.94±0.5	0.64±0.21	<0.001[a*]		
Intergroup analysis		0.22±0.78	0.77±0.82				
p value		0.256[a]	0.001[a*]				
CMAP	Ozone (O_2-O_3)	4.65±0.46	4.59±0.5	0.06±0.14	0.042[a*]	<0.001*	<0.001*
	Corticosteroid	4.57±0.50	3.99±0.41	0.58±0.09	<0.001[a*]		
Intergroup analysis		0.081±0.69	0.60±0.64				
p value		0.554[a]	<0.001[a*]				

SD: Standard deviation; SNAP: Sensory nerve action potential; CMAP: Compound muscle action potential; * *P*-value <0.05 was considered as statistically significant. *P*-values are resulted from repeated measure ANOVA; a: Adjustment method for multiple comparisons was Bonferroni.

TABLE 4
Ultrasonography findings in study groups at baseline and eight weeks after injection

		Time					
		Baseline	After eight weeks	Intragroup analysis		Time	Group* time
Outcome	Group	Mean±SD	Mean±SD	Mean±SD	*p*	*p*	*p*
Volar bulging	Ozone (O_2-O_3)	3.56±0.46	3.51±0.46	0.052±0.14	0.05[a]	<0.001*	<0.001*
	Corticosteroid	3.66±0.69	3.10±0.46	0.57±0.50	<0.001[a]*		
Intergroup analysis		−0.10±0.82	0.41±0.64				
p value		0.588[a]	0.009[a]*				
CSA	Ozone (O_2-O_3)	14.7±2.06	14.6±1.74	0.057±0.82	0.75[a]	<0.001*	<0.001*
	Corticosteroid	15.5±2.29	12.99±1.83	2.51±0.82	<0.001[a]*		
Intergroup analysis		−0.80±2.9	1.66±2.47				
p value		0.240[a]	0.007[a]*				

SD: Standard deviation; CSA: Cross-sectional surface area; * *P*-value <0.05 was considered as statistically significant. *P*-value is resulted from repeated measure ANOVA; a: Adjustment method for multiple comparisons was Bonferroni.

significant improvement in favor of the CS group at eight weeks after injection compared to the O_3 group (p<0.001, Table 2).

Electrodiagnostic studies revealed a significant decrease in both CMAP and SNAP latency eight weeks after injection in both groups (p<0.001, Table 3). A similar finding was also observed in the proximal CSA and volar bulging of the median nerve on ultrasonography in the CS group at eight weeks after injection (p<0.001, Table 4). The interaction effect of time and group on CMAP and SNAP latency, CSA, and volar bulging were statistically significant (p<0.001; Tables 3, 4). These findings imply that in the CS group, the mentioned parameters reduced more sharply compared to the O_3 group eight weeks after baseline (Tables 3, 4).

Compound muscle action potential, SNAP, CSA, and volar bulging showed considerable improvement in favor of the CS group compared to the O_3 group at eight weeks after injection (p<0.001; Tables 3, 4).

Two (9.5%) patients receiving O_3 and two patients receiving CS reported transient pain after the injection. Hypopigmentation was evident in two patients who received CS.

DISCUSSION

The results show that O_2-O_3 injection (10 mcg/mL) could improve perceived pain and function reported by patients, comparable to CS injection after eight weeks. Nonetheless, symptom severity was significantly lower in the CS group at the end of the study. Electrodiagnostic parameters (CMAP and SNAP) were significantly improved during the course of follow-up in participants who underwent CS injection, while no significant improvement was obtained in the O_2-O_3 arm. Ultrasonographic indices (median nerve CSA and volar bulging) improved eight weeks after the injection, with the superiority of CS over O_2-O_3.

A wide extent of nonsurgical treatments have been proposed for CTS. Conservative management is preferred in almost all nonsevere cases. Nonsteroidal anti-inflammatory drugs, wrist splints, and job modification are among the noninvasive options for managing CTS. Corticosteroid injection is shown to be promising in most mild to moderate cases, although the results are controversial among different studies. Graham[31] demonstrated that patients with CTS who underwent CS injections experienced relief for a limited period, while only 10% of them experienced permanent relief. On the contrary, Agarwal et al.[32] reported long-term improvement in electrodiagnostic parameters and function secondary to methylprednisolone injection. Since local steroid injections may induce systemic effects, including loss of bone density or hyperglycemia, caution should be exercised in high-risk patients.[33] Local O_2-O_3 injection is proposed to be a comparable alternative in these cases; however, evidence is limited in this field.[19] Oxygen-O3 therapy is believed to be effective partly due to its moderation in oxidative stress, which plays a pivotal role in inflammatory conditions.[19] Pain relief in conditions such as low back pain and knee osteoarthritis is reported by two studies.[28,34]

Zambello et al.[35] demonstrated the effectiveness of O_2-O_3 injection in treating CTS in more than 90% of the participants for one year. It should be taken into account that patients had multiple O_2-O_3 injections, and it was not a controlled trial. Their results were somewhat similar to our study regarding improvement in the intensity of pain. In another more recent uncontrolled study, sensory nerve conduction and motor distal latency along with symptom severity (BCTQ questionnaire) were improved after eight sessions of O_2-O_3 injections.[12] Contrary to these findings, the present study showed no significant changes in the electrodiagnostic and ultrasonographic parameters, although it should be noted that we used a single dose of O_2-O_3 injection. Bahrami et al.[1] compared the effectiveness of the single dose of O_2-O_3 therapy against a control group (volar splint for eight weeks). They revealed significantly improved symptoms in the O_2-O_3 group compared to the control group, while neurophysiological indices were not changed. Another more recent study showed a decrease in VAS and BCTQ scores in both O_2-O_3 and CS groups six weeks after injection.[29] However, as the results of the present study suggest, ultrasonographic and electrodiagnostic parameters were significantly changed after treatment only in the CS group. Elawamy et al.[28] demonstrated improved pain, function, neurophysiological, and ultrasonographic improvement six months after receiving O_2-O_3 injection in systemic sclerosis patients with CTS compared to methylprednisolone. It is worth noting that the dosage of O_2-O_3 was 25 mu-g/mL in 20 mL, and the procedure was done on a special patient population (i.e., systemic sclerosis patients).

The strengths of this study were the randomized controlled design and matching of both arms, addressing possible confounding factors. Both subjective and objective (either clinical or paraclinical) data were obtained. Nonetheless, this study has some limitations. since there is no definite recommended number of O3 applications, it was applied once, and the results of the repeated applications could not be investigated in this study. Furthermore, the study had a low sample size, no control group, and no long-term follow-up. Further studies should include an increased frequency of time points on which clinical and electrodiagnostic or ultrasonographic data are gathered for an extended time for better evaluation of the short-term and long-term effects of each intervention.

In summary, O3 therapy can be effective in reducing pain and improving the physical function of patients, with no significant changes in electrophysiological and ultrasonographic parameters. While in the CS group, a significant enhancement in all assessed parameters was demonstrated.

Ethics Committee Approval: The study protocol was approved by the School of Medicine-Shahid Sadoughi University of Medical Sciences Ethics Committee (date: 19.05.2021, no: IR.SSU.MEDICINE.REC.1400.099). This trial was registered in the Iranian Registry of Clinical Trial (registration ID: IRCT20210920052535N1). A written informed consent was obtained from all participants before enrollment in the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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