INFLUENCE OF OZONATED GEL PHONOPHORESIS ON THE TREATMENT OF CHRONIC LATERAL EPICONDYLITIS: A RANDOMIZED CONTROLLED TRIAL

Samir Ahmed ElSabbahi[1], Ahmed Abd-Elaziz Hefny[2], Mohamed Abdelhaleem Kadah[3], Yasser Ramzy Lasheen[4]

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Abstract

Background: Chronic lateral epicondylitis (CLE), or "tennis elbow," is produced by a degenerative mechanism of the extensor tendon. (CLE) can produce a great monetary and social costs due to lost workdays. Ozone molecules have anti-inflammatory, analgesic, anti-oxidant, immune-modulatory effect, and became an effective treatment tool for musculoskeletal disorders. **Objectives:** This study was done to investigate the effect of ozonated gel phonophoresis on pain intensity, wrist range of motion, hand grip strength and hand activities in patients with chronic lateral epicondylitis. **Methodology:** 40 patients with chronic lateral epicondylitis from both genders participated in this study after signing a consent form. The patients were assigned randomly into two equal groups; group A (study) and group B (control). Group A(study) consisted of 20patients who received ultrasonic with ozonated gel (phonophoresis) (1 MHz, 1 W/cm^2 continuous mode) for 5 min. in addition to the conventional physical therapy program (TENS, hot pack, elbow joint support, stretching and strengthening exercises) 3 times per week for 4 weeks. Group B (control)consisted of 20 patients who received only the conventional physical therapy program,3times per week for 4 weeks. Pain intensity was evaluated by Visual Analogue Scale (VAS), elbow extension and flexion ROM was measured, hand activities were assessed by Quick Disabilities of Arm, Shoulder and Hand (Quick DASH) and hand grip strength was evaluated by hand held dynamometer. Data obtained from both groups pre and post treatment. **Results:** The results of the study showed a significant reduction in pain, wrist flexion and extension, hand grip strength and hand functions in the study group compared to the control group B ($p = 0.001$). **Conclusion:** Ozonated gel phonophoresis in addition to conventional physical therapy is an effective noninvasive physical therapy modality in reducing pain, increasing wrist mobility and epicondylitis., and improving hand function in patients with chronic lateral epicondylitis

Keywords: Chronic lateral epicodylitis, Tennis elbow, Ozonated gel and Phonophoresis.

1 Professor in physical therapy, Department of Basic Science, Faculty of Physical Therapy, Cairo University.
2 Physiotherapist in The General Orgnization of Teaching Hospitals and Institutes, Al-ahrar Teaching Hospital, Zagazig.
3 Professor in Orthopedic Surgery Department, Faculty of Medicine, Cairo University, Egypt.
4 Assistant Professor in physical therapy, Department of Basic Science, Faculty of Physical Therapy, Cairo University.

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INTRODUCTION

Forearm common extensor tendon degeneration with ongoing symptoms is referred to as chronic lateral elbow tendinopathy. One of the most prevalent overuse symptoms in primary care is this one. 1% to 3% of the population suffers from chronic lateral epicondylitis (CLE), primarily middle-aged adults without a gender difference. Due to missed workdays, chronic lateral epicondylitis (CLE) can result in significant social and financial hardship **(Kun-Longet al., 2020).**

Ultrasound is produced by a transducer composed of a piezoelectric crystal which converts electric energy into mechanical energy in the form of oscillations which generate acoustic waves **(Machet et al, 2002)**. It has been used for many years to treat musculoskeletal disorders such as tendonitis, epicondylitis, tenosynovitis, bursitis, and osteoarthritis.While passing through tissues of varying resistance levels, these waves are transformed into heat. Ultrasound is also used to enhance percutaneous absorption of medications in phonophoresis applications (**Ferdi et al, 2020; and Okan et al.,2020).**

Phonophoresis is a process of local administration of topical medicines under the influence of ultrasound which drive the drug molecules into the tissues causing an enhanced penetration. It is considered painless, noninvasive and has fewer side effects as it administered locally at the site of pain **(Byl. et al;**

1995).When compared to simple topical treatment, phonophoresis delivers higher local concentrations of the drug, increasing permeability both through structural changes in the skin and through the convection mechanisms built into the ultrasound effect.**(Cagnie, B et al;** 2003)

Ozone is popular with its anti-inflammatory and analgesic action; it helps in the synthesis of biologically active substances such as interleukins, leukotrienes and prostaglandins which is valuable in reducing inflammation and pain. (Naik et al., 2016).Ozone has been used in various conditions for management of pain, and it is supposed to serve as a complementary and low-risk mode of treatment (Al-Jaziri et al., 2008).

Joint problems that cause acute and chronic pain can both be quickly and effectively relieved by intra-articular ozone injections. As a result, it might be a better alternative to anti-inflammatory medication because of its quick beginning of action, subsidence of swelling, drop in temperature, and improvement in joint mobility. It has been shown to have positive effects on knee osteoarthrosis, low back pain, and lumbar sciatic pain **(Anzolin AP,et al,2021).**

When ozone is added to gels and oils, it improves their stability and storage capabilities, makes ozone gas handling and storage easier, prevents quick deterioration, enables outpatient treatment, and lowers the hazards associated with using it in gaseous form in excessive or inadequate doses.**(Sadowska et al, 2008)**

The available literature indicates that ozone is only occasionally used in physical therapy. There aren't many studies done on topical treatments for knee osteoarthritis and discomfort. We want to evaluate a novel CLE approach in this study. To lessen the suffering and impairments of individuals with chronic lateral epicondylitis, ozonated gel phonophoresis therapy may be a useful treatment.

Ozone therapy is a potential minimally invasive, conservative treatment that can be used alone or in conjunction with other therapies to help people with musculoskeletal diseases perform better and experience less pain. According to various studies, the effectiveness and safety of ozone therapy have primarily been researched in cases of knee osteoarthritis and low back pain.**(De Sire et al, 2021)**

Despite improvements in CLE therapy, there are currently no set criteria in place **(Kun-Long et al, 2020)**. Therefore, the purpose of this study was to determine if topical ozonated gel phonophoresis was successful in treating chronic lateral epicondylitis patients' discomfort and enhancing their mobility and functional abilities.

SUBJECTS AND METHODS

Study Design

It is a single-blinded randomized controlled trial. It was conducted at AL-AhrarZagazig Teaching Hospital from December 2022 till May 2023. The participants in this study signed an informed consent form. The study was approved from the research ethics committee of faculty of physical therapy, Cairo University with registration number (P.T.REC/012/004131).Clinical Trial.gov ID: NCT05872165

Participants:

Forty patients with chronic lateral epicondylitis from both genders participated in this study, they were selected from outpatient clinic of AL-Ahrar Zagazig Teaching Hospital.

The patients were diagnosed and referred by the orthopedist based on clinical and radiological examination. Their age ranged from 30 to 50 years, Pain onset was more than 3 months. All participants were medically stable and without analgesics treatment or any medication which may cause misleading results. All patients had body mass index between 18.5 and 29.9 kg/m2. The participants were randomly divided into two equal groups.

Group A (study):

Consisted of 20 patients who received ultrasonic with ozonated gel as a coupling medium (phonophoresis) (1 MHz, 1 W/cm2 continuous mode) for 5 min, in addition to the conventional physical therapy program 3 times per week for 4 weeks.

Group B (control):

Consisted of 20 patients who received the conventional physical therapy only 3times per week for 4 weeks included TENS, hot pack, stretching exercises for the wrist extensors muscles,strengthening exercises for wrist extensors and flexors muscles and wrist rest splint.

Inclusion criteria:

Patients met the following criteria were included in the study:

All patients were diagnosed as chronic lateral epicondylitis from both genders.Patients with chronic lateral epicondylitis were diagnosed and referred by orthopedist.Positive clinical manifestation in all patients.Patients age was ranged from30 to 50 years (**Giray et al.,2019**).Pain onset was more than 3 months. All participants were medically stable and without analgesics treatment or any medication which may cause misleading results. All patients had body mass index between 18.5 and 29.9 kg/m^2 **(Stasinopoulos D, et al; 2005).**

Exclusion Criteria:

The patients with one or more of the following criteria were excluded.Patients with elbow instability, elbow surgery, shoulder or elbow fractures, Arthritis and effusion of the elbow, skin diseases or open wound on elbow area, intra articular injection from duration less than 3 months,

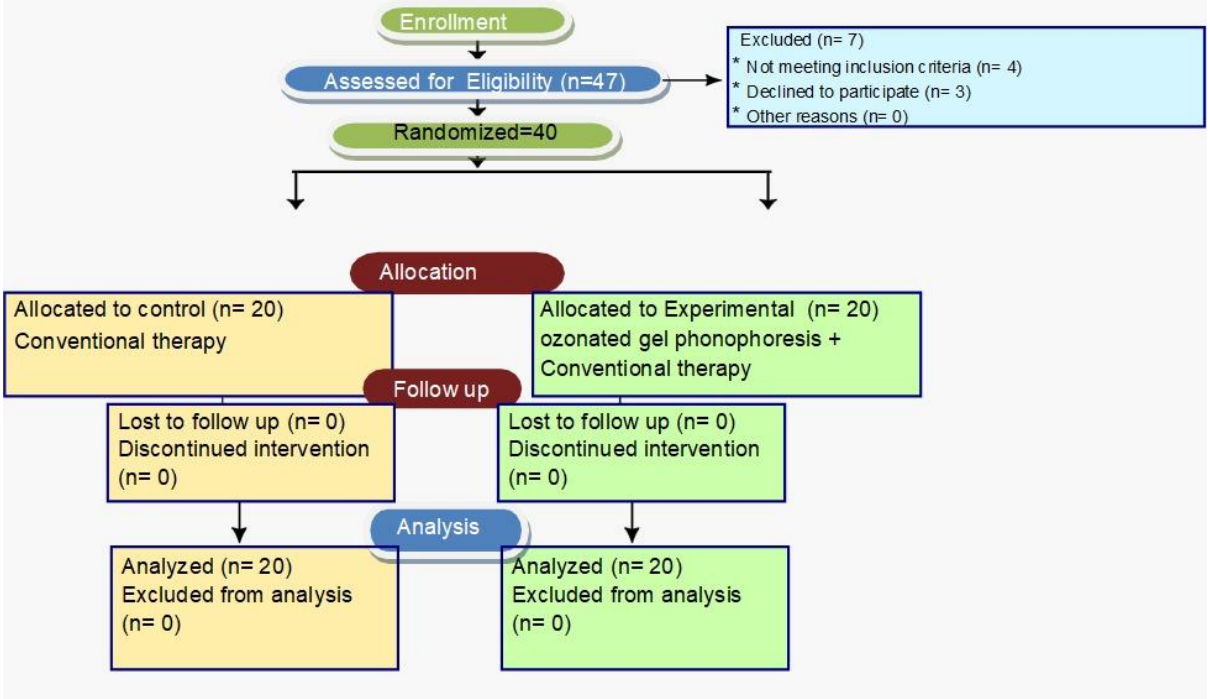
entrapment of the radial nerve Pregnancy, history of cancer, Systemic diseases such as rheumatoid arthritis, Reiter's syndrome, or diabetes. Severe medical and neurological or psychiatric disorders.

Sample size

The sample size calculation was done by using the G*power software (G power program version 3.1, Heinrich-Heine-University, Germany). The minimum proper sample size is 40 subjects, they were divided into 2 groups (Study group A), and (Control group B)20 subjects in each group.

Randomization

Random assignment was performed using a computerized random number generator. sealed, opaque, and numbered envelopes were prepared containing participant group assignment. Another investigator, then, opened the envelope containing the concealed group allocation to assign each participant into the standard care group or the intervention group.



Outcome measures

Pain intensity was evaluated by Visual Analogue Scale (VAS), elbow extension and flexion ROM was measured, hand activities were assessed by Quick Disabilities of Arm, Shoulder and Hand (QuickDASH) and hand grip strength was evaluated by hand held dynamometer. Data obtained from both groups pre and post treatment.

Assessment procedure

1- Visual Analogue Scale (VAS)

Each patient was asked to make a handwritten mark on a 100 mm line (10cm) that exactly corresponded to his/her pain. This line represents a continuum between no pain or discomfort (zero), to the worst pain (10). Measurements from the starting point of the scale to the patients' marks were recorded and interpreted as their pain intensity. The results were interpreted as: no pain (0–4 mm), mild pain (5-44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm)**(Jensen et al., 1986).**

2- Measurement of ROM of wrist movement

For measuring wrist flexion, the fixed arm of the goniometer was positioned parallel to the forearm, and the mobile arm was positioned parallel to the radial side of the patient's hand. The participants were instructed to bend their wrist joint 3 times, and the mean ROM of the 3 attempts was recorded. For measuring wrist extension, the goniometer was placed similar to the setting for wrist flexion, and the participants were instructed to extend their wrist 3 times, and the mean ROM of the 3 attempts was recorded.

3-Hand grip strength

the participants were in a seated position with their back on the backrest of a chair and their feet on the ground. Participants were asked to place their arms by their sides with their elbows in a 90° flexion position. Participants were asked to keep their forearms and wrists in a neutral position. Each participant was then instructed to squeeze the digital hand dynammeter as hard as possible for 3 seconds. After at least 4 minutes of rest, the test was repeated

2 more times, and the mean handgrip strength of the 3 attempts was recorded.

4- Assessment of hand activities

The Quick Disabilities of Arm, Shoulder and Hand (QuickDASH) Questionnaire was used to evaluate hand activities Arabic version (**Alnahdi AH, 2021**). The QuickDASH has five response options for each item from 0=no difficulty to perform or no symptoms to 5=unable to do. If at least 10 out of the 11 items are completed, the responses are summed to form a raw score, and then converted to a 0-100 scale. A higher score reflects greater disability **(Gummesson C, et al;2006)**.

-Treatment procedures:

For study group(A):

patients received Ultrasonic with ozonated gel as a coupling mediumin addition to conventional physical therapy.

- Ultrasonic with ozonated gel (natural material composed of a suspension of medical grade ozone a mixture of oxygen and ozone in the ratio of 0.25% and 99.75% respectively and Olive oil)as a coupling medium (phonophoresis-1 MHz, 1 W/cm2 continuous mode) for 5 min.patient sit on relaxed position affected arm on the bed.Putting small amount of ozonated gel as a medium and appling the ultrasound head on lateral aspect of affected elbow for 5 min

- The treatment was applied over 3time per week for 4 weeks.

For control group (B):

received the conventional physical therapy only 3times per week for 4 weeks included TENS, hot pack, stretching exercises for the wrist extensors muscles, strengthening exercises for wrist extensors and flexors muscles and wrist rest splint

1- TENS

Biphasic square wave impulses at a frequency of 100 Hz and pulse duration of 300 µs were used for a total duration of 30 minutes. Stimulation was provided by carbon rubber surface electrodes (4 cm × 3 cm) secured to the skin with adhesive tape above elbow joint on the site of pain one electrode on the lateral side and the other electrode on the left side of elbow with intensity 20 to 40 m Am**.(Sivaramakrishnan A, et al; 2018)**

2-Electerical Hot pack for 20 min.

Patient in a relaxed position, the hot pad was put on the affected elbow for 20 min.

3-Stretching and strengthening exercises.

Stretching:

Static stretching to forearm extensors was applied for 30 sec. total six repetitions with rest of 30 seconds between each session was given.The patient position was supine lying position with elbow rested on the bed, wrist joint was free outside the bed. Therapist supported the elbow joint with one hand and the other hand stretched forearm extensors.

4- Strengthening exercise:

The patient was asked to make wrist extension slowly and maintain the position. Active motion of wrist extension with elbow flexed 90 degrees, 2-3 sets of 10 repetitions was started, progressing to 5 sets of 10 repetitions as tolerated. When the subject performed repetitions without overcompensation of other muscles 1 pound of weight was added and performed 3 sets of 10 repetitions progress to 5 sets. Then add 1 pound of weight and progress to 5 sets. Then add 1 pound of weight and progress till 3 pound weight. As tolerance improved elbow is taken into extension.Strengthing exercise for hand grip muscles to increase hand grip power the patients were asked to grasp a hand dynamometer from sitting with elbow flexed then instructed to squeeze on it as much as he can for few seconds then relax and repetitions.

5-Elbow splints. The patient put on the Tynor Elbow Support For 4 weeks after the physical therapy session.

STATISTICAL ANALYSIS

Unpaired t-test was conducted for comparison of ageand BMI between groups and Chi-squared test was used for comparison of sex distribution. Normal distribution of data was checked using the Shapiro-Wilk test. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups.Mixed MANOVA was performed to compare within and between groups effects on VAS, Quick DASH, elbow extension and flexion ROM and hand grip.Bonferroni corrections were carried out for subsequent multiple comparison. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA).

RESULTS

***- Subject characteristics*:**

Table (1) showed the subject characteristics of group A and B. There was no significant difference between groups in age, BMI and sex distribution($p > 0.05$).

Table 1. Comparison of subject characteristics between group A and B:

	Group A	Group B	Statistics	p-value
Age, mean ± SD (years)	40.15 ± 6.20	40.05 ± 6.12	(t= 0.28)	0.78
BMI, mean ± SD (years)	24.01 ± 1.07	23.61 ± 1.31	(t= 1.06)	0.29

Sex, n (%)				
Female	9 (45%)	9 (45%)	($\chi^2 = 0$)	1
Male	11 (55%)	11 (55%)		

SD, Standard deviation; t, unpaired t value;χ^2, Chi squared value; p value, Level of significance.

Effect of treatment on VAS, Quick DASH, elbow extension and flexion ROM and hand grip:

Mixed MANOVA revealed that there was a significant interaction of treatment and time (F = 260.76, p = 0.001, partial eta squared = 0.97). There was a significant main effect of time (F = 1307.73, p = 0.001, partial eta squared = 0.99). There was a significant main effect of treatment (F = 72.42, p = 0.001, partial eta squared = 0.91).

Within group comparison

There was a significant decrease in VAS and Quick DASH of group A and B post treatment compared with pretreatment (p < 0.001). The percent of change of VAS and Quick DASH of group A was 66.67 and 63.66% respectively; and that of group B was 25.93 and 16.23% respectively. (Table 2).

There was a significant increase in wrist extension and flexion ROM and hand grip of group A and B post treatment compared with pretreatment (p < 0.001). The percent of change of wrist extension and flexion ROM and hand grip of group A was 38.82, 50 and 50.80% respectively; and that of group B was 19.57, 23.68 and 19.17% respectively. (Table 3).

Between group comparison

There was no significant difference between groups pre treatment (p > 0.05). There was a significant decrease in VAS and Quick DASH of group A compared with that of group B post treatment (p < 0.001). There was a significant increase in wrist extension and flexion ROM and hand grip of group A compared with that of group B post treatment (p < 0.01).(Table 2-3).

Table 2. Mean VAS and Quick DASH pre and post treatment of group A and B:

	Group A	**Group B**		
	Mean±SD	**Mean±SD**	**MD**	**p value**
VAS				
Pre treatment	85.85 ± 4.92	86.40 ± 5.31	-0.55	0.73
Post treatment	28.70 ± 3.54	64.00 ± 4.21	-35.3	0.001
MD	57.15	22.4		
% of change	66.57	25.93		
	p = 0.001	***p = 0.001***		
Quick DASH				
Pre treatment	81.60 ± 5.65	81.65 ± 6.04	-0.05	0.97
Post treatment	29.65 ± 2.51	68.40 ± 4.96	-38.75	0.001
MD	51.95	13.25		
% of change	63.66	16.23		
	p = 0.001	***p = 0.001***		

SD, Standard deviation; MD, Mean difference;p value, Probability value.

Table 3. Mean wrist extension and flexion ROM and hand grip pre and post treatment of group A and B:

	Group A	Group B		
	Mean±SD	**Mean±SD**	**MD**	**p value**
Wrist extension ROM (degrees)				
Pre treatment	45.60 ± 4.10	46.50 ± 4.32	-0.9	0.50
Post treatment	63.30 ± 2.72	55.60 ± 3.85	7.7	0.001
MD	-17.7	-9.1		
% of change	38.82	19.57		
	p = 0.001	***p = 0.001***		
Wrist flexion ROM (degrees)				
Pre treatment	40.40 ± 2.60	39.90 ± 3.75	0.5	0.62
Post treatment	60.60 ± 2.11	49.35 ± 3.13	11.25	0.001
MD	-20.2	-9.45		
% of change	50	23.68		
	p = 0.001	***p = 0.001***		
Hand grip (lb)				
Pre treatment	43.90 ± 14.36	47.20 ± 11.85	-3.3	0.43
Post treatment	66.20 ± 9.61	56.25 ± 12.84	9.95	0.009
MD	-22.3	-9.05		
% of change	50.80	19.17		
	p = 0.001	***p = 0.001***		

SD, Standard deviation; MD, Mean difference; p value, Probability value.

DISCUSSION

This study looked at how individuals with chronic lateral epicondylitis responded to ozonated gel phonophoresis in terms of pain severity, wrist range of motion, hand grip strength, and hand activities.

statistical analysis which showed no statistical difference in the pretreatment evaluation. Comparing the general characteristics of patients of both groups revealed that there was no significance difference between groups in age and BMI ($p > 0.05$).

Both groups showed good post-treatment outcomes measures but group A (study) showed significant improvement in all variables compared to group B (control).

The findings of this study are consistent with those of Ulusoy GR et al. (2019), who looked at the effectiveness of corticosteroid and ozone injections in treating 80 individuals (56 women and 24 men; an average age of 45.8 7.5) with persistent lateral epicondylitis pain. While corticosteroids were given once a week for three times, ozone was injected 6–8 times at 3-day intervals. They found that the ozone group outperformed the corticosteroid group in terms of pain scores at the third, sixth, and ninth months after injection ($p< 0.001$ for all). The results demonstrated that for CLE patients who are not responding to conventional medication, ozone injections can be a helpful therapeutic option.

Also, the result of this study matched with the findings of **Martinelli et al (2020) who** studied the safety and effectiveness of intramuscular para-vertebral injections of O_2–O_3 (O_3 concentration of 16 mcg/mL once a week) in 168 patients affected by cervico-brachial pain, they found significant pain reduction at follow-ups after 1, 2, 3, 4, and 5 years.

The findings of Beyaz et al. (2018), who used intra-discal ozone injections to treat 44 patients with

chronic neck discomfort caused by disc herniation, provide additional support for the findings of the current investigation. Their results showed a considerable reduction in pain compared to preoperative levels in a follow-up examination of their VAS pain scores, and there were no problems noted. Furthermore, paravertebral O3/O2 injection is a trustworthy and efficient treatment for neck discomfort brought on by cervical disc disease, according to Ucar et al. (2022).

We assume that the noticeable improvement of pain VAS, as well as wrist flexion and extension, hand grip strength and hand functions are based upon the well-evidenced favorable ozone molecule biological properties. Ozone molecule has as anti-inflammatory, analgesic, anti-oxidant, immune-modulatory effect, and increases blood supply **(Seyam O, et al ; 2018).**According to Moretti M. (2012), ozone therapy causes tissue hyper-oxygenation and has become a useful therapeutic option for treating musculoskeletal problems.

Ozone treatment has been used in the rehabilitation of individuals with back pain, myofascial pain syndrome, tendonitis, and tendon injuries. Local injections of ozone are already used as a therapeutic option for musculoskeletal diseases.**(Muto M , et al; 2008- Simonetti L, et al; 2003)**

Ozone therapy produces therapeutic effects by improving tissue oxygenation, accelerating the use of glucose in cellular metabolism, improving protein metabolism, increasing erythrocyte activity, inhibiting inflammatory mediators, decreasing prostaglandin synthesis, and reducing oxidative stress in biological tissues. **(Agasarov LG, et al; 2022).**

The results of the current study were consistent with those of **Bahrami MH et al. (2019),** who examined the efficacy of ozone injection for the treatment of carpal tunnel syndrome. Two parallel groups of 40 individuals with mild to intermediate carpal tunnel syndrome were included. The resting volar wrist splint was worn by both members of the intervention group for 8 weeks, while they both received a single dose of local ozone injection and used the same splinting technique. The median nerve conduction study, the Boston questionnaire (BQ), the visual analog scale (VAS) for pain, the intensity of symptoms, and functional status were reassessed 10 weeks after the treatment. Both groups saw significant improvements in all metrics, including VAS, symptom severity, and functional status, with the highest changes in VAS. In comparison to the control group, the VAS was significantly reduced in the ozone group.

The current study's findings revealed a considerable improvement in the study group and a significant decrease in pain intensity in both groups. This could be explained by the use of TENS, which is based on the Gate Control Theory. It does this by stimulating the 83 inhibitory interneurons in the substantia gelatinosa of the spinal cord's dorsal horn and by stimulating the large-diameter (A-beta) primary sensory afferents, which block the transmission of nociceptive signals from the small-diameter A-delta and C fibers.**(Khadilkar et al,2008)** .

CONCLUSION:

Ozonated gel phonophoresis in addition to conventional physical therapy is an effective noninvasive physical therapy modalityin reducing pain, increasing wrist mobility and grip strength, and improving hand function in patients with chronic lateral epicondylitis.

RECOMMENDATIONS:

1-Further studies are required to determine the effect of ozonated gel on different musculoskeletal disorders.

2- To compare the effectiveness of ozonated gel with other forms of treatment for chronic lateral epicondylitis, more research is necessary.

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