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Original Article

AN INSTITUTIONAL EXPERIENCE WITH TOPICAL GLYCERYL TRINITRATE FOR TENNIS ELBOW: A RANDOMIZED TRIAL.

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Abstract
Objective
This study is conducted to analyze the efficacy of glyceryl trinitrate in the treatment of tennis elbow

Method
90 participants were divided into treatment groups and placebo groups. The placebo group received placebo patches, and the treatment group was given glyceryl trinitrate patches. The participants of the study were selected if the pain, as well as the tenderness, was evident with pain-stimulating maneuvers. The pain was evaluated using a visual analog scale before the treatment and after the treatment. A criterion was specified to determine the outcome of the study.

Results
A substantial difference in the VAS (Visual Analogue Scale) score of pain was observed in the 3rd week of follow-up between the two groups. In the treatment group, the VAS score reduced significantly from 9.2 to 5.28 ($p < 0.00001$), indicating a marked improvement in symptoms. In contrast, the control group showed a minimal reduction in the VAS score from 9.13 to 8.48 ($p = 0.18$), with no significant change in pain levels. The statistical analysis demonstrated that the difference in pain reduction between the treatment and control groups was highly significant.

Conclusion
The topical application of GTN patches is effective in reducing pain and tenderness associated with lateral epicondylitis.

Recommendation
Based on the findings of this study, the topical application of glyceryl trinitrate is recommended as a first-line treatment for tennis elbow, given its significant effect in improving pain and elbow function.

Keywords: *Topical Glyceryl Trinitrate (GTN), Lateral Epicondylitis (LE), Visual Analog Scale (VAS)*
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Introduction
Tennis elbow was first reported in the German literature in the 1880s. [1] The occurrence of tennis elbow has been reported in about 50% of non-professional tennis players, which accounts for 1 to 3% of the total population [2] LE occurs equally irrespective of gender, considering race it is more common amongst whites, it occurs mostly in the dominant arm, the age range of the patients reporting tennis elbow is about 30 to 50 years. [3] The occurrence of lateral epicondylitis is due to repetitive bending back of the wrist repetitively. The cause of the pain in the lateral elbow in lateral epicondylitis is due to manual extension of the muscles [4,5] Although the symptom of epicondylitis overlaps with other conditions as well. [6,7] A thorough evaluation of the history, functions, and symptoms is required to diagnose lateral epicondylitis. In certain cases, patients undergo diagnostic imaging to confirm the occurrence of lateral epicondylitis when they are irresponsive toward the treatment. The treatment of this condition is quite difficult considering the repetitive strain on the muscles.[8]

In long-term tendinopathies, the nitric oxide is given as a patch in terms of 1.25 mg for a full day. It significantly decreases pain, relieves any other symptoms, and improves the functional abilities of the Achilles tendon [9,10] and LE [11,12]

The present study aims to analyze the efficacy of glyceryl trinitrate in the treatment of tennis elbow.

Materials and methods
Study design
It was a hospital-based parallel randomized double-blind control trial.

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Study setting
Patients over 18 years of age who had pain around their elbows were selected from ortho OPD at UPUMS Saifai, between Jan 2017 to Aug 2018 duration period.

Participants
The following categories of patients were recruited for the study: The patients who had chronic pain and tenderness in the elbow, wrist extension was not possible, they demonstrated mill's sign that they were unable to move the wrist from flexion to complete extension with the forearm in pronated position [13] and they could not lift chair with one hand and the forearm in the pronated position.[14]
Patients who had surgery in the elbow region or had effusion of the elbow, periarticular fracture, infection, radiculopathy, allergy to adhesive tapes, or history of steroid injection were excluded.
A total of 90 patients with lateral epicondylitis were taken for study and randomized into two equal study groups with 45 patients in each group.

Intervention
The treatment group received a glycryltrinitrite patch that delivered 1.25mg drug every 24 hours, each GTN patches (nitroderm 5mg, Novartis) were cut into 4 pieces and applied to the area over maximum tenderness once a day.
The placebo patches were also similarly applied to the patients either till the end of the study or till the symptoms subsided. Investigators and patients were blinded to which patch was given to the patients.
The patients were thoroughly evaluated for their symptoms, history, and functional abilities of the lateral epicondyle at 03 weeks and 06 months for treatment outcomes using VAS and Verhaar criteria et al [15]. The VAS is a scale of 1 to 10 which measures the pain, before and after the treatment received.

Outcomes
According to Verhaar et al criterion.[15] excellent indicated that there was no pain and the patient was satisfied with the treatment. Good indicated there was pain occasionally due to heavy lifting and other exercises, the patient was satisfied with the treatment and there was no loss of function. Fair indicated that the patient was not satisfied, had tenderness and pain, and could lift heavy weights. Poor indicated that the patient was not satisfied and there was pain and tenderness.

Randomization
Sequence Generation: The random allocation sequence was generated using a computer-based random number generator, ensuring that each participant had an equal chance of being assigned to either the treatment or control group. The type of randomization used was simple randomization, where each of the 90 participants had a 1:1 allocation ratio, meaning each had an equal probability of being allocated to the treatment group (glyceryl trinitrate patches) or the control group (placebo patches).
Allocation Concealment Mechanism: The random allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes (SNOSE). The envelopes were prepared by an independent statistician who had no involvement in the study's conduct. Each envelope contained the allocation information and was opened only after a participant's consent was obtained and their eligibility was confirmed, ensuring that neither the participants nor the enrolling staff knew the allocation in advance.
Implementation: The random allocation sequence was generated by an independent statistician. The participants were enrolled by clinical staff at the Orthopaedics Department of Uttar Pradesh University of Medical Sciences. Once enrolled, participants were assigned to the respective intervention groups according to the allocation sequence by the study coordinator, who opened the sealed envelopes in sequence.

Blinding
Blinding was implemented to maintain the study's integrity, designed as a double-blind trial where participants, care providers, and outcome assessors were unaware of the group allocations. Participants did not know whether they received the active glyceryl trinitrate or placebo patches, care providers who administered and monitored the interventions were blinded, and outcome assessors were also blinded to ensure unbiased evaluation of results. Identical-looking patches were used for both groups to maintain blinding throughout the study.

Statistical analysis
The average and standard deviation of the VAS score and Verhaar et al, the score was calculated, and the Whitney U test was used to compare both the scores amongst two groups. The p-value was determined to evaluate the effectiveness of both treatments.

Ethical clearance
The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Results
Out of the 90 patients studied 13(14.44%) patients were between 20 to 30 years, 30 (33.33%) patients were between 31 to 40 years, 25 (27.77%) were between 41 to 50 years, and 22 (24.44%) patients were between 51 to 60 years. The mean age was 41.8 years (20-55) in the treatment group with a standard deviation of 41.8+/-8.92 and the mean age was 40.6 years (20-56) in the control group with a standard deviation of 40.6+/- 9.97

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Table no.1: Age distribution among the groups

Age groups	Treatment n (%)	Control n (%)	Total n (%)
20-30 yrs	5 (11.1)	8 (17.8)	13 (14.4)
31-40 yrs	16 (35.6)	14 (31.1)	30 (33.3)
41-50 yrs	13 (28.9)	12 (26.7)	25 (27.8)
51-60 yrs	11 (24.4)	11 (24.4)	22 (24.5)
Total	45 (100%)	45 (100%)	90 (100%)
Mean ± SD	41.8 ± 8.92	40.66 ± 9.97	41.23+/-9.42
t-test value – 0.571, p-value – 0.571			

Distributions of treatment and control group participants according to the involvement of elbow joint side

In the control group out of 45 17 (37%) patients were nondominant sided and rest 28 (62.2) were dominant sided and in the treatment group out 45 the 20(62.2) patients were nondominant sided and rest 25(55.6) are dominant side, it means the patient's dominant side of the elbow is more affected then non-dominant in my study over lateral epicondylitis

Table 2: Comparison among treatment and control group participants for the outcome based on Visual Analogue Scale – at baseline, 3 weeks, and 6 months

Group	Baseline	3 weeks	6 months	P Value
Treatment	9.2 ± 0.86 (8-10)	5.28 ± 1.16 (2-7)	1.75 ± 1.31 (0-5)	< 0.00001
Control	9.13 ± 0.84 (7-10)	8.48 ±1.17 (4-10)	8.6 ± 1.73 (2-10)	0.18
P Value	0.35	< 0.00001	< 0.00001	

**Mann-Whitney U test, (an insignificant decline from baseline in the control group)*

In the treatment group at 03 weeks there is a marked difference in symptoms from baseline and 03 weeks to 06 months statistically there is a significant difference in symptoms and the control group there is a slight decline in symptoms from baseline to 03 weeks and statistically there is not any significant difference in symptoms from 03 weeks to 06 months. It means in the treatment group there is a significant difference in symptoms.

Table no. 3: Comparison of participants for the outcome - Outcome Measurement Grade by Verhaar et al criteria. At 3 weeks and 6 months according to the intervention groups

Treatment group				
Follow Up	Excellent n (%)	Good n (%)	Fair n (%)	Poor n (%)
3 weeks	1 (2.2)	23 (51.1)	21 (46.6)	0
6 months	32 (71.1)	13 (28.8)	0	0
Control group				
Follow Up	Excellent n (%)	Good n (%)	Fair n (%)	Poor n (%)
3 weeks	0	1 (2.2)	6 (13.3)	38 (84.4)
6 months	1 (2.2)	3 (6.6)	4 (8.8)	37 (82.2)

Comparative outcome at 03 weeks and 06 months by Verhaar et al scale.

3 weeks

In this study in the control group, outcome measurement at 3 weeks, showed poor results were 38 (84.4%), fair 6 (13.3%), good 1 (2.2%) and there is no one in the excellent group. In the treatment group outcome measurement at 3 weeks there is no one in poor, fair 21 (46.7%), good 23 (51.1%), and 1 (2.2%) in the excellent group, according to the measurement at 3 weeks the poor patients in higher in the placebo group and fair and good patients in the treatment group.

6 months

In the control group outcome measurement at 6 months poor patients were 37 (82.2%), fair 4 (8.9%), good 3 (6.7%), and 1 (2.2%) excellent group. The total number of patients is 45 (100%) and in the treatment group

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outcome measurement at 6 months there is no one in the poor and fair, 13 (28.9%) and 32 (71.1%) in the excellent group. According to the measurement, at 6 months in the control group, there are more patients in the criteria under poor (82%), and in the treatment group, there are more patients in the criteria under excellent (71.1%). There is good efficacy in the treatment group.

Discussion

Management of lateral epicondylitis has been a therapeutic challenge in the past. The goal of an orthopedic surgeon is to reduce the pain and tenderness after treatment of lateral epicondylitis and to avoid complications.

In the study, the mean age of patients in the control group was 40.67 years with a standard deviation of 9.97, and in the treatment group, 41.80 years with an SD of 8.92 which is comparable with the mean age of 43.5 years with an SD of 11 in the control group and 42.9 years with SD of 10.2 in a study by [16]. In a study by [12] the mean age was 46 years (range 30 to 74). Thus, it can be said that the results of the study are more or less comparable with other studies in the literature [12,13,14].

In the study out of 45 patients in the control group 17(37.8%) had non-dominant side involvement and 28(62.2%) patients had dominant side involvement, in the treatment group 20 (44.4%) had nondominant side involvement, and 25(55.6%) patients had dominant side involvement which is comparable with right side involvement in 3 patients and left side involvement in 17 patients and right side involvement in 15 patients and left side involvement in 5 patients in the study by[16]. In another study of the 14 subjects, 8 were men, 13 were right-handed, and 9 had LE affecting their dominant arm [17]thus it can overemphasize that right-sided patients are more commonly affected than males. There was a substantial difference reported between the treatment group and the control group in the

In the study, the VAS score at baseline was 9.13 ± 0.84 in the control group and 9.2 ± 0.86 in the treatment group which is comparable with the baseline VAS score of 8.05 ± 1.53 in the treatment group and 8.80 ± 1.28 in the control group in the study by 16]. In the present study, the VAS score at 3 weeks follow-up was 8.49 ± 1.18 in the control group and 5.29 ± 1.160 in the treatment group which is comparable with a VAS score of 3.15 ± 1.53 in the treatment group and 6.45 ± 0.75 in the control group in a study by [16]. 6 months follow-up VAS pain scores in the study were 8.60 ± 1.737 in the control group 1.76 ± 1.317 in the treatment group which is comparable with the VAS score of the study by [16] so it can be said that the results of the study are more or less comparable with other studies in literature.

In the present study, successful treatment was reported by all 45 patients (100%) in the treatment group and 4 patients (8.9%) in the control group which is comparable with the successful treatment of 95% of the patients treated with GTN in a study by [16] results of the current study are more or less comparable with other studies in the literature.

The study demonstrates that the topical application of glyceryl trinitrate (GTN) patches is significantly more effective than a placebo in reducing pain and improving function in patients with lateral epicondylitis (tennis elbow). The treatment group, which received GTN patches, showed a substantial reduction in pain as measured by the Visual Analogue Scale (VAS), with statistically significant improvements from baseline to the 3rd week and sustained benefits at the 6-month follow-up. In contrast, the control group receiving placebo patches showed minimal changes in pain levels, indicating no significant therapeutic effect. These findings suggest that GTN patches could be a valuable first-line treatment for managing pain and enhancing recovery in patients with tennis elbow, providing a non-invasive alternative with a clear benefit over a placebo. However, further studies with larger sample sizes and longer follow-up periods are recommended to confirm these results and explore the long-term safety and efficacy of this intervention.

Generalizability

The findings of this study may be generalized to a broader population of patients with lateral epicondylitis, given the use of a randomized, double-blind design and the inclusion of participants with varying ages and clinical characteristics. However, since the study was conducted in a single medical institution in India and involved a relatively small sample size, caution should be taken when applying the results to diverse settings or populations. Future research in multiple centers with larger, more diverse populations is needed to strengthen the generalizability of these findings across different demographics and healthcare environments.

Conclusion

This study concluded that topical use of glyceryl trinitrate achieves good functional outcomes in the treatment of lateral epicondylitis.

Limitation

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of a comparison group also poses a limitation for this study's findings.

Recommendation

Although a significant finding has been observed in this study. More such studies in a large cohort are required to confirm the findings. Topical application of glyceryl trinitrate should be the first line of treatment in the case of tennis elbow as significant improvement in the pain and functioning of the elbow is observed.

Acknowledgment

We express our gratitude towards the hospital staff to the patients participating in the study for their co-operation.

List of abbreviation

VAS- Visual analog score
TE- Tennis elbow
GTN- Glyceryl trinitrate.
LE- Lateral epicondylitis

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No funding was received.

Conflict of interest

The authors have no conflicting interests to declare.

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