

# Research Article/Özgün Araştırma

A Comparison of the short-term effects of steroid injection, prolotherapy and home-based physiotherapy in patients with chronic lateral elbow tendinopathy

# Kronik lateral dirsek tendinopatili hastalarda steroid enjeksiyonu, proloterapi ve fizyoterapinin kısa dönemdeki etkilerinin karşılaştırılması

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### Abstract

**Aim:** This study aims to compare the effects of steroid injection (SI), prolotherapy, and home-based physiotherapy on pain and function in short-term in chronic lateral elbow tendinopathy (LET) patients.

**Materials and Methods:** Patients with chronic LET admitted to the orthopedic clinic between 2022 and 2023 were divided into SI (n=17), prolotherapy (n=17) and home-based physiotherapy (n=17) groups. Visual Analogue Scale (VAS), Quick Disability Assessment of Arm, Shoulder and Hand Problems (QuickDASH), and Health Assessment Questionnaire (HAQ) for pain and function before, two, and six weeks after treatment were compared.

**Results:** Second and sixth-week VAS, QuickDASH and HAQ were significantly lower in SI and prolotherapy than home-based physiotherapy group (p=0.001). In the sixth week, sufficient improvement was achieved in VAS, QuickDASH and HAQ in SI compared to prolotherapy and home-based physiotherapy (p=0.001,  $\eta^2=0.30-0.42$ ).

**Conclusion:** SI, prolotherapy, and home-based physiotherapy improved elbow pain and function in short-term, but SI was greater effective. SI may be effective for short-term improvement in chronic LET patients.

**Keywords:** Elbow tendinopathy; Injections; Steroids; Prolotherapy; Physiotherapy.

## Öz

**Amaç:** Bu çalışmanın amacı, kronik lateral dirsek tendinopatili (LDT) hastalarda steroid enjeksiyonu (SE), proloterapi ve ev-tabanlı fizyoterapinin kısa dönemde ağrı ve fonksiyon üzerindeki etkilerini karşılaştırmaktır. **Gereç ve Yöntem:** 2022-2023 yılları arasında ortopedi kliniğine başvuran kronik LDT'li hastalar SE (n=17), proloterapi (n=17) ve ev-tabanlı fizyoterapi (n=17) gruplarına ayrılmıştır. Tedavi öncesi, ikinci ve altıncı hafta ağrı ve fonksiyon için Görsel Analog Skalası (GAS), Kol, Omuz ve El Sorunları Hızlı Anketi (QuickDASH) ve Sağlık Değerlendirme Ölçeği (SDÖ) karşılaştırıldı.

**Bulgular:** İkinci ve altıncı hafta GAS, QuickDASH ve SDÖ değerleri SE ve proloterapi grubunda ev-tabanlı fizyoterapi grubuna göre anlamlı şekilde düşüktü (p=0.001). Altıncı haftada GAS, QuickDASH ve SDÖ'de SE grubunda proloterapi ve ev-tabanlı fizyoterapiye göre etkili iyileşme sağlanmıştır (p=0,001,  $\eta^2$ =0,30-0,42).

**Sonuç:** SE, proloterapi ve ev-tabanlı fizyoterapi kısa dönemde dirsek ağrısı ve fonksiyonunu iyileştirmektedir, ancak SE daha etkilidir. SE kronik LDT'li hastalarda kısa dönemde iyileşme için etkili olabilir.

**Anahtar kelimeler:** Dirsek tendinopatisi; Enjeksiyonlar; Steroidler; Proloterapi; Fizyoterapi.

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Bu makale araştırma ve yayın etiğine uygun hazırlanmıştır. **Thenticate** intihal incelemesinden geçirilmiştir.

# Introduction

Lateral elbow tendinopathy (LET) or lateral epicondylitis is a clinical problem that occurs at the fibro-osseous junction of the common extensor tendon in the outer lateral region of the elbow.<sup>1</sup> The aetiology of LET is unknown, but micro-tears in the common extensor tendon usually occur due to overuse of the hand and repetitive grasping.<sup>2,3</sup> Accordingly, the main complaints seen in patients with LET are moderate to severe pain that significantly affects activities of daily living and inability to perform functional activities.<sup>4</sup> Clinical examination is usually the gold standard for diagnosing pain in the outer lateral region of the elbow, with resistant wrist extension being sufficient to make the diagnosis. However, in some cases, it needs to be supported by magnetic resonance imaging (MRI) findings.<sup>5</sup> In patients with persistent pain and other symptoms for the last three months or more. the process is considered chronic LET.<sup>6</sup>

Most patients with LET can be effectively treated with conservative treatment methods.<sup>6,7</sup> There are many conservative treatment modalities for LET, primarily extracorporeal shock wave therapy (ESWT), high-intensity laser therapy, physiotherapy; and then steroid injection, prolotherapy, autologous blood transfusion, platelet-rich plasma, botulinum toxin, ozone-oxygen solution, and hyaluronic acid.<sup>6,8,9</sup> Steroid injection, which is a conservative method used in patients with LET, has been reported to have a positive effect by providing early improvement in pain and other symptoms.<sup>10</sup> However, it is not clear whether the effects of steroid injection in patients with chronic LET will be sufficient for symptom relief.<sup>6</sup> Prolotherapy has also become a new conservative treatment option in chronic LET as a regenerative application in recent years.<sup>1</sup> Investigations in recent years have indicated that prolotherapy can be effective in reducing pain and improving function by stimulating the healing process in chronic musculoskeletal problems such as LET.<sup>6,11</sup> Physiotherapy techniques used in chronic LET include Cyriax manual therapy, ultrasound, transcutaneous electrical stimulation (TENS), kinesiological taping, eccentric wrist extensor muscle strengthening, stretching, soft tissue

mobilization, deep friction massage, and cold application.<sup>4,12-14</sup>

The evidence for the superiority of steroid injection, prolotherapy, and physiotherapy applications used in treating LET in pain and function needs to be clarified.<sup>2,6,7,11</sup> There is also a need for interventions such as prolotherapy and physiotherapy that can be an alternative to steroid injections that are frequently used in the clinic in patients with chronic LET.<sup>15,16</sup> Therefore, this study aimed to compare the short-term effects of steroid injection, prolotherapy, and home-based physiotherapy on elbow pain and function in patients with chronic LET.

# Materials and Methods

## Type of the study

The study was planned as a retrospective study.

## The sample size of the study

study consisted of data The from retrospectively reviewed files, including elbow pain and function of patients who met the inclusion criteria and were treated with three treatment methods. The data of 65 patients admitted to a private hospital's orthopedics and traumatology polyclinic between January 2022 and April 2023 due to pain on the lateral outer side of the elbow and who were diagnosed with chronic LET as a result of MRI examinations and pain on palpation in the humeral lateral epicondyle on clinical examination by a specialist orthopaedist were retrospectively analyzed. After the review, 51 patients with complete data, including before the treatment, second-week, and sixth-week after treatment outcomes, were divided into steroid injection (n=17), prolotherapy (n=17), and home physiotherapy (n=17) groups. Inclusion criteria were pain of at least 4 according to the Visual Analogue Scale (VAS) for the last three months and increased signal intensity at the common extensor tendon origin on MRI. Exclusion criteria were defined as exposure to local trauma that may be related to LET in the last three months, surgery around the elbow in the last six months, history of injection for LET in the last six months, diabetes, inflammatory arthropathy, and systemic comorbidities.

All patients included in the study were taught a standard home-based physiotherapy exercise program by а specialist physiotherapist, including stretching for the extensor muscles of the wrist, eccentric strengthening of the extensor muscles of the wrist, friction massage, and cold application, and all patients were given information and follow-up chart as а home-based physiotherapy program (Table 1). All patients were asked to perform the home-based physiotherapy program twice a day for a total of 6 weeks. The home-based physiotherapy exercise program was demonstrated and taught to all patients by the same specialist physiotherapist and given as a home-based program.<sup>17</sup> The wrist extensor stretching exercise was shown to the patients with the elbow in elbow extension and forearm in pronation with the wrist in full flexion. All patients were shown that the wrist extensor stretching exercise should be performed for 30 seconds and six repetitions.<sup>4</sup> Eccentric strengthening training for the wrist extensor muscles was taught by demonstrating that it should be done with an elastic resistance band as six repetitions x 2 sets.<sup>18</sup> The exercising arm was positioned on the bed with the elbow in full extension, the forearm in pronation, the wrist in full extension, and the hand hanging over the edge of the bed. Patients were demonstrated to slowly flex their wrists while counting to 30 in this position against resistance and then return to the starting position with the help of the other hand. When the patients could perform the eccentric exercises without mild pain or discomfort, the load of the elastic resistance band was increased.<sup>19,20</sup> For the friction massage, the application of deep friction massage along the common extensor tendon was demonstrated to patients.<sup>21</sup> At the end of the home-based physiotherapy program, the cold application was taught by demonstrating its application from proximal to distal along the common extensor tendon with a pressurized massage.<sup>6</sup> All patients were advised to wear protective bracing for approximately 3-4 hours daily.<sup>12</sup>

In the steroid injection group, in addition to home-based physiotherapy, the skin was stained with povidone-iodine and ethyl alcohol. Approximately 0.5 cm anterior and 0.5 cm distal to the lateral epicondyle were marked with the patient sitting with the elbow flexed 90 degrees and the forearm pronated. The injection site was entered with an 18gauge needle and advanced. A solution prepared with 2 ml of 4% lidocaine and 1 ml of triamcinolone (5 mg/ml triamcinolone hexacetonide) was injected without exiting the skin, and the injection was completed by withdrawing and redirecting.<sup>22</sup>

In the prolotherapy group, in addition to home-based physiotherapy the skin was again stained with povidone-iodine. Approximately 0.5 cm anterior and 0.5 cm distal to the lateral epicondyle were marked with the patient sitting with the elbow flexed 90 degrees and forearm pronated. Injection with 5 ml of 30% dextrose, 2.5 ml of 4% lidocaine, and 2.5 ml of 0.4% sensorcain was administered around the epicondyle and tendon with an 18-gauge needle.<sup>23</sup> The specialist orthopedist who diagnosed LET performed all the steroid and prolotherapy injections. Injections were administered once after the first evaluation in the steroid injection or prolotherapy groups during the study period.

# Data collection tools

Demographic data of all patients were recorded. The results of the VAS used to evaluate elbow pain and the Quick Disability Assessment of Arm, Shoulder and Hand Problems (QuickDASH) and Health Assessment Questionnaire (HAQ) used to evaluate elbow function were examined and recorded before treatment, two weeks after treatment, and six weeks after treatment.

Visual Analogue Scale: VAS is one of the most commonly used scales for assessing adult pain. In our study, all patients were asked to mark the severity of their activity pain on a 10 cm VAS with 0 and 10 markers, and the marked part was recorded in mm.<sup>24</sup>

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Table 1. A standardized home-based Physiotherapy program.

1) Stretching for the extensor muscles of the wrist

- Bring the wrist to full flexion with the help of your fingers, with the elbow in full extension, as shown in the picture on the side.
- Perform 6 repetitions x 30 seconds



#### 2) Eccentric strengthening of the extensor muscles of the wrist

- The exercising arm was positioned on the table with the elbow in full extension, the forearm in pronation, the wrist in full extension, and the hand hanging over the edge of the table, as shown in the picture on the side.
- Slowly flex your wrists 30 second in this position against resistance and then return to the starting position with the help of the other hand.



		• Perform 6 repetitions x 2 sets													
	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
1st week								1st week							
2nd week								2nd week							
3rd week								3rd week							
4th week								4th week							
5th week								5th week							
6th week								6th week							
3) Friction massage					4) Cold pack application										

- Place your thumb along the common extensor tendon.
- Apply enough pressure friction massage to feel mild pain for nearly three to five minutes.



- Place a coldpack on the distal half of the forearm and apply a pressurized massage starting from this position towards the proximal part of the common extensor tendon.
- Repeat for 3-5 minutes.



	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday		Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
1st week								1st week							
2nd week								2nd week							
3rd week								3rd week							
4th week								4th week							
5th week								5th week							
6th week								6th week							

Remember to fill in the blanks on the follow-up charts after doing the exercises

Quick Disability Assessment of Arm, Shoulder and Hand Problems: QuickDASH is a Likert-type scale to assess physical function in patients with upper extremity musculoskeletal disorders. QuickDASH consists of 11 items, and each question is scored between 1 and 5. A score of 1 indicates no strain, and a score of 5 indicates inability to perform the specified activity. The QuickDASH total score ranges from 0 to 100 (0) points=no impairment and 100 points=severe impairment). Lower scores indicate a better functional level.<sup>25</sup>

Health Assessment Questionnaire: HAO is a scale that assesses the patient's upper extremity fine movements, lower extremity locomotor activities, and activities involving the upper and lower extremities in the last are 20 questions week. There in subcategories, including dressing, standing up, eating, walking, hygiene, reaching, grasping, and daily tasks. Each question is scored between 0 and 3 (0=not difficult at all; 1=somewhat difficult; 2=very difficult, and 3=cannot do). The total score is calculated by dividing the total score of the items marked by the number of items marked. Scores between 0 and 1 on the scale generally indicate mild to moderate difficulty, a score between 1 and 2 indicates moderate to severe disability, and a score between 2 and 3 indicates severe disability.26

## **Data analysis**

SPSS (Version 25; IBM, Armonk, NY, USA) program was used to evaluate the data

obtained statistically. Data were presented as mean and standard deviation. Analysis of variance test (ANOVA) was used to compare the groups when normal distribution data were provided; Kruskal Wallis analysis was used when non-normal distribution data were provided. Repeated measures ANOVA test was used for repeated measurements. The statistical significance level was accepted as *p*<0.05.

## **Ethics committee approval**

Ethics committee approval of the study was obtained from the Muş Alparslan University Scientific Research and Publication Ethics Committee (19.04.2023-90203-4/71). The study was conducted under the principles of the Declaration of Helsinki. Informed consent form was obtained from all patients.

## Results

When demographic data were analysed, there was no difference between the groups in age and body mass index (BMI) (p>0.05). In the steroid injection and prolotherapy groups, 52.9% (n=9) of the patients were female and 47.1% (n=8) were male. In the home-based physiotherapy group, 58.8% (n=10) were female and 41.2% (n=7) were male. In the steroid injection and prolotherapy groups, 94.1% (n=16) of the patients had dominant limb involvement, while 5.9% (n=1) had nondominant involvement. In the home-based physiotherapy group, 88.2% (n=15) of the patients had an affected dominant limb, while 11.2% (n=2) had a non-dominant limb (Table 2).

	Steroid (n <sup>:</sup>	Injection <sup>1</sup> =17)	Prolot (n <sup>:</sup>	herapy <sup>2</sup> =17)	Physio (n	otherapy <sup>3</sup> =17)	p
Age (year)	Mean (	95% CI)	Mean (	95% CI)	Mean	- 1	
Body mass index	36.17 (32	2.85-39.49)	37.58 (33	3.88-41.29)	37.52 (3)	3.25-41.80)	0.772
$(kg/m^2)$	29.24 (27	7.83-30.65)	29.34 (27	7.64-31.04)	29.54 (2)	7.98-31.11)	0.957
	n	%	n	%	n	%	
Sex							
Female	9	52.9	9	52.9	10	58.8	
Male	8	47.1	8	47.1	7	41.2	
Dominant extremity							
Right	14	82.4	15	88.2	15	88.2	
Left	3	17.6	2	11.8	2	11.8	
Affected extremity							
Dominant	16	94.1	16	94.1	15	88.2	
Non-dominant	1	5.9	1	5.9	2	11.8	

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One-way analysis of variance (ANOVA), kg: kilogram, m: meter, p: Independent group comparison analysis value, CI: 95% confidence interval

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There was no difference between the groups in elbow pain and elbow function in pretreatment evaluations (p>0.05). In the second week of post-treatment evaluations, VAS elbow pain, QuickDASH, and HAQ elbow function were significantly lower in the steroid injection group compared to both prolotherapy and home-based physiotherapy groups

and in the prolotherapy group compared to the home-based physiotherapy group (p=0.001). At six weeks after treatment, VAS elbow pain, QuickDASH, and HAQ elbow function were significantly lower in the steroid injection and prolotherapy group compared to the home-based physiotherapy group (p=0.001) (Table 3).

**Table 3.** Comparison of the groups regarding elbow pain and function before, 2nd, and 6th weeks after treatment.

	Steroid Injection <sup>1</sup>	Prolotherapy <sup>2</sup>	Physiotherapy <sup>3</sup>	
Variables	(n=17)	(n=17)	(n=17)	$p^{1}$
	Mean (95% CI)	Mean (95% CI)	Mean (95% CI)	
VAS (mm)				
Before treatment	79.05 (74.28-83.82)	75.29 (70.23-80.35)	73.29 (68.52-78.06)	0.208 (F=1.624)
2nd week after treatment	13.58 (9.32-17.84)	27.76 (20.14-35.38)	50.11 (40.57-59.65)	0.001*1-2, 1-3, 2-3 (F=27.356)
6th week after treatment	6.01 (3.84-8.15)	11.05 (5.43-16.68)	31.29 (20.09-42.49)	0.001*1-3, 2-3 (F=14.940)
$p^2$		0.001 ( $\eta^2$ =0.38)		
HAQ				
Before treatment	1.03 (0.93-1.12)	1.11 (1.05-1.18)	1.13 (1.06-1.19)	0.108 (F=2.334)
2nd week after treatment	0.33 (0.24-0.42)	0.61 (0.51-0.71)	0.88 (0.75-1.02)	0.001* <sup>1-2, 1-3, 2-3</sup> (F=28.359)
6th week after treatment	0.10 (0.09-0.22)	0.33 (0.24-0.42)	0.73 (0.53-0.94)	$0.001^{*1-3, 2-3} (F=22.752)$
$p^2$		$0.001 (\eta^2 = 0.30)$		
QuickDASH				
Before treatment	49.86 (44.07-55.65)	44.24 (41.26-47.23)	46.92 (43.94-49.89)	0.137 (F=2.072)
2nd week after treatment	12.02 (8.26-15.78)	24.72 (22.08-27.36)	36.89 (31.11-42.66)	0.001*1-2, 1-3, 2-3 (F=38.265)
6th week after treatment	4.67 (2.47-6.87)	12.42 (7.80-17.04)	28.47 (20.65-36.29)	0.001*1-3, 2-3 (F=21.806)
<i>p</i> <sup>2</sup>		$0.001 (\eta^2=0.42)$		· · · ·

One-way analysis of variance (ANOVA), p': p value for the difference between independent groups, CI: 95% confidence interval, HAQ: Health Assessment Scale, QuickDASH: Quick Disability Assessment of Arm, Shoulder and Hand Problems

Repeated measures analysis of variance,  $p^2$ : p value for difference in dependent groups,  $\eta^2$ : Effect size p<0.05 statistically significant difference

The change in VAS pain level in the groups at the sixth week after treatment compared to pretreatment was  $73.05\pm2.28$  mm in the steroid injection group,  $64.23\pm4.14$  mm in the prolotherapy group, and  $42\pm5.40$  mm in the home-based physiotherapy group (Figure 1). The change in QuickDASH elbow function score was  $45.18\pm11.91$  points in the steroid injection group,  $31.82\pm1.56$  points in the prolotherapy group, (Figure 2). The change in HAQ score was  $0.87\pm0.15$  points in the steroid injection

group,  $0.78\pm0.11$  points in the prolotherapy group, and  $0.39\pm0.42$  points in the home-based physiotherapy group (Figure 3).

#### Discussion

In this study, which aimed to compare the effects of steroid injection, prolotherapy, and home-based physiotherapy on short-term elbow pain and function in patients with chronic LET, steroid injection was found to be more effective than prolotherapy and home-based physiotherapy in improving short-term pain and function in patients with chronic LET.

Prolotherapy was more effective than homebased physiotherapy in improving elbow pain and function in the short term.



Figure 1. Changes in VAS pain level at the 6th week after treatment compared to pre-treatment in the groups



Figure 2. Changes in QuickDASH elbow function scores in the groups at the 6th week after treatment compared to pretreatment



Figure 3. Changes in HAQ elbow function scores in the groups at the 6th week after treatment compared to pre-treatment.

Elbow pain is the most common symptom in individuals with chronic LET.<sup>3</sup> In a study conducted in patients with chronic LET, it was found that steroid injection and prolotherapy relieved elbow pain in the early period. However, prolotherapy provided more extended pain relief than steroid injection in the later period.<sup>27</sup> Another study compared the 6-week follow-up of steroid injection and prolotherapy and found that steroid injection was more effective in pain relief.<sup>3</sup> The effects of a physiotherapy using muscle energy techniques and steroid injection treatments were compared in patients with chronic LET, and it was reported that steroid injection was more effective than physiotherapy intervention in relieving pain six weeks after treatment.<sup>28</sup> However, a study showed that a total of 8 sessions of 30 minutes of physiotherapy, including grip exercises, wrist extensors, supinator-pronator and biceps and triceps brachii strengthening, shoulder and bench press, and elbow manipulation, provided pain relief similar to steroid injection in patients with LET.<sup>29</sup> In a study that included manual therapy, therapeutic exercise, sensorimotor grip, and posture correction, progressive resistance exercise for the wrist extensor and general muscles, upper extremity strengthening training and lasted four sessions

per week for six weeks, physiotherapy was found to be more effective in relieving pain than prolotherapy injection.<sup>30</sup> In this study, steroid injection was found to be more effective in relieving pain in patients with chronic LET than both prolotherapy and homebased physiotherapy at two weeks and prolotherapy and home-based physiotherapy at six weeks after treatment. These results are in accord with recent studies indicating that steroid injection was highly influential early after the intervention. The home-based physiotherapy program applied to all groups in this study may have contributed to pain levels, and the short-term efficacy of steroid injection in the short term in chronic LET patients may explain pain-relieving than prolotherapy or home-based physiotherapy.

The common goal of conservative treatment methods such steroid injections. as prolotherapy, and physiotherapy used to improve functional outcomes in patients with LET is to increase the patient's functional level.<sup>4,7,16</sup> A study comparing the effects of prolotherapy and steroid injection on elbow function in patients with chronic LET found that patients who received steroid injections eight weeks after the intervention had better elbow function scores.<sup>15</sup> Similarly, it was reported that steroid injection and prolotherapy

improved elbow function in both groups in the first and third-month measurements after application in patients with LET. However, the steroid group had a better elbow function score.<sup>31,32</sup> Studies comparing steroid injection and physiotherapy interventions determined that steroid injection was more effective than physiotherapy regarding elbow functions in the sixth week after treatment.33,34 However, physiotherapy is also reported to be effective compared to routine drug treatment prescribed in patients with chronic LET. Eccentric strengthening, range of motion exercises, and stretching have been shown to provide positive results in patients at 6-week follow-up.<sup>8</sup> In this study, steroid injection administered to patients with chronic LET improved elbow function more than prolotherapy and homebased physiotherapy at two weeks and prolotherapy and home-based physiotherapy intervention at six weeks after treatment. This result may have occurred due to the effectiveness of the home-based physiotherapy program given to all of the patients in our study, based on the findings in the general literature, and the relief of pain in a short time. Informing the patients to avoid painful and strenuous activities, which is one of the primary factors in the occurrence of LET, and providing recommendations may have contributed to the functional improvement of the elbows of the patients in our study. In addition, although there is insufficient evidence for its physiologic effects,<sup>19</sup> we think that the wrist eccentric exercise used in our study also contributed to the healing process in all patients.

# Limitations

This study has several limitations. The first and most important one is that we could not obtain sufficient information about the patient's compliance with the home-based physiotherapy program, which was taught to the patients in our study and had an exercise follow-up chart. Our second limitation is that we could not perform long-term follow-up in the study. Lastly, we could not record medication use after the interventions.

## Conclusion

This study has identified that steroid injection, prolotherapy, and home-based physiotherapy were found to improve pain and function in patients with chronic LET in the short term. However. steroid injection improved elbow pain and function more effectively than prolotherapy and home-based physiotherapy in the short term. If pain and elbow function improvement is aimed in a short time in patients with chronic LET, the use of steroid injection in combination with a standard home-based physiotherapy program may be more effective and may be appropriate. In future studies, long-term follow-up comparisons of steroid injection and prolotherapy interventions combined with a structured physiotherapy program are needed.

# **Ethics Committee Approval**

Ethics committee approval of the study was obtained from the Muş Alparslan University Scientific Research and Publication Ethics Committee (19.04.2023-90203-4/71). The study was conducted under the principles of the Declaration of Helsinki.

# **Informed Consent**

Informed consent form was obtained from all patients.

# Author Contributions

All authors have participated in the conception and design, data collecting, literature review, drafting the article, or revising it critically for important intellectual content. Resources/materials: HZ. Data analysis and interpretation: GB. The final version of this article was read and approved by all authors.

# **Conflict of Interest**

The authors have no conflicts of interest to declare.

# **Financial Disclosure**

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# **Peer-review**

Externally peer-reviewed

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