



ISSN: 2230-9926

Available online at <http://www.journalijdr.com>

# IJDR

International Journal of Development Research

Vol. 12, Issue, 04, pp. 55244-55249, April, 2022

<https://doi.org/10.37118/ijdr.23042.04.2022>



RESEARCH ARTICLE

OPEN ACCESS

## TREATMENT WITH PLASMA RICH IN PLATELETS IN LATERAL EPICONDYLITIS: SYSTEMATIC REVIEW

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### ARTICLE INFO

#### Article History:

Received 10<sup>th</sup> January, 2022

Received in revised form

26<sup>th</sup> February, 2022

Accepted 20<sup>th</sup> March, 2022

Published online 27<sup>th</sup> April, 2022

#### Key Words:

Platelet-rich Plasma;  
Lateral Epicondylitis; Treatment;  
Efficiency.

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### ABSTRACT

**Introduction:** Therapies using platelet-rich plasma (PRP) are becoming widely used, especially in sports medicine, where early return to function is a major concern. Assuming these therapies are based on a biological stimulus that accelerates the recovery of degenerated tissues, thus allowing for an early return to activities, their use has spread to a multitude of orthopedic pathologies, but clear proof of their clinical effectiveness is yet to be demonstrated. For these reasons, the present study aimed to evaluate, through a systematic review, the use of platelet-rich plasma in the treatment of lateral epicondylitis of the elbow. **Methods:** Two reviewers independently performed a search with the same descriptors and in the Pubmed, Medline and Embase databases, for studies published until July 2, 2019. The following descriptors were used: "Lateral epicondylar tendinopathy"; "Treatment"; "Platelet-rich plasma"; "Efficacy". The following filters were used to reach the expected final result: "Randomized Controlled Trial"; "Randomized Clinical Trial"; "MetaAnalysis"; "Systematic Reviews"; "Clinical Trial"; "Cohort". **Results:** There was a very strong correlation between the searches of the two researchers ( $k=0.801$ ). In the end, 36 complete studies remained, of which 20 were included. As general characteristics, a total of 819 patients treated with Platelet Rich Plasma (PRP) were included in this review. Mean age, dominant side, and disease duration ranged from 34 to 50 years, 57 to 85%, and 5 to 18 months, respectively. The percentage of men ranged from 18 to 57%. The average satisfaction rate was 86%, and complications were reported with an average of 6.02%. Heterogeneity was observed in relation to the study design. The selected articles presented the following characteristics: randomized clinical study, meta-analysis, systematic review and cohort study. The predominance in the literature surveyed was the absence of a gold standard in the treatment of lateral elbow epicondylitis, even with positive results in most studies that used PRP. **Conclusion:** In this review, it was evidenced that medical advances in using PRP therapy are a reality, the clinical results presented by the studies do not demonstrate consensus on its effectiveness and do not guarantee the success of the therapy in face of side effects such as pain. However, its results are promising. Further studies with level of evidence I and II, in number of relevant patients, are still needed to definitively answer this question.

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**Citation:** Herison Franklin Viana de Oliveira, Francisco Robson Queiroz Rego, Kennet Wandersson Leite Silva, Vinicius Herison Franklin Viana de Oliveira Buenos Aires and Epiácio Leite Rolim Filho. "Treatment with plasma rich in platelets in lateral epicondylitis: Systematic review", *International Journal of Development Research*, 12, (04), 55244-55249.

## INTRODUCTION

Lateral elbow epicondylitis is a commonly diagnosed condition of the athlete's elbow, having been associated with the term "tennis elbow". Despite this classic description related to the sport of tennis, only 5 to 10% of patients with epicondylitis practice this sport. Elbow tendinosis is more common in non-athlete patients, with a prevalence of approximately 1% to 3% in the general population (1-10). The condition occurs mainly in patients whose activities require repetitive movements of supination or pronation of the forearm with the elbow extended.

Individuals between the ages of 35 and 50 years are the most affected, with similar involvement in both sexes and with a predominance of the dominant limb (1-7). The etiology of lateral epicondylitis is unknown. It is believed to have a multifactorial component, initially occurring due to microlesions at the origin of the extensor musculature of the forearm, evolving due to a combination of mechanical overload and abnormal microvascular responses, with the formation of immature repair tissue and angiofibroblastic hyperplasia. The most frequent involvement of the short radial extensor tendon of the carpus, which may also involve the common extensor tendon of the fingers (8-15). Diagnosis is basically made by observing the patient's history and clinical examination. The main complaint is pain

mainly in the topographical location 5mm distal and anterior to the lateral epicondyle, extending to the dorsum of the forearm and with incapacity for sports practice and substantial loss of professional productivity. (11-15). Numerous methods have been advocated for the treatment of elbow tendinosis, including rest, nonsteroidal anti-inflammatory medication, bracing, physical therapy, extracorporeal shock wave therapy, acupuncture, botulinum toxin application, corticosteroid injection (previously considered the gold standard, but now controversial), injection of autologous blood, application of platelet-rich plasma, as well as various types of surgical procedures. (2-18). As of 2003, the first experimental trials using humoral mediators as a possible treatment for adequate tendon repair were reported. Platelets have shown a role in the inflammatory response by collaborating with growth factor secretion and repair cell recruitment (7-12). Together with platelets, alpha granules form a unit with inactivated growth factors; these are transformed into growth factor beta, endothelial growth factor, platelet growth factor and epithelial growth factor (7-12). All these factors together cooperate for the recruitment, proliferation and differentiation of cells involved in tissue regeneration (11-19).

In 2011, Thanasis et al, carried out a study where 28 patients were randomly divided into two groups; the first group received an application of 3 ml of autologous blood and the second group received 3 ml of platelet-rich plasma (PRP). In this investigation, they concluded that platelet-rich plasma was an effective treatment for chronic elbow epicondylitis compared to the application of autologous blood alone; however, there were still no studies with a strong enough level of evidence in the literature. Currently, therapies with platelet-rich plasma (PRP) are being used increasingly in the treatment of musculoskeletal soft tissue injuries, such as muscle tendinopathies, ligamentous and tendinous pathologies. These therapies can be used as the main treatment or as an adjunct procedure (application after surgical repair or reconstruction). Platelet-rich plasma (PRP) is produced by centrifuging a quantity of the patient's own blood and extracting the active platelet-rich fraction. The platelet-rich fraction is applied to the injured tissue; for example, by injection at the site. These platelets have the ability to produce a variety of growth factors and are expected to improve tissue healing. For all these reasons, the main objective of the present study was to evaluate, through a systematic review, the treatment with platelet-rich plasma in lateral epicondylitis (LE). Thus, this study aims to carry out a systematic review of the results obtained in treatment with platelet-rich plasma for patients with lateral epicondylitis of the elbow, as well as patient satisfaction and major complications.

## METHODS

**Search strategy:** Two reviewers independently performed a search with the same descriptors and in the Pubmed, Medline and Embase databases, for studies published until July 2, 2019. The following descriptors were used: Lateral epicondylar tendinopathy; Treatment; Platelet-rich plasma; Effectiveness. The following filters were used to reach the expected final result: "Clinical Trial"; "Randomized Controlled Trial"; "Randomized Clinical Trial"; "Meta-Analysis"; "Systematic Reviews"; "Cohort".

### Eligibility and selection criteria

The studies found were submitted to the following inclusion criteria:

- Studies related to the proposed topic;
- Studies with evidence level I and II;
- Studies published in indexed journals;
- Articles in languages: English, Spanish and Portuguese;
- Research carried out on humans;
- Articles available in full version.

Exclusion criteria were:

- Simple case report studies or methodology with low reliability, outside the framework of the inclusion criteria.

**Investigated variables and extracted data:** Two independent investigators took part in the searches. Which followed the same criteria in the selected studies, collecting the following data: study design; objective and outcome of the study.

## RESULTS

**Identification of studies and characteristics:** According to the search strategy, 122 studies were found with the aforementioned descriptors, which were again evaluated according to their design and relevance according to the type of study filters and inclusion criteria. There was a very strong correlation between the searches of the two researchers ( $k=0.801$ ). In the end, 36 complete studies remained, of which 20 were included (Table 1).15-34. As general characteristics, a total of 819 patients treated with PRP were included in this review. Mean age, dominant side, and disease duration ranged from 34 to 50 years, 57 to 85%, and 5 to 18 months, respectively. The percentage of men ranged from 18 to 57%.

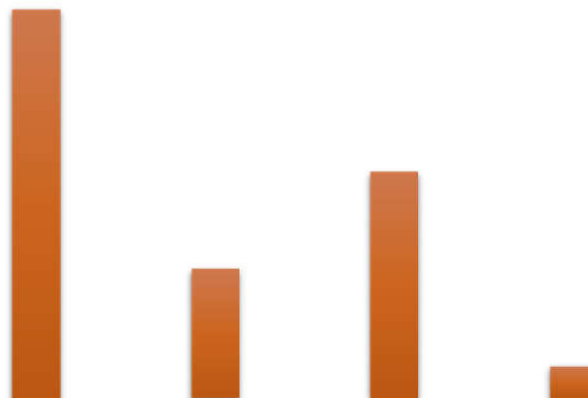


Figure 1. Number of articles according to study design



Figure 2. Representation of the number of articles that reported positive and negative results with the use of PRP in the treatment of lateral epicondylitis

The average satisfaction rate was 86%, and complications were reported averaging 6.02%. Heterogeneity was observed in relation to the study design (Figure 1). The results were positive in 90% (18) and negative in 20% of the articles (2) included (Figure 2). The selected articles presented the following characteristics: randomized clinical study, meta-analysis, systematic review and cohort study. The predominance in the literature surveyed was the absence of a gold standard in the treatment of lateral elbow epicondylitis, even with positive results presented with the use of PRP. The studies collected can be seen in Table 1 below.

Table 1. Representation of the articles collected in the study

STUDY	DESIGN STUDY	OBJECTIVE	OUTCOME CLINICAL
Arthroscopic debridement versus Platelet-Rich Plasma Injection: A Prospective, Randomized, Comparative Study of Chronic Lateral Epicondylitis With a Nearly 2-Year Follow-Up. Merolla et al (2017)	Clinical Randomized Trial To	compare the efficacy of autologous platelet-rich plasma (PRP) injections and lateral release arthroscopic in the treatment of chronic lateral epicondylitis.	(1) PRP injections and arthroscopic release of the extensor radialis carpi brevis are effective in the short and medium term; (2) patients with PRP had a significant worsening of pain at 2 years; (3) arthroscopic release ensured better long-term results in time to pain relief and grip strength recovery; and (4) both procedures were safe and well accepted by patients.
Platelet rich plasma versus steroid on lateral epicondylitis: meta-analysis of randomized clinical trials. Mi et al (2017)	Meta-analysis of a randomized clinical trial.	Compare the results of platelet-rich plasma versus steroid in lateral epicondylitis.	Treatment of EL patients with steroids can mildly relieve pain and significantly improve elbow function in the short term (2-4 weeks, 6-8 weeks). PRP appears to be most effective in relieving pain and improving function in the medium term (12 weeks) and long term (half a year and a year).
Autologous whole blood or corticosteroid injections for the treatment of epicondylopathy and plantar fasciopathy? Tsikopoulos et al (2016)	Meta-analysis of a randomized clinical trial.	PRPS or corticosteroid injections for the treatment of epicondylitis and plantar fasciitis.	Corticosteroids were marginally superior to PRP in pain relief in plantar fasciitis at 2-6 weeks. PRP provided significant clinical relief in epicondylopathy within 8-24 weeks.
Treatment of elbow epicondylitis with platelet rich plasma versus local corticosteroids. Martínez-Montiel et al (2016)	Clinical Randomized Trial.	Treatment of epicondylitis of the elbow with platelet-rich plasma versus local corticosteroids.	The results show that platelet-rich plasma provided better results from the perspective of pain control and effect duration.
Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis: systematic review and network meta-analysis. Arirachakaran et al (2016)	Systematic review and network meta-analysis.	Platelet-rich plasma versus autologous blood versus steroid injection in lateral epicondylitis.	This network meta-analysis provided additional information that PRP injection may improve pain and decrease the risk of complications, whereas steroid injection may improve pain, disability scores, and pressure pain threshold, but has a risk of complications.
Platelet-rich plasma versus corticosteroid injection for lateral recalcitrant epicondylitis: clinical and ultrasonographic evaluation. Gautam et al (2015)	Clinical Randomized Trial	Platelet-rich plasma versus corticosteroid injection for lateral epicondylitis.	PRP appeared to allow biological healing of the lesion, whereas corticosteroids appeared to provide short-term symptomatic relief, but resulted in tendon degeneration.
Platelet-Rich Plasma Compared With Other Common Injection Therapies in the Treatment of Chronic Lateral Epicondylitis. Rodik et al (2016) Epud (2014)	Systematic review	Platelet-rich plasma compared to other common injection therapies in the treatment of chronic lateral epicondylitis.	Consistent findings from randomized controlled trials suggest Level 1b evidence in support of PRP injection as a treatment for EL.
Impact of platelet rich plasma over alternative therapies in patients with lateral epicondylitis (IMRPOVE) Chiavaraset al (2014)	Multicenter randomized controlled trial	Randomized, multicenter study comparing autologous platelet-rich plasma, autologous whole blood, dry needle tendon fenestration, and physical therapy exercises isolated on pain and quality of life in patients with lateral epicondylitis.	Ongoing study, with no published clinical results.
Strong evidence against platelet-rich plasma injections for chronic lateral epicondylar tendinopathy: a systematic review. de Vos et al (2014)	Systematic review	review the literature on the effectiveness of PRP injections in chronic lateral epicondylar tendinopathy.	There is strong evidence that PRP injections are not effective in the treatment of chronic lateral elbow tendinopathy.
Platelet-rich therapies for musculoskeletal soft tissue injuries. Moraes VY et al (2014)	Systematic review	Evaluate the effects (benefits and harms) of platelet-rich therapies for the treatment of musculoskeletal soft tissue injuries.	There is currently insufficient evidence to support the use of PRP in the treatment of musculoskeletal soft tissue injuries. Researchers contemplating RCTs should consider the coverage of studies currently underway when assessing the need for future RCTs in specific conditions. There is a need for standardization of PRP preparation methods.
The effect of platelet-rich plasma on clinical outcomes in lateral epicondylitis. Ahmad et al (2013)	Systematic review	Evaluate the evidence for the application of platelet-rich plasma (PRP) in lateral epicondylitis.	This review highlights the limited but evolving evidence for the use of PRP in lateral epicondylitis; however, more research is needed to understand the concentration and preparation that facilitate the best clinical outcome.

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Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Mishra et al (2014) Epud (2013)	Randomized controlled trial.	To assess the clinical value of tendon needling with PRP in patients with chronic lateral epicondylitis compared to an active control group.	No differences significant were found at 12 weeks in this study. At 24 weeks, however, clinically significant improvements were found in patients treated with leukocyte-enriched PRP compared to an active control group. There were no significant complications in the 2 groups.
Treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoid, or saline: a randomized, double-blind, placebo-controlled trial. Krogh et al (2013)	Randomized controlled trial.	Compare the treatment of lateral epicondylitis with platelet-rich plasma, glucocorticoids, or saline solution.	Neither PRP injection nor glucocorticoid was superior to saline in terms of pain reduction in EL in the primary endpoint at 3 months. However, glucocorticoid injection had a short-term pain-reducing effect at 1 month, in contrast to other therapies. EL injection of glucocorticoid reduced both color Doppler activity and tendon thickness compared to PRP and saline.
Comparative effectiveness of injection therapies in lateral epicondylitis: a randomized systematic review and network meta-analysis of controlled trials. Krogh et al (2013)	Systematic review and meta-analysis and meta-analysis	Assessing the comparative efficacy and safety of different injection therapies in patients with lateral epicondylitis	This systematic review of a network of randomized clinical trials found a paucity of evidence from unbiased trials to substantiate the treatment recommendations on injection therapies for lateral epicondylitis.
Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis: a randomized controlled clinical trial. Thanasis et al (2011)	Randomized controlled clinical trial.	Platelet-rich plasma versus autologous whole blood for the treatment of chronic lateral elbow epicondylitis.	Regarding pain reduction, treatment with PRP seems to be an effective treatment for chronic lateral epicondylitis of the elbow and superior to autologous blood in the short term. The definition of indication details, better concentration of PRP, number and time of injections, as well as the rehabilitation protocol, can increase the effectiveness of the method.
Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Gosens et al (2011)	Randomized controlled clinical trial.	Platelet-rich plasma versus corticosteroid injection in lateral epicondylitis	Treatment of patients with chronic lateral epicondylitis with PRP reduces pain and significantly increases function, exceeding the effect of corticosteroid injection even after a 2-year follow-up. Future decisions to apply PRP for lateral epicondylitis should be confirmed by further follow-up of this study and should take into account possible costs and harms, as well as benefits.
Growth factor-based therapies provide additional benefit beyond physical therapy in resistant elbow tendinopathy: a prospective, single-blind, randomized trial of autologous blood injections versus platelet-rich plasma injections. Creaney et al (2011)	Clinical Randomized Trial	Autologous blood injections versus platelet-rich plasma injections in lateral epicondylitis.	In patients who are resistant to first-line physiotherapy, such as eccentric loading, autologous blood injections or PRP are useful second-line therapies to improve clinical outcomes. In this study, up to seven out of ten difficult-to-treat patients benefit from a surgery-sparing intervention.
Positive effect of an autologous platelet concentrate in lateral epicondylitis in a randomized double-blind controlled trial: platelet-rich plasma versus corticosteroid injection with a 1-year follow-up. Peerbooms et al (2010)	clinical trial Randomized	Platelet-rich plasma versus corticosteroid injection with 1-year follow-up in lateral epicondylitis.	Treating patients with chronic lateral epicondylitis with PRP reduces pain and significantly increases function, exceeding the effect of corticosteroid injection.
A systematic review of four injection therapies for lateral epicondylitis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. Rabago et al (2009)	Systematic review	Evaluate existing evidence of prolotherapy, polidocanol, autologous whole blood, and platelet-rich plasma injection therapies for EL.	There is strong evidence for the use of all therapies. New studies are needed to define who stands out over the other.
Treatment of chronic elbow tendinosis with buffered platelet-rich plasma. Mishra et al (2006)	Study Cohort	Treatment of chronic elbow tendinosis with buffered platelet-rich plasma.	Treating patients with chronic elbow tendinosis with platelet-rich plasma buffered significantly reduced pain in this pilot investigation. Further evaluation of this new treatment is recommended. Finally, platelet-rich plasma must be considered before surgical intervention.

## DISCUSSION

Lateral epicondylitis is a disease whose etiology is still not completely understood, of multifactorial origin. Histopathological studies have shown that this is tendinosis due to a combination of mechanical overload and abnormal microvascular responses. Therefore, the treatment becomes a challenge, with the use of various therapeutic techniques, from the conservative ones, most recommended in most cases, to surgical intervention. Among the varied possibilities of conservative treatment, there is a lot of discussion in the literature about the best option to be used. In this study, we aim to evaluate the efficacy and safety of using platelet-rich plasma in the treatment of lateral elbow tendinosis in comparison with other similar therapeutic methods. The factors evaluated mainly involved functional improvement, decreased pain and fewer side effects. Autologous platelet-rich plasma is a biological, non-toxic and non-immunoreactive product, derived from the patient's own blood, produced by centrifugation and extraction of the active fraction rich in platelets. It can be applied to damaged or degenerated tissues, where, after activated, it releases high concentrations of platelet-derived growth factors, which promote an acceleration of tissue healing from an inflammatory reaction with consequent angiogenesis, fibroplasia, collagen synthesis and tissue remodeling (1-14). The present study showed that the treatment of lateral epicondylitis with PRP injection can be a promising non-surgical alternative. Its use has been shown to improve tissue repair in tendinosis in several animal models and in vitro (6-20), and has recently shown significant and lasting improvements in pain and function in several studies involving humans (21-29). A possible explanation for the long-lasting effect of platelet-rich plasma is the fact that it provides changes in the properties of the new tendon formed from tissue healing and remodeling, so that the cells become able to perceive and respond early when subjected to a new mechanical overload. (1-12). Conservative therapies, such as the use of nonsteroidal anti-inflammatory medication and local corticosteroid infiltrations, work to suppress inflammation. However, histopathological studies have shown that the pathophysiological process in lateral epicondylitis is not an inflammation, but a fibroblastic response and vascular, using an angiofibroblastic degeneration, called tendinosis. Among the techniques widely used for the treatment of epicondylitis is the application of corticosteroids. According to Smithed et al, the improvement observed in patients treated with corticosteroid injection has partial and temporary efficacy (13). For these reasons, this therapy was not adopted as a first choice. Thus enabling the growth of PRP as an alternative increasingly widespread in conservative treatment.

A recent randomized clinical trial by Gosens et al with a 2-year follow-up demonstrated a significant reduction in pain and a significant improvement in function in patients with lateral epicondylitis at 1 and 2 years with PRP when compared to corticosteroids (30). Corroborating this systematic review, the beneficial effects of using platelet-rich plasma are longer lasting compared to other techniques. A systematic review and meta-analysis of randomized clinical trials by Arirachakaran et al compared clinical outcomes between the use of platelet-rich plasma, autologous blood and corticosteroids. Providing additional information that injecting PRP can improve pain and decrease the risk of complications, while injecting corticosteroids can improve pain, disability scores and pressure pain threshold, however, its use has a risk greater number of complications (19). In a study by Gautam VK et al, 30 patients aged between 18 and 60 years with recalcitrant lateral epicondylitis without response to oral medication or non-invasive treatment received infiltration of PRP and corticosteroids. Patients were assessed using the visual analogue pain scale (VAS), arm, shoulder and hand impairment scale (DASH), Oxford Elbow Score, Mayo Score, handgrip strength, and ultrasound performed by a musculoskeletal sonographer. The scales evaluated showed significant improvement in both groups within 6 months. However, in the group in which corticosteroid was applied, the scores reached the peak of improvement within 3 months and deteriorated over 6 months,

indicating recurrence of symptoms in 46.7% of patients submitted to corticosteroids. As for the ultrasonographic findings, a greater number of patients were observed with a reduction in the thickness of the common extensor tendon and cortical erosion of the lateral epicondyle in those treated with the application of corticosteroids (20). On the other hand, according to Krogh et al, comparing the use of platelet-rich plasma, glucocorticoids and saline injections, there was no greater reduction in pain with PRP or glucocorticoid injections when compared to the application of saline solution for patients with chronic lateral epicondylitis after a 3-month interval. Among the results found, glucocorticoid injection had a better short-term pain-reducing effect compared to the other two therapies at the end of 1 month, showing reduced activity on color Doppler and on tendon thickness. *Todavia, sem diferença estatisticamente significativa entre os 3 grupos após 3 meses.* (27). Outro estudo por Vos et al em 2014, concluiu que há fortes evidências de que as injeções de PRP não são eficazes no tratamento da tendinopatia crônica lateral do cotovelo (23). In the current literature, it is still complex to definitively assess PRP. Although several studies have been carried out aiming at the use of PRP for the treatment of tendinosis, and the vast majority are favorable, there are conflicting results possibly related to differences in study protocols, platelet concentration or separation techniques, outcome measures and/or groups of comparison.

## CONCLUSION

Based on the evidence presented, most studies - many of them with a reliable level of evidence - have demonstrated that the use of PRP is favorable and beneficial in the treatment of lateral epicondylitis (15-22,24-34). A significant clinical improvement was observed in most of the included studies, both in terms of pain by the visual analogue scale (VAS) and functional scores, with the use of one or two applications of platelet-rich plasma (19-33). This systematic review also provided additional information that PRP infiltration has a minimal risk of adverse effects compared to other similar therapies, establishing itself as a promising option in conservative treatment. Despite the findings, it is still not possible to state that this is a gold standard recommendation regarding other treatment options. In this sense, new randomized clinical trials are needed, with a complex and reliable methodology that will definitively answer the use of platelet-rich plasma in lateral epicondylitis of the elbow.

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