

## Extended-release triamcinolone provides prolonged relief for patients who failed standard corticosteroid injection for knee osteoarthritis; a pragmatic retrospective study



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### ARTICLE INFO

#### Keywords:

Cortisone  
Steroid  
Kellgren-Lawrence  
Knee pain  
Long-acting

### ABSTRACT

**Objective:** Identify if extended-release triamcinolone has a longer duration of action in a cohort of patients who have had limited duration of relief from prior corticosteroid injection.

**Design:** Retrospective analysis of patients with knee osteoarthritis.

**Setting:** Academic outpatient musculoskeletal practice.

**Subjects:** One hundred and fifty patients (age  $67.5 \pm 13.7$ , 68.2% female) with knee osteoarthritis who had subjectively insufficient relief from a standard corticosteroid injection.

**Methods:** Ultrasound-guided knee injections of extended-release triamcinolone were administered to all patients by experienced practitioners. The primary outcome measure was comparative duration of subjective relief from extended-release triamcinolone, compared to the patients' duration from their prior standard corticosteroid injection. The secondary outcome was the duration of relief from extended-release triamcinolone.

**Results:** Patients reported  $7.1 \pm 8.7$  additional weeks of relief from extended-release triamcinolone ( $t = 6.50$ ,  $p < 0.001$ ), with lower Kellgren-Lawrence score being the only factor associated with increased comparative duration of relief ( $B = -2.39$ ,  $p = 0.042$ ). No factors were associated with duration of pain relief from extended-release triamcinolone.

**Conclusions:** This retrospective study suggests that injection of extended-release triamcinolone is associated with prolonged pain relief in patients who have had insufficient duration of pain relief from a standard corticosteroid injection. Those with lower Kellgren-Lawrence grades were more likely to have an increased comparative duration of relief.

### 1. Introduction

Corticosteroid injections are a common medical procedure, with millions of intra-articular injections performed each year [1]. Amongst other pathologies, osteoarthritis remains one of the most common indications for these injections [2,3]. Specific to knee osteoarthritis, corticosteroid injections are commonly performed by physicians [4], but duration of relief is limited [5]. Multiple studies have demonstrated efficacy for these injections, but the duration varies significantly based on injection location, corticosteroid type, and study performed, but they all tend to last a few months at most [5]. Efficacy is consistently reported

around 3–7 days [5,6] but the effect tends to decrease afterwards for about 4–6 weeks [7,8]. With a short duration of action, patients often require frequent repeat intra-articular corticosteroid injections. Previous studies have shown that repeat steroid injections every 3 months can lead to side effects such as cartilage breakdown [9]. This provides the challenge of identifying a longer lasting pain relief from steroid injections to avoid subsequent injections to prevent long-term side effects.

Recently, extended-release triamcinolone has become available, with a few studies demonstrating longer duration of relief than standard triamcinolone [10], with sustained relief on a second injection [11]. The longer duration of triamcinolone extended release is due to the

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<https://doi.org/10.1016/j.inpm.2022.100103>

Received 23 March 2022; Received in revised form 21 April 2022; Accepted 4 May 2022

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composition of triamcinolone contained within PLGA microspheres which biodegrade over time allowing for slower drug release into the joint capsule than standard TA injections alone [12]. This suggests that extended-release triamcinolone may play a role in patients for which standard corticosteroids have lost their duration of efficacy. The aforementioned studies unfortunately included all-comers, including patients who may not have previously had a standard corticosteroid injection; the standard injection may have worked just as well. Many patients, however, anecdotally begin to “fail” standard corticosteroid injections as their osteoarthritis progresses – would they still benefit from extended-release triamcinolone? For patients who fail standard corticosteroid injections who are poor candidates for knee arthroplasty, or are trying to delay the surgical intervention, this could identify an alternative treatment option.

## 2. Theory

This study was undertaken to identify if a subset of patients who had limited relief from standard corticosteroid injections would have any additional relief from extended-release triamcinolone. Specifically, this retrospective study aimed to identify if patients who had limited relief from a prior corticosteroid injection (less than two months' duration) had a greater duration of pain relief from extended-release triamcinolone.

## 3. Materials and methods

### 3.1. Patient inclusion

Institutional review board approval from the University of Utah (IRB #00071733) was obtained for this study. This retrospective study was performed by electronic chart review from 2018 to 2020 of successive patients to an academic sports medicine clinic who received extended-release triamcinolone injections in the knee for osteoarthritis. These injections were only administered after inadequate duration of relief from standard corticosteroid injections (defined as less than 2 months' subjective relief). Thus, all eligible patients “failed” standard corticosteroid injections. All patients in the initial review were considered based on the following inclusion criteria: 1) knee osteoarthritis diagnosis based on radiographic findings, 2) received intra-articular injection of extended-release triamcinolone (32 mg in 5 mL), and 3) contained documentation describing the duration of relief from a prior standard corticosteroid injection. There was no prescribed protocol for physical therapy, analgesics, or other treatments; clinicians were allowed to exercise their clinical judgment. Exclusion criteria included: 1) inability to report relief (e.g. cognitive impairment), 2) those in which other diagnoses may account for the knee pain (e.g. overlying lumbar radiculopathy), 3) concurrent rheumatologic disorders affecting the knee, 4) prior knee injection (of any type) within 1 month of extended-release triamcinolone injection, and 5) undergoing extended-release triamcinolone injection while still having relief from previous injection. Only the first extended-release triamcinolone injection was included in the analysis.

All patients received the injection under ultrasound guidance via a superolateral approach by one of six fellowship-trained, board-certified, sports medicine physicians. No greater than 5 mL of 1% lidocaine was used for local anesthetic prior to the extended-release triamcinolone injection in all patients. Any significant suprapatellar joint effusion seen on ultrasound (deemed “significant” by the provider, generally at least 5 mL), was aspirated and recorded. Chart extraction revealed subjective self-reported duration of improvement for prior corticosteroid injections and self-reported duration of improvement from extended-release triamcinolone at a follow-up visit. Bilateral knees were treated as a single patient, as no patient in this review noted differences in improvement between sides. The *a priori* primary outcome variable was increased duration of subjective pain relief for extended-release triamcinolone compared to that of the patient's prior corticosteroid injection (i.e., difference in durations of pain relief between the two procedures; positive

values indicated longer duration of pain relief by extended-release triamcinolone). Secondary outcome variables included: 1) duration of patient-reported pain relief by extended-release triamcinolone (continuous), 2) 1 or more months more pain relief of extended-release triamcinolone compared to standard corticosteroid (dichotomous with yes/no), and 3) 3 or more months of pain relief from extended-release triamcinolone (dichotomous with yes/no). The following variables were used as covariates in regression analyses: sex, Kellgren-Lawrence score [13], body mass index (BMI), and age.

### 3.2. Statistical analysis

Descriptive statistics were calculated for the patients' demographics and outcome variables, using means and standard deviations for continuous variables and frequencies and percentages for categorical variables. A dependent *t*-test was used to compare the duration of pain relief from a prior corticosteroid injection to that of extended-release triamcinolone. Multivariate linear regression analysis was performed to identify if any of the covariates above was associated with the primary outcome variable (increased duration of subjective pain relief for extended-release triamcinolone compared to that of the patient's prior corticosteroid injection). In addition, multivariate linear and logistic regression models were used for the continuous and dichotomous secondary outcome variables, with the same set of covariates. All statistical analyses were performed using Stata 17.0 (College Station, TX), with an  $\alpha$  level set at 0.05.

## 4. Results

Fig. 1 outlines the patients included in the study. Of the 150 patients who received injections of extended-release triamcinolone for knee osteoarthritis, 109 (72.2%) patients reported the duration of relief from their prior corticosteroid injection and 85 (56.3%) patients had follow-up data for the duration of relief for their extended-release triamcinolone injection. Of the 150 patients, 63 (41.7%) had data on both the duration of relief from prior corticosteroid injections and extended-release triamcinolone. Of these 63 patients, the average time between previous standard corticosteroid injection and the extended-release triamcinolone injection was 5.8 months with the range of 1.3–29.5 months. A total of 9 patients did not have any explicit documentation regarding timing of prior administration of a standard corticosteroid injection. Chart review identified that 3 patients completed physical therapy and 9 patients were on opioids after injection of extended-release triamcinolone. Of the 9 patients who were taking opioid medications, 4 patients had K-L grade 4 osteoarthritis, 2 patients K-L grade 3, 3 patients K-L grade 2, and 1 patient K-L grade 1. Their average difference in duration of relief between extended-release triamcinolone and standard corticosteroid injections was 6.2wks (range –6 to 16). Table 1 outlines demographic information of patients with knee osteoarthritis.

Patients reported  $1.9 \pm 2.4$  (range 0–8) and  $8.6 \pm 8.1$  (range 0–52) weeks of relief from their prior corticosteroid and their extended-release triamcinolone injections, respectively. Individual durations of relief are seen in Fig. 2, based on KL score. Table 2 demonstrates durations of relief. Of those who reported both the last corticosteroid relief duration and extended-relief triamcinolone duration of relief ( $n = 63$ , 41.7% of 150 patients), the extended-release triamcinolone injection lasted an average of  $7.1 \pm 8.8$  (range –6 to 50) weeks longer, which was statistically significant ( $t = 6.38$ ,  $p < 0.001$ ). Within this subset of 63 patients, 46 had at least KL grade 3; the extended-release triamcinolone lasted an average of  $5.5 \pm 6.0$  weeks longer ( $t = 6.10$ ,  $p < 0.001$ ).

Linear regression modelling revealed that lower Kellgren-Lawrence score (less osteoarthritic change) was significantly related to a greater duration of pain relief from extended-release triamcinolone compared to duration from the last corticosteroid injection ( $B = -2.49$ ,  $p = 0.037$ ). The negative B coefficient suggests that those with lower Kellgren-Lawrence scores had longer duration of pain relief. No other covariates

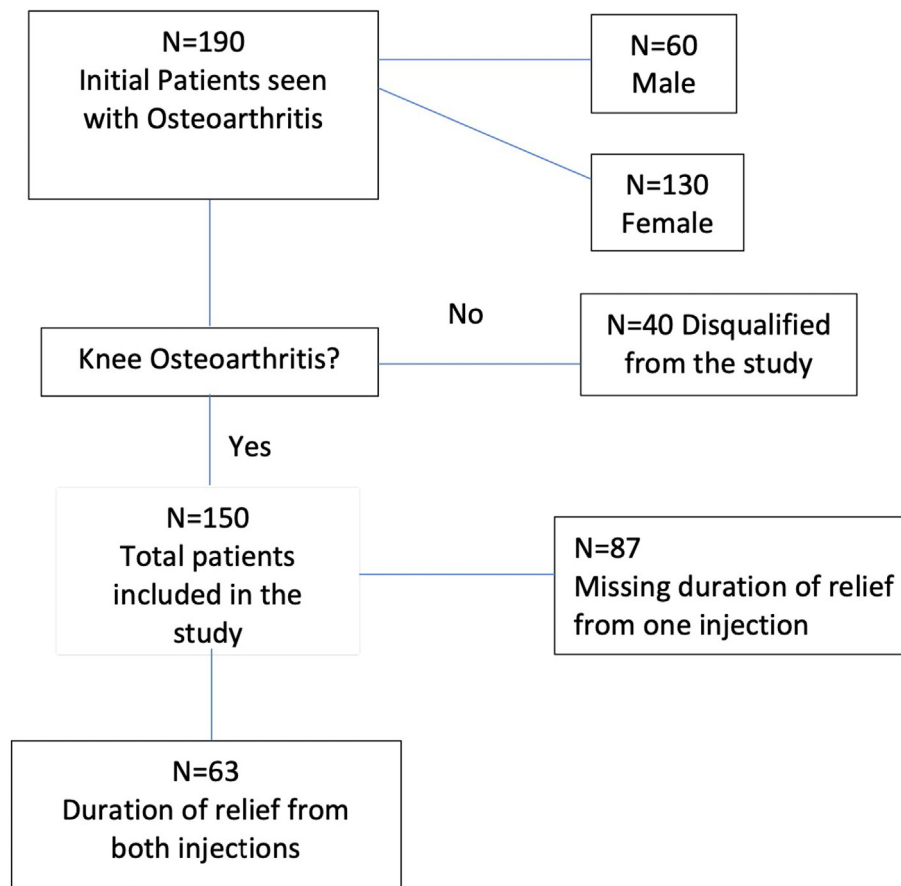


Fig. 1. Flow diagram of patients included in this study.

**Table 1**  
Demographic information of subjects, n = 150.

		n	%	Mean	SD	Median	IQR	
Sex	Female	103	68.7%					
	Male	47	31.3%					
Laterality	Right	47	31.3%					
	Left	49	32.7%					
	Bilateral	54	36.0%					
Kellgren-Lawrence grade	1	10	6.7%					
	2	35	23.3%					
	3	47	31.3%					
	4	54	36.0%					
	Unavailable	4	2.7%					
Joint effusion aspirated (mL)		22	14.7%	24.8	23.3	20	10	
Body mass index					33.3	9.8	31.4	14.9
Age					67.5	13.7	67	17

were significantly associated with a greater duration of pain relief (sex, age, or BMI;  $p > 0.05$ ).

With regards to the regression models on the secondary outcome variables, including duration of pain relief by extended-release triamcinolone, and 1 or more months and 3 or more months of pain relief from extended-release triamcinolone, none of the covariates were significant to the models ( $p > 0.05$ ).

### 5. Discussion

This study is the first to examine the effects of extended-release triamcinolone on patients who have failed standard corticosteroid injections. Failure is categorized by loss of expected relief from these corticosteroid injections. Failure may also be present in patients after

subsequent injections of standard corticosteroids fail to provide adequate relief. The results of this retrospective study suggest that extended-release triamcinolone can provide significantly greater length of relief in a subsequent injection. Patients who have minimal duration of pain relief from standard corticosteroid injections often have limited nonsurgical options. Hyaluronic acid [14] and platelet rich plasma (PRP) [15,16] have not been studied much in higher-grade knee osteoarthritis and are likely ineffective, and genicular nerve ablation is still in its infancy and may have potential benefits [17] to patient but has unknown long-term effects.

Prior studies examining extended-release triamcinolone have shown mildly improved pain-relief compared to standard triamcinolone or placebo [7,10]. These prior studies examined patients without recent injections, though the duration of prior injections were not recorded. The



**Table 2**

Factors relating to duration of relief from injections. ERT = Extended-release triamcinolone.

	N	%	Mean	SD	Median	IQR
Standard corticosteroid duration of relief, weeks	109		1.9	2.4	1	3
ERT duration of relief, weeks	85		8.6	8.1	8	11.5
Three months of relief from ERT	Yes	31	36.5%			
	No	54	63.5%			
ERT duration is at least one month longer than standard corticosteroid	Yes	38	60.3%			
	No	25	39.7%			

Although the mechanism has not been fully elucidated, it may be related to alterations in the hypothalamic-pituitary-adrenal axis, intra-articular glucocorticoid tolerance, increasing chondral injury, or alterations in the biomechanics of the joint [21]. Thus, extended-release triamcinolone may have a resistance to this phenomenon and be more likely to work on repeated injections. Third, individual patient factors may explain the increased duration of extended-release triamcinolone compared to standard corticosteroid injections. Lower Kellgren-Lawrence scores were associated with increased relative duration of relief; thus, there may be a subset of patients who may not have as advanced osteoarthritis but are non-responsive to standard corticosteroids. This could be due to patient-to-patient differences in pharmacogenetics, activity levels, functional demands, or cartilage wear location. Finally, this study only examined pain, and did not examine range of motion or function.

As with all studies, strengths and limitations exist. This study examined a relatively large number of patients with knee osteoarthritis. All injections were performed by numerous fellowship-trained, board-certified, experienced sports medicine providers using ultrasound guidance which has been associated with higher accuracy than blind injections [22]. Although ultrasound guidance was utilized for the injections in this study, which ensured accuracy, this may cause some difficulty in reproducing results in facilities where providers are not trained in ultrasound-guided injections. Finally, the anesthetic used has shown not to adversely affect the extended-release triamcinolone efficacy [23]. The limitations of this study revolve around the retrospective nature of this study, namely selection bias, patient report bias, and recall bias in this cohort. Prior injections could not be examined; failure could have come from inaccurate injections (guidance methods were not recorded), amounts of previous injections, differences in corticosteroid dosage, or types of injectate. Thus, this study cannot differentiate the comparison of extended-release triamcinolone to a single standard corticosteroid preparation (a head-to-head comparison). As this was a retrospective study, radiographs were not obtained at the time of each injection, thus Kellgren-Lawrence scores may have advanced with time and not properly categorized as time elapsed. Patient-reported pain relief is also a subjective term and no objective measure was utilized, but was used similarly amongst all patients. Other confounding variables, such as prior trauma, occupation, smoking status, and medication usage, were not included. As there was no prescribed prospective protocol, secondary interventions may have confounded the relief seen with the injections. Finally, this study was performed in a single center, which may limit the generalizability of the study.

## 6. Conclusions

This study demonstrates that extended-release triamcinolone may have significantly greater duration of pain relief in patients who have had minimal relief from standard corticosteroid injections for knee osteoarthritis. More specifically, in our patient population, patients who fail standard corticosteroid injections but have lower Kellgren-Lawrence

scores are more likely to have prolonged relief compared to the amount of time of pain relief they receive from standard corticosteroid injections. Future prospective studies are warranted to better define the pain relief from extended-release triamcinolone in this cohort.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgements

None.

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