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Economic Impact of Ketorolac vs Corticosteroid Intra-Articular Knee Injections for Osteoarthritis: A Randomized, Double-Blind, Prospective Study

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ABSTRACT

Background: Knee osteoarthritis is a disabling disease that costs billions of dollars to treat. Corticosteroid gives varying pain relief and costs $12 per injection, whereas ketorolac costs $2 per injection, per institutional costs. The aim of this study was to compare ketorolac with corticosteroid based on pain relief using patient outcome measures and cost data.

Methods: A total of 35 patients were randomized to ketorolac or corticosteroid intra-articular knee injection in a double-blind, prospective study. Follow-up was 24 weeks. Osteoarthritis was evaluated using Kellgren–Lawrence grading. Visual analog scale (VAS) was the primary outcome measure. A query of the institutional database was performed for International Classification of Diseases, Ninth Revision codes 715.16 and 719.46, and procedure code 20610 over a 3-year period. Two-way, repeated measures analysis of variance and Spearman rank correlation were used for statistical analysis.

Results: Mean VAS for ketorolac and corticosteroid decreased significantly from baseline at 2 weeks, 6.3-4.6 and 5.2-3.6, respectively and remained decreased for 24 weeks. There was no correlation between VAS and demographics within treatments. There were 220, 602, and 405 injections performed on patients with the International Classification of Diseases, Ninth Revision codes 715.16 and 719.46 during 2013, 2014, and 2015, respectively. The cost savings per year using ketorolac instead of corticosteroid would be $2259.40, $6182.54, and $4159.35 for 2013, 2014, and 2015, respectively, with a total savings of $12,601.29 over this period.

Conclusion: Pain relief was similar between ketorolac and corticosteroid injections. Ketorolac knee injection is safe and effective with a cost savings percentage difference of 143% when compared with corticosteroid.

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Knee osteoarthritis (OA) can be a disabling disease that affects up to 9 million adults in the United States [1,2]. The cost and disability associated with OA treatment can have a large impact on society. In the years 2008-2011, the estimated annual cost to treat OA and joint pain was $62.1 billion with lost wages estimated to $80.1 billion annually [3,4]. Over the next 25 years, the projected population affected with OA in the United States will increase to 67 million people [3]. With the rising cost for this disabling condition, more cost-effective treatments are needed.

Conservative treatment includes patient education, exercise, weight loss, nonsteroidal anti-inflammatory drugs, analgesic medications, bracing and/or orthoses, and intra-articular injections [5]. Intra-articular injection therapy has been studied using corticosteroids, platelet-rich plasma, and viscosupplementation [6-12]. The results are varied; however, general consensus is that corticosteroid intra-articular knee injection has been considered the gold standard [13-16]. In several studies, corticosteroid injections give varying amounts and durations of pain relief [13-17].

As an adjunct in multimodal pain control after total knee arthroplasty, ketorolac has been used successfully in the posterior

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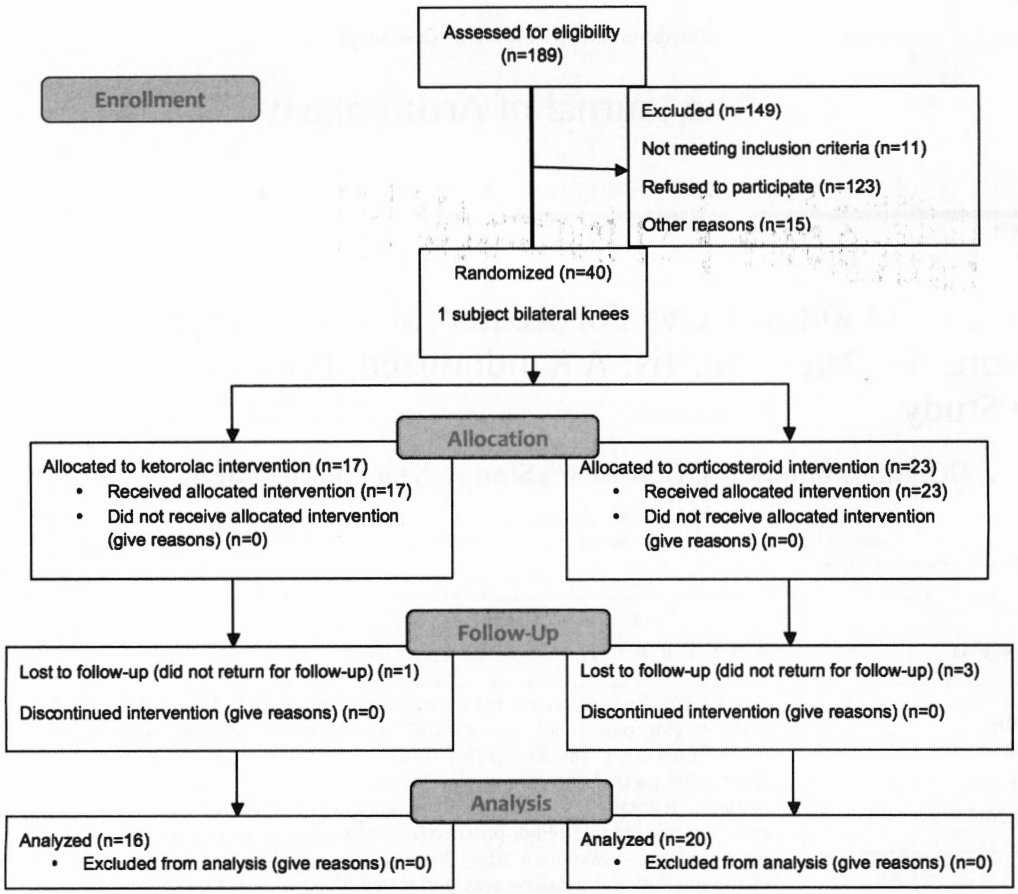

Fig. 1. Subject randomization flow diagram.

capsular injection [18]. In addition, ketorolac intra-articular knee injection has been studied as an adjunct with hyaluronic acid, but not alone in the management of knee OA [19]. Ketorolac is a nonsteroidal anti-inflammatory drug that inhibits the cyclo-oxygenase enzyme system and prostaglandin synthesis. These are key pathways involved in the inflammatory cycle of OA and targets to provide nonoperative pain management for knee OA.

To the author's knowledge, ketorolac intra-articular knee injection has not been performed as a standalone nonoperative treatment for knee OA. To determine whether ketorolac intra-articular knee injection is an appropriate adjunct in the nonoperative treatment of knee OA, we asked the following: (1) what is the effect of ketorolac compared with corticosteroid, the gold standard, with regard to the amount and duration of pain relief; (2) is there any difference in validated patient outcome measurements between both the treatment groups; (3) does body mass index (BMI) or the radiographic stage of knee OA play an effect on pain relief between the treatment groups?; and (4) what is the cost differential if any when comparing ketorolac with corticosteroid.

Materials and Methods

Inclusion and/or Exclusion Criteria

This study was designed as a prospective, double-blinded, randomized, controlled clinical trial. Institutional review board approval was obtained before proceeding with the study. This study was registered at ClinicalTrials.gov (NCT02295189). All subjects included in the study gave informed consent before enrollment. All source data were maintained per institutional review board protocol.

Inclusion criteria were an age of at least 18 years with a clinical diagnosis of knee OA. Knee OA was defined as pain in the knee with weight bearing combined with radiographic evidence of knee OA. The degree of radiographic knee OA was evaluated using the Kellgren–Lawrence (KL) grading scale [20]. The grading scale is a 0-4 scale defined as follows: KL Grade 0, no radiographic features of OA present; KL Grade 1, unlikely narrowing of the joint space, possible osteophytes; KL Grade 2, small osteophytes, possible narrowing of the joint; KL Grade 3, multiple, moderately sized osteophytes, definite joint space narrowing, some sclerotic areas, possible deformation of bone ends; and KL Grade 4, multiple large osteophytes, severe joint space narrowing, marked sclerosis, and definite bony end deformity.

Exclusion criteria were evidence or history of inflammatory or neuropathic arthropathy, insufficiency of the collateral ligaments or cruciate ligaments, current infection, recent knee intra-articular corticosteroid or viscosupplementation injection (<3 months), pregnant and/or lactating, allergy or hypersensitivity to the study medications, current use of anticoagulation medications, inability to make own decisions regarding the informed consent, and inability to read and/or understand English. All patients who satisfied the inclusion criteria and did not meet the exclusion criteria were enrolled, and consent was obtained.

Preparation and Injection

Enrolled subjects were randomized to treatment with use of a computer system by the pharmacist who prepared the injections.

Table 1
Demographics.

Demographics	Corticosteroid (N = 20)	Ketorolac (N = 16)
Age[a] (y)	65	53
Gender		
Male	9	7
Female	11	9
BMI[a] (kg/m^2)	30.6	32.5
Laterality		
Left	9	9
Right	11	7
Kellgren–Lawrence grade[a]	3	3

BMI, body mass index.
[a] Reported as the mean.

Once randomized, each subject's injection was prepared and wrapped with an opaque covering to blind the subject and the investigator who performed the knee injections. Injections contained either 2 cc of ketorolac tromethamine (Toradol, 15 mg/cc; APP Pharmaceuticals, LLC, Schaumburg, IL) in 8 cc of bupivacaine hydrochloride (0.5%) without epinephrine or 2 cc of triamcinolone acetonide (Kenalog-40, 40 mg/cc; Bristol-Myers Squibb, Princeton, NJ) in 8 cc of bupivacaine hydrochloride (0.5%) without epinephrine. The superolateral site on the knee was sterilely prepped in standard fashion before injection. The injection was performed under ultrasound guidance (GE LOGIQ e Ultrasound; General Electric Healthcare; Little Chalfont, Buckinghamshire, United Kingdom) by a single investigator who was blinded to treatment and outcomes.

Data Collection

All data collection was performed by a technician who was also blinded to treatment. The study technician recorded all outcome measures onto a separate case report form for each encounter. Data collected included demographics and validated patient outcome measures. Demographics included height, weight, BMI, laterality, and age. Patient outcome measures included visual analog scale (VAS), Western Ontario and McMaster University Osteoarthritis Index (WOMAC), Knee Society Score, Tegner/Lysholm Knee Scoring Scale, Short Form-36, and University California Los Angeles activity score. Subjects provided outcome measures at each clinic visit that included baseline and then 2 weeks, 6 weeks, 3 months, and 6 months after injection. A query of the institutional database was performed for International Classification of Diseases, Ninth Revision codes 715.16 and 719.46 and procedure code 20610 over a 3-year period.

Statistical Analysis

Owing to non-normal distribution of data, nonparametric tests were used. Inclusion of at least 32 subjects ensured 80% power to detect a significant difference in VAS of 1.6. It has been shown for rotator cuff disease that the minimal clinically important difference for VAS is 1.37 cm [21]. Estimated dropout rate of 20%, implied a sample of 20 subjects per group. Stata 13.0 was used to perform the power analysis. Two-way, repeated measures analysis of variance, Mann–Whitney rank sum test, *t*-test, the chi-square test, and Spearman rank correlation were used for analysis. A P value < .05 was considered significant.

Results

Thirty nine patients, including 40 knees, met inclusion criteria. All were enrolled, had baseline measurements, and received an injection. Four patients were removed from the study owing to noncompliance with follow-up or subject request. After withdrawal, data were available for 36 knees (35 patients); 16 in the ketorolac group and 20 in the corticosteroid group, 1 was bilateral (Fig. 1). Demographics are summarized in Table 1. No significant differences were found in demographics between the 2 treatment groups with respect to age, gender, laterality, BMI, and KL grading.

Mean VAS for both ketorolac and corticosteroid decreased significantly from baseline at 2 weeks, 6.3-4.6 ($P = .003$) and 5.2-3.6 ($P = .003$), respectively and remained decreased throughout the 24 weeks (Fig. 2). Data were normalized for VAS over time with no difference between the 2 treatments ($P = .98$). There was no correlation between VAS and age, gender, BMI, or KL grade within treatments ($P > .05$).

Mean WOMAC score for both ketorolac and corticosteroid increased from baseline at 2 weeks, 49-53 ($P = .003$) and 53-68 ($P = .003$), respectively (Fig. 3). Corticosteroid appeared to have higher function scores than ketorolac at final follow-up. There was no correlation between WOMAC and age, gender, BMI, or KL grade within treatments ($P > .05$). There was no significant difference in KS pain and function, Short Form-36, Tegner/Lysholm, and University California Los Angeles scores between ketorolac and corticosteroid throughout the 24 weeks ($P > .05$).

The institutional costs per injection of triamcinolone and ketorolac are $12.28 and $2.01, respectively. The cost percentage

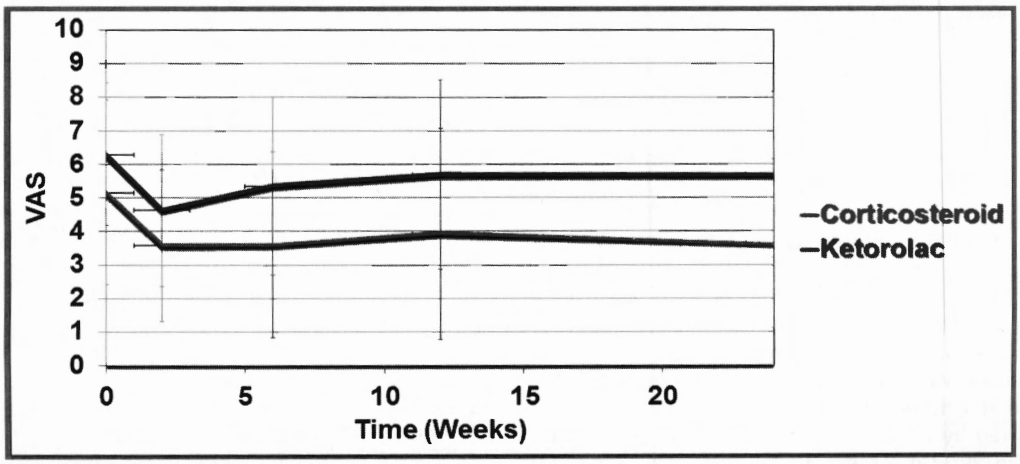

Fig. 2. Mean visual analog scale (VAS) for ketorolac and corticosteroid over time.

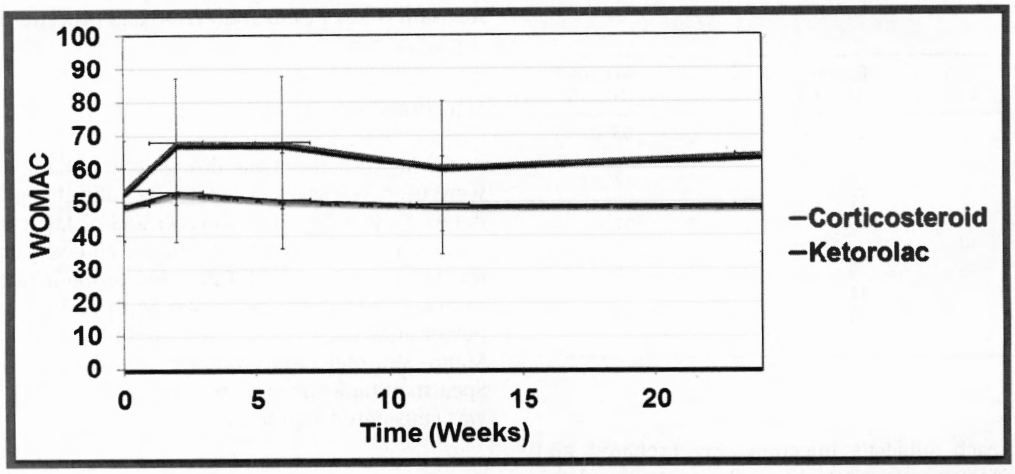

Fig. 3. Mean Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score for ketorolac and corticosteroid over time.

difference is 143% between the 2 injections; with ketorolac being more cost-effective. There were 220, 602, and 405 injections performed on patients with the International Classification of Diseases, Ninth Revision codes 715.16 and 719.46 during 2013, 2014, and 2015, respectively. The cost savings per year using ketorolac instead of corticosteroid would be $2259.40, $6182.54, and $4159.35 for 2013, 2014, and 2015, respectively, with a total savings of $12,601.29 over this period.

Discussion

The cost to treat knee OA and joint pain is significant as the population in the United States is projected to continue to increase [3]. With the rising cost for knee OA, more cost-effective treatments are needed. This study showed that ketorolac intra-articular injection decreases pain and increases function similarly to corticosteroid.

Corticosteroid intra-articular injection has been a mainstay of therapy for nonoperative management of knee OA and has been the gold standard for comparison of other injections. Corticosteroid injection has been shown to be significantly more effective than placebo in relieving pain, but, the beneficial effect has been small and short lasting [6,13-17,22]. This study confirms previous studies with reduction in pain scores in the first 2 weeks after injection, and this was sustained over 6 months. In addition, WOMAC scores were increased after injection with corticosteroid.

Intra-articular knee injection with ketorolac has shown promising pain reduction after arthroscopy and in combination with other agents in human subjects [23]. Ketorolac intra-articular injection combined with hyaluronic acid has been found to decrease knee pain compared with hyaluronic acid alone [19]. Randomized trials investigating multimodal periarticular injections, which include ketorolac, after total knee arthroplasty have shown significantly lower postoperative visual analog pain scores with comparable pain relief to peripheral nerve blocks [18,24,25]. In this study, ketorolac intra-articular knee injection showed similar reduction in pain scores and duration of relief to corticosteroid. Patient functional outcome scores were also increased with ketorolac similar to corticosteroid.

Ultrasound guidance was used for precise placement of the intra-articular knee injections. Direct palpation using anatomic landmarks is preferred by most providers, but accuracy can vary from 50% to 93% [26-29]. Ultrasound-guided intra-articular knee injections have been shown to reduce pain scores and increase effect compared with the direct palpation method [26-29]. In addition, injection into the superolateral site under ultrasound guidance has been shown to be 100% accurate [29]. By using this technique and the superolateral portal, we were able to confirm that all injections were delivered into the intra-articular space minimizing our errors in drug delivery, which would skew the results.

In this study, we showed that pain relief and function were similar between ketorolac and corticosteroid, but, the costs of injections differ. At our institution, the cost per injection of hyaluronate, triamcinolone, and ketorolac is $71.03, $12.28, and $2.01, respectively. The percentage difference in the cost of hyaluronate compared with ketorolac is 189% more costly and that in the cost of triamcinolone compared with ketorolac is 143% more costly. At our institution, using ketorolac instead of corticosteroid knee injection would be a total savings of $12,601.29 over a 3-year period. The use of ketorolac vs other injections would provide a significant cost savings for clinics that perform a high volume of injections.

There are multiple limitations to this study, including a small number of patients and short follow-up time. To minimize this, a power analysis was performed to show a difference in VAS of 1.6 with 80% power [19,30]. The 6-month follow-up point in this study is longer than most of the corticosteroid intra-articular injection studies [13-16]. In addition, the cost difference between corticosteroid and ketorolac may not be significant for clinics based on volume and ability to buy injections in bulk. Because there was no bupivacaine injection control, it is possible that bupivacaine alone provided the increased pain relief and function and not the corticosteroid or ketorolac.

Conclusions

This is the first study comparing knee intra-articular injection of ketorolac with that of corticosteroid. Ketorolac intra-articular knee injection is safe and effective and is 143% cheaper per injection compared with corticosteroid for OA.

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