The Journal of Arthroplasty 31 (2016) 1667–1673

Contents lists available at ScienceDirect

The Journal of Arthroplasty

journal homepage: www.arthroplastyjournal.org

Health Policy & Economics

Hyaluronic Acid Injections in Medicare Knee Osteoarthritis Patients Are Associated With Longer Time to Knee Arthroplasty

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ARTICLE INFO

Article history:
Received 18 September 2015
Received in revised form
11 January 2016
Accepted 15 January 2016
Available online 29 January 2016

Keywords:
hyaluronic acid
corticosteroid
knee osteoarthritis
intra-articular injections
knee arthroplasty

ABSTRACT

Background: Few nonoperative treatment options for knee osteoarthritis (OA) are available, but there is ongoing debate about the effectiveness of intra-articular (IA) hyaluronic acid (HA) injections. We investigated whether the formulation of IA HA, or its combined use with IA corticosteroid (CS), may be contributing to some of the reported variation in clinical outcomes.
Methods: The 5% Part B Medicare data (2005-2012) were used to identify knee OA patients who underwent knee arthroplasty (KA). The time from diagnosis of OA to KA was compared between patients with (HA) and without (no HA) IA HA use, using quantile regression with propensity score adjustment. These were further stratified by type of IA HA. Patient factors associated with time to KA were also assessed using Cox regression.
Results: The "HA" cohort was associated with a longer time to KA of 8.7 months (95% confidence interval: 8.3-9.1 months; $P < .001$) compared with the "no HA" cohort, with extended time to KA in the bio-engineered Euflexxa IA HA cohort. Patient factors associated with longer time to KA included women, younger patients, minority patients, patients with fewer comorbidities, and IA CS injection use. Patients with both IA HA and IA CS had an additional 6.3 months (95% confidence interval: 5.5-7.0 months; $P < .001$) to KA over those with only IA HA.
Conclusion: In a large cohort of elderly patients undergoing KA, there was a significant longer time from diagnosis of OA to KA in those receiving IA HA. It is unclear if the extended time may lead to less KA utilization.

Nearly 27 million adults in the United States have clinical osteoarthritis (OA) [1]. A large proportion of adults aged 60 years and older are estimated to have radiographic knee OA (37.4%) and symptomatic radiographic knee OA (12.1%) [2]. Knee OA is 1 of the 5 leading causes of disability among noninstitutionalized elderly adults [3]. Those impaired by OA can encounter more pain during activity and physically intensive work, leading to loss of work productivity [4-6] and also reduced quality of life [6,7].

Although there is a limited armamentarium of treatment options for addressing the clinical effects of knee OA, there continues to be a lack of consensus on the clinical effectiveness of intra-articular (IA) hyaluronic acid (HA) [8-19]. Clinical practice guidelines released in 2013 by the American Academy of Orthopaedic Surgeons [8] did not recommend the use of HA for patients with symptomatic knee OA. On the other hand, the guidance from other professional societies was neutral or conditionally recommended the use of HA [9,16,19]. The American College of Rheumatology conditionally recommended HA use in patients who had an inadequate response to initial therapy [9], whereas the Osteoarthritis Research Society International guidelines indicated that a number of studies revealed positive effect sizes for pain but required the role of the physician in determining whether a specific therapy may have its merits in the context of its

One or more of the authors of this paper have disclosed potential or pertinent conflicts of interest, which may include receipt of payment, either direct or indirect, institutional support, or association with an entity in the biomedical field which may be perceived to have potential conflict of interest with this work. For full disclosure statements refer to http://dx.doi.org/10.1016/j.arth.2016.01.038.

This study was funded in part by Ferring Pharmaceuticals, Inc.

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http://dx.doi.org/10.1016/j.arth.2016.01.038
0883-5403/

risk-benefit profile and the patient profile [16]. Recent meta-analyses and systematic reviews have identified beneficial effects of IA HA compared to saline as a placebo control [12,20,21], although some have questioned the objectivity of the findings [22]. A draft technology assessment directed by the Agency for Healthcare Research and Quality (AHRQ) stated that no conclusions can be drawn from the available literature on delay or avoidance of unicondylar or total knee arthroplasty (TKA) through the use of IA HA [10], even though trials with older patients showed a small and statistically significant effect on function, but the average effects did not meet the minimally clinically important difference. The draft AHRQ assessment also noted some gaps in the existing evidence in terms of the lack of studies examining the effect of IA HA on delay or avoidance of knee arthroplasty (KA) among those aged 65 years and older, as well as studies that compare large numbers of treated and untreated individuals.

There has also been debate about the effectiveness of IA corticosteroid (CS). The 2013 American Academy of Orthopaedic Surgeons clinical practice guidelines cast uncertainty about their effectiveness [8,23]. In contrast, the American College of Rheumatology conditionally recommended IA CS, and, in particular, "strongly" recommended their use if a patient does not have a satisfactory clinical response to full-dose acetaminophen [9]. The Osteoarthritis Research Society International guidelines also stated that IA CS was an appropriate treatment modality for all knee OA individuals [16].

The lack of consensus on IA injections prompted us to investigate whether the formulation of IA HA, or its combined use with IA CS, may contribute to some of the reported variation in clinical outcomes observed in previous systematic reviews. We analyzed nationally representative Medicare administrative data to address the following research questions: (1) Is there an effect of IA HA on the time from the diagnosis of knee OA to KA and is there a difference in effect size between a specific bioengineered HA (Euflexxa) and other HA formulations (non-Euflexxa HA [NE-HA])? (2) Are there demographic factors that may influence the time from diagnosis of knee OA to KA? (3) Does the use of IA CS further influence the time from diagnosis of OA to KA?

Methods

This study used a retrospective, observational study design based on the 5% sample of Part B Medicare data (carrier/physician claims) from 2005 to 2012. The 5% sample is compiled by the Centers for Medicare and Medicaid Services based on selecting beneficiary records with selected digits in their Health Insurance Claim number. Patients with knee OA were identified from the Medicare data based on the presence of *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code 715.x6 (knee OA). If patients were coded with nonspecific OA (ICD-9-CM codes 715.x8, 715.x9, or 715.x0) and knee pain (ICD-9-CM code 719.46), they were also included in the study [24]. To limit the study to "newly diagnosed" knee OA patients to the extent possible, it was required that these patients did not have a diagnosis of knee OA in the prior 12 months. As a result, if patients did not have at least 12 months of enrollment in Medicare before the knee OA diagnosis, they were excluded. Patients were also excluded if they were aged <65 years because they would be enrolled in Medicare for their physical disabilities, end-stage renal disease, or Lou Gehrig's disease. Health Maintenance Organization enrollees and those not enrolled in both parts A and B of Medicare were also excluded from this study because of their incomplete claim history.

After their diagnosis of knee OA, patients were identified for having used IA HA treatment based on the presence of Healthcare Common Procedure Coding System (HCPCS) Q and J codes for HA (these products have received Food and Drug Administration approval). These included Q3030, Q4083-Q4086, J7315-J7317, and J7319-J7326. This also required the concurrent diagnosis codes of 711.x6, 712.x6, 715.x6, 716.x6, 717.x, 718.x6, 719.x6, 836.x, or 844.x to limit the injections to the knee joint. Patients who subsequently received a KA were further identified based on Current Procedure Terminology-4 codes 27446 or 27447, respectively. The KA patients were then stratified into those who received at least 1 IA HA (HA group) and those who did not (no HA group) before the KA.

The time from knee OA diagnosis to KA was compared between the "no HA" and "HA" cohorts for all patients from 2005 to 2012. A subgroup analysis of patients from 2007 to 2012 was performed when specific Euflexxa IA HA codes were effective; the IA HA cohort was further stratified into those who received Euflexxa IA HA (HCPCS codes Q4085 or J7323; "Euflexxa HA" cohort) and those who did not ("NE-HA" cohort). Confounding factors, such as gender, age, socioeconomic status, extent of comorbidities, race, census region, and year of knee OA diagnosis, were evaluated. Any use of IA CS, prescription of nonsteroidal anti-inflammatory drug (NSAID), or physical therapy (PT) between the knee OA diagnosis and KA were also considered as confounding factors. The patients' socioeconomic status was determined based on whether they received state subsidies for their Medicare insurance premium (ie, with Medicare buy-in). Each patient's comorbid history was evaluated using the Charlson score based on their diagnosed conditions in the 12 months before their knee OA diagnosis. The Charlson score predicts the 10-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with the condition. Scores are summed to provide a total score to predict mortality. Patients were categorized into 1 of 4 comorbidity score categories: 0 (none), 1-2 (low), 3-4 (moderate), and $\geq$5 (high).

IA CS was identified using HCPCS J codes J0702, J0704, J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2650, J2920, J2930, J3300, J3301, J3302, and J3303. These required concurrent coding of a variety of knee conditions (ICD-9-CM diagnosis codes 711.x6, 712.x6, 715.x6, 716.x6, 717.x, 718.x6, 719.x6, 836.x, 844.x) to limit the injections to the knee joint. Prescription NSAID use was identified using V58.64, J3490 (Celebrex) or J1885 (Ketorolac), whereas PT use was identified using CPT codes 97012, 97014, 97016, 97022, 97032, 97034, 97035, 97036, 97110, 97112, 97113, 97116, 97140, 97150, 97530, or G0151.

Quantile regression was used to compare the difference in median time from knee OA diagnosis to KA between the various cohorts, adjusting for differences in potential confounding patient factors, including the use of IA CS, NSAIDs, or PT (factors described previously). The use of median time rather than average time was due to the non-normal distribution of times to KA. Multivariate Cox regression was also used to identify the risk factors for increased hazard to receive KA after the knee OA diagnosis, with adjustment for the confounding patient factors. Subgroup analyses were also performed to evaluate the effects of IA CS. The difference in median time from knee OA diagnosis to KA were compared between those who did and did not receive IA CS before the KA within the "HA" cohort, as well as within the "no HA" cohort.

Propensity scores were used to account for the potential bias in the selection of treatments for knee OA. Propensity scores are increasingly used with observational data to account for potential differences in baseline characteristics or measured covariates of the patient groups or to account for misspecification of the relationship between the risk factors and outcomes [25]. The propensity score for each patient, which is the probability of receiving IA HA, was calculated using logistic regression conditioned on the confounding factors (eg, age, gender, and so forth as described previously). The