Osteoarthritis and Cartilage

OARSI
OSTEOARTHRITIS
RESEARCH SOCIETY
INTERNATIONAL

Long term use of analgesics and risk of osteoarthritis progressions and knee replacement: propensity score matched cohort analysis of data from the Osteoarthritis Initiative

CrossMark

N. Hafezi-Nejad †[*], A. Guermazi ‡, F.W. Roemer ‡§, J. Eng †, B. Zikria ‖, S. Demehri †

† Russell H. Morgan Department of Radiology, Johns Hopkins University, Baltimore, MD, USA
‡ Quantitative Imaging Center, Department of Radiology, Boston University School of Medicine, Boston, MA, USA
§ Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany
‖ Department of Orthopedic Surgery, Johns Hopkins University, Baltimore, MD, USA

ARTICLE INFO

SUMMARY

Objectives: To determine the association between the long-term use of analgesics and progression of osteoarthritis (OA) as evidenced by up to 3-years follow-up worsening of radiographic Kellgren –Lawrence (KL) grade and incidence of knee replacement (KR).
Design: Using nearest neighbor matching of the propensity scores with caliper in the Osteoarthritis Initiative (OAI) cohort, 173 index (Analgesic +) and 173 referent (Analgesic −) subjects were included. Analgesic + and − subjects had analgesics in all and none of their visits, respectively. Analgesic + and − subjects were balanced in their demographics, baseline, first, second and third year body mass index (BMI), Western Ontario and McMaster (WOMAC) total score, Physical and Mental health summary scales (SF-12), Physical Activity Scale for the Elderly (PASE) and Charleston Comorbidity Scale. Analgesic + and − subjects were also matched for baseline radiographic KL grade. Interval increase in the KL grade and incidence of KR were defined as the outcome.
Results: Included subjects had average 6.5 years of follow-up. By the third year, 44 subjects had an interval increase in the KL grade; 29 in Analgesic + and 15 among Analgesic − subjects ($P = 0.024$). By the eighth-year, 41 subjects had their first KR; 29 in Analgesic + and 12 among Analgesic − subjects ($P = 0.005$). Hazard Ratio (HR) of OA progression and KR for Analgesic + subjects was 1.91 (1.02−3.57) and 2.57 (1.31−5.04), respectively.
Conclusions: Long-term use of analgesics may be associated with radiographic progression of knee OA and increased risk of future KR.

Introduction

Background and rationale

Knee Osteoarthritis (OA) is one of the most prevalent chronic joint disorders in the United States[1]. Knee OA has a progressive course, which is associated with gradually worsening symptoms such as chronic pain, stiffness and restricted range of motion[2]. Knee replacement (KR) is recognized as the ultimate outcome in the progression of OA[3]. Various medical treatments can be offered prior to KR in order to improve symptoms and function[4]. Several guidelines have been published to standardize the recommendations regarding the medical therapy and use of analgesics in OA patients[4−7]. Analgesics are the largest group of medications that are prescribed for OA patients. A variety of analgesics including non-steroidal anti-inflammatory drugs (NSAIDS), Cyclooxygenase II (COX II) inhibitors, acetaminophen, salicylates and narcotic analgesics are used for symptom relief[8−18]. Selective and non-selective NSAIDS, acetaminophen and narcotic analgesics are the most commonly used analgesics[12,19−21]. Despite short-term pain relief, the long-term effect of various analgesics on OA progression and outcome is not clear[17,22]. Previous *in vitro* and animal studies have reported that use of analgesics and NSAIDs has deleterious effects

* Address correspondence and reprint requests to: N. Hafezi-Nejad, Russell H. Morgan Department of Radiology, Johns Hopkins University School of Medicine, 601 N. Caroline Street, JHOC 4240, Baltimore, MD 21287, USA. Tel: 1-443-600-3265.
E-mail addresses: nhafezi1@jhmi.edu, nimahn@gmail.com (N. Hafezi-Nejad).

on the structural progression of OA[23,24]. Results of recent observational studies were more controversial. While some reports have confirmed animal studies on negative effects, others have claimed a protective role, especially for the selective COX-II inhibitors[11,25–27].

Recent studies and pre-specified hypothesis

Recently, Lapane et al. evaluated the use of NSAIDs on symptoms and OA progression among subjects with knee OA[28]. Interestingly, long-term use of NSAIDs was associated with decreased joint space narrowing (JSN). In contrast, another first line analysis of the Osteoarthritis Initiative (OAI) cohort by Pelletier et al. reported a lower joint space width among analgesic + subjects[29]. In addition, patients with OA have great variations in their use of analgesics[19–21,28,30]. Many are using more than one analgesic at a time and switches are common among common types of analgesics[18–21].

Objectives

In this study, our objective was to investigate the long-term use of analgesics in association with radiographic progression of OA and subsequent KR as the ultimate structural outcome of knee OA.

Methods

Study design, setting and participants

For this analysis, we used the data from the OAI. The OAI is a cohort of 4796 subjects with or at risk of OA, which are regularly followed on an annual basis. Datasets are available for public access through the OAI website at the http://www.oai.ucsf.edu. Details of the study participants, enrollments, evaluations and follow-ups are also available for public access from the OAI website. The primary hypothesis of the study was to find the maximum number of the index (Analgesic +) and referent (Analgesics −) subjects which have the most similar follow-up assessments except their exposure to analgesics.

Exposure: long-term use of analgesics

Our definition of Analgesic + was documented use of analgesics in all available follow-ups. Physician-prescribed medications were adjudicated and were present in the OAI datasets. Following a recently published study, we used prescription analgesics as it's more reflective of its regular use especially in clinically relevant doses (compared to non-prescription analgesics)[28]. For comparison, we aimed at selecting our referent subjects from those with no report of prescription analgesics in neither of their follow-up visits. Thus, we checked the Medication Inventory Form (MIF) of each subject. Out of the total 4796 participants, 2654 subjects had analgesics in their MIF in "some" of the visits. The remaining 2142 subjects had analgesics in their MIF in "all", or "none" of the follow-up visits.

Outcomes: radiographic Kellgren and Lawrence (KL) grade and KR

We had two distinct outcomes of interest. First, increase in the follow-up KL grade compared to the matched baseline KL grade (only between grade changes) as a measure of radiographic OA progression[31]. Second, KR was chosen as the ultimate outcome of OA[3]. Following the previous study[28], the increase in KL grade was evaluated up to the third year of follow-up. The higher KL grade of the two knees was selected as the variable of interest for each participant[32]. KR incidence was assessed throughout the 8 years of follow-up using the latest updated datasets that were present

online (Datasets were accessed at November 2014). For the purpose of consistency and to avoid issues that may arise from inconsistent or unstandardized readings, we used OAI's central readings of X-rays for KL grade.

Matching variables

In order to define matched referents, for every index, we found one matched referent using nearest neighbor matching of the propensity scores with calipers. For every index, we selected the one best referent who matched with the index in not only the baseline, but the follow-up variables as well (except radiographic KL grade, which was matched only for the initial baseline values). Therefore, we attempted to find subjects with a similar course of OA while having different exposures (long term use of analgesic vs no analgesics: Analgesic +/−). Variables that could possibly affect the probability of using analgesics were considered in finding the matching referents[33]. Choice of the possible confounding variables was based on previous OA risk prediction models which were validated on the OAI cohort's population[3,34–36]. Demographic variables, body mass index (BMI), Western Ontario and McMaster Questionnaire (WOMAC) total score, Physical Summary Scale (PSS) for the Medical Outcome Study (MOS) 12 item short form (SF-12) health survey, mental summary scale (MSS) for the MOS 12 item short form (SF-12) health survey, Physical Activity Scale for the Elderly (PASE) score, and Charlson comorbidity score included the matching variables. Index and referent subjects (Analgesic + and Analgesic −) were selected to have initial matched KL grades, to compare follow-up changes in radiographic KL grades. The greater WOMAC score of the two knees was selected as the variable of interest for each participant[37]. After excluding 384 subjects with missing values in either the demographics, KL grades or the Charleston comorbidity scales, 1758 subjects remained. No participant had missing values in neither the exposure nor the outcome. Following exclusion of the above incomplete index cases, 125 of the remaining 61,405 variable-values, which were accounting for 0.002 of all values, were missing. These 125 missing values were imputed using expectation maximization (EM) technique, which provided us with one completely imputed dataset (no remaining missing values)[38,39].

Propensity score matching

The imputed dataset was used for the purpose of matching. In order to determine referent subjects (Analgesic −) for each index (Analgesics+), we searched the dataset for the one nearest neighbor, non-replaced match[40]. The index (Analgesic +) and referent (Analgesic −) subjects had analgesics in all and none of their visits, respectively. To select the best available referents, propensity score matching was utilized. A 1:1 greedy matching algorithm was employed similar to the method described by Rosenbaum et al.[41]. For every participant in the index (Analgesic +), one best-matched referent (Analgesic −) participant was selected. Using greedy matching algorithm, we found the first best match pair and then moved to find the next best match in a hierarchical manner. Best match was defined as subjects with the highest digit match on their propensity scores, which were calculated using logistic regression analyzes to predict the probability of exposure (long-term use of analgesics). A caliper of 0.1 was employed in finding the highest digit match of the propensity scores. As mentioned earlier, out of the total 4796 participants, 2654 subjects had analgesics in their MIF in "some" of the visits. The remaining 2142 subjects had analgesics in their MIF in "all", or "none" of the follow-up visits; 384 subjects were excluded due to having missing values in either the demographics, KL grades or the Charleston comorbidity scales, and 1758 subjects remained. By exclusion of