Intra-articular corticosteroid injections increase the risk for knee replacement surgery: a multi-centre longitudinal observational study using data from the Osteoarthritis Initiative

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Running headline (max 40 characters): IACs increase the risk of knee surgery

27 **Abstract**

28 **Aims**

29 Recent studies have suggested that corticosteroid injections in the knee may harm the joint, resulting
30 in cartilage loss, and possibly speeding up osteoarthritis progression. The aim of this study was to
31 assess whether patients with (or at risk for) symptomatic knee osteoarthritis and whom undergo
32 corticosteroid injections have an increased risk for knee replacement surgery.

33 **Patients and Methods**

34 We used data from the Osteoarthritis Initiative, a multi-centre observational cohort study that
35 followed 4796 participants with (or at risk for) knee osteoarthritis on an annual basis with follow-up
36 available up to 108 months. Increased risk for symptomatic OA was defined as frequent knee
37 symptoms (pain, aching, or stiffness) without x-ray OA and two or more risk factors, while OA was
38 defined by the presence of both femoral osteophytes (clinic interpretation) and frequent symptoms
39 in 1 or both knees. Missing data were imputed with multiple imputations using chained equations.
40 Time-dependent propensity score matching was performed to match cases at the time of first
41 injection with controls. The effect of corticosteroid injections on knee replacement surgery was
42 estimated using Cox proportional-hazards survival analyses.

43 **Results**

44 After removing patients lost to follow-up, 3822 participants remained. In total, 249 (31.3%) of the 796
45 treated participants and 152 (5.0%) of the 3026 untreated participants had knee replacement surgery
46 during follow-up. In the matched cohort, Cox proportional-hazards regression resulted in a hazard
47 ratio of 1.57 (95% CI: 1.37 – 1.81, $p < 0.001$) and every injection increased the absolute risk of knee
48 replacement surgery by 9.4% at 108 months of follow-up compared to untreated patients.

49 **Conclusion**

50 Corticosteroid injections seem to be associated with an increased risk for knee replacement surgery
51 in patients with (or at risk for) symptomatic knee osteoarthritis. These results suggest that a
52 conservative approach regarding administering corticosteroids in the knee joint should be
53 recommended.

54 **Take home message**

- 55 • Corticosteroid injections seem to be associated with an increased risk for knee replacement
56 surgery in patients with (or at risk for) symptomatic knee osteoarthritis.
- 57 • These results suggest that a conservative approach regarding administering corticosteroids
58 in the knee joint should be recommended.

Introduction

The predominant symptom of knee osteoarthritis (OA) is pain. Pain is the symptom that drives individuals to seek medical care, and contributes to functional limitations and reduced quality of life. The principles of OA treatment are to alleviate pain and stiffness to maintain function, with current consensus guidelines recommending the use of a combination of physical therapy, analgesia, and surgical intervention where necessary.¹ Intra-articular corticosteroid injections (IACs) are a frequently-used treatment regimen for pain relief from symptomatic knee OA as these inhibit inflammation and reduces pain, although only for a limited period of time.^{2,3} Although IACs are regularly used in daily clinical practice, literature shows contradicting results on the potential long-term complications of IACs.⁴⁻⁶ It therefore remains unclear whether IACs can be safely used in the management of knee pain in patients with OA. Corticosteroids have been reported to exhibit a time- and dose-dependent effect on articular cartilage. High doses and/or injection frequencies (i.e. >3 mg/dose or 18-24 mg/cumulative total dose in vivo) have been shown to be associated with significant gross cartilage damage and chondrocyte toxicity, while low doses and/or injection frequencies (i.e. <2-3 mg/dose or 8-12 mg/cumulative total dose in vivo) have shown increased cell growth and recovery from articular cartilage damage.⁷ Two randomized controlled trials have been published that investigated the effect of long-term IACs on articular cartilage damage.^{4,5} Raynauld et al. reported no long-term harmful effect of IACs on the anatomical structure of the knee after two years of repeated injections (every three months for two years), while McAlindon et al. showed that an identical treatment scheme (IACs every three months for two years) resulted in cartilage volume loss with no long-term difference in knee pain after two years compared to saline injections.^{4,5} However, the negative effect on cartilage volume was small and possibly not clinically relevant. In response to McAlindon et al., others argued that IACs are mainly used for acute symptomatic episodes of pain and that repeated IACs at 3-month intervals do not reflect common standard clinical practice, reducing the generalizability of the results.⁸

More recently, Zeng et al. studied the effect of IACs on the radiographic Kellgren and Lawrence (KL) grade and joint space width worsening in patients with KL grade 2 or 3.⁶ They concluded that in these patients IACs increase the risk of KL grade worsening and joint space width worsening by a 3-fold compared to patients that did not received IACs. Radiographic assessment of OA progression by means of the KL grade or joint space width worsening can be valuable, however the presence of radiographic features of OA does not necessarily have to be correlated to knee pain and vice versa.⁹ Knee pain is the main reason patients ultimately undergo knee replacement surgery. Therefore, the aim of this study was to assess whether patients with (or at risk for) symptomatic knee osteoarthritis and whom undergo corticosteroid injections have an increased risk for knee replacement surgery.

Patients and Methods

Study design

We used data from the Osteoarthritis Initiative (OAI) database, available for public access at <https://data-archive.nimh.nih.gov/oai/>. The OAI is a multicentre, longitudinal cohort study that included patients with (or at risk for) symptomatic femoral-tibial knee OA. Enrollment occurred between February 2004 and May 2006 in four centres with an annual follow-up up to 108 months. The present study was conducted and reported according to STROBE guidelines.¹⁰

Participants

The OAI cohort consisted of 4674 participants divided into a progression cohort (n=1390, 30%) and an incidence cohort (n=3284, 70%). The progression cohort consisted of patients with symptomatic knee OA, defined as definite tibial-femoral osteophyte (OARSI atlas grade 1-3) at baseline (clinic interpretation) and pain, aching, or stiffness on the most days of the month in the past year. The incidence cohort consisted of patients without symptomatic knee OA (OARSI atlas grade 0), but with an increased risk of symptomatic OA in one or both knees. Increased risk for symptomatic OA was defined as frequent knee symptoms without visible OA on x-ray images, osteophytes present in one

or both knees but not in combination with frequent symptoms in the same knee, and at least two additional risk factors for OA (knee symptoms in the past 12 months, overweight, history of knee injury, history of knee surgery, family history with OA related knee replacement, Heberden's nodes, repetitive knee bending as current daily activity, and age between 70 – 79).

General inclusion criteria include men and women as from 45 to 79 years of age, living in the US of America. Exclusion criteria included inflammatory arthritis, contraindication of 3-Tesla magnetic resonance imaging and bilateral end-stage knee OA. After 108 months, 899 participants were lost to follow-up. The OAI study protocol is available at <http://data-archive.nimh.nih.gov/binaries/content/documents/ndacms/resources/oai/oai-study-protocol/oai-study-protocol/ndacms%3Aresource>.

Variables

At baseline and annual follow-up visits (12 to 108 months) a large core set of variables was collected including general patient characteristics, knee OA status, quality of life measures, and functional scores. We extracted all patient characteristics (age, gender, history, physical activity, body mass index (BMI), care access etc.), clinical variables (knee symptoms, radiographic signs of OA, hand OA), quality of life measurements (12-Item Short Form Survey (SF-12)), and functional scores (Knee injury and Osteoarthritis Outcome Score (KOOS), Western Ontario and McMasters Osteoarthritis index (WOMAC)) from the OAI, at each follow-up visit.

For each follow-up visit we assessed whether patients reported to have received IACs and whether patients underwent knee replacement surgery. In case of bilateral IACs, the first knee that received an injection was selected. For all other patients, the left or right knee was randomly selected.

Statistical methods

Because of the annual follow-up visits, the exact time of both the injections and knee replacement surgery were unknown so we approximated it by taking a random time point between the follow-up visit the injection or knee replacement surgery status was reported and the preceding visit.

Patient characteristics at baseline had a small percentage of missing values (<1%) except the KOOS Function in Sport and Recreation (KOOS FSR) subdomain that had 25% missing values. The extracted data also had systematic missing variables due to patient withdrawal and/or no consent to study extension, these patients were excluded from the analysis. This reduced the dataset to 3822 patients in total. Remaining missing values were imputed using multivariate imputation by chained equations creating 10 independent imputed datasets. We performed time-dependent propensity score matching (tdPSM) to match patients at time of first injection with available controls at any given time-point using a 1:1 matching algorithm and nearest neighbor matching with a caliper of 0.05.¹¹ The propensity score was defined as the probability to receive a IACs based on patient characteristics (age, gender, BMI, physical activity, health care access, treatment centre, education, family history with OA, occupation), clinical variables (medication use, hand OA at baseline, knee symptoms at baseline, radiographic confirmed OA), quality of life scores (SF-12 subscales), and functional scores (KOOS and WOMAC). Covariate balance was assessed by calculating standardized mean differences (SMD) between patients and controls. Balance equal to or smaller than 0.10 SMD were assumed to have appropriate balance and were visually inspected using balance plots.¹² Balance was assessed for every annual follow-up visit for all imputed datasets. The overall balance of all follow-up visits and the imputation sets combined was evaluated by calculating the average standardized absolute mean difference (ASAMD).¹³

The effect of IACs on the risk of knee replacement was estimated using Cox proportional hazards survival analyses with cumulative IACs as a time-dependent covariate and time to (total or partial) knee replacement surgery as the dependent variable. The Cox proportional hazards survival analyses were performed for each imputation dataset and the estimates were pooled using Rubin's Rule.¹⁴

To get an idea of the clinical relevance of the estimated effect, the absolute risk increase per injection was derived from the Cox proportional hazard model.¹⁵ All analyses were performed in R (version 3.5.2, The R Foundation for Statistical Computing, Vienna, Austria), using packages ‘mice’, ‘MatchIt’, and ‘cobalt’.

Sensitivity analyses

As a sensitivity analysis, the effect of IACs on the risk of knee replacement was also estimated in the unmatched cohort. Moreover, the progression and incidence cohort were analyzed separately to detect potential differences between the two sub cohorts.

Results

After removing patients lost to follow-up, 3822 patients remained with a mean age of 61 (range: 45 - 79) at baseline and 58% was female. At 108 months of follow-up, 20.8% (n=796) received one or more IACs with 1.55 injections (range: 1 - 8) on average while 10.5% (n=401) received knee replacement surgery. Of the 796 patients that received IACs, 249 (31.3%) had knee replacement surgery during follow-up. In contrast, of the 3026 patients that were not treated with IACs, 152 (5.0%) had knee replacement surgery during follow-up (Figure 1). The baseline characteristics are displayed in Table 1.

tdPSM resulted in 1366 matched patients in total for every imputed dataset (683 patients at time of the first treatment were matched to 683 control patients at different time-points that were at risk of receiving IACs). Because the annual follow-up visits were matched sequentially, 113 treated patients (of the 796) were matched as controls before they received their first injection. Some controls had multiple time-points matched to two different treated patients, (i.e. at one-year follow-up, two treated patients receive their first injection and were matched to a single control at 4- and 8-years follow-up) resulting in 23 double matches. In total, 1343 unique patients were matched (Figure 1). At every time-point, most characteristics were well balanced with SMDs below 0.10 (Figure 2). The overall covariate balance was appropriate with an ASAMD of 0.072 (SD=0.005).

The hazard ratio (HR) for knee replacement surgery was estimated to be 1.57 (95% CI: 1.37 – 1.81, $p<0.001$) for each cumulative IAC. Every IAC increased the absolute risk of knee replacement surgery by 9.4% at 108 months of follow-up compared to patients that did not received IACs. Sensitivity analysis of the unmatched cohort showed a HR of 2.15 (95% CI: 1.96 – 2.38, $p<0.001$) for each cumulative IAC. The incidence- and progression sub cohorts pooled HRs were estimated to be 1.78 (95% CI: 1.42 – 2.23, $p<0.001$) and 1.41 (95% CI: 1.19 – 1.67, $p<0.001$), respectively (Figure 3).

Discussion

Our study showed that IACs in the knee joint seem to be associated with an increased risk for knee replacement surgery in patients with (or at risk for) symptomatic knee OA. The HR is 1.57 (95% CI: 1.37 – 1.81) for each next IAC. That is, at 108 months of follow-up, every IAC increased the absolute risk to receive knee replacement surgery by 9.4% compared to similar patients that did not receive IACs. Results from our study are in line with previous studies that showed that IACs have a detrimental effect on knee cartilage, possibly speeding up OA progression.^{4,6,7}

Zeng et al. studied the association between IACs and KL grade- and joint space width worsening using OAI data and reported a HR of 3.02 (95% CI: 2.19 – 4.16) and 4.67 (95% CI: 2.92 – 7.47) for KL worsening and 2.93 (95% CI: 2.13 - 4.02) and 3.26 (95% CI: 1.78 - 5.96) for joint space width worsening for initial and continuous IACs, respectively, which is higher compared to our results. This difference can be explained by differences in population, treatment, outcome, and duration of follow-up. Zeng et al. only included patients with a KL score of 2 or 3 with a maximum of 48 months of follow-up, did not estimate the risk per cumulative injection, and used radiographic OA progression as their outcome of interest.

Our results can possibly be explained by several or combined hypothetical scenarios. First, corticosteroids have been shown to induce chondrocyte toxicity resulting in gross cartilage loss and inflammation.⁷ Cartilage loss can increase knee pain and increase the probability that patient and physician will opt for knee replacement surgery. Moreover, local anaesthetics, such as bupivacaine or

203 lidocaine, that are being injected with corticosteroids have been shown to be chondrotoxic, especially
204 in an already inflamed or damaged knee joint and can also contribute to cartilage loss.¹⁶ Second,
205 although we corrected for several patient characteristics like education, occupation, and care
206 coverage, patients that received IACs might (on average) be more likely to receive medical treatment
207 because they experience pain differently and/or are more prone to seek medical attention.^{17,18} As a
208 result, they could be more likely to receive knee replacement surgery compared to patients with the
209 same pain and functional levels. Third, pain reduction might increase patient movement but could
210 also provoke peak stress because the patient does not feel pain anymore and strains the joint. This
211 could potentially lead to increased degradation of the cartilage.

212 The strength of our study is the large number of included patients that were followed for 108 months
213 in an observational setting using data from the OAI. The OAI database was structurally built to
214 document the natural history of knee OA across a wide range of subjects with different degrees of OA
215 severity and patient characteristics, using regular follow-ups and standardized questionnaires. This
216 enabled us to analyze and compare patient characteristics, clinical variables, standardized quality of
217 life scores and functional scores, both at baseline and time of treatment. Because patients that
218 received IACs had in general higher pain scores and lower functional scores compared to patients that
219 have not received IACs, we used tdPSM to create matches of patients at time of first injection, instead
220 of regular propensity score matching that achieves covariate balance at baseline.^{11,19} This resulted in
221 comparable patients at time of treatment, eliminating changes that occurred between inclusion/start
222 of the study and the first IAC injection (i.e. a patient that reported their first IAC injection at the fifth
223 follow-up visit might have a lower functional score compared to a control that was similar in function
224 at baseline). Some potential limitations should also be discussed. First, we used tdPSM to account for
225 bias, but there is always a risk of residual confounding due to unmeasured and not included variables.
226 However, the relationship between injections and knee replacement surgery appears to be robust;
227 the sensitivity analyses that were performed showed similar effects. Second, treatment regimens
228 regarding IACs and/or knee replacement surgery might have changed during follow-up. This might

reduce the generalizability of our results. We noticed a small increase in IACs and knee replacement surgery with time during the 108 months of follow-up, however, this could also be due to the increasing age of the cohort and/or continued progression of OA. Third, a proportion of the patients that were treated with IACs were also treated with hyaluronic acid injections in the knee joint (of the 288 patients that received a hyaluronic acid injection, 218 also received IACs (76%). We analyzed the effect of hyaluronic acid on our results by including it once as a covariate in the propensity score model and once as a variable in the Cox proportional hazard model. In both cases, hyaluronic acid did not alter the effect found in our analysis. Fourth, a portion of the OAI had incomplete follow-up of IAC received, therefore we excluded 852 patients from our analysis. This was essential because the missing values were (in case of incomplete follow-up) structural and could not be assumed to be missing at random. To check if the analysis had impact on our results, we additionally performed a last observation carried forward imputation as sensitivity analysis to impute the subsequent missing values. This method showed a similar result compared to our analysis. Fifth, in our study we used knee replacement surgery as the ultimate endpoint of OA progression. Ideally, to assess the association between IACs and knee replacement surgery it would be desirable to include radiographic evidence of cartilage deterioration (e.g. Kellgren-Lawrence grade or cartilage volume) to our matching algorithm to further improve the balance between the two groups. Unfortunately, the OAI did not acquire MRIs and radiographs annually, and if available, these had a large portion of missings. Nevertheless, we do not expect that the inclusion of radiographic evidence changes our conclusions as we did include a wide range of disease progression variables (pain-, functional-, and quality of life scores) in our model to account for potential imbalances between the two groups.

Conclusion

IACs seem associated with an increased risk for knee replacement surgery (for each cumulative IAC received) in patients with (or at risk for) symptomatic knee osteoarthritis. These results suggest that

a conservative approach regarding administering corticosteroids in the knee joint to treat osteoarthritis-related pain should be recommended.

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Author Contributions

Idea and conceptualization of the study: SW, MR, TvT, GH. Data collection, validation and analyses: SW, GH. Drafting of the manuscript: SW, MR, TvT, GH. Final approval of the version to be submitted: SW, MR, TvT, GH.

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Conflict of interest

The authors declare no competing financial interest.

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336

337   **Figure 1**

338   Flowchart showing patient selection. Of the 796 patients that received IAC injections
339   during follow-up, 683 patients were matched at their first injection with 683 controls.
340   The dotted line represents 113 patients treated with IACs that would receive
341   treatment later during follow-up but were matched as controls. IAC, intra-articular
342   corticosteroids; KRS, knee replacement surgery; tdPSM, time-dependent propensity
score matching.

Figure 2 Covariate balance at each time-point before and after propensity score matching, pooled for the imputation sets. The red lines indicate the standardized mean difference between intervention and control group before matching. The blue lines indicate the standardized mean difference between intervention and control group after matching. Dotted vertical lines represents -0.10 and 0.10 standardized mean difference, a standardized mean difference between these lines indicates good balance between patients that received IAC injections and patients that did not receive IAC injections. BMI, body mass index; OA, osteoarthritis; KOOS; Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; FSR, function in sport and recreation; WOMAC, Western Ontario and McMasters Osteoarthritis index; SF-12, 12-Item Short Form Survey.

Figure 3 Hazard ratios with 95% confidence intervals. Values higher than 1 demonstrate that IAC injections have an increased risk for knee replacement surgery compared to those that have not received IAC injections. Results are shown for the primary analysis, the unmatched cohort, the incidence cohort, and the progression cohort. IACs, Intra-articular corticosteroids; KRS, knee replacement surgery.

359 Table 1 Characteristics of participants in the overall cohort and the propensity matched datasets at time of first IAC.

360

	Missing at baseline (%)	Entire cohort at baseline (n=3822)			Matched cohort at time of first IAC [†] (n=1366)			361
		Treated (n=796)	Control (n=3026)	SMD	Treated (n=683)	Control (n=683)	SMD	
Age	0.0	62.4 (8.9)	60.9 (9.1)	0.00	68.4 (9.6)	68.4 (9.8)	0.00	
Gender, female (%)	0.0	63.4	57.1	0.11	62.7	62.1	0.01	
BMI	1.9	29.8 (4.8)	28.3 (4.7)	0.00	29.7 (4.8)	29.7 (5.3)	0.00	
Physical activity(PASE) [0 – 400]	0.0	159.9 (83.8)	164.7 (82.2)	0.00	141.2 (75.2)	141.9 (81.2)	0.00	
Care coverage (%)	0.0	97.7	96.6	0.06	98.8	98.6	0.01	
Education (>college graduate) (%) †	0.0	56.0	62.9	-0.11	56.3	57.1	-0.01	
Family history of knee replacement surgery (%)	1.5	16.3	14.6	0.04	15.8	15.8	0.00	
Occupational activities (%)	0.0	72.4	72.4	0.00	72.6	72.2	0.01	
Medication use (%)	0.0	69.8	51.1	0.32	87.3	88.5	-0.03	
Hand OA at baseline(%)	0.0	23.8	21.1	0.05	23.7	23.9	0.00	
History of knee surgery at baseline(%)	0.0	21.8	12.1	0.21	21.2	20.8	0.01	
Knee symptoms at baseline(%)	1.0	64.0	43.6	0.34	62.2	61.3	0.02	
Radiographic OA at baseline* (%)	1.0	53.0	38.5	0.24	52.0	51.8	0.00	
KOOS Knee related QoL* [0 – 100]	0.0	57.7 (22.3)	68.9 (20.9)	0.00	50.5 (20.3)	50.5 (22.5)	0.00	
KOOS Knee symptoms* [0 – 100]	0.0	79.2 (18.2)	87.9 (13.9)	0.00	71.7 (18.8)	71.8 (20.1)	0.00	
KOOS Pain* [0 – 100]	0.0	76.0 (19.8)	86.4 (16.1)	0.00	66.7 (19.4)	66.7 (22.1)	0.00	
KOOS FSR* [0 – 100]	24.7	58.2 (27.0)	73.5 (24.8)	0.00	49.4 (26.5)	49.0 (27.3)	0.00	
WOMAC stiffness* [0 – 8]	0.0	2.2 (1.8)	1.4 (1.5)	0.05	2.6 (1.8)	2.6 (1.9)	0.00	
WOMAC pain* [0 – 20]	0.0	3.9 (3.8)	2.1 (3.0)	0.00	5.7 (4.0)	5.6 (4.4)	0.00	
WOMAC disability* [0 – 68]	0.0	11.5 (12.7)	6.9 (10.2)	0.00	16.9 (12.6)	17.1 (14.2)	0.00	
SF-12 Physical scale [0 – 100]	0.0	46.5 (9.4)	50.1 (8.4)	0.00	42.2 (9.9)	42.2 (10.3)	0.00	
SF-12 Mental scale [0 – 100]	0.0	53.8 (8.5)	53.7 (7.7)	0.00	54.1 (9.0)	54.0 (9.2)	0.00	

362 † Education is categorized in ‘less than high school graduate’, ‘high school graduate’, ‘some college’, ‘college graduate’, ‘some graduate school’, ‘graduate degree’. * Knee specific variable available for both left and
363 right knee. SMD lower than 0.1 is considered appropriate balance.¹³, † Time-dependent propensity score matching resulted in 1366 matched patients in total for every imputed dataset (683 patients at time of the
364 first treatment were matched to 683 control patients at different time-points that were at risk of receiving IACs). Because the annual follow-up visits were matched sequentially, 113 treated patients (of the 796)
365 were matched as controls before they received their first IAC.

366 SMD, standardized mean difference; IAC, intra-articular corticosteroid injection; BMI, body mass index; OA, osteoarthritis; KOOS; Knee injury and Osteoarthritis Outcome Score; QoL, quality of life; FSR, function in
367 sport and recreation; WOMAC, Western Ontario and McMasters Osteoarthritis index; SF-12, 12-Item Short Form Survey.