Impact of Hyaluronic Acid Injections on Utilization of Pain Management Medications

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ABSTRACT

Objectives: Little evidence has been available, from real-world clinical practice, on how the use of pharmacotherapy with pain medications changes in patients who begin using hyaluronic acid (HA) injections. We aimed to examine the impact of the initiation of HA injections on the utilization patterns of pain management modalities in patients with knee osteoarthritis (OA).

Study Design: Retrospective pre-post design utilizing Truven Marketscan Commercial Claims and Encounters data from 2004 to 2011.

Methods: The first HA injections received by patients aged between 18 and 64 years during the study period were identified from the data. Utilizations of 3 pharmacotherapies commonly used in the treatment of knee OA—nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections, and opioids—in the 6-month pre- and post periods were assessed. These were measured as an average number of prescriptions per patient, and as proportions of patients using at least 1 of these agents. The independent variable in the study was a use of HA injection. Paired sample t test and McNemar’s test were used to assess pre-post changes.

Results: There were statistically significant decreases in the utilization of NSAIDs and in steroid prescriptions, along with a significant reduction in the proportion of patients filling these prescriptions during the post period (P <.001). In addition, the number of patients getting any opioid prescriptions reduced significantly during the post period (P <.001).

Conclusions: The study results suggest that HA treatment may help reduce the use of other pain medications such as steroids, NSAIDs, and opioids.


In the United States, nearly 30 million adults suffer from various forms of osteoarthritis (OA), of which knee OA is among the leading causes of disability.2,4 Patients with knee OA may encounter severe pain, leading to disability-related productivity losses,2,4 reduced quality of life,2 and increased financial burden.3 A number of treatment options are available for these patients to mitigate pain, improve daily functioning and disability, and perhaps delay progression of knee OA.6 Treatment for pain management in knee OA includes oral medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, and intraarticular injections such as hyaluronic acid (HA).

HA is a complex glycosaminoglycan sugar, a normal component of synovial fluid and cartilage in the knee.7 The purpose of HA in the knee joints is to provide viscoelastic properties to the synovial fluid—lubrication, shock absorption, and the prevention of wear of articular cartilage.7 In many OA patients, synovial inflammation is an important component of the osteoarthritic cascade. In these patients, concentration of HA polymer in the joints decreases as the knee OA progresses, leading to lower ranges of HA molecular weight. These lower ranges of HA lead to inflammation.7 Treatment with HA injections (viscosupplementation) has been shown to help restore synovial fluid properties in the knee, leading to less pain and improved clinical outcomes.8,9,10 A recent network meta-analysis by Bannuru et al, which included 137 studies with 33,243 patients with knee OA, reported that HA injections were the most efficacious treatment for reducing pain-related outcomes.10 Additionally, an economic benefit of HA injections, post treatment of knee OA, has been reported in a prospective multi-center study in France11 and in other studies with decision analytic models comparing costs of HA therapy with those of conventional care.12 Results of a recent study have suggested that a longer time to total knee replacement (TKR) is associated with use of HA injections; on average, patients who used HA had a longer time to TKR, and the time to TKR increased with additional courses of HA injections.13

However, little evidence exists on how treatment with pain medications and anti-inflammatories (NSAIDs, opioids, and
PRACTICAL IMPLICATIONS
Hyaluronic acid (HA) treatment may help reduce the use of pain medications (such as steroids, nonsteroidal anti-inflammatory drugs, and opioids) among patients with knee osteoarthritis. It was concluded from the study findings that:

- This research provides insights on the impact of HA injections on pharmacy budgets and also the potential abuse of narcotics for pain management.
- Our results indicate that treatment with HA injections has the potential to effectively reduce pain with improvement in clinical outcomes.

corticosteroid injections) is affected when patients receive HA injections in real-world clinical practice. This study aimed to examine the impact of initiating HA injections on the utilization patterns of 3 other pain-management modalities commonly used in patients with knee OA: NSAIDs, corticosteroid injections, and opioids.

METHODS
Study Design and Database
This retrospective pre-post study utilized Truven Marketscan Commercial Claims and Encounters data. All commercially insured patients who received an HA injection between January 1, 2004, and December 31, 2011, were identified. The first HA injection received by patients during this time was described as the index HA injection. The time period of 30 days after the index HA injection was categorized as the treatment period. The 6-month periods before and after the treatment period were categorized as the pre- and posttreatment periods, respectively.

Inclusion and Exclusion Criteria
Patients were included if they: (a) were aged between 18 and 64 years on the date of their index HA injection (as the database did not cover Medicare-eligible patients); (b) were continuously eligible for the overall study period (the year before and the year after after HA injection); and (c) had an outpatient visit with a knee OA diagnosis during the overall study period. Patients who had a TKR during the 1-year period before the index HA injection were excluded from the study; however, the study did include patients who had a TKR in the post treatment period.

Variables
The main outcomes of interest were the utilization patterns of 3 pharmacotherapies commonly used in treating knee OA: NSAIDs, corticosteroid injections, and opioids. These patterns were analyzed in the 6-month pre- and post periods. Utilization was measured as an average number of prescriptions per patient, and as a proportion of patients using at least 1 of these agents. The independent variable in the study was the use of an HA injection. Demographic variables such as age, gender, and region were also assessed.

Statistical Analysis
Descriptive statistics were used for demographic variables. Age was categorized into 3 groups (18-44, 45-54, and 55-64 years) and regions were categorized as Northeast, North Central, South, and West. In order to assess the average number of prescriptions per patient, a paired sample t test was used to analyze a pre-post change. A McNemar’s test was used to assess a pre-post change in proportion of patients using at least 1 of these agents (NSAIDs, corticosteroid injections, or opioids). In addition, analysis was stratified based on patients who had TKR and those who had no TKR in the posttreatment period. All these analyses were performed using SAS for Windows, Version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS
Of the 386,636 identified patients who received HA injections between January 1, 2004, and December 31, 2011, a total of 152,953 patients were included in the final analysis after applying the inclusion and exclusion criteria. The majority of the patients (53.4%) were aged 55-64 years; 35.4% and 11.2% were aged 45-54 years and 18-44 years, respectively. Females and males represented 62.1% and 37.9% of the patients, respectively. The Southern region was most prominently represented with 43.7% of the patients, while the North Central, West, and East regions had 31.3%, 14.2%, and 5.8%, respectively.

During the 30-day initial treatment period, 436,000 HA injections were administered. Most patients received either 1 or 3 injections, per treatment recommendations. Further, an additional 50,000 injections were administered in the follow-up period, which were mostly carried over from the initial treatment period.

Results of the overall analysis are presented in the TABLE. The monthly trends in number of prescriptions filled and proportions of patients filling the prescriptions over time are shown in the FIGURE. Overall, our results demonstrated a statistically significant decrease in the utilization of NSAID prescriptions during the post period. Analysis showed a 10% reduction in the average number of NSAID prescriptions filled (P <.001) and a 15% reduction in the number of patients getting any NSAID prescriptions (P <.001). In addition, the average number of NSAID
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prescriptions among TKR patients and non-TKR patients went down significantly, by 11% and 9% respectively ($P < .001$). The number of TKR patients and non-TKR patients getting any NSAID prescriptions was also reduced by 5% and 16% respectively ($P < .001$). There was a consistent increase in the number of NSAID prescriptions filled and in the proportion of patients filling prescriptions during the pre-period leading up to HA index date, followed by a consistent decrease in the post period (Figure).

Likewise, a significant decrease in the utilization of steroid injections was found during the post period. The average number of steroid injections filled and the number of patients getting any steroid injections went down by 55% and 57%, respectively (both $P < .001$). Further, the average number of steroid injections among TKR patients and non-TKR patients was reduced by 63% and 54%, respectively (both $P < .001$). The proportions of TKR and non-TKR patients getting any steroid injections also decreased, by 60% and 56%, respectively (both $P < .001$). The Figure shows similar trends for both, the number of steroid prescriptions filled and proportion of patients filling the prescription. There was a consistent steep increase during the pre-period followed by a consistent steep decrease during the post period.

Interestingly, utilization of opioids increased in the post period. Overall, the average number of opioid prescriptions filled increased by 12% ($P < .001$) but the number of patients getting any opioid prescriptions fell by 6% ($P < .001$). Subgroup analysis indicated that there was a 175% ($P < .001$) increase in the average number of opioid prescriptions among TKR patients (representing nearly 7.5% of the study population) and a 6% decrease ($P < .001$) among non-TKR patients (representing nearly 92.5% of the study population). The proportion of TKR patients getting any opioid prescription increased by 85%, while the proportion of non-TKR patients using opioids decreased by 15% ($P < .001$). The explanation for the sharp increase in the opioid use among patients who had TKR surgery during the post period is that in the United States, a majority of patients receive a short-term opioid prescription following orthopedic surgery for postoperative pain management. The Figure shows that both the 6-month run-up in opioid prescriptions and the proportion of patients filling those prescriptions plateau after initiation of HA injection. Similar trends were observed in patients with no TKR. However, there were increases in the number of prescriptions filled and in the proportion of patients filling the prescriptions among TKR patients after the initiation of HA injection.

Limitations
This was a retrospective observational study with pre- and post-intervention design. Its findings should be considered in light of certain limitations. Since this study is observational in nature, it would be difficult to draw any causal inferences. Limited details were available about each intervention. Furthermore, the use of Truven MarketScan data restricted the study population to those aged between 18 and 64 years. Hence, findings of this study cannot be generalized to patients 65 years and older. Further research in the form of randomized control trials should study the impact of HA injections, to substantiate the causal inferences.

Table. Comparisons by Pharmacotherapy (no-TKR vs TKR)

<table>
<thead>
<tr>
<th>Pharmacotherapy</th>
<th>Number of prescriptions/patient: mean (SD)</th>
<th>Proportion of patients filling prescription (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-Period</td>
<td>Post Period</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs (NSAIDs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (N = 152,953)</td>
<td>0.90 (1.51)</td>
<td>0.81 (1.51)</td>
</tr>
<tr>
<td>Patients with no TKR in the post period (n = 141,469)</td>
<td>0.87 (1.49)</td>
<td>0.79 (1.51)</td>
</tr>
<tr>
<td>Patients with TKR in the post period (n = 11,484)</td>
<td>1.16 (1.72)</td>
<td>1.03 (1.57)</td>
</tr>
</tbody>
</table>

Steroid injections

| Overall (N = 152,953)        | 0.56 (0.74) | 0.25 (0.59)          | <.001 | 43.6%      | 18.9%       | <.001 |
| Patients with no TKR in the post period (n = 141,469) | 0.54 (0.73) | 0.25 (0.59)          | <.001 | 42.4%      | 18.5%       | <.001 |
| Patients with TKR in the post period (n = 11,484) | 0.81 (0.86) | 0.30 (0.61)          | <.001 | 58.7%      | 23.7%       | <.001 |

Opioids

| Overall (N = 152,953)        | 1.12 (2.61) | 1.25 (2.88)          | <.001 | 34.8%      | 32.7%       | <.001 |
| Patients with no TKR in the post period (n = 141,469) | 1.09 (2.57) | 1.02 (2.60)          | <.001 | 34.3%      | 29.2%       | <.001 |
| Patients with TKR in the post period (n = 11,484) | 1.46 (3.03) | 4.02 (4.33)          | <.001 | 41.0%      | 75.9%       | <.001 |

TKR indicates total knee replacement.

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Figure. Trends in Numbers of Prescriptions Filled and Proportions of Patients Filling Prescriptions Over Time

HA, hyaluronic acid; NSAID, nonsteroidal anti-inflammatory drug; Rx, prescription; TKR, total knee replacement; Trt, treatment with HA injection.
CONCLUSIONS

Overall, the results of this study suggest that in the real-world setting, HA treatment may help reduce the use of anti-inflammatory and pain medications, such as steroids, NSAIDs, and opioids, among patients with knee OA. Although an increase in opioid use was found during the post period in the overall study population, this appeared to be predominantly driven by patients who used opioids for postoperative pain following TKR surgery. Nevertheless, an analysis of the patients without TKR during the post period, representing 92.5% of the main study population, demonstrated lower opioid use compared to the pre-period. This study provides a real-world perspective around the utilization of pharmacotherapeutic options for pain management among patients with knee OA following HA treatment.

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REFERENCES


