Intra-articular injection of hyaluronic acid after arthroscopic surgery fails to provide additional benefit for symptomatic degenerative arthropathy patients: a systematic review and meta-analysis of randomized controlled trials

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- **Objective:** This study aimed to provide the evidence of the role of addition hyaluronic acid immediate after arthroscopy in pain relief and functional recovery.

- **Methods:** A multiple databases search of the PubMed, the Cochrane Library, and Embase was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria to identify randomized controlled trials that evaluate the effect the hyaluronic acid compared with placebo addition immediately after arthroscopy for degenerative arthropathy. Data related to postoperative pain using the visual analog scale, and functional scores, were extracted and analyzed using the RevMan software.

- **Results:** A total of five randomized controlled trials were included in this study. All patients showed significant pain relief after surgery at 2 weeks and 2 months, but no statistically significant differences between the hyaluronic group and control group were observed at 2 weeks and 2 months, respectively. This meta-analysis did not find a difference of WOMAC score between the two groups at 2 weeks (MD: 3.07; 95% CI: -0.66 to 6.81; I² = 39%; P = 0.11) and 2 months (MD: 5.47; 95% CI: -0.69 to 11.62; I² = 57%; P = 0.08), respectively.

- **Conclusion:** For patients with symptomatic degenerative arthropathy, adding hyaluronic acid immediately after arthroscopic surgery did not appear to provide patients with more pain relief and better functional recovery.

Keywords: degenerative arthropathy; knee arthroscopic surgery; hyaluronic acid; viscosupplementation

Introduction

Knee arthroscopy is the replacement choice for patients with symptomatic degenerative arthropathy who have failed conservative treatment, such as intra-articular loose bodies and meniscal pathology. Postoperative joint pain and swelling are the main problems affecting enhanced recovery after surgery, which is thought to be a disorder of the joint environment caused by the trauma of surgery (1, 2, 3). Arthroscopic surgery involves...
Hyaluronic acid is widely used as a joint viscosupplementation in the conservative treatment of osteoarthritis for its lubricating role for joint, although a consensus has not been reached. Studies have found its ability to downregulation of matrix metalloproteinases and cytokines through interleukin-1β-mediated expression (10, 11), which is critical in postoperative anti-inflammation and delaying the progress of osteoarthritis. Given the aforementioned properties and the fewer side effects associated with intra-articular administration, it is considered possible to be beneficial to add a dose of HA immediately after surgery. Pain is the main factor affecting the recovery of patients, and the use of painkillers after surgery is widely accepted by surgeons. Considering the adverse effects of systemic analgesics, the use of topical analgesics for pain control warrants further investigation. Therefore, the role of HA in postoperative pain relief is worth considering among patients with symptomatic degenerative arthropathy.

Therefore, we performed this systematic review and meta-analysis of randomized controlled trials (RCTs) to provide evidence for the use of HA immediately after knee arthroscopy. We hypothesize that a dose of HA added immediately after surgery may be beneficial for postoperative rehabilitation of symptomatic degenerative arthropathy and postoperative pain relief.

Methods

Search strategy

Two independent reviewers performed this systematic review and meta-analysis according to the PRISMA (which stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. This study has been registered with PROSPERO (CRD42022364674). The electronic databases of PubMed, Embase, and Cochrane Library were searched for articles from study inception to December 2, 2022. The following keywords were used: ((hyaluronic acid) OR (viscosupplementation)) AND (arthroscopy)) AND (knee). References from retrieved articles were also explored. The title and abstract of all retrieved articles were screened, and full-text reviews were performed for potentially eligible studies. All disagreements reached consensus through discussion.

Eligibility criteria

Studies were included if they met the criteria as follows: (i) RCT comparing immediately intra-articular HA versus placebo or control group after knee arthroscopy for degenerative arthropathy; (ii) outcomes measured function and pain with VAS scores; (iii) published in English; and (iv) full text of studies available. The exclusion criteria consisted of (i) letters, comments, case reports, reviews, animal studies, cadaveric studies, biomechanical studies, and study protocols; (ii) abstracts only; and (iii) repeated studies and data.

Assessment of methodological quality

Two reviewers independently assessed the methodological quality of included studies based on the modified Coleman Methodology Score (mCMS) (12, 13). This score grades studies from 0 to 100 based on items, such as inclusion criteria, sample size calculation, randomization, follow-up, patient analysis, blinding, similarity in treatment, treatment description, group comparability, outcome assessment, description of rehabilitation protocol, clinical effect measurement, and the number of patients treated. The grading was considered as follows: studies with a score of >85 were considered excellent; 70–84, good; 55–69, fair; and ≤54, poor (12). Any disagreements were resolved by discussion.

Assessment of risk of bias

The Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate the risk of bias of the included studies (14). The type of bias included in this assessment includes selection, performance, detection, attribution, and others. The same two reviewers independently performed the assessment, and all discrepancies reached consensus by discussion with a third senior arthroscopy surgeon author.

Data extraction

Two reviewers independently extracted the data from each study using a predefined data sheet. General characteristics of the studies were collected, including first author, year of publication, country of investigation, study design, sample size, age, gender, body mass index, and follow-up duration. For outcome measurements, visual analog scale (VAS) score for pain, Western Ontario and McMaster University Osteoarthritis Index (WOMAC) score, International Knee Documentation Committee (IKDC), Tegner score, and Lysholm score were recorded. Whenever necessary, we tried to contact the author for missing data; if it failed, we calculated the missing values from available data using formulas in the Cochrane Handbook for Systematic Reviews of Interventions (14).
Figure 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study selection flowchart. HA, hyaluronic acid.

Table 1  Study characteristics. Values are presented as mean ± s.d. where available.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Anand et al. (6)</th>
<th>Baker et al. (19)</th>
<th>Filardo et al. (18)</th>
<th>Hempfling (8)</th>
<th>Yoon et al. (17)</th>
</tr>
</thead>
<tbody>
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<td>Ireland</td>
<td>Italy</td>
<td>Germany</td>
<td>Korea</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Sample size, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>24</td>
<td>49</td>
<td>45</td>
<td>40</td>
<td>23</td>
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<td>24</td>
<td>49</td>
<td>45</td>
<td>40</td>
<td>24</td>
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<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
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<tr>
<td>Treatment</td>
<td>43.5 ± 12.2</td>
<td>46.5</td>
<td>39.0 ± 10.4</td>
<td>40.8 ± 9.6</td>
<td>47.7 ± 13.2</td>
</tr>
<tr>
<td>Control</td>
<td>43.3 ± 11.7</td>
<td>44.1</td>
<td>40.8 ± 9.6</td>
<td>46.7 ± 14.3</td>
<td></td>
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<tr>
<td><strong>Sex, male-female ratio, n</strong></td>
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<td></td>
<td></td>
<td></td>
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<td>Treatment</td>
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<td>34:15</td>
<td>8:37</td>
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<td></td>
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<tr>
<td>Control</td>
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<td>36:13</td>
<td>12:33</td>
<td>7:17</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
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<td>NR</td>
<td>26.2 ± 3.7</td>
<td>NR</td>
<td>27.0 ± 3.6</td>
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<tr>
<td>Control</td>
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<td>24.1 ± 3.2</td>
<td>26.2 ± 4.9</td>
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<td><strong>Follow-up, months</strong></td>
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<td>6</td>
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<td>3</td>
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<tr>
<td>Viscosupplementation</td>
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<td>Durolane</td>
<td>Hymovis</td>
<td>Viscoseal</td>
<td>Jointseal</td>
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<tr>
<td>Dosage</td>
<td>50 mg/10 mL</td>
<td>60 mg/3 mL</td>
<td>24 mg/3 mL</td>
<td>50 mg/10 mL</td>
<td>5 mg/10 mL</td>
</tr>
<tr>
<td>Placebo</td>
<td>Bupivacaine</td>
<td>Bupivacaine</td>
<td>no</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>Dosage</td>
<td>50 mg/10 mL</td>
<td>50 mg/10 mL</td>
<td>77</td>
<td>77</td>
<td>74</td>
</tr>
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<td>mCMS</td>
<td>74</td>
<td>74</td>
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</table>

NR, not reported; mCMS, modified Coleman Methodology Score; DB, debridement; MN, meniscectomy.

**Statistical analysis**

A meta-analysis was conducted to show the S.M.D. (standardized mean difference) for continuous variables and the risk ratio in dichotomous variables. Data at the 2-week and 2-month postoperative time points were pooled for the meta-analysis. The minimum clinically important difference (MCID) was introduced to evaluate effect of the intervention and compare potential differences between the two groups. Based on the previous studies, the MCID for improvement in VAS for pain, WOMAC, IKDC, Tegner score, and Lysholm score was set at 20% (15, 16). If a meta-analysis was not possible because of lack of variables, a qualitative description of the outcomes was performed. Publication bias was not investigated because the methods are unreliable with 5 studies. Heterogeneity between studies was quantified using the $I^2$ statistic. $I^2$ value of 25%, 50%, and 75% were considered to indicate low, medium, and high heterogeneity, respectively. For studies with high heterogeneity ($I^2$ value >50%), a random-effect model using the DerSimonian and Laird’s approach was adopted; otherwise, the fixed-effect model using the method of inverse of the variance was used. Forest plots were used to illustrate outcomes. $P < 0.05$ was considered statistically significant and the 95% CI was used to report all pooled statistics. Review Manager (RevMan software, version 5.4.1, The Cochrane Collaboration, 2020) was used to perform the statistical analysis.
Results

Identification of studies
A total of 676 studies were retrieved from PubMed, Embase, and Cochrane Library databases. After removal of 149 duplicates, 527 studies remained to screen. According to the inclusion and exclusion criteria, 509 studies were excluded after reading the titles and abstracts, and 13 studies were excluded after reading the full texts. No additional study was found after screened for the references of the included studies. Finally, five RCTs were included in the study (Fig. 1) (6, 8, 17, 18, 19).

Study characteristics
The five included studies, comprised a total of 363 patients who were enrolled, including 181 in the treatment group and 182 in the control group. All patients underwent arthroscopic surgery for degenerative arthropathy, including irrigation, debridement, and/or partial meniscectomy. No patients underwent meniscal suture, anterior cruciate ligament reconstruction, or microfracture. All patients in the treatment group received an additional dose of HA immediately after surgery, while patients in two studies (6, 19) received 10 mL of 0.5% bupivacaine as control group and patients in another three studies (8, 17, 18) were treated with surgery alone. Four HA formulations were used in the five included studies, with doses of 3 mL and 10 mL and concentrations ranging from 0.05% to 2%. Details of the study characteristics are presented in Table 1.

Assessment of literature and methodological quality and risk of bias
All of the included studies had level of evidence one. Quality assessment using mCMS showed that five studies were of good quality, ranging from 74 to 77. Figure 2 reveals the risk of bias summary and graph of five included studies. The included studies showed a low risk of bias, and no study reported a high risk of bias in any item. Two studies reveal unclear risk of bias for random sequence generation. The performance bias was recorded adequately in four studies and unclear in one. The other bias was recorded adequately in one study and unclear in four.

Minimum clinically important difference
Based on the previous studies, the MCID for changes in VAS for pain, WOMAC score, IKDC score, Lysholm score, and Tegner score was set at 0.2 using the distribution...
method (15, 16). Thus, in the present work, based on the baseline value of each outcome in the included studies, the value of MCID for VAS for pain was calculated as 0.72, WOMAC score as 5.77, IKDC score as 10.13, Lysholm score as 12.57, and Tegner score as 0.69.

**Pain improvement**

All included studies reported pain improvement at 2 weeks after operation, as indicated by pooled data from four studies, including 313 patients; the total mean improvement was 1.95 in the treatment group and 1.85 in the control group (6, 8, 18, 19). MCID for pain improvement exceeded in both groups, but meta-analyses of pain at rest, pain on weight bearing, and pain on movement also did not show differences in improvement (P = 0.98, P = 0.70, and P = 0.71, respectively) (Fig. 3).

Three studies including 233 patients reported pain improvement within 2 months after operation (6, 18, 19). The total mean improvement was 2.00 and 1.78 within groups, respectively, both exceeding MCID, whereas meta-analyses of pain at rest, pain on weight bearing, and pain on movement showed similar results between groups (P = 0.65, P = 0.27, and P = 0.97, respectively) (Fig. 4).

**Functional improvement**

In total, three studies including 190 patients reported WOMAC score (6, 17, 19). Two weeks after operation, the total mean improvement was 11.72 in the treatment group and 8.23 in the control group, both of the two groups exceeded the MCID for WOMAC score. We found no statistically significant difference in the total mean improvement between groups (MD: 3.07; 95% CI: -0.66–6.81; P = 39%; P = 0.11). The 2-month WOMAC score improved significantly in both the treatment and control groups (17.37 and 12.36, respectively). Although the total mean improvement was higher in the treatment group, a statistical difference between groups was not confirmed (MD: 5.47; 95% CI: -0.69–11.62; P = 57%; P = 0.08) (Fig. 5).

The 2-month Lysholm score (17, 19), Tegner score (17, 18), and IKDC score (17, 18) were reported in two studies, respectively. The total mean improvement of Lysholm score was 18.87 in the treatment group and 16.10 in the control group. The treatment group resulted in a Tegner score mean improvement of 0.87, as compared with 0.48 for control group. As for the IKDC score, the total mean improvement was 21.74 in the treatment group and 17.30 in the control group. Except for the control group, whose Tegner score did not reach the MCID, all the aforementioned scores in the two groups reached the preestablished MCID. Although the three scores improved better in the treatment group, there was no significant difference between the groups (P = 0.36, P = 0.44, and P = 0.18, respectively) (Table 2).

**Discussion**

The main finding of this meta-analysis is that adding one dose of vucosupplementation at the end of arthroscopic

![Figure 4](https://example.com/fig4.png)

**Figure 4**

Meta-analysis comparing improvement in the visual analog scale (VAS) score for pain within 2 months after surgery of the immediate injection of vucosupplementation group versus the placebo injection group. IV, inverse variance.

![Figure 5](https://example.com/fig5.png)

**Figure 5**

Meta-analysis comparing improvement in the total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at (A) 2 weeks and (B) 2 months after surgery of the immediate injection of vucosupplementation group versus the placebo injection group. IV, inverse variance.
Table 2  Analysis of functional improvement.

<table>
<thead>
<tr>
<th></th>
<th>Lysholm score</th>
<th>Tegner score</th>
<th>IKDC score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>72</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Control</td>
<td>73</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Improvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>18.87</td>
<td>0.87</td>
<td>21.74</td>
</tr>
<tr>
<td>Control</td>
<td>16.10</td>
<td>0.48</td>
<td>17.30</td>
</tr>
<tr>
<td>Statistics</td>
<td></td>
<td></td>
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<tr>
<td>M.D.</td>
<td>2.16</td>
<td>0.41</td>
<td>4.88</td>
</tr>
<tr>
<td>95% CI</td>
<td>2.47–6.80</td>
<td>−0.63 to 1.46</td>
<td>−2.32 to 12.09</td>
</tr>
<tr>
<td>P</td>
<td>0%</td>
<td>63%</td>
<td>54%</td>
</tr>
<tr>
<td>P</td>
<td>0.36</td>
<td>0.44</td>
<td>0.18</td>
</tr>
<tr>
<td>MCID</td>
<td>12.57</td>
<td>0.69</td>
<td>10.13</td>
</tr>
<tr>
<td>Favorable outcome</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

MCID, minimum clinically important difference; M.D., mean difference; IKDC score, International Knee Documentation Committee score.

Treatment for symptomatic degenerative arthropathy failed to provide additional pain relief within 2 weeks and 2 months compared with operation alone with placebo injection. Furthermore, functional score improvement demonstrated the effectiveness of the operation, with no statistically significant differences in the total mean improvement of WOMAC scores, Lysholm scores, Tegner scores, or IKDC scores between the two groups, although the total mean improvement was higher in the treatment group.

Both the treatment group and the control group showed significant improvement in pain and functional outcomes at 2 weeks and 2 months after surgery compared with those before surgery. Most patients with symptomatic degenerative arthropathy, who have failed conservative treatment such as rehabilitation and nonsurgical treatment, endure mild-to-moderate pain, which is mainly caused by chronic synovial inflammation, friction of foreign bodies and damaged tissues in the joint (20, 21). Arthroscopic debridement and lavage could remove foreign bodies, hyperplastic and degenerative tissues, which could lead to significant symptomatic relief within 2 months (22, 23). Most patients can start rehabilitation exercise immediately after surgery, of which pain and swelling are main factors affecting recovery. Some surgeons believe that changes in the intra-articular environment caused by operation are the cause of early postoperative joint pain and swelling (2, 24, 25), so it is proposed that the addition of HA may improve the early postoperative pain and swelling (7, 9). Previous studies have yielded inconsistent results (6, 8, 17, 18, 19). Our study found significant improvement in pain and functional outcomes in both groups compared with pre-operation, but no difference between the two groups was found. We thought that although the procedure removes synovial fluid that protects and lubricates the joint and changes the intra-articular environment, the benefit to the patient of the procedure itself may outweigh the harm of reduced synovial fluid which may be re-secreted within several days.

HA is widely used as a viscosupplementation in the conservative treatment of osteoarthritis. Studies have proven that HA has lubricating, anti-inflammatory, and pain-reducing properties (3, 26, 27, 28, 29). In addition, local injection could avoid potential toxicity related to a systemic administration. Based on these features, the use of HA after arthroscopy seems reasonable with the aim of reducing pain and promoting enhanced rehabilitation; however, contradictory results from previous studies do not seem to fully support this hypothesis, for the characteristic features of HA added in different studies were not the same (6, 7, 8, 9, 17, 18, 19). Several possible influencing factors could not be fully addressed in our meta-analysis, including the intervention in the control group and different brands, concentrations, and doses of HA in the treatment group. Intra-articular bupivacaine injection after operation is believed to have an analgesic effect (30, 31). Both Anand et al. and Baker et al. investigated the effects of postoperative addition of HA and bupivacaine, but their findings were diametrically opposed (6, 19). Anand et al. found that the effect of HA did not appear until 3–6 weeks after operation, and the difference was found to increase (6). Baker et al. did not show similar results using another long-acting HA preparation of a higher concentration and lower dosage (19). Another interesting finding is that studies with no additional benefit of HA injection after surgery used preparations of higher concentration and smaller volumes. Therefore, whether the effect of postoperative addition of HA is caused by HA or fresh liquid environment deserves more research.

The cavity of the knee joint generally contains a small amount of synovial fluid between 0.5 and 3 mL. In pathological conditions, additional synovial fluid with different composition and content is produced by the stimulated synovial membrane. The role of synovial components such as inflammatory cytokines and protein molecules in the evolution of knee diseases has been widely studied (10, 32, 33, 34, 35). Degenerative arthropathy has lesser levels of synovial fluid compared to traumatic or immune joint diseases, but inflammatory factors are highly expressed in the joints that require surgery including degenerative arthropathy. Inflammatory factors such as interleukin 6 could promote the increase of capillary permeability and allows more macromolecules to enter the joint cavity, which could contribute to the pain and discomfort preoperation and accelerate the process of osteoarthritis (32, 35). Therefore, the intervention of synovial fluid as a new direction of the treatment of arthropathy has been paid more attention.

Arthroscopy could clear the degenerative tissue and synovial fluid and play a role in refreshing the joint microenvironment. The renewal of joint environment after operation depends on the secretion regulation of joint tissues. However, acute inflammation caused by...
surgical stress is inevitable, which is also the main factor affecting the early recovery after surgery (1, 36, 37). Although this study did not find a benefit of HA addition in pain management, the better functional scores in the treatment group may also have benefited from HA addition, which may be the result of HAs role in joint lubrication and stabilizing the internal environment rather than pain relief. HA has a half-life of no more than a week, but its effects can last up to 6 months, and it might work better with arthroscopic surgery (38, 39, 40, 41, 42). Although this study did not confirm the benefit of adding HA immediately after surgery, other studies have confirmed the benefit of adding HA at intervals after surgery.

Limitations

This study has several limitations, which remain to be addressed. First, due to the strict experimental design and inclusion criteria, only five studies were included. Another two studies met the criteria but were excluded with the unextractable data (7, 9). Results were also reported in several conference abstracts, but were excluded because we did not have access to specific data. However, the strict design, inclusion and exclusion criteria make our results more reliable. Second, the treatment was not completely consistent within the treatment group and the control group. The viscosupplementation in the treatment group was of different manufacturers and specifications, as discussed earlier. Bupivacaine was used in two of the control groups and nothing was added in three. The injection of the control groups was widely used as a routine protocol after arthroscopy, which may increase the generalizability of this study. Third, this study lacks subgroup analysis of disease. Patients with different severity of osteoarthritis may benefit from arthroscopy differently. The results of meniscectomy and debridement may also differ. The failure to obtain additional studies and subgroup data limited our analysis. Finally, the lack of data related to shorter follow-up and swelling may be more relevant to the effect of HA after surgery, which can be addressed by design in future studies.

Conclusion

For patients with symptomatic degenerative arthropathy, HA addition immediately after surgery could not provide additional benefit in pain relief and functional recovery, despite the fact that HA addition showed a trend toward greater improvement in functional scores. Given the existing disagreement and the small number of high-quality studies, more studies should be conducted in the future.

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References


ICMJE Conflict of Interest Statement

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.


