EFFICACY OF WEEKLY INTRA-ARTICULAR LOW MOLECULAR SODIUM HYALURONATE INJECTION FOR THREE WEEKS IN THE TREATMENT OF OSTEOARTHRITIS: OPEN RANDOMIZED CLINICAL TRIAL

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Abstract

The primary objective of this study was to determine whether the three-weekly injections improve knee pain and patients' quality of life. The secondary objective was to assess patients' compliance to treatment and risks related to the three-weekly injections of Hyalgan®. The authors conducted a single-blind randomized controlled trial. Osteoarthritis knee participants aged 50 years or older with early osteoarthritis knee or Kellgren-Lawrence grade I to III were randomized to intra-articular injection of three-weekly doses (the intervention group; n = 50) or five-weekly doses of Hyalgan® (the control group; n = 50). The outcomes of the study were measured at baseline, 1, 2, 3, 4, 5, and 8 weeks post-treatment. The weight-bearing after 50 foot-walking and patients' quality of life at the baseline measured by visual analog scale (VAS) and Thai short form 36 (SF-36) health survey score were not significantly different between the two groups (p = 0.430 and 0.239, respectively). The VAS was statistically lower at the 1st and 2nd week in the three-weekly intra-articular injections group (p = 0.009 and 0.005, respectively). The evaluation of overall changes in the Thai SF-36 score also revealed that patients in the three weekly injection group had a higher quality of life compared to the other group (p = 0.0001). The numbers of loss to follow-up in the intervention group were significantly lower than the control group (2 cases vs. 7 cases, p < 0.05). And no complication related to intra-articular injection was found in the two treatment groups. In conclusion, the results of this present study support the hypothesized superiority of managing pain associated with knee OA and increasing patients' quality of life in the three weekly injections over the conservative management of the five weekly injections. More importantly, the safety of the treatment has been warranted.

Keywords: Osteoarthritis knee, Hyaluronic acid, Viscosupplementation, visual analog scale, Thai short form 36 health survey score

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Introduction

Sodium hyaluronate is the main component of joint fluid and cartilage. Knee arthritis causes a reduction in its concentration which results in chronic knee pain. There is evidence that the supplementation of exogenous sodium hyaluronate can alleviate the pain by restoring the viscoelastic properties of the synovial fluid and stimulates synoviocytes to synthesize endogenous hyaluronic acid.

Low-molecular weight viscosupplementation has been widely used for the treatment of early osteoarthritis knee (OA) (classification based on Kellgren-Lawrence grade I-III). Patients treated with the supplement benefit from the long-term safety and decreased risk of adverse serious gastrointestinal effects, the complications from prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs). A five-weekly injection of sodium hyaluronate has shown to be effective for pain relief in this group of patients. It is global standard practice to provide the five-weekly injections in patients diagnosed with knee osteoarthritis. However, there are some drawbacks from the course of treatment. For example, the whole course is relatively long for the duration. The intra-articular knee injection itself is considered to be painful, and patients are also exposed to a chance of intra-articular bleeding and infection or septic reactions knee.

To avoid these complications and shorten the length of treatment, management with appropriate numbers of injection course should be proposed. As such, the authors designed a randomized controlled trial (RCT) comparing efficacy and effectiveness between a shorter of three-injection course and the standard course. The primary objective of this trial was to determine whether the three-weekly injections improve clinical outcomes of patients. Our primary hypothesis was that treatment with the three-weekly injections would result in reduced weight-bearing pain after 50-foot walking as well as an improvement in patient quality of life at eight weeks. Our secondary outcome was that incorporating the three-weekly injections into the management of knee osteoarthritis would enhance patients’ compliance to treatment without increasing risk of septic or pseudo-septic reactions.

Patients and methods

The study was a two-arm RCT with randomized assignment to intra-articular injection of three-weekly doses (the intervention group) or five-weekly doses of Hyalgan (the control group). The study was started at Buddhachinaraj Phitsanulok Hospital; between July 1, 2016, and June 30, 2017. The study was approved by the Research and Ethics committee at the study center (IRB reference number: 030/59). The sample size was calculated based on whether there is a difference in the efficacy of the three-weekly doses injection and five-weekly doses (hypothesis testing of an equivalence trial). The α was set at 0.05, and β at 0.2 to determine a standard deviation (S) of 10 as well as the clinically acceptable margin of the outcome of 7. The total expected sample size was 48 cases per arm with an additional of 2 cases assigned to each group to compensate any attrition along the follow-up period.

All patients presenting with knee osteoarthritis were screened for eligibility on their first visit at the study hospital. To be included in the study, patients had to be 50 years of age or older and have early osteoarthritis knee or a grade on the Kellgren-Lawrence (KL) of I to III. (The Kellgren-Lawrence ranges from grade 0 to IV, with higher grade indicating more severe of knee osteoarthritis). Patients with a history of allergy to Hyaluronic acid, severe degenerative spine, severe Genu Varus and Genu Valgus as well as those with septic arthritis, inflammatory arthritis, and previous use of intra-articular steroid within six months were excluded from the study. The information on screening, randomization, and follow-up was presented in Figure 1. Informed consent was obtained for all participants.
A simple random sample was performed to assign patients
to the intervention group and the control group. A list of
eligible patients on their first visit was obtained from a
screening nurse every day during the study period. Each
patient was marked with a specific number (1 and 2).
Patients with number 1 were assigned to the intervention
group and 2 to the control group, respectively. Patients in
the intervention group received three-weekly intra-articular
injections of Hyalgan® (4 ml dose at the 1st and 2nd week
follow by 2 ml dose at the 3rd week). The control group ob-
tained a 2 ml-weekly dose for the consecutive five weeks.
Sodium Hyaluronate or Hyalgan® 500 – 730 kilodalton
(kDa) is the Food and Drug Administration (FDA) approved
the drug for the treatment of osteoarthritis of the knee joint
since May 1997 and have been used extensively in Thailand.

To eliminate confounding factor causing by investigators’
expectations, a single-blind technique was established.
During the procedure, each patient was asked to lie on an
examination table in the supine position with their knees
extended; then the injection site was marked along the
superolateral corner of the patella. A well-trained orthopedic
surgeon was the only person who performed the intra-articular
injection procedures for all participants. Acetaminophen
was a sole pain reliever provided after the procedure.
Participant demographic and clinical characteristics, for
example, age, gender, body mass index (BMI), side of affected
knees, signs and symptoms at first visit, and KL grade were
documented. The primary outcome was a composite of two
components: measures of the weight-bearing after 50
foot-walking (visual analog scale of 0 – 10 cm.) and patients’
quality of life (Thai SF-36 health survey score). For
the secondary outcome, patients’ compliance to treatment
measured by follow-up rates and the occurrences of
complication from the intra-articular injection (e.g., septic or
pseudo-septic reactions knee) were recorded. Trained
examiners who were unaware of the group assignments
administered the tests at the baseline, 1st, 2nd, 3rd, 4th, 5th, and
8th week.

Data were analyzed with the Statistical Package for the
Social Sciences (SPSS) version 17.0. Descriptive statistics
were calculated for the patient demographic and clinical
characteristics. Differences in data were tested using
Chi-square tests for categorical variables and one-way
ANOVA for continuous variables. A two-sided significance
level of 0.05 was used to test both primary and secondary
hypotheses.

Results

Patients were recruited between July 1, 2016, and June
30, 2017 (see Fig. 1 for information on screening,
randomization, and follow-up). Of 112 eligible patients, 12
(11%) were excluded before randomization. Five patients
received intra-articular steroid within six months before
the recruitment; three had rheumatoid arthritis, and four had
a severely degenerative spine. Of patients who underwent
randomization, 91% were followed for eight weeks. Two
patients from the intervention group were lost to follow-up,
and seven were from the control group. None of them had a
complication related to intra-articular injection. Of the study
participants who underwent randomization, patients in the
three-weekly injections group had a BMI that was
statistically higher than another group (p < 0.05) with the mean
BMI of 27.2 (SD±4.33) compared to 24.89 (SD±3.73).
There were no statistically significant differences in age,
gender, or concerning pre-treatment symptoms. The weight-
bearing after 50 foot-walking and patients’ quality of life at
the baseline measured by visual analog scale (VAS) and
Thai SF-36 health survey score were not significantly different
between the two groups (p = 0.430 and 0.239, respectively).
Table 1 shows a comparison of the baseline characteristics
of enrolled patients.
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>3 weekly injections (N=50)</th>
<th>5 weekly injections (N=50)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.16 ± 7.45</td>
<td>65.24 ± 8.78</td>
<td>0.961</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>27.2 ± 4.33</td>
<td>24.89 ± 3.73</td>
<td>0.005</td>
</tr>
<tr>
<td>Diagnosis Osteoarthritis (years)</td>
<td>4.54 ± 6.23</td>
<td>3.27 ± 3.95</td>
<td>0.484</td>
</tr>
<tr>
<td>Position</td>
<td></td>
<td></td>
<td>0.419</td>
</tr>
<tr>
<td>Right knee</td>
<td>22</td>
<td>27</td>
<td>0.419</td>
</tr>
<tr>
<td>Left knee</td>
<td>28</td>
<td>23</td>
<td>0.419</td>
</tr>
<tr>
<td>Kellgren-Lawrence grade</td>
<td></td>
<td></td>
<td>0.369</td>
</tr>
<tr>
<td><strong>I</strong></td>
<td>10</td>
<td>5</td>
<td>0.369</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.213</td>
</tr>
<tr>
<td><strong>II</strong></td>
<td>36</td>
<td>41</td>
<td>0.369</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.213</td>
</tr>
<tr>
<td><strong>III</strong></td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Sign &amp; Symptoms</td>
<td></td>
<td></td>
<td>0.213</td>
</tr>
<tr>
<td>Pain</td>
<td>50</td>
<td>50</td>
<td>0.430</td>
</tr>
<tr>
<td>Swelling</td>
<td>4</td>
<td>2</td>
<td>0.213</td>
</tr>
<tr>
<td>VAS</td>
<td>5.62 ± 2.07</td>
<td>5.92 ± 1.70</td>
<td>0.430</td>
</tr>
<tr>
<td>SF-36</td>
<td>416.6±121.6</td>
<td>414.6±130.1</td>
<td>0.239</td>
</tr>
</tbody>
</table>

Data were tested by Chi-square tests
* statistically significant (p < 0.05)
The authors determined the efficacy of the study intervention and found that the VAS after a 50-foot walk in both groups decreased significantly between the 1st and 8th weeks ($p < 0.05$). The VAS was statistically lower at the 1st and 2nd weeks in the three weekly intra-articular injections group ($p = 0.009$ and $0.005$, respectively). The results for the VAS after the 50-foot walk in both groups are shown in Table 2. The trends of mean VAS scores after the 50-foot walk are illustrated in Figure 2.

**Table 2.** Patients' Visual analog scale after 50-foot walking (VAS) evaluation after treatment with 3rd and 5th weekly intra-articular sodium hyaluronate

<table>
<thead>
<tr>
<th>Week</th>
<th>3 weekly injections (N=50)</th>
<th>5 weekly injections (N=50)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.62 ± 2.07</td>
<td>5.92 ± 1.7</td>
<td>0.430</td>
</tr>
<tr>
<td>1</td>
<td>3.88 ± 1.76</td>
<td>4.88 ± 1.90</td>
<td>0.009*</td>
</tr>
<tr>
<td>2</td>
<td>3.14 ± 1.51</td>
<td>4.08 ± 1.74</td>
<td>0.005*</td>
</tr>
<tr>
<td>3</td>
<td>3.06 ± 1.77</td>
<td>3.5 ± 1.46</td>
<td>0.189</td>
</tr>
<tr>
<td>4</td>
<td>2.88 ± 1.61</td>
<td>3.04 ± 1.38</td>
<td>0.588</td>
</tr>
<tr>
<td>5</td>
<td>2.63 ± 1.72</td>
<td>2.59 ± 1.55</td>
<td>0.921</td>
</tr>
<tr>
<td>8</td>
<td>2.38 ± 1.65</td>
<td>2.37 ± 1.65</td>
<td>0.993</td>
</tr>
<tr>
<td>average</td>
<td>3.38 ± 2.00</td>
<td>3.83 ± 2.03</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

Data were tested by one-way ANOVA

* statistically significant ($p < 0.05$)

**Fig 2.** Patients' mean Visual analog scale after 50-foot walking (VAS) evaluation after treatment with 3rd and 5th weekly intra-articular sodium hyaluronate.
The results from a week-by-week analysis of patients' quality of life measured by Thai SF-36 score were similar for both groups ($p > 0.05$) (Table 3). However, the changes in the Thai SF-36 score between pre- and posttreatment were statistically significant ($p < 0.05$). The evaluation of overall changes in Thai SF-36 score also revealed that patients in the three weekly injection group had a higher quality of life compared with the other group ($p = 0.001$). Figure 3 demonstrates changes in patients' quality of life over the eight weeks of the study.

**Table 3.** Patients' Thai SF-36 health survey score evaluation after treatments with 3 and 5-weekly intra-articular sodium hyaluronate

<table>
<thead>
<tr>
<th>Week</th>
<th>3 weekly injections (N=50)</th>
<th>5 weekly injections (N=50)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>51.8±16.3</td>
<td>52.1±15.2</td>
<td>0.239</td>
</tr>
<tr>
<td>1</td>
<td>53.9±15.9</td>
<td>57.4±16.2</td>
<td>0.107</td>
</tr>
<tr>
<td>2</td>
<td>55.4±16.8</td>
<td>58.7±16.2</td>
<td>0.106</td>
</tr>
<tr>
<td>3</td>
<td>58.2±17.1</td>
<td>59.2±16.7</td>
<td>0.148</td>
</tr>
<tr>
<td>4</td>
<td>60.7±17.8</td>
<td>59.3±17.5</td>
<td>0.208</td>
</tr>
<tr>
<td>5</td>
<td>60.3±17.6</td>
<td>59.8±16.9</td>
<td>0.114</td>
</tr>
<tr>
<td>8</td>
<td>60.7±17.5</td>
<td>60.5±15.8</td>
<td>0.202</td>
</tr>
<tr>
<td>average</td>
<td>60.7±17.5</td>
<td>60.5±15.8</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

Data were tested by one-way ANOVA

* statistically significant ($p < 0.05$)

![Total SF-36](image)

**Fig 3.** Patients' Thai SF-36 health survey score evaluation after treatment with 3 and 5-weekly intra-articular Sodium hyaluronate
Our secondary hypothesis examined whether incorporating the three weekly injections course in the management of knee OA would improve patients’ compliance to treatment without increasing risk of septic or pseudo-septic reactions knee. The authors found that the numbers lost to follow-up in the intervention group were significantly lower than in the control group (2 cases vs. 7 cases, \( p < 0.05 \)) (Figure 4). No complication, related to intra-articular injection, was found in the two treatment groups.

![Graph showing number of patients after treatment with 3 and 5-weekly intra-articular Sodium hyaluronate](image)

**Figure 4.** Number of patients after treatment with 3 and 5-weekly intra-articular Sodium hyaluronate

**Discussion**

OA is a chronic disease that involves cartilage degradation, bone remodeling and bone overgrowth. Patients with OA usually suffer from pain and long-term disability. To date, pharmacologic treatments including analgesics and NSAIDs are recommended along with various nonpharmacologic modalities such as exercise and weight reduction.\(^{(5,7,9-13)}\)

However, most currently available pharmacologic treatment has its own limitations regarding tolerability and durability. Long-term use of NSAIDs can cause serious complications consisting of upper gastrointestinal bleeding and renal failure. As an alternative, the potential benefit of intra-articular injection of low molecular weight hyaluronic acid in alleviating pain associated with OA is of increasing interest. Many studies have investigated the efficacy and safety of intra-articular hyaluronic acid, especially for knee OA. The compiled available evidence suggests a positive effect of this drug in reducing pain and improving function.\(^{(12)}\)

In Thailand, the standard practice provides a five weekly injection course of hyaluronic acid among patients diagnosed with knee OA. However, the long duration of treatment is more likely to expose patients to a chance of intra-articular bleeding and infection or pseudo-septic knee reactions.\(^{(10)}\) To investigate the benefit of a shortened course of intra-articular hyaluronic acid injection, the authors gathered qualitative data from a randomized, single-blind comparative study to determine the efficacy and effectiveness of the three weekly injections compared with those of five weekly injections.

The results of this present study supported the hypothesized superiority of managing pain associated with knee OA and increasing patients’ quality of life in the three weekly injections over the conservative management of the five weekly injections. As has been noted in the study, the onset of knee pain relief following hyaluronic acid treatment in the three-weekly-injection group was rapid and apparent within the 1\(^{\text{st}}\) and 2\(^{\text{nd}}\) week of starting treatment. It also demonstrated significantly superior results in controlling pain and improving patients’
quality of life over the eight-week duration. More importantly, the safety of the treatment has been justified because the participants did not report any signs of complications related to the intra-articular injections. In addition, a higher rate of patients’ compliance to treatment was demonstrated in the intervention group.

In comparison with the earlier trials, reports have shown that the three weekly intra-articular injections of Hyalgan® and the five weekly injection did not exhibit any significant difference in pain relief among patients with knee OA. In our study, the authors increased Hyalgan® from a 2 ml to a 4 ml dose. The higher viscosity improved the visco-elastic properties of synovial fluid and alleviated pain more effectively. However, both present and related studies showed a concordant result pertaining to significant pain relief after five weeks of hyaluronic acid treatment. Notably, this study evaluated the short term outcomes of intra-articular hyaluronic acid treatment. Thus, it should not be compared with studies that investigated long term outcomes of such treatment. The authors declare they have no conflict of interest regarding the publication of this article. The randomized controlled trial is appropriate as an optimal method to establish the efficacy of a new intervention compared with the control treatment. Nonetheless, in this study, important limitations were observed regarding its relatively short observation period as well as the high attrition of eligible participants. These limitations might have introduced bias in the study’s results. We suggest a future study to develop a management approach to prevent losses from follow-up and enhance patient adherence, especially for those with chronic diseases like OA. The approach includes ensuring good communication between study staff and participants, accessibility to the clinic, effective communication channels, incentives to continue and ensuring that the study is of relevance to the participants.

Conclusion

In conclusion, this trial shows that the three weekly injections of Hyalgan® were effective over eight weeks. Additionally, the treatment was also superior to the five weekly injections regarding reducing VAS pain, increasing quality of life, improving patients’ compliance to treatment and the safety of the treatment has been justified. However, this present study only examined short term outcomes in a small sample size. Further studies to elucidate long-term effects of three weekly injections in a larger number of patients should be conducted.

References

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