Effect of Regenerative Injection Therapy on Function and Pain in Patients with Knee Osteoarthritis: A Randomized Crossover Study

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Abstract

Objective. We assessed the effectiveness of regenerative injection therapy (RIT) to relieve pain and restore function in patients with knee osteoarthritis.

Design. Crossover study where participants were randomly assigned to receive exercise therapy for 32 weeks in combination with RIT on weeks 0, 4, 8, and 12 or RIT on weeks 20, 24, 28, and 32.

Patients. Thirty-six patients with chronic knee osteoarthritis.

Interventions. RIT, which is made up of injections of 1 cc of 15% dextrose 0.6% lidocaine in the collateral ligaments and a 5 cc injection of 20% dextrose 0.5% lidocaine inside the knee joint.

Outcome Measures. The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms (WOMAC) score (range: 0–96).

Results. Following 16 weeks of follow-up, the participants assigned to RIT presented a significant reduction of their osteoarthritis symptoms (mean ± standard deviation: −21.8 ± 12.5, P < 0.001). WOMAC scores in this group did not change further during the last 16 weeks of follow-up, when the participants received exercise therapy only (−1.2 ± 10.7, P = 0.65). WOMAC scores in the first 16 weeks did not change significantly among the participants receiving exercise therapy only during this period (−6.1 ± 13.9, P = 0.11). There was a significant decrease in this groups’ WOMAC scores during the last 16 weeks when the participants received RIT (−9.3 ± 11.4, P = 0.006). After 36 weeks, WOMAC scores improved in both groups by 47.3% and 36.2%. The improvement attributable to RIT alone corresponds to a 11.9-point (or 29.5%) decrease in WOMAC scores.

Conclusions. The use of RIT is associated with a marked reduction in symptoms, which was sustained for over 24 weeks.

Key Words. Knee Osteoarthritis; Regenerative Injection Therapy; Exercise Therapy; Pain Management; Randomized Controlled Study

Introduction

Osteoarthritis (OA) of the knee is the most frequent form of arthritis in older adults. Symptomatic knee disease occurs in approximately 6% of U.S. adults over the age of 30 and in 10% over the age of 55 [1]. The risk of disability from knee OA was suggested to be comparable with the risk attributed to cardiovascular diseases and greater than any other medical condition in the elderly [2]. Most of the available therapies for OA address the symptoms of the condition but not its underlying mechanisms. Moreover,
treatments for the management of OA are often associated with suboptimal adherence (physical therapy, topicals) [3,4], limited control over symptoms (physical exercise, acetaminophen) [5], tolerability and safety issues (nonsteroidal anti-inflammatory drugs [NSAIDS], opioids, corticosteroids) [1,3–9], and uncertainty about long-term effectiveness (hyaluronic acid) [6,10]. Surgery, including arthroscopic knee surgery and knee replacement, is sometimes used when noninvasive options are noneffective. The outcome of some surgical approaches has nevertheless been reported to be indistinguishable from placebo surgery [11,12].

Ligament laxity and a varus–valgus motion have recently been suggested to contribute to the development of knee OA [13,14]. Regenerative injection therapy (RIT) could counter ligament laxity and a varus–valgus motion by strengthening major supporting ligaments in the knee. RIT involves intra-articular injections of a small volume of a proliferant solution (dextrose) at ligament attachments. In some laboratory conditions, RIT resulted in increases in ligament mass, ligament thickness, cross-sectional strength, and osteotendinous junction strength [15–17]. In clinical case studies, magnetic resonance imaging and ultrasound attest to tissue repair postinjection [18,19]. The underpinning mechanisms potentially responsible for these effects include the elimination of nerve fibers associated with neovascularization [20–22], inflammation and tissue repair, increase in cross-sectional area of ligaments and tendons [15,16,23], and the disruption and subsequent healing of the collagen fibril [20,21,24]. Although RIT already displayed promise as a treatment option for knee OA [25,26], its effectiveness has not yet been studied using a standardized functional outcome and a randomized controlled study design. We conducted a randomized controlled trial with a crossover to test the hypothesis that combining RIT with an exercise program is superior to exercise alone to improve function and pain in patients suffering from knee OA. Using a crossover design has the advantage of offering a good control over potentially confounding variable despite requiring a relatively small sample [27].

Methods

This open-labeled randomized controlled trial was conducted from November 2007 to October 2008. We used a two-period crossover design, meaning that participants were randomly assigned to two groups, A and B, and that the experiment was conducted over two consecutive time periods separated by a washout phase. In period 1, group A received the experimental treatment and group B received the comparative treatment. In period 2, treatment allocation was inverted. Each participant gave written informed consent before the study. The administration of treatment as used in this study was approved by Health Canada (trial registration number: HC-9427-B2716-21C) and is published on the ClinicalTrials.gov public site under the identifier NCT01206634. The study received ethical approbation by the Vitalité Health Network Research Ethics Board.

Participants

Patients recruited for this study were referred to an anesthesiologist by an orthopedic surgeon for pain management. To be included in the study, participants had to have had a diagnosis of knee OA, experience pain in the knee for a minimum of 6 months, be capable to understand and execute physiotherapy exercises, and be 18 years or older. Patients were excluded if they presented any of the following: previous operation of the referring knee, infection of the skin surrounding the knee or of the articulation, abnormal coagulation, allergy to lidocaine, pregnancy, or breast-feeding.

Group Assignment and Intervention

We randomly assigned participants who met the study criteria to one of two study groups in a 1:1 ratio using opaque sealed envelopes in blocks of six. Each envelope contained a description of the intervention of assignment. For group A, the intervention was composed of a home-based exercise program for 32 weeks in combination with RIT on weeks 0, 4, 8, and 12. Intervention for group B included the home-based exercise program for 32 weeks in combination with RIT on weeks 20, 24, 28, and 32. For all the study participants, the exercise program was composed of four strengthening exercises (isometric quadriceps exercises, leg extension exercises with quadriceps roll, strait leg raise, and sitting end-range knee extension) for which the participants were asked to perform three sets of 10 repetitions daily. The participants were instructed on how to do the exercises by a senior physiotherapist, who also reviewed the exercises every 4 weeks. The same program was maintained throughout the study.

The injections were performed as described elsewhere [28,29]. The osteotendinous junction of both insertion sites of the collateral ligaments was identified. The patients then received injections of 1 cc of a 15% dextrose and 0.6% lidocaine solution free of adrenaline in each of eight administration sites in the collateral ligaments (see Appendix). A 5 cc injection of 20% dextrose and 0.5% lidocaine without adrenaline solution was also administered inside the knee joint. The intra-articular injection was performed using the anterior approach. Solutions were prepared by a hospital pharmacist the morning of the injections. The elimination half-life of the solutions is approximately 90–120 minutes [30]. Each infiltration was preceded by a local sterilization composed of three disinfections with a 2% chlorexidine and 4% idopropyl alcohol solution.

Study Variables

Several measures of functional capacity and pain were used. The primary outcome was the Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms (WOMAC version 3.1). This self-administered questionnaire assesses pain, joint stiffness
and disability using 24 items with five-point Likert scales [31]. The WOMAC includes three subscales: WOMAC pain (five items), WOMAC stiffness (two items), and WOMAC function (17 items). Other outcomes included the Brief Pain Inventory (short form), which was administered to assess pain intensity and pain-related functional impairment (physical and emotional) [32]. More specifically, four items assess the intensity of current pain and pain at its least, worst, and average during the past day on scales from 0 (“no pain”) to 10 (“pain as bad as you can imagine”). Seven more items measure pain-related functional interference in different domains (general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life) rated from 0 (“does not interfere”) to 10 (“interferes completely”). The participants also rated their pain with the Wong–Baker Faces Pain Rating Scale, a series of six faces anchored at 0 for “no hurt” and 5 for “hurts worst.” After being instructed that each face is for a person who feels happy because he or she has no pain or sad because he or she has some or a lot of pain, the participants chose the face that best described how they were feeling [33]. The participants also rated their pain with a simple descriptive intensity scale with six adjectives (no pain, mild pain, moderate pain, severe pain, very severe pain, and worst pain possible), a numeric distress scale with anchors 0 for “no pain” and 10 for “unbearable pain,” and a visual analog scale with the words “no pain” and “pain as bad as could possibly be” at the left and right ends of a line, respectively. We also studied each of the measures of pain simultaneously using a combined pain score created by taking the first principal component scores from a principal component analysis of the WOMAC, Brief Pain Inventory, Wong Baker, numeric scale, and visual analog scale for all the subjects and periods. A combined pain score summarizes the results of all pain measures used and alleviates the risk associated with multiple statistical testing. The Timed Up-and-Go Test was used to evaluate functional capacity. The participants started in a sitting position (with hands resting on the arms of an armchair of standard height), stood, walked 3 m, turned around, and walked back to sit down on the chair again. The timing started when the participant’s back came off the chair, and stopped when their buttocks touched the seat of the chair [34]. For all of the outcomes analyzed, lower scores indicate a more desirable outcome (less pain or better physical function). The patients’ severity of knee OA was assessed by a radiologist using the Kellgren–Lawrence grading scale. Anteroposterior radiographs of the knee had been taken prior to enrollment in the study.

Personnel

It was not possible for the participants and administrators of treatment to be masked to group allocation. However, the research assistants responsible for administrating measurement instruments were masked to group allocation. All RIT injections were administered by RD, an anesthesiologist with over 10 years of experience with the administration of this type of treatment. The same senior physiotherapist oversaw the exercise program throughout the study.

Follow Up

The participants met with the research assistants (research nurses and family medicine residents) at the onset of the study, every 4 weeks of the subsequent 32 weeks of intervention and 4 weeks after the intervention. At each of those visits, the participants were asked to fill in measurement questionnaires. The research assistants also investigated the presence of side effects or complications and reminded the participants that the research protocol restricted them from taking any anti-inflammatory medication throughout the 32 weeks of intervention. The participants were nevertheless permitted to continue using other medications. At the onset of the study, the participants received a study calendar detailing each of their appointments. In addition, the patients received an appointment card at the end of each visit. This card provided the time of the next visit, contact information, as well as a list of conditions for which the participants should contact the study center. Prior to beginning the study, it was decided that if a participant presented a sustained deterioration of symptoms or function, or experienced undesirable side effects, the presumed contributing part of the treatment would be discontinued.

Data Analyses

Data were analyzed with diagnostic procedures and according to the two-group two-period crossover trial analysis of variance recommended by Jones and Kenward for the analysis of data from crossover studies [27]. The analysis was carried out on the change observed in the variables during period 1 and during period 2. This approach provides an estimate of the treatment-specific effect from the overall study. Diagnostic plots were assessed to ascertain that the assumptions of the test were met. Furthermore, for each period, we compared changes (score at week 16 minus score at week 0 and score at week 36 minus score at week 20) between the two groups using t-tests. Mean within group change between weeks 0 and 16 and between weeks 20 and 36 was also assessed using paired t-tests for all outcomes. We intended to recruit a minimum of 36 participants based on the estimate that a sample of 18 participants per group would provide 80% power of detecting a treatment effect, with the potential for type I error set at 5%. This was based on the hypothesis that RIT would improve the WOMAC score by 40% and that the comparison treatment would yield no improvement in this cohort of patients with chronic knee OA.

Results

Figure 1 presents the evolution of participants from enrollment to completion of the study. Of 60 patients assessed for eligibility, 45 were considered eligible and were recruited. Twenty-one participants were randomly
assigned to study group A and 24 to group B. Data are presented for the 18 participants who completed the study in each group. Although there were 11 men in group A and eight in group B, there were no meaningful differences between baseline characteristics of participants in both groups (Table 1).

Primary Outcome

Following the first study period, the participants assigned to RIT (group A) presented a significant improvement of their overall WOMAC scores, whereas the overall WOMAC scores did not change significantly among the participants in group B (Table 2). The WOMAC scores of group B nevertheless improved significantly during the second period (during which they received RIT). Although there was no further change in the overall WOMAC scores among group A, the improvement they had achieved in period 1 was sustained throughout period 2 (Figure 2). After the two study periods, the overall WOMAC scores improved by 21.1 points (47.3%) from baseline in group A and by 13 points (36.2%) in group B (relative improvement = change from baseline to end of follow-up / mean baseline score for the group). Based on the overall crossover experiment, the improvement estimated to be attributed to RIT alone corresponds to a 11.9-point (or 29.5%) decrease in the overall WOMAC scores.

Similar observations can be made for each of the WOMAC subscales. At the end of period 1, scores on the WOMAC pain, stiffness, and function subscales had improved among the participants in group A, but only WOMAC pain had improve significantly in group B. The participants in group A presented no further improvement in their WOMAC subscale scores at the end of period 2. This period led to improvements in each of the WOMAC subscales among participants in group B. RIT was estimated to have had positive effects for each of the WOMAC subscale in the overall design test.

Secondary Outcomes

Whereas only four of eight secondary outcomes improved during period 1 in group B, all secondary outcomes improved significantly in group A. Group A measures remained stable during period 2. Among the group B participants, there was an improvement in the two dimensions of the Brief Pain Inventory questionnaire but not in other outcomes. Although not necessarily statistically significant at the conventional $\alpha < 0.05$ cut point, the overall estimated effects suggested that RIT was associated with an improvement of all secondary outcomes. Figure 3 depicts the mean combined pain score of the participants.
at 4-month intervals throughout the study. It shows a rapid improvement in the combined pain score following the administration of RIT for the two groups. Data for group A also suggest that the improvements can be sustained for 24 weeks following the last session of RIT.

Adverse Event

The RIT regimen was ceased as a precautionary measure in one participant in group B after reports of diffuse edema of both legs at weeks 24 and 28 of follow-up.

Discussion

This study demonstrates that RIT was associated with improvements in WOMAC scores that were markedly more important than those obtained from exercise alone. The statistical analyses suggest that 29.5% of the improvement in WOMAC score can be attributed to RIT, which is considered clinically important [35,36]. The magnitude of improvement noted is also above the clinically relevant threshold identified for rheumatoid arthritis research [37]. Moreover, the crossover design of this study allowed us to observe that the improvement attributed to RIT in the group of patients that received it first was maintained over a long period. Similarly, a previous study reported that 83% of patients treated with RIT considered the injections still had a beneficial effect on their condition when interviewed a median of 30 months posttreatment [26]. Future studies should nevertheless investigate whether patients treated with RIT eventually seek further treatment for knee OA.

Our results are consistent with a number of other studies. For example, Reeves et al. documented a significant reduction in pain and increase in flexibility after dextrose RIT treatment among patients with knee OA [25,38]. RIT was also associated with considerable improvements in two studies of patients with lateral epicondylosis [39]. In addition, it was demonstrated that in cases of chronic low back pain, RIT and cointervention with physiotherapy result in improvements on measures of disability and functional scales [40,41].

Improvements in secondary outcomes were not as notable as those observed for the WOMAC. Responsiveness to change has been suggested to be superior for the WOMAC index than for other commonly used tools assessing pain and function [42]. This may be attributable to the multiple dimensions encompassed within the WOMAC, which makes it a more comprehensive index than tests such as the Get up and Go. The Get up and Go represents only one physical activity, whereas the WOMAC includes items for numerous activities, including using stairs, lifting, and carrying [43].

Table 1  Baseline characteristics of participants in the two study groups

<table>
<thead>
<tr>
<th>Variable (scale range)</th>
<th>Group A (Mean (SD))</th>
<th>Group B (Mean (SD))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants; N</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Gender, male</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Age, years</td>
<td>57.3 (12.6)</td>
<td>56.2 (10.9)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>90.1 (22.2)</td>
<td>92.4 (17.2)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>32.2 (7.2)</td>
<td>34.3 (5.7)</td>
</tr>
<tr>
<td>Knee osteoarthritis at X-ray</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1; N</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Grade 2; N</td>
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<td>1</td>
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<tr>
<td>Grade 3; N</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Grade 4; N</td>
<td>5</td>
<td>5</td>
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<tr>
<td>WOMAC total (0–96)</td>
<td>44.4 (13.7)</td>
<td>36.2 (16.8)</td>
</tr>
<tr>
<td>WOMAC pain (0–20)</td>
<td>9.5 (2.9)</td>
<td>8.7 (4.0)</td>
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<tr>
<td>WOMAC stiffness (0–8)</td>
<td>4.1 (1.7)</td>
<td>3.5 (1.5)</td>
</tr>
<tr>
<td>WOMAC function (0–68)</td>
<td>33.6 (10.7)</td>
<td>26.8 (12.8)</td>
</tr>
<tr>
<td>Pain Intensity (0–10)</td>
<td>4.1 (2.2)</td>
<td>4.1 (1.9)</td>
</tr>
<tr>
<td>Functional impairment (0–10)</td>
<td>4.0 (2.5)</td>
<td>3.2 (1.8)</td>
</tr>
<tr>
<td>Wong–Baker (0–5)</td>
<td>2.7 (1.2)</td>
<td>2.3 (1.1)</td>
</tr>
<tr>
<td>Descriptive (0–10)</td>
<td>5.0 (2.0)</td>
<td>3.9 (1.9)</td>
</tr>
<tr>
<td>Numeric (0–10)</td>
<td>5.0 (2.3)</td>
<td>4.4 (2.4)</td>
</tr>
<tr>
<td>Visual analog (0–100)</td>
<td>48.6 (21.8)</td>
<td>38.3 (24.8)</td>
</tr>
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</table>

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms; Pain Intensity = from the Brief Pain Inventory; functional impairment = from the Brief Pain Inventory; Wong–Baker = Wong–Baker Faces Pain Rating Scale; descriptive = simple descriptive intensity scale; numeric = numeric distress scale; visual analog = visual analog scale.

Figure 3  Change in combined pain score over the 36 weeks for the two study groups. Group A (black circles), received regenerative injection therapy (RIT) at weeks 0, 4, 8, and 12. Group B (empty circles), received RIT at weeks 20, 24, 28, 32. Combined pain score, the first principal component score from a principal component analysis of five measures of pain: Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms, Brief Pain Inventory, Wong–Baker, numeric scale, and visual analog scale. Vertical lines represent 95% confidence interval.
Table 2  Change in functional capacity and pain during the two phases of study for both groups

<table>
<thead>
<tr>
<th></th>
<th>Period 1</th>
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<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td></td>
<td>Overall crossover design test</td>
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<tr>
<td></td>
<td>Change between weeks 16 and 0</td>
<td>t-Test on effect</td>
<td></td>
<td>Change between weeks 16 and 0</td>
<td>t-Test on effect</td>
<td></td>
<td>Estimated change RIT vs control</td>
<td></td>
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<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
<td>Mean</td>
<td>SD</td>
<td>P</td>
<td>95% CI</td>
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<td>-21.8</td>
<td>12.5</td>
<td>&lt;0.001</td>
<td>-6.1</td>
<td>13.9</td>
<td>0.11</td>
<td>0.002</td>
<td>-1.2</td>
<td>10.7</td>
<td>0.65</td>
<td>-9.3</td>
<td>11.4</td>
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<td>WOMAC pain</td>
<td>-5.0</td>
<td>3.3</td>
<td>&lt;0.001</td>
<td>-1.9</td>
<td>3.1</td>
<td>0.04</td>
<td>0.01</td>
<td>-0.5</td>
<td>2.6</td>
<td>0.42</td>
<td>-1.6</td>
<td>2.6</td>
<td>0.04</td>
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<td>WOMAC stiffness</td>
<td>-2.1</td>
<td>1.4</td>
<td>&lt;0.001</td>
<td>-0.8</td>
<td>1.7</td>
<td>0.10</td>
<td>0.02</td>
<td>0.6</td>
<td>1.8</td>
<td>0.23</td>
<td>-1.0</td>
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<tr>
<td>WOMAC function</td>
<td>-14.6</td>
<td>9.1</td>
<td>&lt;0.001</td>
<td>-3.6</td>
<td>10.7</td>
<td>0.21</td>
<td>0.004</td>
<td>-1.2</td>
<td>7.1</td>
<td>0.50</td>
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<td>1.87</td>
<td>0.003</td>
<td>-1.01</td>
<td>1.72</td>
<td>0.03</td>
<td>0.32</td>
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<td>0.29</td>
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<td>2.15</td>
<td>0.002</td>
<td>-0.93</td>
<td>1.69</td>
<td>0.04</td>
<td>0.12</td>
<td>-0.33</td>
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<td>-1.27</td>
<td>1.39</td>
<td>0.003</td>
<td>-0.19</td>
<td>1.09</td>
<td>0.50</td>
<td>0.02</td>
<td>0.00</td>
<td>1.28</td>
<td>1.00</td>
<td>-0.38</td>
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<td>0.001</td>
<td>-0.89</td>
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<td>0.07</td>
<td>0.06</td>
<td>-0.37</td>
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<td>&lt;0.001</td>
<td>-0.83</td>
<td>2.68</td>
<td>0.25</td>
<td>0.04</td>
<td>-0.58</td>
<td>1.93</td>
<td>0.32</td>
<td>-0.76</td>
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<td>0.22</td>
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<td>Visual analog</td>
<td>-29.70</td>
<td>19.38</td>
<td>&lt;0.001</td>
<td>-9.92</td>
<td>19.45</td>
<td>0.10</td>
<td>0.03</td>
<td>-6.76</td>
<td>18.71</td>
<td>0.28</td>
<td>-8.11</td>
<td>20.94</td>
<td>0.21</td>
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<tr>
<td>Combined pain score</td>
<td>-3.38</td>
<td>2.32</td>
<td>0.001</td>
<td>-1.6</td>
<td>1.52</td>
<td>0.006</td>
<td>0.06</td>
<td>-1.06</td>
<td>2.21</td>
<td>0.16</td>
<td>-1.38</td>
<td>2.02</td>
<td>0.05</td>
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<tr>
<td>Timed up and go</td>
<td>-0.72</td>
<td>1.16</td>
<td>0.02</td>
<td>-0.79</td>
<td>1.57</td>
<td>0.04</td>
<td>0.89</td>
<td>0.06</td>
<td>1.00</td>
<td>0.82</td>
<td>-0.18</td>
<td>1.21</td>
<td>0.57</td>
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</tbody>
</table>

Group A = received regenerative injection therapy (RIT) in period 1; Group B = received regenerative injection therapy in period 2; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index of severity of osteoarthrosis symptoms; pain intensity = from the Brief Pain Inventory; Functional impairment = from the Brief Pain Inventory; Wong–Baker = Wong–Baker Faces Pain Rating Scale; descriptive = simple descriptive intensity scale; numeric = Numeric distress scale; visual analog = from the visual analog scale; combined pain score = the first principal component from a principal component analysis of all the aforementioned; SD = standard deviation; CI = confidence interval.
Although speculative, the mechanisms thought to be responsible for the improvements associated with RIT include sclerosing of neovascularity [20–22] and restoration of collagen fibers [20,21,24]. Another potential mechanism suggests that the injection of dextrose results in an increase in ED1+ and ED2+ macrophage indicating inflammation and tissue repair [44]. This is thought to result in increases in the cross-sectional area of ligaments [15,16,23]. Whether the change in cross-sectional area leads to an increase in failure force is nevertheless unclear. Whereas some animal studies reported increases in failure force of injected ligaments [16,45], others found no change in failure force [15,46]. It is also unclear what solution content should be considered the most effective, how often it should be administered, and with which complementary treatment it should be combined. In terms of best practices, it was documented that ultrasound guidance and fluoroscopy could have contributed to improving placement accuracy [47,48]. We opted not to use these technologies given our interest to assess an intervention that could be readily administered in primary care settings. Lidocaine and dextrose are commonly available and relatively inexpensive, contributing to the accessibility of the treatment studied. The long-term consequences of intra-articular lidocaine at a concentration of 0.5% will nevertheless need to be established. Reports published following the completion of this study question the viability of chondrocyte cells after administration of local anesthetics [49,50]. Data presented in these reports are nevertheless mostly based on animal tissue and seem to be both dose- and time of exposure-dependent [49,50].

Limitations of this study include that it was not sufficiently powered for the secondary outcomes. The analyses nevertheless suggested that a larger sample would have resulted in more of the secondary outcomes, indicating a statistically significant improvement attributable to RIT. Some patients were lost to follow-up and therefore could not be included in the analyses. However, two of the four patients lost and for whom we had information reported marked improvements after RIT. This suggests that analyses including patients lost to follow-up would have led to results similar to those presented herein. A placebo or saline injection control group was not selected given placebo injections may lead to inflammation and thus amount to RIT. Placebo injections would be similar to dry needling or needle tenotomy, which has been suggested as an alternative treatment for tendinopathy [51–53]. This does not allow eliminating the potential of confounding the RIT effect with a placebo response, which was demonstrated to be important in patients with knee OA [54]. Although one study suggested that ligament injections of saline have no beneficial effects [16], other studies among patients with low back pain failed to show a difference between injections of an active solution and of saline [55]. Other studies that used saline injections also noted significant improvements in the saline groups, therefore suggesting that the process of needling itself could be an active treatment [41,56,57]. In the current crossover study, the order in which treatments were offered could have influenced the outcomes. For example, although figures suggest that the early improvements following exercise only in period 1 were not maintained throughout all of this period, the exercise program in period 2 may have been an important contributor to the maintenance of improvements noted among patients who received RIT first. Future studies should further investigate the issue of timing of RIT in relation to physiotherapy. Finally, generalizing our results to other populations has to be done while acknowledging that our study participants were composed of relatively younger, heavier, and more male patients with higher severity of knee OA than may be presented in other practices.

During the course of RIT treatment, one participant suffered from diffuse edema of both legs. Although the cause of this symptom is unclear, it was probably due to a cardiovascular condition. The RIT regimen was nevertheless ceased as a precautionary measure. RIT has been studied for pathologies ranging from cervical pain to coccydynia and has never been associated to serious adverse events. Two systematic reviews [39,58] of RIT and a study of complications of RIT [59] reported only minor side effects or discomfort associated with the injections.

In conclusion, this is the first randomized controlled study of knee OA to assess multiple pain and function outcomes following RIT. Our results show a meaningful improvement with RIT alone and further improvements with a combination of RIT and exercise. These results, combined with the low risk, low price, and accessibility of dextrose makes RIT of the knee a viable alternative for the management of knee OA. Further studies should investigate optimal RIT regimens with regard to interval between treatments, concentration of agents, and number of treatments.

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