

# Can combined use of low-level lasers and hyaluronic acid injections prolong the longevity of degenerative knee joints?

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**Background:** This study evaluated whether half-yearly hyaluronic acid injection together with low-level laser therapy in addition to standard conventional physical therapy can successfully postpone the need for joint replacement surgery in elderly patients with bilateral symptomatic tricompartmental knee arthritis.

**Methods:** In this prospective, double-blind, placebo-controlled study, 70 consecutive unselected elderly patients with bilateral tricompartmental knee arthritis were assigned at random to either one of two conservative treatment protocols to either one of the painful knees. Protocol A consisted of conventional physical therapy plus a sham light source plus saline injection, and protocol B consisted of protocol A with addition of half-yearly hyaluronic acid injection as well as low-level laser treatment instead of using saline and a sham light source. Treatment failure was defined as breakthrough pain necessitating joint replacement.

**Results:** Among the 140 painful knees treated with either protocol A or protocol B, only one of the 70 painful knees treated by protocol B required joint replacement, whereas 15 of the 70 painful knees treated by protocol A needed joint replacement surgery ( $P < 0.05$ ).

**Conclusion:** We conclude that half-yearly hyaluronic acid injections together with low-level laser therapy should be incorporated into the standard conservative treatment protocol for symptomatic knee arthritis, because it may prolong the longevity of the knee joint without the need for joint replacement.

**Keywords:** knee osteoarthritis, hyaluronic acid injection, low-level laser, outcome

## Introduction

The clinical efficacy of intra-articular injections of hyaluronic acid have been documented since the 1990s.<sup>1,2</sup> Intra-articular injections of hyaluronic acid tend to have a longer duration of action than intra-articular injections of steroids and have less severe side effects.<sup>3</sup> Intra-articular steroids can have serious systemic effects, particularly if the patient has multiple concomitant medical comorbidities, which are not uncommon in the elderly population. Further, clinicians are often reluctant to use intra-articular steroids in elderly patients who are immunocompromised and/or at risk of infection, those with diminished joint position sense and peripheral neuropathy, and those who are prone to fluid retention because of renal, cardiac, or liver dysfunction.

Use of low-level laser dates back to the 1960s and the seminal work of Endre Mester. Since then, further scientific research has demonstrated a positive effect of low-level laser on fibroblast<sup>4</sup> and collagen synthesis at the cellular and molecular level, leading in recent years to use of low-level laser therapy (LLLT) in many clinical applications.<sup>5</sup>

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When managing knee osteoarthritis, most clinicians and surgeons use nonsteroidal anti-inflammatory agents and conventional physical therapy, consisting of ultrasound, transcutaneous electrical therapy, and short wave therapy. However, these conservative treatments only offer short-term symptomatic benefits, and many elderly patients do not tolerate nonsteroidal anti-inflammatory medication well.

The purpose of the current prospective, randomized, double-blind, placebo-controlled cohort study was to assess whether combined use of half-yearly injections of hyaluronic acid together with LLLT can impact the natural course of the degenerative process, prolong the longevity of the degenerative knee joint, and postpone knee replacement surgery, given that many elderly patients are at high surgical risk and/or are reluctant to undergo surgery.

## Materials and methods

All subjects signed their informed consent before study entry, and the study followed the principles outlined in the Declaration of Helsinki. The study population consisted of 70 consecutive unselected elderly patients with a mean age of 75 (range: 70–80) years and documented radiographic changes of tricompartmental disease in the knee, with no evidence of osteonecrosis on magnetic resonance imaging and evidence of synovitis causing inflammation and pain in the affected knee joint. All of the patients had grade 3 Kellgren-Lawrence joint degeneration on knee radiographs. Exclusion criteria included a previous history of knee joint surgery, history of sepsis in the affected joint, genu varum or genu valgum of more than 20 degrees, presence of osteonecrosis on magnetic resonance imaging of the affected knee joint, and evidence of synovial osteochondromatosis. Patients who suffered from autoimmune disease such as rheumatoid arthritis and those who had chronic lower limb muscle weakness, eg, following a cerebrovascular accident, were also excluded.

Upon entry to the study, each patient drew an envelope determining which knee joint would receive which protocol. The treating rehabilitation specialist was blinded as to which knee would receive which protocol. Protocol A involved combined use of conventional physical therapy with five weekly injections of saline and sham irradiation for 180 seconds. Protocol B consisted of standard physical therapy as in protocol A with half-yearly intra-articular hyaluronic acid injections and LLLT with use of 810 nm wavelength lasers from an aluminum gallium arsenide semiconductor laser device with 5.4 J per point and a power density of 20 mW/cm<sup>2</sup>. The regimen consisted of three treatment sessions per week for 6 consecutive weeks. Each treatment session lasted 180 seconds

and the sham light source used in protocol A had a similar irradiation frequency and application time.

At the initial visit, care was taken to document the range of motion, sites of tenderness, and presence and extent of deformity in the affected knees, and patients with significant genu varum or genu valgum were excluded. We used the well-known and validated WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) score<sup>6</sup> to assess the disability caused by osteoarthritis at the initial and all subsequent follow-up visits.

All patients had bilateral knee arthritis and were treated in a randomized manner with both protocol A and protocol B. The five intra-articular doses of hyaluronic acid (Hyalgan, Fida, Italy) were administered 1 week apart, on a half-yearly basis. All physical therapy, LLLT, and intra-articular injections were administered by David Ip to maintain a consistent application technique or nonstandard application of physical therapy machines as well as technique of hyaluronic acid injection to guard against compromising the validity of clinical results obtained.

## Results

The study was conducted between 2008 and 2015 after an enrolment period of 2 years. The male to female ratio was 1:2.5. All 70 subjects completed the study protocol. Altogether, 140 painful knees were treated with protocol A or protocol B. No side effects or discomfort were documented during either treatment regimen. Any flare-ups of pain during the mean 7 years of follow-up were treated by physical therapy and LLLT. Failure was defined as intolerable breakthrough pain necessitating joint replacement surgery. The WOMAC score was used to monitor the clinical progress of all painful joints during follow-up, and the level of pain was monitored by scores on a visual analog scale.

The WOMAC questionnaire is a well-known validated tool for assessment of pain, stiffness, physical function, social function, and emotional function in patients with osteoarthritis of the knee. The possible range of pain scores is 0–20, where the maximum pain subscore is 20, the score range for stiffness is 0–8, maximum stiffness receives a subscore of 8, and the score range for physical function is 0–68. In our study, we paid particular attention to the pain and stiffness subscores because these are the symptoms most commonly warranting surgery. All patients had bilateral symptomatic knee arthritis and served as their own controls.

The five pain questions in the WOMAC questionnaire assess pain experienced in five situations, ie, walking on a flat surface, going up or down stairs, at night while in bed, sitting

or lying, and standing upright. The patient's response to each question produces a score that is then summed to derive an aggregate score for each dimension. The WOMAC pain score can be derived using a 0–10 visual analog scale (often with a score range of 0–50), a 0–100 visual analog scale (commonly reported with a score range of 0–500), an 11-point numeric rating scale (commonly reported with a score range of 0–50), or a Likert scale (commonly reported with a score range of 0–20). We used a Likert scale in this study with a score range of 0–20, where 20 represented maximum pain. Pain was the most important outcome of interest in this study, with special attention paid to pain subscores. The second most important outcome was stiffness, in particular stiffness subscores.

The mean WOMAC subscore for pain upon entry to the study for the 70 knees treated with protocol A was 13 (range: 12–15) and the mean stiffness subscore was 6 (range: 5–7). The mean WOMAC subscore for pain for the 70 knees treated with protocol B was 14 (range: 12–16) and the mean stiffness subscore was 5 (range: 4–6). After a mean follow-up of 7 (range: 6.5–7.5) years, the mean WOMAC subscore for pain in group B was 6 (range: 5–7) and the mean stiffness subscore was 4 (range: 3–5). Only one patient had early deterioration of the WOMAC pain subscore back to 13 at the 2-year point and subsequently underwent joint replacement surgery.

On the other hand, the mean WOMAC pain subscore after a mean follow-up of 7 years for the 70 knees treated with protocol A was 11 (range: 10–12) and the mean stiffness subscore was 4 (range: 3–5). Fifteen knees treated with protocol A required joint replacement surgery, and the difference in the proportions of knees requiring total joint replacement between protocol A versus B was statistically significant ( $P < 0.05$ ).

The data in this study were roughly normally distributed, so are reported as the median without the need for non-parametric statistical methods. The level of statistical significance was calculated using the  $P$ -value obtained by means of chi square testing. The result of the current statistical analysis rejected the null hypothesis that the difference could have been arisen by pure chance at  $P < 0.05$ .

## Discussion

Hyaluronic acid is a polysaccharide composed of repeating disaccharide units, ie, 1,4-glucuronic acid and 1,3-N-acetylglucosamine. It belongs to the group of glycosaminoglycans, but unlike chondroitin sulfate or keratan sulfate, the hyaluronic acid is not sulfated. Hyaluronic acid is synthesized by bioactivity of hyaluronan synthase, which has been reported to have three isoforms in humans.<sup>7</sup>

Hyaluronic acid is one of the major space-filling molecules in the extracellular matrix of the articular cartilage, which has a viscoelastic function to help protect the joint during periods of loading. Natural hyaluronic acid is organized within the extracellular matrix by specific interactions with other matrix macromolecules. High molecular weight hyaluronic acid at a high concentration in solution can also form entangled networks through steric interactions and self-association between and within individual molecules. Such networks have properties that are different from those of individual hyaluronan molecules. They can resist rapid, short-duration fluid flow through the network, thereby having elastic properties that can distribute load or shear forces within the network.<sup>8</sup> This type of structure is ideally suited to the dynamic periodic peak joint loading conditions to which the knee is subjected as part of the normal human gait, thereby acting as a shock absorber.

In addition to having shock-absorbing and viscoelastic properties that may well help to preserve degenerative knee joints in the elderly, hyaluronic acid injections have been shown to have anti-inflammatory and analgesic properties. In previous animal models of arthritis,<sup>9</sup> the mechanism of pain suppression was shown to be related to the effect of these injections on suppressing prostaglandin and bradykinin levels. In addition, higher molecular weight hyaluronic acid injections offer even more pain-relieving effects in arthritic joints.<sup>10</sup>

The authors are not aware of any long-term follow-up studies that have investigated whether long-term half-yearly injections of five intra-articular injections given on a weekly basis can alter the natural history of wear, pain, and inflammation of the knee joint to a point where joint replacement surgery can be postponed, particularly in the high-risk elderly.

The basic science underling LLLT is that it involves the use of near infrared light to alter the cellular function such as helping in normalizing the energy usage of body cells, ie biomodulation. Over the years, there have been many placebo-controlled studies showing the favorable anti-inflammatory effects of LLLT.<sup>11,12</sup>

Standard physical therapy, such as therapeutic ultrasound, has no biomodulating or regulatory effects on the microcirculation or on the genes involved in energy metabolism and oxidative phosphorylation that stimulate increased production of adenosine triphosphate, which in turn regulates other cellular processes leading to normalization of biological function at the cellular level.<sup>13</sup>

The majority of studies of LLLT in patients with knee arthritis have been short-term, and the authors are unaware of any long-term study assessing whether long-term use of LLLT can decrease the need for knee joint replacement surgery.

This present long-term study of combined use of chronic yearly hyaluronic acid injections coupled with LLLT yielded promising results in terms of increasing the longevity of degenerative knee joints, deferring knee joint replacement, or avoiding surgery altogether. This combined long-term use of hyaluronic acid injections plus LLLT has never to date been reported in the literature, let alone any assessment as to whether this improved protocol can potentially reduce the need for joint replacement. In general, any protocol that examines how to reduce health care costs, surgical risk, and patient outcomes, as demonstrated for instance by WOMAC scores, has the potential to be useful to the health care community and cut down the tremendous financial burden faced by health care administrators, especially in countries with a rapidly aging population.

## Conclusion

The current prospective, double-blind, placebo-controlled study showed a statistically significant improvement in joint preservation in elderly patients with degenerative arthritis affecting all three compartments of the knee joint. Over a mean 7 years of follow-up, we demonstrated that use of hyaluronic acid injections (targeting inflammation in the interior of the knee joint) combined with LLLT (targeting inflammation in the exterior of the knee joint) is a rational method for treating symptomatic degenerative knee arthritis, which is becoming increasingly common with increasing longevity of population in many societies and placing a huge burden on health care expenditure.

Larger long-term studies are needed to explore whether once-yearly hyaluronic acid injections can have clinical efficacy similar to that of half-yearly injections in the management of degenerative knee joints. Also, further studies need to be undertaken to ascertain whether it was LLLT, the injection regimen, or a combination of the two that is most beneficial in elderly patients. Finally, the possibility that the current protocol may also benefit younger middle-aged patients suffering from degenerative knee arthritis need to be explored. It should be highlighted that further studies using lasers of similar wavelength, power density, application

method, and application time, are needed to make any clinical comparisons meaningful.

## Disclosure

The authors declare that there is no existing nor potential conflict of interest in the publication of the current article.

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