Knee osteoarthritis: Comparison between ultrasound-guided and landmark-guided hyaluronic acid injection in terms of perceived pain

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Abstract
Knee osteoarthritis is a widespread disability that represents a large proportion of the population with significant effects on affected individuals, health care systems and extensive socio-economic costs. It is a pathologic condition that affects the entire joint, including the cartilage, the hypochondriac bone, the ligaments, the synovial membrane and the surrounding muscles and not exclusively the articular cartilage as previously established. Clinically, the knee joint is the most common form of osteoarthritis, followed by the extremities of the hand and hip.

The present study aimed to compare the perceived pain in the diagnosis of knee osteoarthritis by using ultrasound-guided hyaluronic acid injection versus the classical anatomically-guided hyaluronic acid injection. The sample of the present study consisted of 48 patients suffering from osteoarthritis of the knee who visited the Orthopedic Outpatient Clinics of the General Panarkadikon Hospital, in Tripoli, Greece, between November 2019 and June 2020. Of these, 24 patients constituted the ultrasound (US) group, and 24 patients, the anatomically-guided (LMG) group by using randomization of the total sample.

For this study, the Visual Analogue Scale (VAS) was used. The Cronbach’s Alpha reliability index of the questionnaire is 0.73. The analysis was performed with the IBM SPSS v.25 statistical program.

The pain intensity was related to the method used (p<0.001). In particular, the ultrasound group showed a statistically significantly less pain than the anatomically-guided group. According to the VAS scale, pain in the ultrasound group ranged from 0 to 3, in contrast to the LMG group, which ranged from 3 to 5. This correlation was found to be statistically significant.

The use of the ultrasound-guided hyaluronic acid injection seems to be more comfortable for the patients, compared to the anatomically-guided hyaluronic acid injection.

Keywords: Knee osteoarthritis, ultrasound-guided injection, landmark-guided injection, hyaluronic acid

1. Introduction
Osteoarthritis is a common form of degenerative joint disease that primarily affects the western population. The knee is the main peripheral joint that is affected, resulting in progressive loss of function, pain and stiffness. Hardening of the bone surfaces under the cartilage, followed by the development of new bone and cartilage at the edges of the joint (osteophytes) as well as fibrosis of the joint follicle accompanies this pathology. It is estimated that 10% of the population over the age of 50 will be affected [1]. Knee osteoarthritis is a widespread disability that represents a large proportion of the population with significant effects on affected individuals, health care systems and wider socio-economic costs [2]. It is a pathologic condition that affects the entire joint, including the cartilage, the hypochondriac bone, the ligaments, the synovial membrane and the surrounding muscles and not exclusively the articular cartilage as previously established [3]. Clinically, the knee joint is the most common form of osteoarthritis, followed by the extremities of the hand and hip [4, 5]. In terms of disease burden, osteoarthritis of the knee accounts for about 85% of all osteoarthritis incidents [6]. In general, osteoarthritis is associated with ageing, as well as with a variety of both modifiable and non-modifiable risk factors, including obesity, lack of exercise, genetic predisposition, bone density, occupational injury, and trauma [7].
In particular, for osteoarthritis of the knee, strong evidence suggests that the main risk factors may be female gender, obesity and a previous knee injury [8]. Knee misalignment can also be a major risk factor [9], and knee muscle weakness is likely to be a lower risk factor [10]. The symptoms depend on the cause of the problem, with the most common symptom being knee pain. The pain can be blunt, acute, continuous or intermittent and can range from mild to desperate. During the objective examination, the doctor may notice a tingling, muscle weakness, swelling, permanent contraction, and decrease in active or passive movements. It is also characterized by stiffness after inactivity of the joint, limited mobility, difficulty in walking and climbing stairs. These disabilities, combined with the negative psychological effects, can lead to a reduced quality of life [11]. Knee pain is widespread in the general population and accounts for one-third of the musculoskeletal problems in the primary care setting [12]. Pain is the predominant symptom which is an important clinical decision factor for the use of health services, and it is better framed in a bio-psychosocial model [13]. The International Society for the Study of Pain defines pain as an emotional and sensory disturbance that is usually associated with the destruction of body tissues [14]. Pain is also defined as a psychological experience that includes a personal, subjective sense of harm, a harmful stimulus that signals the current or impending destruction of body tissues, and a set of reactions to protect the body from damage [15]. In support of the above two definitions, it is stated that pain is a complex subjective phenomenon, with each individual having a unique perception of it, influenced by biological, psychological and social factors [16].

The present study aimed to confirm that pain is a subjective feeling, and that varies from person to person, so it is necessary to develop methods that will reduce or/and eliminate the feeling of pain. For knee osteoarthritis treatment, the American College of Rheumatology (ACR) guidelines recommend early non-pharmacological treatment (including patient education, physiotherapy, weight loss, exercise, or assistive devices), in combination with various medications. For pain relief, analgesics can be administered for the treatment of osteoarthritis of the knee [17]. If the pain persists, non-steroidal anti-inflammatory drugs (NSAIDs) may be used to treat osteoarthritis of the knee, but safety concerns can sometimes outweigh the benefits [18]. The addition of intra-articular injections of hyaluronic acid (HA) and steroids as individual therapies may serve as an alternative to treatment with multiple drugs when they are contraindicated, poorly tolerated or ineffective, but these treatments are also uncertain. With dosage and injection regimen [19, 20]. Also, platelet-rich plasma (PRP) aims to balance the pro-inflammatory and catabolic state to the anti-inflammatory and anabolic state. As a result, pain is relieved, and function is improved in patients with knee osteoarthritis [21]. However, none of these treatment options can reverse or repair degenerative cartilage or bone [22]. Surgery should be indicated either in cases where all appropriate non-invasive options have failed to provide adequate relief of symptoms [23], or when there is strong evidence of pre-existing mechanical abnormalities or severe osteoarthritis [24].

The first studies on the use of hyaluronic acid in human knee osteoarthritis were performed by Peyron and Balasz where they injected 1, 2, and 3 mL of hyaluronic acid into 23 knees and observed positive results in knee pain response and function in 74% of the patients studied. Treatment with two 2 mL hyaluronic acid injections in each knee showed the best results in treating pain [25]. Hyaluronic acid is a polysaccharide found in the extracellular matrix, especially in soft connective tissues. This polymer plays an important role in maintaining the normal functioning of the joints, providing support and lubrication and helping to regulate biochemical processes [26]. Numerous studies support the benefit and safety of repeated treatment with intra-articular injection of hyaluronic acid. The study of Pagnano et al. showed that sodium hyaluronate with a molecular weight of 500-730 kDa is well tolerated and effective after either multiple treatments or a single treatment because it relieves pain and reduces the rate of joint structure deterioration [27]. Regarding the process of intra-articular injection, one method that seems to be gaining ground in recent years is the intra-articular injection guided by ultrasound, as opposed to simple injections guided by anatomical points. Musculoskeletal ultrasound was first applied by rheumatologists in the 1980s and soon spread to other related specialties, including orthopedics [28]. However, there is a need for further investigation into the benefits of ultrasound in the area of knee osteoarthritis pain during hyaluronic acid injection.

2. AIM
The present study aimed to compare the perceived pain in the diagnosis of knee osteoarthritis by using ultrasound-guided hyaluronic acid injection versus the classical anatomically-guided hyaluronic acid injection.

3. Material and Methods
The sample of the present study consisted of 48 patients suffering from osteoarthritis of the knee and visited the Orthopedic Outpatient Clinics of the General Panarkadikon Hospital, in Tripoli, Greece, between November 2019 and June 2020. Of these, 24 patients were assigned to the ultrasound (US) group, and 24 patients were placed into the anatomically-guided (LMG) group. The exclusion criteria were: patients under 18 years of age, patients with malignancies, individuals who had undergone knee surgery. For this study, the Visual Analogue Scale (VAS) was used, in which the patient was asked to mark a point on the 10 cm long line, which corresponds to the degree of pain. The left edge of the line corresponds to “no pain”, and the right edge corresponds to “unbearable pain - the worst pain you can imagine”. Precisely, points from 1 to 4 correspond to mild pain, 5 to 6 to moderate pain and from 7 and above to severe pain. The Cronbach’s Alpha reliability index of the questionnaire is 0.73. Randomization was performed in a ratio of 1: 1 (US: LMG), calculating the minimum number of 10 people per group as shown by Power Sample analysis. The analysis was performed with the IBM SPSS v.25 statistical program. All patients who came to the Outpatient Orthopedic Clinic were examined immediately with an Esaote Mylab 70 X-vision ultrasound and a direct sound transmitter at 12 MHz. Immediately after, the patients were examined radiologically, and an orthopaedic doctor performed ultrasonography and a physical examination for the diagnosis of the knee osteoarthritis.

In the present study, patients underwent an ultrasound and usually observed osteophytes and points of double margin and often a collection of fluid in the joint. After the diagnosis, the orthopedist informed the patients about the possible administration of hyaluronic acid to the joint and received their consent. The orthopedist then chose one of the two methods of intra-articular injection into each patient’s knee and then performed a sterile technique to prevent infections
and finally applied the VAS scale with the help of a nurse to record the intensity of the pain. Accurately, in the case of hyaluronic acid injection guided by anatomical points (LMG) in the knee, the soft spot points were used, where the needle was inserted to the knee to suction the excess liquid and then infused the hyaluronic acid. The most critical guide points are the upper and lower lip (pole) of the patella, the tibial bulge and the lower surface of the tibia. In the other case, he performed an intra-articular injection of hyaluronic acid using ultrasound, during which the knee joint was imaged through ultrasound, resulting in higher accuracy and better management of the needle. In both cases, when there was a large amount of fluid in the knee joint, where the liquid was removed and then followed by intra-articular injection of hyaluronic acid so that the injection would be more effective.

3.1 Statistical analysis
Statistical analysis was performed using IBM SPSS v.25. Initially, the researchers conducted a descriptive statistical analysis of the sample. Then, crosstabs correlation analysis was performed to find out the correlation between the needle insertion and the pain it caused. Finally, an Independent samples T-test was conducted to find the difference in pain sensation between the two methods of needle guidance when injecting hyaluronic acid into the knee joint.

3.2 Ethical considerations
This study complied with the fundamental ethical principles regarding the conduct of the research (complete confidentiality, the safety of the material, anonymity and written consent of the participants). Finally, the study protocol was in line with the Helsinki Declaration and was approved by the Ethics Committee of the University of Peloponnese (School of Health Sciences).

4. Results
Forty-eight patients, ten men and thirty-eight women with a mean age of 75.5 years (62 to 89) constituted the sample of the study. All patients were diagnosed with osteoarthritis of the knee after having undergone ultrasound (US) and/or magnetic resonance imaging (MRI). Of these, 24 patients underwent hyaluronic acid infusion using ultrasound, and 24 patients followed the standard anatomical point infusion method. There was no significant difference between the two groups for age and gender. The intensity of pain was not related to either age (p = 0.27) or gender (p = 0.22). According to the results given in Table 1, the pain intensity is related to the method used (p< 0.001). In particular, with the use of ultrasound-guided hyaluronic acid insertion, the pain caused is statistically significantly lower compared to the anatomically-guided method. Pain, according to the VAS scale in the case of the ultrasound group ranged from 0 to 3, in contrast to the LMG group, which ranged from 3 to 5. This correlation was found to be statistically significant (Table 2).

5. Discussion
Osteoarthritis of the knee is traditionally considered a progressive disorder of the articular cartilage in the knee joint [29]. The main annoyance of the patients is the presence of pain in the knee joint, and it is considered a significant decision to come to the Outpatient Department of the Orthopedic Clinic for relief of symptoms. Initially, it is recommended the use of simple analgesics. If the pain persists, non-steroidal anti-inflammatory drugs could be given, followed by intra-articular injections. In the final stage, surgery is performed, since the previous treatment techniques have failed to respond [17, 20, 23]. In clinical practice, there are two methods used for intra-articular injection, the classical method guided by anatomical points (LMG) and the intra-articular injection guided by ultrasound (US). The results of this study clearly show that the intra-articular injection of hyaluronic acid guided by ultrasound achieved a significant reduction in pain, compared to the infusion guided by anatomical points. Direct comparison of the results in this study with the results of other studies cannot be performed. This is probably due to the differences in manipulations and the clinical experience of each physician performing the intra-articular injection. However, the method using ultrasound showed similar results to other studies in the literature in patients with osteoarthritis of the knee. Thus, several studies support the higher accuracy of ultrasound-guided hyaluronic acid injections over the conventional anatomical-guided injection [30, 31] and intra-articular injection into the knee joint with superiority. Also, according to Luenders et al., the anatomy of the knee is particularly susceptible to ultrasound imaging, and therefore most knee structures can be accurately imaged using ultrasound [32]. In particular, studies have shown that the accuracy of intra-articular injection in the knee is significantly improved (approximately 98% accuracy in 1100 injections) with the help of ultrasound guidance [33, 34]. One study found that patients who received intra-articular hyaluronic acid with ultrasound guidance were associated with a significantly reduced rate of knee arthroplasty compared to infusion of anatomically guided hyaluronic acid injections, especially in obese patients [35].

Regarding the pain symptom, one study showed that ultrasound-guided intra-articular injections were superior to anatomically-guided injections in all therapeutic measures. Specifically, injection pain was 58% less, the score from the Visual, Numerical and Functional Analogue Pain Scale (VAS) was 42% less, and the response rates increased by 107% and the non-response rates decreased by 52%. Additionally, the study showed that intra-articular knee osteoarthritis injections performed with ultrasound guidance could improve the cost-effectiveness ratio [36].

In 2012, the same researchers concluded that ultrasound-guided injections showed improved patient outcomes, such as less procedural pain, higher suction volume, a higher rate of successful diagnostic arthrocentesis, and enhanced response

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Table 1: Comparison of the pain provoked by each method, using Independent Samples T-test

<table>
<thead>
<tr>
<th>Method</th>
<th>Patients n</th>
<th>Pain mean ± sd</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>24</td>
<td>1.29±0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LMG</td>
<td>24</td>
<td>4.25±1.51</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Crosstabs correlation between pain and method used

<table>
<thead>
<tr>
<th>Pain (VAS score) Method</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>7</th>
<th>8</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (n)</td>
<td>6</td>
<td>8</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>LMG (n)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>total</td>
<td>6</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td>48</td>
</tr>
</tbody>
</table>

P-value < 0.001
to corticosteroid injection, compared to anatomically guided injections [37]. However, the study by Cunningham et al. showed that there is no improvement in the results of ultrasound-guided intra-articular injection guided by ultrasound [38]. This difference is probably because in that particular study was used an intra-articular injection exclusively, while in the study of Sibbit et al., was used first a synovial fluid suction and then the intra-articular injection. This procedure is considered important because it increases the effectiveness of the intra-articular concentrations of the injectable drug that will follow. Thus, the study by Sibbit et al. further emphasizes the need for complete articulation and decompression of the joint before intra-articular drug injection [37].

It is worth noting that the above two studies concerned with the intra-articular administration of corticosteroids and not hyaluronic acid, resulting in the need to investigate the effectiveness of hyaluronic acid infusion by ultrasound-guided injections.

Regarding corticosteroids that act to eliminate the inflammatory response in intra-articular and periarticular structures, the accuracy of intra-articular injection can be particularly crucial for hyaluronic acid, as this therapeutic agent directly provides several protective properties in the fluid, such as shock absorption, traumatic energy dissipation and lubrication [39]. Two main explanations can justify the reduction of pain with the use of ultrasound versus injections directed at anatomical points. The first is that there is better control and the direction of the needle tip is away from pain-sensitive structures [40, 41]. In particular, Im et al. showed that ultrasound increased the accuracy of needle placement, and this increased its efficiency within the joint, which could reduce pain [42]. Another explanation is that the cold effect of the ultrasound gel, the pressure from the ultrasound transducer as well as the patient observing the ultrasound image, whose attention may have been distracted to it, on a neurocognitive level, has as resulting in a significant reduction in pain and stress [43, 44]. Ultrasound represents one of the most practical options because it is safe, fast, relatively cheap, well accepted by patients and does not emit radiation.

6. Conclusions

The results of the present study have shown that the use of ultrasound as a guiding method of intra-articular injection of hyaluronic acid is an effective way to reduce the intensity of pain, compared to the classical process guided by anatomical points. However, the present study has limitations, such as the pain subjectivity that varies from patient to patient as well as previous exposure to a similar stimuli. Therefore, further research and clinical trials may be needed to clarify the ideal parameters that help reduce pain with the use of ultrasound as well as research to study both methods in the same patients at different times.

7. References


