Ultrasound guided injection with Collagen-based Medical Device: real-life evaluation of efficacy and safety in hip osteoarthritis

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Abstract

Aims: Data regarding the treatment of hip osteoarthritis (OA) with collagen-based extracellular bio-scaffolds are lacking. We evaluated the treatment of hip OA with ultrasound guided intraarticular injections of Collagen-based Medical Device (CMD).

Material and methods: Forty-four patients with Kellgren-Lawrence grade (KLG) I or II were selected, and 20/44 randomly selected patients (CMD group), were treated with 2 weekly consecutive ultrasound guided intraarticular injections of CMD (MD-HIP, Guna S.p.a. Milan, Italy). An additional 24/44 patients were treated with oral non-steroidal anti-inflammatory drugs (NSAIDs) daily (NSAIDs group). Clinical assessment, X-rays and ultrasound evaluation were performed at baseline, and after 1 month in both groups, and after 3 months in the CMD group. Outcome measures were general pain VAS (0-10), the whole WOMAC score, and the WOMAC specific subscores. Results: CMD and NSAIDs group were homogenous for age, gender, VAS pain and WOMAC scores. The CMD group had significant improvement of the VAS pain (p<0.0001), global WOMAC score (p<0.0001) and WOMAC function (p<0.0001) from baseline to the 1st month, with further improvement from the 1st to the 3rd month (p<0.001; p<0.01; p<0.03, respectively). Significant improvement in WOMAC pain (p<0.0001) and WOMAC stiffness (p<0.0001) was detected at 1st month, with no significant change at 3rd month. In the NSAIDs group significant improvement in WOMAC function was detected after 1 month (p=0.021) only. No adverse events were recorded in the CMD and NSAIDs group. Conclusion: The ultrasound guided intraarticular hip injections of CMD resulted in significant improvement in VAS pain and WOMAC scores compared to treatment with oral NSAIDs.

Keywords: hip osteoarthritis; treatment; injections; collagen; ultrasound

Introduction

Osteoarthritis (OA) is a degenerative cartilage disease which is frequent in the general population [1]. It is well known that OA is a significant burden on health systems and on patients’ families [2]. Patients affected by OA frequently complain of pain with consequent disability and significant impairment of quality of life [2]. Sedentary life contributes to the increase of the joint discomfort and favors disease advancement, in particular when the patient is obese [3]. Moreover, the significant prevalence of metabolic diseases as well as the progressive aging of our population might have a further impact on OA development and evolution [4].

The OA pathogenesis and, in particular the complex interaction between systemic and local factors, is not fully understood. Therefore, there are continuing efforts to develop a targeted therapy, aiming to maintain and recover articular function [5-8]. However, a great deal of works has shown the role of inflammation in OA pathogenesis [9]. Primary OA that involves knees and hip joints may be treated with systemic [9,10] and/or local intra-articular (i.a.) drugs such as corticosteroids (CS), [5-8,11,12], or other compounds such as Hyaluronic Acid (HA) or Platelet-Rich Plasma (PRP) [13-15]. Intra-articular treatment has obtained significant results in knee OA.
However, the disease may still flare, requiring the use of supporting treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or CS. In hip OA, Disease Modifying Anti-Rheumatic Drugs (DMARDs) have been employed but their efficacy has been a matter of debate since only a slight benefit has been seen compared to placebo [5-8,10]. For hip OA, the i.a. treatment with CS and other compounds has demonstrated a satisfactory analgesic effect with rapid functional recovery [11-13,17-27]. Furthermore, OA patients that are characterized by chronic clinical features are those at risk for a rapid progression of cartilage damage. Indeed, a warning has been issued about the use of several courses of i.a. CS since it has been hypothesized that repeated i.a. CS use may foster cartilage degradation [17]. In the last two decades, the progress in Functional Tissue Engineering allowed the development of collagen-based extracellular bio-scaffolds [28] that have been used in knee OA [29] and in other degenerative diseases [30,31] but without published data about their use in the treatment of hip OA.

The aim of our work was to evaluate, in a real-life retrospective setting, the short-term effect of an ultrasound (US) guided i.a. treatment with Collagen-based Medical Devices (CMD) in patient with hip OA as well as to understand its impact in the prompt functional recovery of the patient.

Material and methods

The medical charts of 120 hip OA patients undergoing different treatment strategies were revised (Institute of Rheumatology, University of Belgrade). A subgroup of 44 patients with hip OA Kellgren-Lawrence grade (KLG) I or II [32], failing to respond previously to conventional treatment with NSAIDs, pain killers, Symptomatic Slow Acting Drugs for Osteoarthritis (SYSADOAs) were selected. A subgroup of 76 patients with either more severe hip OA (KLG III or IV [33], or with suspicive hip synovitis [34]) were excluded. Out of 44 patients with KLG I or II, we randomly selected 20 patients (CMD group) to be treated with two weekly consecutive US guided intraarticular (i.a.) injections of CMD (200 μg of swine origin Type-I Collagen-based with auxiliary substance class III CMD (MD-HIP, Guna S.p.a. Milan, Italy), and 24 patients were treated with NSAIDs daily administration (only NSAIDs group). MD-HIP injections used in our study is a standard approved medicine for the treatment of the patients with the hip OA (Certificate no. QCT-0114-19, issued by Instituto Superiore di Sanita, Italy).

Demographic data, and clinical outcome measures were analyzed. The visits were performed before the first i.a. injection (baseline), one month and three months after the second i.a. injections. X-ray of the hip was done at baseline to check if the data from the database about Kellgren-Lawrence grade (KLG) I or II were correct. The two CMD injections were inoculated into the hip joint cavity, first injection at baseline, and second one week after the baseline. The inoculation of the CMD was controlled using the US guidance of the needle and observation of the drug inoculation into the joint cavity by detecting the Power Doppler signal at the tip of the needle during the injection of the drug (fig 1).

The control group, extracted from the same database, consisted of 24 patients with hip OA with the similar clinical features. This group did not receive hip i.a. treatment with corticosteroids or CMD. Clinical assessment, were performed in these patients at baseline and after 1 month. At each visit, general pain VAS (0-10), the whole WOMAC score as well as the WOMAC specific subscores (WOMAC pain, stiffness, and function) were used as outcome measures [35] for all patients. All patients from CMD group signed the informed consent for the hip interventional maneuver.

Ethical statement

Ethical approval for retrospective data analyses and publication was obtained from the Ethics committee of the Institute of Rheumatology, Belgrade, Serbia (Decision no. 132/49). Ethical considerations of the research conformed to the Declaration of Helsinki.

Statistical analysis

Each continuous variable mean (±standard deviation) was reported. In order to evaluate change in VAS (1-10) in whole WOMAC score, and WOMAC specific subscores in time with MD, a GEE (Generalized Estimating Equation) linear regression model was used. To compare the change difference in VAS in the whole WOMAC score, and WOMAC specific subscores in time between injection of MD and oral administration of NSAIDs a GEE
A linear regression model was used adjusting for baseline score value. Significance level was set to 5%.

**Results**

Out of 120 hip OA patients undergoing different treatment strategies, 44 patients with KLG I or II were selected. None of the KLG I or II selected 44 patients were previously treated with any i.a. hip injection. All 44 patients had hip OA characterized by hip pain and reduced joint function. Twenty, out of these 44 patients (age range 49-79), were randomly selected for the treatment with two weekly consecutive i.a. hip injections of CMD, and other 24/44 patients (age range 54-72) were treated with NSAIDs only. At baseline, both groups were homogeneous for age, gender, VAS pain and WOMAC scores.

Baseline outcome measures and the dynamic evolution of VAS, whole WOMAC score, and WOMAC specific sub-scores in CMD group (baseline, 1 month and 3 months) are presented in Table I and in figure 2.

The results of VAS, whole WOMAC score, and WOMAC specific subscores in the NSAIDs group are presented in Table II and figure 3.

The CMD group had significant improvement of the VAS pain (p<0.0001) and global WOMAC score (p<0.0001) from baseline to the 1st month visit, with further improvement at 3 months visit (VAS pain from 1st to 3rd month p<0.001; global WOMAC score from 1st to 3rd month p<0.03).

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**Table I. The dynamic evolution of VAS and WOMAC scores globally, and on each WOMAC subdomain in the CMD group at baseline, after 1 month, and after 3 months**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 month</th>
<th>3 months</th>
<th>p value (b vs 1mt)</th>
<th>p value (1 vs 3 mts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS at rest</td>
<td>4.56</td>
<td>2.89</td>
<td>2.62</td>
<td>&lt;0.0001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WOMAC total</td>
<td>54.08</td>
<td>42.16</td>
<td>32.38</td>
<td>&lt;0.0001</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>WOMAC pain</td>
<td>10</td>
<td>6.88</td>
<td>6.36</td>
<td>&lt;0.0001</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td>2.53</td>
<td>1.24</td>
<td>1.08</td>
<td>&lt;0.0001</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC function</td>
<td>43.74</td>
<td>34.09</td>
<td>32.28</td>
<td>&lt;0.0001</td>
<td>&lt;0.03</td>
</tr>
</tbody>
</table>

Out, b, baseline; CMD, Collagen-based Medical Device; 1mt, 1 month; 3 mts, 3 months; N.S., not significant; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; VAS, Visual Analog Scale.

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**Table II. The dynamic evolution of VAS and WOMAC scores globally, and on each WOMAC subdomain in the NSAIDs group at baseline, and after 1 month**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>1 month</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS at rest</td>
<td>4.56</td>
<td>2.89</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC total</td>
<td>38.75</td>
<td>36.95</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC pain</td>
<td>6.58</td>
<td>6.33</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC stiffness</td>
<td>3.33</td>
<td>3.50</td>
<td>n.s.</td>
</tr>
<tr>
<td>WOMAC function</td>
<td>49.12</td>
<td>46.33</td>
<td>0.021</td>
</tr>
</tbody>
</table>

NSAIDs, Nonsteroidal Anti-inflammatory Drugs; n.s., not significant; WOMAC, The Western Ontario and McMaster Universities Osteoarthritis Index; VAS, Visual Analog Scale.
function assessment showed a significant recovery of function at 1st month visit (p<0.0001) with further improvement at 3rd months visit (p<0.03). Regarding the NSAIDs group, a trend in WOMAC function improvement was detected after 1 month (p=0.021), while all other parameters did not show any statistically significant improvement.

No local or systemic adverse events were recorded in the CMD group during the 3 months’ observation period. In the group treated with NSAIDs (according to OA guidelines), no local or systemic adverse events were recorded during the one month follow up period.

Discussion

Our results showed that the CMD i.a. injections may help in controlling hip pain and stiffness, allowing satisfactory recovery of function during the observational period of three months.

Intraarticular injection technique for hip OA is not standardized [21]. In particular, only a few authors have used an US guided approach which significantly increases the drug deposition accuracy and treatment efficacy [18,19,26,36-38] thus reducing the risk of mistakes and complications linked to the injection technique [18,38-40]. Indeed, US hip evaluation prior to treatment may identify capsular distension suggesting the presence fluid effusion. This additional information should help in assessing hip status and treatment options. In our study, the US guidance of the needle enabled precise i.a. compound delivery which may have contributed to the efficacy of the treatment with i.a. CMD [18,37,38] Our data showed that CMD injected patients significantly improved their hip joint function.

In our patients, the i.a. CMD treatment has elicited a satisfactory short-term result allowing the patient to control pain and stiffness, thus recovering the function. However, data on a potential chondroprotective effect of CMD are not available. Moreover, we were not able to find any data in the literature related to the patients with hip OA treatment with CMD.

In hip OA patients with a KLG ranging from I to IV, Dallari et al [41] evaluated the efficacy of intra-articular PRP injections compared with HA or PRP/HA. They detected a significant improvement at 6 months of WOMAC total and VAS scores for both compounds, but the HA results were less significant than PRP hip i.a. injection. Conversely, Di Sante et al [42] in severe hip OA showed that i.a. PRP had an immediate effect on pain which was not maintained at longer term follow-up. In patients injected with i.a. HA, the functional WOMAC and the VAS score obtained the best result in the long-term analysis than the PRP group which presents only significant improvement in VAS scores 4 weeks after treatment. The treatment with both compounds, in elderly patients with hip OA, has been proven to be safe and without risks.

Our study has some limitations. We included only 44 hip OA patients with KLG I or II and then randomly selected 20 for the CMD i.a. treatment, comparing them with 24 remained patients who were treated only with oral NSAIDs. The number of patients was small, and it was not a real double-blind study since patients treated with oral NSAIDs did not receive i.a. placebo injections. Our data are derived from a real life situation, and the hip OA was in an early phase (KLG I or II).

Conclusion

By using the technique of US guidance of the needle during i.a. delivery of the drug we assured a precise and safe delivery of the CMD into the hip joint. The US guided i.a. hip injections of CMD resulted in significant improvement in VAS pain and WOMAC scores compared to treatment with oral NSAIDs.

Our results suggest that in OA patients i.a. hip injections of CMD may contribute to the pain control and the recovery to a satisfactory functional status. Prospective randomized controlled studies are needed to assess the efficacy and safety of CMD in the treatment of patients with hip OA.

Conflict of interest: none

References


