The Efficacy of Diacerein with and Without Diclofenac Sodium on Knee Pain Severity and Walking Time in Patients with Knee Osteoarthritis

Tarek S. Shafshak, MD¹; Enas M. Shaheen, MD²; Naglaa Hussein, MD³; Ahmed A. Hafez, MSc⁴

¹,²,³,⁴Department of Physical Medicine, Rheumatology & Rehabilitation, Faculty of Medicine, Alexandria University, Egypt

Abstract: Diacerein (4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid) appeared promising in osteoarthritis (OA) treatment for its IL-1β inhibitory properties. However, it is a slow-acting disease-modifying drug, and its effect would appear after few weeks of its intake. Therefore, it was suggested to be prescribed in combination with NSAID during the early few weeks of its administration. Objective: To assess the efficacy and safety of diacerein with and without diclofenac in patients with knee OA. Participants: Sixty patients with primary knee OA. Methods: Clinical, laboratory and relevant radiological examination were performed. Patients were divided randomly into 3 groups. Group I (n=20) received diacerein (50 mg twice daily); Group II (n=20) received oral diclofenac sodium (75 mg/day); and Group III (n=20) received both diacerein and diclofenac in the previous doses. Medications were given for 2 months. Assessment of pain severity (VAS) and the 20 meters fast walking time were done before treatment and at 1 and 2 months after treatment. Patients were observed for adverse reactions during the study. Results: There was a drop out of 10 patients in group II. Following treatment, there was significant improvement in pain severity in group I and III (p = 0.033 and 0.048; respectively); and in the walking time in group I (p = 0.001), with no inter-group differences. Few side effects were reported. Mild diarrhea was found in 40% and urine discoloration in 100% of patients of groups I and III. Nausea was reported in 20% of patients of groups II and III. Heartburn was reported in patients of group II (20%) and group III (25%). Conclusion: Diacerein improved knee pain and the walking time with mild adverse reactions. Adding diclofenac to diacerein appeared of no additional benefit, when assessment was done 1 and 2 months after drug intake. The findings recommend using diacerein (in those who can tolerate it) for treating knee OA, especially when NSAIDs are contraindicated.

Keywords: Pain; Osteoarthritis; Knee joint

1. Introduction

Knee osteoarthritis (OA) is the commonest arthritis seen in Egypt;¹ and is characterized by progressive articular cartilage degradation.² Recent reports demonstrated that cytokines, in particular IL-1β, have a role in the pathogenesis of OA.³ Diacerein (4,5-diacetyloxy-9,10-dioxo-anthracene-2-carboxylic acid), a slow-acting disease-modifying drug for OA with IL-1β inhibitory properties, has shown a promise in OA treatment; and appeared to have a role in slowing progression of OA compared to standard treatment with non-steroidal anti-inflammatory drugs (NSAIDs).⁴ It appeared effective in reducing pain and improving function in symptomatic knee OA.⁵ As it is a slow-acting disease-modifying drug, its effect would appear after few weeks of its intake. Therefore, it was suggested to be prescribed in combination with NSAID during the early few weeks of its administration. However, the efficacy and safety of diacerein intake with NSAIDs remained unclear. The aim of the present study was to assess the safety and efficacy of diacerein with and without diclofenac sodium in patients with knee OA.

2. Methods

2.1 Participants:

The present prospective study was conducted on sixty patients with knee pain due to primary knee OA. The duration of study was two years from July 2011 to July 2013. Inclusion criteria were: Patients aged above 50 years with knee pain and knee radiologic osteophytes; besides one of the following features: Morning stiffness < 30 minutes, and/or joint crepitations.¹ Exclusion criteria were: Patients with knee instability, inflammatory arthritis, hyperuricemia, bleeding tendency, increased body weight (>80 kg), associated knee bursitis, contraindications to NSAIDs (e.g. gastropathy, peptic ulcer, renal insufficiency, liver disease, hypertension, bronchial asthma, …), severe functional impairment (e.g. chest problems, ischemic heart disease, heart failure,…), haemarthrosis and/or any problem interfering with walking (e.g. neuropathy, stroke, spinal cord lesion, brain lesion, amputation, ankle-foot or hip problems,…).

2.2 Clinical and radiological examination:

Full history taking, thorough clinical examination and relevant radiological and laboratory investigations were performed to confirm the diagnosis of knee OA; and to rule out any of the exclusion criteria.

2.3 Intervention:

Patients were divided randomly (i.e. randomized controlled trial) into three equal groups: Group I (n=20): received diacerein (osteoacerein, Novartis) 50 mg capsules given twice daily for 2 months. Group II (n=20): received diclofenac sodium (75 mg capsule) taken once per day for 2 months. Group III (n=20): received both diacerein and diclofenac sodium in the previous doses for two months. Patients were asked not to take any other analgesic 24 hours before the start of the study and until its end.
Following patients’ grouping, patients were evaluated before treatment for: 1) Pain severity [using the visual analogue scale (VAS) for pain]; and 2) The twenty meters fast walking time (using a stopwatch). In patients with bilateral knee OA, pain severity was taken for the most painful knee. Reassessment of pain severity and the walking time were done in all patients one month and two months after the start of treatment, in the same way as before treatment. The assessor was blind to patient’s grouping. Also, at each reassessment, patients were examined for any drug adverse reaction or undesirable side effect. In addition, patients were asked to report about any new complaint (e.g. headache, abdominal or chest pain, nausea, gastrointestinal disturbance, skin reaction, short breath, …) any time during the study. It was planned that patients showing any serious adverse reaction to medication would be dismissed.

The procedures followed were in accordance with the ethical standards of the regional committee on human experimentation and with the Helsinki Declaration of 1975. All patients signed informed consent form; and the study was approved by the local ethical committee at the place where the research was done.

2.4 Statistics:
Statistical analysis was carried out using SPSS statistics software version 20. Categorical variables were described using frequencies and percentages. Fisher’s exact (FEP) test and Monte Carlo test (MCP) were used for testing associations between categorical variables. Quantitative data were given as median (minimum-maximum). Non-parametric statistical tests of significance were applied; Kruskal-Wallis test (H) was used to compare more than two independent groups and Friedman test (X²) was used to compare more than two dependent groups. Any significant Kruskal-Wallis or Friedman comparison was followed by adjusted post-hoc pair-wise comparisons. Statistical significance was accepted as p <0.05. All applied statistical tests of significance were two-tailed.

3. Results
There was a drop out of ten patients in group II, even though they did complain from adverse reaction prior to withdrawal from the study. The remaining patients continued the study.

3.1 Patient characteristics:
There was no differences between groups regarding muscle wasting (MCP= 0.820). Other patients’ characteristics are displayed in table 1. The only significant difference between the three groups was in knee effusion (P = 0.016); table 1.

3.2 The changes in pain severity and walking time:
Pain severity and the 20 meters fast walking time are displayed in table 2. Regarding pain severity, there was a significant improvement after treatment in group I (table 2). Post hoc paired comparisons revealed that median VAS was higher before receiving treatment than 2 months after treatment. In group III, there was a significant difference in pain severity between before, 1 month and 2 months after treatment (P = 0.048), but no statistical significant pair wise comparison was found. There was no significant difference in pain severity after treatment in group II. On the other hand, inter-group comparisons revealed no significant difference between the three groups as regards to the changes in pain severity (table 3).

Regarding the 20 meters fast walking time, there was a significant difference between before treatment, one month after and two months after treatment (P = 0.001) in group I. Post hoc paired comparisons revealed that the median for the fast walking time was significantly higher before receiving treatment than two months after treatment in group I (table 2). However, there was no significant change in the 20 meters fast walking time in the other two groups.

Regarding inter-group comparison for the walking time, there was no significant difference between the three groups when comparing the walking time before treatment to that after one month of treatment (table 3). However, there was a significant difference between the three groups when comparing the walking time at one month to that at two months after treatment (p = 0.006, table 3). Also, the median difference in the walking time between before treatment and two months after treatment was significant between the three groups (p = 0.008, table 3). Post hoc pair wise comparisons revealed that the decrease in the walking time at two months after treatment compared to that before treatment was significantly higher in group I compared to group III (table 3).

3.3 Frequency of adverse reactions:
No serious adverse reaction was observed in any group. The recorded non-serious side effects are displayed in table 4.

4. Discussion
In the present study, there was apparent improvement in the pain VAS after drug intake in the three studied groups. However, there was only significant improvement in pain severity after treatment in group I and group III (P = 0.033, and 0.048; respectively). The lack of any significant pain relief after therapy in group II (diclofenac group) might have been due to the low number of patients who continued the study in this group (n=10) and/or the low dose given (half the maximal dose of diclofenac).

On the other hand, group comparison revealed no significant difference between the three groups regarding the change in pain severity. This might suggest that diacerein alone was as effective as diclofenac sodium in relieving osteoarthritic knee pain; and that there was no definite additional benefit on combining both drugs for 1 or 2 months. This would also recommend using diacerein alone in patients with osteoarthritic knee pain, especially when there is contraindication to NSAIDs. The use of adjusted p value (for height, occupation and knee effusion by linear regression model) in inter-group comparison, in addition to the lack of any significant difference between groups in the other patients’ characteristics would suggest group uniformity. This would render group comparison in this study reliable.
Louthrenoo et al.\textsuperscript{8} found that diacerein was as effective as piroxicam in the treatment of symptomatic knee OA and concluded that diacerein had a better safety profile and an added advantage of carry-over effect.

Baliga et al.\textsuperscript{9} reported that there was a statistically significant early reduction in the mean VAS scores in knee OA patients given diacerein Modified-Release (MR) 100 mg and conventional diacerein 50 mg for 8 weeks.

Singh et al.\textsuperscript{10} concluded that the use of diacerein and diclofenac sodium together decreased pain and improved function significantly more than diclofenac sodium alone in knee OA. The pain relieving effect of diacerein plus diclofenac (group III) of the present study is consistent with the finding of Singh et al.\textsuperscript{10} However, diacerein alone appeared as effective as diclofenac plus diacerein in the present study.

Zheng et al.\textsuperscript{11} concluded that diacerein was as effective as diclofenac sodium in treating patients with knee OA. This agrees with inter-group comparisons in this study. However, intra-group changes following treatment in this study suggest that diacerein alone might be better than diclofenac alone when assessment was done two months after therapy.

In the present study, diacerein alone (but not diclofenac alone or diacerein combined with diclofenac) improved the walking time two months after therapy. The finding that diacerein alone was better than diacerein plus diclofenac sodium in improving the walking time two months after therapy; might suggest that diclofenac sodium might have interfered with the structure modifying effect of diacerein, if they were taken together for two continuous months.

Furthermore, it should be noted that the lack of efficacy of diclofenac sodium in improving the walking time might have been also due to the low dose of diclofenac sodium (75 mg per day, which is half the maximum daily dose) and/or the low number of patients in this group. It should be noted that the effect of diacerein on the walking time was not previously addressed.

Regarding the observed adverse reactions during the two-month period, it was generally mild. But combined intake of diacerein and diclofenac sodium might increase side effects. Diarrhea was seen in 40% of patients who were taking diacerein (groups I and III). This does not contradict the findings of others.\textsuperscript{12} However, the risk of diacerein intake for > 2 months was not investigated in this study.

\textbf{In conclusion}, diacerein appeared as effective as diclofenac sodium in improving pain severity. Diacerein, unlike diclofenac sodium, was effective in improving the walking time. Either diacerein or diclofenac sodium showed little side effects. However, it seemed that the addition of diclofenac to diacerein might increase side effects. In light of this study, it may be recommended to give diacerein (osteoacerein) for patients with knee OA to control their knee pain for up to 2 months without serious or intolerable side effect, especially in those who have contraindication to NSAIDs.

\textbf{Recommendations}: Further studies are needed to investigate the long term effects of diacerein with and without NSAIDs on a large number of patients with OA. Also, it is recommended to reassess patients every 2 weeks during the first month (i.e. before diacerein exerts its effect).

\textbf{References}

\begin{itemize}
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\textbf{Table 1: Demographic and clinical data of the studied patients.}
Comparison between the three studied groups regarding pain VAS and the 20 meters fast walking time (inter-group comparison).

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
</tr>
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<tbody>
<tr>
<td>n=20</td>
<td>n=10</td>
<td>n=20</td>
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Age (years)
Median (Min-Max)
Gradual
Sudden
Acute

Onset n (%)
Bilateral
Right
Left

Side involved n (%)

Mild effusion n (%)
Yes
No

Tenderness n (%)
Yes
No

Crepitus n (%)
Palpable
Audible
Rt palpable/ Lt palpable
Rt palpable/ Lt audible

Knee Alignment
Normal
Genu varum
Genu valgum

H: Kruskal Wallis test; MCp: Monte Carlo test; FEp: Fisher Exact test. *Significant

Table 2: Pain visual analogue scale and the 20 meters fast walking time in the studied groups before and after treatment (intra-group comparison).

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before treatment</th>
<th>After Treatment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>After 1 month</td>
<td>After 2 months</td>
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</tbody>
</table>

Pain (VAS, in mm)
Group I (n=20)
Group II (n=10)
Group III (n=20)

Walking time (sec)
Group I (n=20)
Group II (n=10)
Group III (n=20)

Table 3: Comparison between the three studied groups regarding pain VAS and the 20 meters fast walking time (inter-group comparison).

<table>
<thead>
<tr>
<th>Assessment</th>
<th>G I (n=20)</th>
<th>G II (n=10)</th>
<th>G III (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=20</td>
<td>n=10</td>
<td>n=20</td>
<td></td>
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</tbody>
</table>
| Pain (VAS, in mm)
Before treatment versus After 1 month
10 (40-90) | 0 (-20-40) | 20 (20-90) |
| After 1 month versus After 2 months
0 (-40-50) | 5 (-60-50) | 5 (0-40) |
| Walking time (sec)
Before treatment versus After 1 month
1.5 (-12-6) | 5.3 (-13-13) | -1 (-21-8) |
| After 1 month versus After 2 months
Before 2 months
2.5 (-2-16) | 5.3 (-3-6) | 0 (-21-13) |

Table 4: The frequency of adverse reactions.

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Patient's groups</th>
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<tbody>
<tr>
<td></td>
<td>G I (n=20)</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Heartburn</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>-</td>
</tr>
<tr>
<td>Mild Diarrhea</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Urine discoloration</td>
<td>20 (100%)</td>
</tr>
</tbody>
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Note: Minimum and maximum appear in parentheses below the medians. Medians with differing subscripts within rows are significantly different at the adjusted p < 0.05 based on post hoc paired comparisons. *p Significant