

INTRA-ARTICULAR INFILTRATIVE THERAPY ASSOCIATED WITH ALPHA LIPOIC ACID AND VEGETABLE SAFFRON EXTRACT VS INTRA-ARTICULAR INFILTRATION THERAPY ONLY, IN MODERATE-TO-SEVERE ARTHROSIC PAIN

**TERAPIA INFILTRATIVA INTRARTICOLARE INTEGRATA
CON ACIDO ALFA LIPOICO ED ESTRATTO VEGETALE DI ZAFFERANO
VERSO LA SOLA TERAPIA INFILTRATIVA
NEL DOLORE ARTROSICO MODERATO-SEVERO**

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SUMMARY

Controlled clinical trial, open, which evaluates analgesic activity induced by intra-articular infiltrative therapy associated with alpha lipoic acid and vegetable saffron extract vs intra-articular infiltration therapy only, in patients with moderate to severe shoulder, knee or hip arthrosic pain.

The main objective of the research is to evaluate the effective analgesic benefit of the association.

The secondary goal reviews the benefits obtained regarding the joints' range of motion and functionality, then physical wellness and sleep quality.

Key words

Intra-articular infiltration, alpha lipoic acid, Crocus sativus L., shoulder-knee-hip arthrosis, analgesia, physical well-being, articular, sleep quality, mobility

RIASSUNTO

Studio clinico controllato, in aperto, che valuta l'attività antalgica indotta da terapia infiltrativa intrarticolare associata ad acido alfa lipoico ed estratto vegetale di zafferano verso la sola terapia infiltrativa intrarticolare, in pazienti con dolore artrosico di spalla, ginocchio o anca, di intensità moderata-severa. L'obiettivo primario dello studio è valutare l'effettivo vantaggio antalgico dell'associazione.

Gli obiettivi secondari valutano i benefici ottenuti su mobilità e funzionalità articolare, benessere fisico e qualità del sonno.

Parole chiave

Infiltrazione intrarticolare, acido alfa lipoico, Crocus sativus L., artrosi di spalla-ginocchio-anca, analgesia, benessere fisico, articolare, qualità del sonno, mobilità

INTRODUCTION

Intra-articular and peri-articular infiltrative therapies represent safe and effective analgesic therapies in musculoskeletal, joint and soft tissue diseases.

There are two types of infiltration:

- intra-articular infiltration: the drug (hyaluronic acid, cortisone, local anesthetic) is injected directly into the joint;

- peri-articular infiltration: the drug (low weight hyaluronic acid, cortisone, local anesthetic) is injected near the joint.

Corticosteroids and hyaluronic acid are the most commonly used drugs.

The efficacy of cortisone-based preparations is short-lived; they are usually used to provide short-term relief, even if the benefit period is unpredictable due to the large variability of the disorder. Hyaluronic acid, whose intra-articular administration is able to improve the elasticity and functionality of the synovial fluid, is widely used.

Hyaluronic acid's action performs at the level of the joints, which translates, from a clinical point of view, into decreased pain and an improvement of the joint function, sustained even longer in time in the case of cross-linked hyaluronic acids. The maximum clinical efficacy in the post-infiltrative period is different, because the drugs used and the possible combinations are different.

Alpha-lipoic acid, also known as thioctic acid, is a coenzyme involved in basic biochemical reactions of energy metabolism¹ (pyruvate dehydrogenase, alpha-ketoglutarate dehydroge-

nase). It is also a powerful biological antioxidant,² which is both hydro and liposoluble, and is able to contribute to the regeneration of other physiological antioxidants: vitamin C and E, coenzyme Q10 and glutathione.³ These activities enable it to prevent the formation of free radicals and, therefore, the processes of senescence of cells and tissues, in particular by protecting the nervous and cardiovascular tissues.^{4,5}

It is found naturally in both plant and animal food sources.

Derivatives of saffron stigmas (*Crocus sativus* L.) contain carotenoids (crocin and its derivatives) and safranal: the biological activity⁶ of these components, as evidenced by some studies, can improve the conditions of discomfort that may derive from mild and moderate stress⁷ and anxiety disorders.⁸

The clinical trial aims to compare the analgesic efficacy of two treatment plans. The first performed with intra-articular infiltrative therapy associated with alpha-lipoic acid and saffron vegetable extract tablets of 1100 mg, the second with only intra-articular infiltrative therapy, in patients with moderate-to-severe osteoarthritis of shoulder, knee or hip.

MATERIAL AND METHODS

Statistical analysis

All the variables detected in the data collection form are shown in descriptive tables. In particular, the continuous variables are presented as averages, SD, median, minimum and maximum, while the moderate and nominal variables are shown in

contingency tables with the frequencies and the respective percentages. When appropriate, the homogeneity of the variables with respect to the two treatment groups was assessed by the Chi-square test (qualitative variables) or the ANOVA test (quantitative variables).

Study characteristics

Open label, randomized and retrospective trial. The study population is represented by 60 patients aged between 50 and 89 years, of both sexes, with shoulder arthritis, knee and hip pathology presenting, at the first visit, average pain values of the last 24 hours ≥ 4 measured using an NRS (Numerical Pain Assessment Scale). Patients were in line with inclusion criteria and in absence of trial treatment contraindications. They are divided (after signing a informed consensus) into two general groups both of 30 units:

- First group: intra-articular infiltration therapy associated with oral alpha lipoic acid and vegetable saffron extract 1100 mg tablets (1 tablet once a day);

- Second group: intra-articular infiltration therapy.

The follow-up has a duration of 60 days. There is a baseline inclusion visit and follow-up visits after 7, 15, 30, 45 and 60 days. After an initial baseline visit, the following parameters were considered for all patients:

1 The level of analgesia according to the NRS scale (pain intensity at rest and load and/or movement)

2 Physical well-being

3 Functionality of joints

4 Quality of sleep

5 Joint mobility

The comparison of the results obtained in the course of treatment will be evaluated using the numerical assessment scale at 11 points (0-10 NRS) and the ADL scale assessing autonomy in daily living activities. The normality of data distribution will be evaluated by Kolmogorov-Smirnov tests.

The comparison of the temporal trend of the variables will be performed via the ANOVA test for repeated measurements (normal variables) or non-parametric tests for abnormal variables (e.g. Friedman).

STUDY OBJECTIVES

Primary objective

To compare the antalgic activity obtained by the intra-articular infiltrative therapy associated with alpha lipoic acid and saffron vegetable extract compared to infiltrative therapy alone, in patients with arthritic shoulder, knee or hip pain, using a numerical 11-point assessment scale (0-10 NRS) and daily living activities ADL autonomy rating scale.

Secondary objectives: to evaluate the benefits obtained in terms of mobility, physical well-being, joint function and quality of sleep.

Study population

60 patients aged between 50 and 89 years, of both sexes, in line with inclusion criteria.

Inclusion criteria

- Patients diagnosed with arthritis of the shoulder, knee or hip;
- With the presence of average daily pain ≥ 4 measured with NRS and re-

ported in last 24 hours, attributable to the arthritic pathology;

- Able to comply with the study treatment;
- Aged 18 or over;
- Who have signed the informed consent.

Exclusion criteria

- Participation in other research projects that are in conflict or that could confuse the results of the study;
- Absence of informed consent, or withdrawal of consent, for participation in the study;
- Presence of concomitant psychiatric pathological conditions that could interfere with the state of consciousness or with the ability to judge;
- Contraindications of any kind to the use of the treatment in question;
- Concomitant execution of antalgic treatments with neurosurgical/ablative techniques, or by bone marrow neurostimulation, or with loco-regional anaesthetic techniques (including peridural or spinal analgesia), or by using vertebro/kyphoplasty or other invasive techniques with relevance to pain.

Release from follow-up

- For reasons connected to the study treatment (adverse event);
 - For reasons not connected to treatment (death due to illness, transfer of the patient to another treatment facility);
 - For reasons connected to the patient (withdrawal of consent, poor compliance);
 - For various reasons (protocol violations, administrative problems);
- The study requires the reporting of release from follow-up, the date, and

the related reasons.

Assessments

The patient included in the study protocol must be monitored and evaluated in the manner and times described in the protocol.

The information necessary for this purpose is contained in the patient data sheet drawn up at the time of enrolment and consist of:

- Patient personal data (age, sex);
- Study inclusion and exclusion criteria based on the checklist;
- Patient information and obtaining of informed consent in reference to participation in the study;
- Assignment of treatment.

Baseline evaluation

- Summary medical history, which includes the indication on the arthritic pathology, the date of its first diagnosis, the secondary localizations present at that time, and the previously performed treatments;
- Possible concomitant diseases in progress;
- All treatments (analgesic and non-analgesic) in place before visit 1;
- Adverse reactions due to antalgic treatments prior to the start of the study;
- Performance status in daily living activities expressed with the ADL scale;
- Information related to the patient's pain: how many months the patient suffers from pain due to arthritis of the shoulder, knee or hip, the intensity of the average and worst pain experienced in the last 24 hours (with NRS, on patient's indication), the characteristics and type of pain (nociceptive), neuropathic, mixed).

Post-baseline control evaluations

At 7, 15, 30, 45 and 60 follow-up days.

- Measure the amount of average and worst pain related to the last 24 hours (with NRS, on patient's indication);
- Reporting of recourse to additional therapy to support the treatment with the study drugs under starting from the previous visit;
- Addition of fixed, variable pain therapy plan (additional therapy and rescue) and other therapies decided upon to visit;
- Reporting of any change in the study drug and its causes;
- Performance status expressed with the ADL scale;
- Upon indication of the patient, any adverse reactions correlated with pain therapy and any other adverse events;
- Report of any early termination of the study and its related causes.

Populations analysed

The main population for efficacy evaluation is the Intent-to-treat population (ITT) composed of all eligible, randomised patients, with the evaluation of the primary efficacy variable at baseline and at least one post-baseline detection. One "Per-protocol population" also evaluated, to support the ITT population composed of patients who have concluded the study regularly, without protocol violations, and who have taken the same type of treatment for the duration of the study.

For the evaluation of tolerability, we take into consideration the "Safety population" consisting of patients who have been given at least one dose of the study treatment assigned to them.

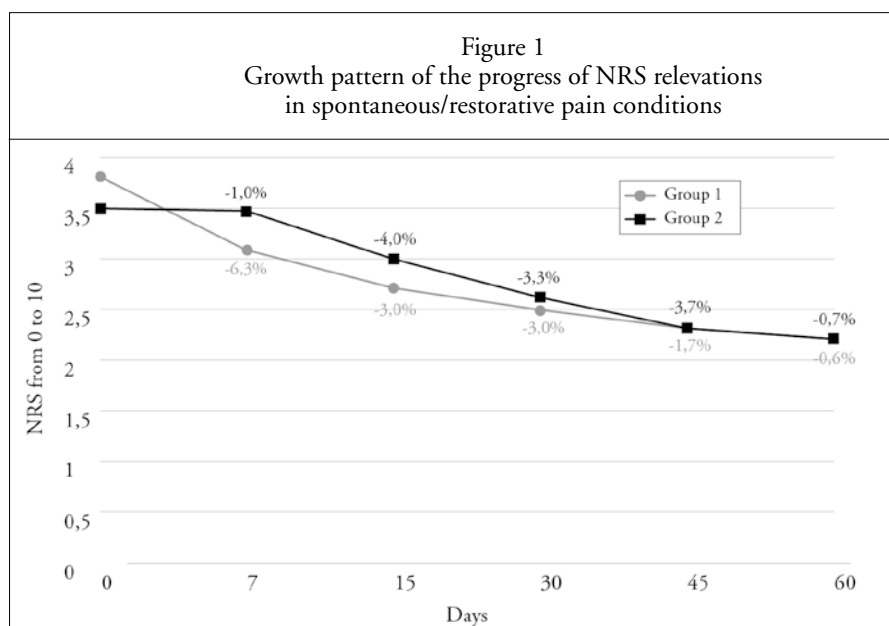
RESULTS

In spontaneous pain/rest conditions, both groups showed significant improvement over the 2 months of treatment ($P < 0.001$) (Figure 1). A repeated two-way variance analysis (interaction in the treatment time) was used. The two groups as the factor between the subjects (treatment) and the six measurements at the time point during the treatment were considered as internal factors (time).

Spontaneous pain/rest intensity was measured by 11 points NRS scale and it shows a decreasing temporal evolution for both treatment groups. In the first group the NRS average value changes from 3.7 to 3.1 (-6.3%) during the first observation week, then it goes down to 2.8 (-9.3%) during the second one and to 2.5 (-15.3%) at 30 days, reaching 2.3 (-17%) at

30 days, reaching 2.3 (-17%) at 45 days and 2.2 (-17.6%) at the end of the observation period. In the second group, treated with infiltrations only, the NRS average value changes from 3.5 to 3.4 (-1%) during the first observation week, it goes down to 3.0 (-5%) during the second one and to 2.7 (-8.3%) at 30 days, reaching 2.4 (-12%) at 45 days and 2.3 (-12.7%) at the end of the observation month. The comparison between treatments was not statistically significant at any visit.

As shown in Figure 1, the group of patients treated with intra-articular infiltrative therapy associated with oral alpha lipoic acid and saffron vegetable extract Tabs 1100 mg / day (group 1) therapy, during the 60-day observation span had a of the NRS scale score equal to 2.92% on average. The group of patients treated with intra-articular infiltrative thera-



py alone (group 2) had a reduction of the NRS scale score equal to 2.54% on average over the 60-day observation period.

The data shows that on average, group 1 had a greater reduction of the NRS score of 0.38%, compared to group 2.

Under load/movement pain conditions both groups showed significant improvement over the 2-month treatment ($P < 0.001$). Group 1 significantly reduced the NRS average value compared to the control indicated by the factor effect between subjects ($P < 0.001$).

A repeated two-way variance analysis (interaction of time in the treatment) was used. The two groups as the factor between the subjects (treatment) and the six measurements at the time point during the treatment were considered as internal factors (time). If time-dependent changes were significant at each stage, the Dunnett test was used as a post-hoc test to compare the decrease in pain intensity with baseline values. If the treatment-dependent changes were significant, t-tests were used to compare the differences between the two treatments for each time point. P values of ≤ 0.05 were considered to indicate statistical significance. The data is given as means \pm SEM.

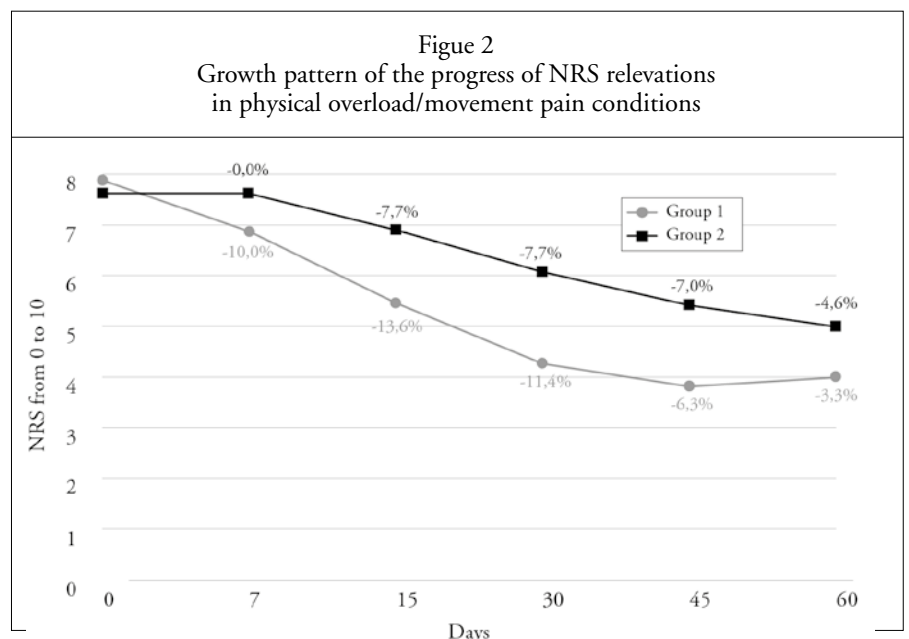
The intensity of the load/movement pain, measured using the 11-point NRS scale, showed a decreasing temporal trend for both treatment groups; for group 1, the NRS average value went from 7.9 to 6.9 (10% reduction) during the first week of observation, then fell to 5.3 (-23.6%) during the second week, and to 4.2 (-35%) at 30 days, reaching 3.8 (-41.3%) at

45 days; for group 2, the NRS average value remained unchanged during the first week of observation (score 7.8), then fell to 7.0 (-7.7%) during the second week, and 6.9 (-15.4%) at 30 days, reaching 5.4 (-22.4%) at 45 days, and finally 4.9 (-27.0%) at the end of the observation. The comparison between the two treatments was statistically significant ($P < 0.001$) at all four check-ups. As highlighted in *Figure 2*, group 1 had a reduction of the score on the NRS scale equal to 8.92% on average, while group 2 reduced the score on the NRS scale by 5.4% on average. The difference in average percentage score is 3.54% greater in favour of group 1.

At the baseline visit for both treatment groups, almost all patients reported reduced or poor physical well-being. The start of treatment shows a progressive and constant improvement

of the conditions of the patients, in particular group 1. The percentage of patients in group 1 with improved physical well-being increased from 33.3 percent in the first week of observation, to 90 percent in the second week and remained so until the 30th day, and then reached 96% at the 45 days of observation. At the end of the period, however, there was a trend reversal with the percentage reduced to 73.3. For group 2 patients who were only treated with infiltrative therapy, no improvement in physical well-being was recorded after the first week of observation. In the second week, 60 percent showed an improvement, at 30 days the percentage rose to 80 percent. Later, there was a downturn of the trend at 45 days, which was reduced to 40 percent, and then to only 26.6 percent at the end of the observation period (*Figure 3*).

At the baseline visit for both treat-

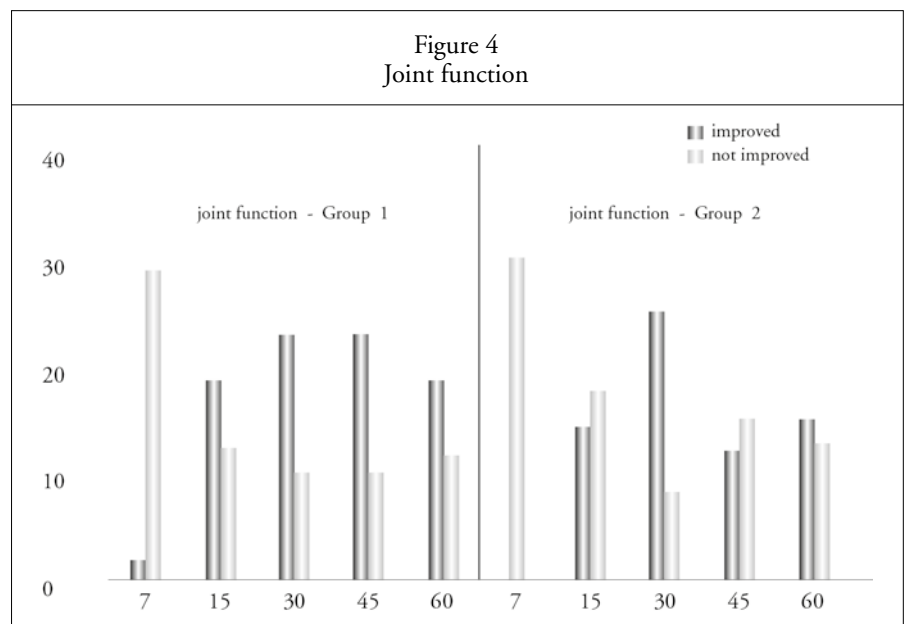
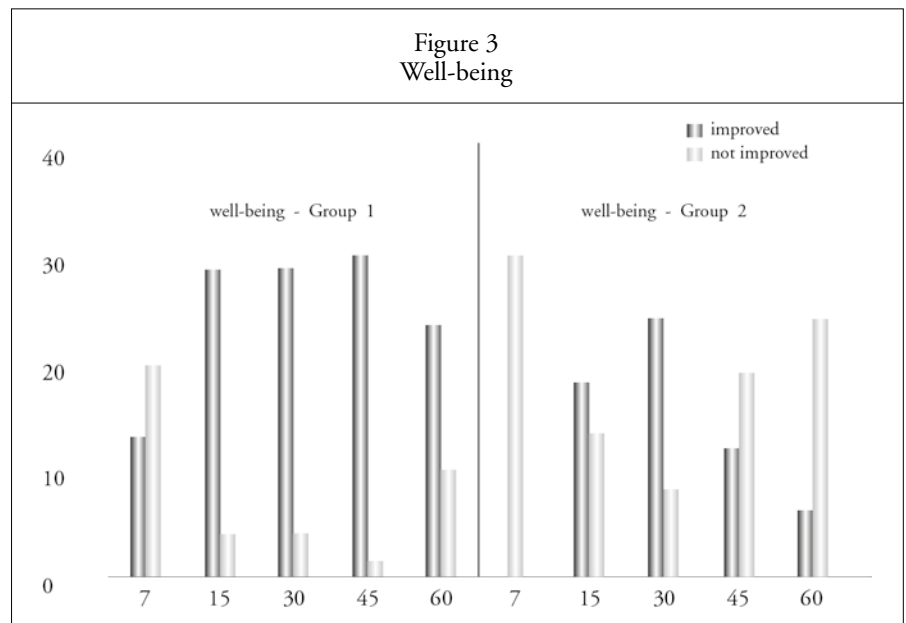


ment groups, almost all patients reported reduced, poor or absent joint functionality. The percentage of patients in group 1 with improved joint functionality was 3.3 percent in the first week of observation, 63.3 percent in the second week and 70 percent at the 30th day. It remained the same at the 45th day, but at the end of the observation period, there was a trend reversal with the percentage reduced to 63.3. For group 2 patients who were only treated with infiltrative therapy, no improvement was recorded after the first week of observation. In the second week, 36.6 percent showed an improvement and, at 30 days, the percentage rose to 73.3 percent. Later, there was a downturn of the trend at 45 days, which was reduced to 40 percent, and then to 50.0 percent at the end of the observation period with up-and-downs (Figure 4).

At the baseline visit for both treatment groups, almost all patients reported deeply disturbed sleep and several awakenings. During the treatment there was a quality of sleep continuous improvement with reduction of night awakenings, almost until the reversal. The percentage of patients with restful sleep was different between the treatment groups. In the first one it grew rapidly during the first half of the observation period (66%-7 days, 90%-15 days, 96.6%-30 days, 100%-45 and 60 days), while for group 2 patients who were only treated with infiltrative therapy, the quality of sleep was improved slowly (66%-7 days, 73.3%-15 days, 76.6%-30 days, 96.6%-45 and 100%-60 days) (Figure 5).

At the baseline visit for both treatment groups, almost all patients reported reduced mobility or need for

assistance. Patients of group 1 gradually improved, but the improvement didn't last until the end of the follow



up. Particularly, the percentage of patients with improved mobility reased from 3 percent in the first week of

observation, to 30 percent in the second week, to 40 percent at 30 days. Later, there was a downturn of the

trend at 45 days (30%), until 6% at the end of period.

For group 2 there was not mobility improvement during the first week, then the percentage of patients with improved mobility raised to 6.6% in the second week and remained so until the end of the observation period. No patient complains of mobility worsening.

The comparison between treatments was significant to the second week examinations ($P < 0.05$) and to the third week ($P < 0.05$) (Figure 6).

CONCLUSION

The primary objective proposed in the study was to evaluate the pain related to osteoarthritis of the shoulder, knee or hip, using a numerical 11-point evaluation scale (0-10 NRS) and the autonomy in daily living rating scale (ADL). The secondary objectives concerned the benefits in terms of mobility, physical well-being, joint functionality and sleep quality. The intensity of spontaneous/resting pain shows a decreasing temporal course for both treatment groups and although the group treated with alpha lipoic acid and saffron vegetable extract 1100 mg tablets (group 1) showed a greater improvement, the statistical analysis did not show a significant difference between the values found in all the follow-up intervals. On the other hand, the analysis of the values selected in the load/movement pain condition, namely when the pain is decidedly greater, was more significant.

At the end of the 60 days, group 1 had a score reduction of 8.92% (NRS

Figure 5
Sleep quality

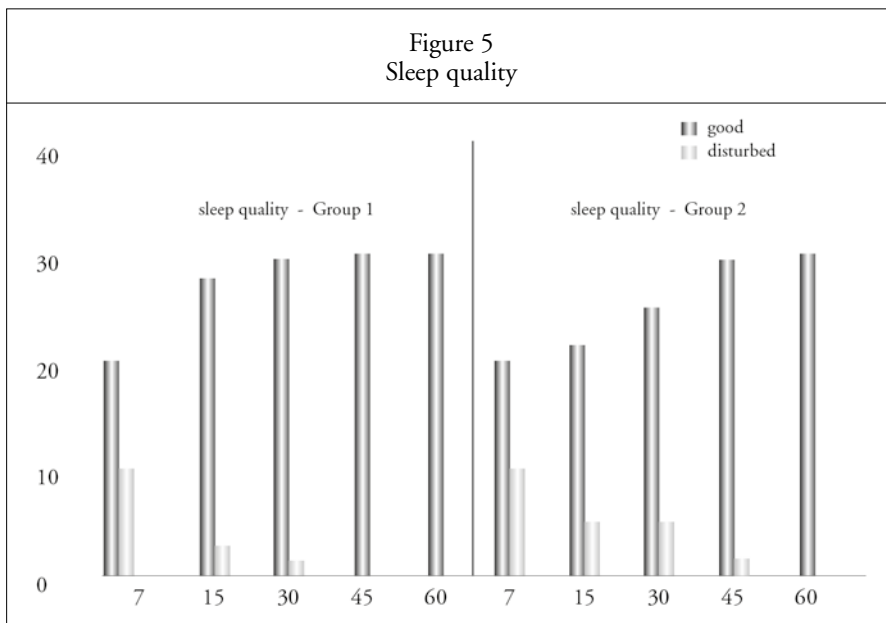
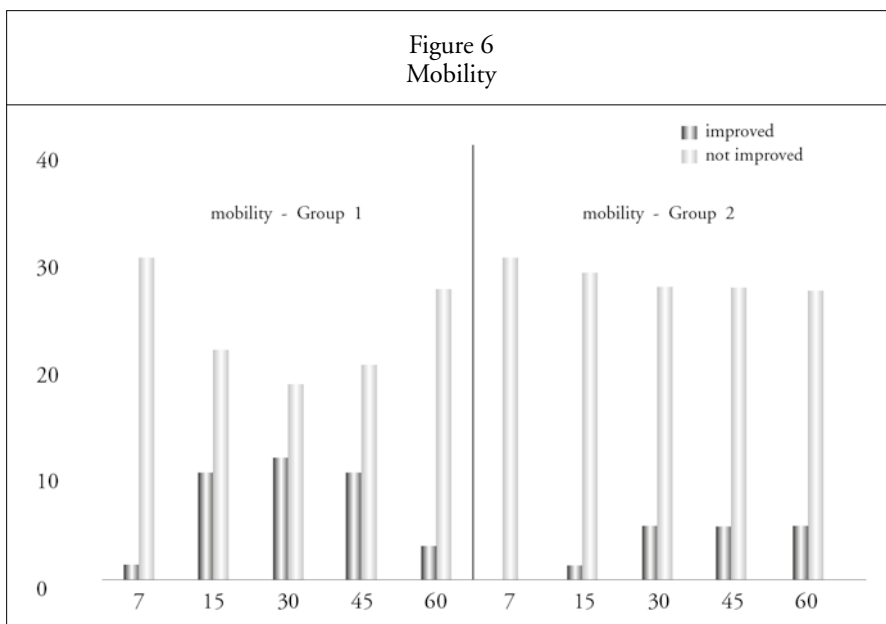


Figure 6
Mobility



scale) on average, while group 2 (patients who were only treated with intra-articular infiltrative therapy) had a reduction of the lowest NRS scale score, of 5.4% on average. At the end of the observation period, there was a high percentage of group 1 patients with improved physical well-being (73.3%), compared to the lower percentage of group 2 (26.6%).

Mobility also improved, with values statistically significant between the two groups during some follow up intervals. The quality of sleep, although better in both groups, evolved faster in group 1.

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