# Efficacy of a comprehensive rehabilitation programme combined with pharmacological treatment in reducing pain in a group of OA patients on a waiting list for total joint replacement

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## Abstract

### Objectives

*It has been shown that combined rehabilitation and pharmacological treatment reduce pain in subjects with osteoarthritis (OA), although the efficacy of either therapy alone may be limited. We studied the effects of a comprehensive rehabilitation programme alone and together with pharmacological treatment in relatively young OA patients awaiting total joint replacement (TJR).*

### Methods

*Forty-four OA patients randomly divided into two groups underwent three weeks of comprehensive day hospital rehabilitation treatment alone (group A) or in combination with acetaminophen 1g three times a day. Pain intensity was measured using a visual analogue scale (VAS) before and during treatment, and for four weeks afterwards, and compared between the groups using Student's t-test for unpaired data.*

### Results

*In group A, pain intensity was not reduced after the first week of treatment (T0 vs. T1: p=0.739), but was significantly reduced from the end of the second week to the end of the observation period (p<0.01). In group B, pain intensity was significantly reduced (p<0.01) from the first week of treatment to the end of the observation period. The differences in the VAS score variations from T0 between the two groups were statistically significant throughout the study period (T0–T1: p=0.004, T0–T2: p=0.041, T0–T3: p=0.035, T0–T4: p=0.009, T0–T5: p=0.011, T0–T6: p=0.014 T0–T7: p=0.015).*

### Conclusion

*Rehabilitation is effective in reducing pain even in patients with severe OA on a waiting list for TJR, but its efficacy is boosted by adding appropriate pharmacological treatment.*

**Key words**

pain, osteoarthritis, rehabilitation, acetaminophen, total joint replacement

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## Introduction

Hip and knee osteoarthritis (OA) are the most common joint disorders affecting the elderly throughout the world. There is still no known cure for OA, and the current management of patients with hip and knee OA remains the controlling pain and disability, both of which have a a considerable societal and public health impact (1, 2). Approximately 12% of American adults aged 65 years or over have OA, which is the most frequent cause of chronic non-cancer (2). In Europe, 19% of the subjects responding to a telephone-based survey had chronic pain and two-thirds (21%) of them used non-medication treatments such as physical therapy (3).

When the pain and the related disability of OA can no longer be borne, total joint replacement (TJR) may be used to relieve pain and improve function. The use of TJR for OA has increased over the last 20 years throughout the world, even in relatively young subjects (4), and the number of revisions of total hip or knee arthroplasty and deep infections increased steadily between 1990 and 2002 (5). Both represent a very considerable economic burden (5, 6), and the subjects undergoing TJR were about twice as likely to report current joint pain as those who did not (6).

All of these data underline the fact that TJR is not always completely successful and that, among the subjects who survive for 10–20 years beyond the original surgery, many need revision; all possible therapies should therefore be attempted to postpone TJR for as long as possible.

As comprehensive hospitalised rehabilitation (7, 8) and appropriate drug therapy are both well-established treatments for controlling pain and disability in patients with OA of the hip or knee (9, 10), we studied the efficacy of a comprehensive rehabilitation programme alone or combined with pharmacological treatment in reducing pain in a group of young OA patients on the waiting list for TJR.

## Materials and methods

The study was designed to evaluate the efficacy of a comprehensive in-patient rehabilitation programme alone or combined with pharmacological treatment in controlling the pain of patients with severe OA of the hip or knee on the waiting list for TJR. The only inclusion criterion was being on the waiting list for the surgical replacement of a major lower limb joint affected by OA. The exclusion criteria were the presence of other forms of pain such as neuropathic pain or other diseases in which pain is the major complaint (visceral disorders; fibromyalgia, arthropathies and other rheumatological diseases such as rheumatoid arthritis, diabetic neuropathy). Patients receiving drugs that could influence pain levels (tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRIs] etc.) were also excluded, as were those with gastrointestinal problems or known acetaminophen intolerance.

Seventy-nine patents were interviewed and, after being given an exhaustive explanation of the methods and purposes of the study, 44 agreed to enter the study. They were informed that they could leave the study and undergo TJR at any time. The enrolled patients were randomly divided into two groups (see Table I), both of which underwent a 15-working day protocol (three weeks) of comprehensive rehabilitation consisting of strengthening exercises, flexibility and endurance training, and physical therapy (thermotherapy and transcutaneous electrical nerve stimulation, TENS) of the painful joint in a day hospital (DH). The 22 patients in group B also received pharmacological treatment (acetaminophen 1 g three times a day).

Following the DH rehabilitation programme, the patients in both groups were allowed to take acetaminophen 1 g a maximum of three times a day in the case of pain relapse.

Pain was assessed weekly by means of a visual analogue scale (VAS). This was chosen as the only pain measurement because of its relative simplicity and the fact that it allowed the patients to complete the related questionnaire (Fig. 1) at home and post it to us during the 4-week post-treatment follow-up period (during the period of rehabilitation, the VAS was administered by a research nurse).

### *Ethical issues*

The ethics committee approved the study and suggested that a doctor involved in the study should always be

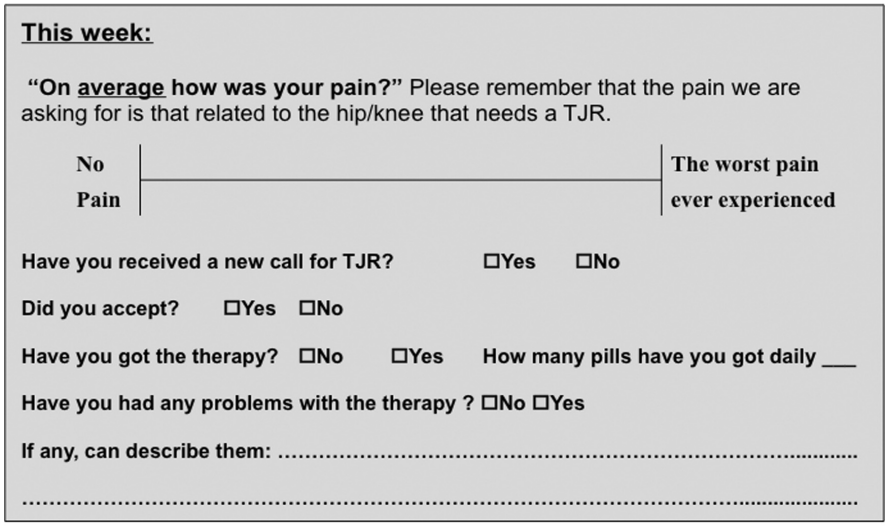


**Fig. 1.** Weekly questionnaire used for home assessment of VAS and therapy.

available for consultation. Rescue treatment with acetaminophen plus codeine 30 mg was also suggested in the case of the failure of previous treatment with acetaminophen alome. For these reasons, it was also suggested that a doctor should call the patient in the case of continuous home treatment for more than one week, or in case of a switch from acetaminophen to acetaminophen plus codeine.

*Statistical analyses*

Student's *t*-test for unpaired data was used to compare the age, height and weight of the two groups. Gender distribution and joint involvement were compared by means of the $\chi^2$ test. These statistical analyses indicated that the two groups were clinically and demographically homogeneous at baseline.

## Results

There were no significant differences between the two groups in terms of age ($p$=0.664), height ($p$=0.644), weight ($p$=0.201), gender ($p$=0.545) or the joint involved ($p$=1) (Table I).

Pain intensity was measured using the VAS before treatment (T0), at the end of each week of treatment (T1 to T3), and at the end of each of the four weeks of follow-up (T4 to T7). Comparison of the scores at T0 (Student's *t*-test for unpaired data) confirmed that the groups were homogeneous as there was no statistically significant between-group difference ($p$=0.244) (Fig. 2).

There was no significant difference in pain intensity after the first week of treatment in group A (T0 *vs*. T1: $p$=0.739), but there were statistically significant reductions in pain intensity from the end of the second week of treatment to the end of the follow-up period ($p$<0.001). In group B, there was a statistically significant reduction in pain intensity from the first week of treatment, and this was maintained until the end of the follow-up ($p$<0.001).

Although the VAS scores of the two groups were not significantly different at T0 (group A: 6.3±1.2; group B: 6.7±1.3, $p$=0.244), in order to normalise the data and remove the numerical difference, the subsequent analyses were based on the variations in VAS scores rather than the absolute values. Student's *t*-test for unpaired data revealed statistically significant differences in the VAS score variations between the two groups at all of the considered time points (T0–T1: $p$=0.004; T0–T2: $p$=0.041; T0–T3: $p$=0.035; T0–T4: $p$=0.009; T0–T5: $p$=0.011; T0–T6: $p$=0.014; T0–T7: $p$=0.015) (Fig. 3).

## Discussion

The results of this study show that rehabilitation alone can be effective in reducing pain, but that combining it with appropriate pharmacological treatment can increase its efficacy even in a group of patients with severe OA on a TJR waiting list. To the best of our knowledge, this is the first published study of this subgroup of OA patients.

OA is the most prevalent joint disease, and a major cause of disability because of the presence of chronic pain (11). According to a 1998 epidemiological study, approximately 16% of the adult population in the UK experience pain in more than three joints lasting more than one week over the course of a 1-month period (12). Although there is no unequivocal definition of OA, pain is the pivotal clinical feature in the American College of Rheumatology's classification criteria for OA of the hand, hip and knee (13, 14), and joint pain is therefore the most prominent and important sign.

It has been shown that rehabilitation and pharmacological treatments substantially reduce pain in patients with OA of the hip or knee, but either may have limited effects alone. A long lasting efficacy has been obtained through Spa-therapy with mud which persisted for up to 1 year (15). Water- (16) and land-based rehabilitation protocols (17) have provided positive results, but seem to have only short-term beneficial effects in patients with mild-moderate hip and/or knee OA and substantially none in disabled OA patients aged 60 years or older. In this group of elderly patients, only a slight change was obtained from participating in an aerobic or a resistance exercise programme plus a health education programme (18). These data suggest that rehabilitation programmes should not stand alone but should be part of a broader treatment approach for OA that has to include pharmacotherapy (18).

The different results obtained from a stand-alone rehabilitation approach can be explained by the difference in the treated population: it is more effective when the OA is less severe, and less effective in severe forms such as in the case of patients on a waiting list for TJR. This bias in the literature has been highlighted by two recent Cochrane reviews that pointed out a substantial lack of studies with clearly defined patient subgroups (8, 16), and it is true not only in terms of age stratification, but also in terms of gender because females aged 65–74 years report more hip and knee pain (19, 20). In this context, our data

**Table I.** Demographic and clinical data.

| CODE | Group | Age (yrs) | Height (cm) | Weight (kg) | Gender | Joint | Pain onset | Concomitant pathologies |
|---|---|---|---|---|---|---|---|---|
| 1F | A | 71 | 172 | 70 | M | hip dx | 1998 | DIA |
| 2F | A | 66 | 160 | 75 | F | hip sx | 2001 | OP |
| 3F | A | 59 | 162 | 58 | F | hip sx | 2003 | DIA, HC |
| 4F | A | 71 | 158 | 60 | F | hip dx | 2001 | |
| 5F | A | 59 | 171 | 61 | F | knee dx | 2000 | VAL |
| 6F | A | 57 | 181 | 90 | M | knee sx | 2001 | DIA |
| 7F | A | 63 | 178 | 74 | M | hip sx | 2003 | HC, HT |
| 8F | A | 71 | 159 | 65 | F | hip dx | 2000 | HT |
| 9F | A | 69 | 171 | 78 | F | hip dx | 1998 | OP |
| 10F | A | 57 | 166 | 60 | M | knee dx | 1998 | VAL |
| 11F | A | 62 | 160 | 82 | M | hip dx | 2001 | HT |
| 12F | A | 59 | 179 | 88 | M | hip sx | 1997 | HC |
| 13F | A | 55 | 171 | 64 | F | knee dx | 2001 | VAL |
| 14F | A | 67 | 163 | 73 | M | hip dx | 2001 | |
| 15F | A | 69 | 180 | 76 | M | knee sx | 2003 | HT |
| 16F | A | 71 | 159 | 65 | F | hip dx | 2000 | |
| 17F | A | 69 | 172 | 70 | M | hip dx | 2003 | OA Knee left |
| 18F | A | 56 | 162 | 80 | F | knee dx | 1998 | OB, OP |
| 19F | A | 67 | 159 | 63 | F | hip dx | 2004 | HP, OP |
| 20F | A | 64 | 180 | 92 | M | hip sx | 1998 | HT |
| 21F | A | 69 | 184 | 86 | M | knee dx | 2001 | |
| 22F | A | 59 | 161 | 54 | F | hip dx | 2002 | |
| 1F+T | B | 55 | 188 | 80 | M | hip dx | 2002 | CAR, HT |
| 2F+T | B | 63 | 165 | 79 | M | hip dx | 2001 | CAR, DIA, HT |
| 3F+T | B | 59 | 173 | 80 | F | hip sx | 2000 | OP |
| 4F+T | B | 73 | 169 | 82 | M | hip dx | 1998 | DIA, HT |
| 5F+T | B | 71 | 172 | 91 | M | hip dx | 2003 | DIA, GO, OA |
| 6F+T | B | 65 | 158 | 61 | F | hip sx | 1999 | |
| 7F+T | B | 68 | 171 | 75 | F | knee sx | 1997 | VAR, OA |
| 8F+T | B | 59 | 174 | 59 | M | hip dx | 2003 | |
| 9F+T | B | 71 | 176 | 87 | M | hip dx | 2002 | HT |
| 10F+T | B | 69 | 182 | 89 | M | hip sx | 2002 | |
| 11F+T | B | 67 | 164 | 58 | F | knee dx | 2001 | |
| 12F+T | B | 72 | 164 | 81 | M | knee dx | 2000 | |
| 13F+T | B | 68 | 162 | 49 | M | knee dx | 1998 | CAR, COPD |
| 14F+T | B | 73 | 165 | 70 | F | hip sx | 2002 | |
| 15F+T | B | 61 | 156 | 70 | F | knee dx | 2001 | |
| 16F+T | B | 59 | 184 | 91 | M | hip sx | 2003 | HC |
| 17F+T | B | 72 | 171 | 84 | M | hip sx | 2004 | DIA, HB, HC, HT |
| 18F+T | B | 69 | 187 | 96 | M | hip dx | 2000 | HC, HP |
| 19F+T | B | 67 | 154 | 61 | F | knee dx | 2000 | KB, VAR |
| 20F+T | B | 57 | 167 | 81 | F | knee sx | 2002 | KB, VAR |
| 21F+T | B | 57 | 158 | 81 | F | hip dx | 1997 | DIA, OP, HB |
| 22F+T | B | 54 | 182 | 89 | M | hip sx | 2000 | COPD |
| Group A Mean±SD | | 64.1±5.6 | 168.5±8.7 | 72±11.1 | 11M, 11F | 7 knee, 15 hip | | |
| Group B Mean±SD | | 65 ±6.3 | 170.1±10 | 77±12.7 | 13M, 9F | 7 knee, 15 hip | | |

A: physiotherapy group; B: physiotherapy + drug group; CAR: cardiomyopathy; COPD: chronic obstructive pulmonary disease; DIA: diabetes; GO: gout; HB: hip bilateral; HC: high cholesterolemia; HT: hypertension; KB: knee bilateral; OA: diffuse osteoarthritis; OB: obesity; OP: osteoporosis, VAL: knee valgus, VAR: knee varus.

can help as it suggests that a comprehensive rehabilitation programme can control pain in a subgroup of relatively young OA patients (mean age 65 years) but with severe OA.

The very large number of pharmacological treatments used to treat OA range from NSAIDs and selective COX-2 inhibitors to so-called adjuvants such as antidepressants and others. The World Health Organisation (WHO) has proposed three pain treatment levels depending on pain intensity and response to treatment. Acetaminophen is the main reference level 1 treatment currently used in clinics (13, 14, 21-23), but this level is all too often rapidly exceeded or even not considered because it is thought to be unable to control severe pain. However, as suggested by AAOS (24), OARSI (25) and ESCISIT guidelines (26), this belief has been mainly fostered by the unsatisfactory results obtained when the period of treatment is too short or the dose is inappropriate.

It has also been recently reported that NSAIDs have more effective analgesic activity than acetaminophen (27), although this is only true when the joint disease has a strong inflammatory component because the acetaminophen better analgesic than anti-inflammatory activity. It has been shown that joint inflammation is associated with prostaglandins not only in the periphery, but also in the spinal cord and central nervous system, and that they play a pivotal role in pain-induced functional remodelling of the spinal cord (28, 29). Acetaminophen has very weak anti-inflammatory action, but a very good and recognised antinociceptive effect on central prostaglandins (30). Inflammatory flags are almost always absent in painful OA (13, 14) which suggests that, in such cases, the analgesic effect of acetaminophen is more important than its anti-inflammatory effect. This is supported by the statistically significant reduction in pain intensity observed in this study when pharmacological treatment was combined with a rehabilitation programme.

Our findings also indicate that a comprehensive rehabilitation strategy is useful in reducing pain (Fig. 2). However, this became statistically significant only after the second week of treatment, although it was maintained throughout the study. These findings are of course positive but the comparison of our treatment groups (Fig. 3) showed that the addition of pharmacotherapy led to more rapid and statistically better pain control from the first week of treatment. It is worth noting that both groups share a progressive loss of efficacy over time. Due to this parallel progressive loss of efficacy after an intensive rehabilitation period of three weeks, continuous home based physiotherapy could counteract this progressive loss of efficacy.

Good nursing management before surgery can improve the post-operative outcomes of hip and knee TJR (31)

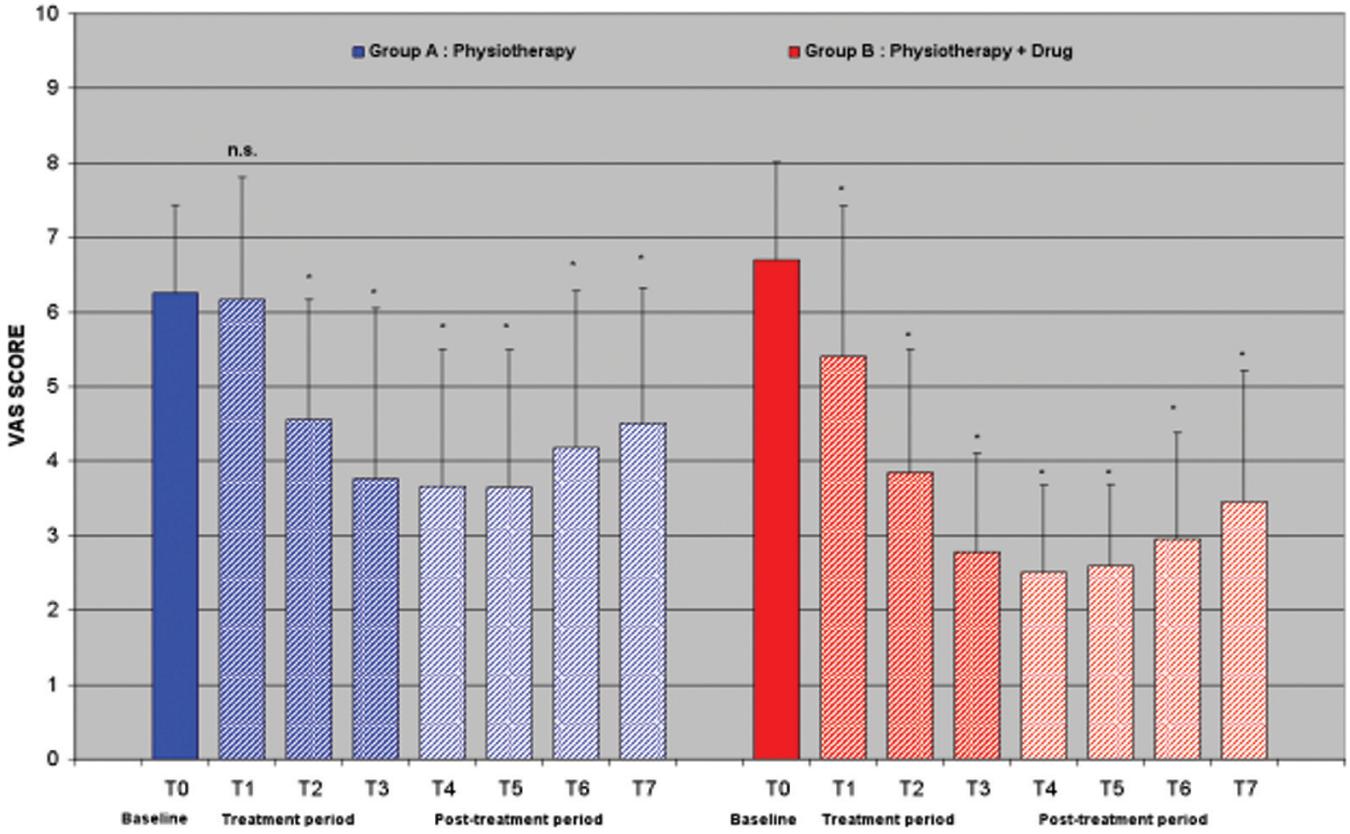


**Fig. 2.** VAS score in the two groups weekly assessed for the duration of the study.
On the top of each bar, statistical significativity *vs*. basal value of group is reported. n.s.: non statistically significative; *: $p<0.001$.

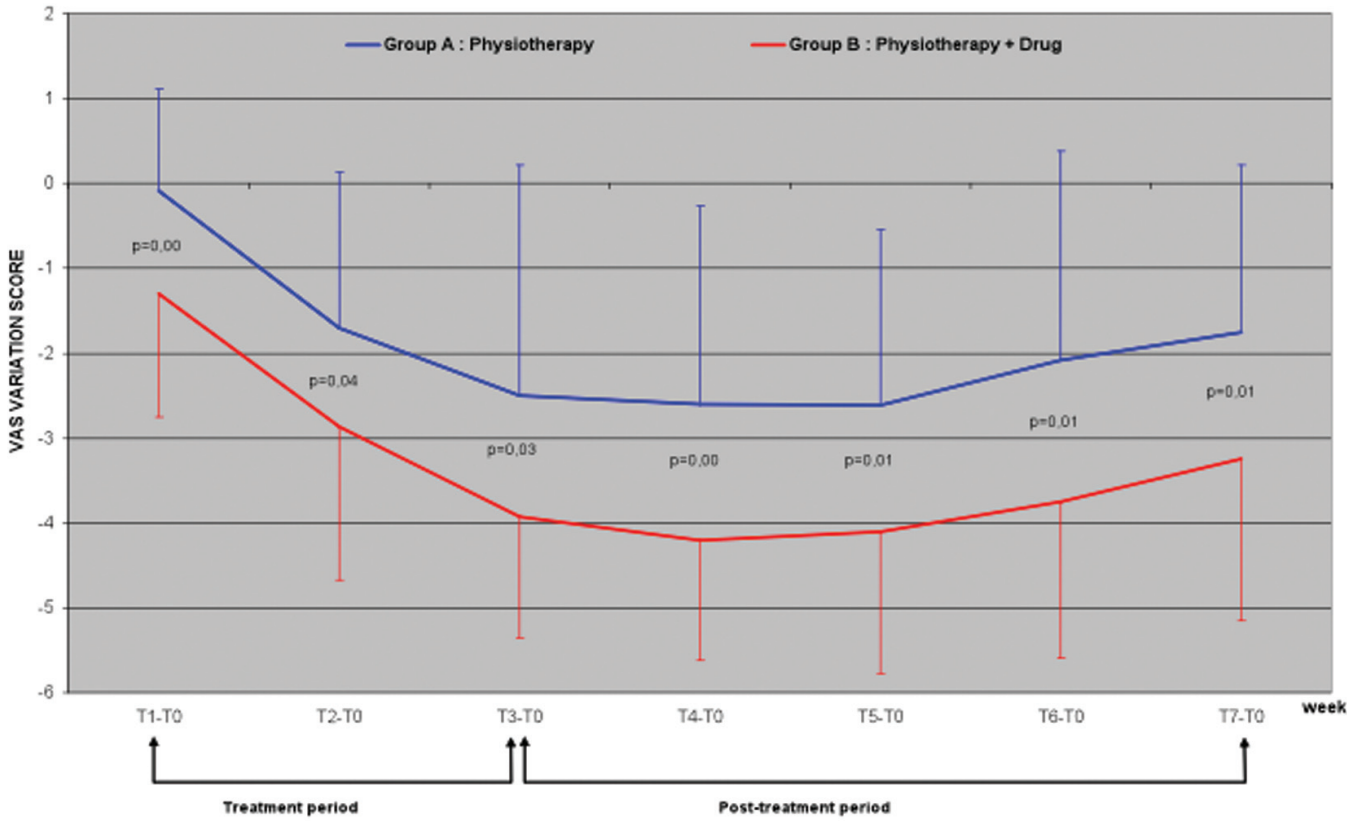


**Fig. 3.** VAS score variations in the two groups. Statistical significance between the two groups is reported.

and, in this context, it is fundamental to achieve the best possible pain control because it has been clearly shown that pre-emptive analgesia and perioperative pain control also improve post-surgical pain (32). Furthermore, NSAIDs and selective COX-2 inhibitors have serious side effects (33-35), whereas acetaminophen is considered safest drug for level 1 pain therapy (25, 36-38). Our results support this view as there were no reported side effects and none of the patients withdrew from the study because of unexpected events. The combination of durable efficacy and lack of side effects enables patients to undergo TJR in better condition without unnecessarily high levels of pain or undesired side effects.

In conclusion, our findings demonstrate that:

1. stand-alone comprehensive rehabilitation can reduce pain even in the case of severe OA in a subgroup of relatively young patients on a waiting list for TJR;
2. the therapeutic efficacy of rehabilitation can last for at least four weeks after the end of the training programme;
3. better pain control can be obtained by integrating the rehabilitation programme with level 1 pharmacological treatment (*i.e.* acetaminophen at a full dose of 3 g/day);
4. pain is reduced earlier and to a greater extent when the two forms of treatment are combined;
5. the combined treatment can allow patients awaiting TJR to pass the pre-surgery period without unbearable and unnecessary pain.

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