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Research article

Intermittent intravenous clodronate in knee osteoarthritis

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Abstract

Aim: This 1-year, longitudinal, open label, randomized, controlled study assessed the clinical effects of intravenous (IV) courses of clodronate versus IV acetaminophen in patients with moderate-to-severe symptomatic knee osteoarthritis (OA).

Method: Outpatients aged 40–80 years, with moderate-to-severe knee OA (Kellgren-Lawrence radiological classification grade II/III) and baseline VAS pain score >50 were enrolled. Patients with steroid/bisphosphonate intake or local infiltrations with steroid or hyaluronic acid in the previous 3 months were excluded. The patients were randomized in a 2:1 ratio to receive IV clodronate 300 mg/day or IV acetaminophen 1000 mg/day, both for 10 days every 3 months for 1 year.

Results: Of 122 patients (females 107, males 15; mean age ± SD, 74.3 ± 5.1 years) 82 received clodronate and 40 acetaminophen. WOMAC total score (mean ± SD) was significantly lower at every time point with clodronate (3 months 70 ± 11.24; 6 months 55.2 ± 21.7; 12 months 33.5 ± 11) versus acetaminophen (3 months 78 ± 11.5; 6 months 66 ± 20.4; 12 months 70.9 ± 20.4; $P < 0.01$ vs clodronate). The Lequesne index and VAS pain scores were also lower with clodronate than acetaminophen ($P = 0.02$ and $P = 0.01$ respectively). No systemic or severe side effects were observed.

Conclusion: Intermittent IV administration of clodronate reduced subjective knee pain effectively and improved functionality in patients with established knee OA. No systemic or severe side effects were observed, suggesting that IV clodronate, at the dosages used, has an excellent safety profile over 1 year with a similar tolerability profile to acetaminophen.

Key words: intravenous clodronate; knee osteoarthritis

INTRODUCTION

Osteoarthritis (OA) is an inflammatory chronic, progressive disease that particularly affects weight-bearing joints such as spine, hips and knees, and is a major cause of morbidity and reduced quality of life.[1]

OA is the most common of the rheumatic disorders and affects the quality of life of millions of people each year.[2, 3] In the US, approximately 10% of adults aged 25 years or older have clinical OA, with a higher prevalence in women, particularly those aged 50 or over, and in older adults.[4] Rates of radiographically defined OA are much higher with about one third of all adults and at least 80% of older adults having OA confirmed by radiography.[4]

OA is associated with an extremely high economic burden due to disability, comorbid disease, cost of treatment and the high prevalence of the disease.[5] The main economic burden associated with OA is related to pharmaceutical treatment, hospitalization for joint replacement surgery, and indirect costs resulting from reduced work-productivity and home-care costs.[5] Moreover, the prevalence of OA is increasing, with the number of patients with OA rising by nearly 30% over the past 10 years, due to an aging population and increased obesity rates.[5, 6]

Historically, OA has been considered a disease of articular cartilage; however, more recent evidence suggests that subchondral bone is also involved in the pathophysiology, in disease initiation and progression,[7] with both erosion of cartilage and remodelling of subchondral bone leading to clinical disease (pain, loss of function and disability). Indeed, these change in the subchondral bone may even occur before cartilage changes in OA.[7] Increased local bone turnover, decreased bone mineral content and stiffness, and decreased trabecular numbers have been observed in subchondral bone in patients with OA compared with healthy individuals.[8] OA is also characterized by the formation of osteophytes (bony outgrowth at the joint margins), synovitis and increased concentration of inflammatory proteins in the synovial fluid.[9] Secondary synovitis may trigger clinical symptoms and further contribute to damage of the cartilage and subchondral tissue and to joint damage in general.[10-12]

OA symptoms are managed using non-steroidal anti-inflammatory drugs (NSAIDs), analgesics and a range of non-pharmacological interventions.[13] However, NSAIDs and acetaminophen are associated with a gastrointestinal and cardiovascular safety issues[14] and do not target the actual disease process itself or prevent the ongoing progressive degradation of cartilage. Therefore, those individuals who fail to gain adequate benefit from medical management and have refractory pain and disability ultimately become candidates for joint replacement surgery.[13]

Bisphosphonates are analogues of inorganic pyrophosphate and inhibitors of bone resorption.[15] Several studies have shown that treatment with bisphosphonates such as clodronate can reduce the pain associated with a range of painful diseases involving the bone.[15-20] In addition, in patients with OA, bisphosphonates have been shown to be effective in improving symptoms and bone and inflammatory markers.[21-23]

Clodronate is a non-aminobisphosphonate currently registered in Europe for treating postmenopausal osteoporosis. Intravenous (IV) clodronate was shown to be effective for treating painful episodes of erosive osteoarthritis of the hands.[24] It has also been shown to reduce synovial fluid concentration of inflammatory mediators and significantly reduce pain in patients with synovitis secondary to knee osteoarthritis.[25] The aim of this randomized study was to evaluate whether patients with painful knee OA can also benefit from treatment with IV clodronate.

METHODS

Study Design

This was a 1-year, open-label, randomized, active controlled study conducted at a single centre – the Rheumatology Unit of the Magenta Hospital in Italy – in an outpatient setting. Patients who fulfilled the inclusion criteria were randomized in a 2:1 ratio into two groups. The patients were randomized to a 10-day course of IV clodronate 300 mg/day or IV acetaminophen 1000 mg/day, both given every 3 months for 1 year. Patients attended the clinic at baseline/screening visit and then for follow-up at 3 months, 6 months and 1 year. During the study period, no intra-articular injections and no substitution or change in the dose of NSAIDs in use at baseline were performed.

The study protocol was study performed in accordance with the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from each participant.

Patients

Patients were eligible for inclusion if they were aged between 40 and 80 years, and had moderate-to-severe knee OA (Kellgren-Lawrence radiological classification grade II or III[26]) and a visual analogue scale (VAS) pain score >50 on a 0–100 mm scale. Patients were excluded from the study if they had a previous diagnosis of rheumatoid arthritis or other connective tissue inflammatory disease, had taken steroid or anti-resorptive drugs such as bisphosphonate intake in the previous 3 months, had received previous local administration of steroid or hyaluronic acid, or had renal, cardiovascular, neurologic, psychiatric or neoplastic disease. NSAIDs were permitted if taken but no variation in dose or frequency was tolerated during the study period.

Study Endpoints

The primary outcome measure of treatment efficacy was the WOMAC consisting of 24 questions to assess pain, stiffness and physical function on a VAS that ranged from 0 to 100, with a lower score indicating improvement (i.e., less pain, less stiffness and less limitation of physical function).[27, 28]

Secondary outcomes included the Lequesne index score for knee osteoarthritis and VAS pain score (0-100 mm). The Lequesne index is a 10-question interview-style survey given to patients with osteoarthritis of the knee. It has five questions pertaining to pain or discomfort, one question dealing with maximum distance walked, and four questions about activities of daily living. The total Lequesne questionnaire is scored on a 0 to 24 scale, with lower scores meaning greater function (less functional impairment).[29-31]

Statistical Analysis

Intention to treat (ITT) analysis was carried out in order to include all the randomized patients within the analysis. This study was planned with one control per two experimental patients. For a Type I error probability of 0.05 and a Type II error probability of 0.1, 64 experimental patients and 32 control individuals were necessary to found a true difference in the experimental and control means of 15 in the WOMAC score.

Power sample size was established with PS software Version 3.0. Descriptive values of the data are presented as mean ± SD; a *P* value <0.05 was considered statistically significant. Statistical differences were estimated by Student t Test for independent or paired samples when needed. General linear model (GLM) with ANOVA for repeated measures was performed when required. Statistical analyses were performed with SPSS 13 for Windows statistical package software.

RESULTS

Patient Disposition and Baseline Characteristics

Out of 265 outpatients screened from January 2010 to July 2010, 122 consecutive patients (females 107, males 15; mean age 74.3 ± 5.1 years) were enrolled and randomized to treatment and comprised the ITT analysis group; 82 patients were randomized to clodronate and 40 to acetaminophen (**Figure 1).** All patients completed the 1-year follow-up.

Patient demographics and baseline characteristics are shown in **Table I**.

Table 1: Patient demographics and baseline clinical characteristics in the intention to treat (ITT) population

NS, not significant; WOMAC, Western Ontario and McMaster Universities Arthritis Index

	Clodronate 300mg (*n* = 82)	**Acetaminophen 1000mg (*n* = 40)**	***P* value**
M/F	13/69	2/38	NS
Age, years mean ± SD	71.4 ± 3.2	69.2 ± 1.8	NS
Weight, kg, mean ± SD	68.1 ± 5.6	72.4 ± 3.7	NS
Height, m, mean ± SD	167.5 ± 15.2	163.3 ± 12.8	NS
WOMAC score, mean ± SD	71.5 ± 11.4	72.2 ± 0.7	NS

Efficacy

IV clodronate was associated with a significantly greater improvement in the primary efficacy measure compared with IV acetaminophen: the WOMAC total score was significantly lower at every time point with clodronate (3 months 70 ± 11.24, 6 months 55.2 ± 21.7, 12 months 33.5 ± 11) compared with acetaminophen (3 months 78 ± 11.5, 6 months 66 ± 20.4, 12 months 70.9 ± 20.4; $P < 0.01$ versus clodronate for all time points) (**Figure 2**).

The Lequesne index and VAS pain score were also lower with clodronate than with acetaminophen at all time points ($P = 0.02$ and $P = 0.01$ respectively) (**Figures 3 & 4**).

Tolerability

No systemic or severe side effects were observed in either group. All patients continued acetaminophen or clodronate for the complete study duration. In general, the administration of clodronate was well tolerated with a predictable and manageable side-effect profile that included mild acute-phase responses resulting in self-limiting, transient (few days), flu-like symptoms (low-grade fever, fatigue, arthralgia or myalgia, nausea, and increased bone pain). No side effects were observed with acetaminophen (**Table II).**

Table 2: Side effects observed in patients receiving clodronate or acetaminophen during the study

	Patients, n (%)	
Adverse event	**Clodronate 300mg (*n* = 82)**	**Acetaminophen 1000mg (*n* = 40)**
Bone pain	12 (14.6)	1 (2.5)
Nausea	1 (1.25)	2 (5)
Fatigue	1 (1.25)	0 (0)
Fever	2 (2.50)	0 (0)
Vomiting	1 (1.25)	1 (2.5)
Myalgia	15 (18.75)	1 (2.5)

DISCUSSION

The findings from this 1-year, open label, comparative study suggest that intermittent IV clodronate is more effective than IV acetaminophen in terms of improving WOMAC, Lequesne and VAS pain scores and was well tolerated in patients with moderate-to-severe OA.

The demonstrated efficacy of clodronate on pain and functionality is not unexpected given the probable involvement of chondrocytes in the pathogenesis of the disease. The aetiology of OA is unclear but increasing evidence suggests that in addition to chondrocyte involvement, synovial activation is also thought to be implicated due to the elevated

numbers of macrophages and inflammatory markers observed in the synovium of many patients – even in those with early OA.[11] Many studies have confirmed the presence of degradation products of cartilage due to local inflammation, particularly the urinary C-terminal cross-linking telopeptides of type II collagen (CTX-II).[32-35]

After administration, clodronate accumulate in the bone and induce phagocytic cell apoptosis, thereby modulating macrophage-mediated production of proinflammatory cytokines and nitric oxide [NO]) and inhibiting matrix metalloproteinases (MMPs).[36] MMPs are known to play a key role in the inflammatory process and cause degradation of the cartilage and radiological joint damage during OA.[37, 38]

Despite some earlier animal models in which some bisphosphonates were demonstrated to have no effect on acute inflammation,[39] clodronate has demonstrated anti-inflammatory and anti-arthritic effects.[18, 40] As a non-aminobisphosphonate, preclinical data suggest that clodronate may have advantages over aminobisphosphonates in terms of increased anti-inflammatory effect.[39] For example, an *in vitro* study showed that clodronate, but not aminobisphosphonate alendronate, was metabolised into the ATP analogue $AppCCl_2p$.[41] The metabolite $AppCCl_2p$ reduce macrophage production of proinflammatory cytokines such as tumour necrosis factor α (TNFα) and interleukins (IL-1β, IL-6), as well as NO.[36, 41] Aminobisphosphonates, on the other hand, appear to have a proinflammatory effect, at least in the short term.[39]

There is some evidence that aminobisphosphonate treatment may reduce cartilage degradation in some patients thereby slowing radiological progression of OA by preserving the structural integrity of subchondral bone.[21] However, data are inconsistent.[23, 42] Large, long-term studies of risedronate in patients with knee OA showed that significantly lower risk of radiographic progression over 2 years was apparent only in patients in whom CTX-II was normalized at 6 months.[23, 43] Clearly, more research is required into the identification of specific patients who will most benefit from bisphosphonate treatment.

Although our study was not designed to show any effect on disease progression, our findings do show that clodronate can provide a marked improvement in pain and functionality in moderate-to-severe OA and these data support those from earlier studies demonstrating the pain-relieving actions of clodronate in arthritis and corticosteroid-induced osteoporosis, erosive osteoarthritis, complex regional pain syndrome type I and osteoporotic vertebral fractures.[16-18, 24]

Limitations of this study include its small open-label design, lack of blinding and absence of radiological outcome measures or specific quality of life assessments.

CONCLUSIONS

Significant reductions in the WOMAC Lequesne and VAS pain scores in patients with knee OA versus acetaminophen demonstrate the analgesic efficacy and improvements in function achieved with intermittent clodronate over 1 year. Clodronate was also well tolerated. These promising data warrant confirmation in larger, controlled, longer-term, blinded, prospective studies on the effects of IV clodronate on osteoarthritic pain and functionality. Studies evaluating the effect of IV clodronate on NSAIDs use, long-term impact on disease progression and subsequent improvement in quality of life in OA should also be undertaken to clarify the role of this agent in the management of OA.

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Figures

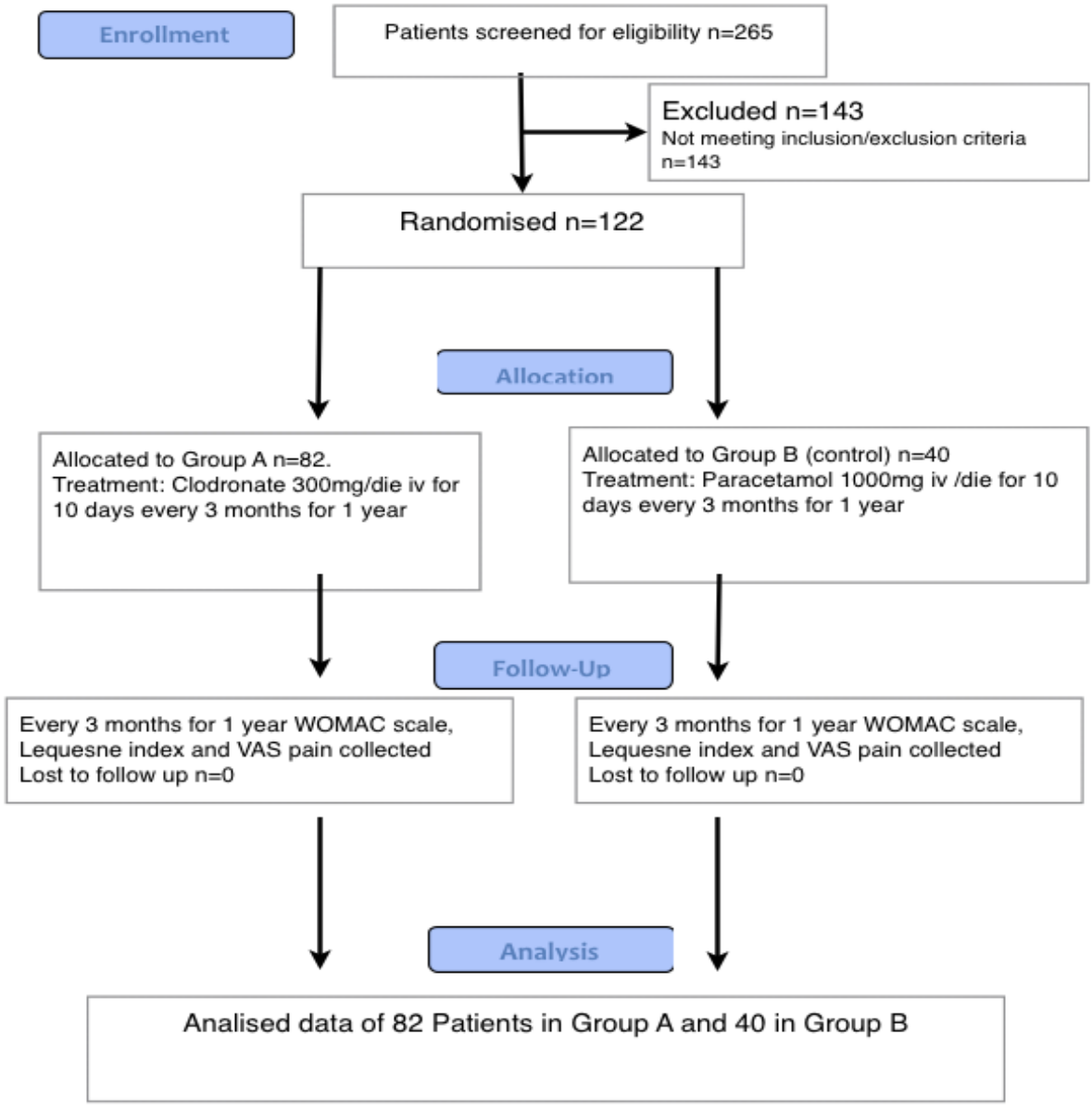

Figure 1: Patient disposition and flow through the study

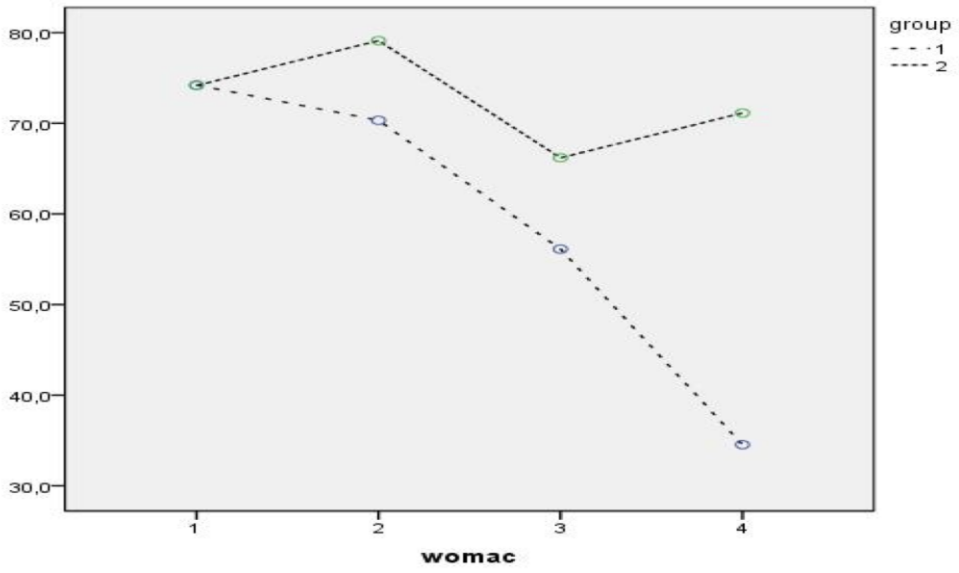

Figure 2: Western Ontario and McMaster Universities Arthritis Index (WOMAC) score in patients with OA treated with clodronate or acetaminophen therapy from baseline to 1 year.

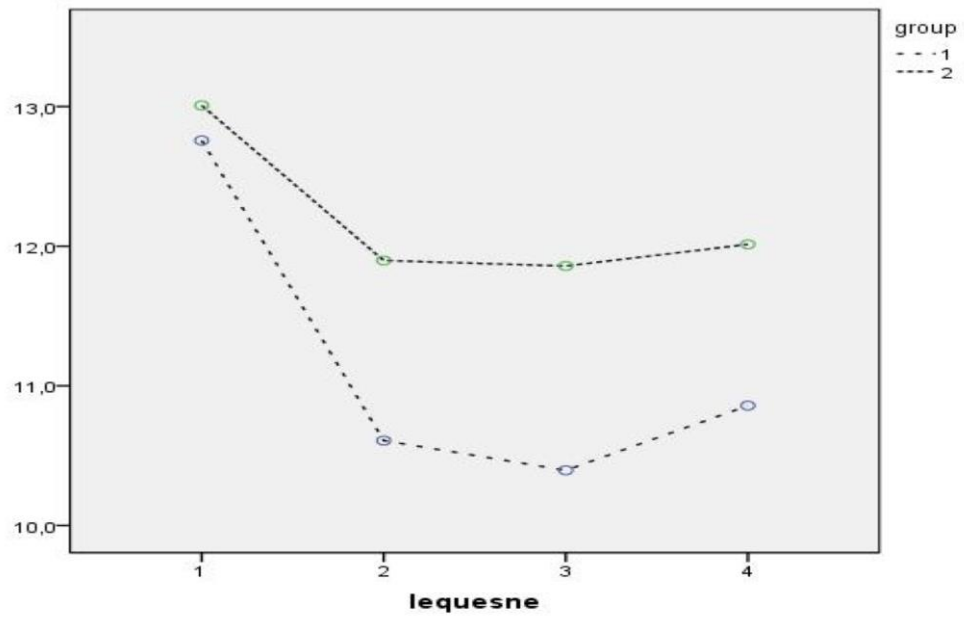

Figure 3: Lequesne index score in patients with osteoarthritis (OA) treated with clodronate or acetaminophen from baseline to 1 year.

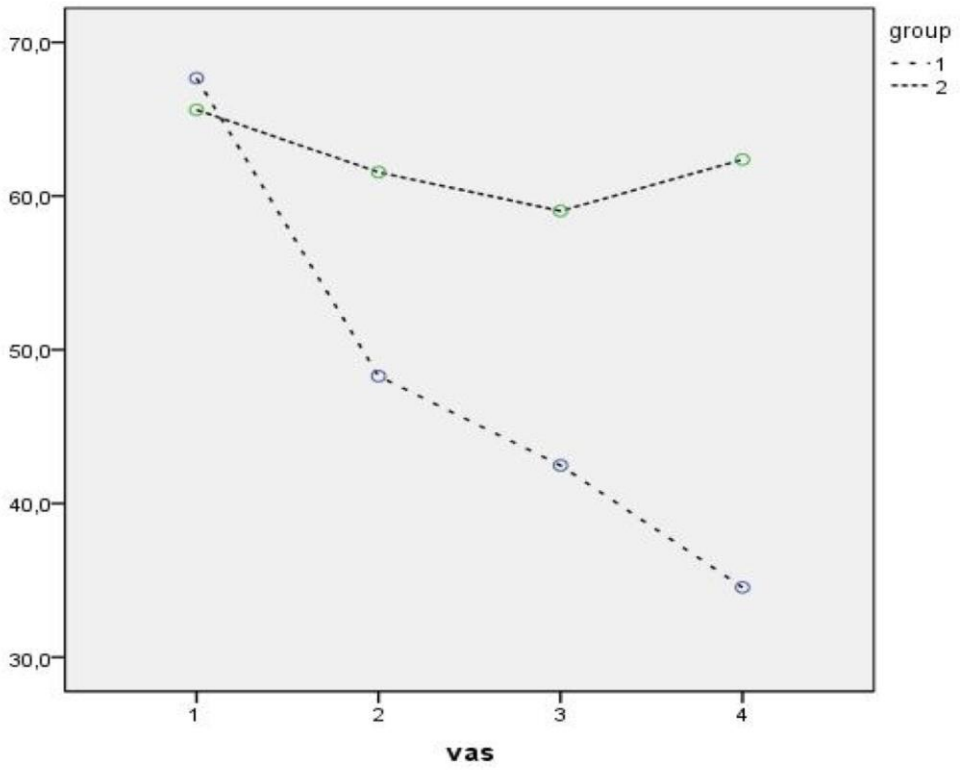

Figure 4: Visual analogue scale (VAS) pain score in patients with osteoarthritis (OA) treated with clodronate or acetaminophen from baseline to 1 year.