

**Research Article**

**Combined therapy in osteoarthritis of the knee, doubleblind  
randomized clinical trial**

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**IRCT Number: IRCT2012102610799N2**

**ABSTRACT**

**Background:** Osteoarthritis is the most common joint disease during which knee joints are affected more than the other joints. Various drugs are used to treat osteoarthritis that each with advantages and disadvantages. The purpose of this study was to compare the efficacy of single and combination of acetaminophen, naproxen and omega-3 with a special focus on knee osteoarthritis.

**Methods:** In a randomized clinical trial, 156 patients with moderate osteoarthritis, in 6 groups of 26 persons with acetaminophen, naproxen, acetaminophen + naproxen, acetaminophen + omega-3, naproxen + omega-3, acetaminophen + naproxen + omega-3 therapy. With acetaminophen 1000 mg was used every 8 hours, naproxen 500 mg every 12 hours and omega-3 1000 mg every 8 hours for 6 weeks. Twelve patients missed the study. Before the start of the treatment and at the end of treatment, we evaluated the results of the treatments using Visual Analogue Scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).

**Results:** Patients pain, physical function, joint stiffness and WOMAC ranking in all treatment groups significantly decreased after the treatment. WOMAC ranking after the treatment between groups was significantly different and triple-drug therapy yielded better results than one-drug therapy.

**CONCLUSION:**

The least cost of treatment is attributed to acetaminophen and the highest cost of treatment is attributed to acetaminophen + naproxen + omega-3. The best results of therapies of knee osteoarthritis was attributed to naproxen + omega-3.

The study showed that adding omega-3 will increase the efficacy, reduce joint stiffness and reduce severity of the side effects of these drugs. The efficacy of omega-3 may be due to anti-inflammatory effect through competitive inhibition of the arachidonic pathway.

**Keywords:** Knee Osteoarthritis, Omega -3, Naproxen, Acetaminophen, Joint Stiffness.

## INTRODUCTION

Osteoarthritis (OA), also known as degenerative joint disease, is the most common knee pathology in older people and the commonest reason for knee pain and disability in this age-group. It is highly prevalent and the leading cause of chronic disability in the elderly (1). The characteristic of knee OA is pain. Joint pain from knee OA is activity-related. Pain comes either during or just after joint use and then it gradually resolves (2). Stiffness of the affected joint may be prominent, but morning stiffness is usually brief (< 30 min). Knee range of motion is restricted and associated with joint crepitation. Knee tenderness may be seen in physical examination. Joint effusion is not common (3). Diagnosis of OA is based on clinical symptoms, physical examination and radiological findings. The radiologic hallmarks of osteoarthritis include decreased joint space, marginal osteophytosis, subchondral cyst formation, and subchondral sclerosis (4). According to diagnostic criteria of the American College of Rheumatology (ACR), if knee pain occurs with osteophyte and at least 1 of 3: age > 50 years, joint stiffness < 30 minutes, and crepitation on active motion of the knee, this diagnostic approach has 91 percent sensitivity and 86 percent specificity in diagnosis of knee OA (5). The treatment of osteoarthritis is usually for controlling symptoms, especially pain, and improving the quality of patient's life. The treatment includes non-pharmacologic treatment, pharmacologic treatment (acetaminophen local or systemic utilization of non-steroidal anti-inflammatory drug(s) (NSAIDs) and intra-articular injection of corticosteroids and hyaluronan products) and surgery. Acetaminophen is considered as the first line of knee osteoarthritis oral treatment in cases having slight to average pain (6). Some studies have shown that a NSAID has a more efficient effect on controlling knee osteoarthritis pain, than acetaminophen. On the other hand, some other studies have not shown any meaningful difference between acetaminophen and some NSAIDs in controlling

osteoarthritis disease (7, 8, 9, 10, 11). Although, these common treatments are effective in reducing osteoarthritis symptoms, but the control of the disease by these drugs, especially NSAID(s) is accompanied by serious complications such as gastrointestinal bleeding and cardiovascular complications (6). The utilization of natural complements having less complication, such as omega-3 and glucosamine can be one of the proper ways of controlling osteoarthritis. Omega-3 contains unsaturated fatty acids which have powerful regulatory features on immune system and beneficial effects on cardiovascular system. In addition, several clinical and experimental studies have shown anti-inflammatory effects of omega-3. In these studies, the use of omega-3 in the treatment of chronic inflammatory disease has caused a decrease in the function of the disease and a lower dosage need of anti-inflammatory drugs (12). It has been also shown that, omega-3 has obvious anti-inflammatory effect in some disease such as rheumatoid arthritis, ulcerative colitis and dysmenorrhea (13). There is not complete study on the effect of omega-3 in the treatment of osteoarthritis. However, it is stated in a research that, the addition of omega-3 to glucosamine has caused a better improvement than glucosamine alone, in patients with knee osteoarthritis (14). According to the rule of inflammatory processes in the incidence of osteoarthritis and beneficial features of omega-3 on the immune system, especially its anti-inflammatory effects and also the contradictions in the comparison of acetaminophen effectiveness with NSAIDs in controlling osteoarthritis. The aim of this study was to compare the effect of acetaminophen and naproxen as NSAID(s) and combinational usage of these drugs, single or combined with omega-3, in controlling the symptoms of knee osteoarthritis. The WOMAC and VAS have been used to measure the physical functions, morning stiffness and pain during and at the end of the treatment.

## MATERIALS AND METHODS

In this double blind randomized clinical trial study (With the international RCT number: IRCT2012102610799N2), the patients aged 45 to 65 having referred to Yasuj's Shahid Mofateh Clinic with knee pain were examined. The inclusion criteria were:

1. The level of pain more than 3 on visual analogue scale.

2. Radiologic scale of 2-4 on the Kellgren & Lawrence scale (15)

The informed consent was given before the start of the treatment. History and physical examinations were performed. On the account of having possibilities of entering the research and tendency for cooperation, anterior and lateral radiography views of the knee was performed.

If OA of knee was confirmed by the radiographic findings and clinical symptoms, then the patients were randomly classified in 6 groups. Finally, 156 patients in 6 groups were treated from which 12 patients were excluded due to complications and personal issues. Each group was treated for 6 weeks and wash out period of 4 days.

Criteria diagnoses of knee OA are based on American Association of Rheumatoid Standards. VAS must be more than 30 millimeters. Pain intensity in knee OA were measured by VAS and WOMAC. The WOMAC index which is used to assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis. The WOMAC consists of 24 items divided into 3 subclasses:

1-Pain (5 items): during walk, using stairs, in bed, sitting or lying, and standing

2-Stiffness (2 items): after first walk, later in the day

3-Physical function (17 items): stair use, rising from sitting, standing, bending, walking, getting in/out of a car, shopping, putting on/talking off socks, rising from bed, lying in bed, getting in/out of bath, sitting, getting on/off toilet, heavy household duties, light household duties (21).

In every item, the choices include:

0-None 1-Mild 2-Moderate 3-Severe 4-Extreme  
Scale lengths of every subclass are: A-Pain 20(5\*4) B-Stiffness 8(2\*4) C-Physical function 68(17\*4). The sums of these scale lengths are 96. There are high scale lengths of WOMAC, indicated low health status (high severity of disease) (16).

The validity and reliability of the Persian versions of WOMAC Osteoarthritis Index in Iran was done by Naderian et al in 2012. In this study, Cronbach's alpha coefficients and interclass correlation efficiencies for WOMAC OA index ranged from 0.63 to 0.94 (17).

Treatment groups were: 3000 mg acetaminophen (500mg tablets made by Chimidaru Company, 2 tablets every 8 hours) day was given to Group 1, 1000mg naproxen (500mg tablets made by ParsDaru Company, every 12 hours) to the Group 2, naproxen (500mg every 12 hours) and omega-3 (1000mg tablets made by Zahravi Iran Company, every 8 hours) to the Group 3, acetaminophen (1000mg every 8 hours) and omega-3 (1000mg every day) to the Group 4, acetaminophen (1000mg every 8 hours) and naproxen (500mg every 12 hours) to the Group 5, and acetaminophen (1000mg every 12 hours) + naproxen (500mg every 8 hours) + omega-3 (1000mg every 8 hours) were given to the Group 6.

We measured the pain severity by visual analogue scale and joint stiffness, physical functions and pain severity of patients by WOMAC before and after the treatment.

Inclusion criteria included patients having idiopathic knee osteoarthritis which aged 45 to 65 and had moderate knee pain, pain more than 30 millimeters by visual analogue scale and radiologic index of 2-4 by Kellgren-Wellander Scale.

Exclusion criteria were rheumatoid diseases, infectious arthritis, previous articular damage, old knee bones fractures and other articular abnormalities, overuse of alcohol, hepatic failure, heparin use, steroid use during the past 2 months, use of oral steroid in 8 days, gastrointestinal bleeding, renal failure, pregnancy or breast

feeding, allergy to drugs used in research, severe pulmonary insufficiency, knee prosthesis or knee surgery during the past 3 months. The data was collected by data registry forms and history recording method. Physical examination of the cases by a physiatrist and knee radiographies were reported by a radiologist.

For the final diagnosis of knee OA in the study, diagnostic criteria of ACR were used. Data were coded and entered in the computer and analyzed using SPSS software, version 21 and the use of one-way variance test and post-hoc Turkey's test. This study was conducted by the international Clinical Trial Number (IRCT number: IRCT2012102610799N2).

Overall, 166 patients entered the study from which 156 finished the treatment and 12 persons missed the treatment due to personal problems. In the end, patients were taken under treatment in 6 groups for 6 weeks.

**RESULTS**

The 156 patients participating in the study were classified into 6 groups, 144 patients continued the treatments and 12 patients left the study. The 36% were male, and 64% were female. WOMAC ranking and pain, physical function, stiffness was significantly different in the 6 groups before and after the treatments ( $p < 0.05$ ). WOMAC ranking were significantly different in the 6 groups after the treatments ( $p < 0.05$ ). But, the difference between pain, physical function, stiffness was not significant in the 6 groups after the treatments ( $p < 0.05$ ). The comparison of every two groups, revealed that WOMAC ranking was significantly different between the single treatment and two and three drug therapies (Table 1). Additive omega-3 causes a decrease in WOMAC ranking in all groups, but leads to a significant decrease in the three drug therapy. The highest complications among the treatment groups was gastrointestinal upset which was seen in two drug therapies.

**Table 1-**The comparison of WOMAC ranking in the 6 groups after the treatment

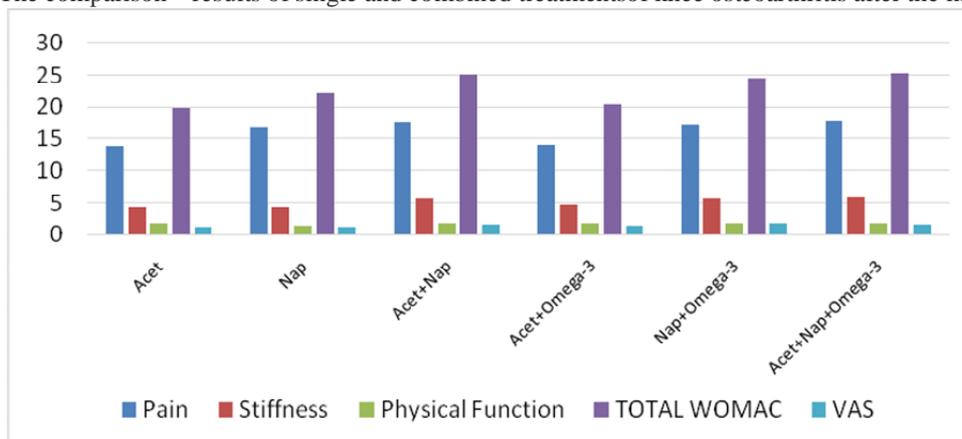
Acet.-Nap-Omega	Nap- Omega	Acet.-Omega	Acet.-Nap	Nap	Groups
10.45 0.043*	8.65 0.096	9.56 0.083	5.4 0.225	Dif:5.12 Sig:0.25	Acet.
13.76 0.032*	4.98 0.146	8.23 0.091	5.12 0.233	-----	Naproxen
7.56 0.101	8.64 0.172	10.12 0.071	-----	-----	Acet.-Nap
10.02 0.122	5.48 0.416	-----	-----	-----	Acet.-Omega
10.94 0.117	-----	-----	-----	-----	Nap- Omega

$P < 0.05$  \*

According to the results, pain severity, physical functions, joint stiffness and WOMAC score of the patients before and after the treatment was significantly different in all 6 groups.

But joint stiffness of the patients in the groups receiving omega-3 in their medications was meaningfully different than the single medication groups or groups who did not use omega-3 ( $P < 0.05$ ) (Table 2).

**Diagram 1-**The comparison results of single and combined treatments of knee osteoarthritis after the interventions.



**Table 2-** The comparison rankings result of the treatments and cost in the 6 groups

*Rank Cost of treatment	Ranks of treatment	** The sum of Ranks of treatment	Score of VAS	Score of WOMAC	Physical function WOMAC	Stiffness WOMAC	Pain WOMAC	Treatment
1	5	12	(3)1.25	(3)19.9	(1)1.79	(3)4.2	(2)13.9	Acet.
2	4	11	(3)1.21	(2)22.1	(2)1.46	(3)4.2	(1)16.69	Nap.
3	2	6	(2)1.53	(1)25.1	(1)1.78	(1)5.7	(1)17.5	Acet.+Nap.
4	3	10	(3)1.34	(1)20.5	(1)1.7	(2)4.6	(2)14	Acet.+Omega
5	1	5	(1)1.71	(1)24.5	(1)1.69	(1)5.6	(1)17.2	Omega+Nap.
6	2	6	(2)1.56	(1)25.4	(1)1.7	(1)5.8	(1)17.7	+Acet.+Nap. Omega

**DISCUSSION AND CONCLUSION**

Many studies are carried out to compare the effects of acetaminophen and naproxen (as a NSAID) in several countries which had different and sometimes contrasting results (7, 8).

This study compares the results of different treatments to detect an effective treatment. Combined treatment of naproxen and omega-3 yielded the best treatment result and acetaminophen had the best cost-effective treatment.

In this study, there were a meaningful decrease in physical functions, pain severity, joint stiffness, WOMAC score and visual analogue scale (pain severity from 10), after the treatment in comparison to before it in all groups. And this shows that all the treatments were effective in controlling osteoarthritis disease of the knee. This result is consistent with Altman et al (2000) and

Nisha et al (2000), who say that acetaminophen is the first drug for knee or femur osteoarthritis patients which can be used with dosage of 1gr, 4times a day(18,19).

Naproxen also had effective role in controlling knee osteoarthritis. This is agree with Harrison,s study ,which found that NSAIDs are the most common drugs for treating the pain of osteoarthritis (1).It also conforms to Shiff et al (2004) study which argue that, naproxen relieves the pain of osteoarthritis compared to the placebo(20).In the clinical trial of Bradly et al (1992), no difference was seen between response to acetaminophen and ibuprofen in patients having joint stiffness with joint inflammation signs(7). In Altman et al, (1999) study, acetaminophen and ibuprofen were equally effective in patients having slight to average pain due to joint stiffness. However, ibuprofen preceded acetaminophen in the

treatment of severe knee pain(8). It is also shown that diclofenac, as an NSAID has performed better at severe levels of disease than acetaminophen in sedating pains and improving knee joint functions, However, there was no difference between these two drugs at the low levels of the disease (11). The results of this study slightly conform to these studies. Like Bradley's study, this research shows no difference between the medication effect of acetaminophen and ibuprofen (7). On the other hand, these results partially conform to Altman and Pincus's, in a way that at the low levels of the disease, there was no difference in the effectiveness of acetaminophen and diclofenac in Pincus's study (7) or ibuprofen in Altman's study. The reason for the lack of a complete match between researches is the slight, average and severe levels of the disease.

In this research, the results of physical functions, pain severity, joint stiffness, WOMAC score and visual analogue scale (after the treatment) showed more decrease by combinational medications with omega-3. But it did not show any statistically meaningful difference, that demonstrates the complementary effect of omega-3 in the treatment of knee osteoarthritis. There is no complete study of omega-3 effectiveness in the treatment of osteoarthritis. However, it is stated in a research that adding omega-3 to glucosamine sulfate improves the symptoms in knees and hips (morning stiffness, pain) higher than glucosamine alone (14). Also in another research, the addition of omega-3 as complementary to NSAID was effective in neck and back pain(21). In an in vitro model of cartilage inflammation, therapeutic potential of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) were examined. The results support the hypothesis that EPA and DHA are anti-inflammatory through competitive inhibition of the arachidonic pathway. The efficacy of these compounds is likely to be even greater at more physiologic levels of IL-1B. We suggest that EPA and DHA, particularly EPA, have exciting therapeutic potential for

preventing cartilage degradation associated with chronic inflammatory joint disease (22). In rheumatoid arthritis, many studies report improvements in morning stiffness and joint tenderness with regular intake of fish oil supplements for up to three months(23).

This observation may be the first study which observes the effect of omega-3 in combination with acetaminophen and naproxen on knee osteoarthritis. Also, considering that osteoarthritis is more prevalent among the elderly and noticing the beneficial effect of omega-3 on cardiovascular and immune system of human body, especially among the elderly, the use of omega-3 as a complement in the treatment of knee osteoarthritis and acetaminophen and naproxen as the main medication is suggested.

The highest incidence of complications across all treatment groups are gastrointestinal disorders, which is agree with other studies such as Golden et al(24).

#### ACKNOWLEDGEMENTS

Researchers are grateful to the Research Council of Medical Faculty of Yasuj University of Medical Sciences, people participating in the project, management, and Shahid Mofateh's staffs.

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