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Full Length Research Paper

Evaluating the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis

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The present study was aimed to evaluate the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis. 204 patients with knee osteoarthritis were enrolled in a randomized clinical trial. After a 1-week washing period, the groups received ginger extract (103 cases) or placebo (101 cases). A responder was defined by a reduction in pain of > 15 mm on a visual analog scale (VAS) or by 20% reduction in the mean score of each index of the Western Ontario and Mc Master Universities (WOMAC) criteria after 6 weeks. Pain reduction according to VAS was more significant in ginger group than placebo ($p<0.05$). Although pain reduction according to WOMAC was greater in ginger than placebo group, the difference was not statistically significant. Reduction in morning stiffness and difficulty were statistically greater in the ginger than the placebo group ($p<0.05$). Also there was no difference between the two groups in side effects of therapy. In conclusion, the results showed that ginger extract is effective in reducing pain, stiffness and difficulty in patients with knee osteoarthritis, therefore is recommended as a safe drug for these patients.

Key words: Osteoarthritis, ginger, pain, stiffness, knee, randomized clinical trial, human.

INTRODUCTION

Osteoarthritis (OA) is the most common articular disease and an important cause of pain and disability in most countries (Nisha, 2001; Felson, 2006). Nowadays, the therapy for OA is focused on controlling the symptoms, since there is no established cure for the disease (Hochberg et al., 1995; Pendleton et al., 2000; Lozada and Mustafa, 2001). Although many medical programs and drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) have been evaluated on controlling the symptoms, they often showed adverse side effects. Therefore many researches still continue to find drugs or modalities with fewer side effects and significant improvement in the symptoms. Zingiber, a species of Zingibraceae family (also called gingers) (Trease GE and WC 1983) is one of the most commonly used herbal supplements. Its medical effects have been shown since ancient times. For example, it has been used for more than 2000 years in China to help treat stomach upset, nausea, vomiting and diarrhea (Altman, 1992; Ali et al., 2008). It has also been shown to be effective in relieving symptoms of osteoarthritis (Altman et al., 1986; Srivastava and Mustafa, 1992; Bliddal et al., 2000; Wigler et al., 2003; Frondoza et al., 2004; Chrubasik et al., 2007; Ali et al., 2008), the mechanism of which is suspected to be via anti-inflammatory properties by inhibiting the activation of tumor necrosis factor alpha (TNF-α) and cyclooxygenase expression (Altman RD 2001; Frondoza et al., 2004; Ali et al., 2008). Since studies evaluating the effects of ginger on osteoarthritis-related symptoms have had mixed results, this double–blind, placebo–controlled

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clinical trial study was designed to evaluate the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis (OA).

MATERIALS AND METHODS

Patients with knee OA in concordance with the American College of Rheumatology classification criteria, using the decision tree format that includes radiographs (Grznna et al., 2005) and with knee pain on standing that was between 40 mm and 90 mm on a 100 mm visual analog scale (VAS) (Wewers and Lowe, 1990) during the last 24 h, who had referred to the rheumatologic clinic of Imam-Ali hospital of Zahedan from September 2006 to may 2008, were assessed for eligibility in the study. The exclusion criteria were: age less than 18 years, rheumatoid arthritis, fibromyalgia, gout, recurrent or active pseudo-gout, cancer or other serious diseases, signs or history of liver or kidney failure, asthma requiring treatment with steroids, treatment with oral corticosteroids within the prior 4 weeks, intra-articular knee depo–corticosteroids within the previous 3 months, intra-articular hyaluronate within the previous 6 months, prior treatment with immuno-suppressive drugs within the previous year, significant injury to the knee within the previous 6 months, fever > 38°C, and those with diseases of hip or lumbosacral joint and refusal to participation. Three hundred and twenty patients meeting the above criteria were enrolled in the study and randomly were allocated into 2 groups of 160 patients, being matched in age and gender. They were provided with an oral and written informed consent form. University review board approved study. After a 1-week washout period for anti–inflammatory and analgesic medications, the 2 groups were given 1 capsule of ginger called zintoma or placebo (twice daily) for 6 weeks, respectively.

The zintoma capsules contained 250 mg of powdered ginger (from *Zingiber officinale*, Zingibraceae) and the placebo capsules, being matched with the zintoma capsules, contained starch (Gol–daru drug manufacturer, Isfahan, Iran). Since ginger powder was covered with the capsule layer, the patients could not get aware of the smell or color of the powder. It must be mentioned that a resident of internal medicine who was blind to the kind of capsules gave the drug or placebo to the patients. Patients were permitted to take acetaminophen (not from a special manufacturer) up to 4 g/day and aspirin as anti-coagulation up o 325 mg/day during the whole study. The patients were also advised to use the minimum numbers of stairs during their daily activities. Furthermore, some kinds of knee exercises were taught to all patients and they were recommended to perform the knee exercises 3 times a day, each time including 15 repetitions of each exercise.

Patients were visited and assessed at the beginning of the study and after 6 weeks. The efficacy parameters were: 1) experiencing at least 15- mm reduction in knee pain between baseline and the final visit on standing during the preceding 12 hours and after walking 50 meters, as measured by a 100mm VAS, 2) experiencing at least 20% reduction in the mean score of any index of the Western Ontario and Mc Master universities (WOMAC), including pain, stiffness and difficulty (each index was given 1 to 4 points according to its severity) (Bellamy et al., 1988). They were also asked about their daily performance of the exercises they learned. If they performed the exercise program 3 times a day, their performance quality was assumed to be complete. If they performed it 2 times or only once a day, they were classified as moderate or minimal exercise performance quality, respectively. Data were gathered and analyzed using the SPSS (version 13) and STATA (version 8) software. For monovariate analysis Fischer exact test, chi-square test, independent and paired t-tests, Pearson's correlation coefficient and odds ratio were used. All analysis was performed with a minimum significance level of 5%. For multivariate analysis logistic regression was used. To select a model the backward elimination procedure was used. Asymptomatic standard errors were used to find confidence intervals for parameters in the model.

RESULTS

In total, 320 patients were firstly enrolled in the study, of which 116 patients were lost during the follow up period due to non-compliance to treatment or not coming for further evaluation or due to taking non steroidal anti-inflammatory drugs (NSAIDs). 204 patients completed the study. No patient was excluded due to side effects of the drug. There was also no significant difference in age, gender, body mass index (BMI), smoking, duration of pain, VAS on standing and after 50 meters walking and in WOMAC indexes between those who did not complete the study and those who completed it. 103 patients were enrolled in the ginger and 101 patients in the placebo group, respectively. The mean age was 48.4±11.1 in the ginger group (ranging from 38 to 75 years) and 45.74±12.5 in the placebo group (ranging from 37 to 73 years). There were 20 male and 83 female patients in the ginger group and 20 male and 81 female patients in the placebo group. BMI was 25.6±2.4 and 25.2±2.4 in the ginger and placebo groups, respectively.

There were also no significant differences between the remaining patients of the two groups in VAS and WOMAC indexes at the beginning of the study (Table 1). After the 6^{Th} week, the groups showed significant differences in VAS and WOMAC indexes, when compared with each other (Table 2).

According to VAS (100 mm), pain reduction was significantly greater in the ginger group, both on standing (OR = 1.76) and after 50 meters walking (0R = 2.054) ($P<0.05$). WOMAC indexes also showed greater improvement in the ginger group in pain (OR = 2.56), stiffness (OR = 2.01) and difficulty (OR = 2.56), when compared with the placebo group after the 6^{th} week of treatment ($P<0.05$). 60 patients took acetaminophen during the study with the maximum amount of 2 g/day and the mean amount of 1g/day, of which 36 patients were in the ginger and 24 were in the placebo group, but there was no difference between the two groups in taking acetaminophen. Furthermore, by excluding those patients who had taken acetaminophen, no difference was found in the results of the study while comparing the two groups (Table 3).

Pain reduction was less prominent while taking acetaminophen alone compared with ginger plus acetaminophen. The results showed that although acetaminophen improved pain, but it had no effect on the final results of comparing the 2 groups. In total, 11.3% of patients did not do any exercise, including 8.9% of the placebo and 13.6% of the ginger group. Minimal exercise performance was noted in 34.7 and 35% of the placebo and the ginger group, respectively. 16.8% of the placebo and 17.5% of the ginger group performed the exercises

Table 1. The mean duration of OA and the VAS and WOMAC indexes in the two groups at the beginning of the study.

Variables	Ginger extract (mean (±S.D) n = 103	Placebo (mean ±S.D) n = 101	P-value
Duration of OA* (years)	3.9 ± 5.5	3.5 ± 4.4	0.555
VAS** (100 mm) on standing	57.3 ± 15.2	58.1 ±14.7	0.517
VAS (100 mm) after 50 m walking	59.8 ± 16.0	61.2 ± 16.5	0.584
Pain	2.9 ± 0.5	2.9 ± 0.5	0.546
Stiffness	2.1 ± 0.7	2.0 ± 0.6	0.440
Difficulty	2.6 ± 0.4	2.60 ± 0.5	0.652

*OA: osteoarthritis, ** VAS: visual analog scale.

Table 2. Results of secondary parameters in the intent to treat analysis.

Parameter time point	Mean	Placebo (n = 101)		Ginger extract (n = 103)		Change	Between group differences	P-value
		S.D	Change	Mean	S.D			
VAS (100 mm) on standing	58.1	14.7	-13.3	57.3	15.2	-18.6	5.3	0.008
Baseline 6th week	44.8	18.6		38.7	18.5			
VAS (100 mm) after walking 50 m	61.2	16.5	-14.7	59.8	16.0	-20.3	5.7	0.012
Baseline 6th week	46.5	18.8		39.4	16.6			
WOMAC (pain)	2.9	0.5	-0.4	2.9	0.5	-0.6	0.2	0.066
Baseline 6th week	2.4	0.7		2.2	0.8			
WOMAC (stiffness)	2.0	0.6	-0.1	2.1	0.7	-0.3	0.2	0.003
Baseline 6th week	1.8	0.6		1.4	0.6			
WOMAC (difficulty)	2.6	0.5	-0.3	2.6	2.0	-0.5	0.2	0.003
Baseline 6th week	2.2	0.6		0.4	0.6			

*WOMAC: western Ontario and Mc Master Universities criteria.

moderately and 39.6 and 34% performed the complete exercise program in the placebo and ginger group, respectively. Logistic regression analysis of multi-variables showed physical activities to be effective in reducing pain and difficulty, but not on reducing stiffness.

Our results also showed that pain reduction was related to the duration of the disease. Those with OA lasting for more than 3 years showed little improvement in pain (P-value = 0.152; independent sample t-test). Besides, results of VAS and WOMAC indexes did not show any relation with age, gender and smoking after the 6th week (P-value > 0.05 in all instances). There was no significant difference between the two groups

Table 3. Results of secondary parameters in the intent to treat analysis after excluding those who had taken Acetaminophen.

Clinical variable	Improvement by treatment	Ginger (%)	Placebo (%)	OR* (95% CI)	P-value
Pain	Positive	44 (65.67)	34 (44.16)	1	0.010
	Negative	23 (34.33)	43 (55.84)	2.43 (4.76-1.23)	
Stiffness	Positive	30 (44.7)	20 (25.9)	1	0.018
	Negative	30 (44.7)	57 (74.1)	2.31 (4.66-1.15)	
Difficulty	Positive	43 (64.1)	29 (37.6)	1	0.002
	Negative	24 (35.8)	48 (62.3)	2.98 (5.85-1.50)	

* OR: Odd's Ratio.

in side – effects and the most common were dyspepsia and heart burn (7 cases in the placebo group and 5 in the ginger group).

DISCUSSION

Knee osteoarthritis is a progressive disease and the fourth and the eighth cause of disability in women and men, respectively (Murray and Lopez, 1997). Medical treatments frequently have serious complications (Long et al., 2001). Gastrointestinal complications of non-steroidal anti-inflammatory drugs lead to mortality in some patients (Long et al., 2001). More Than 200 anti-inflammatory drugs have been evaluated for treating OA, but each has minimal to severe side effects (Wigler et al., 2003). Therefore, it seems better to evaluate those drugs, which both improve the symptoms and have little side effects. So ginger has been evaluated in the present study. Our results showed ginger to be more effective in reducing knee pain on standing and immediately after walking 50 meters, and also more effective in improving WOMAC indexes, comparing with placebo ($P<0.05$). In a report by Altman and Marcussen (2001) on 247 patients with knee OA, 63% of patients receiving ginger and 50% of patients receiving placebo reported reduction of knee pain on standing ($P<0.05$) (Altman et al., 1986). Our results showed reduction of pain in 50.5 and 36.6%, respectively ($P<0.05$). In the mentioned study, WOMAC indexes improved in the ginger group more significantly and Stiffness showed the highest degree of improvement, but our study showed the least improvement in stiffness.

In a cross-sectional double-blind clinical trial performed by Bliddal et al. (2000), the effects of ginger, ibuprofen and placebo on patients with knee OA in whom the mean duration of the disease was 7.7 years, were compared together. The study reported ginger and ibuprofen to be more effective than placebo during the first stages of the trial, but there was no significant difference between the two drugs and placebo at the end of the study (Bliddal et al., 2000). In Mustafa and Srivastava's study 1992, 28 patients with rheumatoid arthritis, 18 Patients With osteoarthritis and 10 patients with muscular complaints were given ginger at the dose of 1 to 2 g for 3 months to 2-5 years. 55% of patients with OA reported reduction in pain and 50% reported reduction in articular swelling (Srivastava and Mustafa, 1992).

Wigler et al. (2003) found ginger to be significantly more effective than placebo in reducing pain in patients with OA, according to VAS.In our study, the severity of destructive changes in knee joint and the amount of improvement after treatment were not evaluated and the knee X-Rays were just used to establish the diagnosis and ruling out the other diagnoses causing knee pain. However, the severity of articular destruction may play a role in the amount of improvement after treatment.Some of the other interfering factors are those diseases in association with OA, which can cause knee pain. Although we tried our best to get sure that the pain had been raised from knee OA, it is possible that those conditions might have been missed in some cases and not found by physical examination and X-rays.

WOMAC is one of the most sensitive approaches used is evaluating knee OA and is widely used in clinical trials (Wolfe F, 1999). In 1999, Wolfe showed that most patients with OA had some musculoskeletal complaints, especially low back pain, and some had non musculoskeletal complaints such as fatigability and depression, which can interfere with the results of WOMAC test (Wolfe F, 1999). Therefore it is essential to interpret the results with caution (Laurent et al., 2006). One of the non-medical treatments for OA is reassuring. Maintaining a regular contact with the patient, for example via telephone has been shown to have some effects in reducing pain (Laurent et al., 2006). In our study, we did not contact the patients and were not aware of their socio-economic conditions during the treatment course. These may interfere with the results of our study.

The durations of our study and some other previous studies were 6 weeks. We did not evaluate the effects after 6 weeks. Of course, the results will be more realistic if the evaluating period lasts longer. Many studies have shown physical exercise and changing life-style to be of the essential treating methods. Also muscular weakness is directly correlated with the severity of pain (Felson, 2006). The combination of exercise and weight loss (mean 4.6 kg) has been shown to be effective in relieving

pain (Felson, 2006). In our study, exercising was effective in relieving pain according to both VAS and WOMAC indexes (except for morning stiffness) independent of ginger consumption ($p<0.05$). Therefore the improvement found in the placebo group can be mostly attributed to physical exercises.

Patients were informed about physical exercise and how to reduce the pressure on the joints, but we could only assess the amount of daily exercises by questionnaires and could not assess their perseverance on other recommendations such as the number of stairs they went up or down each day. These could also affect our results. The patients' jobs and their daily activities are also shown to be effective on the results (Felson, 2006), but we did not assess their jobs. Giving a fixed dose of the drug to all patients, without paying attention to the weight may also be important in interpreting the results. We believe that the differences between our results and the previous studies are mainly due to the differences in the duration of the disease, the amount of physical exercises by the patients, the extent of articular destructions at the beginning of the study, their perseverance on the recommendations, the dose of the drug and other diseases causing knee pain.

During our study, those patients with the less duration of the disease showed more improvement. So we can conclude that if the treatment is started earlier in the course of the disease and before the formation of complete knee joint destruction, the results will be much better, although serial imaging is necessary to confirm it. NSAIDs are of the drugs being widely used in OA. They have established gastrointestinal side effects, being sometimes dangerous, especially in elderly (Bliddal et al., 2000). Ginger-related side effects are minimal and include dyspepsia, heartburn, diarrhea, and mouth and throat irritation (Frondoza et al., 2004), but ginger had no important side – effects during our study. Regarding the fact that physical exercise, strengthening the muscles and changing life-style have independent effects on the patients' symptoms (Felson, 2006), we recommend all patients with knee OA to perform exercises and to change their life styles. Also, since ginger is an available plant with minimal adverse reaction and favorable effects on relieving the symptoms of patients with OA, we recommend it as a safe drug in controlling the symptoms of knee OA.

Further studies are also required to evaluate the long term and more detailed effects of ginger on OA, using serial radiographs.

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