Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(4):623-627

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Strontium ranolate effect on knee osteoarthritis

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ABSTRACT

Osteoarthritis (OA) is a joint disease that most commonly accompanied with pain and joint deformity which eventually leads to disability. Burden of OA will be accounted second in women and fourth in men in Iran. Most therapies of knee osteoarthritis are symptomatic treatment. Recently, strontium ranolate are used as a new agent for handling of post menopausal osteoporosis and provided reduces in hip and vertebral fractures risks. Beneficial effects of this treatment are showed in spine OA as well. This study was designed to evaluate short-term effects of strontium ranolate on treating of knee OA in Iran. Study was performed as a randomized double blind clinical trial. Symptomatic knee OA cases at Kellgren – Lawrence based stages I, II and III were enrolled in study following exclusion of systemic disease as well as joint disease. These patients randomly divided into 2 groups and each group was treated with placebo and Strontium ranolate at the dose of 2 mg per day. Then cases were followed for 12 weeks via Visual Analog Scale (VAS) and Western Ontario and McMaster universities (WOMAC) questionnaires associated with subsequent statistically analyzes. Statistically significant differences in the rate decline of pain, stiffness, functionality and eventually total scores as well as VAS scores were revealed between strontium ranolate and placebo therapy. Given the proven positive effects, strontium ranolate recommended as one of treatment bases in association with weight loss and muscles physiotherapy as well as healthy use of joints.

Keywords: knee osteoarthritis, strontium ranolate

INTRODUCTION

OA is one of the causes of pain and disability as well as the most common muscloskeletal disease around the world. OA causes progressive degeneration of cartilage and joint space loss. The most commonly affected joints are knees, hips, spine and small joints of the fingers. Due to uncertain correlation between clinical syndromes and radiologic findings, estimation of OA prevalence is not easy. However, OA prevalence is higher in females and increases with age.[1] Knee osteoarthritis is the most common joint disease that causes pain and joint deformity and eventually leads to an inability. The disease classically refers to focal articular cartilage lesion with a hypertrophic response in the bone and subcondral region. Prevalence of symptomatic knee OA is 5.4% and 16% in men and women over 80 years respectively. Approximately 11% of symptomatic knee OA cases are at the ages over than 64 years.[2] Most drugs for knee OA treatment are symptomatic therapy. In recent decades, many studies on the medications with modulating effects on articular structurality have been done. Dedicated treatments of knee osteoarthritis are usually provided for pain control and quality of life improvement as well as progressive arthetopathy prevention. OA therapy is divided into two groups. First non- pharmacotherapy which includes some educational efforts on healthy use of joints, muscle physiotherapy, aerobic exercise and weight loss in obese patients, heat therapy and acupuncture. Second pharmacotherapy includes topical and oral NSAID, such as acetaminophen and intra-articular injections of corticosteroids and hyaluronic products and supplements such as glucosamine condroitin sulphate.[3] Mentioned therapies haven't any modulating effect on joints and have not preventive effect on articular destructive progress. These therapies only reduce pain and joint malfunctioning. As a new FDA approved drug, Strontium

ranolate has been used for the treatment of post menopausal osteoporosis in last few years which reduced the risk of hip and vertebral fractures. Its beneficial effects on spine osteoarthritis have been also demonstrated.[4] Since the strontium molecule is similar to calcium, so it is easily take in the body and participate in bones and teeth building.[5] Strontium stimulates new bone formation as well as reduction in bone resorption.[6] It also enhances the stimulatory effects of insulin-like growth factor (IGF1) on the synthesis of glycosoaminoglycans and proteoglycans.[7, 12] Also, studies have shown that strontium reduces levels of C-Terminal telopeptide urinary collagen type 2 (u-CTX-II) significantly, a biomarker for cartilage damage with high tissue specificity.[4,11] additionally, calcium-sensing receptors are stimulated by strontium, leading to the differentiation of preosteoblast to osteoblast and consequence bone formation. It also stimulates osteoblasts to secretion of osteoprotegerin (OPG) which inhibits osteoclast formation via preosteoclast through the receptor activator of nuclear factor kappa-B ligand (RANKL) pathway.[7] Additionally, mesenchymal stem cell differentiation to osteoblast could be conducted by strontium in bone marrow.[8] Progression inhibition in animal model osteoarthritis particularly through the downregulation of cartilage key proteases as well as Interleukin-1 beta (IL-1β) was already shown by means of strontium.[9] Two objectives were often followed in knee osteoarthritis surveys. One is focused on disease-modifying drugs developing which can be assessed by measuring of joint space loss and another goal is related on short-term response to treatment of knee osteoarthritis to improve joint function, pain and patient functioning during daily activities which those criteria assessed using VAS and WOMAC questionnaires.[10] Due to limited research on the effects of strontium on knee osteoarthritis and different pathophisyologic mechanisms of spinal osteoarthritis in compared with knee osteoarthritis, study was designed to evaluate short-term effects of strontium on the clinical improvement of knee osteoarthritis.

EXPERIMENTAL SECTION

This study was conducted as a double blind randomized controlled clinical trial (RCT). The study population included patients with knee OA attending to rheumatology clinic of a university hospital during one year. OA of patients were characterized using American College of Rheumatology (ACR) standards and enrolled cases were in all stages of kellgren & Lawrence scaling system (I, II and III) except stage IV. Exclusion criteria were the presence of knee and hip implants, use of glucosamine sulfate and chondroitin during past 6 months, grade IV osteoarthritis (complete destruction of the joints), renal failure, Coagulopathies and anti-coagulant use. Patients randomly assigned to two groups (strontium prescribed and placebo) based on computerized random number selection and each group was treated with placebo and Strontium ranolate at the dose of 2 mg per day respectively. Strontium ranelate was obtained from les laboratories servier industrie (French) as 2 g sachets. The sachet dissolved in a glass of water and administered orally. Placebo also obtained from School of Pharmacy, Zanjan University of Medical Sciences, Zanjan, Iran. The study period was 3 months. Baseline blood tests including CBC, diff, Bun, Cr, ALT, AST, ESR and both knee PA and lateral view radiography were obtaind from all patients.

Additionally, all cases were assessed by questionnaires for baseline WOMAC and VAS values obtaining. The OA patients were evaluated by WOMAC questionnaire via three indicators: pain, stiffness and functional limitation which contain five, two and seventeen questions respectively. Each patient was asked to give scores from 0 to 100 for each question. Every case was emphasized to avoid from any analgesic consumption during study enrolling. Initial experiments were repeated at the end of the third month of treatment to rule out possible side effects. After completion of the study, WOMAC and VAS scores at baseline and the end of the third month were obtained and a difference in the mean of the pain, stiffness and functionality score at the level of at least 20% decline was considered as drug efficacy cut off point between the groups. A method of evaluation that is widely used for evaluating patients with knee osteoarthritis is WOMAC questionnaire that are used to assess pain and disability. Reliability of questionnaire was standardized for cases. Meanwhile, the university ethics committee approval was obtained for this study.

RESULTS

Analysis was performed on 76 cases. There was no statistically significant difference between groups in terms of age (P_{value} = 0.238). Minimum age was 35 years and maximum age was 70 years. Mean of weight, height and BMI had not statistically significant difference in both groups. On the other hand, the two groups were similar in weight and height at the baseline. The differences among osteoarthritis intensity were not statistically significant between two groups using Kellgren Lawrence scoring (P_{value} = 0.425). According to kolmogorov-smirnov test, the data of WOMAC questionnaire were normally distributed and therefore parametric tests were used. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores in both groups (Strontium and placebo recipients) using t-test did not show statistically significant differences at baseline (Table 1).

Table 1. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores

Baseline score	Strontium mean ± sem	Placebo mean ± sem	P_{value}
Pain	301.9 ± 98.3	276.3 ± 122.7	0.318
Stiffness	94.3 ± 57.4	91.05 ± 60.7	0.809
Functionality	955.3 ± 302.3	882.1 ± 364.1	0.344
Total WOMAC	1351.6 ± 418.8	1249 ± 521.8	0.350
VAC	81.9 ± 19.2	73.1 ± 21.5	0.064

The pain, stiffness and functionality scores as well as VAS and total WOMAC scores at baseline and end of study decline were statistically significant in the Strontium group using Paired t-test (Table 2).

Table 2. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at baseline and end of study

Variable		Strontium mean ± sem	Placebo mean ± sem
Pain	pain scores at baseline	301.9 (98.3)	276.3 (122.7)
	pain scores at end of study	225.2 (122.7)	259.2 (117.8)
	pain scores decrease	76.73 (95.3)	17.02 (108.3)
	P_{value}	0.001	0.339
Stiffness	Stiffness scores at baseline	94.3 (57.4)	91.05 (60.7)
	Stiffness scores at end of study	72.6 (60.03)	90 (117.8)
	Stiffness scores decrease	21.6 (51.2)	1.05 (46.01)
	P_{value}	0.013	0.889
Functionality	Functionality scores at baseline	955.3 (302.3)	882.1 (364.1)
	Functionality scores at end of study	740.4 (377.4)	786.8 (338.07)
	Functionality scores decrease	214.8 (289.2)	95.3 (292.7)
	P_{value}	0.001	0.052
Total WOMAC	Total WOMAC scores at baseline	1351.6 (418.8)	1249.5)521.8)
	Total WOMAC scores at end of study	1038.36 (531.8)	1136.1 (493.4)
	Total WOMAC scores decrease	313.2 (378.9)	113.4 (395.6)
	P_{value}	0.001	0.085
Total VAS	Total VAS scores at baseline	82.02 (19.5)	73.1 (21.5)
	Total VAS scores at end of study	68.1 (20.6)	70.9 (23.8)
	Total VAS scores decrease	13.9 (18.6)	2.2 (26.01)
	P_{value}	0.001	0.559

While the number of cases with stiffness score decrease (P_{value} = 0.05) was statistically significant between groups but it wasn't occurred about pain (P_{value} = 0.168), functionality (P_{value} = 0.247), total WOMAC (P_{value} = 0.243) and VAS (P_{value} = 0.154) scores decrease at drug efficacy cut off point (Table 3).

Table 3. Comparison of pain, stiffness and functionality scores as well as VAS and total WOMAC scores at drug efficacy cut off point (at least 20% decline)

Variable	Number of cases in Strontium group (n=38)	Number of cases in Placebo group (n=38)	P_{value}
Pain	55.3% (n=21)	39.5% (n=15)	0.168
Stiffness	53.1% (n=17)	28.6% (n=10)	0.041
Functionality	505 (n=19)	36.8% (14)	0.247
Total WOMAC	47.4% (n=18)	34.2% (n=13)	0.243
VAS	44.7% (17)	28.9% (n=11)	0.154

Additionally the percentage fall in scores of pain, stiffness, function and total WOMAC were statistically significant (Table 4).

Table 4. Comparison of mean reduction in pain, stiffness, functionality and total WOMAC scores

Variable	Strontium mean ± sem	Placebo mean ± sem	P_{value}
Pain	25.5% (33.1)	10.3% (73.6)	0.008
Stiffness	21.5% (52.3)	15.2% (74.4)	0.024
Functionality	22.6% (28.9)	2.9% (46.4)	0.03
Total WOMAC	24% (26)	1.3% (45.8)	0.01

Standard deviations were indicated numbers in parentheses.

Mean reduction in pain, stiffness, function, WOMAC and VAS scores was not statistically significant based on gender except about male stiffness (P_{value} = 0.026) and female pain (P_{value} = 0.038) scores decline (Table 5).

Table 5. Comparison of mean reduction in pain score, stiffness, function, WOMAC and VAS scores based on gender

Gender	End of study scores drop off in comparison with baseline scores	Strontium mean ± sem	P_{value}	Placebo mean ± sem	P_{value}
Male	Pain	101.6 (72.84)	0.120	0.00 (42.42)	0.088
	Stiffness	44.16 (65.30)	0.136	40 (14.14)	0.026
	Functionality	206 (258.7)	0.655	115 (49.49)	0.446
	Total WOMAC	351.8 (288.6)	0.246	75 (21.21)	0.066
	VAS	16.6 (16.3)	0.173	15 (49.49)	0.529
Female	Pain	72.06 (99.20)	0.039	17.9 (3.3)	0.038
	Stiffness	17.4 (48.2)	0.222	3.3 (46.1)	0.223
	Functionality	216.5 (298.3)	0.098	94.2 (300.8)	0.098
	Total WOMAC	306.03 (397)	0.055	115.5 (406.6)	0.055
	VAS	12.96 (19.12)	0.078	3.19 (25.04)	0.073

End of study scores drop off in comparison with baseline scores of stiffness, function, WOMAC and VAS in cases younger than 50 years were not statistically significant except about pain scores in placebo group (P_{value} = 0.049) while this statistically significant difference was ocurred about stiffness and total WOMAC scores at the cases older then 50 years (Table 6).

Table 6. Comparison of mean reduction in pain score, stiffness, function, WOMAC and VAS scores based on age

Age	End of study scores drop off in comparison with baseline scores	Strontium mean ± sem	P_{value}	Placebo mean ± sem	P_{value}
Up to 50 years old	Pain	105.08 (74.6)	0.068	29.7 (121.5)	0.049
	Stiffness	14.5 (61.5)	0.640	3.8 (59.5)	0.643
	Functionality	286.5 (305)	0.301	159.5 (328)	0.295
	Total WOMAC	406 (384.7)	0.194	193.1 (449.2)	0.183
	VAS	17.5 (20.05)	0.213	5 (29.3)	0.185
Over 50 years old	Pain	63.6 (102.1)	0.060	6.7 (98.2)	0.059
	Stiffness	24.9 (46.7)	0.035	1.19 (32.6)	0.029
	Functionality	181.7 (281.5)	0.088	43.3 (257.1)	0.086
	Total WOMAC	270.3 (375.9)	0.043	48.9 (343.9)	0.041
	VAS	11.7 (17.9)	0.058	0.000 (23.4)	0.067

Decrease of VAS score in Strontium group was statistically significant at patients with OA grade I. Though statistically significant decrease of scores were happened in both groups (Strontium and placebo) for functionality score in OA grade II cases and for pain, stiffness and VAS scores in OA grade III patients (Table 7).

Table 7. Comparison of mean reduction in pain score, stiffness, function, WOMAC and VAS scores according to the severity of osteoarthritis

OA severity	End of study scores drop off in comparison with baseline scores	Strontium mean ± sem	P_{value}	Placebo mean ± sem	P_{value}
GradeI	Pain	86 (20.7)	0/956	81.6 (176.3)	0/970
	Stiffness	0.000 (42.42)	0.956	1.6 (33.2)	0.953
	Functionality	286 (253.6)	0.818	356 (591.5)	0.861
	Total WOMAC	372 (266.8)	0.868	436 (792.8)	0.903
	VAS	20 (23.4)	0.459	0.000 (50)	0.569
GradeII	Pain	26 (87.04)	0.571	0.033 (121.6)	0.545
	Stiffness	2 (41.3)	0.729	8.6 (49.6)	0.719
	Functionality	150.2 (171.8)	0.046	23.13 (217.7)	0.037
	Total WOMAC	178.2 (238.7)	0.138	14.1 (343.6)	0.112
	VAS	4.5 (14.2)	0.633	0.066 (31.5)	0.584
GradeIII	Pain	96.7 (102.4)	0.012	19.8 (88.4)	0.012
	Stiffness	34.9 (54.07)	0.015	4.2 (45.9)	0.014
	Functionality	227.4 (337.2)	0.384	145.1 (265.9)	0.376
	Total WOMAC	359.2 (440.4)	0.112	160.7 (346.4)	0.106
	VAS	16.08 (18.5)	0.047	16.08 (18.5)	0.046

No changes were observed in ALT, CBC, ESR, BUN and Cr of cases after 3 months follow-up at both groups. Additionally, 4 patients were excluded from study due to sever nausea and vomiting and data analysis was performed on 76 cases without any side effects.

DISCUSSION

Reginster et al study is the only survey about the Strontium effects on patients with knee osteoarthritis which has been published yet. Mentioned study was performed with larger sample size and longer follow-up period. But it was

focused on modulating effects of strontium on cartilage destruction inhibition via stimulation of collagen type II, glycosoaminoglycans and proteoglycans synthesis. This study also showed a significant effect of strontium on the pain and total WOMAC scores at a dose of 2 g per day, but not at dose of 1 g per day. The participants in our study were younger (mean of age = 53.2 years) than Reginster et al study (mean of age = 62.4 years). Additionally our female participants were more (84.2% in compare with 71%). Also most patients in our study were in Grade III (60.5%) while the most patients were in Grade II in Reginster et al study (61%). In addition Reginster showed statistically significant difference in pain and total WOMAC scores only. However, differences may be partly justified with regard to the demographic characteristics which are handeled different responses to a drug in these studies. Pain killing mechanism of Strontium is not well defined.[13]

CONCLUSION

As amatter of fact, these results make an assumption that Strontium regenerate destractive joint and make pain relief. Therefore, Strontium Ranolate is a candidate agent to use in knee OA patients in according to presented study.

Acknowledgement
Authors are thankful to Dr Noorodin Musavinasab for his kind support.

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