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Calcitonin Injection and Functional Status of Females With Knee Osteoarthritis

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Abstract

Background: Osteoarthritis (OA) is one of the most common diseases of both bone and cartilage. Since calcitonin may have positive effect on both of them.
Objectives: The current study aimed to evaluate the effect of weekly calcitonin injection on patients with knee osteoarthritis using Western Ontario and McMaster universities arthritis index (WOMAC) questionnaire.
Methods: The current prospective cross sectional study, randomly recruited 28 eligible female participants aged 55 - 70 from outpatients referred to rehabilitation clinics. These patients were in stages II and III based on Kellgren-Lawrence grading scale. Patients were requested to fill out the multidimensional WOMAC questionnaire on the day of enrollment into the study (baseline examination) and five weeks after completion of their treatment with calcitonin. Paired T-test was used to assess mean differences of the questionnaire.
Results: Compared to baseline, significant improvement in WOMAC score was observed after five weeks of treatment. Pain, joint stiffness, functional activity and total score of WOMAC showed improvement of 80.6%, 25.3%, 41.9% and 47.91% respectively, which were statistically significant (P value < 0.001). Pain, activity and stiffness improved respectively according to the mean differences and confidence interval.
Conclusions: The study results showed that calcitonin can provide proper outcomes such as increased locomotor activity. Although WOMAC parameters increased in all age groups, it had great effect just on 55 - 60 years age group. Therefore, improvement of quality of life and proper rehabilitation, which are the main factors in osteoarthritis patients, were almost achieved in this study.

Keywords: Knee Osteoarthritis, Calcitonin, Pain Assessment, Rehabilitation

1. Background

Osteoarthritis (OA) is known as the most common disease of the locomotor system, associated with radiological alterations; it is detected in a great number of patients over 50. Pain, the main symptom of OA, has significant influence on quality of life and is regarded as an important factor of disability (1). Conservative treatment regimens for osteoarthritis alleviate the symptoms but do not cure the disease and mostly target pain, inflammation and elimination of the risk factors (2, 3). Thus, currently there are no reliable accepted treatments capable of changing the course of OA (4). Although it is not well realized or documented which factors begin or drive this disease, bone and cartilage degradations are regularly coupled tightly in the pathogenesis of OA (5, 6), in which subchondral bone turnover, sclerosis of the subchondral plate, trabecular thinning and articular cartilage loss are the main parameters (5). Considering the strong relationship between the subchondral bone and the articular cartilage, an ideal therapeutic approach should adjust the metabolic activity of bone and cartilage. In contrast to other antiresorptive agents, calcitonin affects both of them (7). Calcitonin is a small, 32-amino-acid, peptide secreted in response to additional calcium in plasma (8); it fulfills several criteria, including minimal toxicity at therapeutic doses (9), analgesic effect on the clinical management of the disease (10), anti-inflammatory features (11, 12), positive effect on the morphology and metabolism of both subchondral bone and articular cartilage (13). The last benefit is achieved by reducing the increased turnover of the subchondral bone, decreasing the severity of cartilage injuries and changing the biochemical complex and supramolecular organization of the OA cartilage matrix (14). Although previous re-

searches showed its effects on experimental models of OA, a few researches focused on its role as a treatment of OA in clinics (1). In addition, previous clinical trials were limited to administration of oral, subcutaneous and intra nasal formulations of calcitonin (15).

2. Objectives

The current study aimed to evaluate the therapeutic effects of calcitonin injection on an elderly group of females with OA.

3. Methods

In this prospective cross-sectional study, 28 eligible females aged 55 - 70 were randomly recruited from outpatients referred to the rehabilitation clinics under study, Shiraz, Southern Iran. These patients were in stages II and III based on Kellgren-Lawrence grading scale (16), with no proper response to regular treatment in the last six months. Patients with a history of knee surgery, knee trauma, severe OA of knee, rheumatologic or systemic disease, congenital bone disease affecting knee and severe osteoporosis of the knee were excluded from the study. Diagnosis was confirmed by anterior-posterior and lateral view of knee X-rays and the severity of OA was estimated by Kellgren-Lawrence grading scale.

3.1. Study Design

The Western Ontario McMaster universities arthritis index (WOMAC) is a condition-specific questionnaire, developed to assess OA of the hip or knee (17, 18). It has a multidimensional scale with 25 items grouped into three dimensions: pain (six items), stiffness (two items) and physical function (seventeen items). Each item has different scores ranging from 0 to 4 (0: no pain, 1: mild pain, 2: moderate pain, 3: severe pain, 4: very severe pain). Therefore, it is graded in a numerical rating scale ranging from 100 (no symptoms) to 0 (extreme symptoms). The original questionnaire was translated into Persian; it was valid, reliable and sensitive to the changes in the health status of patients with hip or knee OA (13, 17).

Patients were requested to fill out the multidimensional WOMAC questionnaire on the day of entry into the study (baseline examination) and five weeks after completion of their treatment with calcitonin.

In the treatment course, every patient received two vials of calcitonin (fifty international units (IU) of calcitonin per one milliliter) intramuscularly at the buttock site once a week for five weeks.

3.2. Ethics

The study protocol was approved by the ethics committee under the code: 914307. All patients signed separate written informed consent (approved by the ethics committee of Shiraz University of Medical Sciences) before participation in the current study.

3.3. Statistical Analysis

Paired sample T-test was used to compare the mean differences of WOMAC three dimensions before and after treatment. All the statistical analyses were performed through the SPSS statistical software (version 18.0) and P value < 0.05 was considered as statistically significant.

4. Results

According to Table 1, finally 28 patients with the mean age of 58.46 $\pm$ 1.4 years were included in the study. Significant increase in WOMAC parameters were detected after five weeks of treatment. Pain, joint stiffness, functional activity and total score of WOMAC showed statistically significant differences (P value $<$ 0.001) (Table 1). Participants experienced considerable changes in WOMAC perceptions of pain (80.6%), joint stiffness (25.3%), functional activity (41.9%) and the total score improved about 47.9%.

Table 1. The aWOMAC Scale Parameters Before and After the Treatment With Calcitonin[a]

WOMAC Parameters	Baseline	After Five Weeks	P Value
Pain	234.82 (94.4)	424.10 (124.1)	P< 0.001
Stiffness	130.36 (48.3)	163.39 (43.8)	P< 0.001
Activity	791.96 (210.7)	1124.10 (270.9)	P< 0.001
Total	1157.14 (324.7)	1711.60 (445.4)	P< 0.001

Abbreviation: WOMAC, Western Ontario McMaster universities arthritis index.
[a]Values are expressed as mean (SD).

Compared to baseline, the most improvement in WOMAC score in pain, stiffness and functional activity was observed in 55 - 60 age group (total P value $<$ 0.001) with the most mean difference and the least confidence interval (mean difference: 160.13; 95% (CI): -794.09 to -450.64) while the least improvement was observed in the 65 - 70 age group (total P value= 0.09) with the least mean difference (Tables 2 and 3). Although functional activity had increased, it did not improve statistically in the 60 - 65 and 65 - 70 age groups. Moreover, joint stiffness improvement was statistically significant just in 55 - 60 years age group (P value $<$ 0.001). Pain had great improvement in the 55 - 65 years patients.

Table 2. Mean Differences and Confidence Intervals of Pain, Stiffness and Activity According to Age Group[a]

Age Group, y	Pain	Stiffness	Activity	Total
55 - 60	209.21 ± 49.5	34.21 ± 14.6	374.94 ± 107.4	622.36 ± 160.13
60 - 65	185 ± 89.80	35.0 ± 29.4	250.0 ± 396.3	470.0 ± 430.9
65 - 70	100 ± 82.47	25 ± 19.99	212.50 ± 179.47	337.50 ± 274.63
Total	189.28 ± 40.43	33.03 ± 11.27	332.14 ± 102.7	554.46 ± 138.76

Abbreviation: CI, 95% confidence interval.
[a]Values are expressed as mean difference ± CI.

Table 3. Mean Value and Standard Deviation of aWOMAC Score Parameters Before and After the Treatment According to the Age Group[a]

Age Group, y	Baseline	After Five Weeks	P value
55 - 60	1155.26 (345.66)	1777.63 (391.30)	< 0.001
60 - 65	1220 (216.79)	1690 (487.21)	0.09
65 - 70	1087.50 (400.26)	1425 (655.10)	0.09

Abbreviations: SD, standard deviation; WOMAC, Western Ontario McMaster universities arthritis index.
[a]Values are expressed as mean (SD).

5. Discussion

The best approach to treat OA should consider both cartilage and bone (1, 7). As already mentioned, regarding the dual effect of calcitonin on bone and cartilage, this agent is considered as an appropriate candidate to treat OA. Previous clinical trials by Tanko et al. showed that salmon calcitonin had efficacy and safety after three months in postmenopausal females aged 55 - 85. They showed that calcitonin can reduce urinary collagen type II degradation product in a dose dependent manner (9, 19).

The current study demonstrated that weekly injection of 100 IU calcitonin for five weeks significantly improved daily performance and quality of life. Calcitonin reduced the pain and stiffness and increased activity. Although activity parameter had the highest mean difference and high confidence interval, it made the improvement less significant. Overall, pain, activity and stiffness statistically improved, respectively (Table 2). Moreover, it was noticed that calcitonin can improve the WOMAC parameters in the 55 - 60 years age group significantly in comparison to older age groups. Therefore, by increase of age the effect of calcitonin become less in WOMAC parameters. This different influence can be due to prolonged duration of inactivity, which leads to joint contracture and muscle disuse atrophy.

Manicourt et al. conducted a randomized clinical trial, in which oral calcitonin with 0.5 and 1 mg daily doses was administered; then the clinical and functional efficacy were evaluated by Lequesne-Algofunctional index after 84 days. The P value showed significant reduction in median functional disability score in 0.5 and 1 mg calcitonin groups on days 42 and 84. They noted that both placebo and 1mg calcitonin groups had significant pain score reduction on days 42 and 84; whereas the 0.5 mg group had pain reduction on day 84. They showed that the percentage of response in 1 mg calcitonin group was 71%; while in placebo and 0.5 mg calcitonin groups were 50% and 46%, respectively (20). Since the placebo had great effect on pain perception in patients with OA, pain score could not be a reliable variable in the questionnaire. Moreover, the drug selected as the placebo in the study could affect the results. There are different reasons that could lead to such results; the measuring unit of calcitonin and different outcomes are also different in comparison to the current study.

In another study by Armagan et al. 30 patients received 200 IU/day nasal calcitonin besides home exercise program, compared with just exercise program group. Visual analogue scale (VAS), WOMAC and 20-m walking time were used for the clinical assessment. They showed that pain severity significantly reduced VAS scores, WOMAC scores and 20-meter walking time in a six-month follow-up of patients who received calcitonin. Besides clinical assessment, Armagan et al. showed that 200 IU nasal calcitonin had beneficial influence on magnetic resonance imaging (MRI) parameters (femoral condyles and tibial plateaus) and biologic cytokines (21). Similar to the current study findings, they noted that patients had their best improvement in WOMAC activity and pain parameters.

In another study, 200 IU/day nasal calcitonin was administered to 30 patients who developed OA due to gonoarthritis for 10 months. Clinical effects were assessed by European league against rheumatism (EULAR) criteria and VAS score. This study showed that salmon calcitonin had anti-osteoarthritic effects and beneficial influence on knee OA (10). But they used flavonoids and naproxen sodium besides calcitonin in their study; therefore, the definite effect of calcitonin could not be evaluated.

Esenyel et al. conducted a study in which postmenopausal females in stages II and III, based on Kellgren-Lawrence grading scale, were encouraged to use nasal spray 200 IU once daily for three months. Esenyel et al. used WOMAC questionnaire to evaluate the effect of nasal spray. In the study, pain, stiffness and physical function improved 62%, 48% and 49% respectively after three months (1). Similar to the current study, pain and function had great improvement but the current study did not notice such a great influence of calcitonin on joint stiffness. The differences between the results can be due to the formulation, dose and duration of calcitonin administration. In the current study, patients received 100 IU calcitonin weekly for five weeks compared to the study by Esenyel et al. (1) that used 200 IU calcitonin daily for three months. Therefore, the current study showed that even short time administration of calcitonin can be effective in moderate to severe OA.

The current study had some limitations including the absence of control group and lack of placebo administration besides long time follow-up. Moreover, the WOMAC questionnaire assesses the subjective variables; hence, potential existence of bias should be considered. As a suggestion for future investigations, the study can be conducted on a larger sample in a randomized controlled clinical trial.

It should be noted that European committee for medicinal products for human use (CHMP) postulated that long term usage of calcitonin in clinical trials could be accompanied by increased risk of cancer from 0.7% to 2.4% in comparison to the placebo group. It is shown that the risk is higher in the patients who received intra nasal calcitonin. However the Canadian healthcare organization claimed that there is no increasing risk in long term use of calcitonin and it may be just an association (22, 23). Therefore, short term use of calcitonin, particularly low dose injection has no association with cancer.

5.1. Conclusions

To sum up, as confirmed by the current study and other mentioned investigations, calcitonin even in short term and low dose has useful effects such as increased locomotor activity and a decreased urge for analgesic use by reducing pain. Therefore, improvement of function and quality of life, which are the main factors in patients with OA, were almost achieved in the current study.

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Footnotes

Authors' Contribution: Study concept and design: Alireza Ashraf and Mahdie Karimizadeh; analysis and interpretation of data: Mahdie Karimizadeh and Attiyeh Vasaghi; drafting of the manuscript: Attiyeh Vasaghi, Mahdie Karimizadeh, Alireza Ashraf; critical revision of the manuscript for important intellectual content: Attiyeh Vasaghi, Alireza Ashraf; statistical analysis: Attiyeh Vasaghi.

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