The effect of calcitonin on pain and serum beta-endorphin levels in patients with bone metastasis

Sema ÖNCÜL[1], Alp ARACI[2], Yılmaz BASER[1] , Şükran ATİKCAN[1], Nermin ÇAPAN[1], Nadi ÖZDAMAR[3]' Ferah TOKMAK[3]

[1]Ankara Atatürk Chest Disease Thoracic Surgery Center; [2]Medical Advisor, Sandoz; [3]Radio-Oncology Department, Ankara Oncology Hospital, ANKARA - TURKEY

Salmon calcitonin has an analgesic effect on bone pains. This effect is more significant during the therapy of bone pains particularly due to malignancy. In this clinical study the analgesic effect and the effect on serum beta-endorphin levels of salmon calcitonin, given intramuscularly for 14 days and at 100 IU/day dosage in a double blind placebo controlled manner, were evaluated.

In salmon calcitonin group, all patients out of 15 (100%) who completed their therapy, showed an analgesic effect which had been evaluated by both the physician and the patient. In placebo group, all patients' bone pain continued or progessed during the study. In salmon calcitonin group, beta-endorphin levels were increased for all patients except one case at the end of the study (mean difference was +108.3%; $p<0.05$). In placebo group beta-endorphin levels were decreased in 6 patients, out of 9 cases (mean difference was 14.9%; $p>0.05$). No side effects were seen during the therapy for both groups.

It was concluded that salmon calcitonin therapy is beneficial for the patients who have bone metastasis, as a bone pain reducing process. [Turk J Med Res 1993; 11(1): 27-31]

Key Words: Cancer, Pain, Beta-endorphin, Calcitonin

The patients with primer malignancy have bone metastases frequently (1). Most of these patients have an extreme bone resorption and bone pain (2). As referenced in many studies, salmon calcitonin (sCT) has analgesic effect on bone pains, related with bone metastases (3-5).

The mechanism of analgesic effect is not realized definitely, but some hypothesis are reported.

1. sCT increases the level of beta-endorphin (6).
2. It inhibits enzyme cyclooxygenase, which catalyzes production of prostaglandins (7).
3. It acts as a central neuromodulator (8).

Among these hypotheses, the beta-endorphin increasing effect has been accepted mostly. There are some studies, showing that the analgesic effect is related to the increase of serum beta-endorphin levels (9-11). In this clinical study the analgesic effect and the effect on serum beta-endorphin levels of salmon calcitonin, administered intramuscularly for 14 days at 100 IU/day dosage in a double blind placebo controlled manner, were evaluated in a larger study group.

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Correspondence Yılmaz BASER
Ankara Atatürk Chest Disease & Thoracic Surgery Center
ANKARA

MATERIALS AND METHODS

The study was started with 30 patients with bone metastasis due to primary malignancy and completed with 24 patients. Three patients were excluded from the study inadequate cooperation related to pain evaluation. Two patients died because of brain metastasis. One patient was excluded from the study because of having a progressive sensorial loss due to spinal artery syndrome.

The study was performed in a double blind placebo controlled manner. Miacalcic® ampoules (100 IU) were used for salmon calcitonin group and identical placebo ampoules were used for placebo group. All drug material were packed in identical packages, having 15 ampoules in each. On every package a study code was printed. Code explanation was done after the study was over by Sandoz.

In the sCT group all out of 15 patients and in the placebo group 9 out of 15 patients completed the study. 100 IU/day sCT ampoules or identical placebo ampoules were administered intramuscularly for 14 days.

The Patients

At the beginning of the study all patients had slightly or moderate bone pains. The patients who had severe bone pains were not included into the study (more than "8" in the visual analog scale evaluated by both the physician and patients).

There were 7 females and 8 males in the salmon calcitonin group and 3 females and 6 males in the placebo group. The mean ages were 50±9 in the salmon calcitonin group and 54±11 in the placebo group.

The mean body weights were 65±12 kgs in the salmon calcitonin group and 63±6 kgs in the placebo group.

The distribution of patients' primary tumours are presented in figure 1.

The diagnosis of metastases were obtained by using bone scintigraphy (19 cases), computerized axial tomography (2 cases) and radiography (3 cases).

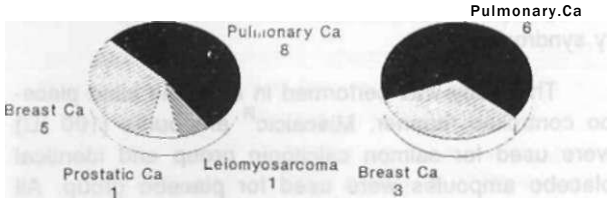
In the salmon calcitonin group, out of 15 patients 6 had multiple metastases including cranial, costal, sternal, vertebral and pelvic metastases, 3 had costal, 3 had vertebral, 2 had pelvic and 1 had cranial and humeral metastases. In the placebo group out of 9 patients 5 had costal and cranial, 2 had costal, 1 had clavicular and 1 had pelvic metastases.

The evaluation of bone pain

Patients' bone pains had been evaluated by both the physician and the patients before morning visits 08.00AM. The evaluation had been made by the same physician for each patient.

During the evaluation of the severity of bone pain by the patients, "Scott-Huskinsson's Vertical Visual Analog Scale" was used. The test was performed at the 1st, 3rd, 7th, 11th and 14th days of the study.

During the evaluation of the severity of bone pain by the physician, the physician observed the patients verbal or facial responses by:



Salmon calcitonin group n=15 Placebo group n»9

Figure 1. Primary tumors.

— performing a local digital compress externally on the area of skin above the bone metastasis,

— observing the patient, during his/her passive and active movements of the limbs (if bone metastasis is on the extremities),

— observing the patient, during inspiration and expiration or during coughing (if bone metastasis is on the costa),

—observing, how it provoked the severity of pain with vertebral column movements (if bone metastasis is on the vertebra).

Regarding the patients' responses, the physician noted the severity of pain in between "1" to "10", as "0" indicates "no pain" and "10" indicates "very severe pain" at the 1st, 3rd, 7th, 11th, and 14th days of the study.

Laboratory

ESR (Erythrocyte Sedimentation Rate), white blood differential, serum calcium, serum inorganic phosphorus, serum alkaline phosphatase and serum beta-endorphin levels were detected at the beginning and also at the end of the study. "Beta-endorphin 1125 RIA kit (Du Pont NEN Products)" was used for detecting beta-endorphin levels collected in the morning, during basal excretion period of beta-endorphin.

RESULTS

In salmon calcitonin group, all 15 patients (100%) who had completed their therapy, showed an analgesic effect which had been evaluated by both the physician and the patient (Figure 2). In placebo group, all patients' bone pain continued or progressed during the study (Figure 3). In salmon calcitonin group, the mean value of pain was decreased from 6.02±2.2 to 2.2±1.2 evaluated by visual analog scale and from 6.2±1.8 to 2.2±1.5 graded by the physician. In salmon calcitonin group, the analgesic effect had been started approximately at the 3rd day of the therapy. In placebo

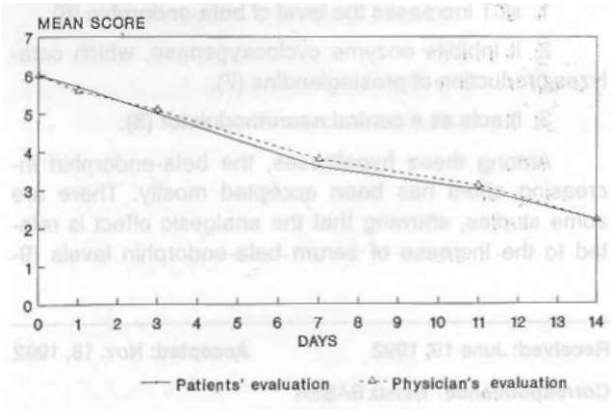


Figure 2. The evaluation of analgesic effect (Salmon calcitonin group).

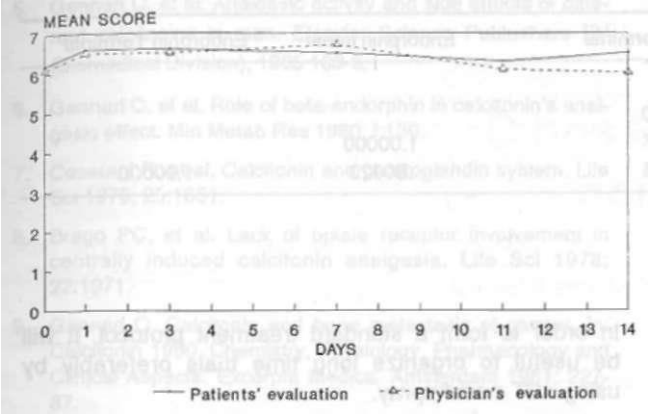


Figure 3. The evaluation of analgesic effect (Placebo group).

group, the mean value of pain was increased from 6.2±1.9 to 6.5±2 evaluated by visual analog scale and unchanged as 6.1 ±1.7 graded by the physician.

The analysis of laboratory results indicates that after 14 days of therapy, serum calcium and beta-endorphin levels were changed significantly in salmon calcitonin group. There was no significant difference on the other parameters.

The statistical evaluations were performed by Student's t test. In salmon calcitonin group, the mean serum calcium value was significantly decreased at the the end of the study when compared to the mean initial value. The mean value of serum calcium was 9.6±1.3 mg/dl before the study and 8.4±0.9 mg/dl at the end of the study ($p<0.05$). In placebo group, the mean serum calcium value significantly increased at the end of the study. The mean value of serum calcium was 8.1 ±0.5 mg/dl before the study and 9.1 ±0.6 mg/dl at the end of the study ($p<0.05$). The latter value was also significantly different than the end serum calcium value of salmon calcitonin group ($p<0.05$).

In both salmon calcitonin and placebo groups, the mean initial alkaline phosphatase levels were increased [21 ±2.8 K.A.U. (King Armstrong Unit) in salmon calcitonin group and 20±4.1 K.A.U in placebo group]. At the end of the study the mean alkaline phosphatase levels were decreased in salmon calcitonin group (19.8±3.7 K.A.U.) and increased in placebo group (20.7+4.2 K.A.U.). These differences were not statistically significant.

In salmon calcitonin group, the mean values of serum inorganic phosphorus were 3.77±0.84 mg/dl at the beginning and 3.38±0.6 mg/dl at the end of the therapy ($p>0.05$). In placebo group, the mean values of serum inorganic phosphorus were 4.05±0.9 mg/dl at the beginning and 4.5±1.1 mg/dl at the end of the therapy ($p>0.05$). These differences were not statistically significant.

In salmon calcitonin group, beta-endorphin levels were increased for all patients except one case, (mean difference was +108.3%; $p<0.05$). In placebo group beta-endorphin levels were decreased for 6 patients, unchanged for 1 patient and increased for 2 patients out of 9 cases (mean difference was 14.9%; $p>0.05$) (see figure 4,5). No side effects were seen during the therapy for both groups.

DISCUSSION

In salmon calcitonin group, the decrease of serum calcium level was an expected result. This hypocalcémie effect of sCT has been regarded as an indicator of its potency (12). In placebo group, the increase of serum calcium level is probably an indicator of osteolysis due to tumor.

The results support the hypothesis that sCT increases the serum beta-endorphin levels (13). It is possible that this increase is related to the clinical analgesic effect of the drug, as demonstrated in the present study.

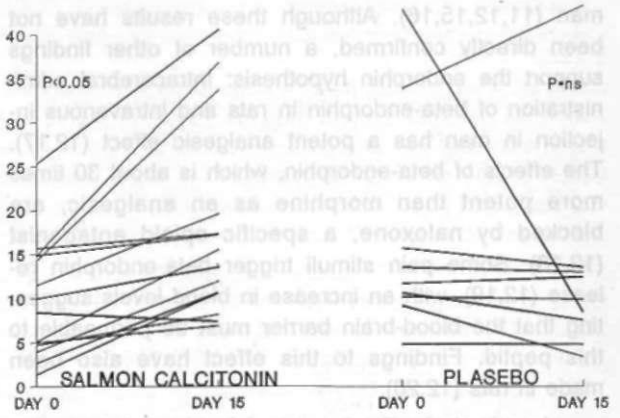


Figure 4. The effect of salmon calcitonin on beta-endorphine levels.

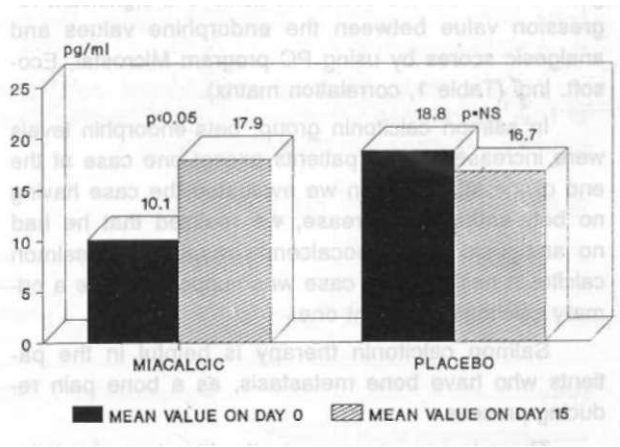


Figure 5. The effect of salmon calcitonin on beta-endorphine levels.

Table 1. Correlation matrix

	Pain Score Initial	Pain Score Terminal	Endorphin Initial	Endorphin Terminal
Pain Score Initial	1.00000			
Pin Score Terminal	-.27675	1.00000		
Endorphin Initial	.09475	-.18197	1.00000	
Endorphin Terminal	.41900	-.23726	.80920	1.00000

Critical value (1-tail, .05) - +or -.44218
Critical value (2-tail, .05 - +/- .51235

In literature it is mentioned that, the analgesic effect of calcitonin might be distinct from its anti-osteolytic effect since, whereas the hypocalcémie effect after intravenous infusion using a minipump was not sustained for longer than 24-48 hours, the analgesic effect was maintained for some time longer (12,14).

In our study, we detected increased levels of serum beta-endorphin in the sera of patients treated with salmon calcitonin. In literature it is mentioned that, plasma levels of beta-endorphin (but not of beta-lipoproteins) were reported to be raised after intravenous adiministration of at least 50 I.U. salmon calcitonin in man (11,12,15,16). Although these results have not been directly confirmed, a number of other findings support the endorphin hypothesis: Intracerebral administration of beta-endorphin in rats and intravenous injection in man has a potent analgesic effect (12,17). The effects of beta-endorphin, which is about 30 times more potent than morphine as an analgesic, are blocked by naloxone, a specific opioid antagonist (12,18). Some pain stimuli trigger beta-endorphin release (12,19), with an increase in blood levels suggesting that the blood-brain barrier must be permeable to this peptid. Findings to this effect have also been made in rats (12,20).

In our study, the increased levels of beta-endorphin, detected in the sera of patients treated with salmon calcitonin, were seemed to be related to the analgesic effects but we could not achieve a significant regression value between the endorphine values and analgesic scores by using PC program Microstat, Ecosoft. Inc. (Table 1, correlation matrix).

In salmon calcitonin group, beta-endorphin levels were increased for all patients except one case at the end of the study. When we evaluated the case having no beta-endorphin increase, we realized that he had no analgesic and hypocalcémie response to salmon calcitonin neither. This case was supposed to be a primary calcitonin resistant one.

Salmon calcitonin therapy is helpful in the patients who have bone metastasis, as a bone pain reducing process.

There is no consensus in the literature about the duration of therapy for patients with bone metastases. In order to form a standard treatment protocol, it will be useful to organize long time trials preferably by using sCT nasal spray.

Kalsitoninin kemik metastazlı hastalarda ağrı ve serum beta-endorfin düzeyleri üzerine etkisi

Somon kalsitoninin kemik ağrıları üzerinde analjezik etkisi vardır. Bu etki özellikle malignansilere bağlı ağrılarda daha belirgindir. 14 gün süreyle i.m. olarak 1001U/gün dozunda çift kör kontrollü olarak yapılan bu çalışmada somon kalsitoninin analjezik etkisi ve serum beta-endorfin düzeylerine etkisi değerlendirildi.

Kalsitonin grubunda tedaviyi tamamlayan 15 hastanın hepsinde (%100) hem hekim hem de hasta tarafından değerlendirilebilen bir analjezik etki izlendi. Plasebo grubunda hastaların kemik ağrıları devam etti. Kalsitonin grubunda biri hariç tüm hastalarda serum beta-endorfin düzeyleri arttı (ortalama fark %+108.3; p<0.05). Plasebo grubunda 9 vakanın 6'sında beta-endorfin seviyeleri azaldı (ortalama fark %14.9; p>0.05). Çalışma süresince her iki grupta da yan etki izlenmedi.

Somon kalsitonin tedavisinin kemik metastazı olan hastalarda kemik ağrısını azaltıcı bir yöntem olarak yararlı olduğu sonucuna varıldı.
[TurkJMedRes 1993; 11(1): 27-31]

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