

Calcitonin Promotes Faster Healing of Spinal Fractures in Osteoporotic Patients

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ABSTRACT

AIM: To delineate the effect of calcitonin on the healing of osteoporotic spinal fractures in non-operative treatment and compare it to another treatment for the same pathology (bisphosphonates)

METHODS: This was a prospective double blind study. We evaluated data derived from the medical files of two comparable groups of osteoporotic patients: Group A (calcitonin + calcium) and Group B (bisphosphonate). Both groups were originally diagnosed with osteoporosis in the time of fracture and were both treated conservatively with a brace and osteoporotic medication. Radiography was used to evaluate fracture consolidation. Profile views of radiographical images were taken in the time of diagnosis and 3, 6, 9, and 12 months after that. CT was performed to evaluate bone union 6 and 12 months after surgery. QUALEFFO-41 was used as an evaluation scoring tool in order to appraise problems affecting day to day activity, access mobility issues and general well being.

RESULTS: Average periods of bone union in the calcitonin group were significantly shorter and at 12-month follow-up, the proportion of patients with bone union was better in the calcitonin group. Patients the calcitonin group were stopping pain medication earlier and they were discarding their braces sooner. T scores of group A at the end of the study follow up were statistically significant.

CONCLUSIONS: The implementation of Calcitonin shows a favorable outcome in spinal pathological fractures with an increase in fracture consolidation and improved quality of life.

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Key words: Osteoporosis; Osteoporotic fractures; Osteoporotic fractures treatment; Calcitonin; Nasal calcitonin

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INTRODUCTION

With advancing age, abnormalities in the bone remodeling process (like net reduction in bone formation) change the bone's material properties as well as its structure^[1]. This coupled with increased bone turnover and bone resorption, accelerates progressive skeletal decay. This disparity between the volumes of bone formed and resorbed ultimately produces regions of stress that are susceptible to micro-damage, potentially increasing fracture susceptibility and probability.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture^[2,3]. These fractures are associated with considerable morbidity and economic burden, particularly in developed countries. In 2000 alone there were an estimated 9 million osteoporotic fractures worldwide, resulting in a loss of 5.8 million disability-adjusted life-years^[4]. The incidence and costs of these fractures and their sequelae continue to rise with an ever aging population. Costs related to osteoporotic fractures in the United States alone are anticipated to reach \$25.3 billion by 2025^[5]. The most insidious osteoporotic fractures are the spinal ones, because of their gradual onset, frequently remaining clinically undetected, and seldomly being related to major traumatic events^[6].

In postmenopausal women, bone turnover increases dramatically and remains elevated for up to 40 years after cessation of ovarian

function, leading to progressive loss of bone mass^[7,8]. Additional slower age-related bone loss affects elderly men and women both. This process yields osteoporotic bones vulnerable to fracture. Some of the factors that contribute to the decay of the aging skeleton -- eg, the increase in the rate of remodeling, the increased resorption, the decreased tissue mineral content -- are to some degree reversed by anti-resorptive drugs and calcitropic Hormones like calcitonin^[9,10].

Calcitonin (also known as thyrocalcitonin) is a 32-amino acid linear polypeptide hormone that is produced in humans primarily by the parafollicular cells (also known as C-cells) of the thyroid^[11]. It acts to reduce blood calcium (Ca^{2+}), opposing the effects of parathyroid hormone (PTH)^[12]. The hormone participates in calcium (Ca^{2+}) and phosphorus metabolism. In its skeleton-preserving actions, calcitonin protects against calcium loss from skeleton. The calcitonin receptor, found on osteoclasts^[13], and in kidney and regions of the brain, is a G protein-coupled receptor, which is coupled by Gs to adenylate cyclase and thereby to the generation of cAMP in target cells. Calcitonin was extracted from the ultimobranchial glands (thyroid-like glands) of fish, particularly salmon. Salmon calcitonin resembles human calcitonin, but is more active. At present, it is produced either by recombinant DNA technology or by chemical peptide synthesis. The pharmacological properties of the synthetic and recombinant peptides have been demonstrated to be qualitatively and quantitatively equivalent^[14]. Currently the substance comes in oral, injectable and nasal preparations. The usual treatment regimen for osteoporosis with nasal calcitonin is 100-200 IU per day.

METHODS

This was a prospective double blind study approved by the ethics committee of our institution. We evaluated data derived from the medical files of two comparable groups of osteoporotic patients, Group A included 21 patients suffering from osteoporotic spinal fractures that were treated with calcitonin 200 IU and a supplement containing calcium 500 mg+400 IU vitamin D on a daily basis and Group B comprised of 18 patients treated with bisphosphonate alendronate 70 mg once per week and a supplement containing calcium 500 mg+400 IU vitamin D on a daily basis. Both were originally diagnosed with osteoporosis after a gradual onset of back pain and kyphosis that led to a radiological confirmation of collapsed vertebrae (osteoporotic fractures) and were treated for this pathology. All patients were instructed to abstain from use of non-steroid anti-inflammatory drugs (NSAIDs) for the duration of the study and to only use paracetamol as pain medication. All patients were treated conservatively with a use of TLSO brace.

The time period investigated spanned 3 years starting from 2008 and ending in 2011. All patients included in the research were followed up for a minimum of 1.9 and a maximum of 2.5 years.

Patients that were diagnosed with other type of pathologic fractures (e.g. myeloma, metastasis) were excluded from the research. Patients that were already under treatment for osteoporosis and patients that underwent surgery were excluded from the research. Our cohort included new diagnosis of osteoporosis on the basis of a pathological fracture diagnosed radiologically, ensuing into a consequent positive DEXA scan. Dual Emission X-ray Absorptiometry (DEXA) findings^[21] 15 were considered positive for a T score below the value of -2.5. The second parameter investigated was Treatment Efficacy which was expressed by T score sequences in a minimum of 4 and a maximum of 8 years follow up. We catalogued the initial T score on the date of diagnosis and a final T score on the date of the study completion.

Physicians performing the follow ups were considered to be

blinded to the patients treatment and group allocation. Physicians performing the statistics and evaluating the research data were also blinded to the treatment and only knew the group allocation but not its meaning.

We implemented the Quality of Life Questionnaire QUALEFFO-41 (International Osteoporosis Foundation, IOF, 10 December 1997) as an evaluation scoring tool in order to appraise problems affecting day to day activity, access mobility issues and general well being. The lower the QUALEFFO score the better the Quality Of Life. QUALEFFO consists of 5 domains, and scores can be calculated individually for each domain.

The validation of mobility and well being was instrumental in delineating possible difference in the quality of life of patients in our groups that could correlate to the clinical data collected. Radiography was used to evaluate fracture consolidation. Profile views of radiographical images were taken in the time of diagnosis and 3, 6, 9, and 12 months after that. CT was performed to evaluate bone union 6 and 12 months after surgery. In this study, we defined bone union as bone formation and remodeling of the involved vertebra without any further signs of collapse, as well as bridging of any displaced segments. Evaluation of bone union was blinded and performed by 3 surgeons. Fracture consolidation was used to define the period of bone union if at least 2 of the observers concurred.

All adverse events were reported together with an assessment of their severity (mild, moderate, or severe).

Statistical analysis of the data was performed using SPSS 13.0 for Windows (SPSS Inc, Chicago, Illinois). Values are presented as Mean±Standard Deviation. Comparison of was done by Mann-Whitney/Wilcoxon Two-Sample non-parametric Test (Kruskal-Wallis test for not normally distributed data). A critical *P* value of <0.05 was used for all hypothesis testing. All reported *P* values are two-sided.

RESULTS

Table 1 shows the demographic characteristics of our cohort. There were no significant demographics differences between the two groups. There was no significant difference in the number of patients who had sustained fractures and the age of original diagnosis.

Average periods of bone union evaluated by radiographical imaging and by CT in the calcitonin group were significantly shorter than those in the bisphosphonates group ($P<0.05$; Table 2). At 12-month follow-up, the proportion of patients with bone union was 84% (evaluation by radiographical imaging) and 82% (CT) in the calcitonin group, and 74% and 68% in the bisphosphonates group, respectively. The rate of bone fusion evaluated by radiographical imaging and CT in the calcitonin group was significantly higher than that in the bisphosphonates group ($P<0.05$; Table 2).

Patients in group A were stopping pain medication earlier than their group B counterparts and they were discarding their braces sooner (Table 2). The T scores of group A patients at the end of the study follow up were statistically significantly improved compared to the same final values for patients in group B (Table 2).

Quality Of Life general score (mean) was 31.30 (range 7-82) for group A and 63.50 (range 20-97) for group B with the difference being statistically significant ($p=0.000$) in favour of the calcitonin group. This falls in line with previous studies that correlate the effect of calcitonin on pain and mobility. Patients in Group A were discarding their brace earlier than their group B counterparts exhibiting greater confidence in mobility and with their pain diminishing significantly earlier.

Adverse Effects. There were no adverse reactions effects/events in either group.

Table 1 Demographic, stratification and research data. Fracture categorization according to severity and location.

Stratification	Cohort	Group A	Group B
Individuals	39	21 (53.9% of cohort)	18 (46.1% of cohort)
Gender	37 female (94.9%); 2 male (5.1%)	20 female (95.2% of group) 1 male (4.8% of group)	17 female (94.4% of group) 1 male (5.6% of group)
Age on diagnosis [mean] (range)	62.81 (38-91)	62.94 (38-91)	61.18 (44 - 82)
Fracture sites total (n)	45	25 (55.6% of group)	20 (44.4% of group)

Table 2 Statistical analysis for T scores (baseline – final), fracture consolidation and quality of life.

Stratification	Group A	Group B	p value
Individuals	21 (53.9% of cohort)	18 (46.1% of cohort)	
Age on diagnosis [mean] (range)	62.94 (38-91)	61.18 (44 - 82)	0.133
T score baseline (range)	-3.28 (-2.48 to -5.68)	-3.59 (-2.56 to -5.24)	0.000
T score final (range)	-2.78 (-2.20 to -5.30)	-3.11 (-2.50 to -4.30)	0.000
Fracture sites total n	25 (55.6% of group)	21 (44.4% of group)	0.128
Lumbar Fractures	9	6	
Thoracic Fractures	16	15	
Time to consolidation (weeks) [mean] (range)	9.1 (8.2 - 13.5)	12.8 (9.1 - 20.3)	0.000
Brace discarded (weeks) [mean] (range)	8.9 (7.4 - 11.3)	14.1 (10.2 - 21.5)	0.000
Pain medication stopped (weeks) [mean] (range)	6.1 (5.5 - 8.2)	11.2 (9.9 - 19.8)	0.000
Quality of life score [mean] (range)	31.30 (7 - 82)	63.50 (20 - 97)	0.000

DISCUSSION

The National Institutes of Health (NIH) Consensus Development Conference on Osteoporosis in 2000 recognized the role of both bone mass and other factors that affect bone strength^[16]. The conference characterized osteoporosis by reduced bone strength, which reflects both bone density and bone quality. Further, bone quality is influenced by a number of variables, including turnover, damage accumulation, and mineralization, as well as architecture and geometry.

Osteoporosis usually involves more than just one vertebra that exhibit reduced structural strength and is one of the more common causes of vertebral collapse in the spine. This leads to osteoporotic vertebral fractures that usually have a gradual onset, frequently remain clinically undetected, and seldomly will they be related to traumatic events^[17].

Osteoporotic vertebrae display “sub-optimal” bone architecture^[18], leading to an uneven load distribution. Compared to the architecture of a healthy vertebra, trabeculae of osteoporotic vertebrae are less numerous, thinner, sparse and more axially oriented (at the cost of transverse orientation structure) making them particularly vulnerable to unusual multidirectional loading. Moreover, longer and thinner trabeculae are more vulnerable to buckling and more readily perforated by osteoclasts^[19]. With increased vulnerability to buckling being extremely important for high loads, this biomechanical model explains the reduced compression strength osteoporotic vertebrae exhibit. This is also supported by the suggestion that fractures of osteoporotic vertebrae may be caused by loads that are higher than normal and also caused by infrequent loads in unusual directions. Pollintine *et al*^[20] used stress profilometry to study the load shift between the two columns of osteoporotic vertebrae and proved it to be significant.

The load distribution between the different cancellous and cortical parts of the vertebral body is also affected by osteoporosis. The contribution of the cancellous mass (spongiosa) in load transfer depends strongly on the location within the vertebra^[21]. Close to the endplates, the spongiosa does most of the load bearing, but towards the centre of the vertebra the load becomes more evenly distributed, the main reason being the architecture within the spongiosa. Moving from the endplates toward the centre of the vertebra, the shell curves

inward, while simultaneously the outer trabeculae angle from the endplate towards the shell, resulting in the mid-transverse shell “collecting” the load from the outer trabeculae. The contribution to load support of the spongiosa is larger in the healthy vertebra than in the osteoporotic one^[22].

There is a lifelong, strong relationship between bone morphology and physiological or external loading throughout life^[23,24]. Vertebral fractures may originate from actions like forward flexion, lifting, and exertion of loads that may not be “physiological” but are also not normally traumatic^[25]. The aforementioned changes in pathologic vertebrae architecture may lead to an increased vulnerability.

Calcitonin is a widely used medicament in osteoporotic patients that is easily administered through the nasal route. It has been on the market since the end of the original studies in the late 70's^[26] and it is a very cost effective treatment with the lowest cost in all countries produced. Moreover, the use of nasal calcitonin is patient friendly, easily followed and the patient response ratios are excellent^[27]. No severe adverse effects have been associated with its use^[27].

There have been numerous studies investigating its efficacy in osteoporosis and fracture pain and several studies that investigate its effectiveness in fracture healing in in-vitro and animal models both^[28-32]. Very few reports of its actual fracture healing effect in humans exist and these are mostly case reports^[33-38]. Nonetheless, the use of calcitonin as an easily followed osteoporotic treatment in conjunction with previous studies in animals, deems a thorough look into its bone healing effect needed.

It has been suggested that bone neuropeptides can act as direct regulators of osteoblastic function^[39]. Calcitonin gene-related peptide (CGRP) has been identified as the causative neuropeptide for callus angiogenesis and it has been proven that vascularization plays an important role in callus maturation^[40,41]. Calcitonin's action in fracture healing is promoted by the indirect positive response of vascular endothelium cells, monocytes and histiocytes^[40,41]. Calcitonin also contributes to the production of other promotive substances of bone matrix, like neutral proteases^[40,41].

In some clinical studies it has been established that there is a clinical and radiological improvement in patients with recent fractures of the peripheral skeleton, acceleration in the formation of radiologically visible callus and clinical improvement especially in Paget's disease patients with multiple fractures^[42-45]. Calcitonin

has also been used in clinical settings of patients with injuries of the musculoskeletal system, such as incorporation of bone grafts after local injections of calcitonin, restoration of bone cysts after dental extractions and an improvement in delayed fracture healing after local administration of calcitonin in patients with neglected fractures^[45-48].

Our study was looking into the effect of calcitonin on fracture consolidation in an elderly population suffering from osteoporotic vertebral fractures that were not treated operatively. The statistically significant differences in the time of fracture consolidation, brace discard and pain improvement show great promise although should be considered carefully and warrant further study. The results of our study should be a pointer for further pilot studies better delineating the effect of calcitonin on fracture healing.

Limitations to our study are the small number of our cohort. Nonetheless, we should point out that this is the biggest cohort that has been investigated for a similar reason. The inclusion of spinal fractures only is another limitation and a possible research that would look into the effect of calcitonin in different fracture sites might be the next step forwards.

Our study suggests that the use of calcitonin attenuates the healing of fractures in the spine in a quicker and more favorable way than bisphosphonates. Moreover, the improvement in quality of life, mobility and the lack of adverse effects make this a promising suggestion. This might be used as a clinical indication for further studies that will result in a possible treatment guideline.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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