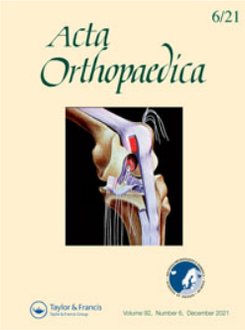

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Effect of nasal salmon calcitonin on post-traumatic osteopenia following ankle fracture

A randomized double-blind placebo-controlled study in 24 patients

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With the aim of preventing postfracture osteopenia, we randomized 24 patients with internally fixed ankle fractures to 3 months of treatment with placebo or 200 IU nasal salmon calcitonin (sCT) in a prospective, double-blind design. 3 patients were excluded, leaving 11 patients in the placebo group and 10 in the sCT group for study. Bilateral measurements of bone mineral content (BMC) in the coronal plane of the proximal tibia were performed by dual photon absorptiometry (DPA) postoperatively within 7 days of the fracture and after 1.5, 3 and 6 months. 3 months after the fracture, BMC in the injured legs had decreased by 14% in the placebo group and 2.1% in the sCT group. This difference was not statistically significant. In the healthy legs, a statistically significant intergroup difference was seen 6 weeks after the fracture, caused by a tendency towards a decrease in BMC of 4.6% in the placebo group, while BMC in the sCT group had increased by 7.4%. Nasal sCT may to some extent, but in this study not significantly, reduce postfracture osteopenia, and cause a significant effect on BMC in the healthy leg.

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It is well known that a 20–50% loss of bone mineral occurs in a fractured bone with a partial recovery after healing, but even 10 years after a tibial shaft fracture a significant reduction in bone mineral can be detected, close to the former fracture (Nilsson 1966, Andersson and Nilsson 1979, Ulivieri et al. 1990, Petersen et al. 1992, 1997, Karlsson et al. 1993, Kannus et al. 1994). The histomorphologic changes in the proximal tibia following tibial shaft fractures consist of an increase in the number of osteoclasts and osteoblasts which looks like a high turn-over disease of bone (Obrant and Nilsson 1984).

Calcitonin inhibits bone resorption through a direct effect on osteoclasts (Chambers and Azria 1988), and it has therefore mainly been used to treat bone diseases characterized by increased bone turn-over. In a prospective randomized study, we investigated the effect of nasal salmon calcitonin (sCT) on postfracture osteopenia in the proximal tibia, following ankle fractures in a double-blind placebo-controlled design.

Patients and methods

24 patients with an ankle fracture as the only injury, treated by open reduction and internal fixation were randomized, using block randomization (blocks of size 4) to postoperative treatment with either sCT or placebo in a prospective, double-blind study. The participants received nasal placebo or 200 IU nasal sCT (Miacalcic® nasal spray, Sandoz) given daily as 1 puff in 1 nostril in the evening. Treatment was given for 12 weeks and without calcium supplements. The patients had been treated at the Department of Orthopedics, Rigshospitalet, Copenhagen, and all were included in the study within 7 days. Patients with previous lower extremity fractures, diseases known to affect bone metabolism or with alcohol abuse were excluded. 3 patients were excluded during the study. In the calcitonin group 1 patient died of pulmonary embolism, 1 in each group stopped taking medication. This left 11 patients in the placebo group and 10 in the sCT group for study (Table 1). The project was approved by the Danish National Board of Health and the local committee on ethics and written informed consent was obtained from the patients before inclusion in the study.

The fractures were classified according to the Lauge-Hansen system (1942) and all were pronation-eversion (PE) or supination-eversion (SE) types, most SE-types being classified as SE-IV fractures (Table 1). After surgery all injured extremities were immobilized in a plaster cast for 6–8 weeks. Weight bearing in the cast was allowed 3 weeks postoperatively, with the exception of 3 patients in each group, who were

Table 1. Baseline characteristics

	Placebo	Calcitonin
n	11	10
Age	33 (19–58)	34 (23–55)
Female/male	6/5	5/5
Fracture type (SE/PE)	6/5	5/5
Days until inclusion	3.9 (2–7)	3.5 (2–6)
Weeks of cast immobilization	6.0 (6–6)	6.2 (6–8)
BMC value in injured leg (g/cm)	4.73	5.29
range	(1.78–6.75)	(2.51–6.76
BMC value in healthy leg (g/cm)	4.77	5.11
range	(1.95–6.64)	(2.25–6.68)

not allowed to bear weight during the period of cast immobilization.

Blood and urine (U-) samples were obtained at inclusion and repeated on day 7 and after 3 months. Concentrations of serum (S-) ionized calcium, S-parathyroid hormone, S-phosphate, S-alkaline phosphatase and S-osteocalcin were measured. In the urine samples obtained as a number 2 urinary spot sample in the morning after overnight fasting, U-hydroxyproline was measured.

Measurements of bone mineral content (BMC) in the coronal plane of the proximal tibia were performed by dual photon absorptiometry (DPA), using a custom-made knee scanner (GT-50, Tibia-1a, Gammatec A/S, Værløse, Denmark), specially designed for bone mineral measurements of the proximal tibia. The scanner uses the radiation peaks of 44 and 100 KeV from a ^{153}Gadolinium source and scanning was performed with a pixel size of 2 mm × 2 mm (Petersen et al. 1993, 1996a, b). After scanning, a region of interest was selected for measurement of BMC (g/cm). The patients were scanned within 7 days of the fracture and after 1.5, 3 and 6 months.

Statistics

Nonparametric tests for unpaired (Mann-Whitney) and paired data (Wilcoxon) and nonparametric two-way analysis of variance (Friedman) were used. P-values below 0.05 were considered significant. The 95% confidence intervals (95% CI) were calculated for absolute and percentage changes in BMC. The study was designed to determine whether sCT was a potent inhibitor of posttraumatic bone loss. An analysis of statistical power, performed with a fixed type-1 error probability of 5%, showed that, if a decrease in BMC (0–3 months) was totally prevented by sCT, the number of patients needed in each group to reach a statistical power of 80% was 12. Thus, the design of the study was suitable for evaluating an almost total preventive effect of sCT, but lacked statistical power to rule out a moderate effect of sCT on bone loss in the fractured legs.

Results

In general, nasal sCT appeared well tolerated. When comparing intergroup changes in biochemical parameters we found no statistically significant differences.

BMC of the proximal tibia in the injured legs decreased in both groups and after 3 months BMC was decreased by 14% in the placebo group and 2.1% in the sCT group (Table 2). In the healthy legs, a tenden-

Table 2. Prospective changes in BMC (g/cm) of the proximal tibia, following ankle fractures in the sCT and placebo groups. Changes in BMC are evaluated, using the Friedman test and calculation of the 95% confidence interval (95%CI) for the mean percentage changes

	Postop	6 weeks	3 months	6 months	P-value [a]
Injured legs					
Calcitonin (n 10)					
Mean (range)	5.29 (2.51–6.76)	5.05 (3.87–6.80)	5.01 (3.73–6.41)	4.89 (2.19–6.60) [c]	0.14 [c]
Change (95%CI)		–1.5 (–16 ; 13)	–2.1 (–16 ; 12)	–6.9 (–28 ; 14) [c]	
Placebo (n 11)					
Mean (range)	4.73 (1.78–6.75)	4.34 (0.89–6.27)	4.14 (0.78–6.25)	4.24 (0.77–6.00) [b]	0.02 [b]
Change (95%CI)		–11 (–22 ; –11)	–14 (–26 ; –1.4)	–10 (–25 ; 4.7) [b]	
Healthy legs					
Calcitonin (n 10)					
Mean (range)	5.11 (2.25–6.68)	5.29 (3.62–6.68)	5.38 (3.60–6.73)	5.33 (3.10–6.82) [c]	0.78 [c]
Change (95%CI)		7.4 (–6.4 ; 21)	8.6 (–5.3 ; 23)	6.2 (–14 ; 27) [c]	
Placebo (n 11)					
Mean (range)	4.77 (1.95–6.64)	4.60 (1.51–6.60)	4.70 (1.49–6.75)	4.69 (0.93–6.66) [b]	0.23 [b]
Change (95%CI)		–4.6 (–9.4 ; 0.3)	–2.2 (–14 ; 9.7)	–1.7 (–18 ; 15) [b]	

[a] Friedman test
[b] n 10
[c] n 9

Table 3. Comparison of the mean (standard error) changes in BMC (g/cm) between groups, using calculation of the 95% confidence intervals (95%CI) for the difference between the mean

ΔBMC, months	Placebo (n 11)	Calcitonin (n 10)	Difference (95%-CI)
Injured legs			
1.5–0	–0.39 (0.13)	–0.24 (0.21)	0.15 (–0.36 ; 0.66)
3–1.5	–0.20 (0.12)	–0.04 (0.15)	0.16 (–0.25 ; 0.57)
3–0	–0.59 (0.16)	–0.28 (0.21)	0.31 (–0.23 ; 0.85)
Healthy legs			
1.5–0	–0.18 (0.07)	0.17 (0.15)	0.35 (0.20 ; 0.68)
3–1.5	0.08 (0.12) [a]	0.09 (0.14)	0.01 (–0.38 ; 0.41)
3–0	–0.12 (0.15) [a]	0.27 (0.17)	0.39 (–0.09 ; 0.86)

[a] n 10

cy towards a decrease in BMC of 2.2% was seen in the placebo group 3 months after the fracture, while BMC in the sCT group had increased by 8.6% (Table 2). We found no statistically significant effect of sCT on postoperative changes in BMC in the injured legs, but in the healthy legs found a significant difference between the sCT and placebo groups regarding the changes in BMC from baseline to 6 weeks postoperatively (Table 3).

Discussion

The reduction of BMC in the injured legs in the placebo group was in good agreement with the degree of bone loss reported by previous studies (Finsen and Benum 1989, Petersen et al. 1992). In the injured legs of the sCT group, the decrease in BMC was only half of that seen in the placebo group. However, we found no statistically significant intergroup difference regarding the changes in BMC.

The preventive effect of calcitonin on immobilization osteopenia has been evaluated in several animal studies. The effect varied from no effect (Ekeland et al. 1983, Skerry and Lanyon 1993) to increased mechanical properties of both intact and fractured bones (Karachalios et al. 1992), as well as a preventive effect on bone loss, measured as ash weight (Tuukkanen et al. 1990).

To our knowledge, no previous studies using quantitative densitometric measurements of bone mineral have evaluated the effect of sCT on postfracture bone loss, following fractures in humans, but other studies have used different techniques. In a study by Mallet et al. (1986), 19 children with femoral fractures were randomized to 4 weeks of treatment with sCT injections or no treatment. No effect of sCT on biochemical markers of bone turnover was observed, but the treatment prevented bone loss, judged from plain radiographs. The effect of sCT injections, combined with oral calcium supplementation on 10 successive days in each month for 1 year, in postmenopausal women with Colles' fractures, was evaluated in a recent study by Crespo et al. (1997). Radiogrammetric measurements of the metacarpal index, which concern only cortical bone mass, were performed at baseline and after 1 year of treatment. A significant effect of sCT was found and, in the treatment group, the metacarpal index increased by 13%, while in the placebo group a 7% decrease was found. Since no measurements were performed between baseline and the 1-year follow-up and no measurements were performed in the healthy contralateral extremities, the data are difficult to interpret or to compare directly with our study. Minaire et al. (1987) evaluated the effect of sCT on bone loss following recent paraplegia by histomorphometry and found a decrease in bone resorption without effect on bone formation, compared to an untreated control group.

Not surprisingly, the bone loss following ankle fractures was smaller than that seen after tibial shaft fracture (Andersson and Nilsson 1979, Ulivieri et al. 1990, Petersen et al. 1997). Nevertheless, an ankle fracture induces a decrease of 1–2% per week in BMC during the first 3 months after the fracture (Petersen et al. 1992). Although ankle fractures heal relatively fast, the time after removal of the cast is often characterized by swelling, stiffness and strain-related pain in some patients, while others have an uneventful and fast recovery (Philips et al. 1985, Jacobsen et al. 1994). Due to variations in the period after cast removal and the fact that not all patients came for the planned BMC measurement at the 6-month follow-up, the analysis of the intergroup changes was not extended to include the 6-month follow-up.

3 months of treatment using sCT without calcium supplementation, to prevent the development of post-traumatic osteopenia, appeared well tolerated by the

patients. In our study, 200 IU of nasal sCT given daily could not inhibit the development of posttraumatic osteopenia in the injured legs, following ankle fractures, but a statistically significant effect was observed in the healthy contralateral legs. Additional studies with sufficient statistical power are needed to evaluate the amount of effect of nasal sCT on posttraumatic osteopenia.

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Andersson S M, Nilsson B E. Changes in bone mineral content following tibia shaft fractures. Clin Orthop 1979; 144: 226-9.

Chambers T J, Azria M. The effect of calcitonin on the osteoclast. Triangle 1988; 27: 53-60.

Crespo R, Revilla M, Crespo E, Villa LF, Rico H. Complementary medical treatment for Colles' fracture: a comparative, randomized, longitudinal study. Calcif Tissue Int 1997; 60: 567-70.

Ekeland A, Myhre L, Underdal T. Effects of salmon calcitonin on mechanical properties of healing and intact bone and skin in rats. Acta Orthop Scand 1983; 54: 462-9.

Finsen V, Benum P. Osteopenia after ankle fractures. Clin Orthop 1989; 245: 261-8.

Jacobsen S, Honnes de Lichtenberg M, Jensen C M, Tørholm C. Removal of internal fixation-the effect on patients' complaints: A study of 66 cases of removal of internal fixation after malleolar fractures. Foot Ankle Int 1994; 15: 170-1.

Kannus P, Järvinen M, Sievänen H, Oja P, Vuori I. Osteoporosis in men with a history of tibial fracture. J Bone Miner Res 1994; 9: 423-9.

Karachalios T, Lyritis G P, Giannarakos D G, Papanicolaou G, Sotopoulos K. Calcitonin effects on rabbit bone. Acta Orthop Scand 1992; 63: 615-8.

Karlsson M K, Nilsson B E, Obrant K J. Bone mineral loss after lower extremity trauma. Acta Orthop Scand 1993; 64: 362-4.

Lauge-Hansen N, Ankelbrud I. Genetisk diagnose og reposition. Munksgaard, Copenhagen 1942.

Mallet E, Lefort J, Caulin F. Prevention of trabecular bone loss in children's femoral fracture: effects of treatment with calcitonin. Clin Sci (Suppl. 13) 1986; 70: 82

Minaire P, Mallet E, Levernieux J, Schoutens A, Attali G, Caulin F. Immobilization bone loss; preventive effect of calcitonin in several clinical models. In: Osteoporosis 1987 (Eds. Christiansen C, Johansen J S, Riis BJ). Copenhagen 1987: 603-10.

Nilsson B E. Posttraumatic osteopenia. A quantitative study of the bone mineral mass in the femur following fracture of the tibia in man using Americium-241 as a photon source. Acta Orthop Scand (Suppl. 91) 1966; 37.

Obrant K J, Nilsson B E. Histomorphologic changes in the tibial epiphysis after diaphyseal fracture. Clin Orthop 1984; 185: 270-5.

Petersen M M, Olsen C, Lauritzen J B, Lund B. Changes in bone mineral content in the proximal tibia following ankle fracture. Eur J Exp Musculoskel Res 1992; 1: 77-80.

Petersen M M, Olsen C, Lauritzen J B, Lund B. Bone mineral content assessed by dual photon absorptiometry in the proximal tibia: normative data and measurements in orthopedic conditions. Eur J Exp Musculoskel Res 1993; 2: 121-6.

Petersen M M, Jensen N C, Gehrchen P M, Nielsen P K, Nielsen P T. The relation between trabecular bone strength and bone mineral density assessed by dual photon and dual energy X-ray absorptiometry in the proximal tibia. Calcif Tissue Int 1996a; 59: 311-4.

Petersen M M, Olsen C, Lauritzen J B, Lund B, Hede A. Late changes in bone mineral density of the proximal tibia following total or partial medial meniscectomy: a randomized study. J Orthop Res 1996b; 14: 16-21.

Petersen M M, Gehrchen P M, Nielsen P K, Lund B. Loss of bone mineral of the hip assessed by DEXA following tibial shaft fractures. Bone 1997; 20: 491-5.

Philips W A, Schwartz H S, Keller C S. A prospective, randomized study of the management of severe ankle fractures. J Bone Joint Surg (Am) 1985; 67: 67-78.

Skerry T M, Lanyon L E. Immobilisation-induced bone loss in the sheep is not modulated by calcitonin treatment. Bone 1993; 14: 511-6.

Tuukkanen J, Jalovaara P, Väänänen K. Calcitonin treatment of immobilization osteoporosis. Acta Physiol Scand 1990; 141: 119-24.

Ulivieri F M, Bossi E, Azzoni R, Ronzani C, Trevisan C, Montesano A, Ortolani S. Quantification by dual photon absorptiometry of local bone loss after fracture. Clin Orthop 1990; 250: 291-6.