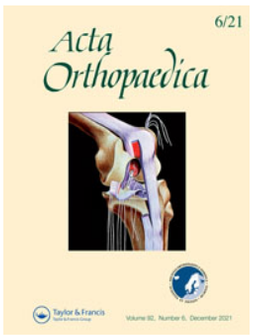

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Clodronate increases mineralization of callus after Colles' fracture

A randomized, double-blind, placebo-controlled, prospective trial in 32 patients

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ABSTRACT – In a randomized study of 32 postmenopausal women with a Colles' fracture, we studied whether 8 weeks of treatment with clodronate, a bisphosphonate, could prevent posttraumatic osteopenia. The patients were treated with a plaster splint for 4 weeks. The bone mineral density (BMD) of the forearm bones was measured at 2 levels with dual-energy x-ray absorptiometry (DEXA) 2, 6 and 12 months after the fracture.

At 2 months, in the clodronate group, there was a median 53% higher BMD in the fracture region of the radius than in the uninjured radius. In the placebo group, we found a 33% higher BMD in the fractured radius at that level than in the uninjured radius. This increase in BMD of the fractured radius, caused by clodronate, was statistically significant. At 12 months, the BMD of the fracture side had been reduced by 17% and 12%, respectively, at that time it was still significantly increased in the clodronate group alone. In the ulna at the same level, we found no significant changes in BMD in either group on either side at any time.

At 2 months, at the level between the distal and middle thirds, in the fractured radius, the median BMD was 7% lower in the clodronate group and 6% lower in the placebo group than in the uninjured radius. Although the reduction in BMD at that level was significant, there was no difference between the two treatment groups. At this level, the ulna on the fractured side showed a similar pattern, with a 5% lower BMD in the clodronate group and a 4% lower BMD in the placebo group. This osteopenia showed a small but significant progression on the fractured side after 6 and 12 months.

■

The bisphosphonates have considerable effects on mineralization and resorption of bone. These drugs have been used in diseases with increased bone turnover, such as Paget's disease of bone, bone tumors, and osteoporosis (Fleisch 1993, Giannini et al. 1993, Kanis et al. 1993). In particular, they are characterized by a marked inhibitory effect on osteoclastic bone resorption. Thus, earlier investigators showed that bisphosphonates can reduce disuse osteopenia in rats (Tarvainen et al. 1994), plate osteopenia in rabbits (Nyman et al. 1993a) and postmenopausal osteopenia in humans (Harris et al. 1993). Furthermore, an increase in the calcium content of fracture callus by the bisphosphonate clodronate has been reported in rats (Nyman et al. 1993b, Madsen et al. 1998). This could have implications for bone strength after the fracture. The aim of this study was to find out whether clodronate, a bisphosphonate, has a positive effect on forearm BMD after a wrist fracture in postmenopausal women. Previous authors (Adolphson et al. 1993) have demonstrated that the posttraumatic osteopenia is present already at plaster removal. Therefore we have chosen the time of withdrawal of bisphosphonate treatment to make the first BMD measurements.

Patients and methods

We included 32 otherwise healthy, postmenopausal women having a mean age of 62 (50–76) years

Table 1. Radiographic classification of 32 Colles' fractures according to Lidström (1959), Older et al. (1965) and Frykman (1967). 1 fracture (clodronate group) could not be classified

	Lidström					Older				Frykman							
Group	2A	2B	2C	2D	2E	1	2	3	4	1	2	3	4	5	6	7	8
Clodronate (n 16)	5	6	1	1	2	0	7	5	3	1	0	0	1	1	3	3	6
Placebo (n 16)	6	7	2	1	0	1	9	4	2	1	0	1	0	3	5	1	5

with a displaced Colles' fracture. None of the patients had previously had forearm fractures or had undergone hormone therapy. The other exclusion criteria were: serious intercurrent diseases, especially of the liver, kidney or hematopoetic organs, medication with antacids or iron therapy and alcoholism or drug abuse. Patients suffering from joint diseases—e.g., rheumatoid arthritis and osteoarthrosis—were also excluded. The study was approved by the Karolinska Institute local ethics committee and the Swedish Medical Products Agency. The patients gave their oral informed consent before inclusion in the study.

All patients who were admitted to our emergency department and fulfilled the inclusion criteria were asked whether they wanted to participate. After consent, they were randomized, using block randomization (block of size 8), to treatment with either clodronate capsules, (Bonefos) 400 mg or placebo capsules twice daily per os; this treatment started within 48 hours after the fracture. The study was double-blind, the code being revealed after the last patient had had the final radiographic examination. Treatment was given for 8 weeks and it did not include calcium supplements. The patients were instructed to take the morning capsules at least 30 minutes before breakfast and to take the afternoon capsules at least 30 minutes before or after ingesting food or drink in order to increase the resorption of drug. The patients were also told not to take other drugs at the same time that might reduce the resorption of clodronate. They were also given paracetamol 500 mg for pain relief.

Radiographs were taken of the wrist initially, after reduction, at 10 days, 4 and 8 weeks after the trauma. All patients were treated with closed reduction under local anesthesia and application of a below elbow dorsal plaster splint. They were immobilized for 4 weeks. There was no difference in age or type of fracture between the treatment groups (Table 1). Clinical examinations were done at 10 days, 4, 8 and after 12 weeks. The patients were interviewed about any serious side-effects. Pain was recorded on a visual analogue scale (VAS). Measurements of the consumption of paracetamol also indirectly indicated pain. Grip-strength was recorded with a balloon vigorimeter.

The BMD of the forearm bones on both sides was measured in the coronal plane by a dual-energy x-ray absorptiometer, DEXA (DPX-L^{TM}, Lunar Co., Madison, Wisconsin, USA) (Mazess et al. 1989). The values are expressed as areal BMD, g/cm^2. The ultradistal radius and ulna (including the entire callus region of the radius) were scanned and also the diaphyseal region, e.g., the intersection between the distal and middle thirds of the forearm (33%-level). To facilitate measurements of the same locations on both radii, the olecranon was used as a reference on both arms, because of possible shortening on the fracture side. The uninjured forearm was scanned at the corresponding levels and the median BMD, both of the radius and ulna, were calculated. The patients were scanned again after 2 months and the measurements were repeated after 6 and 12 months.

To estimate the measurement error of DEXA, we made double measurements, with complete reposition of the forearms and the scanner, in another group of 12 patients with a Colles' fracture. The measurement error was 3.6% in radial BMD at the ultradistal level, and 1.3% in radial BMD at the 33%-level.

Statistics

We used nonparametric tests for paired (Wilcoxon signed-rank test) and unpaired data (Mann-Whitney U-test). Differences were considered signifi-

Table 2. Bone mineral density (BMD) in the forearms, given as percentage of the values of the contralateral arm, in 32 patients after a Colles' fracture. Median values (25–75 percentiles) are given. Difference in median % and calculation of the 95% confidence interval (95%CI) for the median percentage changes between forearms at 2 months and longitudinal differences in both forearms. Externally fixated patients are excluded. –sign indicates bone loss

	2 months			6 months				12 months			
	Fract.	Control	diff %	Fract.	diff % 2–6 months	Control	diff % 2–6 months	Fract.	diff % 2–12 months	Control	diff % 2–12 months
Radius											
Clodronate											
Ultradistal	0.39	0.24	53[a]	0.34	-13[a]	0.24	-1	0.33	-17[a]	0.24	-3
lower range (95%CL)	0.32	0.22	(37)	0.28	(-19)	0.21	(-5)	0.25	(-24)	0.23	(-5)
upper range (95%CL)	0.42	0.28	(58)	0.37	(-2)	0.30	(2)	0.35	(-8)	0.29	(2)
33%-level	0.50	0.54	-7[a]	0.49	-4[a]	0.56	-1	0.47	-5[a]	0.54	-1
lower range (95%CL)	0.44	0.47	(-9)	0.44	(-6)	0.48	(-2)	0.43	(-8)	0.48	(-3)
upper range (95%CL)	0.56	0.61	(-2)	0.55	(-2)	0.62	(1)	0.55	(-4)	0.61	(0)
Placebo											
Ultradistal	0.31	0.23	33[a]	0.29	-10	0.22	-3	0.29	-12	0.23	-1
lower range (95%CL)	0.30	0.22	(23)	0.25	(-16)	0.21	(-4)	0.25	(-18)	0.22	(-5)
upper range (95%CL)	0.33	0.27	(48)	0.36	(2)	0.28	(1)	0.34	(2)	0.27	(0)
33%-level	0.51	0.56	-6[a]	0.50	-3	0.55	-1	0.49	-3	0.56	-2[a]
lower range (95%CL)	0.46	0.50	(-12)	0.43	(-5)	0.47	(-4)	0.42	(-6)	0.48	(-3)
upper range (95%CL)	0.56	0.60	(-2)	0.54	(1)	0.59	(0)	0.56	(0)	0.58	(0)
Ulna											
Clodronate											
Ultradistal	0.21	0.21	-1	0.22	4	0.21	2	0.22	7	0.21	4
lower range (95%CL)	0.18	0.19	(-8)	0.19	(-5)	0.20	(-1)	0.19	(-1)	0.20	(-2)
upper range (95%CL)	0.24	0.23	(8)	0.26	(18)	0.23	(6)	0.26	(22)	0.24	(7)
33%-level	0.52	0.56	-5[a]	0.52	-1[a]	0.56	-1	0.53	-2	0.58	-1
lower range (95%CL)	0.50	0.54	(-8)	0.50	(-4)	0.51	(-4)	0.49	(-4)	0.51	(-4)
upper range (95%CL)	0.64	0.67	(-3)	0.63	(0)	0.67	(1)	0.63	(0)	0.66	(2)
Placebo											
Ultradistal	0.20	0.20	-3	0.19	1	0.20	-1	0.20	1	0.20	-1
lower range (95%CL)	0.18	0.19	(-10)	0.18	(-1)	0.18	(-5)	0.19	(-3)	0.18	(-4)
upper range (95%CL)	0.22	0.22	(3)	0.20	(6)	0.21	(2)	0.21	(9)	0.22	(1)
33%-level	0.57	0.60	-4[a]	0.55	-4[a]	0.58	-2	0.56	-2[a]	0.58	-2
lower range (95%CL)	0.52	0.55	(-6)	0.51	(-6)	0.52	(-4)	0.54	(-4)	0.55	(-3)
upper range (95%CL)	0.60	0.64	(0)	0.58	(-1)	0.62	(0)	0.58	(-1)	0.63	(2)

Areal BMD (mg × cm^{-2}).
[a] $p < 0.05$

cant at $p < 0.05$. The median values (25–75 percentiles) were calculated for absolute values of BMD and the 95% confidence intervals (95% CI) for percentage changes in BMD. The study was designed to determine whether clodronate 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 BMD was entirely prevented by clodronate, 12 patients would be needed in each group to reach a statistical power of 80% (Petersen et al. 1998). Thus, the design of the study was suitable for evaluating an almost complete preventive effect of clodronate, but it lacked statistical power to rule out a moderate effect of clodronate on BMD in the fractured forearms.

Results

Clodronate was usually well tolerated. Some gastrointestinal symptoms (slight diarrhea) were re-

Table 3. Radiographic position and clinical function, expressed as range of motion of the fractured wrist during treatment. Initially (IN), after reduction (AR), 10 days, 4, 8 and 12 weeks. Median values are given. Range of motion in percentage of the uninjured wrist

Time	Radial shortening		Dorsal angulation		Extension + flexion		Radial + ulnar deviation		Pronation + supination	
	Clodronate	Placebo	Clodronate	Placebo	Clodronate	Placebo	Clodronate	Placebo	Clodronate	Placebo
IN	2.5	3.0	110	110						
AR	0.0	0.0	95	90						
10 d	1.0	1.0	100	95						
4 w	2.0	3.0	105	95	36	42	36	47	40 [a]	71
8 w	3.0	4.0	105	95	64	65	64	71	79 [a]	92
12 w					76	76	82	74	89	94

Radial shortening (mm), dorsal angulation (degrees). Range of motion (degrees).
[a] $p < 0.05$

ported in 4 patients (2 in each treatment group) but did not require cessation of therapy. The dominant forearm was fractured in 17 patients. 2 fractures (both in the clodronate group) were reduced and operated on again with external fixation because of redislocation on the 10-day radiographic examination. These patients were excluded from further measurements. All other patients completed the study.

At 2 months, on the ultradistal level, which includes the fracture region, there was a median 53% higher BMD of the fractured than of the uninjured radius in the patients treated with clodronate (Table 2). In the placebo group, we found a median 33% higher BMD of the fractured radius at that level, compared to the uninjured radius. This increase in BMD, caused by clodronate, was significant ($p = 0.01$). At 12 months, the BMD of the ultradistal radius on the fracture side had been reduced by 17% and 12%, respectively; at that time it was still significantly increased in the clodronate group alone. There was no significant change in BMD with time in the ultradistal, uninjured radius. In the ulna at the same site, we found no significant change in BMD in either group on either side at any time.

At 2 months, on the 33%-level, we found a median 7% lower BMD of the fractured radius, compared to the uninjured radius, in the patients treated with clodronate. In the placebo group, we found a median 6% lower BMD of the fractured radius than of the uninjured radius. Although the reduction in BMD of the radius at that level was significant in both groups, a posttraumatic effect, we saw no significant difference between the two treatment groups. At this level, the BMD of the ulna showed a similar pattern, with a 5% lower BMD in the clodronate group and a 4% lower BMD in the placebo group. Again, although the reduction in BMD of the ulna at that level was significant in both groups, there was no significant difference between the groups. The osteopenia at this site showed a small progression on the fractured side after 6 and 12 months. Thus, the BMD of the ulna showed no significant recovery after 6 months. On the contrary, a further reduction in BMD on the fractured side in the placebo group was noted after 12 months.

Increased radial shortening and dorsal angulation after fracture reduction was detected with time in both groups (Table 3). However, there was no significant difference in fracture position between the groups. The patients in the clodronate group had a slower recovery of pronation and supination at 4 weeks ($p = 0.03$) and 8 weeks ($p = 0.03$). However, there was no significant difference in other parameters of range of motion at any time or in clinical function at 12 weeks (Table 3). Finally, there was no significant difference in pain or in grip-strength between the groups at any time and no difference in consumption of paracetamol.

Discussion

The measurement error of DEXA is about 1% in the radius (Barden and Mazess 1989) and 2% in the hip (Lilley et al. 1991). We made double measurements of the radial BMD in 12 patients and found a measurement error of the same order.

The effect of clodronate on mineralization of fracture callus in our study was substantial, the BMD having increased by approximately 20% after 2 months of clodronate treatment. This is in agreement with studies in the rat, where Nyman et al. (1993b) and Madsen et al. (1998) found increased calcium content in the fracture callus. In addition, Goodship et al. (1994) noted increased bone mineral content and increased amount of bridging external callus after treatment with another bisphosphonate (pamidronate) in osteomized ovine bone.

The administration of clodronate did not reduce posttraumatic osteopenia. In animals, Nyman et al. (1995) found that treatment with clodronate for 3 months failed to inhibit the decrease in BMD caused by plate fixation of the intact rabbit tibia. Åstrand and Aspenberg (1999) showed that alendronate, another bisphosphonate, also failed to inhibit the bone resorption caused by instability in rat tibia.

Some of the bisphosphonates have been reported to disturb the mineralization causing osteomalacia (McCloskey et al. 1987, Ott 1993). However, several investigators have found that not even high doses of clodronate impair the mineralization of bone (Nilsson et al. 1990, Kanis et al. 1993). An impairment of bone mineralization by clodronate could cause a more marked redislocation of the fractured radius. Redislocation (expressed as an increased radial shortening or dorsal angulation) can be detected up to the 8-week radiographic examination in both groups (Table 3). No significant difference was found between the groups. As no increased redisplacement took place, this probably means that clodronate did not impair the mineralization.

At 2 months, in the fracture region, we found a 20% higher BMD of the fractured radius in the clodronate group than in the placebo group. This significant increase in BMD, caused by clodronate, could have a protective effect on later fractures. In fact, a marked reduction in incidence of an ipsilateral refracture after previous Colles' and hip fractures has been reported (Finsen and Benum 1986, Finsen et al. 1989).

In conclusion, we found that clodronate increases the mineralization of fracture callus after a Colles' fracture. But we saw no reduction in posttraumatic osteopenia nor was there any difference in pain or in clinical function after 3 months caused by the compound.

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