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Clodronate prevents prosthetic migration

A randomized radiostereometric study of 50 total knee patients

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ABSTRACT – In a double-blind study, we randomized 50 patients to receive peroral clodronate medication or placebo from 3 weeks before until 6 months after a total knee replacement with a cemented NexGen implant. Migration of the tibial components was measured by radiostereometry at 1 year. Clodronate reduced prosthetic migration, as measured by maximum total point motion, from 0.40 mm to 0.29 mm (p = 0.01). This confirms that the early postoperative migration is related to bone resorption and thus the biology of the bone bed. Since early migration is related to late loosening, 6 months of clodronate medication might reduce the risk of loosening.

Postoperative migration in total joint replacements predicts late loosening (Freeman and Plante-Bordeneuve 1994, Kärrholm et al. 1994, Ryd et al. 1995, Stocks et al. 1995). This indicates that the risk of loosening is determined peroperatively (Ritter et al. 1999) or that crucial pathophysiological events occur during the first postoperative months, which determine the risk of late loosening (Mjöberg 1994, Aspenberg and van der Vis 1998).

By radiostereometric (RSA) analysis, it has been established that tibial components migrate postoperatively (Ryd et al. 1986, 1995, Nilsson et al. 1991, Hilding et al. 1995), mostly by sinking into the bone bed. Most implants settle after 6 months to 1 year, but some continue to migrate. All implants followed by RSA and revised due to loosening have shown continuous migration as well as, in general, greater initial migration (Ryd et al. 1995). Further, continuous migration is associated with inducible displacement, i.e., immediate motion between implant and bone on load (Hilding et al. 1995). Since the tibial component of a knee prosthesis, or the cement, rests directly on bone postoperatively, inducible displacement suggests that the superficial layer of the bone has been resorbed and replaced by soft tissue. The uppermost layer of the tibial bone bed is most probably avascular and necrotic, since the capillaries are damaged by saw-cutting, as they would be by fractures. High-pressure lavage may further remove marrow stroma and thereby any remaining capillaries. Finally, cementing can cause thermal and toxic trauma (Toksvig-Larsen and Ryd 1989, Toksvig-Larsen et al. 1991, Mjöberg 1994).

We propose a scenario in which the main event underlying continuing migration and instability is inherent in the removal and replacement of the necrotic bone. Necrotic bone appears to be remodeled without the coupling of resorption with new bone formation, that is seen in normal remodeling. Thus, if the necrotic bone trabeculi upon which the tibial component rests are resorbed before new ones are produced, softening and collapse may occur, similar to the collapse of an osteonecrosis in the femoral head. Once primary stability is lost and a fibrous membrane formed, micromotion

will prevent osseous anchorage from being re-established. The membrane that ensues may then allow further osteolysis with time, due to fluid pressure effects (Robertsson et al. 1997, Aspenberg and van der Vis 1998, van der Vis et al. 1998, 1999) or possibly effects from particles entering the membrane (Horowitz et al. 1991, Kadoya et al. 1997). These secondary phenomena may lead to clinical loosening.

If this scenario is correct, the most efficacious approach to prevent loosening would be not to address pressure generation or particles, but to change the balance between resorption and formation in the crucial remodeling of the necrotic bone bed. This might be accomplished by inhibiting bone resorption with clodronate, a bisphosphonate with proven effect against bone resorption around osteolytic metastases (Kanis and McCloskey 1997). The hypothesis of this study was, therefore, that clodronate given peri- and postoperatively would diminish prosthetic migration during the first postoperative year, as measured by RSA using total point motion as the primary effect variable.

Patients and methods

50 patients were recruited for this study, according to the calculation of statistical power. Inclusion criteria were gonarthrosis stages 3–5 according to Ahlbäck (1968), and age 60–75 years. Exclusion criteria were cortisone or bisphosphonate medication, rheumatoid arthritis or any other systemic illness affecting the skeleton, as well as generally poor health. The patients were informed 4–6 weeks before the operation with a total knee arthroplasty. Written consent was signed. Leiras Oy (Åbo, Finland) provided consecutively numbered bottles of tablets, either clodronate 400 mg (Bonefos) or placebo, the contents blinded to both patient and investigator.

3 weeks before the operations, the patients started to take 4 tablets 1 hour before breakfast every day, continuing until 6 months after the operation. 5 patients were operated on with simultaneous bilateral knee prostheses, but only the first operated knee was included in the study. The operations were performed by the first author (MH) with

Figure 1. The NexGen implant design version with tibial pegs used in this study.

cemented NexGen implants (Figure 1) (Zimmer, Warsaw, USA). The operative technique was standardized, using the 5-in-1 instrumentation and high pressure pulsatile lavage before cementation with Palacos cum gentamicin. Tantalum markers of 0.8 mm were implanted in the proximal tibia (8–10 markers) and in the plastic insert (4 markers). Radiographs for RSA were taken the first postoperative day, at 6 weeks, 6 months and 1 year. Two films were taken simultaneously at a 90° angle with the knee inside a calibration cage, according to RSA standard. The digitization of the radiographs and the calculations by the programs X-ray, kindat and winRSA were performed in Lund. The accuracy was 0.2 mm (translations) and 0.3° (rotations). The protocol of this study was approved by the Ethics Committee of Uppsala University and the Swedish Medical Products Agency.

Statistics

For power analysis, we assumed the migration to be 0.5 mm MTPM in the control group and a reduction in migration of 0.2 mm MTPM by clodronate treatment. Standard deviation was estimated to be 0.2 mm, the significance level chosen was 0.05 and the power 80%. With a two-sided test, 50 patients were required. With a one-sided test, a loss of 10 patients could be tolerated. Results were analyzed according to the intention-to-treat principle (Hollis and Campbell 1999), so that

Table 1. Migration of tibial components at 1 year postoperatively, with or without clodronate treatment, analyzed according to intention to treat. Mean and *SD*

	Clodronate (n 25)		Control (n 24)		P-value
MTPM, mm	0.29	*0.11*	0.40	*0.16*	0.01
Rotation (degrees)					
x-axis	–0.10	*0.16*	0.28	*0.28*	0.01
y-axis	0.10	*0.30*	0.07	*0.29*	0.8
z-axis	0.02	*0.14*	0.02	*0.21*	0.4
Translation (mm)					
x-axis	0.00	*0.08*	0.00	*0.11*	0.9
y-axis	0.01	*0.05*	–0.05	*0.10*	0.1
z-axis	0.03	*0.08*	–0.07	*0.09*	0.1

Table 2. Migration of tibial components at 1 year postoperatively, with or without clodronate treatment. Analyzed according to protocol; infected cases and those who did not take the medication were excluded. Mean and *SD*

	Clodronate (n 21)		Control (n 24)		P-value
MTPM, mm	0.28	*0.10*	0.40	*0.16*	0.004
Rotation (degrees)					
x-axis	–0.07	*0.14*	–0.28	*0.28*	0.001
y-axis	0.10	*0.27*	0.07	*0.29*	0.9
z-axis	–0.04	*0.09*	0.02	*0.21*	0.2
Translation (mm)					
x-axis	0.01	*0.06*	0.00	*0.11*	0.7
y-axis	0.00	*0.05*	–0.05	*0.10*	0.05
z-axis	–0.02	*0.07*	–0.07	*0.09*	0.04

all patients were considered to belong to the group to which they were originally randomized, whether or not they took their tablets. Maximum total point motion (MTPM) at 1 year was chosen as the primary effect variable before the study was started, but the results of segment motion in 6 degrees of freedom at 1 year are also presented. The Student's t-test (two-tailed) was used to compare the groups treated with clodronate and placebo, since all 7 variables from the RSA are continuous and approximately normally distributed at 1 year. P-values less than 0.05 were considered significant.

Results

1 patient was lost from follow-up. By analyzing the remaining 49 patients, the clodronate-treated group showed significantly less migration, as expressed by MTPM (Table 1). If we exclude 4 patients who did not take the medication or developed an infection, the difference between the groups increases (Table 2; Figure 2).

The patient who was lost from follow-up was in the placebo group and died of pancreas cancer, not diagnosed before the operation. 2 patients sustained an infection in their operated knees, related to other disease and diagnosed about 6 months postoperatively. Both were in the clodronate-treated group. None has needed revision, and 1 seems to have been successfully cured by antibiotics. 3 patients in the clodronate group were not able to take the medication, 2 due to gastrointestinal side-effects and 1 due to a complicated postoperative course. This patient later acquired 1 of the 2 infections.

Discussion

Tibial components in total knee arthroplasty migrate postoperatively. Most of the migration occurs during the first 6 weeks. It then continues at a gradually slower rate up to 1 year, whereafter most implants become stable (Ryd et al. 1986, 1995, Nilsson et al. 1991, Hilding et al. 1995). In a large long-term study where 158 knees were followed by RSA up to 10 years, all cases that eventually loosened had shown continuous migration,

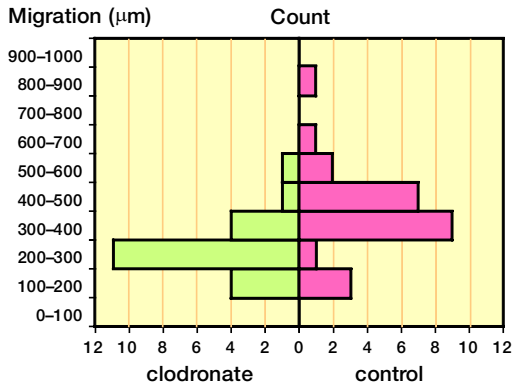

Figure 2. Frequency distribution of migration MTPM (in μm) in the clodronate-treated (green fields) and control groups (red fields). 2 noncompliers and 2 infected patients are excluded.

but also a significantly larger migration as early as 6 months postoperatively (Ryd et al. 1995). It was concluded that loosening is a process that starts very early, and that the risk of loosening can be estimated from the migratory pattern.

The early migration of tibial components could have two reasons, namely, crushing or resorption of the bone on which it rests. Reduction of migration by an osteoclast inhibitor, such as clodronate, indicates that resorption is a cause of initial migration. During normal remodeling, bone resorption does not lead to mechanical failure, since it is linked to new bone formation, by the so-called coupling phenomenon. In necrotic bone, however, this mechanism is disturbed or absent (Glimscher and Kenzora 1979). Thus, the effect of clodronate indicates that the bone adjacent to the prosthesis has been, at least in part, necrotic.

Will the long-term fixation be improved in the clodronate-treated group? It is too early to say, but there are reasons to be hopeful. Osteoclast inhibition can be assumed to preserve the necrotic bone stock adjacent to the implant, until its function has been taken over by newly formed bone. The clodronate treatment was only given for 6 months, but the effect on migration was still present at 1 year postoperatively. Maintaining the initial stability is probably crucial since once an implant is stabilized, it does not start to migrate later on (Ryd et al. 1995).

Our results do not indicate that clodronate would be efficient as treatment of incipient loosening (continuous migration) or fully developed clinical loosening. Once a membrane is established and an implant is unstable, the situation seems to be very different. Fluid pressure generated by instability has a strong osteolysis-activating effect (Aspenberg and van der Vis 1998, van der Vis et al. 1998, 1999), and there is also some evidence that wear particles entering the membrane may activate osteoclasts (Horowitz et al. 1991, Kadoya et al. 1997). Finally, increasing fatigue may be an alternative explanation of continuous migration (Taylor and Tanner 1997). However, both fluid pressure and particles are strong inhibitors of bone formation, and bone formation is not affected by clodronate (unless severely overdosed, when bone formation is suppressed) (Adami and Zamberlan 1996). Clinical loosening with osteolysis may therefore be an entirely different process than the initial remodeling that we have interfered with in this study. Osteoclast inactivation by clodronate should be regarded as prophylaxis at present and it may not be effective when secondary osteolytic factors have been allowed to enter the scene.

The relationship between early migration and future loosening has also been established for the stem (Freeman and Plante-Bordeneuve 1994, Kärrholm et al. 1994) and the cup (Stocks et al. 1995) in the hip. This suggests the same underlying mechanism for early osteoclastic bone resorption. Therefore, perioperative clodronate medication might also affect early fixation of prostheses in the hip.

Can our results be expected to be valid also for other bisphosphonates? Bisphosphonates accumulate in the bone matrix and are ingested by the osteoclasts where they interfere with enzyme systems which eventually leads to apoptosis. The intracellular action differs entirely between clodronate and aminobisphosphonates such as alendronate or pamidronate (Adami and Zamberlan 1996). Clodronate has been in clinical use for 15 years as a potent inhibitor of local bone resorption around osteolytic metastases (Kanis and McCloskey 1997), but is not yet approved for treatment of osteoporosis. The idea of using bisphosphonates to inhibit bone resorption at a bone implant interface has been tested in animal models with differing results (Shanbhag et al. 1997, Åstrand and Aspenberg 1999). Alendronate has been shown to inhibit the local osteopenia (stress-shielding effect) that develops in the proximal femur after total hip replacements (Lyons et al. 1998), but the implication of this finding on fixation is unclear. We do not believe that the effects of clodronate can be immediately extrapolated to other bisphosphonates.

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