Clinical and radiological outcome of total hip replacement five years after pamidronate therapy

A TRIAL EXTENSION

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Bisphosphonates reduce peri-prosthetic bone loss in the short term after total hip replacement but the mid- and longer term effects are not known. The aims of this randomised trial were to examine the effect of a single dose of 90 mg of pamidronate on the clinical and radiological outcome and peri-prosthetic bone mineral density in 50 patients (56 hips) over a five-year period, following total hip replacement.

At five years, 37 patients (42 hips) returned for assessment. The Harris hip scores were similar in the pamidronate and placebo groups throughout the study. Also at five years, four patients, two from each group had osteolytic lesions on plain radiography. These were located around the acetabular component in three patients and in the femoral calcar in one. The femoral and acetabular peri-prosthetic bone mineral density in the pamidronate group and the control group was similar at five years.

Pamidronate given as a single post-operative dose does not appear to influence the clinical outcome or prevent the development of osteolytic lesions at five years after total hip replacement.

Peri-prosthetic osteolysis contributes to aseptic loosening after total hip replacement (THR). At present, the only established treatment for osteolysis is revision surgery. As a result, many strategies of treatment are being developed in the hope that these may reduce the incidence of, or arrest the progression of, osteolysis. Potential approaches include the use of surfaces, such as hard-on-hard bearings or highly cross-linked polyethylene which have a low rate of wear,^{1,2} improvement of fixation of the implant by the use of osteoconductive or osteo-inductive surface coatings,³ or pharmacological intervention to preserve peri-prosthetic bone mineral density (BMD).⁴ The role of pharmacological and biological agents in modulating the progression of established osteolytic lesions is also being explored.⁵⁻¹⁰

To date, the most extensively investigated group of drugs with a potential role in modulating bone loss and osteolysis is the bisphosphonates, which have powerful anti-osteoclastic activity.¹¹ We, and other investigators, have found that they reduce early bone loss after total joint replacement.¹²⁻¹⁷ In a recent meta-analysis of six studies which met the eligibility criteria, Bhandari et al⁴ concluded that bisphosphonates preserved bone mass in the early period after surgery. However, they also highlighted the short-term nature and a lack of

relevant outcomes such as clinical function, quality of life and survivorship data, in these studies.

In a previous paper we concluded that a single post-operative infusion of 90 mg of pamidronate reduced femoral bone loss and active turnover of systemic bone over a period of two years, but did not enhance early stability of the implant.¹³ The aims of this five-year clinical trial were to study the longer term effects of treatment with pamidronate on the clinical and radiological outcome, and on peri-prosthetic bone loss as measured by dual-energy x-ray absorptiometry (DEXA).

Patients and Methods

Between April and October 1998, 50 patients with a diagnosis of primary or secondary osteoarthritis were recruited for the study. Those with inflammatory arthritis, disorders affecting bone turnover, or an intake of drugs affecting bone turnover within the preceding 12 months were excluded. The investigation was approved by the local research ethics committee. All patients gave written informed consent.

All patients received a 'hybrid' THR with a cemented femoral component (Ultima-TPS; DePuy Ltd, Leeds, United Kingdom) and a cementless press-fit acetabular component

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Table I. Details of the treatment and control groups

	Treatment	Control	p-value
Number of patients	18	19	
Number of bilateral THRs*	2	3	
Mean age in years (range)	58 (32 to 73)	57 (28 to 71)	0.795
Male:Female	12:6	10:9	0.508
Mean body mass index in kg/m ² (range)	27 (19 to 38)	29 (24 to 37)	0.155
Mean pre-operative BMD† in g/cm ² (range)			
Net proximal femur	1.80 (1.43 to 2.07)	1.77 (1.34 to 2.30)	0.727
Net pelvis	1.14 (0.67 to 1.56)	1.12 (0.96 to 1.71)	0.682
Mean component linear wear at five years in mm (range)	0.90 (0.15 to 3.48)	0.60 (0.22 to 3.48)	0.204

* THRs, total hip replacements

† BMD, bone mineral density

(Plasma cup; Braun Ltd, Sheffield, United Kingdom), except two, in whom press-fit stability was not achieved; they received a cemented Charnley acetabular component (DePuy Ltd). Details of the operative procedure and the post-operative regime of mobilisation have been described previously.¹² Patients were randomised to receive either a single intravenous infusion of 90 mg of pamidronate (Novartis Pharmaceuticals UK Ltd., Frimley, United Kingdom) or a placebo using a computer-generated, simple randomisation design. Both were prepared in the hospital pharmacy, supplied as a colourless solution in 500 ml of 0.9% sodium chloride and administered on the fifth post-operative day.

Clinical and radiological assessment. Clinical assessments were made using the Harris hip score¹⁸ pre-operatively and at 12 and 26 weeks and one, two and five years after operation. Standardised supine anteroposterior (AP) radiographs of the pelvis and proximal femur were taken at the post-operative baseline and at 6, 12 and 26 weeks and one, two and five years. The location of any osteolytic lesions around the pelvic implant was categorised using the zones described by DeLee and Charnley,¹⁹ and of any femoral peri-prosthetic osteolytic lesions by the zones described by Gruen, McNiece and Amstutz.²⁰ Measurements of the size of the lesion were made using a metric digital electronic caliper with outside-inside jaws, a manufacturer's precision of ± 0.01 mm and an accuracy of ± 0.02 mm (model KEN-331-1330 K; Kennedy Tools, Sheffield, United Kingdom). Measurements were corrected for magnification by using the known size of the femoral head, and expressed in millimetres as the maximum width and length of the osteolytic lesion. The radiographs were then digitised using a laser digitiser (Lumniscan 200; Lumisys Inc., Sunnyvale, California) and the wear of the acetabular component was measured using EBRA software (EBRA-Cup 1998 release, University of Innsbruck, Austria) by the method described previously.²¹

Bone densitometry. The patients underwent baseline DEXA scans of the proximal femur and hemipelvis one week after operation and had follow-up scans at 6, 12 and 26 weeks and one, two and five years. The scans were acquired and analysed using a Hologic QDR 4500-A fan-beam densito-

meter (Hologic Inc., Bedford, Massachusetts) in 'metal-removal' scanning mode according to an established protocol.²² The BMD was measured in seven contiguous regions of interest around the femoral implant and in four around the acetabular implant.²³ The terms 'net femoral' and 'net acetabular' region of interest defined a global region around each implant. Manual exclusion was performed on areas containing heterotopic bone from the analysis of regions of interest, as described previously.¹²

The DEXA scans acquired at five years were analysed using a Windows version of the Hologic software (version 11.2; Hologic Inc.), while the previous scans were assessed using DOS software (version 8.0; Hologic Inc.). Previous analysis of femoral and acetabular scans in an independent group of 29 patients after THR has determined that no calibration correction is necessary for measurements made using the Windows software.²⁴

Statistical analysis. All analyses were made on a 'per-patient' basis. When a patient had received bilateral THRs, values for the change in the BMD were expressed as the mean change for both hips. Analysis of serial numerical data was made by repeated-measures analysis of variance (ANOVA) and that of categorical data by the chi-squared test. All analyses were two-tailed using a critical p-value of 0.05 and were conducted using SPSS software version 12 (SPSS UK Ltd, Woking, United Kingdom).

Results

Of the 50 patients recruited, 37 (74%) returned for assessment at five years. All had received a hybrid THR. In five, bilateral simultaneous THR had been performed, giving a total of 42 hips available for analysis. The baseline characteristics of the control and treatment groups were similar (Table I). At five years, six patients had died and three were withdrawn for violations of the protocol. Of these three, one had a traumatic fracture in the early post-operative period, one was diagnosed with inflammatory arthropathy and the other one developed temporal arteritis requiring systemic steroid therapy. Two others (one from each group) declined review and two were lost to follow-up.

Clinical and radiological assessment. The median Harris hip scores were similar in the treatment groups throughout the

Fig. 1

Harris hip scores of the patients over five years showing a) the overall score; b) the pain component; c) the functional (including deformity) component and d) the range of movement. The error bars give the median $\pm$ the interquartile range.

study (Fig. 1a). The baseline scores were similar in both groups, and most improvement in scores occurred during the first 12 weeks. At five years there was a trend toward a poorer Harris hip score in the pamidronate group without reaching statistical significance. Examination of the three principal domains of the score (pain, function including deformity and range of movement) showed that this trend lay in the functional component of the summary score, but was also not significant (Figs 1b to 1d). The data from the principal domains also showed that the scores for pain and range of movement underwent the most rapid improvement, with most occurring during the first 12 weeks whereas functional improvement occurred more slowly but continued for up to one year after surgery.

Isolated expansile osteolytic lesions were identified on anteroposterior radiographs of the hip at five years in four patients (two in each group; chi-squared test $p = 0.954$), but none had evidence of loosening on plain radiographs. In three patients (two placebo, one pamidronate) cavitory osteolytic lesions (Fig. 2) were seen in the region of the

Fig. 2

Radiograph of the pelvis showing a small osteolytic lesion in the acetabular dome.

Fig. 3

The mean ($\pm$ SEM) change in regional femoral bone mineral density (BMD) (g/cm^2) over five years in both groups.

Fig. 4

The mean ($\pm$ SEM) change in the regional pelvic bone mineral density (BMD) (g/cm²) over five years in both groups.

acetabular dome, the largest measuring 18 mm x 9 mm. In one patient an osteolytic lesion measuring 4.5 mm x 8.1 mm was noted in the region of the femoral calcar. Three of the patients with osteolysis were asymptomatic and one reported pain. No linear osteolytic lesions were seen in either group.

Bone densitometry. The pre-operative femoral BMD was similar in both groups (Table I). In the placebo group it declined rapidly in the first 12 weeks after surgery in all regions (Fig. 3), followed by a recovery phase in all zones except regions 6 and 7, which showed further decline. Treatment with pamidronate resulted in a consistent trend towards less bone loss in regions 6 and 7 in all the post-operative stages, although this did not reach statistical significance (Fig. 3; region 6, ANOVA, $p = 0.187$; region 7, ANOVA, $p = 0.184$). No differences between the groups

were found for the other regions of interest in the femur over the five-year period.

The pre-operative BMD for the acetabulum was similar in both groups (Table I). In the placebo group the pelvic BMD declined rapidly over the first 12 weeks after surgery in all regions (Fig. 4). Continued bone loss was seen throughout the five years in all regions, except in region 4 in which there was subsequent recovery in the BMD. Bone loss was most severe in the region of the acetabular dome, in regions 2 and 3. Treatment with pamidronate did not influence the loss of BMD over the five-year period (ANOVA, $p > 0.05$ all regional comparisons).

Adverse events. The adverse events in the initial two years after surgery have been described in our previous studies.^{12,13} Over the subsequent three years, five of 19 patients (26%) in the placebo group and seven of 18 (39%) in the

pamidronate group experienced such problems (chi-squared test, $p > 0.05$). In the placebo group two developed hypertension, one had a chest infection, one underwent lobectomy for bronchiectasis and one had a fracture of the ankle and also underwent prostatectomy. In the pamidronate group, diabetes with peripheral neuritis was detected in one patient, one had a peptic ulcer, one had angina which required insertion of coronary stents, one underwent repair of an inguinal hernia, one developed an ear infection, one had a fracture of the neck of the femur on the contralateral side which required screw fixation and one suffered a dislocation of the hip which was treated by closed reduction.

Discussion

Previous studies examining the role of bisphosphonates after THR have had a short follow-up and have focused mainly on peri-prosthetic changes in the BMD.^{12,14-16} Our study evaluated the effect of pamidronate on the clinical and radiological outcome over a period of five years. We found that a single post-operative dose of pamidronate did not affect the clinical outcome after THR, nor did it prevent the development of osteolytic lesions. The incidence of osteolytic lesions in our study population was high (9.5%). Possible reasons for this include the relatively young mean age of the patients (58 years; 28 to 73) and a high mean linear wear of the acetabular polyethylene at five years of 0.90 mm and 0.60 mm in the pamidronate and placebo groups, respectively (Table I).

We have previously described the significant effect of a single dose of pamidronate in preserving acetabular and femoral bone mass at six months after the operation,¹² and that subsequently its efficacy was lost on the acetabular site.¹³ Our data at five years suggest that the effect of this therapy on the femoral side after a single dose was also lost in the long term. However, this loss of significance may have been a result of reduced statistical power at the five-year stage because of the withdrawal of patients, since the trend towards preservation of the bone mass remained (Fig. 3). Using the alternative approach of 'per-hip' analysis (42 hips), rather than 'per-patient' (37), the trend towards preservation of the bone mass for regions 6 and 7 remained significant over the five-year period (region 6, ANOVA, $p = 0.038$; region 7 ANOVA, $p = 0.048$). Wang et al¹⁷ have recently noted a similar loss in efficacy in preservation of the distal femoral BMD at three years after the cessation of treatment with alendronate in total knee replacement. Their data also showed a trend towards preservation of the bone mass in the bisphosphonate group compared with a control group (BMD change -3.9% *vs* -12.2%, respectively, $p = 0.08$). Taken together, these studies suggest that maintenance doses would be required to have a clear effect on the preservation of the peri-prosthetic bone mass in the long term after total joint replacement. However, the impact of preservation of the bone mass in relation to the risk of aseptic loosening remains unknown,²⁵ and such

therapy outside the setting of clinical trials cannot be justified based on current evidence.

The observed lack of an effect in inhibiting osteolysis may be due to a primary inability of pamidronate to influence peri-prosthetic osteolysis, or it may be a function of an insufficient dose. Previous studies in small and large animal models have suggested a potential role for other bisphosphonates in inhibiting osteolysis. Von Knoch et al²⁶ reported a favourable effect of a single dose of zoledronic acid on particle-induced osteolysis in mice. Studies in a rat model by Millett, Alen and Bostrom,²⁷ and in a canine model by Shanbhag, Hasselman and Rubash,²⁸ have also shown that alendronate can inhibit particle-induced osteolysis. However, a clinical study has not shown a similar effect in man.⁹ Rubash et al⁹ found that daily oral administration of 10 mg or 35 mg of alendronate did not have any effect on decreasing the progression of established femoral osteolytic lesions in 123 patients studied over 18 months. The results of these studies suggest that the timing of the administration of bisphosphonate in relation to the development of osteolysis and the type of bisphosphonate used may be important.^{9,27,28} The successful animal studies differ from those in clinical practice in that the bisphosphonate was given at a similar time to the osteolytic stimulus (particles), and that bisphosphonate was started before osteolytic lesions were established.^{27,28} The nearest clinical situation to that of the animal models may be in the commencement of prophylactic administration in patients with established high wear rates of the implant, given before the development of osteolytic lesions.

The regional pattern of the longitudinal peri-prosthetic change in the BMD around a cemented, polished, collarless, double-tapered femoral implant over the period studied has not been described previously. The data from our control and treatment groups suggested that the overall magnitude of bone loss associated with use of this design of implant was small. This may be a reflection of the force-closed design principle,²⁹ allowing more proximal load transfer to host bone than shape-closed implant designs. By contrast, acetabular bone loss was greater than that around the femoral component and was progressive over the five-year period, occurring predominantly at the acetabular dome suggesting a rim-loading pattern of load transfer, as previously proposed for uncemented metal-backed acetabular components.³⁰

Our study has a number of limitations. We recruited 50 patients at the start, but only 37 could be included in the analysis at five years. Also, the study was powered to examine changes in the BMD and not osteolysis. We used plain radiography to assess the osteolytic lesions, and it is possible that the number of lesions detected may be higher with the use of advanced imaging techniques such as CT or MRI.³¹

In summary, although single-dose post-operative pamidronate therapy is effective at reducing bone loss at two years, this effect is not sustained over five years.

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