No effect of Osteoset®, a bone graft substitute, on bone healing in humans

A prospective randomized double-blind study

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ABSTRACT – We studied the effects of a newly marketed bone substitute, Osteoset, on bone healing in a tibial defect in humans. 20 patients undergoing an ACL (anterior cruciate ligament) reconstruction with bone-patella tendon-bone graft were block-randomized into 2 groups of 10 each. In the treatment group, the tibial defect was filled manually with Osteoset pellets, in the control group the defect was left empty. CTs of the defect were taken on the first day after the operation, 6 weeks, 3 and 6 months postoperatively. We found about the same amount of bone in the defect in the Osteoset and control groups after 6 weeks, 3, and 6 months. In the control group, but not in the Osteoset group, the bone volume increased from 6 weeks to 3 months. The Osteoset pellets were almost resorbed after 6 weeks.

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Numerous bone substitutes are to be found on the market (Ladd and Pliam 1999). Osteoset is a synthetic bone graft substitute made of calcium sulfate, like plaster of Paris (Wright Medical 1997a). The product has been approved by the FDA and is CE marked. It can be used alone or in combination with other naturally occurring materials to fill bone voids or gaps (Pecora et al. 1998, Debes et al. 1999, Tay et al. 1999, Wilkins et al. 1999). The effectiveness of calcium sulfate as a vehicle for delivery of local antibiotic treatment has also been shown (Petersen et al. 1999, Turner et al. 2000). The osteoconductive properties of calcium sulfate have been studied in animals for several decades (Peltier et al. 1957, Turner et al. 1999). However, its use in humans has only been evaluated in uncontrolled studies (Sottosanti 1995, Pecora et al. 1998, Wilkins et al. 1999, Mirzayan et al. 2001).

In this prospective randomized trial on humans, we investigated the effects of Osteoset pellets on bone healing in a critical size defect.

Patients and methods

We block-randomized 20 patients undergoing a standard ACL reconstruction into 2 groups of 10 in each. Before surgery, the surgeon knew to which group the patient had been randomized. The study, designed as a double-blind trial for patients and clinicians, had been approved by the local ethics committee. The patients gave their informed consent to participation.

Inclusion criteria. We included patients having a total ACL (anterior cruciate ligament) lesion suitable for reconstruction with a bone-patella tendon-bone graft.

Exclusion criteria. We used several of the manufacturer's contraindications: degenerative and metabolic bone diseases, uncontrolled diabetes mellitus, severe vascular and neurological diseases, uncooperative patients who will not or could not follow postoperative instructions, including those who abused alcohol and/or drugs, hypercalcemia, pregnancy, breastfeeding and an immature skeleton.

The patients were healthy apart from the ACL lesion. Most of them had paticipated in sports in the past. 4 men and 6 women with a mean age of 29 (21–40) years were included in the Osteoset group whereas 6 men and 4 women with a mean age of 31 (19–44) years were included in the control group.

Osteoset

The Osteoset manufacturing process creates a uniform crystalline structure of alpha-hemihydrate calcium sulfate of a specific size and shape (hexagonal) which results in a controlled resorption rate said to be similar to that of new bone formation (Wright Medical 1997b). Osteoset was donated by Pro-Meduc ApS (Frederiksberg, Denmark). The 4.8 × 3.3 mm pellets were supplied sterile for use in a single patient.

Surgery

Two senior surgeons performed the operations with a standardized procedure using a tourniquet. During the operation, the bone-patellar ligament-bone graft was prepared. The defect in the tibial tuberosity, created by an oscillating saw, measured approximately 1 × 1 × 2.5 cm. In the treatment group the tibial defect was filled manually with Osteoset pellets to the level of the cortical bone (about 32 pellets). No graft material was left in the tibial defect in the control group. The peritendium above the defect was sutured and the defect in the patella was left empty in both groups. Prophylactic antibiotics (Cefuroxim) were given intravenously before surgery. No drain was used. All patients followed a standard rehabilitation program, with mobilization on the first day after surgery.

We took CT images of the defect on the first day after the operation, 6 weeks, 3 and 6 months post-operatively to quantify bone formation. In accord with the double blind design, the CTI were evaluated in reverse order.

CT imaging

We used the PICKIR PQ 2000 CT scanner, a width of 2 mm per scan, and took about 10–14 images per defect, which were enlarged and developed by standard procedures. The densities of Osteoset pellets, fibrous tissue, cortical, trabecular and new bone were measured on CT images and expressed in Hounsfield units (Table 1).

Table 1. The densities of various tissues and pellets measured on CT images in Hounsfield units

Tissue type	mean Hounsfield units
Cortical bone	1300
Cancellous bone	450
New bone	400
Connective tissue	180
Osteoset pellets	1300

The Scritel Digitizer (software Jandel Sigma Scan) was used to measure manually the area of the defect on each section. Each section was evaluated 3 times and the mean value calculated. From these measurements we calculated the coefficient of variance to assess the precision of the method.

The defect volume was determined with the formula:

$$V_{defect} = \sum \text{area(section)} \times t$$

V_{defect}: defect volume (mm^3),
$\sum$ area(section): sum of the areas (mm^2),
t: the distance between each section (2 mm).

Reduced defect volume—i.e., new bone formation—calculated by the formula:

$$V_{NB} = (V_{post} - V_{follow\text{-}up}) \times 100\% \; / \; V_{post}$$

V_{NB}: new bone volume, %
V_{post}: the defect volume on the first day after the operation.
$V_{follow\text{-}up}$: the defect volume at 6 weeks, 3 and 6 months.

Statistics

The data are presented as mean (SD). 95% confidence intervals were calculated for the main results. The data were analyzed using unpaired ANOVA on ranks and pairwise multiple comparison procedures (Student-Newman-Keuls method) followed by a t-test of statistical significance. The study was planned to reveal a difference in bone volume of 70% between groups by SD 50%, type I error 5%, and type II error 20%. The coefficient of variance was calculated by Therkelsen's method (1979).

Table 2. Coefficient of variance of estimated bone area, calculated from the measurements

Time of evaluation	Coefficient of variance, %
Postoperative	7.8
6 weeks	16
3 months	14
6 months	11
Mean	12

Table 3. Bone formation in the tibial defect in patients undergoing ACL reconstruction, expressed as percentage of the total defect volume after surgery

Time of evaluation	Percent of new bone volume	
	Osteoset group	Control group
Postoperative	0	0
6 weeks [a]	42	30
3 months [b,c]	44	44
6 months	47	49

[a] No significant difference between the groups (p = 0.06, t-test).
[b] No significant increase in bone formation in the Osteoset group.
[c] Statistically significant increase in bone volume from 6 weeks to 3 months in the control group.

Results

All 20 patients completed the study. No intraoperative or postoperative complications occurred. No prolonged drainage or differences regarding wound healing were observed between the groups. The coefficient of variance showed that the method of evaluation was very precise postoperatively and after 6 months (Table 2).

We found most new bone formation during the first 6 weeks after surgery (Table 3). 42 (CI 33–51)% of the primary defect had filled with new bone in the Osteoset group compared to 30 (CI 22–38)% in the control group (p = 0.06). Later, no statistically significant changes occurred in the Osteoset group, but in the control group, more new bone had formed at 3 months than at 6 weeks (p = 0.01). We observed no new bone formation from 3 to 6 months in either group. None of the defects became completely filled with bone.

In the Osteoset group, 51 (SD 12)% of the defect was filled with pellets postoperatively. We found a positive correlation between the volume of pellets and new bone volume at 6 weeks (correlation coefficient r = 0.78, p = 0.005), but no significant correlation at 3 and 6 months.

Remnants of the pellets were present after 6 weeks, but not after 3 months.

Discussion

Animal studies have showed the effect of Osteoset on bone healing (Debes et al. 1999, Turner et al. 1999). However, in our prospective randomized study, we found no statistically significant effect of Osteoset on bone healing in humans. The study was designed to reveal a great difference of 70% or more on bone formation between groups since a small difference has hardly any clinical significance. Due to lower standard deviations than predicted, we showed a difference of 18% in bone formation between groups of 10 patients each.

The discrepancy between the results of the animal studies and ours in humans may be due to much greater bone healing and remodeling in dogs than in humans with rapid resorption of pellets (Kimmel and Jee 1982). Secondly, the tibial defects in our study were larger than in animal trials. Thirdly, in the canine model, the Osteoset pellets were surrounded by trabecular bone in the entire circumference, but in our model, the pellets had bone contact only with the sides and the bottom of the defect. The pellets had no contact with periosteum.

We showed statistically significant new bone formation in the Osteoset and control groups 6 weeks after surgery, with a tendency towards more bone formation in the Osteoset group (p = 0.06). This early finding may be partly explained by remnants of pellets being detected as bone, which can have made us overestimate bone formation at that time. This may also explain the positive correlation between Osteoset volume and bone formation in the defects after 6 weeks. However, it did not affect our failure to find a difference in bone formation after 3 and 6 months.

These results show the limitations of animal studies and the importance of controlled studies in humans. It should be stressed that our study was performed in healthy bone with optimal healing

capacity. It may be that Osteoset would be more efficacious in unhealthy bone. However, the Osteoset resorption rate seems too rapid for bone formation in humans even during optimal conditions with no micromovement. Nadkami et al. (2000) reported better bone formation on calcium sulfate composites augmented with calcium phosphate, which reduced the resorption rate. Bone substitutes with less rapid resorption than Osteoset may be better in men.

Osteoset was donated by Pro-meduc ApS, Denmark.

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