Implant fixation enhanced by intermittent treatment with parathyroid hormone

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**THE JOURNAL OF BONE & JOINT SURGERY**

The intermittent administration of parathyroid hormone (PTH) increases the formation of bone by stimulating osteoblastic activity. Our study evaluates the possibility that intermittent treatment with PTH (1-34) may also enhance the implant-bone fixation of stainless-steel screws. Twenty-eight rats received one screw in either one (n = 8) or in both (n = 20) proximal tibiae. We administered either PTH (1-34) in a dosage of 60 μg/kg/day (n = 14) or vehicle (n = 14) over a period of four weeks. At the end of this time, the degree of fixation was assessed by measuring the removal torque on one screw in each rat (n = 28) and the pull-out strength on the contralateral screw (n = 20). PTH increased the mean removal torque from 1.1 to 3.5 Ncm (p = 0.001) and the mean pull-out strength from 66 to 145 N (p = 0.002). No significant differences in body-weight or ash weight of the femora were seen. Histological examination showed that both groups had areas of soft tissue at the implant-bone interface, but these appeared less in the PTH group. These results indicate that intermittent treatment with PTH may enhance the early fixation of orthopaedic implants.

**Materials and Methods**

**Implants.** All the screws were manufactured from stainless steel (SS 2333). The threaded part was 1.7 mm in diameter and 3 mm long. The head of the screw was triangular to allow it to fit the chuck used for the measurement of torque. The screws had a hole in the triangular head so that a specially constructed device could be connected for pull-out measurement (Fig. 1).

**Experimental procedure.** Approval of the Institutional Review Board was obtained for the study. In a first series eight Sprague-Dawley rats, weighing between 325 and 340 g, received one screw in the left tibia. These were used for the measurement of removal torque. In a following series of 20 Sprague-Dawley rats weighing between 250 and 350 g, one screw was inserted into each tibia. One was used for removal torque (left) and the other (right) for pull-out strength. The animals were housed at 22°C. Two rats were kept in each cage with free access to standard laboratory food pellets and water. Streptomycin (12.5 mg) was given intramuscularly before surgery.

Under general anaesthesia with 0.6 to 0.7 ml of a mixture of pentobarbital (15 mg/ml) and diazepam (2.5 mg/ml) given intraperitoneally, the medial proximal tibial met-
aphysis was exposed through a longitudinal incision using an aseptic technique. The periosteum was reflected proximally up to the epiphysis. An insertion hole was hand-milled in the cancellous bone, approximately 3 mm distal to the epiphysis, using a regular 1 mm injection needle. Each implant was inserted in the hole and screwed down carefully until its head reached the bone. After insertion of the implant, the skin was sutured using a 4/0-monofilament nylon suture. The animals bore full weight immediately afterwards.

After implantation of the screws the rats were randomly divided into two groups of equal number. One had a subcutaneous injection of human PTH (1-34) (Bachem, Bubendorf, Switzerland) in a dosage of 60 µg/kg body-weight/day dissolved in a vehicle of 0.5 M saline with 2% heat-inactivated rat serum. The second group had an injection of vehicle only. The injections were given once a day, with the exception of Christmas Day, for 28 days between 8 am and 10 am. The rats were weighed once a week, and the doses were adjusted accordingly.

After four weeks the animals were killed with an overdose of pentobarbital. All tissue growing on and around the head of the screw was removed. The fresh unfixed specimens were then used for immediate testing at room temperature.

In all rats, the torque was measured in the left tibia with the screw connected to a freely rotatable chuck which had a 10 cm metal lever arm connecting it to a traction transducer. The transducer was constructed from a brass ring and strain gauges in a four-bridge, and connected to a computer to measure the force applied momentarily. The system was calibrated with weights. The torque was applied manually by a blinded investigator, who aimed at increasing the rotary moment by 1 Ncm/s by looking at the force display, until rotation started. The maximum torque value was recorded.

The right tibia of the rats with bilateral implants was fixed by a clamp and traction was applied through a metal pin passing through the hole in the screw. The pin was connected to the transducer through a horseshoe-shaped metal connector. The transducer was connected to a self-constructed tensile testing device, driven by a servo engine acting on a threaded spindle producing a cross-head speed of 20 mm/min. The pull-out strength was measured as the peak force when the screw loosened from bone.

All the specimens were then prepared for decalcified histology with sections taken parallel to the long axis of the screw hole. One section from the middle of the hole was stained with haematoxylin and eosin. The right femur was collected, ashed at 900°C and the ash-weight registered. The torque and pull-out results were then tested for significance using Student’s t-test.

Results

One rat of the PTH group died shortly after the operation and was excluded. Four pull-out screws (two PTH-treated and two control) as well as five torque screws (three PTH-treated and two control) showed loosening of the implant without discoloration or swelling around it. This was probably due to faulty implantation or postoperative trauma to the large protruding head of the screw, and the samples were excluded from the study. All other implants seemed stable. Macroscopically, the PTH(1-34)-treated screws had dense fibrous tissue around the head of the screw, making it in some cases difficult to remove. This was not seen around the untreated screws.

The removal torque in the PTH-treated group was three times higher than that in the control group (p = 0.001) and the pull-out strength was doubled (p = 0.002). The mean value for removal torque in PTH-treated implants was 3.5 ± 0.15 (sd) Ncm and in the untreated specimens 1.1 ± 0.02 Ncm (Fig. 2). The torque reached its maximum when the screw loosened and rotation started, but it remained almost as high during more than 90° of rotation, indicating that it mainly reflected friction between the screw and the tissue. The mean pull-out strength of PTH-treated specimens was 145.0 ± 42.0 N whereas in the untreated specimens it was 66.0 ± 14.0 (Fig. 2). After failure, the force immediately decreased almost to 0 N. Often the screw threads of the PTH specimens were filled with bone which had been pulled out, whereas only small amounts were seen in the control group (Fig. 1). Treatment with PTH did not influence the body-weight of the rats. The mean body-weight of the control group increased by 16.0 ± 7.0% during the period of injection. In the PTH group the increase was 18.0 ± 5.0%. The mean ash weight of the control group was 0.49 ± 0.05 g and in the PTH group it was 0.54 ± 0.07 g (p = 0.07).

Histological examination showed that both groups had areas of soft tissue at the bone-implant interface, but these seemed less in the PTH group, which also had a higher...
density of trabecular bone around the implant (Fig. 3). No fracture lines or other signs of damage were seen around any of the screws tested for torque.

Discussion

The results indicate that intermittent treatment with PTH may enhance early fixation of orthopaedic implants. At the level of resolution of the equipment used, it was not possible to find a torque load below which there was an elastic deformation without a plastic deformation. Such an elastic range would be expected if there were a direct bond between the implant and the bone tissue with a finite shear strength. Since, however, the torque remained high with continued twisting and thus represented friction, it appears that the considerable torque which developed after treatment with PTH may have been because a larger proportion of the surface of the screw had direct contact with bone. It has been suggested that measurements of surface cover are a less sensitive indicator of bony apposition than mechanical tests. Our study used identical implants in all cases and therefore relies on mechanical testing and qualitative histology.

In contrast to the torsion test, the results of the pull-out test appear to be more dependent on the bone surrounding the implant and less on the properties of the interface, because the threads constitute an efficient load-transfer mechanism. The bone in the vicinity of the implant was therefore splintered and fractured in the pull-out test.

It has been shown that administration of PTH to normal adult rats at a dose of 60 µg and 200 µg/kg/day, respectively, increased the amount of callus and the mechanical strength of fractures after 40 days of healing. To our knowledge, fixation of an implant after administration of
PTH has not previously been studied. Early fixation of orthopaedic implants occurs as part of the response to the trauma of the operation. Thus, if repair of a fracture can be accelerated, this would also apply to fixation of an implant. The action of PTH in our study and the finding of a higher trabecular density in a previous study \(^7\) complies with the concept that intermittent treatment with PTH acts by enhancing recruitment and proliferation of osteoprogenitor cells. \(^7\) In addition, PTH may have increased the ability of committed osteoblasts to synthesise matrix, as supported by the higher pull-out strength.

The mechanism behind the anabolic effect of treatment with PTH is not fully understood. PTH binds to receptors on osteoblasts, and the regulation of immediate early genes through PTH has important functional consequences in the downstream regulation of bone matrix genes and the onset of the differentiation of bone cells. \(^12\) PTH may also enhance the synthesis of insulin growth factor I (IGF-1) as well as the secretion of IGF-1-binding proteins in osteoblast-like cells. These factors are then thought to increase bone formation further. \(^13\) A short-term histomorphometric study, which addressed the mechanism of the anabolic action of PTH in man, was performed in a group of osteoporotic patients. \(^14\) After one month of treatment with PTH the mineralising surface and the rate of formation of bone were increased significantly in the PTH-treated patients. Because of the short time period after initiating PTH and tetracycline labelling, the authors interpreted these data to indicate that the formation of bone was occurring on previously quiescent bone surfaces. The effects on already activated surfaces, i.e., after orthopaedic surgery, may start even earlier.

Since the mechanism behind the anabolic effect of intermittent treatment with PTH is unknown, adverse effects are also unknown. Such treatment, however, for osseointegration and the healing of fractures, would be required for a short time only. This would avoid the risks of the adverse effects associated with chronic medication. The present study shows that intermittent administration of PTH (1-34) at a dose of 60 \(\mu\)g/kg/day enhances removal torque and pull-out strength of a stainless-steel screw after only four weeks. This is, to our knowledge, the first demonstration of the pull-out strength of a stainless-steel screw after only four weeks. This would avoid the risks of the adverse effects associated with chronic medication.

Intermittent treatment with PTH may therefore enhance the incorporation of orthopaedic implants.

The authors thank T. Andreassen for help with the PTH, M. Christensson for help with design and manufacturing of the implants and I. Mårtensson and C. Forslund for technical assistance. This study was financially supported by the Swedish Medical Research Council (project 2031), the Medical Faculty of Lund University and the King Gustaf V Jubileumsfond, the Greta och Johan Kocks, the Alfred Osterlund, and the Tore Nilsson Foundations.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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