

Effects of short-term treatment with corticosteroids and indomethacin on bone healing

A mechanical study of osteotomies in rats

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We studied the effects of short-term therapy with methylprednisolone and indomethacin on healing of intramedullary pinned osteotomies of the femur in rats. When the osteotomy was complete and healing occurred under unstable conditions with callus formation, indomethacin inhibited healing when estimated by mechanical tests of bending moment, energy expenditure before refracture, and bending

rigidity 6 weeks after surgery. No inhibitory effects were seen following corticosteroid treatment. When the osteotomy was incomplete and healing occurred under stable conditions, similar tendencies were observed.

Thus, short-term medication with indomethacin inhibits fracture healing. This was not the case with short-term methylprednisolone.

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Long-term treatment with glucocorticosteroids are known to induce general osteoporosis and increase the tendency for spontaneous fractures. Furthermore, long-term (more than one week) therapy with corticosteroids and nonsteroid antiinflammatory drugs inhibit fracture healing (Blunt et al. 1950, Sissons and Hadfield 1951, Rø et al. 1976, Sudmann et al. 1979, Allan et al. 1980, Keller et al. 1987). However, in some medical conditions only short-term medication with these potent antiinflammatory drugs are used. The consequences of such therapy on bone metabolism are unclear.

We studied the effects of short-term medication with methylprednisolone and indomethacin on fracture healing under unstable and stable conditions.

Material and methods

72 male Wistar rats (Møllergaard, Copenhagen, Denmark) with a median weight of 338 (315-355) g were randomly divided into 2 groups: a complete-osteotomy group and a partial-osteotomy group. These groups were divided into 4 subgroups with 9 rats: NaCl-injection control group, steroid group, indomethacin group, and oral-carboxymethyl-cellulose (CMC) control group. The NaCl group received intramuscular injections of 0.66 mL saline just before surgery and thereafter daily for 3 days. The steroid group was treated with intramuscular injections of methylprednisolone 0.20

mg/100 g body weight (Solu-Medrol, Upjohn, Kalamazoo, MI, USA) just before surgery and thereafter daily for 3 days. The indomethacin and the CMC groups were medicated through an intermittently placed flexible, nontraumatic oro-gastric tube one hour before surgery and then daily for 3 days. There was no need for any kind of sedation before the esophageal intubation. Indomethacin (Indocid, MSD, Rahway, NJ, USA) was used in doses of 0.20 mg/100 g body weight. CMC 10 mg/mL served as the vehicle in the indomethacin group, and thus pure CMC (10 mg/mL) in doses of equal volume as indomethacin was included as a control therapy.

Intraperitoneal anesthesia (0.15 mL/100 g body weight) with a mixture of 25 percent Dormicum (midazolam 5 mg/mL; Roche, Basel, Switzerland) and 25 percent Hypnorm (fluanison 10 mg/mL, fentanyl citrate 0.315 mg/mL; Janssen, Beerse, Belgium), was used. The left femur was exposed through a lateral incision between the lateral vastus and hamstrings muscles.

The complete osteotomy group

A partial transverse osteotomy of the midshaft of femur was made with a fine-toothed diamond circular saw with a thickness of 0.21 mm, mounted on an electrical drill (Kavo EWL 900, Leutkirch/Allgäu, Germany). Soft tissue was protected with a periosteal elevator when making the osteotomy. The femur was then manually broken, and the medullary cavity was

reamed from the osteotomy site to a diameter of 1.5 mm, using steel burrs mounted on the electrical drill. A pointed inoxydable 1.6-mm stainless-steel pin (Synthes, Switzerland) was introduced from the fracture site and drilled through the greater trochanter. Then the osteotomy/fracture was reduced, and the steel pin was driven into the distal fragment. The wound was closed in layers.

The partial osteotomy group

A partial lateral osteotomy of the femur midshaft was made with the same diamond circular saw. The depth of the osteotomy was standardized to 3.0 mm by the use of a stop disc that was fastened to the saw. The greater trochanter was exposed, and the medullary cavity was entered using an awl. It was reamed gradually to a dimension of 1.5 mm, and a 1.6-mm steel pin (Synthes, Switzerland) was driven into the medullary cavity.

8 rats were operated on with partial osteotomy and killed prior to the experiments to obtain initial data on bone dimensions and mechanical characteristics of the partially osteotomized femora.

No rats died in the postoperative phase and they seemed to tolerate the operation well. Unprotected weight bearing was allowed. The weight 6 weeks after osteotomy was 421 (329-479) g. There were no significant differences between the groups, but a tendency for a somewhat reduced weight gain in the steroid group was seen.

6 weeks after the operation, all the rats were killed by CO₂ gas. The left femur was carefully dissected free of all soft tissue and the intramedullary pin was removed. Radiography was performed before and after removal of the intramedullary pin. The outer anteroposterior and lateral diameters of the callus mass were measured by a sliding caliper. The quantity of the callus was expressed as the cross-sectional area, assuming it to be an ellipse. The healing osteotomies were mechanically tested in cantilever bending (Engesæter et al. 1978). A standard hydraulic testing machine was run at a constant rate (0.08 rad/s). The load values were transferred to a chart recorder displaying the load-deformation curve. The strength of the bones was calculated as the bending moment necessary to produce fracture. The bending rigidity was determined from the slope of the linear part of the curve. Energy expenditure was defined as the energy absorbed during loading to fracture.

Delayed union was defined as gross instability at the osteotomy site after the nail had been removed and with no signs of bridging callus on radiographs.

Table 1. The bending moment, energy expenditure, and rigidity of the different osteotomy groups. Median (1.-3. quartiles)

	Moment 10 ⁻¹ Nm	Energy 10 ⁻² Nmrad	Rigidity Nm/rad
<i>Complete osteotomy</i>			
NACL	3.40 (2.56-3.95)	3.27 (2.39-3.73)	2.20 (1.75-2.19)
STEROID	3.05 (2.46-5.21)	3.08 (2.36-5.62)	1.75 (1.75-2.49)
INDOM	0.11 (0-1.55)	0.60 (0-2.35)	0.009 (0-0.50)
CMC	3.11 (2.14-4.77)	5.14 (2.57-6.29)	0.96 (0.48-1.75)
<i>Partial osteotomy</i>			
NACL	4.79 (3.29-5.84)	4.59 (2.54-5.71)	2.49 (2.49-2.93)
STEROID	5.52 (4.35-6.67)	6.47 (4.44-7.30)	2.41 (1.93-3.39)
INDOM	3.33 (2.68-4.39)	4.52 (2.17-7.95)	1.51 (1.03-2.06)
CMC	4.94 (4.31-6.36)	6.10 (5.03-11.62)	2.36 (2.06-3.11)

NACL saline group, STEROID glucocorticosteroid group, INDOM indomethacin group, and CMC carboxy-methyl-cellulose group.

Statistics

Data are expressed as median and 1. and 3. quartiles. The Kruskal-Wallis test was used to compare moment, energy and rigidity in the NaCl-, steroid-, indomethacin-, and CMC- groups. When significant differences were found, differences between each group were calculated using the Mann-Whitney *U*-test. *P* < 0.05 was considered significant.

Results (Table 1)

In the control group of rats (n 8) the outer anteroposterior diameter of the femur was 3.2 (3.10-3.30) mm, the outer transverse diameter 4.2 (4.15-4.35) mm and the inner transverse diameter 2.15 (2.10-2.35) mm. The depth of the partial osteotomy was 3.0 (2.85-3.10) mm. The median moment, energy expenditure and bending rigidity of an intact femur were 6.67 (6.46-6.83) 10⁻¹ Nm, 1.07 (1.02-1.09) 10⁻¹ Nmrad and 2.32 (2.12-2.49) Nm/rad, respectively. Furthermore, the contralateral femur which was operated on with the standardized partial osteotomy, had a median moment, energy and rigidity of 1.58 (1.52-1.68) 10⁻¹ Nm, 0.98 (0.70-1.10) 10⁻² Nmrad and 1.40 (1.03-1.68) Nm/rad, respectively.

Complete osteotomy group

The bending moment at testing 6 weeks after surgery was depressed (P 0.02) by short-term medication with indomethacin, whereas there were no marked differences between the NaCl-, steroid- or CMC-treated groups. Further, in the indomethacin group energy absorbed during loading to fracture was not significantly (P 0.07) reduced compared with the other groups. The energy expenditure in rats receiving steroids was clearly comparable with that in the NaCl-treated group. Bending rigidity was reduced (P 0.003) in the indomethacin group when compared with the other groups. Therapy with methylprednisolone did not essentially influence rigidity. These results were in agreement with the clinical and radiological findings of more frequent delayed union in the indomethacin group (5 of 9) compared with the NaCl group (1 of 9), the steroid group (1 of 9) and CMC group (0 of 9). The median amount of callus (cross-sectional area) 6 weeks after complete osteotomy of the left femur was 58 (53-66) mm² in the NaCl group, 50 (38-59) mm² in the steroid group, 60 (42-73) mm² in the indomethacin group and 64 (48-66) mm² in the CMC group. There were no differences between the subgroups concerning the amount of callus.

Partial osteotomy group

Treatment with indomethacin only marginally reduced the moment when compared with the other groups. In the steroid group the moment was somewhat higher than in the NaCl-treated rats. There were no differences between the groups with regard to energy expenditure. Indomethacin depressed rigidity (P 0.01) when compared with the other subgroups. Steroid therapy did not affect rigidity when compared with NaCl treatment.

Discussion

Intermittent, *short-term* treatment with glucocorticosteroids or nonsteroidal antiinflammatory drugs like indomethacin are commonly used in inflammatory diseases, and when acute bone injury occurs in these patients the medical effects on bone healing are unclear. Furthermore, in orthognathic and orthopedic surgery as well as in neuro-surgery, short-term therapy with corticosteroids may be routinely administered to reduce postoperative pain and swelling and to modify the clinical course after elective surgery or accidental trauma (Skjelbred et al. 1982, Svennevig et al. 1984, Mbugua et al. 1988, Bracken et al. 1990). No adverse

effects of this treatment have been detected in clinical practice. Still, there has been a general opinion that therapy with corticosteroids may be inappropriate in situations where bone healing occurs. This may be based on the fact that *long-term* treatment clearly induces general osteoporosis and spontaneous fractures, development of pseudarthrosis in fracture healing in animals (Blunt et al. 1950, Sissons and Hadfield 1951) as well as suppressed immunological response to infections (Cupps and Fauci 1982). However, *short-term* therapy with glucocorticosteroids may not induce such undesired effects. Several studies have shown that indomethacin inhibits bone formation and remodeling (Sudmann 1975, Rø et al. 1976, Almåsbaek and Røysland 1977, Sudmann and Bang 1979, Sudmann et al. 1979, Allan et al. 1980, Keller et al. 1987, Keller et al. 1989). Some of these studies deal with intact bone systems, and their relevance to the healing of fractures, which in most cases occur by the production of external callus, is uncertain. The consequences of short-term therapy with indomethacin are still obscure.

Fracture healing under unstable conditions occurs in different stages and is characterized by the production of external callus. During first days after fracture an inflammatory response dominates, and possibly vascular and cellular responses with activation and release of cytokines and growth factors are the most important inducers of further processes leading to bone regeneration and healing (Balkwill and Burke 1989, Goldring and Goldring 1990). Thus, inhibition of inflammatory responses by short-term medical treatment may dramatically influence the fracture healing evaluated weeks after trauma. After an initial period of callus formation providing stabilization, healing of unstable fractures enters a stage characterized by cytodifferentiation, bone production and remodeling. These phenomena are also dominant in the case of healing of stable fractures occurring nearly without a gap between fragments and without callus formation. The medical effects under these conditions may differ from those in the inflammatory phase of fracture healing.

In rats the increase in mechanical properties of fractured femora stabilized by intramedullary pinning are nearly completed at 12 weeks after trauma. At 4 weeks, the fractures usually are consolidated and the return of strength is most rapid in the period 4-8 weeks after fracture (Reikerås 1990). We therefore examined the healing bones 6 weeks after trauma.

We found a marked inhibitory effect on bone healing of *unstable* osteotomies when the rats were treated with indomethacin for 3 days. Bone strength, absorbed energy and bending rigidity were diminished in the indomethacin group. In contrast, short-term therapy with methylprednisolone did not suppress the

healing when evaluated 6 weeks after surgery. On the other hand, when the fracture healing occurred under *stabilized* conditions, indomethacin therapy had less distinct effects on healing. Only bending rigidity was significantly reduced, and the bone strength and the energy absorbed until refracture was only to some extent reduced. Methylprednisolone did not influence bone healing under stable conditions. Indomethacin is generally believed to inhibit cyclooxygenase and thereby prostaglandin synthesis, but also to effect the release of oxygen-free radicals and lysosomal enzymes. Glucocorticosteroids inhibit phospholipase AII and also interfere with the cytokine network, essentially at a gene regulatory level (Lee et al 1988, Waage and Bakke 1988, Zanker et al. 1990). Thus, indomethacin and corticosteroids may influence both the inflammatory phase of fracture healing as well as bone metabolism (Sato et al. 1986, Tobias and Chambers 1989, Goldring and Goldring 1990).

In this study, short-term therapy with indomethacin and glucocorticosteroids seemed to have different overall effects on fracture healing under both unstable and stable fracture fixations, possibly reflecting dissimilar modes of action selectively influencing the inflammatory phase, cytodifferentiation and remodeling processes. In a clinical setting where bone healing occurs, these results suggest a preference for short-term glucocorticosteroids to indomethacin when there is a need for treatment with antiinflammatory drugs. Furthermore, the inhibitory effect of indomethacin on bone healing was clearly more pronounced when healing occurred under unstable conditions. Thus, this study also supports the view that antiinflammatory drugs have less inhibitory effects on fracture healing occurring under stable conditions compared to healing in unstable situations.

In conclusion, short-term therapy with indomethacin inhibited healing of fixed but unstable, as well as stable fractures in rat femora. These effects were not seen in the case of short-term treatment with methylprednisolone.

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