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Uncertain effect of indomethacin on physeal growth injury

Experiments in rabbits

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Growth arrest and shortening remain significant sequelae of growth-plate injuries. Nonsteroidal anti-inflammatory agents, known to inhibit callus and bone formation, may be useful to diminish callus-induced growth effects after epiphyseal fracture. In this study, we created a longitudinal osteotomy of the medial distal femoral condyle in 54 rabbits to model a Type IV epiphyseal fracture. We treated half with indomethacin and half with normal saline for 6 weeks. Nineteen animals of each group developed deformity, with indomethacin-treated animals averaging only slightly less angulation than the controls. However, the mean femoral shortening was less in the indomethacin-treated animals as compared with the controls

We have previously investigated the use of transphyseal traction, both to correct (Ray et al. 1978) and prevent (Shindell et al. 1985) deformity following injury across the growth plate. Prompted by the work of Sudmann et al (1982a) on the use of indomethacin to prevent the reformation of bone bridges in rabbits, and rat experiments demonstrating impaired fracture healing in the presence of indomethacin (Allen et al. 1980, Altman et al. 1983, Ro et al. 1976), we have evaluated the inhibition of primary bone bridge formation by indomethacin, using an animal model that mimics the worst type of physeal fracture.

Material and methods

We performed a longitudinal osteotomy of the medial distal femoral condyle in 54 juvenile female rabbits to produce a Salter IV fracture (Figure 1). This was done using an oscillating saw, removing approximately one third of the medial condyle and traversing the growth plate. The osteotomy fragment was freed of soft tissue and replaced in its bed, and the joint capsule, includ-

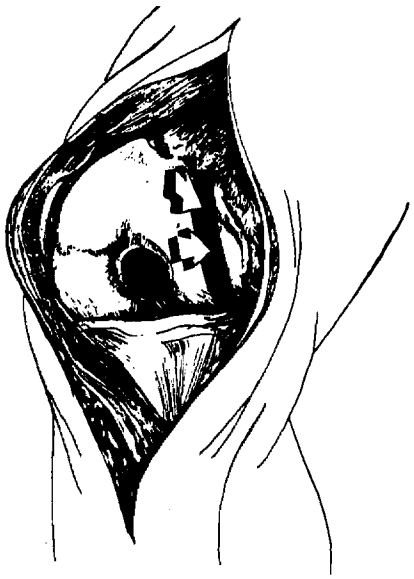

Figure 1. A medial femoral condylar osteotomy was performed on 54 rabbits, as shown above, mimicking a Salter IV fracture. The fragment was replaced in near anatomic position, and the capsule and ligaments were closed in one layer with the skin closed separately.

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ing the medial ligaments, was sutured. All the replaced fragments were securely held in grossly anatomic position, as radiographically confirmed in an earlier contingent of animals. This technique has previously been shown to be reliable in creating a transphyseal bone bridge in dogs (Campbell et al. 1959).

Prior to surgery, we divided the rabbits into two equal groups. In the first group, we administered Sodium Indomethacin Trihydrate (Merck, Sharp & Dohme) 10 mg/kg per day subcutaneously in normal saline beginning immediately before surgery and continuing for 6 weeks. Indomethacin solutions were prepared fresh daily, and doses were adjusted according to rabbit weight gain, as well as to the molar weight of the active drug. We treated the remaining rabbits with equivalent volumes of normal saline.

After death the animals were weighed, and both femurs were excised. Paired radiographs were obtained, from which we measured varus angulation of the distal femur at the intersection of a line drawn through the long axis of the femur and a tangent to the condyles (Figure 2). Length was measured from the tip of the greater trochanter to the central apex of the distal growth plate. Coronal sections of the distal femur were obtained, using Goldner's stain, for histologic studies.

Blood samples were obtained at death in 6 animals to determine serum indomethacin concentration. An additional 3 rabbits were injected with indomethacin for 7 days, as previously described, and serial blood samples were drawn at 2, 4, 6, 12, and 24 hours to construct serum clearance curves. Serum was decanted and frozen within 2 hours of phlebotomy, and the samples were analyzed by high-performance liquid chromatography.

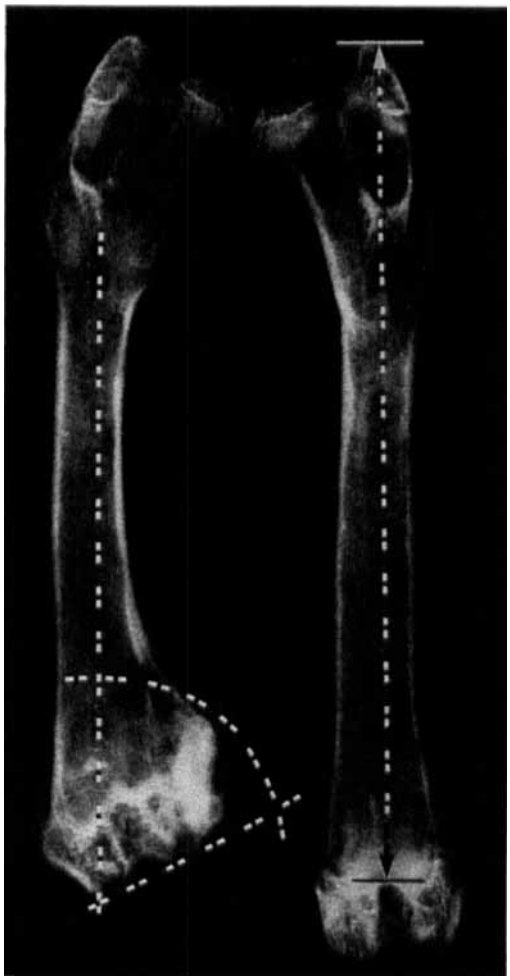

Figure 2. At death, paired radiographs were obtained of the excised femurs. Varus angulation was measured at the intersection of a line drawn tangential to the distal condyles and a second line through the long axis of the shaft. Measurements of femoral length were taken from the tip of the greater trochanter to the central apex of the growth plate.

Results

Of our 54 original rabbits, 10 rabbits were removed because of premature death, fracture, or infection. There was no difference in total weight gain between treatment groups. Nineteen of the 23 remaining indomethacin-treated rabbits developed varus deformity of 24° (8–40°). Of the 21 rabbits treated with normal saline, 19 developed varus deformity of 30° (10–60°). This compared with the normal 8.3° degrees of valgus seen in the unoperated left leg, equal in indomethacin- and saline-treated groups (Table 1).

There was a mean left-right difference of 4.3±1.9 mm in femoral length in the indometha-

Table 1. Deformities after medial femoral condylar osteotomies in rabbits. Valves are mean (SD)

Treatment	Varus (degrees)	Femoral length difference (mm)
Normal saline (n 19)	29.6+(11.3) $P<0.10$	7.8+(3.7) $P<0.001$
Indomethacin (n 19)	24.0+(9.7)	4.3+(1.9)

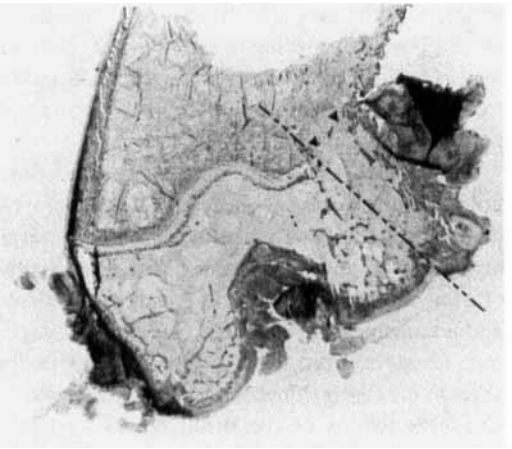

Figure 3. Histologic representation of specimen demonstrating approximate location of original osteotomy (dotted line) and area of predominantly fibrocartilage bridging (triangles).

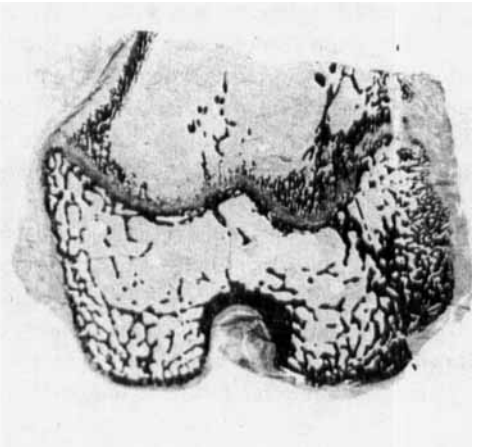

Figure 4. Representative histologic specimen demonstrating approximate location of original osteotomy (dotted line) and area of plate disruption bridged by bone callus (triangles).

cin group, as compared with 7.8±3.7 mm in the control animals ($P < 0.001$). Mean length of the unoperated on legs was comparable at 81 and 82 mm

The histologic sections through the area of bridging showed variable response in both groups, ranging from cartilaginous callus mass to mature trabecular bone. In the 6 animals that did not develop deformity, no plate disruption occurred. The remaining animals demonstrated a pattern of bridge formation that roughly correlated with their deformity; those with less than 20° of deformity often had a fibrocartilage bridge (Figure 3), whereas those with greater than 20° were more often associated with a mature bone bridge (Figure 4). This was consistent in both indomethacin- and normal saline-treated animals. The maturity of bone bridges, when present, appeared equivalent between groups.

Serum indomethacin levels as measured by HPLC averaged 6,640 ng/ml serum at 2 h postinjection, whereas 24-h levels averaged 745 ng/ml. Extraction controls demonstrated 85 per cent recovery. Serum levels resulting in physiologic effects in previously reported studies were in the range of 180 ng/ml (Sudmann and Bang 1979, Sudmann et al. 1982a).

Discussion

Indomethacin has been shown to retard bone formation (Ro et al. 1978). This inhibition is seen in the rate of formation, as well as resorption, yet the point of inhibition is unclear. It is possible that the antiprostaglandin effect may account for the inhibition of bone resorption, because the osteoclasts are stimulated by PGE_2 (Lerner 1980). The mechanism of fracture-healing retardation is less likely to be as directly explained; theories implicate direct effects on osteoblasts, as well as inhibition of preosteoblastic conversion.

The retardation of fracture healing, while usually an undesirable effect, could potentially be put to advantage in the case of injuries across the growth plate. If healing could be slowed down sufficiently, the growth plate could potentially reconstitute across the fracture gap prior to bridge formation. This thesis is supported by observations that cartilage metabolism is unaffected by the dosages of indomethacin used in this study (Aalto and Kulonen 1972). Plate function specifically does not appear affected, as our data and that of others (Sudmann et al. 1982b) would indicate no effect on ordered bone growth.

Although the hypothesis that indomethacin could possibly prevent deformity appears theoretically plausible, our results appear tempered by the degree of initial injury. In this model of a severe Salter IV fracture, we observed a slight nonsignificant decrease in varus angulation in the treated as compared with the control group. We did observe a decrease in left-to-right leg-length discrepancy in the indomethacin-treated group. This suggests an effect of treatment, and a poss-

ible explanation of why Sudmann et al. (1982b) found a decrease of deformity after surgery involving a lesser volume of bone resection and resultant callus. We noted no difference in length of nonoperated on femurs, nor in overall weight gain of animals treated with indomethacin or normal saline. This correlates with prior studies by Sudmann et al. (1982b), showing no effect of indomethacin on ordered growth of adolescent rats despite inhibition of Haversian remodeling in healing bone (Sudmann and Bang 1979).

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Acknowledgement

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