EXAMINATION OF THE RELATIONSHIP BETWEEN FRACTURE REPAIR AND ANGIOGENESIS IN AN NSAID TREATED ANIMAL MODEL

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Introduction

Five to ten percent of all fractures end in delayed or non-union. Reports for three decades have linked NSAIDs to an inhibitory action on fracture repair, yet GPs still prescribe these drugs in up to 50% of fracture patients. The mechanism behind this inhibitory effect has yet to be elucidated. Cancer research has identified that NSAIDs, primarily via a COX-2 pathway, can impede cell proliferation by inhibiting angiogenesis. It is proposed that a similar mechanism occurs in the induction of NSAID induced non-union. We have investigated this hypothesis using a murine femoral fracture model.

Methods

Two hundred and forty animals were randomised into drug (rofecoxib), placebo drug, and sham surgical groups. All animals underwent a standard open femoral fracture treated using a 4-pin external fixator. Outcomes measures involved assessment of repair using digital radiographic and histological means (days 0, 8, 16, 24 and 32), biomechanical testing in conditions of three point bending (days 24 and 32); and assessment of blood flow across the fracture gap using Laser Doppler Flowmetry (days 0, 4, 8, 16, 24, and 32). Data was analysed for statistical differences (SPSS, Version 11.5), with significance being attained when p ≤ 0.05. All experiments were carried out under the agreement of the Northern Ireland License Training Group, Project number PPL 2461.

Results

Initial pilot studies comparing the placebo drug treatment fracture alongside sham surgical model demonstrated the outcome measures of radiographic and blood flow changes at the fracture gap to be both sensitive and specific.

Comparison of data between drug treated and placebo treated animals was then performed. X-ray analysis showed similar healing patterns in both groups, with a stepwise increase in density at the fracture gap, however at the later stages (day 32) the NSAID group had a significantly poorer healing pattern than controls (Graph 1).

Qualitative histological analysis showed that controls healed quicker (significantly more advanced healing at days 24 and 32) (graph 2); while quantitative histological studies demonstrate that at day 8 controls had a more new bone, with the NSAIDs animals having more cartilage. NSAID animals were seen to have more fibrous tissue in the fracture gap at a day 32.

Greater numbers of animals in the NSAID group had failure of treatment with loss of fracture reduction or pin pullout; this occurred early, between days 8 and 16.

Biomechanical testing showed NSAID animals attained statistically less strength and stiffness at day 32. There was no difference in blood flow across the fracture gap between the groups on the day of surgery. Both groups exhibited a similar pattern with an initial drop in flow, then a peak at day 16 and subsequent return to resting levels by day 32. NSAID treated animals however, exhibited a lower median flow from day 4 onwards (significant at days 4, 16 and 24) (graph 3).

Positive correlations have been demonstrated between both histological and radiographic assessments of healing, with increasing blood flow. NSAID animals exhibited lower flows, and also displayed poorer healing radiographically, histologically and biomechanically. Multiple regression analysis demonstrates that this negative effect of NSAIDs on fracture repair is independent to its inhibitory action on blood flow at the fracture site.

Conclusions

COX-2 inhibitors are marketed as having cleaner side effect profiles. They are still widely used when treating trauma patients. Not all animals treated with NSAIDs go on to develop non-union and indeed some heal with similar mechanical properties to control animals. Following the development of a novel method of analysing functional vascularity across a fracture gap we demonstrated that the highly specific COX-2 inhibitor rofecoxib has a significant negative effect on fracture site blood flow alongside inhibiting fracture repair.