Jeffcoach ER, Sams VG, et al. Nonsteroidal anti-inflammatory drugs' impact on nonunion and infection rates in long-bone fractures. J Trauma Acute Care Surg 2014;76(3):779-783.

Design: Retrospective cohort study

Study question: Does the administration of NSAIDs in the setting of acute long bone fractures increase the rate of nonunion and other complications?

Population/sample size/setting/data collection:

- 1901 patients (836 women, 1065 men, mean age 46.6) treated for long bone fractures at the University of Tennessee Medical Center, a Level I Trauma Center, between October 2009 and September 2011
    - Femur, humerus, and tibia were the three fracture types entered into the study
- Medical records were obtained from index admission CPT codes through the hospital medical records department and stored with unique identifiers to protect patient identity
- Medication records were electronically stored but required verification through the pharmacy delivery databanks
- All patients had undergone surgery for their fractures
- Descriptive statistics were abstracted from the medical records, and analysis of data focused on complication rates
    - Complications were defined as nonunion, malunion, and infection
    - Factors in the analysis were NSAID use, Injury Severity Score (ISS), tobacco use, open/closed fracture, fall injury, and motor vehicle crash injury

Results:

- 2 years of data were used in the data set
- NSAID use was administered within 24 to 48 hours of admission; and 92.7% of NSAID was either ketorolac or ibuprofen
- There were 60 complications identified during the followup period available
    - The authors did a logistic regression analysis of the 60 complications, estimating odds ratios (OR) for NSAID use adjusted for ISS, tobacco use, open/closed fracture, fall injury, and motor vehicle crash injury
- Three factors had elevated odds ratios for complications in the adjusted analysis
    - For NSAID use, the adjusted OR was 2.17 (95% confidence interval from 1.15 to 4.10)

    - For tobacco use, the adjusted OR was 3.19 (95% confidence interval from 1.84 to 5.53)
    - For open fracture, the adjusted OR was 3.11 (95% confidence interval from 1.60 to 6.03)
    - The adjusted OR for ISS was 1.01 (95% confidence interval from 0.99 to 1.04)
    - For fall injury, the adjusted OR was 0.37 (95% confidence interval from 0.17 to 0.79)
    - For motor vehicle crash, the adjusted OR was 0.51 (95% confidence interval from 0.27 to 0.96)

Authors' conclusions:

- NSAIDs increase the risk of poor bone healing when administered early in the treatment of long bone fractures
- Smoking also inhibits bone healing of long bone fractures
- NSAIDs should be avoided and smoking curtailed after a long bone fracture occurs
- Some factors could not be assessed, such as techniques used, timing of fracture repair, concurrent injuries, medical condition, and calcium deficiency

Comments:

- Two years of data were obtained, but the timing of the assessment of complications was not uniform and was not very clear
    - Malunion and nonunion would require a longer period of observation than most infections, but the determination that a fracture has not healed would require at least several months
- NSAID use was entered as either present or absent; the dosage of NSAID was not entered as a continuous variable
- The Injury Severity Score (ISS) which was a covariate in the analysis, may not have been correctly analyzed
    - The statistical analysis of ISS was point biserial correlation
    - This treats ISS as a binary variable with only two values, which appear to have been designated as 9.00 versus 10.00
    - ISS is an ordinal variable with values on a scale which usually has a minimum of 0 and a maximum of 75
    - Concurrent injuries, which the authors said were not tested, are reflected in the ISS; for example, any concurrent injuries of the chest, head, or abdomen would figure into the ISS which could have been entered into the analysis of the risk factors for complications
    - There were other binary factors in the logistic regression analysis (tobacco use, open fracture, fall injury and motor vehicle crash injury), and these had

wider confidence intervals than for ISS, whose confidence interval (0.99 to 1.04) was incongruently narrow compared to the other binary variables

- Although the analysis of injury severity is likely to suffer from a dubious analysis, the study did have the strength of having an accurate classification of NSAID use from the pharmacy delivery records, with outcome data drawn from an unbiased source, full participation accomplished by using data from all long bone fractures during the two years of data attainment, and adjustment for confounders (at least minimally)
- The adjustment of the OR for NSAID use also had the advantage of being adjusted for tobacco use
- Overall, even though some of the analysis could have been improved upon, the association between NSAID use during the acute phase of treatment of long bone fractures and poor bone healing is supported by the data, and is biologically plausible from other studies of prostaglandins and bone healing

Assessment: Adequate for some evidence that in the setting of long bone fractures of the femur, tibia, and humerus, NSAID administration in the first 48 hours after injury is associated with poor healing of the fracture, and that tobacco use is also a risk factor for poor fracture healing