Use of Nonsteroidal Anti-Inflammatory Drugs and Risk of Delayed Bone Healing Following Elective Foot Surgery

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Statement of Purpose

To determine if short-term exposure to nonsteroidal anti-inflammatory drugs (NSAIDs) post-operatively results in increased risk of delayed bone healing or nonunions in foot surgeries involving osteotomies of long bones or arthrodesis at or distal to the tarsometatarsal joints.

Methodology and Procedures

This study was approved by the institutional review board of both participating hospitals.

Inclusion Criteria:

- ASA class 1 or 2
- No contraindications to NSAIDs
- Underwent elective surgery involving osteotomies of long bones or arthrodeses at or distal to the tarsometatarsal joint performed between 7/1/2018 – 5/30/2019

Exclusion Criteria:

- Patient history of chronic kidney disease, peptic ulcer disease, gastrointestinal bleeding, or asthma hypersensitive to NSAIDs
- Current anticoagulation therapy
- Pre-existing coagulation disorder or thrombocytopenia
- Suspected or confirmed cerebrovascular disease, cardiovascular disease, hepatic disease, lupus, or connective tissue disorder
- Reported history of NSAID intolerance/hypersensitivity

Surgeries included in this study:

- Osteotomies of the hallux or first metatarsal
- Digital interphalangeal joint, first metatarsophalangeal joint, or first metatarsocuneiform joint arthrodesis
- Lesser metatarsal osteotomies

Surgery was performed by one of three staff podiatric surgeons at the included hospitals.

Peri-operative pain medication:

- Intra-operative single dose of IV ketorolac 15 or 30mg
- Post-operative PO ibuprofen 400-800mg TID
- Regularly prescribed narcotics per surgeon

Patients were queried at their post-operative appointments about their use of NSAIDs for pain control. Patients were followed post-operatively and monitored for clinical signs of delayed or nonunion. Delayed union was defined as lack of bony healing after 90 days while nonunion was defined as lack of bony healing after 9 months.

A retrospective review was performed on patients treated at a single hospital between the dates 1/1/2017 – 6/30/2018, who underwent elective surgery involving osteotomies of long bones or arthrodeses at or distal to the tarsometatarsal joint, and had no peri-operative exposure to NSAIDs to serve as the control group. Their medical records were reviewed for clinical assessments of delayed on nonunion.

Methodology and Procedures (continued)

Statistical analysis was performed on both groups using the Student's t test and Fisher's exact test to assess for any difference between the prospective and retrospective group and any increased risk of delayed or nonunion.

Results

35 patients enrolled in the prospective group and 48 patients in the retrospective control group. In the prospective group, 30 of the 35 patients received intra-operative ketorolac and 22 of the 35 patients reported taking the post-operative ibuprofen. There were three cases of delayed or nonunion in both the prospective and retrospective group ($p = 0.693$). An example of two patients who went onto union are shown in Figures 1 and 2. No statistically significant difference was found between the groups when comparing incidence of diabetes, smoking status (current versus history of), and vitamin D deficiency (see Table 1 below). There was also no statistically significant difference when comparing the two groups for sex ($p = 0.299$), procedure type ($p = 0.734$) or laterality ($p = 0.564$), or average length of follow up ($p = 0.716$).

	Prospective (n = 35)	Retrospective (n = 48)	P-value
Delayed or nonunion	3	3	0.693
Diabetes	4	8	0.548
Current smoker	5	17	0.044
History of smoking	17	26	0.661
Vitamin D deficiency	5	3	0.272

Table 1. Incidence of delayed or nonunion and various comorbidities between the prospective and retrospective groups.

Odds ratios and p-values were calculated to determine if there was and increased likelihood of delayed or nonunion associated with presence of being in the prospective versus retrospective group, age, sex, diabetes mellitus, and smoking status (current versus history). No statistically significant association was found. See Table 2 below.

	Odds ratio	P-value
Prospective vs Retrospective group	1.41	0.688
Age	1.01	0.779
Sex	1.64	0.586
Diabetes Mellitus	3.35	0.194
Current smoker	0.533	0.576
Smoking history	0.925	0.927

Table 2. Odds ratio calculations assessing for association between delayed or nonunion and listed patient factors.

Results (continued)

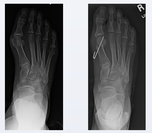
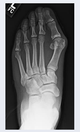
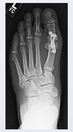


Figure 1. A patient from the prospective group who underwent a chevron bunionectomy fixated with a 0.062" Kirschner wire. Patient received 30mg intra-operative ketorolac and endorsed taking ibuprofen 600mg TID with meals. She healed the osteotomy uneventfully and the Kirschner wire was removed at 3.5 weeks after the procedure.

Figure 2. A patient from the prospective group who underwent a first metatarsophalangeal joint arthrodesis for a symptomatic bunion. Patient received intra-operative ketorolac and endorsed taking ibuprofen 600mg TID with meals. He healed the arthrodesis uneventfully and was discharged from clinic at 8 weeks after the procedure.





Literature Review

NSAIDs have been recommended to be used in conjunction with narcotic pain medication and part of the multi-modal pain control approach. NSAIDs have been shown to have greater reductions in pain scores, allow for early mobilization and weight bearing, and decrease the need for opiate use and associated side effect (1-4). However, there has been much hesitancy to incorporate the use of NSAIDs into the post-operative pain regimen in the orthopedic and podiatric community. This hesitancy stems from concern of increased risk of delayed or nonunions (1, 3-7). There have been gene knock out animal studies that suggest COX-2 inhibitors suppress early fracture healing. (3, 5). As of today, there is no consensus in the literature with regards to use of peri-operative NSAIDs and their impact on bony healing. (3, 7).

These injuries lead to inflammation that is mediated through the production of prostaglandins. Cyclooxygenases catalyze the oxygenation of arachidonic acid to COX-1 and COX-2, both of which are involved in the production of inflammatory modulators, specifically prostaglandins. COX-1 is nonspecific where as COX-2 is generated in response to tissue inflammation (3, 4), as seen in Figure 3.

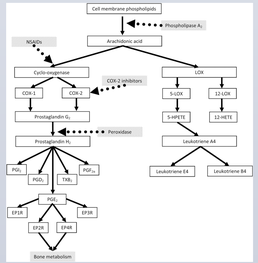


Figure 3. Pathway of arachidonic degradation

Literature Review

Prostaglandins are released in response to osseous injuries. These inflammatory markers promote active bone formation and increase bone mass (3). COX-2 has been shown to be important for microscopic angiogenesis and conversion of endochondral ossification for hard callus formation (3, 4). Theoretically, suppression of COX-2 may lead to decreased bone formation after trauma. However, no consensus has been made in the literature with regards to use of NSAIDs peri-operatively and their effects on bone healing (3, 7).

Analysis & Discussion

Post-operative pain control is a challenge for podiatric and orthopedic surgeons. While multiple studies have advocated for the use of a multi-modal approach to pain control and use of NSAIDs in the post-operative period, there has been much hesitation within this community (1-8).

Many meta-analyses and systematic reviews have been performed to try and form a consensus of the available literature and to also assess the quality of the current literature (3, 7, 8). Wheatley et al performed a meta-analysis on literature reporting the effects of NSAIDs on bone healing. They found that there appeared to be a negative impact of NSAIDs on bone healing in adults, but this could be dose/duration dependent as there as no negative effect reported specifically for short term exposure (8). Doddwell et al published a meta-analysis assessing data on study design, patient characteristics, and risk estimates. They found that there was a significant association between lower quality studies and a higher odds ratio for nonunions. They also noted when looking at the higher quality studies, no statistically significant risk of delayed union or nonunion with exposure to NSAIDs (1). Marquez-Lara et al performed a systematic review assessing the quality of available research on the effects NSAIDs may have on bone healing. They also found that articles that reported a negative relationship between the use of NSAIDs and bone healing were more likely to be lower quality studies (7). Brattwall et al performed a prospective randomized control study comparing the use of etoricoxib (COX-2 inhibitor) and tramadol for post-operative pain control for hallux valgus surgery. Patients were evaluated for objective reports of pain control and satisfaction for the first week post-operatively and CT scans were also performed at 12 weeks post-operatively to assess for osseous healing. They found that patients who received etoricoxib had better pain control when compared to patients who received tramadol. They reported no increased risk of osseous or wound healing with the use of etoricoxib (9).

In our study, both the prospective and retrospective group had three cases of delayed or nonunion, which was found to not be statistically significant. ($p = 0.693$). The groups were found to be similar with respect to incidence of diabetes, history of smoking, and vitamin D deficiency. The only statistically significant differences observed in the groups were the amount of current smokers in the retrospective group and the prospective group had more Caucasian patients. Limitations to this study include the study size and that only clinical signs of delayed or nonunion were monitored for and then followed up with appropriate imaging studies. The retrospective group also consisted of patients only at one facility while the prospective group included two facilities. There were multiple surgeons involved as well.

Analysis & Discussion (continued)

In conclusion, our study aimed to determine if there was any increased risk of delayed on nonunion in elective osseous forefoot surgeries and exposure to NSAIDs in the peri-operative period. Our study found no risk of delayed or nonunion with exposure to NSAIDs following elective osseous surgeries of the forefoot.

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Acknowledgements

Special thanks to Dr. Rachel Nygaard for performing the statistical analysis for this research investigation.

Financial Disclosures

None

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