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Tibia fractures and NSAIDs. Does it make a difference? A Multicenter Retrospective Study

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Highlights:

- We compared healing time for diaphyseal tibia fractures treated with IMN at an institution in the US, where opioids are prescribed for post-operative pain control, to that of an institution outside the US, where NSAIDs are prescribed for post-operative pain control. The difference in healing time between the NSAID and opioid groups was not statistically significant.

- Large prospective randomized studies are necessary to further elucidate the potentially negative effects of NSAIDS on bone healing and to allow the formulation of clear, evidence-based clinical practice guidelines relating to their use in fracture management.

Abstract

Purpose
The purpose of this study was to compare healing time for diaphyseal tibia fractures (OTA/AO 42 A, B, C) treated with intramedullary nailing (IMN) in one geographic cohort using nonsteroidal anti-inflammatory drugs (NSAIDs) for post-operative pain control to that of another geographic cohort using opioid medications. The groups represent differing cultural approaches to post-operative pain control. We hypothesized there would be no difference in healing time.

Methods
Tibia fractures presenting at two level I trauma centers located in different countries between January 1, 2010 and December 31, 2017 were retrospectively screened for enrollment. Fractures classified as OTA/AO 42A, B, or C that were treated with IMN and had radiographic follow up to union were included. At hospital discharge, one cohort (n=190) was prescribed NSAIDs and the other (n=182) was prescribed opioids for pain control. Each analgesic method represented the standard of care for that location. Fracture union was defined as cortical bridging in at least 3 out
of 4 cortices on AP and lateral radiographs. The primary outcome was healing time on radiographic evaluation.

**Results**
There was no statistically significant difference in healing time between the opioid and NSAID groups: 185 vs 180.5 days respectively (p=0.64). Both groups had similar mean age. Student t-tests were run to compare rates of tobacco use, diabetes mellitus (DM), open fractures, and polytrauma between the two groups. The opioid cohort had statistically significant higher rates of tobacco use, DM, and polytrauma. The NSAID cohort, however, had a larger number of open fractures.

**Conclusion**
The difference in healing time between the NSAID and opioid groups was not statistically significant. The deleterious effect of NSAID use on fracture healing has been debated for decades. Numerous animal studies have supported this theory; however, high quality clinical studies in humans have not provided convincing evidence to substantiate this negative effect. Our study suggests that NSAIDs may be used safely and effectively in the acute phase of fracture healing without significantly increasing the risk of delayed union or nonunion. Prospective randomized studies are necessary to rule out the negative effect of NSAIDS on bone healing.

**Keywords:** Tibia fractures, NSAIDs, opioids, bone healing
Manuscript

Introduction

Fracture healing is a complex physiologic process involving the coordination of inflammation, angiogenesis, osteogenesis, and chondrogenesis [1–4]. Many growth factors and cytokines are involved in successful fracture union, and disruption of these signaling molecules can lead to complications or delays in healing. Numerous conditions can influence the fracture healing pathway and lead to nonunion. Patient-dependent factors include medical comorbidities, smoking, medication use, advanced age, alcohol abuse, nutritional deficiency, previous radiation therapy, metabolic disease, and endocrine pathology. Patient-independent factors include fracture comminution, surrounding soft tissue damage, quality of reduction, interposed soft tissue, bone loss, presence of infection, and the type of construct used for fixation.

Prevention of nonunion is paramount in the treatment of fractures, as it places additional burden on the patient and the healthcare system. Nonunion leads to prolonged pain and disability for the patient and increased costs and resource utilization for the healthcare system. With these consequences in mind, it is necessary to identify specific factors that may optimize or hinder the fracture healing environment. One such area that has been studied is the effect of nonsteroidal anti-inflammatory drugs (NSAIDs) on fracture healing.

NSAIDs are effective and generally safe analgesic medications, making them appealing for the management of pain associated with acute fractures. However, they work by directly inhibiting the cyclooxygenase (COX) enzyme, which is critical for production of prostaglandins early in the inflammatory stage of fracture repair. Previous studies in animal models have demonstrated the importance of COX-2 for fracture healing with significant delays in the healing response and differentiation of stem cells following diaphyseal fractures in COX-2 knockout mice models [3,5]. Similar results have been noted in animal models treated with NSAIDs following generation of tibia fractures. These models demonstrate decreased cartilage formation with increased angiogenesis during early fracture fixation [2,6].

Conflicting and inconclusive results are found when comparing outcomes in animal models to those involving humans. Some studies in humans have demonstrated no effect on fracture healing, while others concluded there was a negative effect of NSAID use. The one unifying conclusion in many of these studies is the need for larger prospective, randomized controlled trials to clarify how NSAIDs influence the bone healing process [7,8].

Many physicians, especially in the United States, avoid the use of NSAIDs in treating pain associated with fractures. In the US, common practice is to prescribe opioids for pain management. However, the standard practice outside the US varies widely. In some countries, the standard of care is to prescribe NSAIDs for pain control following fractures. If the suggested deleterious effect of NSAIDs is valid, the healing time and nonunion rate for fractures treated at sites using NSAIDs should be higher than that in the US.

The purpose of this study was to compare healing time for diaphyseal tibia fractures treated with intramedullary nailing (IMN) at an institution in the US, where opioids are prescribed for post-operative pain control, to that of an institution outside the US, where NSAIDs are prescribed for post-operative pain control. We hypothesized there would be no difference in healing time between the two cohorts, which represent differing cultural approaches to post-operative pain control.
Methods

After obtaining IRB approval, tibia shaft fractures presenting at two level I trauma centers (one in Chile and one in the United States) between January 1, 2010 and December 31, 2017 were retrospectively screened for enrollment. ICD-9, ICD-10, and CPT codes were used to identify patients with tibia fractures from the US institution. Chilean patients were identified in a similar manner using the center’s respective hospital record system. Diaphyseal fractures classified as OTA/AO 42A, B, or C that were treated with IMN alone and had follow up to radiographic union were eligible for study inclusion. Tibia fractures classified as OTA/AO 41 or 43 and those lost to radiographic follow up were excluded.

Both institutions used similar surgical technique involving reamed intramedullary nailing. In both cohorts, immediate post-operative pain was managed using opioid medications. Upon discharge, patients in the US cohort were prescribed opioid-based analgesic medications, and patients in the Chilean cohort were prescribed NSAIDs for pain control. Type, dose, and duration of NSAID therapy was recorded.

Follow up radiographs in the Chilean cohort were reviewed by one author (MP). Radiographs in the US cohort were reviewed by three authors (LF, ML, JW) and supervised by senior author (RZ). Fracture union was defined as cortical bridging in at least 3 of 4 cortices as seen on AP and lateral radiographs. Time to union was recorded for all patients. Demographic information including age, gender, smoking status, presence of diabetes, and whether or not patients sustained multiple injuries at the time of tibia fracture (polytrauma) was recorded. The primary outcome in this study was time to fracture union on radiographic evaluation.

A power analysis was performed to determine an adequate sample size for the study. The difference in mean time to union between the two cohorts was anticipated to be small. Therefore, the effect size chosen for the power analysis was 0.3. Alpha of 0.05 and power of 0.8 were selected for a two-tail power analysis. Based on these parameters, each group needed at least 137 patients to adequately power the study.

Results

There were 994 patients with tibia fractures initially identified in the US records and 566 patients with tibia fractures identified in the Chilean records. Patients who did not have radiographic follow up to fracture union, were treated without IMN alone, or had a fracture classified as OTA/AO 41 or 43 were excluded from the study. This left a total of 182 US patients and 190 Chilean patients with diaphyseal tibia fractures classified as OTA/AO 42 A, B, or C, treated with IMN that had a confirmed radiographic union (Figure 1).

All patients in the Chilean cohort were prescribed one of four types of NSAIDs for post-operative pain control at hospital discharge. 119 patients (62.6%) were prescribed ketoprofen, 31 (16.3%) were prescribed meloxicam, 24 (12.6%) were prescribed celecoxib, and 16 (8.4%) were prescribed ketorolac. No patients in the Chilean cohort were prescribed opioid medications at hospital discharge (Table 1).

The mean fracture healing time for the US cohort was 185.0 ± 108.2 days. In the Chilean cohort, mean fracture healing time was 180.5 ± 75.9 days. An independent t-test was performed to compare the two groups, and the difference was not statistically significant (p=0.64; 95% CI, -14.87 – 24.04) (Table 2, Figure 2).
Average age at the time of fracture was 38 years in the US cohort and 39 years in the Chilean group. 68.1% (n=124) of the US cohort were males and 31.9% (n=58) were females; 84.2% (n=160) of the Chilean cohort were males and 15.8% (n=30) were females. US males had an average time to fracture union of 178 ± 98 days; females had time to union of 182.0 ± 77.8 days. In Chilean males, average time to union was 200.6 ± 126 days vs 172.0 ± 65.1 days in females. These differences were not statistically significant (Table 2).

Student t-tests were run to compare rates of tobacco use, diabetes mellitus (DM), open fractures, and polytrauma between the two groups. The US cohort had statistically significant higher rates of tobacco use, DM, and polytrauma. The Chilean cohort, however, had a larger number of open fractures (Table 2).

Discussion

Pain control following orthopedic trauma is a challenge. The goal is to alleviate patient suffering while also minimizing the risks associated with analgesic medications. Orthopedic surgeons in the US often avoid the use of NSAIDs in the fracture setting due to multiple animal studies suggesting a deleterious effect on bone healing. The topic has been debated for decades, and numerous animal studies have supported this theory. However, high quality clinical studies in humans have not provided convincing evidence to substantiate the negative effect of NSAIDs on bone healing [8]. The concept makes intuitive sense, as the mechanism of NSAIDs is to inhibit the cyclooxygenase (COX) enzyme. Inhibition of the COX enzyme decreases levels of prostaglandins which are crucial mediators in the early inflammatory phase of the bone healing process. Again, this theory has been supported most consistently in animal literature, but data in human studies is mixed, limited, and therefore not as clear. For example, some clinical studies in humans have shown that NSAIDs do not affect healing potential of Colles’ fractures or intraosseous periodontal defects [9–11]. In contrast, several other retrospective studies have suggested that patients using NSAIDs after fracture had an increased incidence of nonunion compared to patients that did not [12–14].

Partly as a result of this conflicting data, opioid medications are frequently prescribed instead of NSAIDs following orthopedic trauma. This practice is especially common in the United States. Of all medical specialties in the US, orthopedic surgeons are the third highest prescribers of opioids. Furthermore, opioids are prescribed more in the US than in any other nation [15]. According to Manchikanti and Singh, Americans constitute 4.6% of the world's population, yet we have been consuming 80% of the global opioid supply and 99% of the global hydrocodone supply [16]. We are now dealing with a well-known epidemic, as prescription opioids result in more deaths each year than cocaine and heroin combined [17].

Why has this problem not occurred elsewhere? There are many factors that have contributed to the current state of affairs in the US. One factor involves cultural differences in how clinicians and patients approach pain control. Lindenhovious, et al. looked at patients with hip and ankle fractures treated in the Netherlands who did not receive postoperative opioids. The authors showed that those patients had less postoperative pain and more satisfaction than patients with the same injuries in the U.S. who received opioids [18]. Helmerhorst suggests that “the use of less opioid pain medication by Dutch patients might be explained by cultural differences, differences in health provider training and practice, and psychological differences such as effective coping strategies, greater self-efficacy, and better mood” [19]. Patient expectations may also play a role. Since mandatory pain assessment standards were introduced by the Joint
Commission (JCHAO) in 2011, when it was cited that “pain is the fifth vital sign,” there has been an increased emphasis on repeatedly assessing/rating pain and its correlation to patient satisfaction.

The purpose of our study was to compare healing time for diaphyseal tibia fractures treated with IMN in two groups representing differing cultural approaches to post-operative pain control: one cohort from Chile using NSAIDs and one from the US using opioid medications. We found no statistically significant difference in healing time between the Chilean and US groups, suggesting that NSAIDs may be used safely and effectively in the acute phase of fracture healing without significantly increasing the risk of delayed union or nonunion.

It is important to recognize the large number of patient factors that affect fracture healing rate, including smoking, micro-vascular disease, diabetic status, and baseline nutritional state [6], among many others. Extrinsic factors related to the amount of energy transfer at the time of trauma, such as soft tissue damage, contamination, and vascular injury also affect healing. Additionally, fracture stability following fixation or immobilization and weight bearing at the fracture site both play an important role in the healing process. Complicated multivariate analyses would be required to separate these factors and truly isolate these influences and determine the degree to which each affects fracture healing [6]. This complexity is a key reason why clinical studies in humans on this topic are so difficult.

Our study has several limitations. First, data was collected at two separate institutions, and patients were therefore treated by different surgeons. Confounding variables would likely be reduced if both cohorts of patients were treated by the same surgeon or group of surgeons. However, our retrospective multicenter study was not designed to control for surgeon variables outside of the basic surgical technique of reamed, locked intramedullary nailing. There may also be inherent discrepancies in judgement of fracture healing on x-ray as well as potential bias of the authors interpreting fracture healing in cases at their own institutions. Whelan et al. described the radiographic union score for tibia fractures (RUST) following intramedullary nailing in 2010 [20]. Several studies have subsequently been published suggesting that the RUST score is a reliable and repeatable way to assess tibia fracture healing and offers increased inter- and intra-observer reliability compared with plain radiographs [21,22]. However, for our study, the number of healed cortices was used as it was the method for clinicians to evaluate healing at both locations.

A larger sample size would allow for increased power. However, the power analysis performed prior to study initiation supports that our study was adequately powered. Finally, the two cohorts were not matched with regard to age, sex, comorbidities, smoking status, etc. The US cohort had higher rates of diabetes and tobacco use, both of which have been linked to increased rates of delayed unions and nonunions. It is possible that the deleterious effects of these medical comorbidities in the US cohort were similar to deleterious effects of NSAIDs in the Chilean cohort. If so, the higher rate of comorbidities in the US cohort could have masked the harmful effects NSAIDs in the Chilean cohort leading to a type II error.

In summary, our study contributes to the growing body of literature investigating the effects of NSAIDs on fracture healing. Despite the large amount of data produced on the topic, there is still no clear consensus on the safety of NSAID use following orthopedic procedures [8], and there is no strong clinical or scientific evidence to make clear, evidence-based recommendations regarding their use in fracture care. Pountos advises that clinicians should approach NSAIDs as a risk factor for delayed bone healing and should avoid use in high-risk patients [23]. Likewise, the general consensus among researchers and clinicians seems to be that
NSAIDs may deter fracture healing to some degree, but a short duration of use after a fracture is usually safe in patients who do not have other risk factors for nonunion [24]. More frequent use of NSAIDs in orthopedic trauma patients could reduce the risks associated with introducing patients to opioid medications or increasing pre-existing doses following surgery. It could also potentially contribute to alleviating the epidemic currently facing the US population with regard to opioid addiction and overdose. Nevertheless, large prospective randomized studies are necessary to further elucidate the potentially negative effects of NSAIDS on bone healing and to allow the formulation of clear, evidence-based clinical practice guidelines relating to their use in fracture management.

Conflicts of interest: All authors have no conflicts of interest
References


Figure captions

**Figure 1**

### Chilean Cohort
- 566 patients identified with tibia fractures
- 308 patients excluded with fractures classified as OTA/AO 41 or 43
- 42 patients treated without IMN
- 26 patients lost to follow up
- 190 patients included in final Chilean cohort

### US Cohort
- 994 patients identified with tibia fractures
- 139 patients excluded with fractures classified as OTA/AO 41 or 43
- 94 patients treated without IMN
- 579 patients lost to follow up
- 182 patients included in final US cohort
Figure 2

Time to Fracture Union

Mean time to union (days)

US

Chile
### Table 1 Summary of Results

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cohort</th>
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<tbody>
<tr>
<td>Mean age at Time of Surgery</td>
<td>US</td>
<td>38.08 ± 16.0</td>
<td>39.02 ± 13.75</td>
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<tr>
<td>Sex distribution of Cohort</td>
<td></td>
<td></td>
<td>&lt; 0.005</td>
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<tr>
<td>Male</td>
<td>US</td>
<td>68.1% (124)</td>
<td>84.2% (160)</td>
</tr>
<tr>
<td>Female</td>
<td>US</td>
<td>31.9% (58)</td>
<td>15.8% (30)</td>
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<tr>
<td>Smoker</td>
<td>US</td>
<td>42.3% (77)</td>
<td>13.15% (25)</td>
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<tr>
<td>DM</td>
<td>US</td>
<td>9.3% (17)</td>
<td>5.2% (10)</td>
</tr>
<tr>
<td>Polytrauma</td>
<td>US</td>
<td>37.9% (69)</td>
<td>18.9% (36)</td>
</tr>
<tr>
<td>Open or Closed Fracture</td>
<td></td>
<td></td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Open</td>
<td>US</td>
<td>26.3% (48)</td>
<td>43.6% (83)</td>
</tr>
<tr>
<td>Closed</td>
<td>US</td>
<td>73.6% (134)</td>
<td>56.3% (107)</td>
</tr>
<tr>
<td>Mean Time to Union (days)</td>
<td>US</td>
<td>185.04 ± 108.17</td>
<td>180.46 ± 75.93</td>
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Table 2 NSAID types

<table>
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<tr>
<th>Drug type</th>
<th>% of Cohort by Drug Prescribed</th>
<th>Dosage by Drug Type</th>
<th>Dose in mg</th>
<th>Average length of prescription (days)</th>
<th>Mean time to Union (Days)</th>
<th>SD</th>
<th>95% CI (days)</th>
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<tbody>
<tr>
<td>COX 1 Inhibitor</td>
<td>62.6% (119)</td>
<td></td>
<td></td>
<td>12.1</td>
<td>181.7 ± 62.2</td>
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<td>167.6 - 195.7</td>
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<td>Ketoprofen</td>
<td>62.6% (119)</td>
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<td></td>
<td>12</td>
<td>181.7 ± 62.2</td>
<td></td>
<td>167.6 - 195.7</td>
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<td></td>
<td>2.5% (3)</td>
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<td></td>
<td>9.2% (11)</td>
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<td>COX 2 Inhibitor</td>
<td>37.3% (71)</td>
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<td></td>
<td>13.56</td>
<td>182.2 ± 72.1</td>
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<td>162.7 - 201.7</td>
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<td>Celecoxib</td>
<td>12.6% (24)</td>
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<td>186.3 ± 76.9</td>
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<td>160.0 - 212.6</td>
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<td></td>
<td>54.16% (13)</td>
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<td>Meloxicam</td>
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<td>Non-Selective</td>
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<td>9.0</td>
<td>165.4 ± 84.2</td>
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<td>120.5 - 210.3</td>
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<td>Ketorolac</td>
<td>8.4% (16)</td>
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<td>87.5% (14)</td>
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