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Opioid exposure is associated with nonunion risk in a traumatically injured population: An inception cohort study

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ABSTRACT

Introduction: Certain common medications are associated with an elevated risk of fracture and recent data suggests that medications can also increase nonunion risk. Medication use is a modifiable nonunion risk factor, but it is unknown whether risk accrues solely to chronic medication use or whether there is also risk inherent to acute use.

Methods: Multivariate logistic regression was used in an inception cohort to calculate odds ratios (OR) for fracture nonunion associated with medication use, in context with other risk factors demonstrated to influence nonunion. Patient-level health claims for medical and drug expenses were compiled from a payer database. Patients were included if they had a fracture coded in 2011, with continuous enrollment for 1 month prior to and 12 months after fracture. The database contained demographic descriptors, treatment procedures per CPT codes, co-morbidities per ICD-9 codes, and prescriptions per National Drug Codes. Chronic medication use was defined as $\geq$30 days of prescription prior to fracture with $\geq$1 day afterward; acute use was any other prescription.

Results: Most non-analgesic medications were safe in acute or chronic use, but risk of nonunion was elevated for a wide range of analgesics. Overall, 45,085 fractures (14.6% of fractures) affected patients using chronic opioids. Nonunion OR was elevated for acute and chronic use of Schedule 2 opioids including acetaminophen/oxycodone, hydromorphone, oxycodone, and acetaminophen/hydrocodone bitartrate, as well as Schedule 3–5 opioids including tramadol (all, $p < 0.0001$). The highest ORs were associated with chronic administration of Schedule 2 opioids.

Discussion: Most medications do not increase nonunion risk, but acute and chronic use of NSAIDs or opioids was associated with impaired fracture healing. There is particular risk in prescribing opioid analgesics for fracture, though literature suggests that roughly half of opioid-naïve patients receive such a prescription.

Conclusions: Patients evaluated in this study were not a random sample of Americans; they may approximate a random sample of the Emergency Department population in the United States. Thus, trauma patients may represent a population enriched for nonunion risk factors. Opioids impair recovery from injury; if they also predispose to injury, the ongoing opioid epidemic could presage an increase in nonunion prevalence.

Introduction

Certain medications are associated with a higher risk of bone fracture, including diabetes medications [1], proton pump inhibitors [2], antidepressants [3], antipsychotics [4], anticonvulsants [5], non-steroidal anti-inflammatory drugs (NSAIDs) [6], and opioids [7].

There is also recent evidence, from an inception cohort study of 309,330 fractures, that certain medications that are commonly used at the time of fracture occurrence or orthopedic surgery can increase the risk of nonunion [8]. Medication use is a potentially modifiable risk factor [8], but it is not presently known whether risk of nonunion accrues solely to medications that are used chronically or whether there is also risk inherent to medications used acutely after fracture. Greater clarity and granularity

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regarding the relationship, if any, between medication use and nonunion risk is needed to guide prescribing practices following orthopedic surgery. We hypothesize that nonunion risk associated with medication use accrues only to chronic use prior to fracture. We test this hypothesis in a large payer database of fracture patients in the United States [8], adding detail about medications while retaining all known risk factors in a multivariate model of nonunion risk.

Methods

Database

This study was reviewed and exempted from the need for informed consent by the Institutional Review Board of Duke University Medical Center because patient data were fully de-identified. Data were obtained from Truven Health Analytics (Durham, NC), which compiled patient-level health claims data for medical and drug expenses, together with laboratory test results, hospital discharge, and death data for roughly 90.1 million patients in the United States [9]. Data are submitted by hospitals, managed care organizations, Medicare and Medicaid programs, and approximately 300 large corporations in exchange for benchmark reports. Thus, data primarily represent employed people or their families [9].

Study inclusion was limited to patients with a coded bone fracture in calendar year 2011, if the patient was continuously enrolled in a health plan for a period of 12 months after fracture [8]. Continuous enrollment was required to allow ≥1 year to capture a nonunion diagnosis. Analysis focused on the cohort of patients 18–63 years old when the fracture was sustained. Additional exclusions, as shown in the CONSORT diagram [8] were: cancer-related pathological fracture; flail chest; fracture of a prior malunion; fresh fracture treated with low-intensity pulsed ultrasound (LIPUS); and fracture that affects other than the 18 bones of interest. Variables of interest included patient demographics, treatment procedures per Current Procedural Terminology (CPT) codes, co-morbidities per International Statistical Classification of Diseases and Related Health Problems (ICD-9) codes, and drug prescriptions per National Drug Code Directory (Red Book) codes. The final database contained one row per unique fracture, with comma-separated values for 257 patient variables. There were 309,330 fractures identified in 2011, so the database contained approximately 80.5 million cells [8].

Study design

To facilitate analysis of medication use, we created two additional variables that were not available in the original research [8]. The first variable was the number of days of Medication Use Prior to Fracture (MUPF). The second variable was the number of days of Medication Use Following Fracture (MUFF). For a patient to be defined as a chronic medication user, two conditions had to be met: MUPF ≥30 days; and MUFF ≥1 day. If either condition was not met, the patient was defined as an acute user. If neither condition was met, the patient was defined as a non-user. Acute use could include any use of medications <30 days prior to the date of fracture, or use of a medication beginning at the time of fracture. No patients from the original study [8] were lost due to non-availability of medication data, so the CONSORT diagram from that study is still valid [8]. We also separated opioids into Schedule 2 (high potency) and Schedule 3–5 (low potency), to determine if there was greater risk associated with high potency opioids. The medication Schedule level was defined according to a current classification from the U.S. Food & Drug Administration, CRF, Title 21 (accessed 1 August 2017). Intravenous opioid formulations were excluded from analysis because prescription use is largely restricted to the operative setting (*e.g.*, remifentanil).

Analytic strategy

Our overall hypothesis was that fracture nonunion can be predicted by risk factors derived from patient demographics, as well as CPT, ICD-9, and Red Book codes [8]. Risk factors retained in the present model include all risk factors shown to be important in earlier work, including specific bone fracture type, fracture severity (*e.g.*, open fracture, multiple fractures, high-energy injury, surgical treatment), body-mass index, smoking habit, alcoholism, and comorbid illnesses [8]. The specific hypothesis tested here is that chronic medication use is a significant predictor of nonunion risk, even in context with all other risk factors. Multivariate logistic regression was used to calculate the odds ratio and the associated p value for each risk factor.

Data on medications were pooled into 10 broad categories, as defined by Red Book codes (*e.g.*, antibiotics, anticoagulants, diabetes medications, osteoporosis medications, cardiac medications, diuretics, immunosuppressants, steroids, anticonvulsants, and analgesics). Fracture types analyzed included the 18 most common fracture types. Nonunion odds ratios (OR) were calculated for each medication type separately, for all 18 bones pooled, and for each of 18 bones separately. Statistical analyses used SAS 9.4 (Cary, NC); the critical P-value of significance was set at 0.01, to compensate for multiple comparisons.

Results

A total of 309,330 fractures were evaluated [8], and use of medications was common in this cohort (Table 1). For example, 64.0% of all fracture patients received antibiotics acutely. Most medications had no detrimental impact on fracture healing, although antibiotics, anticoagulants, and bisphosphonates were associated with a significantly higher risk of fracture nonunion when used acutely ($p < 0.0001$), as was insulin and diuretic use ($p \leq 0.0014$). Oral contraceptive use was associated with a significantly lower risk of fracture nonunion ($p = 0.0074$). These findings do not alter the previously identified risk factors for nonunion [8].

Considering non-opioid medications that are commonly used for analgesia (Table 2), the risk of fracture nonunion was increased significantly by acute use of anticonvulsants or butalbital ($p < 0.0001$) or by chronic use of prescription NSAIDs ($p < 0.0001$). Anticonvulsants used chronically or benzodiazepine used acutely also increased risk of nonunion ($p \leq 0.0023$).

Opioid medications as a class (Table 2)—whether Schedule 2 or Schedule 3–5—significantly increased the risk of fracture nonunion following both acute and chronic administration ($p < 0.0001$). A total of 76,940 patient fractures were among chronic analgesic users, representing 24.9% of the entire cohort of 309,330 fractures. Of these, 45,085 fractures (14.6% of 309,330) used opioids chronically and 32,816 fractures (10.6% of 309,330) used NSAIDs chronically. Chronic use cannot be explained as a result of pain from the index fracture, as chronic use was defined as beginning at least 30 days prior to that fracture. Acute use of analgesic medications was present in 198,416 fractures (64.1%) which received opioids acutely and 108,951 fractures (35.2%) which received NSAIDs acutely.

Comparing acute and chronic opioid users (Table 3), there was a significant and substantial difference in healing ($p < 0.0001$). Chronic opioid use roughly doubled the risk of nonunion among all patients, and this effect was fairly consistent across all age increments and both genders, as well as in patients with a diagnosis of smoking or alcoholism. For example, the risk of

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