Research article

The association of opioid use with incident lower extremity fractures in spinal cord injury

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Objective: To determine the association between opioid use and lower extremity fracture risk in men with spinal cord injury (SCI).

Design: Retrospective cohort study.

Setting: Veterans Affairs Healthcare System.

Participants: In total, 7447 male Veterans with a history of a traumatic SCI identified from the Veterans Affairs (VA) Spinal Cord Dysfunction Registry (SCD) from September 2002 through October 2007 and followed through October 2010.

Outcome measures: Incident lower extremity fractures by use of opioids.

Results: In individuals identified from the VA SCD Registry 2002–2007, opioid use was quite common, with approximately 70% of the cohort having received a prescription for an opioid. Overall, there were 892 incident lower extremity fractures over the time period of this study (597 fractures in the opioid users and 295 fractures in the non-opioid users). After adjusting for covariates, there was a statistically significant relationship between opioid use and increased risk for lower extremity fractures (hazard ratio 1.82 (95% confidence interval 1.59–2.09)). Shorter duration of use (<6 months) and higher doses were positively related to fracture risk ($P < 0.0001$).

Conclusions: Opioid use is quite common in SCI and is associated with an increased risk for lower extremity fractures. Careful attention to fracture prevention is warranted in patients with SCI, particularly upon initiation of an opioid prescription and when higher doses are used.

Keywords: Fractures, Opioids, Bone mineral density, Osteoporosis, Spinal cord injuries, Rehabilitation, Veterans

Introduction

Chronic pain following spinal cord injury (SCI) is a frequent and substantial complication and may occur from a number of etiologies.^{1–3} Although not considered first-line therapies for pain relief in SCI, opioids may be used as second- or third-line therapies for refractory pain in this population.⁴

In persons without SCI, a few small studies have suggested that opioid use is associated with low bone mineral density (BMD)^{5,6} and fractures.^{7–9} However, the pathophysiology of osteoporosis in SCI is complex

and differs from that usually encountered with postmenopausal, senile, or isolated disuse osteoporosis,^{10–12} and it is not known whether opioids are related to fracture risk in persons with SCI.

There are a number of mechanisms by which opioids may be associated with fractures. These include adverse effects on the central nervous system leading to an increased risk for falls,^{13–15} the induction of androgen deficiency due to inhibition of gonadotropin-releasing hormones,^{16,17} and by direct interference with osteoblastic bone formation.^{18–20}

Thus, we hypothesized that among patients with SCI who used opioids compared with patients with SCI who did not use opioids, that opioid users would have more

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fractures. Secondly, we hypothesized, based on previous reports of an increased risk of fractures with opioid use in an elderly population without SCI,^{7,21} that this would be particularly true in patients with SCI who were aged 65 and older.

Methods

Participants

We included all male Veterans with a traumatic SCI of at least two years duration identified by the Veterans Affairs (VA) Spinal Cord Dysfunction (SCD) Registry²² during Fiscal Years (FY2002–FY2007). Date of onset of the SCI was obtained from the VA SCD Registry.

Lower extremity fractures that occurred between FY2002 and FY2007 were defined using *International Statistical Classification of Diseases, 9th revision* (ICD-9) codes for fractures of the lower extremity, including: femoral neck (820.x), intertrochanteric (820.21, 820.31), subtrochanteric (820.22, 820.32), pelvis (808.x), femur (820.x, 821.x), patella (822.x), and tibia/fibula (823.x). Only incident fractures were included. A fracture was considered incident (i.e. a new episode of fracture and not coding of follow-up care for a prior fracture), if there were no encounters with the same three-digit ICD-9 codes within a 120-day period prior to the fracture.²³ We excluded 140 fractures that had received codes indicating an external cause of injury (E codes), since these codes are typically assigned for high-force injury mechanisms that cause fractures in persons with normal BMD.

Opioid use

Opioid use was defined as any use within FY2002–FY2007 captured from the VA pharmacy benefits management group prescription database.²⁴

Average daily dose levels were calculated for all opioid prescriptions. To assess the possible effects of opioid dose and to control for dose in the analysis of duration of action, all opioid use was converted to an equianalgesic codeine dose.²⁴ Cumulative opioid exposure was calculated by multiplying these equivalent codeine doses by the quantity prescribed.

Duration of use of opioids prior to the incident fracture was stratified by: 0 days (reference), <6 months, 6 months to ≤1 year, 1 to ≤2 years, 2 to ≤3 years, and ≥3 years,²⁵ and defined as the time starting with the date of initial prescription of the opioid and counting the number of time periods with opioid use following it over the study period.

Covariates

Age, race, duration of SCI, level of SCI, and completeness of SCI (complete/incomplete/unknown) were

obtained from VA SCD Registry Data and the SAS Medical Datasets. To adjust for differences in comorbidities in the opioid users and non-users that might explain differences in fracture rates, Charlson comorbidity indices were calculated. Comorbidities for calculating the Charlson comorbidity index were assessed using medical comorbidity data for the year prior to the end date for each time-point of the study period. Medication use that may be associated with fracture risk (including heparin,²⁶ corticosteroids,²⁷ loop diuretics,²⁸ thiazide diuretics,²⁹ proton pump inhibitors,³⁰ serotonin receptor agonists,³¹ thiazolidinediones³²), pharmacological treatments for osteoporosis (teriparatide, bisphosphonates, calcitonin^{33,34}), calcium,^{35,36} and vitamin D^{37,38} between FY2002 and FY2007 was determined from VA pharmacy-dispensing data and considered as potential covariates.

Statistical analysis

Fracture risk was analyzed using time-to-event analysis. Patients entered the analysis cohort at their first date of VA encounter in the study period. The event of interest was the first fracture in the study period. Endpoints were censored for death, 6 months with no utilization from last known VA encounter,³⁹ or end of study period as appropriate. Time was indicated in 6 months intervals, with a total of 12 time-points.

Bivariate analyses of baseline characteristics of opioid users compared with non-users were analyzed using chi-square tests for categorical variables and *t*-tests for continuous variables. The association between opioid use and incident lower extremity fractures over the time period of the study for the overall cohort was determined using Cox-proportional hazards models. Additional analyses examined the relationship of testosterone use to incident lower extremity fractures, the interaction of testosterone and opioid use with fractures, and associations for those aged 65 and older. Potential confounding variables were investigated using Cox models. Multivariable models were constructed for the selected variables using the backward elimination procedure. All analyses were done using SAS Version 9.2. (Institute Inc., Cary, NC, USA).

The study was approved by the Veterans Affairs Institutional Review Board and principles of the Declaration of Helsinki were followed.

Missing data

There were few missing data with respect to age (<1%), level of injury (2.1%), and Charlson comorbidity indexes (4.2%) in our cohort. To handle the missing variable of age, sensitivity analyses were conducted

excluding the missing values for age. Attempts to fill in missing values for level of injury using ICD-9 codes for paraplegia and tetraplegia did not add new information. Therefore, we imputed paraplegia for the missing data (the largest frequency category) and performed additional sensitivity analyses. For the missing Charlson comorbidity indexes, we imputed the score of 2 (the largest frequency category) and performed additional sensitivity analyses.

In total, 4.5% of our cohort was missing data on race, 22.7% was missing data on completeness of injury, and 13% was missing data on duration of injury. There were no proxies identified for these. Therefore, we added a category of other/missing for the variables of race and completeness of injury and performed additional sensitivity analyses. We characterized duration of injury as 0–10 years, more than 10 years, and included a category for those missing duration of injury.

Results

Table 1 depicts baseline characteristics of the 7447 Veterans included in our database (5106 opioid users and 2341 non-users). Compared with non-users of

opioids, opioid users were younger, more likely to be of race other than White, had a shorter duration of injury, were less likely to have tetraplegia, or to have a complete or unknown extent of injury. Opioid users were also more likely than non-users to have been prescribed heparin, oral corticosteroids, loop and thiazide diuretics, proton pump inhibitors, selective serotonin reuptake inhibitors (SSRIs), thiazolidinediones, and to receive pharmacological treatment for osteoporosis ($P \leq 0.03$ for all) (Table 1). In multivariate models, White race, paraplegia, complete injuries, longer duration of injury and missing duration of injury (>10 years and missing compared with ≤ 10 years), and receipt of osteoporosis therapies were significantly positively associated with incident fractures and thiazide diuretics and the Charlson comorbidity index were significantly negatively associated with incident fractures. These variables were retained in the fully adjusted models.

Oxycodone followed by hydrocodone were the most commonly used opioids in the cohort; morphine and codeine were also frequently used (Table 2). Twelve percent of the opioid users and 13% of those not using an opioid sustained an incident lower extremity fracture.

Table 1 Baseline characteristics of the study population

	Opioid users ($n = 5106$) Mean (SD) or %	Non-users of opioids ($n = 2341$) Mean (SD) or %	P-value
Age	57.18 (12.24)	58.73 (13.43)	<0.01
Race/ethnicity			
White	3827 (74.95%)	1675 (71.55%)	REF
Black	1080 (21.15%)	524 (22.38%)	0.24
Other/unknown	199 (3.9%)	142 (6.07%)	<0.01
Duration of SCI			
0–10 years	1013 (22.97%)	365 (18.00%)	REF
>10 years	3397 (77.03%)	1663 (82.00%)	<0.01
Not Known	696 (13.63%)	313 (13.37%)	0.02
Charlson comorbidity index	4.18 (2.44)	3.50 (1.93)	<0.01
Level of SCI			
Paraplegia	2968 (58.13%)	1194 (51%)	REF
Tetraplegia	2138 (41.87%)	1147 (49%)	<0.01
Completeness of SCI			
Incomplete	2158 (42.26%)	874 (37.33%)	REF
Complete	1751 (34.29%)	973 (41.56%)	<0.01
Not known	1197 (23.44%)	494 (21.1%)	0.03
Other medication use			
Heparin	1624 (31.81%)	388 (16.57%)	<0.01
Oral corticosteroids	2423 (47.45%)	652 (27.85%)	<0.01
Loop diuretics	106 (2.08%)	22 (0.94%)	<0.01
Thiazide diuretics	1185 (23.21%)	355 (15.16%)	<0.01
Proton pump inhibitors	2818 (55.19%)	715 (30.54%)	<0.01
SSRIs	2231 (43.69%)	511 (21.83%)	<0.01
Thiazolidinediones	246 (4.82%)	71 (3.03%)	<0.01
Pharmacological treatment for osteoporosis			
Bisphosphonates	319 (6.25%)	96 (4.1%)	<0.01
Calcitonin	76 (1.49%)	23 (0.98%)	0.08
Teriparatide	2 (0.04%)	1 (0.04%)	1
Calcium	1380 (27.03%)	354 (15.12%)	<0.01
Vitamin D	3032 (59.38%)	856 (36.57%)	<0.01
Any Osteo Tx	3395 (66.49%)	1016 (43.4%)	<0.01

Table 2 Frequency of use of individual opioids

Opioid	Non-fracture cohort (n = 6562) Freq (%)	Fracture cohort (n = 892) Freq (%)
Hydrocodone	1895 (28.89)	212 (23.77)
Codeine	1299 (19.82)	156 (17.49)
Fentanyl	600 (9.15)	66 (7.4)
Hydromorphone	191 (2.91)	29 (3.25)
Meperidine	145 (2.21)	26 (2.91)
Methadone	513 (7.83)	72 (8.07)
Morphine	1375 (20.98)	169 (18.95)
Nalbuphine	12 (0.18)	0 (0)
Opium	42 (0.64)	1 (0.11)
Oxycodone	2330 (35.55)	336 (37.67)
Pentazocine	12 (0.18)	0 (0)
Propoxyphene	802 (12.23)	108 (12.11)
Tramadol	1114 (16.99)	100 (11.21)
Others (buprenorphine, butorphanol, levorphanol)	6 (0.9)	0 (0)

Compared with non-users of opioids, after adjustment for covariates, there was a significant positive relationship between use of opioids and fractures (hazard ratio (HR) 1.82 (95% confidence interval 1.59–2.09). Additional sensitivity analyses performed for missing data for age, race, level of injury, extent of injury, duration of injury, and Charlson comorbidity index as described above did not materially change the results (data not shown). Longer duration of use was significantly inversely related with fracture risk (Table 3) and higher doses (>225 mg/day of codeine equivalents) were significantly positively associated with fracture risk in adjusted models ($P < 0.0001$).

In total, 1217 opioid users and 723 non-users of opioids were aged 65 or older. After adjustment for covariates, there was no significant interaction between older age (age 65+ years) and opioid use on incident fractures ($P = 0.65$). Two-hundred and twenty-four (3%) of the cohort (183 opioid users and 41 non-users of opioids) received testosterone replacement. There was no significant interaction between use of testosterone and opioids on incident fractures ($P = 0.29$).

Discussion

In this large, national cohort of male patients with traumatic SCI, use of opioids was quite common, with approximately 70% having been prescribed opioids

over the 5-year time period of the study. Opioid use was associated with a significantly increased risk for lower extremity fractures, with most fractures occurring when these medications were first prescribed and with higher doses. This fracture risk was independent of age (>65 years) or use of testosterone replacement.

This positive association of opioids with fractures in our cohort with SCI is in accordance with previous reports of increased fracture risk with opioid use in populations without SCI,^{7–9,21,40–42} although it is the first time that this has been examined in SCI patients. In contrast with the non-SCI population,⁷ we did not find an increased risk of fractures with opioid use in our elderly SCI patients, suggesting that all SCI patients prescribed opioids, regardless of age, should be considered at risk for fractures.

Fractures were more common in our cohort in the first six months when the opioid was first prescribed. In accord with these results, a study of Medicare-eligible active and retired employees with employer-sponsored supplemental plans found that the risk of hip fracture was increased when the opioid was first initiated.⁴³ Given our findings with respect to duration of use of opioids and fracture risk, we suspect that the major mechanism by which these fractures occur is mediated through an increased risk of falls, rather than by changes in BMD. Opioids cause impairments in cognition, balance, and coordination, which are risk factors for falls.^{13–15} It is possible that over time our patients partially adapted to the central nervous system effects from opioids that might contribute to falls over time, and that is why the fracture risk decreased over time with use of opioids. In support of this, in non-SCI populations, it has been reported that despite a trend for an increased risk of fractures in opioid users, there are no differences in BMD compared with non-opioid

Table 3 Association of incident fractures with duration of opioid treatment

Duration	HR	95% CI
<6 months	(Ref)	
≥6 months–1 year	0.36	0.26–0.50
1–2 years	0.57	0.43–0.75
2–3 years	0.50	0.36–0.70
≥3 years	0.37	0.27–0.51

users,⁴⁴ although others report that BMD is decreased in opioid users compared with non-opioid users.^{5,6} In accord with a report of patients without SCI given opioids,⁷ we also found that higher doses of opioids were associated with an increased risk for fracture in patients with SCI.

Hypogonadism occurs in 40% or more of patients with chronic SCI,⁴⁵ is itself associated with low BMD,^{46,47} and may be induced by opioids.¹⁷ An association between hypogonadism and opioid prescription has been demonstrated in patients with SCI.⁴⁸ In our series, less than 5% of our cohort received testosterone replacement and testosterone use in our cohort was not associated with fracture risk. However, given both the small numbers on testosterone replacement in our series and the fact that there was unrecognized and/or untreated cases of hypogonadism that we could not assess, further studies of how hypogonadism may influence the risk of fractures in opioid users with SCI are needed.

Most of the patients in our cohort had been prescribed an opioid over the period of our study. These data are in accord with practices described for opioid prescriptions for patients with SCI outside the VA, where in one survey, 60.1% of respondents with SCI reported they had ever been prescribed an opioid and approximately half were currently receiving it.⁴⁹ This high rate of opioid prescription is not surprising, since pain following SCI is highly prevalent and difficult to treat. However, this is potentially concerning since data on their effectiveness for pain relief in SCI are very limited with only very small benefits reported,⁵⁰ and thus opioids are not considered first-line therapies for pain in SCI.⁴ However, we did not determine what proportion of patients was receiving or had previously tried first-line therapies without adequate pain relief. Additionally, a single prescription of an opioid for a short-term painful condition during the study years would cause a subject to be classified as having received opioids. We do not think it is likely that the opioid prescriptions were for treatment of fracture-related pain, as the prescriptions were prior to the first date of care for the fracture.

There are a number of limitations to our study. Data on opioid use were only available beginning in 2002, and our data also exclude any opioids received from non-VA sources. Only lower extremity fractures were included; however, these are the most common fractures that occur in chronic SCI.⁵¹ We could not control for potential confounding by indication, as we did not have data on the indication for use of the opioid. We also could not control for potential covariates not available in

our dataset that may influence fracture risk including, for example, smoking, alcohol use, vitamin D levels, nutritional status, and family history of fracture. In the non-SCI population, lower levels of vitamin D are seen in opioid users compared with non-users.⁴⁴ Our data only indicate whether an opioid was prescribed, not whether or not it was actually taken as prescribed. Women were excluded from our analyses because there were <1% ($n = 26$) women in our SCD registry data. We did not have information on either falls or BMD data in our population, which are central predictors of fracture risk.^{52,53} Finally, we were not powered to determine fracture risk by individual opioid prescribed, as there were too few prescriptions for opioids other than oxycodone, hydrocodone, codeine, or morphine.

Conclusions

Opioids are associated with an increased risk for lower extremity fractures in males with SCI. This is particularly common when opioids are first prescribed for these patients and when higher doses are used. Our results suggest that providers should discuss fracture risk when first prescribing opioids in this population. Further studies of the relationship of medication use to fractures in SCI are needed.

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