Long-term follow-up of opioid use in patients with acetabular fractures

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A B S T R A C T

Introduction: Chronic pain and the pattern of opioid use after skeletal fractures has been a neglected topic in pain medicine. Pelvic and in particular acetabular fractures represent some of the most troublesome injuries for patients with a high incidence of chronic pain after fracture. We examined the long-term opioid analgesic use among patients with acetabular fractures and analysed if potential risk factors would predict a prolonged opioid therapy.

Patients and methods: Data were extracted from medical databases such as the Swedish National Hospital Discharge Register and the National Pharmacy Register. The study period was 2005–2008. Kaplan–Meier analysis constructed the cumulative opioid consumption with 95% confidence intervals (CI). Cox multiple-regression model was used to study risk factors for a prolonged opioid prescription after admission for fracture. An age- and sex-matched control group was included for comparisons.

Results: We identified 1017 patients with isolated acetabular fractures. The proportion of dispensing opioids for these patients was 39%, which was 7 times higher than in the age- and sex-matched non-fracture controls (n = 5077). The median follow-up time was 14 (interquartile range [IQR] 5–24) months. Most patients with opioid use after fracture were male (60%) and the median age was 76 (IQR 61–85) years. The leading mechanism of injury was fall on the same level (52%). At 6 and 12 months after fracture, 41% (95% CI 36–47) and 33% (28–39) were still treated with opioids. The multiple Cox regression-analysis (adjusted for age, sex, type of treatment, and mechanism of injury) revealed that younger patients (age <70 compared with ≥70 years) were more likely to end using opioids (Hazard ratio 2.0 [95% CI 1.5–2.7]). The median daily morphine equivalent dose was 22 (IQR 14–42) mg within the first month after fracture.

Discussion: During follow-up, the frequency of patients on moderate and high doses was falling off. There was no evidence of analgesic tolerance in the majority of the patients who were treated for at least 6 months. To set our findings into perspective, studies of patterns of chronic opioid use among patients with other types of fractures would be valuable.

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1. Introduction

The awareness of chronic pain as an important patient concern has increased the prescription of strong opioid analgesic drugs to non-malignant pain conditions over time. Eriksen et al. reported that in the Danish population, approximately 3% of the adult population and 12% of patients with chronic pain regularly use opioids for the therapy of long-lasting non-cancer pain. The acceptance for the potential long-term benefits of opioids in the spectrum of chronic pain management is increasing, however, there is still substantial concern with regard to abuse, addiction, adverse effects, and the potential problem of dose escalation due to development of analgesic tolerance.

Pelvic and in particular acetabular fractures are a rare entity in the field of skeletal injuries after trauma. Still, they represent some of the most troublesome fractures for patients and surgeons. The golden standard for displaced acetabular fractures is surgery, yet the operative fixation remains a major challenge with a high complication rate and poor functional outcome in a significant amount of patients.

Chronic pain and the pattern of opioid use after skeletal fractures and surgery has been a neglected topic in pain medicine. Previous studies have shown that chronic pain after...
acetabular fractures is a major problem with a high incidence. \textsuperscript{10,18} Therefore, we examined the long-term opioid analgesic use among patients with acetabular fractures. Using data from the National Pharmacy Register we determined the prevalence of long term opioid consumption and the development of tolerance as indicated by increased doses over time. In addition, we analysed if potential risk factors such as age, sex, type of treatment, and mechanism of injury would predict a prolonged opioid therapy.

2. Patients and methods

2.1. Source of data

The Swedish National Hospital Discharge Register (SNHDR) provided data on patients with acetabular fractures. The Register collects information on all inpatient care in Sweden including diagnoses according to the International Classification of Diseases (ICD); As controls, an age- and sex-matched cohort without acetabular fractures was extracted from the Total Population Register. Data on death and emigration for both cohorts were retrieved from Statistics Sweden.

All prescriptions dispensed at pharmacies, with the exception of over-the-counter sales and drugs given to patients during hospitalisation, are stored in the National Pharmacy Register since July 1, 2005.\textsuperscript{1} Over-the-counter sales include some pain medicine such as paracetamol and nonsteroidal antiinflammatory drugs, however opioid analgesics are available by prescription only. Data linkage between the different registers used the personal identification number issued to all Swedish residents.

2.2. Study design

We extracted data from all individuals registered in the SNHDR with ICD-10 codes of acetabular fractures (S324, S3240, and S3241). Relevant surgical intervention codes for open reduction and internal fixation (NE69–99) and total hip joint arthroplasty (NFB29–49) were analysed accordingly. Mechanisms of injury were studied according to ICD E-codes (external codes) and grouped in 6 categories: fall on the same level, fall from height, fall unspecified, transport accident, miscellaneous, and not reported. The study period was July 1, 2005 to December 31, 2008. Each patient in the fracture cohort was matched with 5 individuals by age, sex, and residential area. The control group was extracted from the Total Population Register. None of the controls from the matched cohort did have a fracture of the acetabulum during the observation period.

All opioid analgesics prescribed to the study population and the matched cohort were gathered from the National Pharmacy Register. These data contain the drug name, the day of dispensing, the prescribed amount, and the dosage. The morphine equivalent dose (MED) in milligram (mg) for each opioid was calculated by multiplying the number of pills prescribed by the drug strength. These doses were then converted to the MED using available equianalgesic conversions.\textsuperscript{2,3} The median daily MED dispensed was then calculated for each month. Moreover, the opioid therapy was divided in the following categories: low dose, $\leq 20$ mg MED per day; moderate, $20 < 180$ mg; and high, $>180$ mg.\textsuperscript{2,3} The distribution of patients in the respective categories was calculated for different exposure windows after the fracture: $\leq 1$, 1–2, 3–6, 7–12, and 13–24 months. Opioids have previously been classified as weak (propoxyphene, codeine, tramadol) and strong (oxycodeone, morphine, fentanyl).\textsuperscript{9} Our analysis does not include weak but only strong opioids. We excluded all patients with fractures other than the acetabular fracture at the index hospitalisation or during follow-up, as we did not want to be biased by associated fractures.

The regional ethical review board located at the Karolinska Institutet approved the study (2009/837-31/3 and 2010/0125-32).

2.3. Statistical analysis

Median values with interquartile ranges (IQR) were used as descriptive statistics. Kaplan–Meier analysis constructed the cumulative opioid consumption with 95% confidence intervals (CI). An event was defined as the last opioid prescription. Cessation of opioid therapy was defined as having no new prescription for at least three consecutive months. Three months were chosen as this is the maximum time interval for prescribing opioid analgesics.

We used the Cox multiple-regression model to study risk factors for a prolonged opioid prescription after admission for fracture. The results of the Cox-regression analysis were expressed as hazard ratios (HR) with corresponding 95% CI. If the HR is $>1$, the patients are more likely to end dispensing opioids compared with patients in the reference group. Risk factors studied in the simple Cox model were age, sex, type of treatment (surgical versus non-surgical), and mechanism of injury. All variables were later adjusted for in a multiple Cox model.

Logistic regression analysis compared the group of patients receiving opioid analgesics after the fracture with those who never had any opioid prescription during follow-up. The dependent variable in the model was opioid use (yes/no) and covariates were age, sex, type of treatment, and mechanism of injury. The level of significance was set at $p \leq 0.05$. All statistical analyses were performed using the PASW statistics package version 18 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study participants

We could identify 2127 individual patients with acetabular fractures in the SNHDR. An isolated acetabular fracture without associated fractures was found in 1138 (54%) patients. Some 989 (46%) patients with combinations of acetabular fracture and other fractures were excluded. The crude opioid use among patients with isolated acetabular fracture was 45% ($n = 517$). We excluded 121 (11%) patients who received morphine prescriptions prior to the index hospitalisation, as we wanted to study new opioid use after fracture. This left us with a final sample size of 1017 patients. Of those, had 396 (39%) patients opioid prescriptions after the acetabular fracture (new opioid use). The corresponding age- and sex-matched control group consisted of 5077 individuals. Prescriptions of opioid analgesics was seen in 295 (6%) controls during the same follow-up period.

The majority of the patients with new opioid use after acetabular fracture were male ($n = 237$, 60%). The median age was 76 (IQR 61–85) years and a large proportion of the participants was over 80 years old ($n = 171$, 43%). The mechanism of injury leading to the acetabular fracture was dominated by falls on the same level ($n = 204$, 52%), followed by unspecified falls ($n = 75$, 19%), transport accidents ($n = 47$, 12%), fall from height ($n = 35$, 9%), miscellaneous ($n = 25$, 6%), and not reported ($n = 10$, 2%). Most patients with new opioid use were treated non-surgically ($n = 305$, 77%). The median follow-up time after fracture was 14 (IQR 5–24) months.

3.2. Opioid prescriptions

At 6, 12, and 18 months after the acetabular fracture 100 (41%, 95% CI 36–47), 60 (33%, 28–39), and 36 (28%, 22–34) patients still required opioid prescriptions, respectively (Fig. 1). For those patients, who started on opioid analgesics, the median daily MED
was 22 (IQR 14–42) mg within the first month after the fracture and 21 (IQR 13–42) mg within the second month (Fig. 2). Comparison of the daily MED among individuals who both had prescriptions for continuing treatment from the first to the sixth month indicated that the majority of these patients (72%, 21/29) did not have dose escalations (an increase by more than 30% of the original dose).

Fig. 3 shows the distribution of patients on various doses during different exposure windows. Most patients filled the first opioid prescription within the first month after the fracture (76%). During follow-up, the proportion of patients who stopped with opioid drugs was increasing, whilst the frequency of patients on moderate and high doses was falling off (Fig. 3).

The simple Cox regression-analysis revealed that demographic age under 70 years (HR 2.1), surgery (HR 1.3), fall from height (HR 1.6), and transport accident (HR 2.0) as the mechanism of injury made it less likely to continue opioid analgesic use. After adjustment for all covariates in the multiple Cox model, only younger age remained as a statistically significant predictor for ending opioid use (HR 2.0) (Table 1).

We compared the patients with isolated acetabular fractures and new opioid use (n = 396) with those who did not obtain opioids at all (n = 621). There was no difference concerning age, sex, and mechanism of injury between the two groups (data not shown). However, patients receiving opioid analgesics during follow-up were more likely to have undergone surgery (odds ratio 2.3, 95% CI 1.6–3.3, p < 0.001).

4. Discussion

The use of opioids for pain management in patients with chronic non-cancer pain has continuously increased during the past decades. We studied the long-term opioid prescriptions after fractures of the acetabulum on a nationwide basis in Sweden. Nearly 40% of the patients dispensed opioid analgesics after fracture. The opioid use was 7 times higher than in the age- and sex-matched non-fracture controls. A third of patients still received prescriptions for opioid analgesic drugs one year after the fracture. However, the doses used were rather low and we could not detect any major increased development of tolerance over time, as signalled by increases in dose. We can only assume that pain was the reason for opioid use, since the registers used for this study do not include data on the prevalence of chronic pain. However, using opioid prescription as a proxy for chronic pain may be appropriate.

In a 10 year follow-up study on the outcome of 161 surgically treated patients with acetabular fractures, Briffa et al. reported that complications were common both in the medium- and long-term. The results were variable with a significant amount of patients having either fair or poor outcome (27%).

Pohlemann et al. documented the prevalence of chronic posttraumatic pelvic pain in 83% of the cases with isolated acetabular fractures after 2 years of follow-up. Meyhoff et al. found a high incidence of chronic pain after surgery for pelvic fractures (48%) and acetabular fractures (22 of 45 patients) at a median follow-up of 6 years. The use of opioid analgesics was common among these patients (14%). Other authors confirm the high incidence of chronic pain after acetabular fracture. These findings may partly explain the extended use and prescription of opioids several months after fracture.

In accordance to previous reports, we found a male predominance. Our final study sample that was started on a new opioid treatment is characterized by a high median age and a low proportion of transport accidents. Ferguson et al. showed that the incidence of acetabular fractures in elderly patients is increasing.
Still, our cohort is older compared with other reports.16,4,20 This is explained by differences in patient selection. Whilst some authors described a frequency of up to 70% of associated fractures,16 our study excluded all patients with other fractures. We intended to study the pattern of opioid prescription of a homogenous cohort of patients after an isolated acetabular fracture. Some patients may have been started on opioids due to osteoarthritis, which has been described as a complication in up to 38% of the cases in one report.4

Moreover, we cannot rule out that some patients may have received opioid prescriptions during follow-up due to other diagnoses such as back pain, headache, extremity pain, abdominal pain, or others. Therefore, we included an age- and sex-matched cohort to estimate the opioid use in the general population without the studied fracture type.

We are aware of a considerable use of opioids in the general elderly population, especially in chronic pain.6 As we wanted to study a cohort with novel opioid use after fracture, we excluded all patients that had morphine prescriptions prior to the fracture. We did not collect data on the reason for opioid use in these excluded patients.

After adjustment for covariates in the Cox regression-model, we found only older age to be associated with an increased risk of prolonged opioid use. It is well documented in the literature, that elderly patients with acetabular fractures are more likely to have a poor clinical outcome.16,17,4,19

Long-term opioid therapy has been defined as episodes lasting longer than 3 months.3,14 Continuous use of opioids may increase the risk for tolerance development and dose escalations.2,6 We did not detect an indication of major dose escalations in 72% of patients, at least not during the first 6 months after fracture. There were no patients with high morphine doses after two months and the proportion of patients receiving moderate opioid doses decreased over time.

The median daily MED was between 17 and 27 mg during month 1 and 12 after fracture. Dunn et al. studied 9940 patients who received opioid prescriptions for non-cancer pain. Two thirds of the patients had a diagnosis of back pain or extremity pain and the mean daily MED prescribed was 13 mg. The authors concluded that compared with patients receiving 1–20 mg of opioids per day, patients with 50–99 mg had a 4 fold increase in overdose risk and patients with 100 mg or more per day had a 9 fold overdose risk.5 Mahowald et al. presented a mean opioid use of 25 mg in 230 patients with chronic spine pain. The authors concluded that the treatment was effective and the opioid doses were stable for a prolonged period of time.15 However, other authors examining opioid use among patients with back pain found substantial increases of doses and a limited improvement of pain.6

Our study is limited by the following points. We did not analyse the prevalence of re-surgery during the study period. Dispensing a drug is not always equivalent with the actual drug consumption by the patient. Thus, as a measure of true drug consumption, prevalence, and incidence figures presented maybe an over- or underestimation. Some of the dispensed prescriptions will never be used by patients, resulting in an overestimation. In contrast, additional sources of morphine such as codein (weak opioids) which is transformed in the liver to morphine, were not included in this study, resulting in an underestimation. Our study is limited by the lack of information on clinical pain levels and X-ray findings of the fractures. Our findings do not allow to comment on the adequacy of the prescribed opioid analgesics. However, our data illustrate a broad pattern that helps us to understand long-term prescriptions of opioids in fracture patients. Moreover, we included a matched control group comparing opioid consumption in the general population. All databases in this analysis contain prospectively collected data on a nationwide basis, reducing the risk of systematic bias. The National Pharmacy Register represents a source for national medication history and seems to be rather complete.7 There are no over-the-counter sales of opioid analgesics in Sweden.

In conclusion, we found a significant amount of patients still at risk for opioid prescriptions several months after acetabular fracture. However, the median daily dose used was rather low and patients remaining on opioids displayed a trend towards the use of lower doses over time. Continuation of opioid use was more likely in the elderly. To set those findings into perspective, studies of patterns of chronic opioid use among patients with other types of fractures would be valuable.

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