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## Does Pre-Operative Opiate Choice Increase Risk of Post-Operative Infection and Subsequent Surgery?

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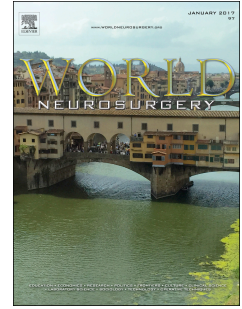
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## Does pre-operative opiate choice increase risk of post-operative infection and subsequent surgery?

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**Abstract:****Background**

Opioids are commonly prescribed for chronic pain prior to spinal surgery and research has shown an increased rate of post-operative adverse events in these patients.

**Objective**

This study compared the incidence of two-year subsequent surgical procedures and post-operative adverse events in patients undergoing lumbar fusion with or without 90-day pre-operative opioid use. We hypothesized that patients using preoperative opioids to have a higher incidence of subsequent surgery and adverse outcomes.

**Methods**

A retrospective cohort study was performed using Optum Pan-Therapeutic Electronic Health Records database including adult patients who had their first lumbar fusion between 2015 and 2018. The daily average preoperative opioid dosage 90 days prior to fusion was determined as morphine equivalent dose (MED) and further categorized into high-dose (MED>100mg/day) and low-dose (1-100mg/day). Clinical outcomes were compared after adjusting for confounders.

**Results**

A total of 23,275 patients were included, with 2,112 (10%) patients using opioids preoperatively. There was a significantly higher incidence of infection compared to non-users (12.3% versus 10.1%;  $P=0.01$ ). There was no association between subsequent fusion surgery (7.9% versus 7.5%,  $P=0.52$ ) and subsequent decompression surgery (4.1% versus 3.6%;  $P=0.3$ ) between opioid users and non-users. Regarding post-operative infection risk, low-dose users showed significantly higher incidence (12.7% versus 10.1%;  $P<0.01$ ), but high-dose users did not demonstrate higher incidence than nonusers (7.5% versus 10.1%;  $P=0.23$ ).

**Conclusion**

Consistent with prior publications, opioid use was significantly associated with a higher incidence of two-year post-operative infection compared to non-use. Low-dose opioid users had higher post-operative infection rates than non-users.

## **Introduction:**

It is estimated that more than 50% of patients undergoing spine surgery have a history of prior opioid use<sup>1</sup>. Research has shown an increase in postoperative complications among these patients that have used opioids preoperatively. These complications include subsequent surgery, extended hospital stays, postoperative chronic opioid use, and pain<sup>2-5</sup>. In 2017, inappropriate opioid use, including overdose, abuse and dependence, accounted for nearly 75% of opioid deaths in the United States, causing an \$80 billion economic burden<sup>6</sup>. Therefore, surgeons and their patients must have a thorough understanding of the potential consequences of preoperative opioid use to enable informed decisions about their treatment plan.

More recent literature suggests infection as another postoperative complication associated with preoperative opioid use<sup>7</sup>. Infection is a dreaded surgical complication that can lead to sepsis, delayed wound healing, pain, and even death. Although an exact relationship between opioid use and postoperative infection has not been established, it is essential that this connection be studied to better understand surgical outcomes.

The high prevalence of opioid prescriptions for patients undergoing spine surgery and the uncertainty of their postoperative complications warrants further investigation. This study assesses preoperative opioid use and various postoperative complications, including infection, pulmonary embolism, subsequent fusion and decompression surgery. Since prior studies have not found that postoperative complications are dosage-dependent, evaluating the relationship between pre-operation opioid dosage and post-operation outcomes is also critical<sup>8</sup>. The objective of this study was to compare the incidence of two-year subsequent surgery procedures and post-operative adverse events in patients that had lumbar fusion with or without 90-day preoperative opioid use. Furthermore, we hypothesize that lumbar fusion patients undergoing pre-operative narcotic use have a higher incidence of subsequent surgery and adverse outcomes.

## **Methods:**

### ***Study Design and setting***

A retrospective, observational cohort study of patients that had lumbar fusion from Quarter (Q) 4 2015 to Q3 2018 was performed using Optum Pan-Therapeutic Electronic Health Records database. Lumbar fusion procedure was the first or index event in this study. Patients' opioid use was measured in the 90 days prior to fusion. Patients were followed for two years' post procedure for occurrence of infection or pulmonary embolism, or a second fusion or decompression procedure (referred to as subsequent fusion or decompression surgery).

### ***Patients***

This study included patients 18 years or older that had a procedure for lumbar anterior or posterior interbody fusion or posterolateral fusion. Patients were required to have 90 days pre and 730 days post-index continuous enrollment in the database for measurement of pre-fusion opioid use and post-fusion outcomes. Patients with a diagnosis of spinal trauma, cancer or infection at the time of fusion were excluded from this study.

Procedures and diagnoses for the inclusion and exclusion criteria were identified using International Classification of Disease (ICD) codes, 10th edition.

### *Data source*

Optum Pan-Therapeutic Electronic Health Records database is a United States-based data source that collects, normalizes, and integrates provider data from different electronic medical record (EMR) platforms (i.e., Cerner, Epic, GE, McKesson, etc.). The data come from 150,000 providers, 2,000 hospitals and 7,000 clinics. It contains approximately 100 million patient lives from each of the U.S. census regions. Thus, the patients from this study were from any of the 2,000 hospitals or 7,000 clinics located across the U.S. that give data to this data source. Because of database privacy policies, the specific number of hospitals or clinics represented in this study cannot be determine.

### *Independent variables*

Opioid use was identified using national drug codes available in the database based on prescriptions written. This measure was used to categorize patients as opioid users or nonusers. Opioid utilization was further measured as morphine equivalent dose (MED) and users were further categorized based on their MED into two categories: 1-100 milligrams (mg)/day (d) MED (low dose) or >100 mg/d MED (high dose). To calculate MED, the daily dosage in mg (unit) was extracted for patients along with the days' supply from the prescriptions table in the database. Conversion factors from prior literature were used for the calculation of MED.<sup>9-15</sup> The following calculation was used to obtain patients' MED within the 90-days before fusion: morphine conversion factor \* average daily dose \* days' supply/ days' supply. .

### *Covariates*

Demographic, clinical and procedure characteristics were collected from the episode of care of the index fusion. Demographic characteristics captured were age, gender, and region. Procedure characteristics were setting of care, year fusion was performed, and number of spinal levels instrumented. The clinical characteristic collected at fusion was deformity diagnosis. Clinical characteristics captured in the 90 days prior to fusion were history of illicit drug use and comorbidities for calculation of the Elixhauser Comorbidity Index score (18).

### *Outcomes*

Outcomes were measured within the 730 days (two years) after the index fusion. Occurrence of infection (comprising general, sepsis, and surgical site infection), pulmonary embolism, subsequent fusion surgery, decompression surgery, and subsequent fusion AND decompression surgery concurrently were collected. ICD-10 codes used to measure the variables above are located in the Supplement.

### *Statistical methods*

All characteristics and outcomes were descriptively analyzed for the overall cohort and by patients' opioid utilization in the 90-days prior to fusion. The unadjusted (not adjusted for confounding factors) two-year cumulative incidence of all outcomes were calculated using a simple proportion and summarized as a percent with 95% confidence interval (CI) for user and nonuser groups. The adjusted two-year cumulative incidence of

all outcomes for opioid users versus nonusers or between nonusers versus 1-100 mg/d MED versus >100 mg/d MED were estimated and compared using logistic regression and marginal standardization approach (recycled predictions).<sup>19</sup> This method provided an estimate of incidence adjusted for confounding factors and the resulting incidence was used calculate difference in incidence between groups (risk difference). All the collected patient/procedure characteristics were included to control for confounding in all analyses. Statistical significance was set at  $P<0.05$ . R statistical software Version 1.2.5033 was used to perform all analyses.

## Results

### *Participants*

This study identified a total of 23,275 patients that met the inclusion and exclusion criteria to be included in the cohort (Figure 1). Of the 23,275 patients, 2,112 (10%) patients were prescribed opioid in the 90 days prior to lumbar fusion and 21,163 were not. Among the opioid users ( $n=2,112$ ), 1,966 (93.1%) patients MED was between 1 – 100 mg/d MED and 146 (6.9%) patients MED was >100 mg/d MED. The mean (standard deviation (SD)) and median MED for the 1 – 100 mg/d MED group was 37.9 (19.7) mg/d and 35 mg/d. For the > 100 mg/d MED group, the respective mean (SD) and median were 241.4 (276.9) mg/d and 166.1 mg/d.

### *Descriptive data*

Table 1 presents the characteristics of all the patients in this study and by their 90-day opioid use prior to fusion. Patients in the user and nonuser group were female (59% for both groups), between 60 – 69 years of age (users, 32.5%, nonusers, 30.9%). More opioid users were from the South (83.5%) and more nonusers were from the Midwest (50.6%). Surgeries were performed mostly inpatient (95%), did not require instrumentation (users, 64.7%, nonusers, 81.1%), and occurred in the year 2016 (users, 45.7%, nonusers 39.0%). Very few patients had a deformity diagnosis at time of fusion (users, 7.3%, nonusers, 8.6%) or history of illicit drug use recorded in the 90 days pre-fusion (users, 6.9%, nonusers, 10.8%). In the user group, most patients had an ECI score of 0 (32.6%) and in the nonuser group, most had a score of 1 – 2 (38.5%).

### *Outcome results*

The unadjusted risk of two-year infection, subsequent fusion or decompression, or fusion with decompression was higher in opioid users than nonusers (Figure 2). Risk and count of infection was 11.5% (243 patients) versus 10.1% (2,144); subsequent fusion, 8.3% (175) versus 7.4% (1,570); subsequent decompression, 5.1% (107) versus 3.5% (742); subsequent fusion and decompression 3.2% (68) versus 2.2% (458). Risk of two-year PE was higher in nonusers, 1.5% (323) versus users, and 1.2% (26). After confounder adjustment, the risk of infection ( $p=0.01$ ), subsequent fusion( $p=0.52$ ), decompression( $p=0.30$ ), and fusion with decompression( $p=0.48$ ) remained higher in the opioid user group (Figure 3). The difference in risk was statistically significant for infection (risk difference (RD) = 2.2%, 95% confidence interval (CI): 0.6% to 3.8%), but not for the other outcomes (fusion, RD = 0.4%, 95% CI: -0.9%, 1.7%; decompression, RD = 0.5%, 95% CI: -0.4%, 1.3%; fusion with decompression, RD = 0.3%, 95% CI: -0.4%, 0.9%). For PE, the risk difference was <0.1% (95% CI: -0.6%, 0.7%).



## Outcomes stratified by MED

There was a statistically significant risk difference of two-year infection between opioid users of 1 – 100 mg/d MED versus nonusers (RD = 2.6%, 95% CI: 1.0%, 4.3%, Figure 4), however, not between users of >100 mg/d MED versus nonusers. The infection risk was not statistically significant (RD = -2.5%, 95% CI: -6.6%, +1.6%,  $p=0.23$  Figure 4). Among the procedural outcomes, opioid users 1 – 100 mg/d MED had similar risk of returning for a fusion (RD = 0.7%, 95% CI: -0.6%, 2.0%), decompression (RD = 0.6%, 95% CI: -0.3%, +1.5%) or both (RD = 0.3%, 95% CI: -0.4%, +1.1%) (Figure 4). Users >100 mg/d MED had similar risk when compared to nonusers, fusion (RD = -2.8%, 95% CI: -6.0%, +0.5%), decompression (RD = -1.1%, 95% CI: -3.3%, +1.1%), both (RD = -1.0%, 95% CI: -2.4%, 0.9%) (Figure 4). Users >100 mg/d MED had similar risk of returning for PE versus nonusers (RD = 1.2%, 95% CI: -1.4%, +3.8%, Figure 4), and the risk difference of PE between users 1 – 100 mg/d MED and nonusers was very small (RD = -0.1%, 95% CI: -0.7%, 0.6%, Figure 4).

## Discussion

Due to the growing body of literature on the detrimental effects of preoperative opioid use on surgical outcomes, we assessed patients with pre-operative opioid use who had a lumbar fusion and two years of follow-up using the national-based Optum Pan-Therapeutic Electronic Health Records database. Our results demonstrated that, after confounder adjustment, preoperative opioid users had a significantly increased risk of postoperative infections compared to non-users. Opioid users had similar risk of undergoing additional fusion or decompression surgery after lumbar fusion as well as similar risk of pulmonary embolism.

Additionally, we investigated the association between preoperative opioid dose and outcomes. We considered MED >100mg/day as “high-dose” opioid use and MED between 1-100 mg/day as “low-dose” opioid use. Interestingly, our cohort revealed that low-dose users had higher rates of postoperative infection and subsequent surgeries than high-dose users, despite not being statistically significant. As for pulmonary embolism, high-dose users showed increased risk, while low-dose users showed similar rates.

The negative impacts of opioid use before spine deformity surgeries have been demonstrated in retrospective and prospective studies, including increased postoperative opioid independence rates, lower patient satisfaction rates, longer hospital stays, less cost-effectiveness of the surgery, and an increased risk of infection after surgery.<sup>20-22</sup> Recent studies also investigated how the duration and dosage of preoperative opioid usage affect surgical outcomes. A longer duration of preoperative opioid use (acute vs. 3-month vs. 6-month duration) has been found to be associated with a higher risk of adverse surgical outcomes and more prolonged hospital stay<sup>4,23,24</sup>; and weaning of chronic opioid use before surgery has shown an effective reduction of postoperative chronic opioid use<sup>2</sup>. Inconsistent findings about the effects of opioid dosage have been reported. Wick et al., identified a threshold dose of preoperative opioid use (29 mg/d) beyond which patients are less likely to achieve the pre-defined minimum clinically important difference after spine surgery and should be considered for opioid weaning. MED > 29mg/day was labeled as “high-dose”; however, patients with MED > 90mg/day were excluded from their study<sup>25</sup>. Virk et al., observed that a higher dose (defined as 30-100 mg/day) has significant adverse effects on surgical outcomes at three months postoperatively and returns to equivalent measurements at six months and 1-year post-surgery<sup>26</sup>.

In this study, we increased the definition of “high-dose” to MED > 100 mg/day, and nonsignificant decreased complication rates, except for pulmonary embolism were observed in this group. Our findings must be considered with caution given the low sample size of this group and potential for the effect of unmeasured confounders. Further studies are warranted to delineate how opioid use influences surgical outcomes to prepare better patients to combat or optimize opioid use.

### **Limitations**

There are some limitations of this study to consider. An electronic healthcare record database was used for this work which can be subject to coding errors and misclassifications within the databases that cannot be corrected. These databases also lack the granularity to collect specific information about the devices used at time of fusion and specifics about subsequent surgery such as location and vertebrae revised. Concurrent use of medications that may interact with opioids and concurrent treatment with non-fusion surgeries at the time of fusion are potential confounders not controlled for in this analysis. Unmeasured patient factors and additional surgical procedure characteristics may also have led to residual confounding. The size of the >100 mg/d MED group was substantially smaller than the 1 – 100 mg/d MED group which limited study power in analyses done with this group. The high-dose user patient number included in the study was very small (N=146, 6.9%) of over 2,000 patients in the study. This small number likely is part of the reason that a significant difference was not found in infection rates.

### **Conclusions:**

In this retrospective study and consistent with prior publications, preoperative opioid users had significantly higher post-operative infection risks than non-users in the two years after spinal fusion procedure. When considering opioid dose, patients taking 1 – 100 mg/d MED had significantly higher risk of two-year postoperative infection. Post-operative infection continues to be a common complication among opioid users. Clinicians should consider the risk of this potential adverse event among patients with planned lumbar fusion surgery taking opioids prior to the procedure.

**Table 1.** Demographic, clinical and procedure characteristics of patients that had fusion with or without prior 90-day opioid use, 2015 – 2018.

**Figure 1:** Flow diagram of inclusion and exclusion criteria for study:

**Figure 2 :** The unadjusted risk of two-year infection, subsequent surgeries and pulmonary embolism, , opioid nonusers (n=21,163) and users (n=2,112).

**Figure 3.** The adjusted cumulative incidence of and difference in two-year infection, subsequent surgeries and pulmonary embolism, opioid nonusers (n=21,163) and users (n=2,112).

**Figure 4.** The adjusted cumulative incidence of and difference in two-year infection, subsequent surgeries and pulmonary embolism opioid nonusers (n=21,163), opioid users 1-100 mg/d MED (n=1,966) and opioid users >100 mg/d MED (n=146) .

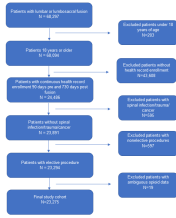
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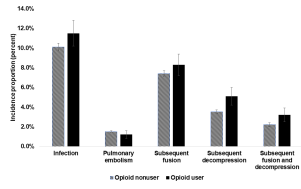
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**Table 1.** Demographic, clinical and procedure characteristics of patients that had fusion with or without prior 90-day opioid use, 2015 – 2018.

	<b>Overall cohort n=23,275</b>		<b>Opioid Users n=2,112</b>		<b>Opioid Nonusers n=21,163</b>	
<b>Age Category, N/%</b>						
18-29	197	0.80%	16	0.80%	181	0.90%
30-39	997	4.30%	78	3.70%	919	4.30%
40-49	2,518	10.80%	219	10.40%	2,299	10.90%
50-59	5,476	23.50%	504	23.90%	4,972	23.50%
60-69	7,226	31.00%	687	32.50%	6,539	30.90%
70-79	5,653	24.30%	512	24.20%	5,141	24.30%
80+	1,208	5.20%	96	4.50%	1,112	5.30%
<b>Female, N/%</b>	13,651	58.70%	1,237	58.60%	12,414	58.70%
<b>Region</b>						
Midwest	10,993	47.20%	290	13.70%	10,703	50.60%
Northeast	2,920	12.50%	5	0.20%	2,915	13.80%
South	7,072	30.40%	1,763	83.50%	5,309	25.10%
West	1,624	7.00%	1	0.00%	1,623	7.70%
Other/Unknown	666	2.90%	53	2.50%	613	2.90%
<b>Inpatient Surgery, N/%</b>	22,054	94.80%	2,013	95.30%	20,041	94.70%
<b>Elixhauser Comorbidity Score Category, N/%</b>						
0	4,598	19.80%	688	32.60%	3,910	18.50%
1-2	8,809	37.80%	665	31.50%	8,144	38.50%
3-4	6,579	28.30%	506	24.00%	6,073	28.70%
5+	3,289	14.10%	253	12.00%	3,036	14.30%
<b>Number of spinal levels instrumented, N/%</b>						
Anterior 1-2	407	1.70%	63	3.00%	344	1.60%
Anterior 3-7	9	0.00%	3	0.10%	6	0.00%
Posterior 2-5	4,220	18.10%	665	31.50%	3,555	16.80%
Posterior 6-11	58	0.20%	8	0.40%	50	0.20%
Posterior 12 or more	11	0.00%	1	0.00%	10	0.00%
Multiple approaches/levels	49	0.20%	5	0.20%	44	0.20%
No instrumentation	18,521	79.60%	1,367	64.70%	17,154	81.10%
<b>Procedure Year, N/%</b>						
2015	2,862	12.30%	221	10.50%	2,641	12.50%
2016	9,223	39.60%	965	45.70%	8,258	39.00%
2017	7,515	32.30%	673	31.90%	6,842	32.30%
2018	3,675	15.80%	253	12.00%	3,422	16.20%
<b>History of Illicit drug use, N/%</b>	2,436	10.50%	146	6.90%	2,290	10.80%
<b>Deformity diagnosis at index, N/%</b>	1,964	8.40%	154	7.30%	1,810	8.60%

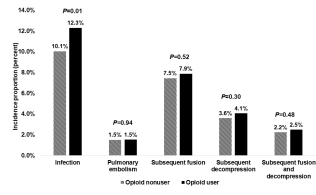


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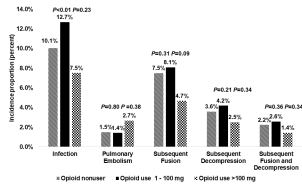


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***Abbreviation list***

1. Morphine equivalent dose (MED)
2. Commercial Claims and Encounters (CCAЕ)
3. International Classification of Disease, 10<sup>th</sup> edition (ICD-10)
4. Electronic Medical Record (EMR)
5. Elixhauser Comorbidity Index (ECI)

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**Credit Author Statement:**

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