

# Comparative Analysis of Length of Stay and Inpatient Costs for Orthopedic Surgery Patients Treated with IV Acetaminophen and IV Opioids vs. IV Opioids Alone for Post-Operative Pain

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## ABSTRACT

**Introduction:** Recovery from orthopedic surgery is oriented towards restoring functional health outcomes while reducing hospital length of stay (LOS) and medical expenditures. Optimal pain management is a key to reaching these objectives. We sought to compare orthopedic surgery patients who received combination intravenous (IV) acetaminophen and IV opioid analgesia to those who received IV opioids alone and

compared the two groups on LOS and hospitalization costs.

**Methods:** We performed a retrospective analysis of the Premier Database (Premier, Inc.; between January 2009 and June 2015) comparing orthopedic surgery patients who received post-operative pain management with combination IV acetaminophen and IV opioids to those who received only IV opioids starting on the day of surgery and continuing up to the second post-operative day. The quarterly rate of IV acetaminophen use for all hospitalizations by hospital served as the instrumental variable in two-stage least squares regressions controlling for patient and hospital covariates to compare the LOS and hospitalization costs of IV acetaminophen recipients to opioid monotherapy patients.

**Results:** We identified 4,85,895 orthopedic surgery patients with 1,74,805 (36%) who had received IV acetaminophen. Study subjects averaged 64 years of age and were predominantly non-Hispanic Caucasians (78%) and female (58%). The mean unadjusted LOS for IV acetaminophen patients was 3.2 days [standard deviation (SD) 2.6] compared to 3.9 days (SD 3.9) with only IV opioids

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( $P < 0.0001$ ). Average unadjusted hospitalization costs were \$19,024.9 (SD \$13,113.7) for IV acetaminophen patients and \$19,927.6 (SD \$19,578.8) for IV opioid patients ( $P < 0.0001$ ). These differences remained statistically significant in our instrumental variable models, with IV acetaminophen associated with 0.51 days shorter hospitalization [95% confidence interval (CI)  $-0.58$  to  $-0.44$ ,  $P < 0.0001$ ] and \$634.8 lower hospitalization costs (95% CI  $-\$1032.5$  to  $-\$237.1$ ,  $P = 0.0018$ ).

**Conclusion:** Compared to opioids alone, managing post-orthopedic surgery pain with the addition of IV acetaminophen is associated with shorter LOS and decreased hospitalization costs.

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**Keywords:** Intravenous (IV); IV acetaminophen; Opioids; Orthopedic surgery; Outcomes; Pain; Post-operative pain

## INTRODUCTION

Pain management in the inpatient setting is generally achieved through the utilization of prescription opioids or, less commonly, non-steroidal anti-inflammatory drugs (NSAIDs). However, in some clinical scenarios, including in the presence of certain comorbid cardiac diseases [1, 2] or in patients who have undergone coronary artery bypass graft surgery [1, 2], NSAIDs may be contraindicated or less desirable, and oral acetaminophen is then commonly used. Among patients on restricted oral consumption for surgical or metabolic reasons, however, the treatment options have historically been limited.

There is also concern that post-operative use of opioids may lead to long-term use and its

associated consequences [3]. Thus new and alternative strategies to help minimize opioid use are being explored. Over the past decade, multimodal pain management approaches have been introduced to utilize multiple pharmacologic and non-pharmacologic treatments to manage pain [4–6]. This has extended into the area of orthopedic surgery with several novel drug developments [7, 8]. Additionally, the recommendation for multimodal approaches was recently adopted by guidelines from the American Pain Society [9].

In November, 2010, an intravenous (IV) formulation of acetaminophen was approved by the Food and Drug Administration to augment clinicians' choices for multimodal analgesia and simultaneously address the issue of managing restricted oral consumption patients. The overall aim of this study was to examine the comparative effectiveness of combination IV acetaminophen (Ofirmev<sup>®</sup>, Mallinckrodt Pharmaceuticals) and IV opioids compared to patients receiving monotherapy with IV opioids following orthopedic surgery. We sought to estimate the impact of IV acetaminophen in terms of: length of stay (LOS), hospitalization costs, inpatient opioid consumption, and potential opioid-related complications.

## METHODS

We performed a retrospective cohort study using data from the Premier Database (Premier, Inc.) between January 1, 2009 and June 30, 2015. This database contains inpatient hospitalization service records submitted from member hospitals across the United States. Individual patients are linked between hospitalizations to allow longitudinal analysis

of multiple hospitalization events per patient within the same institution. The database includes medical record-level details of provider encounters, procedures, and laboratory work as well as hospitalization-level details such as International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis and procedure codes, current procedural terminology (CPT) medical procedure codes, ordered sequencing of events, and variables describing the costs and charges of the institution. The staff at Premier diligently maintains a standardized master charge code table of all possible events in the database records and thus all events from provider encounters to the administration of medications are captured with codes that are identifiable across institutions and repeated hospitalizations.

### **Inclusion and Exclusion Criteria**

We included all patients in the Premier Database with an orthopedic surgical procedure (total hip replacement, total knee replacement, surgical repair of hip fracture, etc.) who received IV acetaminophen or monotherapy with IV opioids starting from the day of surgery and continuing for up to two additional days during the post-operative period. All patients in our study cohort with standardized charge codes for IV opioids and IV acetaminophen beginning on the day of surgery (post-operative day zero) through the first two post-operative days were classified as exposed. Subjects whose IV acetaminophen use continued beyond the second post-operative day were excluded from the analyses to avoid introducing heterogeneity in the IV acetaminophen exposed patient population. Eligible control patients were recipients of IV opioids without the presence of IV

acetaminophen or IV NSAIDs beginning on the day of surgery through the second post-operative day.

We stratified patients into six mutually exclusive categories: total knee replacement, total hip replacement, revision of knee replacement, revision of hip or partial hip replacement, fracture, or other orthopedic surgery (spine, shoulder).

### **Outcomes**

We pre-specified four outcomes of interest for this study: (1) LOS for the surgical procedure hospitalization, (2) total cost of hospitalization, (3) mean dose of opioids [calculated in morphine equivalent doses (MED)], and (4) surgical complication rates. Total hospitalization costs and LOS were captured from the hospitalization summary files. We also calculated the department-level costs of hospitalizations among 14 different departments classified in the Premier Database. The mean opioid dose was calculated from the day of surgery through the second post-operative day. We investigated five groups of complications: Bowel obstruction, nausea/vomiting, respiratory depression, surgical site infection, and urinary tract infection. Each complication was identified utilizing ICD-9-DM diagnosis codes, restricted to those that were classified as not present on admission.

### **Statistical Analyses**

We descriptively compared the IV acetaminophen recipients to the opioid only recipients in terms of age, gender, race, all patient refined-diagnosis related group (APR-DRG) severity of illness, APR-DRG risk of mortality, whether the admission was emergent, and the census region of the

hospital. We used the Chi-square test (for categorical variables) and the Student's *t* test (for continuous variables) to determine whether differences were significant across the exposure categories. We estimated unadjusted differences in the outcomes using the Student's *t* test to compare LOS, hospitalization costs, and mean opioid dose, while unadjusted logistic regression was utilized to compare the differences in rates of each of the potential opioid-related adverse events (AEs). These comparisons of outcomes were performed on the entire cohort as well as stratified by surgery type. We also compared the hospital department-level costs using the Student's *t* test to estimate the differences in costs to individual hospital department budgets.

We performed a two-stage least squares regression instrumental variable analysis overall and by surgery type. Such a regression closely replicates randomization through an exogenous factor (instrument). We estimated each hospital's rate of IV acetaminophen use for all admissions on a quarterly basis as the instrument. We constructed separate adjusted two-stage least squares regression models for LOS, total hospitalization cost, and opioid dose. Use of IV acetaminophen (yes/no) was the main independent variable, instrumented by the time-varying quarterly rate of use of IV acetaminophen. Each model was adjusted for available confounding variables including age, sex, race/ethnicity, APR-DRG severity of illness and risk of mortality indexes, year of surgery, and hospital characteristics: Bed size, whether it was rural or urban, whether it was an academic teaching hospital, and surgeon type (general, orthopedic, or other). All analyses were conducted using SAS for Windows, version 9.3 (SAS Institute Inc., Cary, NC, USA) and STATA 13 (StataCorp LP, College Station, TX, USA).

This study was approved by the Human Subjects Division at the University of Washington by self-determination by the principal investigator.

## RESULTS

We identified 4,85,895 orthopedic surgery patients who were eligible for our study of which 1,74,805 (36%) had been managed with IV acetaminophen and opioids and 3,11,090 (64%) had been managed with IV opioids alone. The subjects in both groups were an average of 64 years of age and slightly more than half were female (58%) and nearly 80% of both groups were white. The IV acetaminophen group contained a higher proportion of elective surgery patients (78.0% vs. 67.7%) and as such the distribution of those patients on the APR-DRG severity of illness and risk of mortality scales was also higher on the minor categories compared to IV opioid monotherapy patients. Surgery type also differed between the groups, with more total knee and hip replacements occurring in the IV acetaminophen group than the opioids group (36.8% vs. 21.4% and 19.2% vs. 12.9%, respectively; Table 1).

Our unadjusted analyses revealed statistically significant differences across all of the outcomes we investigated. The use of IV acetaminophen was associated with  $-0.66$  [95% confidence interval (CI)  $-0.68$  to  $-0.64$ ] shorter days LOS,  $-\$902.7$  (95% CI  $-1005.4$  to  $-800.0$ ) lower hospitalization costs, yet slightly higher opioid dose of 3.1 mg MED (95% CI 2.8 to 3.4). Rates of respiratory depression, surgical site infections, and urinary tract infections were all significantly lower for patients who received IV acetaminophen (all  $P < 0.0001$ ); however, nausea/vomiting ( $P < 0.0001$ ) and bowel

**Table 1** Demographic characteristics of orthopedic surgery patients, comparing IV acetaminophen (Ofirmev) recipients to IV opioid monotherapy recipients

Characteristic	IV opioids ( <i>n</i> = 3,11,090)	IV acetaminophen ( <i>n</i> = 1,74,805)
Age (years), mean (SD)	64.3 (15.6)	63.6 (14.0)
Female, <i>n</i> (%)	1,79,779 (57.8)	1,02,864 (58.8)
Race, <i>n</i> (%)		
White	2,38,421 (76.6)	1,40,748 (80.5)
Black	24,876 (8.0)	14,591 (8.4)
Hispanic	47,600 (15.3)	19,362 (11.1)
Unknown	193 (0.1)	104 (0.1)
APR-DRG severity of illness, <i>n</i> (%)		
Minor	1,36,264 (43.8)	80,801 (46.2)
Moderate	1,30,231 (41.9)	77,862 (44.5)
Severe	36,973 (11.9)	14,462 (8.3)
Extreme	7622 (2.5)	1680 (1.0)
APR-DRG risk of mortality, <i>n</i> (%)		
Minor	2,17,279 (69.8)	1,37,283 (78.5)
Moderate	63,080 (20.3)	28,648 (16.4)
Severe	24,654 (7.9)	7454 (4.3)
Extreme	6077 (1.9)	1420 (0.8)
Elective surgery, <i>n</i> (%)	2,10,663 (67.7)	1,36,318 (78.0)
Hospital region, <i>n</i> (%)		
Midwest	60,685 (19.5)	27,639 (15.8)
Northeast	70,154 (22.6)	28,530 (16.3)
South	1,32,013 (42.4)	1,04,113 (59.6)
West	48,238 (15.5)	14,523 (8.3)
Surgery type, <i>n</i> (%)		
Total knee replacement	66,725 (21.4)	64,399 (36.8)
Total hip replacement	40,140 (12.9)	33,541 (19.2)
Knee revision	5187 (1.7)	4869 (2.8)
Hip revision or partial replacement	26,672 (8.6)	9671 (5.5)
Fracture	64,395 (20.7)	17,928 (10.3)
Other <sup>a</sup>	1,07,971 (34.7)	44,397 (25.4)

APR-DRG all patient refined-diagnosis related group, IV intravenous, SD standard deviation

<sup>a</sup> Shoulder and spine

**Table 2** Unadjusted outcomes of orthopedic surgery patients, comparing IV acetaminophen recipients to IV opioid monotherapy recipients

Outcome	IV opioids ( <i>n</i> = 3,11,090)	IV acetaminophen ( <i>n</i> = 1,74,805)	Difference (95% CI)	<i>P</i> value
Length of stay (days), mean (SD)	3.9 (3.9)	3.2 (2.6)	−0.66 (−0.68 to −0.64)	<0.0001
Hospitalization cost (\$), mean (SD)	19,927.6 (19,578.8)	19,024.9 (13,113.7)	−902.7 (−1005.4 to −800.0)	<0.0001
Morphine equivalent dose (mg), mean (SD)	43.8 (53.4)	46.9 (44.5)	3.1 (2.8 to 3.4)	<0.0001
Opioid-related AEs, OR <sup>a</sup> (95% CI)				
Urinary tract infection		0.596 (0.56 to 0.63)		<0.0001
Respiratory depression		0.518 (0.50 to 0.54)		<0.0001
Surgery site infection		0.754 (0.71 to 0.80)		<0.0001
Bowel obstruction		1.013 (0.99 to 1.04)		0.4
Nausea/vomiting		1.208 (1.16 to 1.26)		<0.0001

*AE* adverse event, *CI* confidence interval, *OR* odds ratio, *IV* intravenous, *SD* standard deviation

<sup>a</sup> IV opioid monotherapy is the reference group

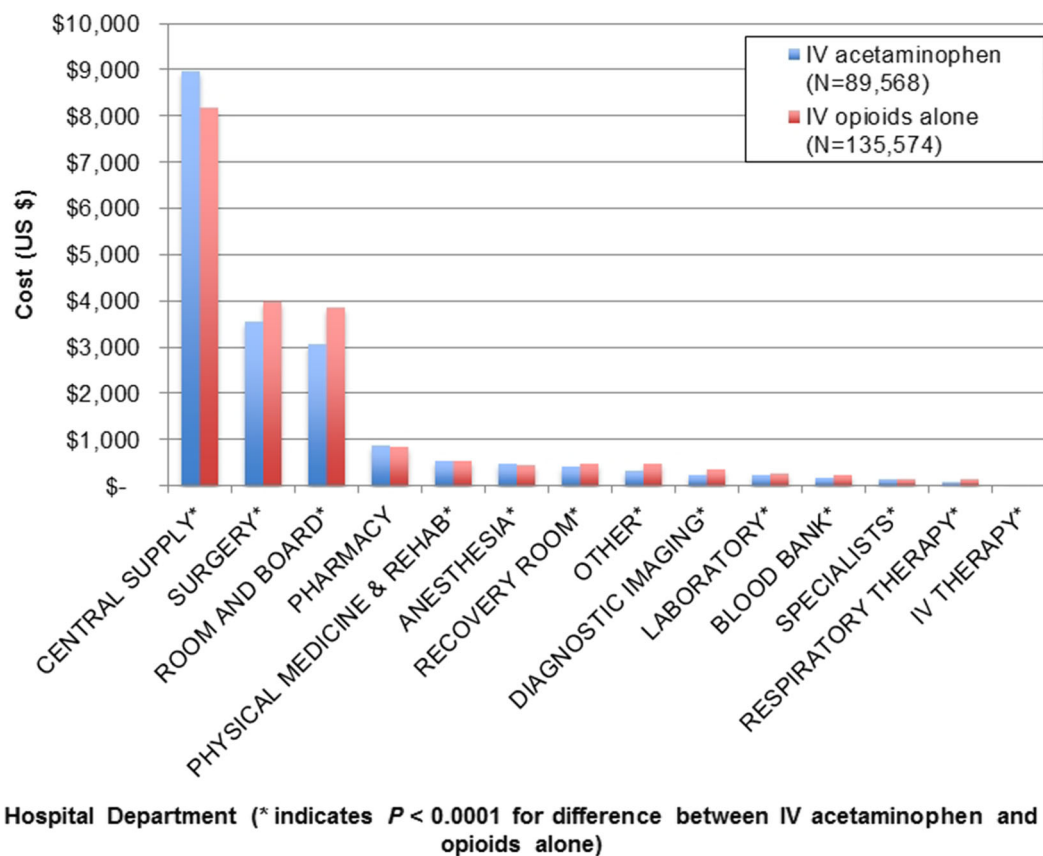
obstruction ( $P = 0.4$ ) were slightly higher (Table 2). Stratification of costs by hospital department revealed statistically significant differences in all departments except pharmacy. The IV acetaminophen group did have higher costs classified under anesthesia (\$15) and central supply (\$763). But these were offset by higher costs in the IV opioid monotherapy group including surgery (\$425), room and board (\$786), diagnostic imaging (\$110), and respiratory therapy (\$53; Fig. 1).

The instrumental variable regressions estimated for LOS, costs, and opioid dose all found statistically significant differences in favor of the group who received IV acetaminophen. Subjects who received IV acetaminophen were estimated to have 0.51 less days in the hospital (95% CI −0.58 to −0.44), cost \$634.8 less (95% CI −1032.5 to −237.1), and used 1.9 mg MED less in opioids

(95% CI −3.0 to −0.75; Table 3). Subgroup analyses by surgery type revealed that LOS was consistently lower across all surgery groups, though only the fracture and other subgroups were statistically and significantly lower. These subgroup analyses also showed that while costs were estimated to be lower for most groups, they were slightly higher for total knee replacements and other surgeries, none of which were statistically and significantly different. Opioid dose was also lower for all groups (non-significant with the exception of other) except MED was slightly higher for knee revisions (1.1 mg,  $P = 0.8$ ; Fig. 2).

## DISCUSSION

We found that post-operative pain control with IV acetaminophen and IV opioids in orthopedic surgeries is associated with statistically and



**Fig. 1** Distribution of costs by hospital department comparing IV acetaminophen recipients to IV opioid monotherapy recipients. *IV* intravenous

**Table 3** Instrumental variable regression estimated outcomes of orthopedic surgery patients, comparing IV acetaminophen recipients to IV opioid monotherapy recipients

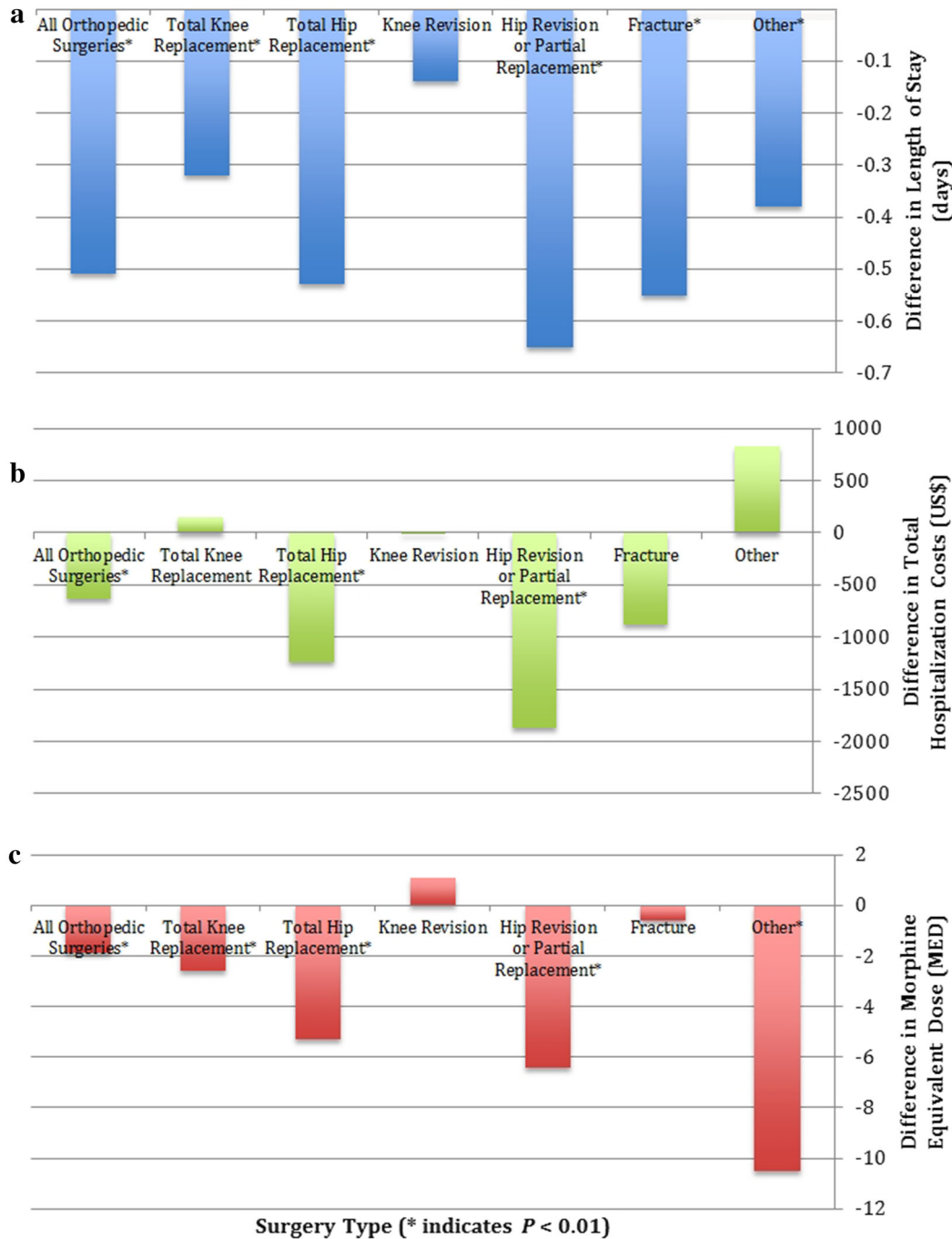
Outcome	Model estimate (95% CI)	P value
Length of stay (days)	−0.51 (−0.58 to −0.44)	<0.0001
Hospitalization cost (US \$)	−634.8 (−1032.5 to −237.1)	0.0018
Morphine equivalent dose (mg)	−1.9 (−3.0 to −0.75)	0.0011

CI confidence interval, *IV* intravenous

significantly shorter LOS, decreased opioid utilization, and lower hospitalization costs compared to IV opioid monotherapy. Reducing the hospital stay by one half day and cost by over \$600 are meaningful to both patients and health systems. Hospital department-level costs were also significantly

different between the groups, with anesthesia and central supply higher for those who received IV acetaminophen and IV opioids but all other departments, with the exception of pharmacy, higher for the group that received IV opioid monotherapy. The largest department-level differences were observed in





**Fig. 2** Instrumental variable regression estimated outcomes between IV acetaminophen recipients and IV opioid monotherapy recipients by surgery type. **a** Length of

stay; **b** total hospitalization costs; **c** morphine equivalent dose. *IV* intravenous

room and board, attributable in part to the LOS difference between the groups, and central supply, which as a catch-all department

pooled across hundreds of hospitals is difficult to characterize. Surgical department cost differences were also high, which could



possibly be attributed to greater surgeon follow-up time for the patients in the IV opioid monotherapy group. Yet it is important for within hospital department budget holders to recognize that cost-shifting may occur in surgical patient populations which ultimately improve overall costs but may negatively impact a given department's budget.

Based on these analyses, introducing IV acetaminophen into the multimodal analgesia protocols for orthopedic surgery centers would be expected to not only decrease costs but also increase patient throughput. Furthermore, finding that 64% of patients had been managed with IV opioids alone (with significant regional variation) speaks current reliance on opioids and an opportunity for patients, clinicians, and hospital systems to increase dialog regarding multimodal analgesia treatment options.

These findings are consistent with prior research in both orthopedic and other surgical procedures [10–13]. The body of literature regarding the use of IV acetaminophen for post-operative pain consistently finds associations with lower costs and shorter LOS for orthopedic surgery patients [10, 12, 13]. Importantly, the population of orthopedic surgery patients in the Premier Database was quite diverse and we observed meaningful differences between the groups of patients who received IV opioid monotherapy compared to those who received both IV acetaminophen and IV opioids post-operatively. We feel that through the use of the instrumental variable approach, our analyses have controlled for selection bias as much as possible outside of a randomized trial, which would be impractical in the size and scope of the population we have currently studied.

## Limitations

This study retains some limitations that should be considered when interpreting our findings. First, we cannot be certain that the differences we observed between IV acetaminophen and IV opioid monotherapy patients could not be explained by unobserved confounding factors. We attempted to account for this through the use of instrumental variable regression, adjusting our models for potentially confounding variables, but unmeasured factors might still play a role in the associations that we reported. Second, the medication use data in Premier is based on the amount and dose charged rather than what was exactly administered to the patient. However, we do not suspect systematic differences in billing of opioids between patients who did or did not receive IV acetaminophen. Third, while we performed unadjusted comparisons of surgical complications, methods do not exist to perform two-stage instrumental variable regressions with logistic regression in the second stage. Therefore, we were limited in our ability to draw conclusions regarding the impact of IV acetaminophen on complications. Finally, the population of patients seen in premier hospitals is not randomly sampled. Therefore, these results may not be generalizable outside of Premier hospitals.

## CONCLUSIONS

We observed clinically and economically important differences in LOS, hospitalization costs, and opioid utilization among orthopedic surgery patients who were managed with IV acetaminophen compared to IV opioids alone. In support of guidelines by the American Pain Society [9], clinicians should consider

multimodal post-operative pain management including IV acetaminophen for orthopedic surgeries.

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**Compliance with Ethics Guidelines.** This study was approved by the Human Subjects Division at the University of Washington by self-determination by the principal investigator.

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