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Original Research Article

Effects of Acetaminophen, NSAIDs, Gabapentinoids, and Their Combinations on Postoperative Pulmonary Complications After Total Hip or Knee Arthroplasty

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Abstract

Objective. Multimodal analgesia has gained popularity in total hip arthroplasty (THA) and total knee arthroplasty (TKA), but large multicenter studies evaluating specific analgesic combinations are lacking. **Design**. A retrospective study using the Premier Healthcare Database (2009–2014). **Subjects**. Adults who underwent elective primary THA or TKA. **Methods**. We categorized day-of-surgery analgesic exposure using eight mutually exclusive categories: acetaminophen (Ac), nonsteroidal anti-inflammatory drugs (Ns), gabapentinoids (Ga; gabapentin or pregabalin), Ac+Ns, Ac+Ga, Ns+Ga, Ac+Ns+Ga, and none of the three drugs. Multilevel models measured associations of the analgesic categories with a composite of postoperative pulmonary complications (PPCs). **Results**. Among 863,139 patients, 75.2% received at least one of the three drugs. In multilevel models, compared with none of the three drugs, Ga use was associated with increased odds of PPCs when used alone (adjusted odds ratio [aOR] = 1.35, 95% confidence interval [CI] = 1.27 to 1.44), combined with Ac (aOR = 1.16, 95% CI = 1.08 to 1.26), or combined with Ns (aOR = 1.28, 95% CI = 1.21 to 1.34). In contrast, the Ac+Ns pair was associated with decreased odds of PPCs (OR = 0.86, 95% CI = 0.83 to 0.90) and lower opioid consumption. Ac+Ns+Ga was not associated with PPCs, whereas it was associated with the lowest opioid consumption on the day of surgery. **Conclusions**. Gabapentinoids, alone and in single combination with either acetaminophen or nonsteroidal anti-inflammatory drugs, were associated with higher PPCs, whereas the Ac+Ns pair was associated with fewer PPCs and an opioid-sparing effect. Ac+Ns+Ga was not associated with PPCs, whereas it was associated with the lowest opioid consumption on the day of surgery.

Key Words: Gabapentinoids; NSAIDs; Acetaminophen; Postoperative Pulmonary; Complications; Total Joint Arthroplasty

Introduction

Joint replacement represents a cornerstone of orthopedic surgery in the United States and , with an aging population and increasing prevalence of obesity, 50% of Americans will experience osteoarthritis in at least one joint in their lifetime [1]. Appropriate acute pain control after surgery is essential to improve early mobilization and participation with physical therapy, and a multimodal approach may lead to a reduction in opioid consumption and related costs [2,3]. However, opioids are routinely administered to manage acute postoperative pain, with adverse perioperative effects ranging from nausea and vomiting to delirium, ileus, and postoperative

pulmonary complications including respiratory depression [4]. Multimodal analgesia involving the use of nonopioid medications in addition to opioids has gained widespread popularity to treat pain and reduce opioid use around joint replacement surgery [5].

Oral and intravenous nonopioid analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 (COX-2) inhibitors, and gabapentinoids, as well as regional analgesics (epidural and perineural infusions), are commonly used to decrease pain and opioid use, reduce opioid-related adverse events, improve patient mobilization, and reduce hospital length of stay [2,3,6]. Several multimodal analgesic protocols have been developed to target various pain pathways in joint replacement surgery [7–9]. Two recent population-based studies showed that combinations of two or more analgesics in joint replacement surgery were associated with lower opioid consumption, fewer respiratory complications, and shorter length of stay (LOS) [5,6]. However, these studies examined heterogeneous combinations of analgesics, making it hard to determine which specific combination is optimal.

Major postoperative pulmonary complications (PPCs) are potentially life-threatening events after total joint replacement [10]. Postoperative respiratory failure has been shown to be a meaningful patient safety indicator associated with poor outcomes, including longer hospital stays, higher costs, and increased 30-day mortality [11–13].

We investigated 1) the utilization of three commonly used nonopioid multimodal analgesics (acetaminophen, NSAIDs, and gabapentinoids) over time and 2) the association of exposure to these analgesics (individually or in combination) on the day of surgery, with PPCs and opioid consumption following elective total hip arthroplasty (THA) or total knee arthroplasty (TKA).

Methods

Data Source and Study Population

Data for 2009 to 2014 were extracted from a widely used inpatient database (Premier Inc., Charlotte, NC, USA) in the United States. This inpatient database comprises patient demographics, hospital characteristics, patient-specific date-stamped billing logs, and International Classification of Disease, Ninth Revision (ICD-9), Diagnosis and Procedure codes. Drug names, strength, dosing, and quantity are also available with day-of-service information. This study was approved by the Duke University Healthcare System institutional review board (Pro00101731) and was exempt from requirements for informed patient consent, as all patient data were fully de-identified.

In this retrospective cohort study, we included adult patients who underwent elective primary THA (ICD-9: 81.51) or primary TKA (ICD-9: 81.54). We excluded patients who had absent charge codes for opioid prescription on the day of surgery, or opioid doses greater than the 95th percentile, indicating extreme outliers.

Study Variables

Exposure

Our main exposure of interest was the use of specified nonopioid analgesics either individually or in combination on the day of surgery, as measured by pharmacy charge codes. We selected three analgesics commonly used in multimodal analgesia protocols: acetaminophen (Ac), NSAIDs (Ns; including COX-2 inhibitors), and gabapentinoids (Ga; gabapentin and pregabalin) [14–16]. We measured day-of-surgery analgesic exposure using eight mutually exclusive categories: Ac, Ns, Ga, Ac+Ns, Ac+Ga, Ns+Ga, Ac+Ns+Ga, and none of the three analgesics. We included both oral and intravenous formulations for Ac and Ns in our exposure definitions. Patients receiving opioid/acetaminophen combination products were not included in Ac to measure the effect of pure acetaminophen administration on outcomes.

Outcomes

The primary outcome was major PPCs, defined by a composite of respiratory failure, pneumonia, re-intubation, pulmonary edema, noninvasive ventilation (NIV), or invasive mechanical ventilation (IMV) [17,18]. Secondary outcomes included intensive care unit (ICU) admission after the day of surgery, LOS, opioid consumption on the day of surgery, and average opioid consumption after the day of surgery (opioid consumption after the day of surgery divided by LOS after the day of surgery). NIV and IMV were identified using either ICD-9 codes or hospital charge codes. We identified ICU admission and opioid consumption using hospital charge codes. Opioid doses were converted to total parenteral morphine equivalents (PMEs) using dose conversion formulae (Supplementary Data) [19].

Covariates

Patient demographic characteristics included age, sex, race (white, African American, Hispanic, other), payor category (managed care organization, Medicaid, Medicare, other), steroid, 28 binary comorbidity indicators using Elixhauser's scheme (except for drug abuse) [20], substance use disorder, and pain conditions [5,6,21]. We controlled for mode of anesthesia (general vs spinal) and receipt of additional nonopioid analgesics on the day of surgery based on hospital charges, including peripheral nerve blocks (single injection or continuous injection), patient-controlled analgesia (PCA), benzodiazepines, ketamine, intravenous lidocaine, dexmedetomidine, dexamethasone, and magnesium. These medications were entered into models as binary variables without considering dose. Hospital characteristics included hospital bed size (<200, 200–499, ≥500),

teaching status, hospital location (rural or urban), and calendar year. The ICD-9 codes and billing descriptions used in this study are listed in the Supplementary Data.

Statistical Analysis

Descriptive statistics were used to examine the study population, with counts (proportions) for categorical variables and means (stand ard deviations) for continuous variables. We used multivariable, multilevel linear, and logistic regression models to examine associations of three analgesics (Ns, Ac, Ga) and their combinations on the day of surgery with the predefined continuous and binary outcomes, respectively [22]. Multilevel models were employed, as patients within the same hospital are more likely to share similar unobserved baseline characteristics or receive similar treatments and therefore have similar outcomes, violating the assumption of independence. We included rand om intercepts for individual hospitals to control for clustering. We considered the nonexposed patients (no receipt of any of the three nonopioid analgesics) the reference group. All covariates were determined a priori based on previous literature and were included in the multilevel models.

We separately performed two sensitivity analyses to confirm the validity of our findings. First, we stratified patients into TKA and THA because of differences in pain levels between the procedures and conducted analyses separately [23]. Second, we tested the potential for effect measure modification in subgroup analysis by restricting to elderly patients aged 65 years or older. A type I error rate of 0.05 was set as the threshold for statistical significance. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

Results

Across 592 hospitals, we identified 863,139 patients who underwent elective primary THA or TKA between 2009 and 2014 (excluding a total of 161,902 patients) (Supplementary Data). Of those, 74,144 (8.6%) patients received acetaminophen (Ac), 27,676 (3.2%) patients received gabapentinoids (Ga), 248,529 (28.9%) patients received NSAIDs, 18,188 (2.1%) patients received Ac+Ga, 152,554 (17.7%) patients received Ac+Ns, 50,102 (5.8%) received Ns+Ga, and 77,842 (9.0%) received Ac+Ns+Ga on the day of surgery, whereas 214,104 (24.8%) patients received none of the three drugs on the day of surgery.

Table 1 shows patient baseline and hospital-related characteristics across the exposure categories. In general, combinations of two or three analgesics were more likely to be used in obese, white patients, those receiving cotreatment with ketamine and dexamethasone, and those treated in teaching hospitals. As shown in Table 2, unadjusted outcomes were generally similar, except for LOS and PMEs on the day of surgery, which were lower in patients who received three analgesics. Yearly trends in the use of the three analgesics and their combinations are shown in Figure 1, A and B, respectively. The Ns-only and none groups decreased over time, whereas the Ac-only group and most combination groups increased over time.

Multivariable Analyses

Figures 2 and 3A–D show fully adjusted estimates of associations between exposure categories and the predefined outcomes. Compared with the group exposed to none of the three analgesics, use of Ga was associated with increased odds of the composite of PPCs (adjusted odds ratio [aOR] = 1.35, 95% confidence interval [CI] = 1.27 to 1.44) (Figure 2). A similar increase was seen in analgesic two-drug combinations that included Ga (aOR = 1.16, 95% CI = 1.08 to 1.26, for Ac+Ga; aOR= 1.28, 95% CI = 1.21 to 1.34, for Ns+Ga). On the other hand , the combination of Ns and Ac showed protective associations with the composite of PPCs (aOR = 0.86, 95% CI = 0.83 to 0.90) and ICU admission (aOR = 0.66, 95% CI = 0.60 to 0.71) and was associated with the lowest average daily PMEs after the day of surgery (−1.4 mg, 95% CI = −1.5 to −1.2 mg). Whereas the combination of the three drugs was not associated with PPCs, it was associated with the lowest PMEs on the day of surgery (−3.3 mg, 95% CI = −3.8 to −2.8 mg). None of the three analgesics, individually or in combination, showed a clinically meaningful difference in LOS.

Findings remained consistent in sensitivity analyses that separately analyzed TKA and THA and included elderly patients (Supplementary Data).

Discussion

In this multihospital study in patients who underwent elective THA and TKA between 2009 and 2014, we found that specific combinations of drugs used for multimodal analgesia may be associated with harmful effect, whereas others may be associated with beneficial effect. Use of gabapentinoids, both individually and in single combination with either NSAIDs or acetaminophen, was associated with increased odds of PPCs. On the other hand , the pair of acetaminophen and NSAIDs was associated with decreased PPCs and opioid consumption on the day of surgery, as well as decreased average daily opioid consumption after the day of surgery. Whereas the combination of the three drugs was not associated with PPCs, it was associated with the lowest PMEs on the day of surgery. We also found that most combinations of nonopioid multimodal analgesics increased in utilization over time.

Previous studies have suggested that combinations of analgesics may lead to reduction of opioid consumption and postoperative complications [5,6]. However, different combinations of analgesics may have different levels

Table 1. Baseline characteristics categorized by three analgesics and their combinations on the day of surgery

	None N = 214,095	Ac N = 74,132	Ga N = 27,676	Ns N = 248,513	Ac+Ga N = 18,187	Ns+Ac N = 152,527	Ns+Ga N = 50,100	Ns+Ac+Ga N = 77,831
Age, mean ± SD, y	66.6 ± 10.8	66.9 ± 10.8	65.6 ± 10.5	65 ± 10.6	66.3 ± 10.6	65.2 ± 10.6	64.3 ± 10.4	64.8 ± 10.3
Male, No. (%)	83,420 (39.0)	28,374 (38.3)	9,331 (33.7)	100,606 (40.5)	5,805 (31.9)	63,185 (41.4)	19,014 (38.0)	31,622 (40.6)
Race, No. (%)								
African American	15,993 (7.5)	5,087 (6.9)	2,410 (8.7)	17,618 (7.1)	1,546 (8.5)	10,955 (7.2)	3,905 (7.8)	5,867 (7.5)
Hispanic	2,540 (1.2)	306 (0.4)	150 (0.5)	2,929 (1.2)	55 (0.3)	855 (0.6)	216 (0.4)	169 (0.2)
Other	34,217 (16.0)	11,245 (15.2)	3,965 (14.3)	32,185 (13.0)	2,879 (15.8)	17,959 (11.8)	5,655 (11.3)	9,714 (12.5)
White	161,345 (75.4)	57,494 (77.6)	21,151 (76.4)	195,781 (78.8)	13,707 (75.4)	122,758 (80.5)	40,324 (80.5)	62,081 (79.8)
Payor category, No. (%)								
MCO	593,64 (27.7)	20,070 (27.1)	6,957 (25.1)	82,529 (33.2)	4,502 (24.8)	50,628 (33.2)	16,479 (32.9)	25,837 (33.2)
Medicaid	6,385 (3.0)	2,033 (2.7)	1,171 (4.2)	7,756 (3.1)	589 (3.2)	3,907 (2.6)	1,621 (3.2)	2,102 (2.7)
Medicare	125,377 (58.6)	44,053 (59.4)	16,720 (60.4)	130,779 (52.6)	11,326 (62.3)	80,343 (52.7)	26,873 (53.6)	41,056 (52.8)
Other	22,969 (10.7)	7,976 (10.8)	2,828 (10.2)	27,449 (11.0)	1,770 (9.7)	17,649 (11.6)	5,127 (10.2)	8,836 (11.4)
CHF, No. (%)	5,544 (2.6)	2,055 (2.8)	1,002 (3.6)	4,577 (1.8)	696 (3.8)	2,667 (1.7)	1,210 (2.4)	1,519 (2.0)
Cardiac arrythmia, No. (%)	6,861 (3.2)	2,622 (3.5)	957 (3.5)	7,208 (2.9)	662 (3.6)	4,508 (3.0)	1,459 (2.9)	2,189 (2.8)
Valvular disease, No. (%)	1,619 (0.8)	602 (0.8)	301 (1.1)	1,358 (0.5)	202 (1.1)	865 (0.6)	341 (0.7)	390 (0.5)
Pulmonary circulation disorder, No. (%)	5,065 (2.4)	1,820 (2.5)	877 (3.2)	4,473 (1.8)	532 (2.9)	2,923 (1.9)	1,060 (2.1)	1,458 (1.9)
Hypertension, No. (%)	141,210 (66.0)	50,099 (67.6)	19,369 (70.0)	156,958 (63.2)	12,635 (69.5)	96,277 (63.1)	32,326 (64.5)	49,185 (63.2)
Peripheral vascular disease, No. (%)	5,065 (2.4)	1,820 (2.5)	877 (3.2)	4,473 (1.8)	532 (2.9)	2,923 (1.9)	1,060 (2.1)	1,458 (1.9)
Paralysis, No. (%)	246 (0.1)	91 (0.1)	36 (0.1)	273 (0.1)	29 (0.2)	163 (0.1)	75 (0.1)	92 (0.1)
Other neurological disorders, No. (%)	7,579 (3.5)	2,741 (3.7)	1,792 (6.5)	8,076 (3.2)	1,075 (5.9)	5,014 (3.3)	2,562 (5.1)	3,108 (4.0)
COPD, No. (%)	32,187 (15.0)	11,476 (15.5)	5,808 (21.0)	33,641 (13.5)	3,617 (19.9)	20,432 (13.4)	8,230 (16.4)	11,495 (14.8)
Diabetes, complicated, No. (%)	39,351 (18.4)	13,616 (18.4)	6,407 (23.2)	41,940 (16.9)	3,852 (21.2)	24,540 (16.1)	9,614 (19.2)	13,479 (17.3)
Diabetes, uncomplicated, No. (%)	2,799 (1.3)	962 (1.3)	1,186 (4.3)	2,317 (0.9)	628 (3.5)	1,401 (0.9)	1,293 (2.6)	1,381 (1.8)
Hypothyroidism, No. (%)	32,938 (15.4)	12,288 (16.6)	4,982 (18.0)	35,792 (14.4)	3,432 (18.9)	22,841 (15.0)	7,839 (15.6)	12,024 (15.4)
Renal failure, No. (%)	11,100 (5.2)	4,588 (6.2)	2,025 (7.3)	7,114 (2.9)	1,657 (9.1)	4,562 (3.0)	1,742 (3.5)	2,691 (3.5)
Liver disease, No. (%)	2,096 (1.0)	570 (0.8)	417 (1.5)	2,146 (0.9)	217 (1.2)	1,129 (0.7)	647 (1.3)	681 (0.9)
Peptic ulcer disease, No. (%)	45 (0.0)	13 (0.0)	6 (0.0)	34 (0.0)	3 (0.0)	16 (0.0)	10 (0.0)	15 (0.0)
AIDS, No. (%)	90 (0.0)	31 (0.0)	24 (0.1)	96 (0.0)	12 (0.1)	55 (0.0)	27 (0.1)	31 (0.0)
Lymphoma, No. (%)	564 (0.3)	222 (0.3)	89 (0.3)	599 (0.2)	55 (0.3)	374 (0.2)	133 (0.3)	201 (0.3)
Metastatic cancer, No. (%)	242 (0.1)	95 (0.1)	34 (0.1)	181 (0.1)	24 (0.1)	90 (0.1)	57 (0.1)	48 (0.1)
Solid tumor without metastasis, No. (%)	921 (0.4)	297 (0.4)	108 (0.4)	991 (0.4)	72 (0.4)	572 (0.4)	176 (0.4)	269 (0.3)
Rheumatoid arthritis, No. (%)	8,396 (3.9)	3,157 (4.3)	1,653 (6.0)	9,082 (3.7)	1,015 (5.6)	5,821 (3.8)	2,462 (4.9)	3,363 (4.3)
Coagulopathy, No. (%)	2,925 (1.4)	927 (1.3)	444 (1.6)	2,705 (1.1)	296 (1.6)	1,755 (1.2)	604 (1.2)	892 (1.1)
Obesity, No. (%)	40,790 (19.1)	14,302 (19.3)	6,746 (24.4)	48,364 (19.5)	4,463 (24.5)	30,692 (20.1)	11,592 (23.1)	17,918 (23.0)
Weight loss, No. (%)	636 (0.3)	185 (0.2)	88 (0.3)	586 (0.2)	51 (0.3)	295 (0.2)	81 (0.2)	142 (0.2)
Fluid/electrolyte disorders, No. (%)	6,348 (3.0)	1,921 (2.6)	869 (3.1)	5,045 (2.0)	596 (3.3)	2,851 (1.9)	1,062 (2.1)	1,651 (2.1)
Blood loss anemia, No. (%)	1,017 (0.5)	263 (0.4)	127 (0.5)	845 (0.3)	58 (0.3)	383 (0.3)	200 (0.4)	176 (0.2)
Deficiency anemia, No. (%)	14,093 (6.6)	4,389 (5.9)	1,901 (6.9)	13,106 (5.3)	1,304 (7.2)	7,539 (4.9)	2,587 (5.2)	3,985 (5.1)
Alcohol abuse, No. (%)	2,526 (1.2)	773 (1.0)	365 (1.3)	2,747 (1.1)	215 (1.2)	1,492 (1.0)	626 (1.2)	939 (1.2)
Psychoses, No. (%)	3,600 (1.7)	1,244 (1.7)	894 (3.2)	3,877 (1.6)	539 (3.0)	2,275 (1.5)	1,142 (2.3)	1,389 (1.8)
Depression, No. (%)	25,083 (11.7)	9,771 (13.2)	5,133 (18.5)	29,914 (12.0)	3,207 (17.6)	19,507 (12.8)	8,043 (16.1)	11,616 (14.9)
Any substance abuse, No. (%)	18,669 (8.7)	5,748 (7.8)	3,060 (11.1)	22,588 (9.1)	1,682 (9.2)	11,525 (7.6)	4,983 (9.9)	6,443 (8.3)
Pain conditions, No. (%)	11,019 (5.1)	4,006 (5.4)	2,801 (10.1)	12,919 (5.2)	1,584 (8.7)	8,932 (5.9)	4,193 (8.4)	5,298 (6.8)

(continued)

Table 1. continued

	None N = 214,095	Ac N = 74,132	Ga N = 27,676	Ns N = 248,513	Ac+Ga N = 18,187	Ns+Ac N = 152,527	Ns+Ga N = 50,100	Ns+Ac+Ga N = 77,831
Steroid, No. (%)	9,449 (4.4)	3,806 (5.1)	1,568 (5.7)	14,120 (5.7)	985 (5.4)	8,651 (5.7)	2,993 (6.0)	3,394 (4.4)
General anesthesia, No. (%)	151,029 (70.5)	57,221 (77.2)	20,639 (74.6)	178,160 (71.7)	14,456 (79.5)	110,867 (72.7)	36,549 (73.0)	57,372 (73.7)
PCA, No. (%)	78,934 (36.9)	17,169 (23.2)	7,056 (25.5)	64,885 (26.1)	2,629 (14.5)	23,108 (15.2)	10,138 (20.2)	6,231 (8.0)
PNB single, No. (%)	54,217 (25.3)	17,611 (23.8)	8,067 (29.1)	64,817 (26.1)	4,342 (23.9)	34,460 (22.6)	12,089 (24.1)	16,784 (21.6)
PNB continuous, No. (%)	17,201 (8.0)	6,057 (8.2)	2,412 (8.7)	21,257 (8.6)	1,582 (8.7)	13,479 (8.8)	4,941 (9.9)	5,913 (7.6)
Benzodiazepine, No. (%)	180,971 (84.5)	61,393 (82.8)	24,398 (88.2)	218,312 (87.8)	14,893 (81.9)	132,952 (87.2)	44,526 (88.9)	63,891 (82.1)
Ketamine, No. (%)	6,952 (3.2)	2,812 (3.8)	1,913 (6.9)	9,666 (3.9)	1,503 (8.3)	6,127 (4.0)	3,413 (6.8)	5,148 (6.6)
Lidocaine, No. (%)	6,298 (2.9)	2,529 (3.4)	1,045 (3.8)	8,761 (3.5)	948 (5.2)	4,117 (2.7)	2,708 (5.4)	3,226 (4.1)
Magnesium, No. (%)	3,290 (1.5)	1,109 (1.5)	390 (1.4)	2,975 (1.2)	237 (1.3)	1,709 (1.1)	675 (1.3)	855 (1.1)
Dexmedetomidine, No. (%)	669 (0.3)	351 (0.5)	91 (0.3)	827 (0.3)	61 (0.3)	523 (0.3)	200 (0.4)	243 (0.3)
Dexamethasone, No. (%)	47,830 (22.3)	20,574 (27.8)	6,295 (22.7)	69,807 (28.1)	4,895 (26.9)	54,795 (35.9)	14,113 (28.2)	22,587 (29.0)
Teaching hospital, No. (%)	82,307 (38.4)	37,663 (50.8)	11,057 (40.0)	93,185 (37.5)	9,472 (52.1)	69,519 (45.6)	21,266 (42.4)	37,692 (48.4)
Rural, No. (%)	27,483 (12.8)	8,191 (11.0)	3,615 (13.1)	29,035 (11.7)	1,791 (9.8)	16,128 (10.6)	4,214 (8.4)	5,518 (7.1)
Bed size, No. (%)								
<200	41,691 (19.5)	15,464 (20.9)	4,581 (16.6)	52,537 (21.1)	3,132 (17.2)	35,184 (23.1)	11,826 (23.6)	15,759 (20.2)
200–499	116,347 (54.3)	36,079 (48.7)	15,239 (55.1)	135,659 (54.6)	9,183 (50.5)	75,038 (49.2)	25,576 (51.0)	41,602 (53.5)
≥500	56,057 (26.2)	22,589 (30.5)	7,856 (28.4)	60,317 (24.3)	5,872 (32.3)	42,305 (27.7)	12,698 (25.3)	20,470 (26.3)
Fiscal year, No. (%)								
2009	38,811 (18.1)	6,333 (8.5)	3,824 (13.8)	41,103 (16.5)	1,040 (5.7)	11,990 (7.9)	5,906 (11.8)	3,839 (4.9)
2010	41,329 (19.3)	8,021 (10.8)	3,773 (13.6)	44,679 (18.0)	1,530 (8.4)	15,741 (10.3)	6,892 (13.8)	5,809 (7.5)
2011	40,910 (19.1)	9,650 (13.0)	4,620 (16.7)	46,685 (18.8)	1,785 (9.8)	19,399 (12.7)	9,110 (18.2)	8,802 (11.3)
2012	36,329 (17.0)	13,817 (18.6)	5,221 (18.9)	42,533 (17.1)	2,775 (15.3)	26,706 (17.5)	9,697 (19.4)	14,433 (18.5)
2013	32,070 (15.0)	17,430 (23.5)	5,137 (18.6)	39,468 (15.9)	4,858 (26.7)	35,139 (23.0)	9,564 (19.1)	19,859 (25.5)
2014	24,646 (11.5)	18,881 (25.5)	5,101 (18.4)	34,045 (13.7)	6,199 (34.1)	43,552 (28.6)	8,931 (17.8)	25,089 (32.2)

Ac = acetaminophen; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; COX-2 = cycloxxgenase-2; Ga = gabapentinoids; MCO = managed care organization; Ns = nonsteroidal anti-inflammatory drugs; PCA = Patient controlled analgesia; PNB = peripheral nerve block.

Table 2. Outcomes by three analgesics and their combinations on the day of surgery

	None N = 214,095	Ac N = 74,132	Ga N = 27,676	Ns N = 248,513	Ac+Ga N = 18,187	Ns+Ac N = 152,527	Ns+Ga N = 50,100	Ns+Ac+Ga N = 77,831
Primary outcome								
Composite of PPCs, No. (%)	13,173 (6.2)	4,471 (6.0)	2,458 (8.9)	12,291 (4.9)	1,605 (8.8)	6,714 (4.4)	3,463 (6.9)	4,875 (6.3)
Secondary outcome								
ICU admission, No. (%)	3,164 (1.5)	867 (1.2)	485 (1.8)	2,343 (0.9)	274 (1.5)	1,105 (0.7)	652 (1.3)	711 (0.9)
LOS, mean ± SD, d	3.4 ± 1.8	3.3 ± 1.5	3.4 ± 1.7	3.0 ± 1.3	3.2 ± 1.6	2.8 ± 1.3	2.9 ± 1.4	2.7 ± 1.3
PMEs on the day of surgery, mg ± SD	72.7 ± 61.7	68.9 ± 60.1	68.8 ± 59.3	68.5 ± 60.6	65.3 ± 56.7	66.5 ± 59.8	69.3 ± 61.4	57.8 ± 53.9
Average PMEs after the day of surgery ± SD, mg/d	21.9 ± 23.7	22.3 ± 25.1	24.3 ± 26.3	21.0 ± 22.3	23.2 ± 25	20.7 ± 21.6	22.1 ± 24.5	20.2 ± 22.4

Composite of PPCs included respiratory failure, pneumonia, re-intubation, pulmonary edema, noninvasive ventilation, or invasive mechanical ventilation.

Ac = acetaminophen; Ga = gabapentinoids; ICU = intensive care unit; LOS = length of stay; Ns = nonsteroidal anti-inflammatory drugs; PMEs = parenteral morphine equivalents; PPC = postoperative pulmonary complications.

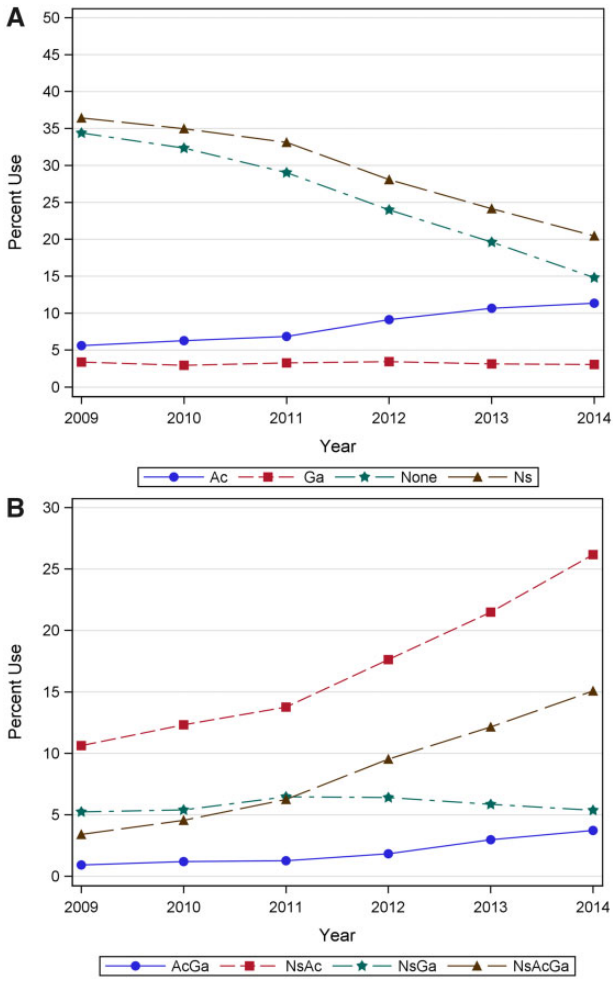

Figure 1. Trends of three analgesics and none of the three (A) and their combinations (B). Ac = acetaminophen; Ga = gabapentinoids; Ns = nonsteroidal anti-inflammatory drugs. Symbols: Ac (circle), Ga (square), None (star), Ns (triangle) in panel A, AcGa (circle), NsAc (square), NsGa (star), NsAcGa (triangle) in panel B.

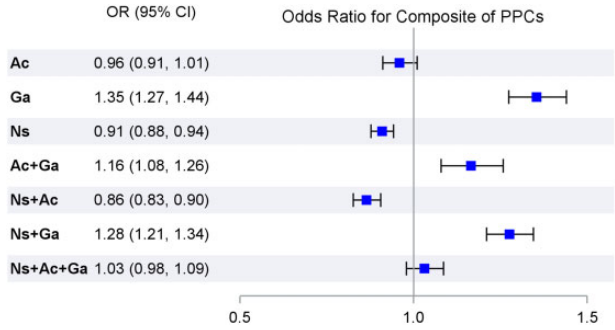

Figure 2. Odds ratio estimates for composite of postoperative pulmonary complications. Ac = acetaminophen; CI = confidence interval; Ga = gabapentinoids; Ns = nonsteroidal anti-inflammatory drugs; OR = odds ratio; PPCs = postoperative pulmonary complications.

of effectiveness in this regard, including synergistic and antagonistic effects [24]. Effective combination therapy requires identification of drugs that provide more beneficial effect when used together, without increasing the incidence of adverse events. From this point of view, we found that the pair of Ac+Ns and the triple combination (Ac+Ns+Ga) were effective in lowering opioid consumption without increasing postoperative pulmonary complications. Interestingly, opioid consumption on the day of surgery was the lowest when the triple combination was used. This supports and extends the findings of a recent network meta-analysis of 135 trials including 13,287 patients who underwent major surgery, which concluded that the pair of Ac+Ns was associated with lower opioid consumption than either analgesic alone [14]. The possible explanation is that the opioid-sparing effects might be more pronounced as the number of treatments for pain management increases [5,6]. In contrast, we also found that findings were inconsistent when gabapentinoids were added to either acetaminophen or NSAIDs. Further research will be required to assess whether the interaction effects of acetaminophen, NSAIDs, and gabapentinoids exist [15].

We found that NSAIDs were associated with decreased odds of postoperative pulmonary complications and with lower opioid consumption when used alone or in combination with acetaminophen. Although the association of NSAIDs with PPCs in THA/TKA has not been

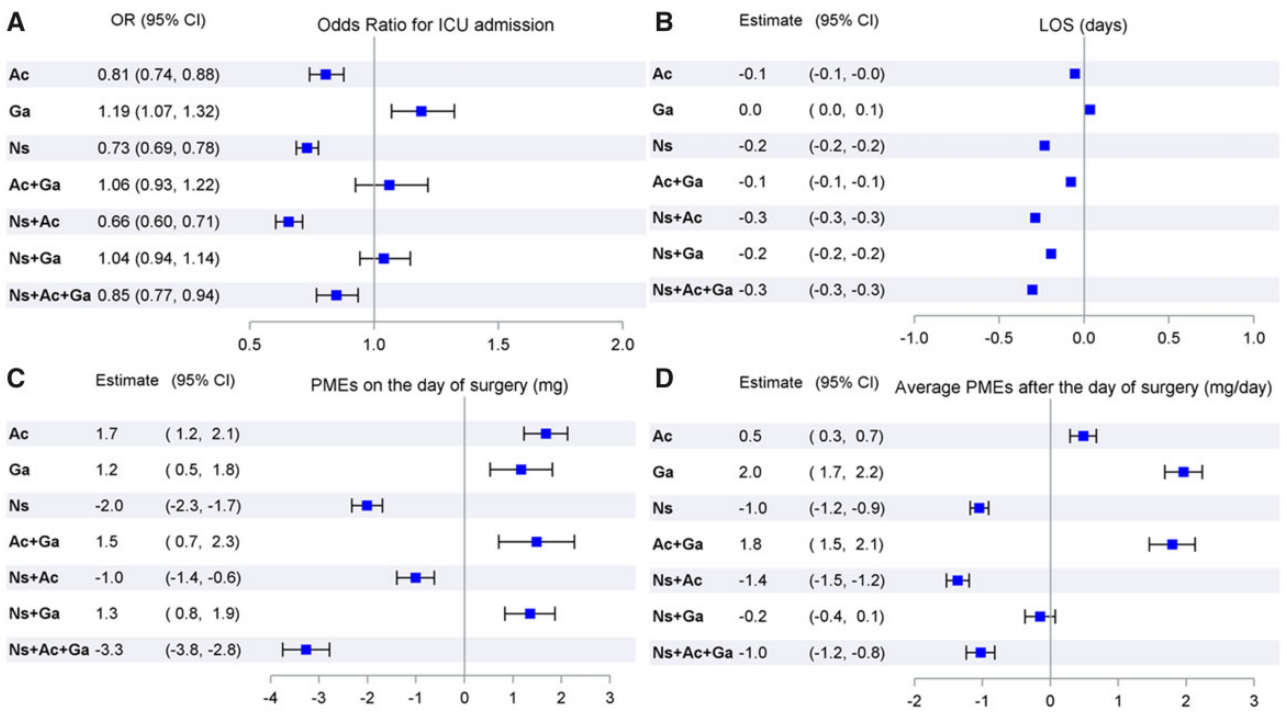

Figure 3. A–D) Estimates for secondary outcomes. Ac = acetaminophen; CI = confidence interval; Ga = gabapentinoids; ICU = intensive care unit; LOS = length of stay; Ns = nonsteroidal anti-inflammatory drugs; OR = odds ratio; PMEs = parenteral morphine equivalents.

assessed thoroughly by previous studies, the greater reduction in opioid consumption on the day of surgery with NSAIDs alone and in the Ac+Ns group might contribute to lower opioid-related postoperative pulmonary complications [25].

Despite widespread use, gabapentinoids are reported to interact with intravenous opioids such that the risk of postoperative respiratory depression is increased [26,27], in addition to more sedation, dizziness, and confusion [28,29]. Our finding that use of gabapentinoids was associated with increased odds of postoperative pulmonary complications in the present study is consistent with results from previous single-center studies [30,31]. When compared with the Ac+Ns pair, the triple combination of Ac+Ns+Ga was not associated with postoperative pulmonary complications. Conceivably, adverse effects of gabapentinoids might offset the protective effect of Ac+Ns. Moreover, in contrast to prior meta-analyses [32,33], we found no opioid-sparing effect of gabapentinoids on the day of surgery. Possible explanations for these mixed results include differences in surgical procedures and patient factors [32]. Given concerns about postoperative pulmonary complications, patients who receive opioids and gabapentinoids may need higher vigilance for signs of respiratory depression in the postoperative period and education for ongoing opioid dose adjustments.

An increased trend in perioperative use of combinations of analgesics has been reported previously [5,6,34]. The increase in use of Ac+Ns and Ac+Ga followed the approval of intravenous acetaminophen by the Food and Drug Administration in 2010; high cost compared with oral acetaminophen may explain the gradual nature of this change. The increased use of analgesic combinations suggests that multimodal analgesic approaches have been gradually implemented, given the recommendations for their use by several professional societies [35,36].

Although we adjusted for a range of covariates and used multilevel models to adjust for between-hospital differences, the present study has several limitations due to its retrospective design using administrative data. First, confounding by indication might occur in the present study. We found that Ac, Ga, and the pair of Ac+Ga and Ns+Ga were associated with higher opioid consumption on the day of surgery. This might be caused by confounding by indication, because patients who had greater acute pain might be more likely to receive those analgesics and opioids, and we were not able to adjust for pain scores. Second, since charge codes had only day-stamped information, distinction of whether co-treatments were given preoperatively, intraoperatively, or postoperatively, especially on the day of surgery, was unavailable. Third, definitions of comorbidities and complications based on the ICD-9 codes may be inaccurate due to coding bias. Fourth, measurement error related to differences between billing data and actual amounts of drugs administered might occur. Fifth, we did not have data on planned (vs urgent) NIV for obstructive sleep apnea or chronic obstructive pulmonary disease in the Premier database. Sixth, LOS in orthopedic surgery is affected by

postoperative care and discharge planning in addition to analgesic choice [37]. Finally, our data do not reflect any changes in stand ard practice since 2014.

Conclusions

The use of gabapentinoids in total hip or knee arthroplasty was associated with increased odds of postoperative pulmonary complications, when used alone or in single combination with either acetaminophen or NSAIDs. In contrast, the paired use of acetaminophen and NSAIDs was associated with beneficial outcomes: fewer postoperative pulmonary complications and reduced opioid consumption. The combination of the three drugs was not associated with postoperative pulmonary complications, whereas it was associated with the lowest opioid consumption on the day of surgery.

Supplementary Data

Supplementary data are available at *Pain Medicine* online.

Authors' Contributions

Tetsu Ohnuma: This author participated in study design, conduct of analyses, interpretation of data, writing of the manuscript, and final approval of the version to be published.

John Whittle: This author participated in study design, revision of the article for intellectual content, and final approval of the version to be published.

Srinivas Pyati: This author participated in study design, revision of the article for intellectual content, and final approval of the version to be published.

Alan R. Ellis: This author participated in study design, conduct of analyses, interpretation of data, revision of the article for intellectual content, and final approval of the version to be published.

Raquel R. Bartz: This author participated in study design, revision of the article for intellectual content, and final approval of the version to be published.

William E. Bryan: This author participated in study design, revision of the article for intellectual content, and final approval of the version to be published.

Marc J. Pepin: This author participated in study design, revision of the article for intellectual content, and final approval of the version to be published.

Karthik Raghunathan: This author led the study team, data analysis and interpretation, writing of the manuscript, and final approval of version to be published.

Vijay Krishnamoorthy: This author participated in study design, interpretation of data, writing of the manuscript, and final approval of the version to be published.

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