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Adverse effect profile comparison of pain regimens with and without intravenous acetaminophen in total hip and knee arthroplasty patients

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Abstract

Background: The use of adjunct, non-opioid agents is integral for pain control following total hip and knee arthroplasty. Literature comparing safety profiles of intravenous acetaminophen versus opioids is lacking.

Objective: To determine whether there is a difference in frequency and type of adverse effects between intravenous acetaminophen–treated and non-intravenous acetaminophen–treated patients. Primary safety endpoints included any adverse effect noted in the electronic medical record post-surgically. Secondary endpoints included changes in laboratory values, vital signs, and pain scores.

Methods: This is a retrospective, matched, cohort study with data collected from electronic medical records. Adverse effects were collected from progress notes, nursing notes, and post-operative notes. Mean pain score was measured by the 11-point visual analog scale over a 72-h period.

Results: A total of 609 patients who underwent a total hip or knee replacement were included. In all, 406 patients were treated with intravenous acetaminophen, and 203 patients received medication management without intravenous acetaminophen. More patients treated with intravenous acetaminophen experienced an adverse effect compared to patients who did not receive intravenous acetaminophen (91.63% versus 84.73%; $p = 0.012$). Mean cumulative acetaminophen exposure was similar in the intravenous acetaminophen group (7704.89 ± 2558.6 versus 7260.1 ± 3016.09 mg; $p = 0.07$). Mean opioid use was similar in the intravenous acetaminophen group as compared to the non-intravenous acetaminophen group (209.61 ± 555.09 versus 163.89 ± 232.44 mg; $p = 0.152$). Significantly higher mean pain scores were found in the intravenous acetaminophen group during the 72-h post-surgery period as compared with non-intravenous acetaminophen-treated patients.

Conclusion: The increased utilization of intravenous acetaminophen in multimodal pain management did not result in an improved safety or tolerability profile or reduced opioid utilization in orthopedic patients.

Keywords

Pharmacoepidemiology/drug safety, anaesthesia/pain

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Introduction

Traditionally, opioids have been the mainstay of management of post-operative acute pain. However, the World Health Organization (WHO) and the American Society of Anesthesiologists (ASA) recommend that whenever possible, use of multimodal pain management therapy should be implemented.[1,2] A multimodal approach includes the use of multiple modalities at lower doses to target different pain pathways, which can minimize adverse effects while

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improving pain outcomes.[3] The ASA recommends that, unless contraindicated, routine use of perioperative non-opioid medications (e.g. non-steroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors) should be implemented. They also strongly agree that acetaminophen, in any form, be considered as part of a post-operative regimen, depending on physician preference and patient-specific factors.[1]

Acetaminophen is widely used to control post-operative pain. Although its mechanism of action is not fully understood, acetaminophen is thought to control pain by inhibiting the synthesis of prostaglandins in the central nervous system and works peripherally to block pain impulse generation.[4] In 2011, an intravenous (IV) formulation of acetaminophen, Ofirmev™ (OFIRMEV; Mallinckrodt Pharmaceuticals, St. Louis, MO, USA) was approved by the US Food and Drug Administration. Intravenous acetaminophen (IVA) is indicated for the management of mild to moderate pain, moderate to severe pain with adjunctive opioid analgesics, and reduction in fever in patients 2 years and older.[5]

Upon availability in the United States, IVA has been widely utilized post-operatively due to its pharmacokinetic and safety profile. There are randomized, double-blinded, placebo-controlled studies that suggest IVA reduces pain intensity and opioid consumption over 24 h.[6,7] IVA's ability to achieve greater peak plasma levels and greater cerebrospinal fluid levels than the oral formulation has been associated with superior analgesic efficacy in the post-operative setting.[8] Although caution should still be exercised in those with hepatic dysfunction, IVA is thought to have less hepatotoxic effects than the oral formulation due to reduced first-pass metabolism.[9] Moreover, administering medication IV after surgery may benefit those with post-operative nausea and vomiting, or those who may not have the option for oral medication based on the type of surgery.[3]

IVA has the potential to fill unmet needs in the post-operative setting, as opioids are associated with adverse effects that may complicate and lengthen surgical recovery, such as vomiting, constipation, respiratory depression, and sedation.[9] Reduction in opioid consumption is generally thought to be associated with fewer of these adverse effects, shorter hospital stays, and an increase in patient satisfaction.[7–10] These adverse effects make it suboptimal to use opioids as monotherapy for the treatment of acute post-operative pain. The advantages of IVA may be offset by the cost of the formulation, which often limits its use. The 24-h cost of oral and IVA, at a dose of 1 g every 6 h, is US$0.12 and US$169, respectively.[4] Data from IVA-treated patients show that the most common adverse effects include nausea (34%), vomiting (15%), headache (10%), insomnia (7%), and pyrexia (5%).[4]

Literature is available regarding the use of IVA but focuses mainly on the effect on adjunct opioid use, efficacy of pain relief, and length of hospitalization.[6,11] One meta-analysis involving IVA in the post-operative setting concluded that there was no statistically significant difference in the rate of adverse effects or liver function test (LFT) abnormalities when comparing IVA to placebo. However, there was insufficient data to conduct a meta-analysis of IVA versus opioids.[12] Another study that evaluated efficacy and safety of IVA to placebo concluded that reduction in morphine consumption did not translate into a lower rate of nausea, vomiting, or constipation, and there was no significant difference between treatment groups regarding the number of patients experiencing adverse effects.[13] This study will focus on the adverse event and safety comparison of IVA use, given its relatively high cost and minimal research available.

Methods

The institutional review board approved this retrospective, matched, cohort study. A retrospective chart review was performed on patients for the period of March 2011 through August 2012 and February 2013 through August 2013. The earlier time period was chosen as IVA was newly available on the market and its use was becoming incorporated into practice. The later time period was chosen when our practice started utilizing IVA in the post-operative setting. Given the retrospective nature of this study, there was no influence on prescribing practices. Some physicians developed their own protocol-based order sets, while others did not. IVA could be ordered either standing or on an as needed basis.

All patients were identified using the institution's electronic medical record. Orthopedic patients, aged 18 years and older, who underwent a total hip or knee replacement were included. Patients who underwent total hip or total knee replacement were pooled via *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) procedure codes (total hip replacement: 81.51; total knee replacement: 81.54). Patients who used IVA were identified using billing data. Initially, patients in each cohort were manually matched in a 1:1 ratio by age, sex, and procedure, depending on whether or not they received doses of IVA as part of routine care. In the second time period, IVA patients were added based on age, sex, and procedure, making the overall ratio 2:1 for IVA relative to non-IVA. Prescribers were limited to using a maximum daily dose of 3 g of acetaminophen, based on the institution's policy. Other demographics assessed included race, sex, height and weight, baseline labs, comorbidities, and length of stay. Exclusion criteria were unmatched patients, those with known allergy or hypersensitivity or contraindication to either opioids or acetaminophen, and pregnant or breastfeeding females.

Data were collected from the hospital's electronic medical records. The primary outcome was any adverse effect or patient complaint noted post-surgically at any point during hospitalization. This was collected by chart review of nursing, pain management, physician, and surgery progress notes. Adverse effects were expressed by number of patients who experienced a given event per group. Secondary

outcomes include change in lab values, vital signs, and pain scores. Lab results and vital signs were collected as surrogate markers for adverse drug events that may have occurred during treatment. Vital signs included blood pressure, respiratory rate, and heart rate. The highest and lowest of the available vital signs were collected. Low blood pressure was defined as systolic blood pressure less than 90 mm Hg or diastolic blood pressure less than 60 mm Hg. Decreased respiratory rate was defined as less than 14 breaths per minute. Lab values above the upper limit of normal were collected and included aspartate aminotransferase (AST > 41 units/L), alanine aminotransferase (ALT > 43 units/L), total bilirubin (Tbili > 1.2 mg/dL), serum creatinine (Cr > 1.1 mg/dL), and blood urea nitrogen (BUN > 21 mg/dL).

Data collected included opioid analgesic IV morphine sulfate equivalents, pain scores prior to and 72 h post-surgery, and length of stay. Pain scores for all patients were electronically documented with assistance from staff pharmacists in the institution. Mean pain scores were measured by the patient-reported 11-point visual analog scale (VAS). A score of 0 indicated *no pain* and a score of 10 indicated *worst imaginable pain*. Pain scores taken post-surgery were listed as time hours, with subsequent pain scores recorded as the number of hours after surgery. Pain scores were averaged at fixed intervals as well as overall throughout the 72-h period.

To accurately compare total and mean opioid use between two groups, IV and oral opioid narcotics were converted to IV equivalents of morphine expressed in milligrams. Conversion was done via a Microsoft Excel opioid dose equivalent spreadsheet provided by Mallinckrodt Pharmaceuticals and utilized by the institution using the following formula: 0.33 (mg oral hydrocodone) + 0.33 (mg oral morphine) + 1.33 (mg oral hydromorphone) + 0.50 (mg oral oxycodone) + 0.05 (mg oral codeine) + 100 (mg IV fentanyl) + 6.67 (mg IV hydromorphone) + 0.12 (mg meperidine) + 1 (mg oral methadone). Fentanyl patches were converted to its equivalent daily IV fentanyl dose in milligrams and then converted to IV morphine. The mean and total dosages of other pain medications were also calculated via sum and average function in Microsoft Excel.

Student's t tests were utilized to compare continuous data, including age, laboratory values, length of stay, mean doses of treatments, and pain scores. Chi-square test was used to compare race. Fisher's exact test was used to compare differences in categorical data, including procedure types, comorbidities, and adverse events. For all tests, a p value of less than 0.05 was considered a statistically significant difference.

Results

There were a total of 609 patients who underwent total hip or knee replacement during the evaluation period and were included in the analysis. Study flow and selection criteria are reflected in the supplementary material (Supplementary Figure 1). In summary, 812 patients were evaluated and 203 were excluded. Of the 609 included, 406 patients were treated with IVA post-operatively and 203 received medication management without IVA. Significantly more patients treated with IVA had a diagnosis of anemia (229 versus 69 patients; $p < 0.0001$). Patients treated with IVA had a higher mean baseline ALT (27.30 ± 19.87 versus 23.56 ± 9.59 U/mL; $p = 0.01$), but mean baseline AST was similar between groups. There were no other significant differences in baseline demographics. All patient demographic results are found in Table 1.

Although the mean cumulative acetaminophen exposure (IV and oral) was higher in the IVA group (7704.89 ± 2558.63 versus 7260.1 ± 3016.09 mg; $p = 0.07$), this finding is insignificant. Patients who were not treated with IVA used significantly higher mean cumulative oral acetaminophen doses (1022.62 versus 7260.09 mg; $p = 0.0001$). A complete list of concomitant, non-opioid medications is listed in the supplementary material (Table 1). No difference in opioid use was observed between patients treated with IVA post-operatively as compared to the non-IVA group (209.61 ± 555.09 versus 163.89 ± 232.44 mg; $p = 0.152$). With the exception of oxycodone and hydromorphone, the use of specific opioid agents was similar among patients in both arms. Despite increase in cumulative total doses of IVA among patients, a reduction in opioid utilization was not observed. A complete list of concomitant opioid medications is listed in Table 2.

Table 3 provides a summary of reported adverse effects among treatment groups, regardless of its relation to acetaminophen use. Overall, significantly more patients treated with IVA experienced an adverse effect compared to patients who did not receive IVA (91.63% versus 84.73%; $p = 0.012$). The mean number of adverse effects experienced in IVA-treated versus non-IVA-treated patients was 1.93 ± 1.13 and 1.52 ± 0.84, respectively ($p < 0.0001$). The most common adverse events included nausea (14.5% versus 10.3%; $p = 0.163$), vomiting (6.7% versus 6.9%; $p = 1.0$), and hypotension (83.5% versus 78.3%; $p = 0.121$). There was not a significant difference in these safety endpoints.

There was no difference in terms of gastrointestinal adverse events between IVA-treated and non-IVA-treated patients (28.8% versus 22.7%; $p = 0.12$). Opioid reversal with naloxone was also similar between both groups (1.48% versus 1.97% patients; $p = 0.7379$). More patients in the IVA-treated group also experienced elevations in LFTs above the upper limit of normal (5.67% versus 1.97% patients; $p = 0.0376$) and decreases in respiratory rate (28.82% versus 0.49% patients; $p < 0.0001$) during the post-operative observation period. Pre- and post-surgical LFTs were only available for 96 patients (16.5% in the IVA-treated group versus 14.29% in the non-IVA-treated group). This may lead to abnormalities in other patients going undetected. There were a few patients whose LFTs exceeded three times the upper limit of normal: six (1.48%) in the IVA group and two (0.99%) in the non-IVA treatment group ($p = 0.73$). Although the difference is not statistically significant, each of these

Table 1. Baseline demographics of IVA and non-IVA groups.

	IVA (n = 406)	Non-IVA (n = 203)	p value
Age			
Mean (SD)	64.6(10.72)	64.7 (10.00)	0.65
Male, n (%)	172 (42.36)	86(42.36)	1
Length of stay, mean (SD)	3.36 (1.10)	3.35 (1.06)	0.96
Height and weight, mean (SD)			
Weight (kg)	90.3 (22.73)	91.03 (24.95)	0.97
BSA (m^2)	2.04 (0.31)	2.03 (0.38)	0.89
Height (cm)	168.40 (11.72)	169.68 (11.37)	0.35
Race, n (%)			
White	361 (88.92)	180 (88.67)	0.73
Black	28 (6.90)	15 (7.39)	
Hispanic	9 (2.22)	5 (2.46)	
Asian	6 (1.48)	2 (0.99)	
Other	2 (0.49)	1 (0.49)	
Procedure (%)			
Total knee replacement	248 (61.08)	124 (61.08)	1
Total hip replacement	158 (38.92)	79 (38.92)	
Comorbidities (%)			
Anemia	229 (56.4)	69 (33.99)	<0.0001
Congestive heart failure	7 (1.72)	4 (1.97)	1
Coagulation deficiency	24 (5.91)	5 (2.46)	0.07
Diabetes	77 (18.97)	42 (20.69)	0.66
Drug abuse	8 (1.97)	0	1
Alcohol abuse	7 (1.72)	2 (0.99)	0.72
Hypertension	275 (67.73)	134 (66.01)	0.71
Hypothyroid	69 (17)	34 (16.75)	1
Obesity	73 (17.98)	39 (19.21)	0.74
Peripheral vascular disease	8 (1.97)	8 (3.94)	0.18
Liver disease	6 (1.48)	3 (1.48)	1
Labs, mean (SD)			
Serum Cr	0.83 (0.21)	0.84 (0.25)	0.53
Serum BUN	18.38 (0.20)	18.39 (0.21)	0.97
Serum AST	25.61 (11.41)	24.54 (7.89)	0.23
Serum ALT	27.30 (19.87)	23.56 (9.59)	0.01
Alk. Phos.	84.23 (24.00)	80.92 (24.14)	0.15
Tbili	0.55 (0.24)	0.52 (0.22)	0.12

kg: kilograms; BSA: body surface area; cm: centimeters; Cr: creatinine; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; Alk. Phos.: alkaline phosphatase; Tbili; total bilirubin, SD: standard deviation, IVA: intravenous acetaminophen.

patients had normal LFTs at baseline. The adverse effect that occurred significantly more commonly in the non-IVA treatment group was lightheadedness (14 (2.96%) versus 12 (5.91%) patients, respectively; $p = 0.032$). All other adverse events were statistically similar between IVA-treated and non-IVA-treated patients.

Among patients who experienced at least one adverse effect, no significant difference was observed in terms of mean opioid exposure (197.75 ± 495.6 versus 166.07 ± 137.66 mg; $p = 0.25$) and mean cumulative acetaminophen exposure (7613.9 ± 2719.77 versus 7077.31 ± 2745.25 mg; $p = 0.14$) of any dosage form. Among patients who experienced two or more adverse effects, there was also no difference in terms of mean acetaminophen (7656.77 versus 7573.17 mg; $p = 0.72$) or opioid (225.23 versus 171.65 mg; $p = 0.22$) doses as compared to those with only one adverse event.

Mean pain scores between the IVA-treated and non-IVA-treated groups over the 72-h period were 3.82 and 3.30, respectively ($p < 0.0001$). Significantly higher mean pain scores were found in the IVA-treated group during the 72-h post-operative observation period as compared with the non-IVA-treated group.

Discussion

This post-surgical population analysis suggests that IVA may not improve the safety profile of patients utilizing this modality in combination with opioids. Adverse effects associated

Table 2. Opioid medication use during post-surgical study period (expressed in IV equivalent of morphine in mg).

	IVA (n = 406)	Non-IVA (n = 203)	p value
Opioids			
Total, mean, mg (SD)	209.61 (552.09)	163.89 (232.44)	0.15
Fentanyl injection, n (%)	365 (90)	179 (88.2)	0.58
Fentanyl injection, mean, mg (SD)	99.9 (543.47)	77.4 (193.18)	0.50
Hydromorphone injection, n (%)	147 (36.2)	57 (28.1)	0.05
Hydromorphone injection, mean, mg (SD)	59.0 (90.54)	107.3 (148.01)	0.91
Hydromorphone oral, n	6 (1.5)	7 (3.4)	0.14
Hydromorphone oral, mean, mg (SD)	44.43 (90.54)	22.85 (148.01)	0.02
Meperidine injection, n (%)	4 (0.1)	4 (2.0)	0.45
Meperidine injection, mean, mg (SD)	4.16 (4.16)	3.33 (3.33)	0.31
Methadone oral, n	2 (0.49)	0	0.55
Methadone oral, mean, mg (SD)	388 (0)	0	N/A
Morphine injection, n (%)	147 (36.2)	78 (38.4)	0.0017
Morphine injection, mean, mg (SD)	69.3 (249.97)	42.8 (69.48)	0.53
Morphine oral, n	1 (0.2)	2 (1.0)	0.26
Morphine oral, mean, mg (SD)	176.82 (0)	59.94 (56.51)	0.06
Oxycodone oral, n	388 (95.6)	186 (91.6)	0.06
Oxycodone oral, mean, mg (SD)	73.54 (71.56)	51.93 (38.66)	0.002

SD: standard deviation; IVA: intravenous acetaminophen; IV: intravenous.

with opioids, including constipation, nausea, lethargy, and decreased respiratory rate, continued to occur despite the addition of IVA to post-surgical treatment regimens. Although the objective of multimodal pain management is to reduce opioid use, thereby reducing opioid-related adverse events and improving the safety profile, this was not observed.

It appeared that opioid use was not reduced with the addition of IVA to treatment regimens. Additive acetaminophen exposure in this multimodal treatment approach did not lead to a significant reduction in opioid usage in the post-surgical period. It is possible that physicians were not aware of reducing opioid prescribing while adding IVA to pain regimens. Continued opioid use is likely contributing to adverse effects, including those gastrointestinal and respiratory in nature. Although adverse effects in each group may be attributed to concurrent opioid use and increased medication exposure, the use of IVA did not significantly improve safety outcomes.

The number of patients with hepatic lab abnormalities was significantly greater in those treated with IVA as compared to those not treated with IVA. Each of the patients with observed LFTs above the upper limit of normal had normal levels drawn at baseline (approximately 1 month prior to surgery). Increases in LFTs may not necessarily increase until several days after an overdose, and the hospital places a 3 g maximum daily dose on acetaminophen. Therefore, these abnormalities are unlikely attributable to IVA.[11]

There are several limitations of this study. We acknowledge that our institutional limitation of IVA dosing was 3 g, rather than 4 g, and this may have affected the ability to reduce opioid exposure. The 4 g dose is recommended in the product labeling for IVA, but we limited prescribers to 3 g after the Johnson & Johnson[5] product information warnings that suggested 3 g as the limit for the oral product.

Another limitation is the possibility of under-reporting of adverse effects in the electronic medical record. In a recently published matched-pairs analysis, Apfel et al.[11] discussed that adverse events in hospitals are likely to be under-reported, which would lessen the likelihood of determining a significant difference. This notion likely applies to our population, which warrants careful interpretation of documented adverse events. Furthermore, physician documentation transitioned from paper to electronic in the midst of the study period in 2012. Although both paper and electronic medical records were reviewed for this study, there is a possibility that documentation of adverse effects were under-reported in the first time period before electronic documentation was implemented.

Finally, due to its retrospective nature, this safety analysis study was not controlled for use of concomitant medications. Therefore, it is not possible to ascertain what medication caused particular adverse effects. Many of the adverse effects noted may be contributed to IVA, opioids, and other concomitant medications. Since physicians were given the freedom to customize post-operative medication regimens among patients in both arms, there may be variability in safety profiles. For example, significantly more patients treated with IVA also used pregabalin which may have attributed to observed adverse effects. In addition to concomitant medication use, there is also significant concern that there may be other differences not accounted for by matching.

Conclusion

The increased utilization of IVA in multimodal pain management did not result in an improved safety or tolerability profile or reduced opioid utilization in orthopedic patients.

Table 3. Number of patients who experienced adverse effects.

	IVA	%	Non-IVA	%	p value
Gastrointestinal					
All	117	–	46	–	–
Nausea	59	14.53	21	10.34	0.163
Vomiting	27	6.65	14	6.9	1
Flatus	10	2.46	3	1.48	0.5594
Constipation	9	2.22	5	2.46	1
Diarrhea	5	1.23	1	0.49	0.6691
Belching	3	0.74	1	0.49	1
Heartburn	2	0.49	1	0.49	1
Abdominal pain	1	0.25	0	0	1
Loss of appetite	1	0.25	0	0	1
Neurologic					
All	73	–	38	–	–
Dizziness	19	4.68	11	5.42	0.6944
Lightheadedness	12	2.96	14	6.9	0.0321
Sedation	11	2.71	4	1.97	0.783
Weakness	11	2.71	1	0.49	0.0701
Confusion	9	2.22	5	2.46	1
Fatigue	4	0.99	0	0	0.3069
Visual hallucination	0	0	2	0.99	0.1107
Headache	2	0.49	1	0.49	1
Trembling	2	0.29	0	0	1
Slurred speech	1	0.25	0	0	1
Blurry vision	1	0.25	0	0	1
Dermatologic					
All	15	–	3	–	–
Itch	8	1.97	3	1.48	0.7594
Rash	3	0.74	0	0	0.5545
Sweating	2	0.49	0	0	1
Flushing	1	0.25	0	0	1
Injection site irritation	1	0.25	0	0	1
Lab/vitals					
All	479	–	164	–	–
Hypotension	339	83.5	159	78.33	0.1208
Decreased RR	117	28.82	1	0.49	<0.0001
LFT > ULN	23	5.67	4	1.97	0.0376
Other					
Unresponsiveness (requiring naloxone)	6	1.48	4	1.97	0.7379
Dry mouth	2	0.49	0	0	1
Congestion	1	0.25	0	0	1
Sore throat	1	0.25	0	0	1
Ear ringing	1	0.25	0	0	1

RR: respiratory rate; LFT: liver function test; ULN: upper limit of normal; IVA: intravenous acetaminophen.

Implementation of strategies to promote safe and effective use is advised for patients in the post-surgical setting.

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Declaration of conflicting interests

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Ethical approval

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Supplementary Material

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