Randomized Trial

A Randomized Trial Comparing the Safety and Efficacy of Intravenous Ibuprofen versus Ibuprofen and Acetaminophen in Knee or Hip Arthroplasty

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Background: All surgical procedures are associated with a degree of pain. The experience of uncontrolled post-operative pain can have significant implications on health care costs. Recent studies have demonstrated that intravenous (IV) ibuprofen is an effective, safe, well-tolerated analgesic when administered for both abdominal hysterectomy and orthopedic surgery. The use of ibuprofen leads to a reduction in pain severity at rest and with movement and also decreases narcotic consumption. IV acetaminophen has also been shown to be effective in alleviating pain for surgical procedures. Given the established safety and efficacy of IV ibuprofen and IV acetaminophen for perioperative pain, we were interested in determining if any potential synergies are afforded by the simultaneous administration of both medications in orthopedic surgery patients.

Objectives: Compare the safety and efficacy of the perioperative administration of IV ibuprofen alone and in combination with IV acetaminophen in total knee or hip arthroplasty.

Study Design: Randomized, single center, trial.

Setting: Tertiary care center in Philadelphia, Pennsylvania, United States.

Methods: Seventy-eight patients undergoing elective knee or hip arthroplasty were randomized into 2 groups. Group 1 received 800 mg of IV ibuprofen at induction, and 800 mg of IV ibuprofen every 6 hours until discharge or for up to 5 days. Group 2 received 800 mg IV ibuprofen at induction and 1000 mg IV acetaminophen at closure, and 800 mg IV ibuprofen plus 1000 mg IV acetaminophen every 6 hours until discharge for up to 5 days. The primary endpoint was demonstrated using the visual analog scale (VAS) pain scores. Secondary endpoints included opioid requirements, quality of recovery scale (QoR), length of post-anesthesia care unit (PACU) stay, antiemetic consumption, opioid consumption, and opioid related adverse events.

Results: Patients in Group 2 had lower VAS scores ($P < 0.002$) by day 3 only. Opioid requirements and adverse events were significantly less in Group 2 which was also statistically significant. Time to discharge from the PACU for Group 1 on average was 55 minutes and 38 minutes for Group 2 ($P = 0.178$) which was not statistically significant although may have clinical significance. Length of hospital stay was also evaluated; however, no statistical significance was noted between the 2 groups ($P = 0.138$). There was no significant difference in QoR scores which were 177 (SD = 15.44) for Group 1 (n = 35) and 179.5 (SD = 16.30) for Group 2 (n = 39).

Limitations: The study is a single center study with the attendant risk of convenience bias. The total number of patients is also small and may call into question the reproducibility of the results. No cost analysis was undertaken as part of this study. Further research should aim at prospectively designed multi-center double blinded randomized control trials with an analysis of the pharmacoeconomics of the use of these agents.

Conclusion: IV ibuprofen combined with IV acetaminophen demonstrated additional benefit in terms of improved pain scores on post-operative day 3 only, fewer potential adverse events related to opioid use, and decreased use of opioids when compared to IV ibuprofen alone.

Key Words: Acute pain, post-operative pain, randomized controlled trial, surgery, NSAID, analgesia, acetaminophen

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All surgical procedures are associated with acute pain and inflammation ranging from mild to severe that causes significant discomfort and stress for the patient. Perioperative pain can lead to various complications and prolong patient immobility and hospital stay (1). Various analgesics are prescribed for perioperative pain, with opioids being the most common class of drugs. Parenteral formulations of these medications are available when the oral route cannot be used (2). Opioids are often used for post-operative pain; however, because of adverse events including respiratory depression, sedation, allergic reactions, and gastrointestinal events, this use is somewhat limited (3,4). Moreover, while opioids can be useful in alleviating the sensation of pain, they do not alter the course of the underlying disease process. Adjunctive agents for pain including non-steroidal anti-inflammatory drugs (NSAIDs) may be used in combination with opioids. These medications not only reduce pain but also control the underlying inflammatory process. In addition, combining NSAID and opioid therapy may help mitigate side effects by reducing the total opioid dose required (5).

Intravenous (IV) ibuprofen is the first and only intravenous NSAID approved in the US for the control of both pain and fever in adults (5,6). IV ibuprofen was shown to be safe and effective for the control of perioperative pain (7-10). The results of a multicenter, randomized, double-blind, placebo-controlled trial of IV ibuprofen for the management of post-operative pain following abdominal hysterectomy were recently reported. This study demonstrated that IV-ibuprofen is an effective analgesic medication, that is safe and well tolerated when administered as an 800 mg dose every 6 hours in patients undergoing total abdominal hysterectomy surgery (7). Another clinical trial that looked at patients undergoing orthopedic or abdominal surgeries, administration of an aqueous ibuprofen formulation at a dosage of 800 mg IV once every 6 hours was associated with a significant reduction in morphine use compared with placebo, as well as reduction in pain severity at rest and with movement (9).

IV acetaminophen is an analgesic and antipyretic agent that has been used outside the US for many years as a first-line agent for the control of pain and fever in adults and children (11). It was recently approved in the US for the management of pain alone or in combination with opioid analgesics, and reduction of fever (12). Since 2005, various studies have been carried out to determine the effectiveness of IV acetaminophen for alleviating pain associated with surgical procedures. These studies clearly showed not only the analgesic efficacy and the safety profile of IV acetaminophen, but also a reduction in the requirements of other analgesics for pain control (13,14). In double-blind clinical trials, single or multiple doses of IV acetaminophen 1 g generally provided significantly better analgesic efficacy than placebo treatment in adult patients who had undergone dental, orthopedic, or gynecological surgeries (15-19). Furthermore, IV acetaminophen 1 g generally reduced need for opioid rescue medication (9,20).

The IV route is especially advantageous in the perioperative setting when patients may not be able to receive oral medications due to NPO status, sedation, or vomiting. Rectal analgesic medications are also available but high variability in absorption via this route often renders these drugs less reliable (16). Given the established safety and efficacy of IV ibuprofen and IV acetaminophen for perioperative pain, we were interested in determining if any potential synergies are afforded by the simultaneous administration of both medications in orthopedic surgery patients. Here we describe the results of our single center, randomized, open-label trial to compare the safety and efficacy of IV ibuprofen used singly and in combination with IV acetaminophen in orthopedic surgery patients.

Methods

Study Design

This study was approved by the Drexel University College of Medicine and Hahnemann University Hospital Institutional Review Board. Adult patients scheduled for total knee or hip arthroplasty who met the requirements for all inclusion criteria and did not meet any exclusion criteria were consented and randomized in a 1:1 ratio to receive either IV ibuprofen (Group 1) or IV ibuprofen in combination with IV acetaminophen (Group 2) (Table 1).

Patients in Group 1 received 800 mg IV ibuprofen at the induction of anesthesia, followed by 800 mg IV ibuprofen every 6 hours until discharge or for a total up to 120 hours (5 days) whichever came earlier.

Patients in Group 2 received 800 mg IV ibuprofen at the induction of anesthesia and 1000 mg IV acetaminophen at the time of surgical wound closure, followed by 800 mg IV ibuprofen plus 1000 mg IV acetaminophen every 6 hours until discharge or up to 120 hours (5 days) whichever came earlier.

All patients had general anesthesia with the choice

of induction and maintenance agents left to the anesthesiologist's discretion. In addition, all patients who underwent a total knee arthroplasty were provided with regional anesthetic blocks; either a femoral nerve block or an adductor canal block. These nerve blocks were acceptable as per the study protocol and are fairly routine for most total knee arthroplasty procedures. A single surgeon completed the procedures and the average length of the surgical procedure was approximately 120 minutes. Following surgery, at the request of the patient, morphine and/or hydromorphone intake was allowed and administered either via IV bolus doses and/or patient-controlled analgesia pump. Variable dosing was given to the patient based upon the severity of pain and response. Given the risk of thromboembolic disease in patients undergoing orthopedic surgery all patients received prophylactic doses of heparin.

The analgesics and procedures involved in this study were all standard of care drugs prescribed and administered by the attending anesthesiologist for control of total knee or hip arthroplasty surgery related pain. Data collected for every patient was recorded in the patient's medical chart as part of their standard medical care. No additional patient procedures or activities were mandated by this study. Patient enrollment, data collection, and analysis were completed within one year.

Table 1. *Inclusion and exclusion criteria.*

Inclusion Criteria
Adult patients age 18 – 65 scheduled for total knee or hip arthroplasty surgery.
ASA physical status I, II, III.
Exclusion Criteria
Impaired cardiac, liver, and/or renal function.
History of substance abuse or chronic pain.
Patients known to be hypersensitive to any of the components of IV ibuprofen or IV acetaminophen.
Patients currently on anticoagulation medications.
Patients less than 18 years of age.
Inability to understand the requirements of the study or be unwilling to provide written informed consent (as evidenced by signature on an informed consent document approved by an Institutional Review Board) and agree to abide by the study restrictions.
Be pregnant or nursing.
Be otherwise unsuitable for the study, in the opinion of the investigator.

Analysis and Methods

Sample size calculations were completed by using the 2 means equation in the Power and Sample Size Calculation program (21). Mean and standard deviation of pain score at rest (12 – 24 hours) from a previously completed study were used to calculate the sample size (10). The mean difference between study and control group was 9.7 and the detectable difference was set at 15. Two-tailed hypothesis testing concluded that each group needed 39 participants to achieve a power of 80%, with an error rate of 5% and therefore a total of 78 patients were scheduled for enrollment in this study.

The effectiveness of IV ibuprofen alone compared to IV ibuprofen in combination with IV acetaminophen was demonstrated by measuring patients' self-assessment of pain intensity using a 100 mm VAS pain score at rest (primary study endpoint). Secondary endpoints included opioid requirements, patients' quality of recovery scale (QoR), which is an important measure of the early postoperative health status of patients, length of hospital stay, length of post-anesthesia care unit (PACU) stay, need for antiemetic medications and safety as determined by the incidence of treatment-emergent adverse events that included gastrointestinal symptoms which included gastritis and nausea and vomiting primarily.

The study investigators prepared and maintained adequate and accurate case report forms (CRF) of the study data obtained from the medical charts. Blinded data were then entered and analyzed in a password-protected computer database.

Statistical Analysis

Data entry and analysis was performed with SPSS (SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp). Demographic and patient characteristics were obtained for all enrolled patients. Mean (SD [standard deviation]) and median (range) were obtained for age, QoR scores, and time to discharge from the PACU. The number of observations and percentages were obtained for gender, ethnicity, type of surgery, and length of hospital stay.

Number of observations, percentages, mean, standard deviation, minimum and maximum values were obtained for all measurements. The data was analyzed using the independent t-test and Chi-squared test. P-values and 95% CI (confidence interval) were obtained to report any statistically significant differences.

Comparisons between the study groups and pain scores were done with the independent t-test. Mean (SD), 95% CI, test-statistics (degrees-of-freedom [df]) and P-values were reported. Comparisons between study groups were based on quality of recovery scores

and time to discharge from PACU, which was completed by performing Mann Whitney U Test. Test statistics, effect sizes, and P-values were reported. Differences between the study groups for length of hospital stay were determined by performing cross-tabulation. Chi-Squared values and *P*-values were reported. Statistical significance was set at 0.05.

Results

The study was completed over the course of 12 months at Drexel University College of Medicine/ Hahnemann University Hospital, Philadelphia, PA. All patients undergoing total knee arthroplasty and total hip arthroplasty were evaluated for inclusion into the study. After appropriate screening and reviewing exclusion and inclusion criteria, a total of 78 patients were enrolled and 39 patients were randomized into each treatment group; Group 1 patients received 800 mg IV ibuprofen at the induction of anesthesia, followed by 800 mg IV ibuprofen every 6 hours until discharge or up to 120 hours (5 days) whichever came earlier, and Group 2 patients received 800 mg IV ibuprofen at the induction of anesthesia and 1000 mg IV acetaminophen at the time of surgical wound closure, followed by 800 mg IV ibuprofen plus 1000 mg IV acetaminophen every 6 hours until discharge or up to 120 hours (5 days) whichever came earlier. After enrollment, 4 patients dropped out of the study. This occurred due to deviation from study protocol (i.e., due to infrequent pain assessments and/or medications being discontinued inadvertently). Due to these factors and inability to follow any data points given the lack of data, these patients were dropped from the study. The remaining 74 patients, 35 in Group 1 and 39 in Group 2, completed all acceptable study procedures and were included in the analysis.

Demographic and patient characteristics of the study population are presented in Table 2. There was no significant difference observed between groups in terms of age or type of surgical procedure.

Opioid requirements and adverse events related to opioids were significantly less in Group 2 which was also statistically significant ($P < 0.001$). Anti-emetic consumption was similar between groups and did not demonstrate statistical significance when both intra-operative and post-operative medications were administered (Table 3).

Table 2. *Patient characteristics of study population.*

	Group 1 (N = 35)			Group 2 (N = 39)		
	n (%)	Mean (SD)	Median (Range)	n (%)	Mean (SD)	Median (Range)
Age	35 (100)	58.3 (8.45)	59 (27 – 69)	39 (100)	57.8 (8.35)	59 (26 – 70)
Gender						
Male	15 (42.9)	-	-	13 (33.3)	-	-
Female	20 (57.1)			26 (66.7)		
Ethnicity						
White	13 (37.1)	-	-	15 (38.5)	-	-
Black	21 (60.0)			24 (61.5)		
Asian	1 (2.9)			0		
Surgery						
Total Knee Arthroplasty	27 (77.1)	-	-	29 (74.4)	-	-
Total Hip Arthroplasty	8 (22.9)			10 (25.6)		

Table 3. *Comparisons between quality of recovery scores, time to discharge from PACU and opioids requirement in PACU.*

	Group 1		Group 2		Test Statistics		Effect size, r	*P*-value
	n (%)	Median (Range)	n (%)	Median (Range)	U	Z		
Time to discharge from PACU (mins)	35 (100)	55 (5 – 321)	39 (100)	38 (11 – 342)	558.0	-1.35	0.15	0.178
Quality of Recovery (QoR40) &*	35 (100)	181 (133 – 197)	39 (100)	184 (128 – 198)	586.5	-1.04	0.12	0.298
Opioids requirement in PACU (IV Morphine Equivalents, mg)	35 (100)	25 (10 – 35)	39 (100)	20 (5 – 25)	1208	-5.68	0.66	< 0.001

*QoR40 survey and validity available online at www.pqrsonline.org

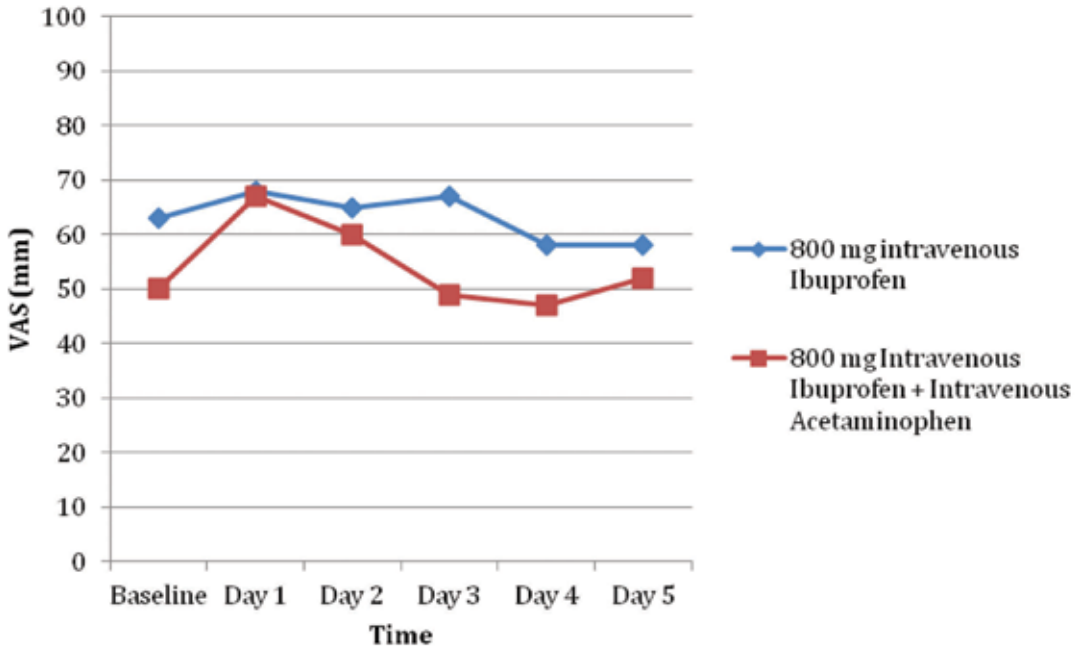

Fig.1. *VAS Preoperative baseline through post-operative day 5.*

Table 4. *Comparisons of VAS at time of preoperative admission to post-operative day 5.*

VAS Scores (Rest)	Group 1		Group 2		95 % CI of difference	t-test (df)	*P*value
	n	Mean (SD)	n	Mean (SD)			
Preoperative	35	6.3 (3.00)	39	5.0 (3.32)	-0.99, 2.83	1.86 (72)	0.067
Day 1	35	6.8 (2.01)	39	6.7 (2.21)	-0.87, 1.09	0.23 (72)	0.822
Day 2	35	6.5 (1.87)	38	6.0 (2.08)	-0.41, 1.43	1.10 (71)	0.274
Day 3	33	6.7 (2.19)	35	4.9 (2.49)	-0.71, 2.97	3.24 (66)	0.002
Day 4	28	5.8 (2.37)	35	4.7 (2.38)	-0.10, 2.31	1.83 (61)	0.071
Day 5	25	5.8 (2.12)	30	5.2 (2.36)	-0.62, 1.82	1.01 (53)	0.607

Pain scores (VAS) were lower at days 3 through 5 in patients randomized into Group 2 (Fig. 1 and Table 4), the difference was only statistically different on Day 3 (6.7 vs. 4.9; $P < 0.002$).

Time to discharge from PACU for Group 1 on average was 55 minutes and 38 minutes for Group 2 ($P = 0.178$). This numerical difference did not reach statistical significance although may have clinical relevance. Length of hospital stay was also evaluated; however, no statistical significance was noted between the 2 groups ($P = 0.138$) (Table 5).

Discussion

Perioperative pain and discomfort is associated with significant morbidity, increased length of hospital stay, and cost of care. Opioid sparing analgesia is an important strategy to help address this problem and IV ibuprofen and IV acetaminophen (used individually) have played a key role in the treatment of post-operative pain in previously completed trials (9,13,14,19,22). However, to the best of our knowledge, the present study is the first randomized controlled trial to assess the potential synergy afforded by co-administration of

Table 5. *Comparisons between duration of hospital stay and adverse events and PONV administration.*

	Group 1 (N = 35) n (%)	Group 2 (N = 39) n (%)	Chi-squared value (df)	*P*-value
Hospital Stay				
1 Day	0	1 (2.6)		
2 Days	2 (5.7)	3 (7.7)		
3 Days	5 (14.3)	0	6.959 (4)	0.138
4 Days	3 (8.6)	5 (12.8)		
5 Days	25 (71.4)	30 (76.9)		
Adverse Events*				
Yes	26 (74.3)	13 (33.3)	10.82 (1)	0.001
No	9 (25.7)	26 (66.7)		
PONV Medication**				
Yes	17 (48.6)	13 (33.3)	1.201 (1)	0.273
No	18 (51.4)	26 (66.7)		

*Adverse events included gastrointestinal disturbance, somnolence, respiratory depression, and/or pruritis.
** PONV medication administration included both intraoperative and post operative administation of medications.

IV ibuprofen and IV acetaminophen in the perioperative setting.

We recognize that this study does have several limitations. It was conducted at a single center with a small population size n = 78. Single center studies are prone to convenience bias; due to this, the results may vary for patients undergoing hip and knee surgeries at other centers where the standard of care may be different. Given the smaller population size and the lack of power in the results, more robust research must be completed to validate these results. Additional larger scale investigations would be needed to confirm the differences observed between the 2 groups. We did not collect data on the use of nerve blocks (i.e., femoral blocks and/or adductor canal blocks) and how they may impact overall pain control. Patients undergoing total knee replacement often have higher pain and often may require more pain control when compared to patients undergoing total hip arthroplasty. This may inherently affect the outcome of the results of the study.

Due to the side effect profile of NSAIDS, they are often contraindicated, which may limit the use in certain patient populations. Ibuprofen is a reversible inhibitor of COX-1 which is responsible for the production of thromboxane which aids in platelet aggregation. It also inhibits PGE2 synthesis, and when specifically examining the gastric mucosa, this may cause gastric mucosal irritation leading to development of ulcers. The activity of ibuprofen on platelets and in prostaglandin synthesis is temporary and this incomplete inhibition may lead to an increased bleeding tendency at peak concentration and a paradoxical increased thrombotic tendency as the effect wears off (5). We did not measure coagulation profiles in this study; this information would be useful as we know that orthopedic surgery is associated with increased incidence of thromboembolic disease and hospitalization costs (23). Additionally, patients did not receive gastric ulcer prophylaxis as we felt that the duration of therapy was short and given the IV route of administration, the risk of development of ulcers is reduced as there is no direct contact with the gastric mucosa leading to irritation. It would be imprudent to use ibuprofen in patients with a known coagulopathy or history of gastric ulcer disease or gastrointestinal bleeding as this may result in a catastrophic bleeding event. Had we compared placebo versus IV acetaminophen alone, we would have obtained valuable information for the management of patients where the use of ibuprofen is contraindicated and future work should focus on delineating this. This study focused on patients undergoing only knee or hip arthroplasty surgeries; therefore, the study conclusions may not apply to other surgical procedures. Moreover, quality of recovery was not statistically significant which may indicate the necessity for a more robust analysis. The time of administration of anti-emetic medications and detailed breakdown of adverse events was not collected in this study which may also provide valuable insight. These may be followed on future studies and may be a potential area of further research. In addition, many patients and clinicians may prefer oral administration for both acetaminophen and ibuprofen postoperatively both for cost effectiveness and ease of administration. Although, this is often a preferable route, reliable bioavailability and subsequent absorption of oral formulations of most medications may be altered

post-operatively in patients. Regarding blinding, both patients and physicians were not blinded to the study. Unblinded studies have the potential for both performance and ascertainment bias; therefore, future work should incorporate a study design that would mitigate against this (24). Since we were following a strict protocol, no additional oral formulations of NSAIDS and/or acetaminophen were provided to the patients included in the study. We did not perform a cost analysis as part of this study. Health care today faces significant resource challenges; therefore, in assessing the utility of a given therapy, the pharmacoeconomics should be concurrently analyzed to determine whether therapy is cost effective. Although we show that there was no statistical difference in length of stay, this finding is limited by the fact that most of our patients were discharged after day 5. This is mainly influenced by routine post-surgical care at our institution which involves inpatient rehabilitation followed by residential rehabilitation placement with the attendant issues of finding a suitable placement. It is important to recognize that pain was not a limiting factor to time of discharge in this study. Finally, confounding variables should be considered when interpreting the results such as the patient inability to report adverse events and the potential for under-treated painful symptoms throughout the study.

The study demonstrated that IV ibuprofen 800 mg combined with IV acetaminophen 1000 mg decreased adverse events related to opioids and opioid consumption, when compared to IV ibuprofen alone in patients undergoing knee and hip arthroplasty surgeries.

The results of the trial demonstrate that co-administration of IV ibuprofen and IV acetaminophen significantly decreased VAS on day 3 post-operatively, and also decreased the incidence of adverse events and opioid consumption. If pain is the only limiting factor to time of discharge, then based on the results of this study, this would be the ideal time to discharge. The results of the study are promising in terms of post-operative pain management in patients undergoing knee and hip arthroplasty, as well as other surgical procedures.

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