IV vs. Oral Acetaminophen as a Component of Multimodal Analgesia After Total Hip Arthroplasty: a Randomized, Blinded, Controlled Trial

FUNDER: Mallinckrodt Pharmaceuticals

PROTOCOL NO.: 2016-209

VERSION & DATE: V3.28.16

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PROTOCOL SYNOPSIS

Protocol Title:	IV vs. oral acetaminophen as a component of multimodal analgesia after total hip arthroplasty: a randomized, blinded, controlled trial
Protocol Number:	2016-209
Protocol Date:	3.28.2016
Sponsor:	Mallinckrodt Pharmaceuticals
Principal Investigator:	Geoffrey Westrich, MD
Products:	IV Acetaminophen
Objective:	1. Does IV acetaminophen reduce pain after THA compared to oral acetaminophen? 2. Does IV acetaminophen reduce opioid consumption after THA compared to oral acetaminophen? 3. Does IV acetaminophen reduce opioid related side effects after THA compared to oral acetaminophen?
Study Design:	Experimental Randomized Controlled Clinical Trial
Enrollment:	154
Subject Criteria:	**Inclusion Criteria:** -Patient undergoing primary total hip replacement -Patient between the age of 1880 -Patient planned for Combined Spinal Epidural anesthesia (CSE) and Patient Controlled Epidural Analgesia (PCEA) -Patient who is English speaking
	Exclusion Criteria: - Non-English speaking patients - Patients receiving periarticular injections - Patients who took opioids preoperatively - Patient with hepatic or renal insufficiency - Patient with hypersensitivity or contraindication to protocol medication -Patient with contraindication for CSE and PCEA -Patient undergoing revision or emergency surgery

Study Duration:	• Both groups will start treatment 30 minutes after surgery every six hours for a total of three days • Between February 2017 and May 2018
Data Collection:	• DOB • Race • Gender • NRS pain scores at rest (patient report on POD1 am, POD 2 am) • Name • Pain NRS at rest (patient interview on POD0,1,2,3,14) • Pain NRS with PT (POD0,1,2,3) • CAM • Opioid Dose • ORSDS • Satisfaction (0-10) • Range of Motion (ROM) • Discharge Time
Outcome Parameters:	**Primary Outcome Parameters:** -Pain with physical therapy (POD 1) via NRS scale (010). -Opioid use (oral morphine equivalents, cumulative, POD 03). -Opioid side effects (Opioid related symptom distress scale, ORSDS, composite score POD 1)
	Secondary Outcomes Parameters: -Pain with physical therapy (POD 03). -Pain at rest (POD 03). -Opioid use on individual days. -Pain OUT questionnaire, POD2. -Progress through physical therapy. -Discharge time. -Patient satisfaction (010 -Likert scale) at discharge. -Confusion Assessment Method (CAM)
Data Evaluation:	The three primary outcomes will be compared between the IV and oral acetaminophen groups with two sample t-tests or Wilcoxon rank-sum tests, depending upon the distribution of the data. Effect sizes will be presented as differences in means or Wilcoxon Mann Whitney odds with 95% confidence intervals. Continuous secondary outcomes measured at a single time point will be analyzed in the same manner as the primary outcomes. Categorical secondary outcomes will be compared using chi-square or Fisher's exact tests, with effect sizes

	presented as risk differences and relative risks with 95% confidence intervals. Outcomes measured at multiple time points will be analyzed using regression based on a generalized estimating equations (GEE) approach. Balance on demographics and baseline characteristics will be assessed by calculating standardized differences (difference in means or proportions divided by the pooled standard deviation) between groups. An absolute value of 0.2 or greater will be interpreted as more imbalance than would be expected by chance (Austin 2009). All analyses will be performed on an intention to treat basis. References: Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity score matched samples. Stat Med. 2009;28(25):3083–107
Statistical Analysis:	**1. Proposed analysis (e.g., student's ttest, ANOVA, chisquare, regression, etc.):** 3 two-sample t-tests **2. Alpha level:** 0.05/3 = 0.0167 (Bonferroni correction) **3. Beta or power level:** > 80% (90% for NRS pain, 80% for opioid use, 82% for ORSDS) **4. Primary outcome variable estimate (mean +/s.d. for continuous outcome, frequency/percentage for categorical variable):** -Mean ± SD NRS pain with activity (POD1) = 1.9 ± 2.0 (Jules 2015) -Mean ± SD opioid use (cumulative POD0POD3) = 105 ± 92 mg OME (Jules 2015) -Mean ± SD ORSDS total score (POD 1) = 0.58 ± 0.50 (Jules 2015) **5. Number of groups being compared (use 1 for paired analysis within the same subjects)**: 2 **6. Effect size or change expected between groups:** -NRS pain with activity (POD1): 1.3 points (Todd 1996) -Opioid use (cumulative POD0POD3): 53 mg OME (50% reduction) -ORSDS total score (POD1) = 0.29 (50% reduction) **Resulting number per group**: 70 **Total sample size required**: 140 + additional 10% to account for attrition = 154

	Who conducted your sample size calculation? Kara Fields References: 1. JulesElysee KM, Goon AK, Westrich GH, Padgett DE, Mayman DJ, Ranawat AS, Ranawat CS, Lin Y, Kahn RL, Bhagat DD, Goytizolo EA, Ma Y, Reid SC, Curren J, YaDeau JD. PatientControlled Epidural Analgesia or Multimodal Pain Regimen with Periarticular Injection After Total Hip Arthroplasty. J Bone Joint Surg Am, May 2015; 97 (10): 789798 2. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996; 27(4): 485–489

1.0 INTRODUCTION

Over 500,000 total hip arthroplasty (THA) procedures were performed in the United States in 2014 [1]. Recent mortality trends associated with opioid use have emphasized the desirability of minimizing use of opioids [2]. Pain management after THA remains problematic and opioids are frequently employed. For example, after THA, 90 mg oral morphine equivalents (OME) was taken over postoperative days (POD) 0-2 despite multimodal analgesia including epidural analgesia [3]. This high level of opioid use was not regimen specific, as THA patients receiving a periarticular injection in lieu of epidural anesthesia used 51% more opioids and experienced higher pain levels [3]. Acetaminophen allows for reduced administration of perioperative opioids [4]. Although acetaminophen has traditionally been administered orally, an intravenous (IV) preparation has recently become available. IV acetaminophen after major orthopedic surgery provides effective analgesia and reduces morphine administration by 33%, compared to placebo [5]. When compared to oral acetaminophen, IV administration has earlier and greater blood-brain barrier penetration and twice the cerebrospinal fluid bioavailability over the first 6 hours [6]. Thus, IV acetaminophen could have improved analgesic effects compared to oral. However, it is not clear whether IV acetaminophen has clinical benefits, such as reduced pain or opioid usage, over oral acetaminophen for THA patients. A recent meta-analysis found IV acetaminophen provided no clinical benefit over oral for total joint arthroplasty [7]. In the study protocol, opioids were only administered upon patient request, in order to promote minimal use of opioids. We hypothesized that IV acetaminophen would reduce 1 or more of the following 3 primary outcomes: (1) pain with activity on POD 1; (2) opioid use (cumulative, POD 0 □ POD 3); and (3) opioid-related side effects (POD 1).

Refrences:

[1] Healthcare cost and utilization project. Washington, DC: U.S. Department of Health & Human Services; 2018.
[2] Collins FS, Koroshetz WJ, Volkow ND. Helping to end addiction over the longterm: the research plan for the NIH HEAL initiative. JAMA 2018;320:129e30.
[3] Jules-Elysee KM, Goon AK, Westrich GH, Padgett DE, Mayman DJ, Ranawat AS, et al. Patient-controlled epidural analgesia or multimodal pain regimen with periarticular injection after total hip arthroplasty: a randomized, doubleblind, placebo-controlled study. J Bone Joint Surg Am 2015;97:789e98.
[4] Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. Br J Anaesth 2005;94:505e13.
[5] Sinatra RS, Jahr JS, Reynolds LW, Viscusi ER, Groudine SB, Payen-Champenois C. Efficacy and safety of single and repeated administration of 1 gram intravenous acetaminophen injection (paracetamol) for pain management after major orthopedic surgery. Anesthesiology 2005;102:822e31.
[6] Singla NK, Parulan C, Samson R, Hutchinson J, Bushnell R, Beja EG, et al. Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. Pain Pract 2012;12:523e32.
[7] Sun L, Zhu X, Zou J, Li Y, Han W. Comparison of intravenous and oral acetaminophen for pain control after total knee and hip arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore) 2018;97:e9751.

2.0 PRODUCT DESCRIPTION

Enrolled patients received either IV acetaminophen (Ofirmev, Mallinckrodt Pharmaceuticals) and an oral placebo or oral acetaminophen and an IV placebo in a randomized, blinded fashion. Patients were randomized in a 1:1 ratio in blocks of size 6 and 8 via a computer-generated randomization schedule (using SAS version 9.4; SAS Institute, Cary, NC) by a statistician not otherwise involved in the trial. Pharmacists dispensed the study medication. Patients, physicians, and research assistants were blinded throughout the study.

3.0 OBJECTIVE OF CLINICAL STUDY

Pain after total hip arthroplasty (THA) is an active field of investigation at HSS. THA is frequently performed at HSS, and patients are often managed with an epidural and multimodal analgesia. IV acetaminophen has favorable kinetics compared to oral, and may improve pain outcomes. If there is a clinically meaningful benefit to IV acetaminophen then IV acetaminophen may be more widely used in THA patients in particular, and among orthopedic patients in general.

4.0 STUDY HYPOTHESES

1. There will be a difference in pain with activity (POD 1) between patients who receive IV vs. oral acetaminophen.
2. There will be a difference in opioid use (cumulative, POD 0 POD 3) between patients who receive IV vs. oral acetaminophen.
3. There will be a difference in opioid side effects between patients who receive IV vs. oral acetaminophen.

5.0 STUDY DESIGN

5.1 Study Duration

- Both groups will start treatment 30 minutes after surgery every six hours for a total of three days.
- Between February 2017 and May 2018

5.2 Endpoints

5.2.1 Primary Endpoint

- Enrolment of 154 patients.

5.2.2 Safety Evaluations:

- If a patient experiences complications, they will be kept at HSS for observation and withdrawn from the study. Such complications that would cause safety and toxicity concerns include local anesthetic toxicity, cardiac toxicity, and central nervous toxicity.

5.3 Study Sites

- Hospital for Special Surgery
  535 E 70th St, New York, NY 10021

6.0 STUDY POPULATION

6.1 Number of Subjects

- 154

6.2 Inclusion Criteria

Subjects of either gender will be included if they:

1. Patient undergoing primary total hip replacement
2. Patient between the age of 1880
3. Patient planned for Combined Spinal Epidural anesthesia (CSE) and Patient Controlled Epidural Analgesia (PCEA)
4. Patient who is English speaking

6.3 Exclusion Criteria

Subjects will be excluded from the study if they:

1. Non-English speaking patients
2. Patients receiving periarticular injections
3. Patients who took opioids preoperatively
4. Patient with hepatic or renal insufficiency
5. Patient with hypersensitivity or contraindication to protocol medication
6. Patient with contraindication for CSE and PCEA
7. Patient undergoing revision or emergency surgery

6.4 Randomization

This is a double blinded study; group assignment is concealed from the patients and the treating physicians. A computer generated randomization table will be generated by a statistician. The table will be used by pharmacy to prepare medications. Patients will be randomized to one of two groups:

Group 1: Postoperative iv acetaminophen 1g q6h / placebo pills q6h for a total of three days.

Group 2: Postoperative po acetaminophen 1g q6h / placebo iv solution q6h for a total of three days.

After entry into the study, the pharmacist will provide to the PACU iv solution for infusion containing identical volume of either normal saline or 1g of Acetaminophen. Additionally, pills will be provided containing either 1g of Acetaminophen, or placebo.

7.0 PROCEDURES

7.1.1 Surgical Procedure

- Total Hip Arthroplasty (THA)

7.1.2 Anesthetic Procedure

Intraoperative.

IV sedation with midazolam (up to 5 mg) and propofol only. No opioids, no ketamine.

Combined spinal epidural anesthesia (CSE) with mepivacaine, 1.5%. Spinal dose: 60 mg. Epidural dose or mepivacaine as needed to achieve desired degree of hypotension.

Intraoperative intravenous medications:

- Dexamethasone, 4 mg.
- Ondansetron, 4 mg.
- Famotidine, 20 mg.
- Ketorolac 1530mg (30 mg unless age >70 years or weight <60 kg)

Postoperative.

IV / oral analgesics

- IV ketorolac 1530mg q 8 hr, for a total of 6 doses (1 dose in OR, 5 doses postop). (30 mg unless age >70 years or weight <60 kg)
- Then, once ketorolac is finished, meloxicam 7.5 15mg PO for POD2,3. (15 mg unless age >70 years or weight <60 kg

PRN analgesics:

- Tramadol 50 mg PO q 6 hr prn mild pain
- Tramadol 100 mg PO q 6 hr prn moderate pain
- Oxycodone 5 mg PO q 3 hr prn severe pain

(at patient request, can proceed to oxycodone 5/10/15 mg if tramadol is viewed as ineffective).

7.1.3 Investigational Product Application

- **Group 1**: Postoperative iv acetaminophen 15min infusion of 1g (100ml vial) every 6 hours starting 30min after surgery for a total of three days (or until discharge, if discharged prior to 3 full days). Patients in this group will receive placebo pills every 6 hours starting 30min after surgery for a total of three days.

- **Group 2**: Postoperative po acetaminophen 1g every 6 hours starting 30min after surgery for a total of three days (or until discharge, if discharged prior to 3 full days). Patients in this group will receive a 15min placebo iv infusion (100ml normal saline) every 6 hours starting 30min after surgery for a total of three days.

7.2 Medical Record Requirements

- Patient undergoing primary total hip replacement
- Patient between the age of 18-80
- Patient planned for Combined Spinal Epidural anesthesia (CSE) and Patient Controlled Epidural Analgesia (PCEA)
- Patient who is English speaking

7.3 Data Collection

The following data will be collected:

Pre-operative/Baseline

- basic demographic data
- patient weight & height, BMI
- Confusion assessment Method (CAM)

Surgical procedure

- date of surgery
- type of surgery

7.4 Schedule of Assessments

Procedures	Pre-Op	POD 0	POD 1	POD 2	POD 3	POD 14	Discharge
Name	X						
DOB	X						
Gender	X						
Race	X						
NRS Pain Scores at Rest (Morning)			X	X			
Pain NRS (0-10) at Rest		X	X	X	X	X	
Pain NRS with PT		X	X	X	X		
CAM	X		X				
Opioid Dose		X	X	X	X		
ORSDS			X	X	X		
Satisfaction (0-10)			X	X	X		
Range of Motion (ROM)						X	
Discharge Time							X

8.0 STATISTICAL ANALYSIS

1. Proposed analysis (e.g., student's ttest, ANOVA, chisquare, regression, etc.): 3 two-sample t-tests
2. Alpha level: 0.05/3 = 0.0167 (Bonferroni correction)
3. Beta or power level: > 80% (90% for NRS pain, 80% for opioid use, 82% for ORSDS)
4. Primary outcome variable estimate (mean +/s.d. for continuous outcome, frequency/percentage for categorical variable):
-Mean ± SD NRS pain with activity (POD1) = 1.9 ± 2.0 (Jules 2015)
-Mean ± SD opioid use (cumulative POD0POD3) = 105 ± 92 mg OME (Jules 2015)
-Mean ± SD ORSDS total score (POD 1) = 0.58 ± 0.50 (Jules 2015)
5. Number of groups being compared (use 1 for paired analysis within the same subjects): 2
6. Effect size or change expected between groups:
-NRS pain with activity (POD1): 1.3 points (Todd 1996)
-Opioid use (cumulative POD0POD3): 53 mg OME (50% reduction)
-ORSDS total score (POD1) = 0.29 (50% reduction)

Resulting number per group: 70
Total sample size required: 140 + additional 10% to account for attrition = 154

Who conducted your sample size calculation? Kara Fields

References:

1. JulesElysee
KM, Goon AK, Westrich GH, Padgett DE, Mayman DJ, Ranawat AS, Ranawat CS, Lin Y, Kahn RL, Bhagat DD, Goytizolo EA, Ma Y, Reid SC, Curren J, YaDeau JD. PatientControlled Epidural Analgesia or Multimodal Pain Regimen with Periarticular Injection After Total Hip Arthroplasty. J Bone Joint Surg Am, May 2015; 97 (10): 789798
2. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996; 27(4): 485–489

9.0 ADVERSE EVENT ASSESSMENT

All Adverse Events (AEs) will be reported in the final study report. Definitions for Adverse Event (AE) used in this study are listed below and are based on FDA and international guidelines:

9.1 Adverse Event (AE)

Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

9.2 Serious Adverse Events (SAE)

Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

9.3 Adverse Event Reporting

All AEs are collected on an Adverse Event Form, either in paper or electronic format. All AEs experienced by the participant during the time frame specified in the protocol (e.g., from the start of intervention through the end of the study) are to be reported, as outlined in the protocol. The reporting requirements to the IRB, to the NIA and to the FDA (in case of drug and device studies) may differ and must be complied with. Please note that the AE form contains a column to indicate whether the event is SERIOUS. Thus, SAEs are a subset of the reported AEs. Routine reporting of AEs is described in the DSMP and may be monthly or quarterly as determined with the NIA staff and /or the DSMB/Safety Officer.

10.0 INVESTIGATOR RESPONSIBILITIES, RECORD AND REPORTS

Data will be collected by an investigator or research assistant. Sources of data include medical records and patient physical assessments/interviews conducted by study personnel. Data will be recorded and managed using REDCap electronic data capture tools hosted at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medical College. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Connection to REDCap occurs via the hospital's encrypted cable and wireless networks, and data will be entered through a password protected computer terminal or iPad.

10.1 Subject Consent and Information

Any information collected electronically will be stored on the REDCap server. The REDCap server and data are hosted by Weill Cornell Medical College CTSC, with the servers physically located in the Payson building of Weill Cornell New York Presbyterian Hospital. Access to this space is limited to members of the Hospital's informatics department. Electronically, several intrusion protection mechanisms, including firewalls and encryption, are in place to protect the server and its data. Any paper based data sheets utilized for the study will be stripped of all personal identifiers whenever possible and stored the department's locked office.

All patients will be identified by a specific study number. Any patient information taken from medical records will be kept strictly confidential. Only the previously mentioned investigators will have access to this information. Thus our research presents a minimal risk of harm to subjects' privacy.

10.2 Subject Data Protection

Informatics staff in the Weill Cornell Medical College CTSC will have access to the REDCap server as needed for administrative purposes. HSS IRB members, upon request, may also review study records and/or data. Data will be released to Mallinckrodt Pharmaceuticals (the study sponsor) and the project's statistician, at designated intervals, including interim analysis (if appropriate) and at end of study. Any identifiers not essential for data analysis will be removed from the data set, which will be sent to the statistician as a password protected, encrypted file. After data analysis, the study data set will be stored as an Excel or SPSS file. A unique feature of REDCap is that data fields marked as protected health information (PHI) can be automatically de-identified when data is exported. We will utilize this option when closing out the study after data analysis, so that no identifiers remain in the stored Excel or SPSS data set. In the REDCap program, the study will be changed from production mode to archive mode. This means the data and study forms will no longer be accessible to REDCap users. Only the research assistant and research manager will have rights to unarchive the study. The study will be maintained in REDCap for the period of time required by hospital/federal regulations, at which point it will be deleted.

Access to the REDCap program is password protected, and access to a specific study's information within the program is limited to the research assistant and other IRB approved study personnel who have been given permission to view and/or enter study data. REDCap program access is authorized by the CTSC; particular study access is granted by the research assistant. For data exports, fields marked as protected health information (PHI) in REDCap will be de-identified, if feasible. All transmission of data will occur via encrypted networks and in password protected files. Any paper based data sheets utilized for the study will have personal identifiers removed whenever possible and will be stored in the department's locked office. Each subject will be assigned a unique study number for identification, and that number will not be derived from or related to information about the

individual. Presentations and publications that result from this study will not contain any individual identifiers other than unique study numbers.

10.3 Staff Information

PI: Geoffrey Westrich, MD

Co Investigators:
(First Name, Middle Name, Last Name, Title)

- Jacques YaDeau, MD, PhD ,IRB Vice Chair
- Philippe Ortiz
- Kara Fields, Volunteer
- Denesy Mancenido, Assistant Director, Research
- Phuong Dinh Mac

APPENDIX A: CASE REPORT FORMS