Project Title: IBUPAP – Combination of Oral Ibuprofen and Acetaminophen (APAP) is Superior to Either Analgesic Alone for Pediatric Emergency Department (ED) Patients with Acute Mild to Moderate Pain

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I. **Project Title: IBUPAP – Combination of Oral Ibuprofen and Acetaminophen (APAP) is Superior to Either Analgesic Alone for Pediatric Emergency Department (ED) Patients with Acute Mild to Moderate Pain**

II. **Hypothesis/Research question:** The combination of oral ibuprofen and acetaminophen (APAP) is superior to either analgesic alone plus placebo for pediatric emergency department patients with acute mild to moderate traumatic/non-traumatic pain.

III. **Goals /Objectives**: Objective #1: Assess level of analgesia with combination oral ibuprofen and APAP therapy on a 10-cm visual analogue (NRS) or FACES pain scale in comparison to either analgesic medication alone plus placebo. Objective #2: Assess antipyretic effects with combination oral ibuprofen and APAP versus either analgesic medication alone plus placebo. Objective #3: Note level of analgesia achieved with each diagnosis(es). Objective #4: Assess the incidence and type of adverse effect(s) of the study medications as well as patients' and parents' satisfaction with achieved level of analgesia.

IV. **Rationale**: Current literature supports ibuprofen and APAP are the most commonly used analgesics in the pediatric ED for acute mild to moderate traumatic/non-traumatic pain. However, the analgesic benefits of combination ibuprofen and APAP in this specific setting does not exist, but instead only as it applies to pediatric patients with postoperative pain. Thus, we have designed a double-blind, randomized, controlled clinical trial to evaluate analgesic efficacy, safety and feasibility of combination therapy to potentially broaden its clinical application in the pediatric ED. We hypothesize that combination oral ibuprofen and APAP therapy is superior to either drug alone and is an excellent analgesic modality for controlling acute mild to moderate traumatic/non-traumatic pain in the pediatric ED.

V. **Literature review**: Pierce and Voss in meta-analysis and qualitative review of 85 studies compared analgesic and antipyretic effects of ibuprofen and APAP (54 contained analgesic efficacy data and 35 contained antipyretic data) in children and adults and demonstrated better fever control and greater pain relief in patients receiving ibuprofen (1). Clark et al randomized 300 hundred pediatric ED patients (aged 6-17 years old) with acute musculoskeletal injuries less than 48 hours prior to admission to weight-based APAP at 15 mg/kg dose, ibuprofen at 10 mg/kg dose or codeine at 1 mg/kg dose (100 patients in each group). The results demonstrated greater analgesics effect of ibuprofen at 60 minutes with greater percentage of patients achieving adequate analgesia based on pre-determined change in pain score (2). Another double-blind crossover trial comparing analgesic efficacy of APAP at 15 mg/kg dose versus ibuprofen at 10 mg/kg dose in pediatric patients with acute migraine showed that ibuprofen was twice as likely as APAP to abort migraine within 2 hours (3). Ibuprofen at 10 mg/kg dose was also found in a randomized, double-blind, multicenter, controlled trial by Bertin et al to have similar analgesic efficacy as compared to APAP at 10 mg/kg dose in pediatric patients (aged 1-6 years old) with pharyngitis/tonsillitis (4) or acute unilateral/bilateral otitis media (5). The evidence supporting the use of combination ibuprofen and APAP in pediatric patients, however, is limited to those with post-operative pain. Ong et al conducted a qualitative systematic review of 21 studies involving 1909 patients comparing the analgesic benefit of

combination non-steroidal anti-inflammatory drug (NSAID) (diclofenac, ketoprofen, ketorolac, tenoxicam, rofecoxib, apirin) and APAP for acute pediatric postoperative pain demonstrating better analgesic efficacy of combination therapy as compared to APAP or NSAID alone in 85% and 64% of studies (6). Similarly, combination NSAID (rofecoxib or ibuprofen) and APAP was again found to require less rescue analgesia in the pediatric population after teeth extraction and tonsillectomy (7, 8).

VI. **Methodology: (A clear outline of to whom, what, where and by whom)**

a. **Study Design**: Prospective, randomized, double-blinded, controlled clinical trial.

b. **Setting**: Urban tertiary care hospital pediatric ED with 40,000 annual departmental visits.

c. **Inclusion/Exclusion Criteria**: Patients with acute mild to moderate traumatic/non-traumatic pain will be screened by the triage nurse, research associate(s), resident(s), fellow(s) and attending physician(s) involved in the study. Enrollment is to be carried out for patients during the weekdays/weekends when pharmacy resident(s) are present in the ED.

Inclusion criteria: ages 3-17 years old presenting to the pediatric ED with mild to moderate traumatic/non-traumatic pain (ie, NRS 1-4, FACES 2). **Exclusion criteria:** (1) documented or suspected pregnancy, (2) parental refusal, (3) allergies to NSAIDS or APAP, (4) inability to tolerate oral medications or contraindications to oral medication route, (5) received analgesics within 4 hours prior to ED presentation, (6) inability to use pain scales.

d. **Randomization:** Patients will be enrolled and randomized upon triage by an assigned nurse dedicated to the study into one of three groups by using a blocks-randomization scheme maintained by the ED pharmacists. Group 1: oral ibuprofen at 10mg/kg dose and placebo of equal volume; Group 2: oral APAP at 15 mg/kg dose and placebo of equal volume; and, Group 3: oral ibuprofen at 10 mg/kg dose and APAP at 15mg/kg dose. Medications including placebo will be given via prefilled syringes of identical volume, color and flavor. Level of analgesia will be assessed at times 0 and 60 minutes from administration of medication(s).

All enrolled patients, health care practitioners, and research associates will be blinded to the study medication(s) given and to the allocation sequence. Pharmacist(s) who are aware of the study medication(s) will not enroll patients. The allocation sequence code will only be revealed to the researchers once recruitment, data collection, and data entry are completed.

e. **Data collection instruments**: The research associates and participating residents will prospectively collect NRS/FACES pain scale scores, antipyretic effects, patient diagnosis(es), adverse effect(s), patient diagnosis(es), and vital signs at times 0 and 60 minutes from administration of medication(s). Patients will be

reassessed for type of adverse effect(s) after administration of study medication(s) with responses noted (eg, nausea, vomiting, dizziness). The research assistants will additionally review the pediatric ED log sheet daily during the enrollment period to make note of those patients excluded from the study based on criteria.

f. **Primary Data Analysis:** An intent-to-treat analysis will be performed using SPSS software. Continuous variables will be compared using analysis of using 2 tests. The primary analysis will utilize a test for differences in mean self-reported pain intensity among groups using analysis of variance. For presence of adverse events adjusted odds ratios will be calculated using 2 tests. Two-sided tests of significance will be used throughout. Baseline characteristics will be measured with descriptive frequencies.

References:

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