Title: A Prospective Randomized Double-Blind Trial Comparing 3 Doses of Oral Ibuprofen in Management of Mild to Moderate Pain of Adult Patients in the ED

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INTRODUCTION:
Ibuprofen is one of the most widely used non-steroidal anti-inflammatory drug (NSAID) for management of mild -to moderate pain in the ED (acute musculo-skeletal pain, headache, dental pain). Ibuprofen as a representative of NSAID's as a class follows the analgesic ceiling concept that postulates that there is a dose of a drug beyond which any further dosage increase results in no additional analgesic effect. Despite this fact, Ibuprofen is commonly used in the ED at doses above its analgesic ceiling (600-800 mg per dose), although this may not offer an incremental analgesic advantage and potentially adds risk of harm. The proposed analgesic ceiling dose for ibuprofen is only 200-400 mg/dose, and about 1200 mg/day. Thus, we propose that administration of Ibuprofen in a dose of 400 mg in the ED is as effective in treating mild-to-moderate acute pain in patients presenting to the ED as 600 mg and 800 mg. To our knowledge, there are no data from EM literature that directly evaluated the analgesic ceiling dose of Ibuprofen for managing pain in the ED.

STUDY DESIGN
A randomized, double-blind trial to determine the analgesic equivalency of orally administered ibuprofen at 400 mg for the treatment of acute pain in comparison to with higher doses of 600 and 800 mg for managing mild-to-moderate pain of adult patients in the ED.

OUTCOME MEASURES
The primary outcome will be reduction in numeric rating scale pain score at 60 minutes from medication administration. Secondary outcomes included rates and percentages of subjects experiencing adverse effects as well as percentage of patients requiring rescue analgesia

STUDY POPULATION
Patients considered for inclusion will comprise adults aged 18 and older years who presented to the ED primarily for management of acute mild to moderate musculoskeletal pain, headache, or dental pain with an intensity of less than 4 on a standard 0 to 10 numeric rating scale and who would routinely be treated with oral iburpofen in our ED as determined by the treating attending or resident physician. Acute pain will be defined in our study as having an onset within 30 days or less. Exclusion criteria will include pregnancy or breastfeeding, active peptic ulcer disease, acute gastrointestinal hemorrhage, known history of severe renal or hepatic insufficiency, allergy to nonsteroidal anti-inflammatory drugs, and patients having already received analgesic medication. For the purposes of this study, ibuprofen will be used without co-administration of any other analgesics, with the exception of rescue medication.

STUDY LOCATION
The study will be conducted at a 711-bed urban community teaching hospital with an annual ED census of greater than 120,000 visits.

DURATION OF ENROLLMENT

Patients pain scores will be recorded at the beginning of the study and at 60 minutes post-administration of medication by utilizing NRS.

DESCRIPTION OF INTERVENTION AND ADMINISTRATION

Once the patient is triaged, an initial pain score will be assessed. Patients will then have an initial evaluation by ED physician and, once deemed eligible for the study, the patient will be randomized to receive oral ibuprofen at a dose of 400mg, 600mg, or 800mg. The on-duty ED pharmacist will prepare 400 mg, 600 mg and 800 mg oral ibuprofen preparations in identical capsules according to predetermined randomization generated in SPSS by the research manager. Demographics, chief complaint and initial pain score will be recorded in the data sheet as well as prior analgesics use. Patients pain scores will be recorded at the beginning of the study and at 60 minutes post-administration by using NRS.

RANDOMIZATION/BLINDING

The research manager and statistician independently of data collection will conduct the programming of the randomization list, confirmation of written consent acquisition, and statistical analyses. ED pharmacy investigators will maintain the randomization list, prepare the medication, and deliver it to the nurse caring for the study participant in a blinded manner. The preparing pharmacist, research manager, and statistician will be the only ones with knowledge of the study arm to which the participant would be randomized. Providers, participants, and the data-collecting research team will be blinded to the medication received. Study investigators will include treating physicians who will assisted in screening and supervising the research fellow, residents, and research coordinators, who will enroll patients and record pain scores and adverse effects at baseline and at 60 minutes.

STATISTICAL ANALYSES

All data will be recorded on data sheets separate from clinical data and entered into Microsoft Excel. The Microsoft Excel spreadsheet will be exported to SPSS 19.0 for statistical analyses. Data will be analyzed by intention to treat and will include frequency distributions, and repeated measures ANOVA to assess a difference in pain scores. The chi-square test will assess the presence or absence of side effects between the three groups. A p-value of < 0.05 will be used to denote statistical significance.