

**Intranasal Ketorolac versus Intravenous Ketorolac for Treatment of Migraine Headaches in Children: A Randomized Clinical Trial**

**NCT02358681**

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## Study Purpose and Rationale:

Acute migraine headaches are common in children and adolescents, accounting for approximately 85,000 emergency department (ED) visits annually in the United States.(7) However, there has been a surprising lack of investigation of non-oral abortive treatment for migraine headaches in children, resulting in substantial variation in practice and undertreatment.(8) Ketorolac is a nonsteroidal anti-inflammatory drug (NSAID) that is frequently administered by the intramuscular (IM) or intravenous (IV) routes in the ED, and is one of the most common treatments administered to children who present to an ED with a migraine or headache.(7) Ketorolac is considered an evidence-based, first-line acute migraine therapy, with most studies completed in adults.(9)

The intranasal (IN) administration of ketorolac may provide an efficacious and painless means of treating acute migraine headaches in children, as this route uniquely uses the nose-brain pathway. The nose-brain pathway is the transport of medications directly to the brain through the olfactory and trigeminal nerves exposed in the nasal cavity. This pathway circumvents the blood-brain barrier and has been shown to produce both faster central nervous system (CNS) effects and higher drug concentrations of other medications in the CNS than that achieved after IV administration alone.(10-13) In addition to the nose-brain pathway, administration of medications by the IN route takes advantages of the highly vascularized respiratory epithelium. Absorption by this means facilitates rapid uptake into the systemic circulation, bypassing first-pass metabolism, and resulting in plasma concentrations comparable to those achieved by IV administration.(14) Both of these mechanisms have been credited as reasons for IN administration's ability to produce clinical effects approaching that of IV administration for different medications. (12,15-17) Although IN ketorolac has similarly been studied and shown to be effective for providing analgesia in adults, there is a gap of knowledge regarding the efficacy of IN ketorolac in treating migraines in children and adolescents.(2,3,6,18-21)

IN ketorolac administration may allow children to receive effective analgesia in an expeditious and painless manner in the ED, as well as in a broader number of settings. The implementation of IN medications decreases the time it takes for a child to receive analgesics in the ED compared to those receiving IV analgesics, as the IN route does not require the additional, technically more challenging step of obtaining IV access.(22) Effective analgesics such as ketorolac are typically administered by the IV and IM route and require children to receive a painful needle stick, an experience that has been identified by them as amongst the medical experiences that they most fear, causing high levels of pain and distress.(23-28) The IN route is a completely needle-free technique, and saves children from both the short and long term consequences of inadequately managed needle stick pain.(29-33) Finally, eliminating the need for IV access to administer analgesics creates the potential opportunity for children to receive more potent and effective analgesics at home or in the office setting, rather than the hospital.

Our overall goal is to determine best-practice management of children with acute migraines. Our specific aims for this study are as follows:

**Primary Aim:** Determine whether intranasal (IN) ketorolac is non-inferior to intravenous (IV) ketorolac for reducing pain in children with acute migraine headaches. We hypothesize that IN ketorolac is non-inferior to IV ketorolac in reducing acute migraine headache pain by a minimum clinically significant difference within 60 minutes of administration.

**Secondary Aim:** Determine whether there is a difference in the time to achieve a clinically significant reduction in pain after receiving IN ketorolac compared to IV ketorolac. We hypothesize that there is no difference between groups in the time it takes to achieve a clinically significant reduction in pain. If we can demonstrate that IN ketorolac is as efficacious as IV ketorolac, this would support the clinical implementation of this novel modality for effectively treating migraine pain, in addition to incurring additional benefits (such as eliminating

unnecessary needle pain and decreasing time to receiving analgesics) that would improve the overall care of children with migraines.

As a sub-study, some of the data obtained will be used to analyze the validity and clinically significant differences between FPS-R and vNRS pain scales for children with migraines.

### **Study Design:**

We will conduct a prospective, double-blinded, randomized, non-inferiority, parallel 1:1 clinical trial of 80 children in a single urban pediatric ED. We will block randomize patients to receive either IN ketorolac (1 mg/kg) and an IV placebo (study group A), or IV ketorolac (0.5 mg/kg, maximum single dose of 30 mg) and an IN placebo (study group B). The volume of the IN placebo will be the same volume the patient would have received if they were receiving IN ketorolac; similarly, the volume of IV placebo will be the same volume the patient would have received if they were receiving IV ketorolac. Normal saline will be used as the placebo for both IN and IV administration. IN administration will be performed in a standardized fashion using a mucosal atomization device (MAD), which is a small plastic device that attaches to the end of a syringe.(47) The MAD converts any solution that is expressed from the syringe through the MAD into an atomized spray that is more readily absorbed and easier to deliver than if the solution was given as drops. All patients will receive an IV line to receive IV fluids as is typical in our ED.

The permuted, block randomization scheme will be predetermined by a third-party uninvolved with any study procedures (KB) using an online randomization program. Study group assignment will be concealed in sequentially-numbered sealed opaque envelopes which will not be opened until a patient has been enrolled. The members of the study team performing the pain assessments, those conducting the 24-hour follow up call, and the patient, will all be blinded to the study group assignment.

The chosen dosage and maximum dose of IV ketorolac are the standard of care for children.(48- 50) The maximum single dose of ketorolac which has been administered by the IN route is 30 mg; this is the maximum single dose of IV ketorolac, as well as the maximum dose of IN ketorolac that has been studied in both adults and children.(3,51) This practice is also consistent with the dosing of other IN sedatives and analgesics, in which the maximum single dose given by the IN route is the same as the as that given by the IV route.(12) The dosage of 1 mg/kg for IN ketorolac was selected based on rationale as explained as follows:

- First, we expect the maximum serum concentration achieved by IN administration to be less than that achieved by IV administration. This is because the maximum serum concentrations after IN administration of ketorolac has been shown to be 60% of those that occur with the same dose administered intramuscularly. Given that intramuscular administration typically achieves serum concentrations less than those achieved after IV administration, it would follow that maximum serum concentrations achieved after IN administration would be even less than those achieved by IV administration (i.e. no more than 60%).

- Second, the dose of medications commonly administered by the IN route are at least double the dose when the medication is given by the IV route. This is due in part to the decreased serum bioavailability of IN administration compared to IV administration. For example, the sedative midazolam is typically dosed 0.1 mg/kg when administered IV, but is dosed 0.2 to 0.5 mg/kg when given by the IN route.10-18. The analgesic fentanyl is typically dosed 1 mcg/kg when administered IV, but is dosed 1.5 to 2 mcg/kg when given by the IN route.

Importantly, there is no increased incidence of adverse events reported with these higher doses when administered by the IN route for other medication, and there is nothing from a molecular perspective that makes the IN absorption of ketorolac significantly different from midazolam or fentanyl. In addition, ketorolac is

less lipophilic than midazolam and fentanyl, which means that we do not anticipate adverse events related to over-absorption through the nose-brain pathway to occur when using this increased dose.

- Third, ketorolac may be administered by the IV route at doses of 1 mg/kg. Giving 1 mg/kg of IV ketorolac is also a well-documented practice when providing analgesia in infants and children. Given that 1 mg/kg is a dose which is already in use for IV administration, it would support the acceptability of also administering ketorolac at 1 mg/kg by the IN route.

**Study Procedures:** We will assess the patient's pain in a standardized fashion using the FPS-R, administered in the patient's primary language. We will assess the FPS-R and vNRS at baseline (within 15 minutes prior to receiving the study drug) and then at 10 minutes, 30 minutes, and 60 minutes (or within 5 minutes of each mark to allow for unpredictable setting of the emergency department) after administration of the study drug for 60 minutes. We will assess pain associated with nasal administration using the same two scales within 15 minutes of study drug administration. The patient will then be assessed at 2 hours (or within 10 minutes) after administration of the study drug and at 24 hours after study drug administration. Pain assessment not required if a valid documented reason is provided. Such reasons may include, but are not limited to: patient is asleep, having a procedure done, or other medically indicated reason that prohibits a pain assessment from being performed. The Data Collection Form will serve as source document for study drug administration time. The Study Physician will sign on the Data Collection Form as a witness.

If the 24-hour mark is during a timeframe that is inconvenient for the patient (e.g. during sleeping hours), the assessment will be made at a point greater than, but as close to as possible to, the 24-hour mark, within 48-hours of study drug administration. We will conduct the 24-hour follow up by telephone if the patient is discharged from the ED, or in person if the patient is hospitalized (the decision to hospitalize will not be dictated by the study). Patients will be reimbursed \$10 for the time and effort spent participating in this study.

**Outcomes: Primary Aim:** To demonstrate that IN ketorolac is non-inferior to IV ketorolac in reducing pain in children with acute migraine headaches, we will compare the mean decrease in pain score of both study groups at 60 minutes after administration of the study drug to each other. The outcome we will use to measure this decrease in pain will be the Faces Pain Scale – Revised (FPS-R). The FPS-R is a 10 point pain scale that has been validated for the use in children greater than 4 years of age in the ED; is one of the self-report measures of pain recommended for research in children; and is commonly used as the primary outcome in ED research.(56,57) IN ketorolac will be considered non-inferior to IV ketorolac if the difference between the mean decreases in pain score of both groups is less than a clinically meaningful difference in pain. The minimum clinically meaningful difference in pain in children when using the FPSR has been shown to be 2 out of 10, and is consistent across all categories of age, sex, ethnicity, and primary language; (58) therefore, the non-inferiority margin (delta) will be set at 2/10. In addition to the FPS-R, we will also assess pain using a descriptive ordinal scale frequently used in headache research.(59) Using this scale, we will ask the patient to describe their headache pain as severe, moderate, mild, or none. We will also use the verbal numeric rating scale (vNRS), which involves asking the patient how much pain they have on a scale from zero to ten. We selected the reduction in pain, rather than pain freedom as recommended by the IHS guidelines, as pain freedom is very seldom achieved in the ED, with only approximately 20% of patients reportedly being pain free upon discharge. (59-61) Prior comparative trials of abortive migraine and headache therapies in the ED have similarly shown that as few as 15% of adults and 7% of children achieve headache freedom after treatment, but greater than 60% experience headache relief.(40,62) As a result, pain freedom from migraine or headaches has been infrequently used as the primary outcome for studies in the ED setting; instead, degree of pain relief has been used.(37-40,63-66) Additionally, we chose the one hour end point based on the IHS recommendations that a time point earlier than two hours should be considered for parenteral study medications (which would apply to both IV and IN routes).(59)

Secondary Aim: To determine if there is a difference in time to achieve a clinically significant reduction in pain after receiving IN ketorolac compared to IV ketorolac, we will use the outcome of time (in minutes) and compare, as appropriate, the mean or median time it takes after administration of study drug in each group to achieve a minimum clinically significant difference in pain (i.e. 2/10 on the FPS-R).

Note that a prior iteration of the protocol stated that this secondary aim was to determine if IN ketorolac was non-inferior to IV ketorolac, with a non-inferiority margin for this aim of 10 minutes. This secondary aim was changed prior to starting patient enrollment (i.e. no patients were enrolled yet) because the number of pain assessments was decreased from assessments at 10, 20, 30, 40, 50, 60, and 120 minutes to 10, 30, 60, and 120 minutes for feasibility reasons. Since we would then no longer be able to assess change in pain score in 10 minute increments, it would not have been possible to accurately assess for non-inferiority based on a non-inferiority margin of 10 minutes. Therefore, the aim was changed to as is currently stated.

Additional efficacy outcomes will include those that are ED-based, and those assessed at a 24- hour follow up:

- i) ED-based outcomes: 1) Receipt of rescue medications at any time during the ED visit; 2) Headache relief in the ED, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none, on the severe/moderate/mild/none pain scale, without the use of rescue medications; 3) Headache freedom in the ED, defined as achieving a headache level of none within 2 hours without the use of rescue medications; and 4) Percentage improvement in pain score between baseline and one hour, defined as (baseline pain score – one hour pain score)/baseline pain score.
- ii) 24-hour follow up outcomes: 1) The patient's overall assessment of efficacy and tolerability, expressed as a dichotomous response to the question, "The next time you come to the emergency department with a headache or migraine, do you want to be given the same medication (that is, the medicine you received first)?"; 2) Sustained headache freedom, defined as achieving a level of none on the severe/moderate/mild/none within 2 hours of medication administration and maintaining this level continuously for 24 hours without the use of rescue medications; 3) Sustained headache relief, defined as change within 2 hours of the patient's description of headache from severe or moderate to either mild or none without the use of rescue medication, and maintaining this level of relief continuously for 24 hours without the use of rescue medications; and 4) Use of rescue medications, if any, during the 24-hour period after initial medication administration after discharge from the emergency department (if yes, which one).

Functional outcomes will be assessed during their ED stay and at the 24-hour follow up. We will use a question standard in headache research, but modified to suit the pediatric population:

"Do you think you could do all of your usual daily activities? Usual daily activities can include things like going to school, doing your homework, doing your chores, playing games (including video games), reading, or playing sports." Available responses will include: a) I think I could do everything I usually do without any problems (or difficulty). b) I think it would be a little bit hard (or difficult) to do everything that I usually do. c) I think it would be very hard (or difficult) to do everything that I usually do, and I could only do the easiest things. d) I don't think I could do any of the things I usually do at all. (59) Safety outcomes will be assessed at the 1- and 2-hour assessments and the 24-hour follow up. We will ask the patient whether they have experienced any new or different symptoms. If they answer in the affirmative, their symptoms will be elicited with an open-ended question.

The procedure for breaking the blind in this study is as follows: In the event of a serious adverse event (defined as a medical occurrence that results in death, is life-threatening, requires inpatient hospitalization, results in

persistent of significant disability/incapacity), not only will this event be reported to the IRB, but it will be reported to the study DSMB within 7 days of the event occurrence for consideration of unblinding. The DSMB will decide whether or not to break the blind based on whether or not they deem it necessary for the care of the subjects or conduct of the study.

We will be conducting a retrospective medical record review to identify a missed eligible population (i.e. patients who are eligible, but are not screened or enrolled). The reason for this review is to ensure scientific credibility by showing that we are not enrolling a biased sample of children. This review is necessary because as patients come to the emergency department 24/7, it is inevitable that some eligible patients will be missed. This population of missed eligible patients will not be subjected to study procedures or interventions. The data points collected for these patients will be retrieved from existing medical records and are both limited and specific. These data points include: age; sex; initial pain score; medications received in the emergency department; and disposition (e.g. home, admission). No personal identifiers will be collected for this population of missed eligible patients. Each of these patients will be de-identified and assigned a unique subject number at the point of data entry. There will be no key that will link the subject number to the patient.

**Study Drugs and Devices:** Ketorolac is a commonly administered NSAID that is used to treat pain in both adults and children, for conditions ranging from headaches, back pain, kidney stones, and fractures. It is typically administered by the IV or IM route, but has been studied when administered IN, mainly in adults, with both its clinical effects and pharmacokinetic properties well described. Ketorolac is commonly administered as part of clinical care for pediatric emergency department patients, and is stored in the usual pharmacy-controlled areas in the pediatric emergency department. The ketorolac which will be administered is the same formulation, and patients being enrolled in this study have already been determined by their treating physician to require ketorolac as part of their usual care.

The mucosal atomization device (MAD) is a plastic device with a foam applicator that aerosolizes a solution into a fine mist into the nasal mucosa. We do not believe that the MAD requires an IND because it does not increase the risk of adverse events associated with IV ketorolac. The MAD has been considered IND-exempt by this IRB in other studies conducted by our group (IRB-AAAI0699 and IRB-AAAL7510). We do not believe that an IND is required. The IND Assistance Program was consulted, and their opinion was that no IND was required (note reflecting this decision has been attached to this submission).

We also do not believe that the intranasal route of administration significantly increases the risk associated with the drug product (i.e. ketorolac). Similar determinations for midazolam and fentanyl (both of which are also not approved for intranasal administration in children) to be suitable for an IND waiver were made by CUMC IRBs 1 and 2 in the aforementioned protocols, and to our knowledge and review of the literature, there is nothing about ketorolac that makes it more likely than midazolam or fentanyl to increase the risk of adverse events when administered intranasally.

**Study Subjects:** Eligible patients will be children 8 to 17 years of age, inclusive, who present to the pediatric ED with a migraine headache as defined by the modified Irma criteria.(43) The Irma criteria are essentially the same as the International Headache Society (IHS) ICHD II criteria with annotation for children, except that the requirement for a minimal number of headache episodes was removed. The reason for this modification, and development of the Irma criteria, was in response to concerns that the ICHD II criteria for diagnosing migraines, even with the annotation for children, still lacked sensitivity not only when used in the pediatric population, but particularly when they presented to the ED. (44,45) This is because many children who are seen in the ED with a headache may present with one of their first episodes; they may indeed have migraines

but will not be diagnosed as such because they cannot fulfill the IHS criteria of requiring five distinct headache events over time.(46)

To demonstrate the appropriateness of using the Irma criteria for diagnosing migraines in children in the ED, one prior study has shown that the original iteration of the Irma criteria is almost twice as sensitive as the ICHD-II criteria with annotation for children for diagnosing migraine headaches in children in the ED setting.(43) Although the original iteration of the Irma criteria requires fulfillment of four criteria, decreasing the requirement to three (i.e. the modified Irma criteria) increased the sensitivity to 95%.(43) We have chosen to use the modified version so that it would be possible to study a more generalizable population of children who present to the ED with likely migraine headaches.

Per the modified Irma criteria, children in our study will be eligible if they have a headache that fulfills at least three of the six following criteria: i) moderate to severe episode of impaired daily activities; ii) focal localization of headache (focal meaning unilateral, bifrontal, bitemporal, or biparietal); iii) pulsatile description; iv) nausea or vomiting or abdominal pain; v) photophobia or phonophobia or avoidance of light and noise; and vi) symptoms increasing with activity or resolving by rest. Additionally, the eligible child must have a headache of moderate to severe pain (defined as 4/10 on the validated Faces Pain Scale – Revised (FPS-R) pain scale) and require any IV medication for treatment of their migraine headache (e.g. ketorolac, metoclopramide, prochlorperazine), as decided by their attending ED physician. We will enroll patients with a headache duration between 1 and 168 hours (i.e. 7 days).

We will exclude patients for any of the following: any contraindication to receiving ketorolac (e.g. known allergy, known peptic ulcer disease, gastrointestinal bleeding, renal impairment, known bleeding disorders); receipt of an NSAID (e.g. ibuprofen) within previous six hours; presence of intranasal obstruction (e.g. mucous or blood) that cannot be readily cleared using suction or nose blowing; inability to speak English or Spanish; unable to complete self-report measures of pain or questionnaires (e.g. developmental delay, neurologic impairment); known underlying hepatic impairment; critical illness; and frequent use of drugs for headache (defined as regular intake of analgesics for acute headaches on more than 10 days per month).

The Data Collection Form will serve as source document for subject eligibility. The Study Physician will sign on the Data Collection Form as a witness.

### **Statistical Procedures:**

We will enroll 80 children (40 in each group) ages 8 to 18 years. We based our sample size on the ability to demonstrate non-inferiority between the IN and IV ketorolac groups' ability to reduce pain. It has been shown that a reduction of 2 on the FPS-R score is the minimum clinically significant difference in pain in children.<sup>56</sup> Therefore, our predetermined margin of non-inferiority is 2. In order to be conservative for the sample size calculation, we based the calculation on a margin of 10% less than our predetermined margin of non-inferiority of 2. The resulting sample size of 80 children, therefore, is based on a margin of 1.8 on the FPS-R pain scale. Using a standard deviation of 2.725 (again, selected using conservative assumptions), a sample size of 40 patients per group provides 90% power to detect non-inferiority using a one-sided two sample t-test with an alpha of 0.05.

We will conduct an intention to treat analysis for all enrolled randomized subjects. We will conduct a one-sided t-test to evaluate the difference between the mean decreases in pain score of the two study groups (primary outcome). The difference between groups, with its 95% CI, will be compared to the pre-determined non-inferiority margin (i.e. 2/10) to establish whether IN ketorolac is noninferior to IV ketorolac. For our secondary outcome (time to clinically significant reduction in pain), we will also compare groups using a two-sample one-

sided t-test. Similar to the analysis for the primary outcome, the difference between groups in the time to clinically significant reduction in pain, with its 95% CI, will be compared to the pre-determined non-inferiority margin of 10 minutes. A Kaplan-Meier distribution analysis will also be used to compare the time to meaningful pain relief in the two treatment groups. For other secondary outcomes, we will compare groups using standard bivariate analyses for categorical and continuous variables and a table describing adverse events by treatment will be reported.

### **Study Medication:**

IND-Exempt

Ketorolac - 1 mg/kg, maximum single dose of 30 mg; Route of administration: Inhalation.

Ketorolac - 0.5 mg/kg, single maximum dose of 30 mg. Route of administration: Intravenous.

### **Potential Risks:**

There are no risks in addition to the usual risks associated with receiving ketorolac for analgesia. There is a chance that a patient may not experience the same degree of pain relief that they may have experienced if they had received IV ketorolac. However, patients will have their pain assessed as per usual standard care, and can receive any additional required analgesics at any point in time if their pain relief is inadequate. The procedures involved in this study do not increase the risk for adverse events normally associated with receiving ketorolac.

### **Potential Benefits:**

There are no potential direct benefits to participating in this study.

### **Alternatives:**

An alternative to participation in this study is to choose not to participate.

### **Data and Safety Monitoring:**

Data will be reviewed on an ongoing basis by the PI with each patient enrolled. On an ongoing basis, the investigators will monitor accrual of study subjects, assess adherence to study protocol, assess data quality, and collect and review adverse events and other subject safety matters. We will submit to the IRB protocol deviations and any requested protocol modifications.

A data safety monitoring board (DSMB) consisting of two physicians unrelated to the study will be formed to evaluate safety and adherence to the protocol. The two physicians will consist of one emergency physician clinician scientist who is familiar with the clinical management of migraine headaches in the emergency department (Dr. Bernard Chang, Department of Emergency Medicine); and a pediatric neurologist who is qualified to understand the management of pediatric migraine headaches (Dr. Robert Fryer, Department of Pediatrics, Division of Neurology). The DSMB will convene after the first 5 subjects have been enrolled. After the first meeting, they will convene on an annual basis. The schedule will be dependent on the rate of enrolment of the first 5 patients.

**Adverse Event Reporting:** An adverse event is any untoward medical occurrence by a subject. For each patient, the investigators will evaluate adverse events after completion of enrollment. All unanticipated problems (i.e. unexpected events, outcomes, or occurrences, at least possibly related to the research, and suggest an increase in risk of harm to subjects or others) will be reported to the IRB. This reporting will be done promptly, but no later than one week after the occurrence or after the PI acquiring knowledge of the unanticipated problem, and will also be reported at time of continuing review.

All data will be maintained on password-protected computers and in locked file cabinets in a locked room to which only authorized study personnel will have access. Only approved research staff will view the clinical information of children enrolled in this study. We will retain study records and documentation for 3 years after the last enrolled patient has completed all study procedures.

History of Changes to Protocol: <https://www.clinicaltrials.gov/ct2/history/NCT02358681>

## References:

1. Boyer KC, McDonald P, Zoetis T. A novel formulation of ketorolac tromethamine for intranasal administration: preclinical safety evaluation. *Int J Toxicol* 2010;29(5):467–78.
2. Singla N, Singla S, Minkowitz HS, Moodie J, Brown C. Intranasal ketorolac for acute postoperative pain. *Curr Med Res Opin* 2010;26(8):1915–23.
3. Pfaffenrath V, Fenzl E, Bregman D, Färkkilä M. Intranasal ketorolac tromethamine (SPRIX(R)) containing 6% of lidocaine (ROX-828) for acute treatment of migraine: safety and efficacy data from a phase II clinical trial. *Cephalalgia* 2012;32(10):766–77.
4. Bacon R, Newman S, Rankin L, Pitcairn G, Whiting R. Pulmonary and nasal deposition of ketorolac tromethamine solution (SPRIX) following intranasal administration. *Int J Pharm* 2012;431(1-2):39–44.
5. Bullingham R, Juan A. Comparison of intranasal ketorolac tromethamine pharmacokinetics in younger and older adults. *Drugs Aging* 2012;29(11):899–904.
6. Garnock-Jones KP. Intranasal Ketorolac. *Clin Drug Investig* 2012;32(6):361–71.
7. Sheridan DC, Meckler GD, Spiro DM, Koch TK, Hansen ML. Diagnostic testing and treatment of pediatric headache in the emergency department. *J Pediatr* 2013;163(6):1634–7.
8. Richer LP, Laycock K, Millar K, et al. Treatment of children with migraine in emergency departments: national practice variation study. *Pediatrics* 2010;126(1):e150–5.
9. Taggart E, Doran S, Kokotillo A, Campbell S, Villa-Roel C, Rowe BH. Ketorolac in the treatment of acute migraine: a systematic review. *Headache* 2013;53(2):277–87.
10. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci* 2002;5(6):514–6.
11. Illum L. Is nose-to-brain transport of drugs in man a reality? *J Pharm Pharmacol* 2004;56(1):3–17.
12. Wolfe TR, Braude DA. Intranasal medication delivery for children: a brief review and update. *Pediatrics* 2010;126(3):532–7.
13. Lötsch J, Walter C, Parnham MJ, Oertel BG, Geisslinger G. Pharmacokinetics of nonintravenous formulations of fentanyl. *Clin Pharmacokinet* 2013;52(1):23–36.
14. Moksnes K, Fredheim OM, Klepstad P, et al. Early pharmacokinetics of nasal fentanyl: is there a significant arterio-venous difference? *Eur J Clin Pharmacol* 2008;64(5):497–502.
15. Chien YW, Su K, Chang SF. Nasal systemic drug delivery. In: *Anatomy and physiology of the nose*. New York: Dekker; 1989. p. 1–26.
16. Lahat E, Goldman M, Barr J, Bistrizter T, Berkovitch M. Comparison of intranasal midazolam with intravenous diazepam for treating febrile seizures in children: prospective randomised study. *BMJ* 2000;321(7253):83–6.
17. Borland M, Jacobs I, King B, O'Brien D. A randomized controlled trial comparing intranasal fentanyl to intravenous morphine for managing acute pain in children in the emergency department. *Ann Emerg Med* 2007;49(3):335–40.
18. Turner CL, Eggleston GW, Lunos S, Johnson N, Wiedmann TS, Bowles WR. Sniffing out endodontic pain: use of an intranasal analgesic in a randomized clinical trial. *J Endod* 2011;37(4):439–44.
19. Brown C, Moodie J, Bisley E, Bynum L. Intranasal ketorolac for postoperative pain: a phase 3, double-blind, randomized study. *Pain Med* 2009;10(6):1106–14.
20. Grant GM, Mehlich DR. Intranasal ketorolac for pain secondary to third molar impaction surgery: a randomized, double-blind, placebo-controlled trial. *J Oral Maxillofac Surg* 2010;68(5):1025–31.
21. He A, Hersh EV. A review of intranasal ketorolac tromethamine for the short-term management of moderate to moderately severe pain that requires analgesia at the opioid level. *Curr Med Res Opin* 2012;28(12):1873–80.
22. Borland ML, Clark L-J, Esson A. Comparative review of the clinical use of intranasal fentanyl versus morphine in a paediatric emergency department. *Emerg Med Australas* 2008;20(6):515–20.

23. Fradet C, McGrath PJ, Kay J, Adams S, Luke B. A prospective survey of reactions to blood tests by children and adolescents. *Pain* 1990;40(1):53–60.
24. Humphrey GB, Boon CM, van Linden van den Heuvel GF, van de Wiel HB. The occurrence of high levels of acute behavioral distress in children and adolescents undergoing routine venipunctures. *Pediatrics* 1992;90(1 Pt 1):87–91.
25. Cummings EA, Reid GJ, Finley GA, McGrath PJ, Ritchie JA. Prevalence and source of pain in pediatric inpatients. *Pain* 1996;68(1):25–31.
26. Van Cleve L, Johnson L, Pothier P. Pain responses of hospitalized infants and children to venipuncture and intravenous cannulation. *Journal of Pediatric Nursing* 1996;11(3):161–8.
27. Goodenough B, Thomas W, Champion GD, et al. Unravelling age effects and sex differences in needle pain: ratings of sensory intensity and unpleasantness of venipuncture pain by children and their parents. *Pain* 1999;80 (1-2):179–90.
28. Carlson KL, Broome M, Vessey JA. Using distraction to reduce reported pain, fear, and behavioral distress in children and adolescents: a multisite study. *J Soc Pediatr Nurs* 2000;5(2):75–85.
29. Broome ME, Bates TA, Lillis PP, McGahee TW. Children's medical fears, coping behaviors, and pain perceptions during a lumbar puncture. *Oncol Nurs Forum* 1990;17(3):361–7.
30. Hamilton JG. Needle phobia: a neglected diagnosis. *J Fam Pract* 1995;41(2):169–75.
31. Pate JT, Blount RL, Cohen LL, Smith AJ. Childhood Medical Experience and Temperament as Predictors of Adult Functioning in Medical Situations. *Children's Health Care* 1996;25(4):281–98.
32. Bijttebier P, Vertommen H. The Impact of Previous Experience on Children's Reactions to Venepunctures. *J Health Psychol* 1998;3(1):39–46.
33. McCarthy AM, Kleiber C. A Conceptual Model of Factors Influencing Children's Responses to a Painful Procedure When Parents are Distraction Coaches. *Journal of Pediatric Nursing* 2006;21(2):88–98.
34. Alfonzo MJ, Bechtel K, Babineau SE. Management of Headache in the Pediatric Emergency Department. *Pediatric Emergency Medicine Practice* 2013;10(7):1–23.
35. Babineau SE, Green MW. Headaches in Children. *CONTINUUM: Lifelong Learning in Neurology* 2012;18 (4):853–68.
36. Friedman BW, Hochberg M, Esses D, et al. A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines. *Headache* 2006;46(6):934–41.
37. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. *Ann Emerg Med* 2008;52(4):399–406.
38. Friedman BW, Mulvey L, Esses D, et al. Metoclopramide for acute migraine: a dose-finding randomized clinical trial. *Ann Emerg Med* 2011;57(5):475–82.e1.
39. Friedman BW, Adewunmi V, Campbell C, et al. A randomized trial of intravenous ketorolac versus intravenous metoclopramide plus diphenhydramine for tension-type and all nonmigraine, noncluster recurrent headaches. *Ann Emerg Med* 2013;62(4):311–4.
40. Friedman BW, Garber L, Yoon A, et al. Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. *Neurology* 2014;82(11):976–83.
41. Dayan P, Chamberlain J, Dean JM, Maio RF, Kuppermann N. The Pediatric Emergency Care Applied Research Network: Progress and Update. *Clin Pediatr Emerg Med* 2006;7(2):128–35.
42. Dayan PS, Holmes JF, Atabaki S, et al. Association of traumatic brain injuries with vomiting in children with blunt head trauma. *Ann Emerg Med* 2014;63(6):657–65.
43. Trottier ED, Bailey B, Lucas N, Lortie A. Diagnosis of migraine in the pediatric emergency department. *Pediatr Neurol* 2013;49(1):40–5.
44. Hershey AD, Winner P, Kabbouche MA, et al. Use of the ICHD-II Criteria in the Diagnosis of Pediatric Migraine. *Headache* 2005;45(10):1288–97.
45. Bigal ME, Arruda MA. Migraine in the pediatric population—evolving concepts. *Headache* 2010;50(7):1130–43.

46. Walker DM, Teach SJ. Emergency department treatment of primary headaches in children and adolescents. *Curr Opin Pediatr* 2008;20(3):248–54.
47. LMA MAD Nasal: Intranasal Mucosal Atomization Device. [Internet]. [cited 2014 Jul 29]. Available from: [http:// www.lmana.com/files/lma-madnasal-eng-ir-fnl.pdf](http://www.lmana.com/files/lma-madnasal-eng-ir-fnl.pdf)
48. Mandema JW, Stanski DR. Population pharmacodynamic model for ketorolac analgesia. *Clin Pharmacol Ther* 1996;60(6):619–35.
49. Forrest JB, Heitlinger EL, Revell S. Ketorolac for postoperative pain management in children. *Drug Saf* 1997;16 (5):309–29.
50. Dsida RM, Wheeler M, Birmingham PK, et al. Age-stratified pharmacokinetics of ketorolac tromethamine in pediatric surgical patients. *Anesth Analg* 2002;94(2):266–70.
51. Drover DR, Hammer GB, Anderson BJ. The pharmacokinetics of ketorolac after single postoperative intranasal administration in adolescent patients. *Anesth Analg* 2012;114(6):1270–6.
52. McAleer SD, Majid O, Venables E, Polack T, Sheikh MS. Pharmacokinetics and safety of ketorolac following single intranasal and intramuscular administration in healthy volunteers. *J Clin Pharmacol* 2007;47(1):13–8.
53. Lewis DW, Winner P, Wasiewski W. The placebo responder rate in children and adolescents. *Headache* 2005;45 (3):232–9.
54. Evers S, Marziniak M, Frese A, Gralow I. Placebo efficacy in childhood and adolescence migraine: an analysis of double-blind and placebo-controlled studies. *Cephalalgia* 2009;29(4):436–44.
55. Fernandes R, Ferreira JJ, Sampaio C. The placebo response in studies of acute migraine. *J Pediatr* 2008;152 (4):527–33–533.e1.
56. Stinson JN, Kavanagh T, Yamada J, Gill N, Stevens B. Systematic review of the psychometric properties, interpretability and feasibility of self-report pain intensity measures for use in clinical trials in children and adolescents. *Pain* 2006;125(1-2):143–57.
57. Tsze DS, Baeyer von CL, Bulloch B, Dayan PS. Validation of Self-Report Pain Scales in Children. *Pediatrics* 2013;132(4):e971–9.
58. Tsze DS, Baeyer von CL, Bulloch B, Dayan PS. Differences in clinically significant changes in pain scale scores based on patient characteristics. Presented at Pediatric Academic Societies May 2013; Vancouver, Canada.
59. Tfelt-Hansen P, Pascual J, Ramadan N, et al. Guidelines for controlled trials of drugs in migraine: third edition. A guide for investigators. *Cephalalgia*. 2012;32(1):6–38.
60. Gupta MX, Silberstein SD, Young WB, Hopkins M, Lopez BL, Samsa GP. Less Is Not More: Underutilization of Headache Medications in a University Hospital Emergency Department. *Headache* 2007;47(8):1125–33.
61. Friedman D, Feldon S, Holloway R, Fisher S. Utilization, Diagnosis, Treatment and Cost of Migraine Treatment in the Emergency Department. *Headache* 2009;49(8):1163–73.
62. Brousseau DC, Duffy SJ, Anderson AC, Linakis JG. Treatment of pediatric migraine headaches: a randomized, double-blind trial of prochlorperazine versus ketorolac. *Ann Emerg Med* 2004;43(2):256–62.
63. Soleimanpour H, Ghafouri RR, Taheraghdam A, et al. Effectiveness of intravenous dexamethasone versus propofol for pain relief in the migraine headache: a prospective double blind randomized clinical trial. *BMC Neurol* 2012;12:114.
64. Talabi S, Masoumi B, Azizkhani R, Esmailian M. Metoclopramide versus sumatriptan for treatment of migraine headache: A randomized clinical trial. *J Res Med Sci* 2013;18(8):695–8.
65. Turkcuer I, Serinken M, Eken C, et al. Intravenous paracetamol versus dexketoprofen in acute migraine attack in the emergency department: a randomised clinical trial. *Emerg Med J* 2014;31(3):182–5.
66. Zhang A, Jiang T, Luo Y, et al. Efficacy of intravenous propacetamol hydrochloride in the treatment of an acute attack of migraine. *Eur J Intern Med* 2014;