Ketorolac for Refractory Migraine in the ED

Specific Care Question :

In the pediatric patient diagnosed with refractory migraine is ketorolac an effective treatment?

Question Originator:

Migraine Therapy in the ED CPG Team

Plain Language Summary from The Office of Evidence Based Practice:

Based on very low quality evidence, the Migraine in the ED CPG Teams makes a ***Conditional* Recommendation** to use ketorolac or valproic acid as the second line treatment, with the potential to use valproic acid if needed based on prior NSAID exposure. Friedman et al. (2014) reported there was no difference when comparing ketorolac vs. valproic acid for pain relief at 2 hours. However, the use of rescue medications was lower in the group who received ketorolac. Although ketorolac appears to have greater efficacy, it should not be used if NSAIDs were recently taken*. If valproic acid is used, pregnancy testing in females must be negative.

*Caution: Ketorolac should not be used if NSAIDs were taken within the following timeframes:

- ibuprofen < 6 hours prior administration
- naproxen sodium < 12 hours prior administration

Although the included studies are methodologically strong, they are only three studies that include a small number of subjects (see Figure 1). Meta- analysis cannot be performed.

- Friedman et al (2014) compared 30 mG IV ketorolac to 1 gram IV valproic acid and found there was:
  - No difference in pain relief at two hours after medication administration. *OR* = 1.91, 95% CI [0.96, 3.79], p= 0.06.
  - Significantly less use of rescue medications when ketorolac was administered OR= 0.48, 95% CI [0.28, 0.83], p= 0.009.
- Brousseau, Duffy, Anderson, & Linakis (2004) compared 0.5 mG/kg; (maximum 30 mG) IV ketorolac to 0.15 mG/kg IV prochlorperazine (maximum 10 mG). The study was stopped early due to the overwhelming benefit of pain relief within two hours in the group treated with prochlorperazine. (*OR*= 4.55, 95% CI [1.37. 15.11], p= 0.01. The odds of having pain relief if treated with prochlorperazine was 4.5 times greater than if treated with ketorolac.
- Meredith, Wait, & Brewer (2003) compared IV ketorolac to nasal sumatriptan and reported pain scores within two hours of treatment. The group treated with IV ketorolac had significantly lower pain scores than subjects treated with nasal sumatriptan *MD* = -40.76, [-60.35, -21.16].

The dose of ketorolac is 0.5 mG/kg IV (max 30mG) and 1 mG/kg IM (max 60 mG)

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Search Strategy and Results:

Studies included in this review:
March 10 2014
EMBASE
'migraine'/exp/mj/dm_dt AND ([internal medicine]/lim OR [neurology and psychiatry]/lim OR [pediatrics]/lim OR [pharmacology and pharmacy]/lim) AND ([infant]/lim OR [preschool]/lim OR [school]/lim OR [child]/lim OR [adolescent]/lim) AND [humans]/lim AND [english]/lim AND [abstracts]/lim AND [embase]/lim AND [2009-2014]/py

Studies included in this review:
Friedman et al., 2014
Brousseau et al., 2004
Meredith et al., 2003

Studies <u>not</u> included in this review with rationale for exclusion:
Duarte 1992- Does not answer the question

Method Used for Appraisal and Synthesis:
Review Manager 5.3.5 (Higgins & Green, 2011).

Updated August 5 2015, August 7, 2015, August 18 2015 March 8 2016, May 16 2016

Characteristics of included study:

Tables:

Brousseau et al., 2004

Methods	Prospective 2-center double-blind RCT
Participants	**Setting:** 2 pediatric EDs within 2 separate children's hospitals **Randomized:** 62 subjects were randomized **Completed:** 60 subjects completed **Age:** mean of 13.8 (SD 3.0) for prochlorperazine, 13.7 (SD 2.6) for ketorolac **Gender:** 18/33 female for prochlorperazine, 18/29 female for ketorolac **Inclusion:** Prensky & Sommer criteria (recurrent headaches with pain-free intervals and at least 3 of the following: 1-an aura, 2-unilateral location, 3-throbbing pulsatile pain, 4-nausea, vomiting, or abdominal pain, 5-relief after sleep, 6-a family history of migraines **Exclusion:** Subjects with any contraindication to use of two study drugs and those unable to complete a Nine Faces Pain Scale **Power analysis:** Sample size was determined by assuming a 30% difference between groups in the proportion of patients classified as experiencing treatment successes represented the minimal limit of clinical significance. A 65% success rate was assumed for the more efficacious treatment. Using an α value of 0.05 and a β value of 0.80, the sample size goal was set at 49 patients per group. At the recommendation of an independent study monitor, it was determined a priori that an interim analysis of the data would be performed at approximately 50% of desired enrollment. Because the interim analysis disclosed a clear difference between the 2 treatments, the study monitor recommended termination of the study at the 50% enrollment point.
Interventions	All subjects received a 10 mL/kg bolus of normal saline solution over a 30-minute period. **Treatment group:** prochlorperazine (0.15 mG/kg; maximum 10 mG) intravenous over 10 minutes **Control group:** ketorolac (0.5 mG/kg; maximum 30 mG) intravenous over 10 minutes
Outcomes	Treatment success = a reduction of 50% or greater in the child's Nine Faces Pain Scale score at 30 or 60 minutes or a complete resolution of symptoms.
Notes	They stopped the study before achieving 49 subjects per group because the prochlorperazine, the "control" treatment was significantly better than the ketorolac the "experimental" treatment.

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	Block randomization performed by hospital pharmacy
Allocation concealment (selection bias)	Low risk	Block randomization performed by hospital pharmacy
Low risk	Low risk	Treating nurse, physician and patient were all blinded. Code for blinding was maintained in the pharmacy and not available to any investigator until completion of the study.
Blinding of outcome assessment (detection bias)	Low risk	Treating nurse, physician and patient were all blinded. Code for blinding was maintained in the pharmacy and not available to any investigator until completion of the study.
Incomplete outcome data (attrition bias)	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	Low risk	

Friedman, et al., 2014

Methods	RCT
Participants	**Setting** ED- proficient bilingual (English and Spanish) staff **Number randomized** : N= 330, 110 per treatment group Ketorolac 30 mG, valproate 1 gram and metoclopramide 10 mG **Number completed:** N= 320, 106 ketorolac, 107 valproate and 107 metoclopramide **Gender:** 14% male **Age:** 34 years (range: 25-44 years) **Inclusion criteria:** Subjects met the criteria of the International Headache Society's International Classification of Headache Disorders 2nd Ed. Also accepted those who did not meet the criteria for • insufficient number of lifetime headaches (<5) • prolonged duration of headache (>72 hrs) **Exclusion criteria:** those who would receive a lumbar puncture in the ED, fever present (>/= to 100.4 degrees F), a new neurologic abnormality, seizure disorder, concurrent use of an investigational medication, pregnancy, lactation, previous enrollment, allergy or intolerance to study medications--

	including hepatic dysfunction, peptic ulcer disease or concurrent use of immunosuppressive medications or monoamine oxidase inhibitors medications **Power analysis:** sample size 100 for each arm of the study
Interventions	Three interventions 1. 1 g of IV valproate vs. 10 mG IV metoclopramide 2. 1 g IV valproate vs. 30 mG IV ketorolac 3. 10 mG of metoclopramide vs. 30 mG IV ketorolac
Outcomes	Primary outcome: Headache relief at one hour Secondary outcomes: 1. Use of rescue medication in the ED- this was considered failure for all other secondary outcomes 2. Patient's overall assessment of efficacy and tolerability - Y/N to "Do you want to receive the same medication the next time you visit the ED with a headache?" 3. Sustained headache relief- four point scale severe, moderate, mild, none within two hours and maintained for 24 hours Functional outcomes 1. Yes/no to "Do you think you could now perform all your usual daily activities?" Assessed at one hour Safety outcomes 1. One hour after medication: assessment of drowsiness on a 3 point scale: (a) no drowsiness. (b) a little bit drowsy, but able to function normally, and (c) too drowsy to function normally 2. Twenty four hours after medication (follow up phone call) 1. Did you feel restless: (a) no restlessness, (b) a little bit restless, or (c) very restless 3. At one, two and 24 hours subjects were asked if they had any other symptom
Notes	Primary outcome: pair wise comparison, Mean difference in pain score (0-10, lower is better) (95% CI) between baseline and one hour Valproate vs. metoclopramide: [- 1.9 (-2.8. -1.1)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving metoclopramide. Valproate vs. ketorolac: [- 1.1 (-2.0, -0.2)] The negative mean difference means that subjects who received valproate had a smaller improvement in pain than subjects receiving ketorolac Metoclopramide vs. ketorolac [0.8 (-1.1, 1.7)] The positive mean difference means that subjects who received metoclopramide had a larger improvement in pain score than subjects receiving ketorolac

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Random sequence generation (selection bias)	Low risk	randomized using an online random number generator, in blocks of six, by the research pharmacy
Allocation concealment (selection bias)	Low risk	The pharmacist placed filled medication vials into the designated container that was numbered in sequence by the randomization schedule. Only the research pharmacist, who was not in the ED knew the allocation. All doses were made to 10 mL to match the volume of ketorolac which came as a 10 mL solution from the manufacturer. Vials were the same.
Blinding of participants and personnel (performance bias)	Low risk	ED nurse who was blinded to the allocation, placed the medication into a 50 mL bag of normal saline for infusion IV drip over 15 minutes
Blinding of outcome assessment (detection bias)	Low risk	Research associates who were blinded to allocation asked subjects questions at 1 and 2 hours after medication was administered. Subjects were contacted at 24 hours after medication administration as well. All data collection tools were standardized
Incomplete outcome data (attrition bias)	Low risk	Used intention to treat analysis
Selective reporting (reporting bias)	Unclear risk	They did not give data that can be used in a meta-analysis for their primary outcomes, but did for their secondary outcomes
Other bias	Low risk	

Meredith, et al., 2003

Methods	Prospective double-blind RCT
Participants	**Participants:** Adults **Setting:** urban emergency department **Number randomized:**29 subjects **Number completed:** 29 subjects **Age:** 33 years (range 18-56 years) **Gender:** 14% male **Inclusion criteria:** Modified International Headache Society (IHS) criteria for migraine without aura was used.

	Exclusion criteria: known allergy to sumatriptan or ketorolac, active peptic ulcer disease, use of an ergotamine containing medication, monoamine oxidase inhibitor or antidepressant, hemiplegic or basilar migraine headache, renal impairment or dialysis dependent, menstruation, pregnancy or nursing. Subjects were excluded if they had taken a non-steroidal anti-inflammatory medication or sumatriptan. Also, if the subject was thought to have a life threatening illness such as stroke (either intracranial hemorrhage or vascular occlusion) meningitis, or encephalopathy. Power analysis: not reported
Interventions	Group 1: Ketorolac IV, 30 mG -n= 13 Group 2: Sumatriptan Nasal, 20 mG - n= 16 All patients rated their pain using a visual analog scale from 0-100. Pain assessment was repeated 1-hour post study medication.
Outcomes	Change in pain score on a visual analog scale (100 mm) left endpoint "no pain" and right endpoint "pain as bad as it could possibly be"
Notes	Used a RMANOVA to compare pre-and post-treatment scores (RMANOVA= repeated measures analysis of variance). They used the term "power analysis" in an unusual manner..

Risk of bias table

Bias	Scholars' judgment	Support for judgment
Low risk	Low risk	Randomization was done by a computer-generated random-number program
Allocation concealment (selection bias)	Low risk	
Blinding of participants and personnel (performance bias)	Low risk	Treating physician, nurse and patient were all blinded. Unblinding did not occur until post treatment pain score was recorded.
Blinding of outcome assessment (detection bias)	Low risk	
Incomplete outcome data (attrition bias)	Low risk	No attrition reported.
Selective reporting (reporting bias)	High risk	They report findings in this way: one hour after treatment the mean pain score was decreased significantly by 61.7 mm (SD = +/- 35.01; power = 80-90% at P </= 0.05
Other bias	Low risk	

Figures:

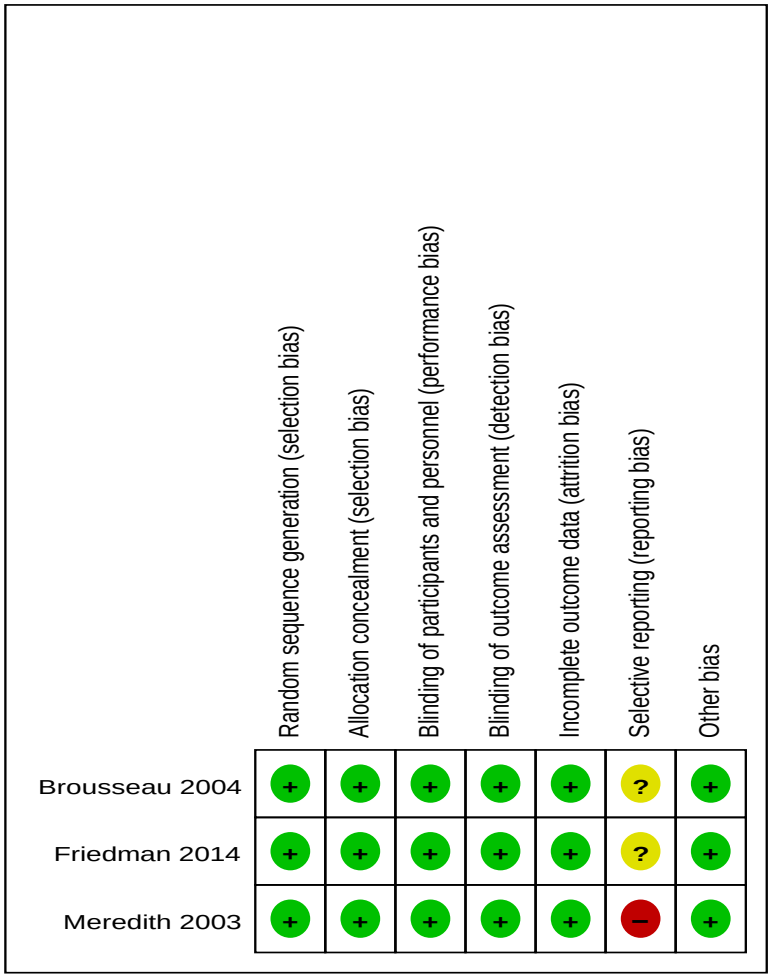

Figure 1. Risk of bias summary: Scholars judgments about each risk of bias item for each included study