COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

Sub-I Name: Valerie Lee **Block: August** **Date: Aug 28, 2010**

Case SIGNOUT:

24 yo F with HbSS with h/o multiple hospitalizations for VOC, acute chest syndrome requiring exchange transfusion, with last hospitalization (4 months ago) for VOC c/b HAP requiring 2 U pRBCs for symptomatic anemia now presenting with left lower rib and lower back pain consistent with VOC. Chest X-ray was negative.
At home, pain usually controlled with NSAIDs. During hospitalizations usually requires dilaudid PCA. She required increasing doses of dilaudid, worsened by concurrent UTI and migraine.

***Clinical Question**: Would the addition of NSAIDs be beneficial for the pain management of this patient?*

Background Info

General recommendations for pain management in VOC: IVF + O2 + opiates

Most recommendations are based upon expert opinion, though there are some smaller RCTs

- Opiate PCA are preferable to Opiate IV injections PRN
- Do NOT use meperidine due to risk of seizures
- Steroid therapy – reduces VOC duration, but may have increased rebound
- Some variable evidence as to benefit of PO/IV NSAIDs

Search Strategy

Database: Ovid-MEDLINE

# ▲	Searches	Results
1	Anemia, Sickle Cell/	14512
2	Pain/	98649
3	1 and 2	710
4	**limit 3 to (english language and randomized controlled trial)**	**41**

Bartolucci P, Murr T, Roudot-Thoravel F, et al. "A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults." **Blood**, 2009 Oct 29; 114(19): 3742-3747.

Senior Medicine Rotation: Based Medicine Project (Cont)

RCT comparing the benefit of adding ketoprofen to standard of care (IVF, O2 therapy, morphine, folic acid [and additional standing acetaminophen]) during acute VOC. 66 patients were randomized to two different groups and treated (as below) and pain levels were checked according to two different scales: VAS and CPS. If they failed therapy (developed ACS or required transfusion), they were taken out of the analysis group due to need for more aggressive treatment. Study to evaluate whether ketoprofen administration can shorten VOC duration by 2 days – 66 patients necessary for adequately powered study to examine this hypothesis.

Group	Criteria or definition	N
Population screened.	Admitted patients to Internal Medicine service at Henri-Mondor Hospital in Paris from August 2000-March 2003	Not noted
Inclusion criteria	>15yo, HbSS, hospitalized for severe VOC (pain/tenderness affecting at least one part of the body that required opioids and not attributable to other causes)	102
Exclusion criteria	VOC > 72 hrs or <24hrs; IVF > 24 hrs; blood transfusion during previous month; **NSAID use in previous 7 days**; pregnancy; h/o drug abuse; HTN; fever>38degreesC; WBC>30 or <4; ACS; severe anemia requiring transfusion at blood transfusion at inclusion; psychiatric disorder/progressive visceral disease; NSAID/ketoprofen contraindication; pts using ASA/valproic acid/macrolides/anti-H2/imidazole/rifampicin/phenobarbital/ carbamazepine/phenytoin/heparin/vitamin K antagonist/ ticlopidine/lithium/methotrexate/IFN-a/diuretics/antiHTN	36
Treatment group	Randomly assigned to receive ketoprofen (300mg continuous IV x 2 days, then 100mg PO q8hrs) in conjunction with morphine	33
No treatment group	Randomly assigned to receive placebo (NS IV x 2 days, placebo pill PO q8hrs) in conjunction with morphine	33

Primary endpoints: Length of VOC from inclusion (fulfillment of 3 out of 4 criteria):

1. Afebrile x 8hrs
2. No pain progression/No need for IV opiates x 8hrs
3. Walking/moving without pain
4. No spontaneous pain or CPS <=1

Secondary endpoints:

1. Amount of morphine used during VOC
2. VAS and CPS scores
3. Treatment failure: ACS or need for blood transfusion

- Are the Results of the Trial Valid?
  - Randomized? Yes
  - All patients accounted for at end? – (see below answer)
  - Intention to treat? Patients were analyzed according to treatment categories, but 7 patients from each group were eliminated due to failing out of the study
  - Blinding? Yes
  - Groups similar at start of trial? Yes
  - Equal treatment of groups? Yes

- Did randomization work? Yes – 54 patients with 66 admissions overall, with no significant difference in age, BMI, VOC duration, morphine dosing, VAS/CPS or lab values before inclusion

Endpoint	Result (experimental v. placebo)	Significance
Duration of VOC (hours)	51(35.5-87) vs. 50 (36-103)	p = 0.61 Kaplan-Meier comparison showed comparable day-by-day success rates
Morphine dose	110 (46-195) vs. 88 (52.5-262.5)	p = 0.64
Median CPS	0.4 (0.2-0.7) vs. 0.4 (0.2-0.7)	p = 0.46
Median VAS	12.6 (4.8-23.2) vs. 9.6 (5.8-33.2)	p = 0.50
Morbidity	**Result**	**Significance**
Treatment Failure	7 patients in experimental: 3 blood transfusions (1 with septic IV), 4 ACS 7 patients in placebo: 5 blood transfusions, 1 ACS, 1 sepsis	Kaplan Meier comparison were comparable, though numbers were low.
Adverse Events (abd pain, infxn, constipation, epigastric pain, facial edema, fever, cytolysis, myocardial repolarization abnormality, n/v, pruritus, somnolence, tachycardia, urinary retention)	16 vs. 19	Most events were felt to be secondary to morphine sulfate as there appeared to be no apparent difference between the groups, though p values were not calculated
Relapse	Numbers not noted	No significant difference between treatment groups (per text)

- Are the Results of the Trial important? Yes and No – this is the first RCT with a larger sample size considering NSAIDs use in the management of pain and has longer followup than other studies in the area. However, it excludes patients who had taken NSAIDs in the week prior to hospitalization, and also has decreased power due to the 7 treatment failures in each group.
    - The treatment was not shown to have a significant advantage over placebo in any of the clinical endpoints.
    - Precision of the estimate of the effect? Due to the 7 person loss from each group, the beta-error rate is increased, however, the authors estimated that if there was a 2 day difference in VOC duration, there was an 82% likelihood of observing this difference.

- Can I apply these results to my patient?
    - Comparison of my patient to trial patients:
        - The patient fits the inclusion criteria (>15yo, HbSS, VOC).
        - Racial/cultural differences – study took place in Paris, cultural differences in the expression of pain, may make the results less applicable to our patient
        - Our pt did take NSAIDs prior to admission, and would not have been included in the study, and this may have been important in determining a category of patients who had previously shown benefit from taking NSAIDs.
        - Additional migraines and other causes of pain which may be appropriately managed by NSAIDs may make study results inapplicable to our patient
    - All clinically important outcomes considered.
        - Duration of pain, severity of pain, and amount of opioid used were most important criteria evaluated and all were examined (as the point of study is to determine opioid-sparing analgesics)
        - No inclusion of renal function or other laboratory tests indicative of NSAID toxicity
    - Should the patient be on NSAIDs?
        - This paper is compelling in that it demonstrates no benefit to NSAIDs, but also demonstrates no increase in AE. The pt has no contraindictations to NSAID use, despite findings, it may still be appropriate to provide a trial of NSAIDs in setting of intractable pain since it may address her other problems as well. Further studies will be needed.

Bartolucci P, Murr T, Roudot-Thoravel F, et al. "A randomized, controlled clinical trial of ketoprofen for sickle-cell disease vaso-occlusive crises in adults." Blood, 2009 Oct 29; 114(19): 3742-3747

Lotternberg and Hassell. "An Evidence-Based Approach to to the Treatment of Adults with Sickle Cell Disease." American Society of Hematology. 2005. 58-65.

Dunlop R, Bennett K. "Pain management for sickle cell disease in children and adults. Cochrane Database of Systemic Reviews." 2006, Issue 2, John Wiley and Sons, Ltd. Chichester, UK DOI: 10.1002/14651858.CD003350.pub2

Perlin et al. "Enhancement of Control with Ketorolac Tromethamine in Patients with Sickle Cell Vaso-Occlusive Crisis." American Journal of Hematology. 1995; 46:43-47.