



Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

20 year old female with a history of sickle cell disease on hydroxyurea with multiple prior admissions for VOC, exchange transfusion in the setting of previous pregnancy, avascular necrosis and retinopathy, now presenting with pain in the lateral abdomen, lower back bilaterally and proximal posterior thighs. Her pain is uncontrolled with her home pain regimen of oxycontin 30mg q12hrs and oxycodone 30mg q6hrs PRN pain. During her previous hospitalizations, she has been managed by PCA in some instances and IV opioids PRN in others.

Clinical Question: What is the appropriate pain management technique in patients with sickle cell disease presenting with a vaso-occlusive crisis that requires IV opiates?

Background:

Vaso-occlusive crises:

- Most common cause for hospital admission in sickle cell patients [1]
- Overall VOCs occur once per year in sickle cell patients
- 5% of pts with SCD are responsible for more than a third of hospital admissions with VOC
- Most commonly involves the back, legs, knees, arms, chest and abdomen [2]
 - Recurrent crises often have same distribution [3]
 - Bone pain tends to be bilateral and symmetric
- A pain crisis often resolves within 5-7 days, but a severe crisis can last weeks to months [4]
 - If a crisis is >7d, consider osteomyelitis, avascular necrosis and compression fracture [5]
 - Often precipitated by infection, dehydration, stress [6]
- Treatment: oxygen, hydration, analgesics, supportive care [7]
- Side effects of morphine: nausea, constipation, pruritis, sedation, hypoventilation, acute chest syndrome [8]

PCA (patient controlled analgesia)

- It may provide superior analgesia and patient satisfaction, but with a higher cost based on cost of equipment, nursing time in putting together analgesia, etc. [9, 10]

Search Strategy: Database: Pubmed

“Sickle cell vaso occlusive crisis” and “analgesia”: 4 results

Article Chosen:

van Beers EJ, et al. “Patient controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial.” Am J Hematol 2007; 82, 955-960.

Group	Criteria or definition	n
Population screened.	Sickle cell disease patients requiring parenteral analgesia for pain during a vaso-occlusive crisis. Measured by pain score of 4 or greater during 4 hours with maximal pain medication (acetaminophen 500mg 6x/day, diclofenoc 50mg TID)	Unknown
Inclusion criteria	Sickle cell disease (HbSS, HbSC, HbSB0, HbSB+); an episode of pain caused by vaso-occlusive crisis necessitating treatment with IV morphine; age more than 17 years.	Unknown
Exclusion criteria	Patients who had already received opioids for more than 24 hours or patients who were allergic or intolerant to morphine	Unknown
Treatment group (PCA group)	Intravenous morphine using a PCA pump: single bolus injection of 5mg morphine followed by patient controlled 0.01 mg/kg bolus injection every 5 minutes. If not adequate, could be increased to 0.02 mg/kg. No continuous infusion	12
Alternate group (CI group)	Dose adjusted CI administration of morphine: single bolus of 5mg followed by 0.03 mg/kg/hr. Increased by 1mg/hr until adequate pain relief was obtained or side effects intolerable. Continuous morphine dosage decreased by 1mg/hr if pain scores were 5 or lower or at patient's request.	13

Primary endpoints: Cumulative and mean hourly morphine consumption, pain intensity score and cumulative side effects during treatment with IV morphine

Secondary endpoints: Length of hospital stay, duration of treatment and quality of life.

Are the Results of the Trial Valid?

- Randomized? Yes, 19 patients were randomized. Six patients had a second episode and underwent crossover to the other group, totaling 25 episodes of vaso-occlusive crises (4 initially PCA, 2 CI). There were 12 in the PCA group and 13 in the CI group
- All patients accounted for at end? Yes, two subjects with VOC withdrew consent and requested treatment with meperidine after randomization
- Intention to treat? Yes
- Blinding? Not blinded.
- Groups similar at start of trial? Yes. Age, sex, number on hydroxyurea treatment, Hg genotype, hemoglobin, percent neutrophils, CRP, HgF, and HgS were similar. The only difference was an average leukocyte count of 15.2 in the CI group compared to 11.3 in the PCA group.
- Equal treatment of groups? Yes
 - Adequate level of pain control was 5 or less on an 11 point verbal response scale
 - Pain scores collected 4 times a day
 - All patients: 500mg acetaminophen 6x daily, 50mg diclofenac TID (or tramadol 50mg TID if intolerance or contraindication)
 - Side effects: includes nausea, pruritis, sedation, lack of BM for one day +10, need for medical intervention for side effects (anti-emetics, anti-histamines) +5.
 - Power of 0.90 by having 12 episodes of vaso-occlusive crisis in each study arm.
- Did randomization work? Yes.

Are the Results of the Trial important?

- Yes, the author's primary aim was to evaluate the efficacy of PCA in sickle cell vaso-occlusive crises. They were able to shown a significant decrease in mean daily dose of morphine, median cumulative dose of morphine and side effects of nausea and constipation in the PCA group compared to the CI group. Cumulative side effects were not significant when corrected for cumulative morphine dose. Furthermore, mean cumulative dose may be partially explained due to the reduced duration of morphine administration in the PCA group. There was no significant difference in pain intensity score, length of stay or duration of morphine administration. Mortality was not assessed as there were no deaths in the study.

- Size of treatment effect? PCA was shown to have a significant advantage over CI based on decreased morphine daily and cumulative dosing, along with less nausea and constipation.
- Precision of the estimate of the effect? Relatively small trial given only 19 patients with 25 vaso-occlusive crisis episodes with only one person requiring altering pain regimen in each group. A larger trial would be beneficial in characterizing the effect.

Endpoint	Result	Significance
Mean daily morphine dose	PCA: 0.5 mg/hr CI: 2.4 mg/hr	P < 0.001
Median cumulative dose	PCA: 33 mg CI: 260 mg	P = 0.018
Pain intensity score (least, mean worst)	PCA: 4.2, 5.3, 6.3 CI: 4.2, 4.9, 5.8	P = 0.14, 0.09, 0.39
Cumulative side effects:		
(1) nausea	PCA: 11; CI: 18	P = 0.045*
(2) constipation	PCA 30; CI 45	P = 0.021*
(3) Pruritis	PCA 5; CI 14	P = 0.42
(4) Sedation	PCA 18, CI 12	P = 0.52
Length of stay	PCA: 6d CI: 9d	P = 0.15
Duration of morphine administration	PCA 4.5 d CI: 7 d	P = 0.21
Quality of life: physical, mental health summary	PCA; 24, 44 CI: 31, 40	P = 0.94 P = 0.94
Adverse Events	PCA	CI
Severe hypoxia due to hypoventilation s/p naloxone	0	1
Intestinal pseudo-obstruction	1	1
Acute chest diagnosed with VOC	0	5 (3 before, 2 after randomization)

*not significance when corrected for cumulative morphine dose

Can I apply these results to my patient?

- My patient presented with inadequate control of pain on home pain regimen of oxycontin 30mg BID and oxycodone 30mg q6hrs PRN, requiring IV pain medication. She met the inclusion criteria. However, the exclusion criteria include a stipulation that patients cannot have opiate medications for more than 24 hours before inclusion in the study. Since the patient has a chronic need for opiate medications at baseline, she would have excluded her from the study even though her medications are used to control chronic low levels pain.
- My patient underwent PCA with IV dilaudid instead of morphine, but in all likelihood all opiates would act similar since this study examined morphine's administration.
- Her PCA was dosed at 0.3mg q6min PRN, which is 0.0058 mg/kg of dilaudid based on a weight of 51.8kg, which is 0.03mg/kg morphine, which is slightly higher than starting doses used.
- Comparison of my patient to trial patients: my patient was at the lower end of the age range of both groups, had the most common hemoglobin genotype, had a baseline Hg within the range (6.4), had a leukocyte count of 13.1 with 36% neutrophils (much lower than average). CRP was not measured. The HgF and HgS were 5.8% and 84.3%, both higher than average.
- All clinically important outcomes considered: Yes
- Should the patient be on a PCA? Likely yes. The benefit of using PCA compared to CI is shown by lower daily and cumulative morphine doses, which contributes to less side effects of nausea and vomiting in PCA controlled patients. Furthermore, there is a slight decrease in the number of days PCA patients spent in the hospital; this may become significant with increased study population size. There were few adverse events in PCA controlled analgesia. In order characterize harms, a larger study with increased sample size would need to be used.

- Technically, these results cannot be generalized to my patient since she does not meet the exclusion criteria, but I believe there is a difference between being on new opioid medication and baseline maintenance medication.

References:

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