COLUMBIA UNIVERSITY MEDICAL CENTER

DIVISION OF GENERAL MEDICINE

Senior Medicine Rotation: Evidence-Based Medicine Project

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Case SIGNOUT:

29 year old woman with a history of HgbSS sickle cell disease, multiple past transfusions, Chronic Renal Insufficiency, and leg ulcers, but no history of acute chest syndrome, who presents to the ER with complaints of Back and LUE pain, consistent with her VOC's. Patient requesting 6mg Dilaudid q3hr for pain control. The patient denies chest pain, and CXR is normal. However, patient's O2 saturation was in the 80's overnight; concerning for development of acute chest syndrome.

Clinical Question: Some studies have reported a dose related association of opiods and the development of acute chest syndrome; what is the best way to minimize opiod levels, while ensuring adequate pain control?

Search Strategy

Database: OVID – Medline.

	1	Anemia, Sickle Cell/	13830
	2	Pain/	89535
	3	1 and 2	626
	4	Acute Chest.mp.	1209
	5	3 and 4	34

Article Chosen:

Van Beers EJ. van Tuijn CF. Nieuwkerk PT. Friederich PW. Vranken JH. Biemond BJ. **Patient-controlled analgesia versus continuous infusion of morphine during vaso-occlusive crisis in sickle cell disease, a randomized controlled trial.**

American Journal of Hematology. 82(11):955-60, 2007 Nov.

Group	Criteria or definition	n
Population screened	SCD patients requiring paraenteral analgesia for VOCs. Repeat visits accepted, but subjects were crossed over to the other group.	27
Inclusion criteria	Patients over 17yrs of age	27
Exclusion criteria	Patients who received opiods for more than 24hrs, or pts allergic to opiods. Study did not report this number.	N/A
PCA group	1 bolus of 5mg Morphine + PCA 0.01mg/kg with 5 min lockout. If not adequate relief, increase to 0.02mg/kg with 5 min lockout. No Background infusion.	12
CI group	1 bolus of 5mg followed by 0.03mg/kg/hr. Based on pain assessment, dose can be increased or decreased by 1mg/hr	13

*All patients received Tylenol 500mg q4 and diclofenac 50mg TID.
**Unit of analysis was a VOC visit. Thus, 19 patients were analyzed, 6 of which were included twice, but were crossed over to the opposite group the second time.

Primary endpoints:

- Cumulative & mean hourly morphine consumption
- Pain intensity:
  - Assessed 4-times a day with verbal response on a scale of 0 (no pain) to 10 (worst pain). Pain level of 5 was deemed as acceptable pain relief.
  - A Visual Analogue Scale (VAS) was also used to compare pain intensity, importance of pain control, and perceived pain control on admission, and on day 2 of treatment.
  - These were rated on scale of 0mm (not important, not under control) to 100mm (very important, totally under control).
- Cumulative side effects during treatment
  - Side effects related to morphine (nausea, constipation, pruritis, sedation) were scored daily on an 11-point scale 0 (no symptoms) to 10 (worst symptoms). If medication was needed for any side effect then 5 points were added to the score.
  - Oxygenation (pulse oximetry) was measured several times daily. A daily mean was calculated.
  - Acute Chest syndrome was defined as per accepted definition (chest pain, New CXR infiltrate, Temperature > 38.2, cough, tachyphnea, wheezing)

Secondary endpoints:

- Length of hospital Stay in days
- Duration of Treatment in days
- Quality of Life: Measured by a survey.

- Are the Results of the Trial Valid?
  - Randomized?
    - Sealed, random envelopes containing the designated delivery system were picked at random and assigned to patients.
  - Patients accounted for at end?
    - Yes. 2 patients, 1 from each arm, withdrew from the study.
  - Intention to treat?
    - Yes, intention was to establish adequate level of pain relief.
  - Blinding?
    - No, this was an open study, since both subjects, and investigators were privy to the type of treatment subjects were getting.

- Groups similar at start of trial?
  - No significant difference in age, sex, hydroxyurea treatment, Hgb level on admission, or HbF (fetal HgB) was found between both groups. Leukocyte count was higher in the continuous infusion group.
  - There was no mention of avg. weight in each group. Since dosing was weight based, and results were reported in totals. If there were a significant difference in weights, then the results would be biased to the 'lighter' group using less Morphine.
- Equal treatment of groups? Yes. Each of the groups received equal care, and same number of visits to assess pain.
- Did randomization work? Yes. No significant difference in group characteristics or pain intensity at baseline.

Results:

Endpoint	Result	Significance	ARR	NNT
1º Morphine Dose:				
Mean Daily Dose (mg/hr)	***0.5 (PCA) vs. 2.4 (CI)***	***P<0.001***		
Mean Daily Dose – First 3 days (mg/hr)	***0.5 (PCA) vs. 3.5 (CI)***	***P<0.001***		
Total Amount (mg)	***33 (PCA) vs. 260 (CI)***	***P<0.018***		
1º Cumulative side effects (Mean Side-effect score)				
Nausea**	***11 (PCA) vs. 18(CI)***	***P < 0.05***		
Constipation**	***30 (PCA) vs. 45(CI)***	***P <0.05***		
Pruritis	5 (PCA) vs. 14 (CI)	P = 0.42		
Sedation	18 (PCA) vs. 12 (CI)	P = 0.52		
Oxygen Saturation (%)	98(PCA) vs. 97 (CI)	P > 0.05		
Acute Chest Syndrome	1 (PCA) vs. 2(CI)	P > 0.05		
1º Pain Intensity:				
Least Pain	4.2 (PCA) vs. 4.2 (CI)	P = 0.14		
Median Pain	5.3 (PCA) vs. 4.9 (CI)	P = 0.09		
Worst Pain	6.3 (PCA) vs. 5.8 (CI)	P = 0.39		
Visual Analogue Scale	Comparable at baseline and at 2 days.	No significant difference		
Perceived Pain Conrtol	Comparable at baseline and at 2 days	No significant Difference		
Importance of Pain control *(Change over 2 days)*	***+2 (PCA) vs. -12 (CI)***	***P < 0.02***		
2º Length of Stay (days)	6 (PCA) vs. 9 (CI)	P = 0.15		
2ºDuration of Treatment (days)	4.5 (PCA) vs. 7 (CI)	P = 0.21		
2º Quality of Life	Comparable at baseline and at 2 days	No significant difference		

**When corrected for Morphine consumption the difference disappeared, confirming the dose response.

- Are the Results of the Trial important?
    - The results are important insofar a to show that less morphine is used if PCA pumps are used in VOC's. However, the results don't demonstrate a clinical advantage (e.g. incidence of acute chest, length of stay) or advantage in reducing pain intensity.
    - Size of treatment effect?
        - There is a significant difference in total amount of morphine used by PCA user as compared to CI users. The absolute mean difference is 227 mg.
    - Precision of the estimate of the effect?
        - Pain intensity (one of the primary endpoints) is a subjective measure and very difficult to assess, and to compare across individuals. However, with a large cohort and numerical assignment of pain, one would hope that the subjectivity will not bias results.
- Can I apply these results to my patient?
    - Comparison of my patient to trial patients.
        - Based on the description of the patient profile, it appears that my patient, a 29year old female with HgbSS type disease would not be different than those subjects studied.
    - Comparison of Treatment Studied
        - We used Dilaudid (Hydromorphone) for pain control rather than morphine. Since the study compared CI vs. PCA of morphine the results cannot be applied fully to our patient scenario. Nevertheless, one can postulate that results, if Dilaudid was studied, should not be much different.
        - Furthermore, the method of delivery chosen for our patient is not strictly continuous infusion. The patient requested dilaudid 6mg q3hr. With a half life of 2-3 hours for that drug, one can approximate that she is receiving a continuous infusion of 2mg/hr of dilaudid. If she were enrolled in that study, she would be receiving 1.8mg/hr of morphine is she was randomized to the continuous group (pt wt = 60 kgs), or 0.6mg morphine per bolus if she randomized to the PCA group.
        - Thus, as far as treatment modality is concerned, it is unclear that IV boluses at a set time can be approximated as CI. Thus I hesitate to apply the results of this study to my patient. Furthermore, this study falls short of showing clinical advantage of using PCA. Thus the utility of this study in this scenario is questionable.
    - All clinically important outcomes considered.
        - The study was set up, and sample size was chosen to detect a reduction of morphine by 50%. As far as that aim is concerned, they achieved their goal. However, **Acute Chest Syndrome**, being by far the most significant adverse outcome of VOC was not taken into consideration in choosing sample size. From the results of this study, it is clear that a larger number of subjects are required to elucidate the difference in the rates of acute chest between both groups.
        - Furthermore, from a hospitalist perspective**, length of stay** is often an important primary endpoint. It seems there is a difference in Length of Stay, albeit non-significant, in patients getting PCA vs. those with CI. A larger study sample, solidifying this difference would have made this study more useful.
    - Likely benefits outweigh potential harms and cost?
        - Since there was no difference in pain levels between two groups, it is unlikely that there is a potential harm in using PCA pumps for VOC's. Use of these pumps varies by institution. To my knowledge, Columbia requires the anesthesiologists to set up the pump. This might be a costly resource to use; however, if LOS is shown to decrease significantly with PCA use, then it might be more cost effective to use PCA.