Critical Review Form

Therapy

Randomized Double-Blind Placebo-Controlled Trial of Two IV Morphine Doses in ED Pts with Moderate to Severe Acute Pain, *Ann EM* 2007;49:445-453

Objective: **"**To compare pain relief and safety of 2 dosages of morphine sulfate (0.10 mg/kg and 0.15 mg/kg) in adult ED patients with acute pain" as measured by the between-group difference in before/after numeric pain rating scale.

Methods: Single urban academic ED randomized "double-blinded" placebo-controlled trial of two morphine dosages in adult patients with acute pain requiring opioid analgesia. Subjects were enrolled around the clock from March 25, 2005 – January 3, 2006. Exclusion criteria included age >65, inability to consent, opioids or tramadol within 7-days, pain for more than 7 days, methadone use, morphine allergy, alcohol intoxication, pregnancy or breast feeding, systolic blood pressure less than 90 mm Hg, weight above 100 kg or concurrent monoamine oxidase inhibitor use.

Randomization occurred in blocks of ten using an online random plan generator. Allocation occurred in the pharmacy with "patient, physician, nurse, and research associate" (quadruple-blinding) all blinded to group assignment throughout the entire study. The first dose of 0.10 mg/kg (max 10 mg) was administered over 5-minutes to both groups. The second dose (of 0.05 mg/kg in the treatment arm or placebo in the control arm) was administered 30-minutes later with the final pain assessment performed at 60-minutes by a 0 (no pain) to 10 (worst possible pain) scale. Satisfaction was assessed by asking patients "How would you rate this pain medication?" with subjects provided the following five descriptors: "poor", "fair", "good", "very good", and "excellent". Safety profiles were assessed by pulse oximetry, respiratory rate, and BP at baseline, 30-minutes and 60-minutes. In addition symptoms of reported nausea, vomiting or pruritis were sought.

The primary outcome was the between group differences in mean before and after change in numeric pain score to 60 minutes among patients in the 0.10 mg/kg arm compared with the 0.15 mg/kg arms. The study was 95% powered to detect difference greater than 1.3 given a standard deviation of three and two-sided α of 0.05.

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes, in blocks of 10 using an on-line random number generator (p 446)
2.	Was randomization concealed (blinded)?	Yes, to patients, physicians, nurses, and research associates (p 446)
3.	Were patients analyzed in the groups to which they were randomized?	Yes, all participants who underwent random assignment were analyzed according to group assignment in an *intention-to-treat* fashion (p 448).
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No demographic (Table 1, p 449) or prognostic baseline numeric pain score differences between groups are noted so the two groups should start with a similar pain prognosis. (Table 2, p 450)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	No, randomization concealed as noted in above.
2.	Were clinicians aware of group allocation?	No
3.	Were outcome assessors aware of group allocation?	No
4.	Was follow-up complete?	Yes, as noted in Figure 1 (p 448) *all* randomized subjects were analyzed through 60-minutes (the study endpoint)
II.	**What are the results (answer the questions posed below)?**	

1.	How large was the treatment effect?	• 280 patients were randomized clinically and statistically. • 9/142 randomized to the higher dose did not receive the 2nd dose. • No clinically or statistically significant difference between 0.10 mg/kg and 0.15 mg/kg dosing was noted by numeric pain score at 30-minutes (3.6 vs. 4.1), 60-minutes (4.5 vs. 5.3) or between 30- and 60-minutes (1.0 vs. 1.4). • The difference between proportions of patients reporting moderate or greater pain relief at 60-minutes was 9% favoring the higher dose of morphine. • Adverse events were similar in the 2 groups (Table 4, p 451) with 12% vomiting, 1-2% itching.
2.	How precise was the estimate of the treatment effect?	The CI's all overlap so there is no difference between groups.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Yes, pain patients in a busy academic ED.
2.	Were all clinically important outcomes considered?	Yes, therapeutic pain response.
3.	Are the likely treatment benefits worth the potential harm and costs?	No benefit was noted to higher morphine dosing.

Limitations

1) **Primarily poor Hispanic and African-American population with limited external validity to other populations. Also, the results cannot be readily extrapolated to pediatric or elderly populations.**
2) **Numeric pain scale questionable Gold standard, but currently it is the best we have.**
3) **Large number of abdominal pain cases.**
4) ***Spectrum bias* is possible in that the median pain score was 10 and subjects with lesser pain may respond differently to narcotic analgesia.**
5) **30-minute delayed dosing of 0.15 mg/kg dose may produce different response than baseline dosing would have.**

Bottom Line

Well-designed, adequately powered, single center RCT showing no clinically significant difference in analgesic effect or side effect profile for 0.10 mg/kg . Morphine IV vs. 0.15 mg/kg Morphine in divided doses. Future research should focus on higher narcotic doses (Morphine >0.15 mg/kg or equipotent hydromorphone) and identify patient characteristics associated with higher analgesic thresholds.