Critical Review Form
Therapy

Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005 Jan 3;182(1):24-7.

Objectives: "to determine the effectiveness of IN naloxone compared with IM naloxone for patients with acute respiratory depression secondary to suspected opiate overdose treated in the pre-hospital setting." (p. 24)

Methods: This prospective, unblinded, randomized controlled trial was conducted in rural and metropolitan Victoria, Australia between January 5, 2002 and December 19, 2004. Patients with suspected opiate overdose with a respiratory rate (RR) of less than 10 and who were not arousable were randomized to receive either 2 mg of intranasal (IN) naloxone (1 mg in each nare) by mucosal atomizer or 2 mg of intramuscular (IM) naloxone. Random allocation was achieved by use of a sealed envelope that was opened after eligibility was determined. Patients whose RR failed to improve to 10 or more within 8 minutes of the initial dose were given an additional 0.8 mg of IM naloxone.

The primary outcome was the response time, defined as the time required for the RR to reach 10 breaths/minute. Secondary outcomes included the proportion of patients whose RR increased to 10 or more within 8 minutes, the proportion of patients with a Glasgow Coma Scale (GCS) score > 11 at 8 minutes, the proportion of patients requiring a rescue dose of naloxone, and the rate of adverse events.

Of 182 patients initially enrolled, 27 were excluded from analysis: 12 regained consciousness prior to naloxone administration, 12 had incomplete data, and 3 had "technical problems." Of the 155 patients included, 71 received IM naloxone and 84 received IN naloxone. The majority of patients were men (72%) and the median age was 28 (range 13 to 57 years). In 65 patients (42%), coingestion of another drug or alcohol was suspected by paramedics. Patients in the two groups were similar with respect to the reported demographic data (Table).

Table. Baseline characteristics of enrolled patients

	IM naloxone	IN naloxone	p-value
Median age	**30**	**28**	**0.7111**
Males (%)	**52**	**59**	**0.8167**
Transported to hospital	**15 (21%)**	**14 (17%)**	**0.6138**
Suspected coingestion	**28 (39%)**	**37 (44%)**	**0.6778**

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. Randomization occurred by random number allocation, though the method of sequence generation was not reported.
2.	Was randomization concealed (blinded)?	Uncertain. Treatment protocols were contained in sealed envelopes that were opened after determining patient eligibility. It is unclear if the envelopes were opaque or if randomization could be subverted in some other way.
3.	Were patients analyzed in the groups to which they were randomized?	No. Patients were analyzed according to the route of the initial dose of naloxone given, regardless of response or need for additional naloxone given by an alternate route. **However 27 patients eligible for inclusion were NOT randomized and hence not included in the analysis.**
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients were similar with respect to age, gender, location of overdose, need for hospital transport, and suspicion of coingestion. We are not given the initial GCS scores or RRs for the groups, so we do not know if they were similar in these respects.
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?	Yes. Patients were not blinded to treatment group and no placebo or sham treatments were used. It is unlikely that performance bias on the part of the patients would have affected the outcomes.
2.	Were clinicians aware of group allocation?	Yes. EMS personnel were aware of the route of naloxone administration, potentially leading to performance bias.
3.	Were outcome assessors aware of group allocation?	Likely yes. Outcomes were based on EMS records, which presumably include documentation by the EMS providers who administered the naloxone, and hence were aware of the route of administration. The authors do not mention if data abstractors were blinded to group allocation or study purpose. This could potentially lead to observer bias.
4.	Was follow-up complete?	Yes. All outcomes were based on the EMS records, so outcome data was available for all patients

		included in the analysis.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	Patients in the IM group had a shorter time to respirations ≥ 10/min compared to the IN group: mean of 6 min (95% CI 5-7 min) vs. mean of 8 min (95% CI 7-8 min), p = 0.006. Patients in the IM group and IN group had similar times to GCS > 11 (p = 0.376), though the times were not provided. The IM group was more likely to have spontaneous respirations by 8 minutes compared to the IN group: 82% vs. 63% (p = 0.0163), for an odds ratio [OR] of 2.6 (95% CI 1.2-5.5). There was no statistically significant difference in percent requiring rescue naloxone (13% in the IM group vs. 26% in the IN group, p = 0.0558; OR = 2.4 [95% CI 1.0-5.7]) or percent with a GCS > 11 at 8 minutes (72% in the IM group vs. 57% in the IN group, p = 0.0829; OR 1.9 [95%0.98-3.7]). Those in the IM group were more likely to have a minor adverse effect compared to the IN group (though this was not statistically significant): 21% vs. 12%, p = 0.1818. There was a significantly higher rate of agitation/irritation in the IM group compared to the IN group (13% vs. 2%, p = 0.0278).
2.	How precise was the estimate of the treatment effect?	See above.
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 and no. While this study was performed partly in rural Australia, where EMS run-times and transport times are likely higher, this would likely NOT have affected the outcomes. The type of opiate ingestions involved in these cases is unclear (IV heroin vs. IN heroin vs. skin-popping, prescription opiates), and

		could potentially affect the outcomes. Overall, these were typically younger patients with opiate overdose, and were likely similar enough to apply the results to our patient population.
2.	Were all clinically important outcomes considered?	No. The authors looked at changes in respiratory rate and GCS, without considering other patient or provider-important outcomes, such as needlestick injuries, incidence/duration of hypoxia, ED length of stay, or cost.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While there was a difference in the primary outcome, time to respirations > 10/min, in favor of the IM group (mean 6 min vs. 8 min) the clinical significance of this is unclear. 74% of patients in the IN group required no additional therapy. There were no major adverse events in either group, and the rate of minor adverse events was not significantly difference statistically. While IM naloxone seems to provide more rapid response in terms of respiratory rate, IN naloxone resulted in less agitation and irritation, which would supports its use.

Limitations:

1) **Major and minor adverse events were not defined in the study, and the method of assessment of these events was not described.**

2) **Initial GCS and RR not provided for the two groups, making prognostic balance an uncertainty.**

3) **The sealed envelopes were not mentioned as being opaque, therefore potentially no allocation concealment was used.**

4) **No blinding or sham treatments, potentially leading to observer bias.**

5) **A large volume of dilute naloxone (2 mg in 5 mL) was used, exceeding recommendations (Wolfe 2004).**

6) **No standardized methods or objective observers were to record times or respiratory rates.**

7) **27 patients eligible for inclusion were NOT randomized and hence not included in the analysis intention to treat analysis principles were therefore not followed.**

8) **The authors do not mention if data abstractors were blinded to group allocation or study purpose.**

Bottom Line:

This randomized controlled trial conducted in Australia demonstrated a shorter time to recovery (RR > 10) in patients receiving IM vs. IN naloxone in opiate overdose (6 minutes vs. 8 minutes), the clinical significance of which is unclear. There was no difference in the proportion of patients requiring a rescue dose of naloxone, and there was a trend towards higher rates of minor adverse events in the IM group (21% vs. 12%), though this was not statistically significant. The study failed to provide baseline RR and GCS scores for the two groups, and hence prognostic balance was not demonstrated. Additionally, the failure to standardize or report the methods by which time was measured may have biased the results. IN and IM naloxone both appear to be safe routes of administration based on this study, and both would be viable options.