Critical Review Form
Therapy

PGY-4

Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose. Addiction. 2009 Dec;104(12):2067-74.

Objectives: **"to determine the effectiveness and safety of concentrated (2 mg/ml) i.n. [intranasal] naloxone compared to i.m. [intramuscular] naloxone for treatment of suspected opiate overdose in the pre-hospital setting." (p. 2068).**

Methods: **This prospective, randomized, unblended trial was conducted at 6 EMS branches in the state of Victoria, Australia from August 1 2006 to January 31 2008. Eligibility required a suspected opiate overdose with altered level of consciousness, pinpoint pupils, respiratory depression (respiratory rate [RR] < 10/min), or Glasgow Coma Scale (GCS) ≤ 12, with no major facial trauma, blocked nasal passages, or epistaxis. All patients who met eligibility were enrolled, with exception that paramedics who had not yet been trained in the study protocol could not enroll patients in the study.**

Block randomization **by EMS branch was achieved by use an online computer program to achieve a random sequence of allocations. Sequentially numbered opaque envelopes were present in each ambulance containing the group allocation. Envelopes were opened after eligibility was determined. Patients were allocated to receive either 2 mg of intramuscular (IM) naloxone or 2 mg of intranasal (IN) naloxone (1 mg per nare administered by mucosal atomization device). Patients who failed to respond by to treatment within 10 minutes were given a "rescue" dose of 0.8 mg of naloxone IM.**

The primary outcome was the proportion of patients who responded to naloxone within 10 minutes of administration, defined as spontaneous RR ≥ 10/min and GCS ≥ 13. Secondary outcomes included time to adequate response, need for hospitalization, requirement of "rescue" naloxone, and adverse events. Adverse events were defined as drug-related (vomiting, nausea, seizure, sweating, tremor, pulmonary edema, increased blood pressure, ventricular dysrhythmia, cardiac arrest, agitation, and paresthesias), administration-related (nasal obstruction, nasal deformity), or study-related (epistaxis, ruptured septum, spitting, coughing, leakage of solution from nasal passages).

During the study period, 266 patients were treated for suspected heroin overdose at the study sites. Of these, 13 were not considered for enrollment, 75 were not eligible, and 6 were excluded for either equipment issues or improvement prior to naloxone administration. 172 patients were included in the analysis: 83 in the IN group, 89 in the IM group. The median age was 29 years and 74% were male.

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. Block randomization of patients according to study site was conducted using a computer program.
2.	Was randomization concealed (blinded)?	Yes. A computer-generated randomization sequence was used. Sequentially numbered randomization envelopes made of thick, non-transparent paper were used to conceal randomization. The envelopes were opened at the scene, after eligibility had been determined.
3.	Were patients analyzed in the groups to which they were randomized?	No. 3 patients in the IN group were excluded from analysis due to missing equipment, while 3 other patients (2 in the IN group and one in the IM group) became more alert prior to naloxone administration and were hence excluded from analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes and no. Patients in the IN and IM groups were similar with respect to mean age (30.6 vs. 31.8), mean treatment time (13.1 vs. 13.4 minutes), percent male (77.1% vs. 70.8%), and concomitant alcohol use (30.1 vs. 34.8%). Patients in the IN group had higher rates of concomitant drug use [21.0% vs. 9.0%, difference 12.7% (95% CI 2.0-23.4)].
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?	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. This could potentially lead to

		observer bias.
4.	Was follow-up complete?	No. All patients treated with IN or IM naloxone included in the analysis had data recorded in the electronic patient case recorded.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• 129 of 172 total patients (75%) achieved adequate response within 10 minutes of initial naloxone administration: 60 (72.3%) in the IN group vs. 69 (77.5%) in the IM group, difference -5.2% (95% CI -18.2 % to 7.7%). • Mean response time was 8.0 min in the IN group vs. 7.9 min in the IM group, hazard ratio (HR) 0.8 (95% CI 0.6 to 1.2). • A multivariate analysis for adequate response time yielded an odds ratio (OR) of 0.7 (95% CI 0.3 to 1.5). • A multivariate analysis for time to adequate response yielded a HR of 0.84 (95% CI 0.6 to 1.2). • Significantly more patients in the IN group required rescue naloxone compared to the IM group: 18.1% vs. 4.5% (difference 13.6%, 95% CI 4.2% to 22.9%). This difference remained significant after controlling for age, gender, and suspected coingestion (OR 4.8, 95% CI 1.4 to 16.3). • There was one major adverse event involving a seizure in a patient receiving IM naloxone. • There was no significant difference between the IN and IM groups with respect to: o Minor adverse events (19.3% vs. 19.1%; difference 0.2%, 95% CI -11.6% to 11.9%) o Hospitalization rates (28.9% vs. 25.8%; difference 3.1%, 95% CI -10.3% to 16.4). o Agitation and/or violence (6.0% vs. 7.9%) o Nausea and/or vomiting (8.4% vs. 7.9%) o Or headache (4.8% vs. 3.3%) • There were no reported needlestick injuries in either group.
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 aspiration, 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 no significant difference in the proportion of patients who achieved adequate clinical response in the IN and IM groups (72.3% vs. 77.5%), significantly more patients in the IN group required rescue naloxone (18.1% vs. 4.5%). It seems reasonable to use IN naloxone as the primary treatment given the ease of administration and lack of clear harm, with the understanding that a significant proportion of these patients will require a rescue dose of naloxone, either IM or IV.

Limitations:

1) **The inclusion criteria required only suspected opiate overdose and were not definitive. There was no requirement that the overdose was witnessed or that opiates or paraphernalia be found on scene. It is possible that some of the enrolled patients did not suffer from acute opiate overdose.**

2) **A nonconsecutive, convenience sample was enrolled. There was no comparison of the enrolled and non-enrolled populations to ensure similarity.**

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

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

5) **The criteria for receiving "rescue" naloxone were not well-defined.**

6) **Six randomized patients were excluded from the analysis: a true intention to treat analysis was not used.**

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

<u>Bottom Line:</u>

This randomized controlled trial conducted in 6 EMS branches in Victoria, Australia demonstrated similar rates of clinical response at 10 minutes to intramuscular and intranasal naloxone administration for acute opiate overdose, as well as similar response times. A significantly higher proportion of patients in the IN group required "rescue" naloxone compared to the IM group, though the criteria used to necessitate rescue naloxone were not well-defined. The failure to standardize or report the methods by which time and respiratory rate were 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.