Critical Review Form
Therapy

Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. Prehosp Emerg Care. 2009 Oct-Dec;13(4):512-5.

Objectives: **"to compare the IV and IN routes of naloxone administration with respect to the time from patient contact and medication administration to clinical effect in patients with suspected narcotic overdose." (p. 513)**

Methods: **A retrospective review of the electronic emergency medical services (EMS) record was undertaken from March 2003 to July 2004. Patients were included if they were given naloxone by EMS for suspected opiate overdose; by protocol this required a respiratory rate (RR) of 8 breaths/min or less. Exclusion criteria included failure to be treated with naloxone or altered mental status felt to be secondary to a cause other than opiate overdose. Prior to March 2004, the authors do not indicate if EMS protocol dictated a preferred route or dosage for naloxone administration. In March of 2004, the EMS protocol was changed to make intranasal (IN) naloxone first-line therapy for opiate overdose. A dose of 2 mg (1 mg per nostril) was recommended by mucosal atomization device, to be repeated in 5 minutes if respiratory depression persisted. Intravenous (IV) naloxone was given as 1 mg slow IV push if there was no response to IN naloxone at 10 minutes.**

The main outcome measures were time from naloxone administration to clinical response and time from first EMS contact to clinical response. Clinical response was defined as an increase in respiratory rate of 6 breaths/min or more, or an improvement in Glasgow Coma Scale (GCS) of at least 6 points. Secondary outcome measures included number of doses of naloxone administered, number of rescue doses given by alternate route, and number of needlesticks reported during care of study patients.

A total of 154 patients met inclusion criteria and were seen during the study period. Of these, 104 were given IV naloxone as first-line therapy, and 50 were given IN naloxone as first-line therapy. Mean ages in the IN and IV groups were 41 and 44 respectively ($p = 0.21$); males represented 71% and 60% of the IN and IV groups respectively, the mean initial GCS scores were 6.2 and 6.90 ($p = 0.28$), and mean initial respiratory rates were 8.6 and 10.9 ($p = 0.06$).

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?	No. This was a retrospective chart review. Route of naloxone administration was determined primarily by EMS protocol. Prior to March 2004 (the first year of the study) the protocol dictated the use of the IV route; the protocol changed to dictate the IN route in March 2004, and thus the IN route was first-line for the final 5 months. Given the protocol change, it is unlikely that selection bias would have played a significant role. Seasonal variation also seems unlikely to affect prognostic balance given the nature of the study.
2.	Was randomization concealed (blinded)?	No. Patients were not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. While patients were not randomized, they were analyzed according to the route of the initial dose of naloxone.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Yes. Patients in the IV and IN groups were similar with respect to mean age (41 vs. 44, p = 0.21), gender (males represented 71% vs. 60%, p =- 0.14), mean initial GCS scores (6.2 vs. 6.90, p = 0.28, and mean initial respiratory rates (8.6 vs. 10.9, p = 0.06).
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 the route of naloxone administration, however performance bias on the part of patients seems unlikely to have affected 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?	Yes. Presumably all cases of opiate overdose administered naloxone during the study period were

		included. As follow-up did not extend beyond information included in the EMS record, follow-up was complete.
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	• Positive clinical response was see in 33 of 50 (66%) of patients in the IN group compared to 58 of 104 (56%) in the IV group (p = 0.3) for a RR of clinical response of 1.18 (95% CI 0.91 to 1.54). • Mean time from administration of naloxone to clinical response was longer in the IN than the IV group (12.9 vs. 8.1 min, p = 0.02), but mean time from patient contact to clinical response was the same for the two groups (20.3 vs. 20.7 min, p = 0.9). • A second dose of naloxone was given to 17 of 50 (34%) patients in the in IN group vs. 19 of 104 (18%) in the IV group (p = 0.05). For 3 patients in the IN group (6%) the 2nd dose was given a different route whereas no patients in the IV group received a rescue dose by another route (p = 0.19). • There were no needlestick injuries reported 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?	Likely yes. These were US patients (Fresno, CA) with acute opiate overdose defined by decreased respiratory rate (8 breaths/min or less). It is likely that rates of coingestion and type/route of opiate administration were similar, though this can not be said with certainty.
2.	Were all clinically important outcomes considered?	No. Follow-up was limited to the duration of the EMS encounter. Outcomes such as length of ED stay, admission rates, additional naloxone dose given in the ED, incidence/duration of hypoxia, and cost of treatment were not considered.
3.	Are the likely treatment benefits worth the potential harm and costs?	Uncertain. While ease and rapidity of IN naloxone administration is appealing, the mean time from patient contact to clinical response was not statistically different

		between the two groups. No complications attributable to IV administration (needlesticks) were observed. However, more patients in the IN group required a rescue dose of naloxone by an alternate route (6% vs. 0%). While this difference was not statistically significant, the study was underpowered to detect such a difference. Additionally, it would be helpful to know the dose of naloxone used in each group, as it is possible that either group was under-dosed. Additional research into the optimal dose of IN naloxone may show more significant benefit.

Limitations:

1) **Dose of naloxone was not standardized and dosages were not provided for either group.**

2) **The study was not randomized. While no differences in stated confounders were observed between the two groups, there is the potential for an imbalance of unknown confounders.**

3) **The study was retrospective and no blinding occurred, either on the part of the patients, EMS personnel, or data abstractors (not specifically mentioned). There is potential for observer bias and data abstraction bias.**

4) **Chart review methods not detailed (Gilbert 1996, Worster 2004), specifically no mention of:**
   a. **Blinding of data abstractors,**
   b. **QA of the data abstraction tool,**
   c. **QA of the data abstractors.**

5) **Outcome beyond the EMS encounter (duration of ED stay, additional naloxone doses given in the ED, total cost of care) were not assessed.**

Bottom Line:

This retrospective chart review of EMS records demonstrated a non-statistically significant increase in the proportion of patients with a positive clinical response for intranasal vs. intravenous naloxone (66% vs. 56%), and no difference in the mean time from patient contact to positive clinical response in the two groups. While these data suggest that IN naloxone is safe and at least as effective as IV naloxone, the study was fraught with methodological flaws, primarily failure to follow recommendations for the performance and reporting of retrospective chart reviews (Gilbert 1996, Worster 2004).