Critical Review Form
Therapy

PGY-2

Intranasal naloxone delivery is an alternative to intravenous naloxone for opioid overdoses. Am J Emerg Med. 2010 Mar;28(3):296-303.

Objectives: **"to investigate whether IN naloxone was noninferior compared to IV naloxone in increasing respiratory rates (RRs) and mental status in patients presenting with suspected opioid overdose in the prehospital setting."**

Methods: **This retrospective chart review was conducted at an urban university-based level I trauma center between January 1, 2005 and December 31, 2007. Patients were included if they met one of the following criteria:**

1) **Admission of opioid use to paramedics or emergency department (ED) physician.**
2) **Witness testimony of opioid use to paramedics or ED physician.**
3) **Evidence of opioid use observed by paramedics (e.g. heroin, prescription narcotics, paraphernalia found on person).**
4) **Positive urine drug screen for opioids.**

Exclusion criteria included cardiac arrest, intubation prior to naloxone administration, sedation prior to naloxone administration, or patients with missing end-point data. Per EMS protocol, included patients received either intravenous (IV) naloxone (0.4 to 2.0 mg) or IN naloxone (1 mg per nostril) at paramedic discretion.

Data was collected from EMS patient care reports (PCRs) by two medical student investigators. The primary outcome measures were changes in Glasgow Come Scale (GCS) and unassisted respiratory rates (RRs) after the administration of IV or IN naloxone. Additionally, the authors looked at rates of requirement for subsequent doses of naloxone.

From a database of emergency medical calls, 344 patients were identified who received naloxone. A total of 67 were excluded due to cardiac arrest, sedation, or missing data. Of the remainder, 181 could not be confirmed as opioid overdose using the specified criteria, leasing 96 confirmed cases. Of these, 55 received IV naloxone, 38 received IN naloxone, and 3 received IM naloxone. For the IV and IN routes, patients were similar with respect to age (median 42 vs. 38, p = 0.44), sex (67.3% male vs. 60.5% male, p = 0.50), initial RR (10/min vs. 10/min, p = 0.60), and initial GCS (4 vs. 3, p = 0.60). There was a higher rate of coingestion in the IV group (58.2%) compared to the IN group (34.2%), p = 0.02, and subjects receiving IN naloxone received a higher dose than those receiving IV naloxone (1.95 vs. 1.71 mg, p = 0.01).

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, and EMS protocol allowed paramedic discretion to determine the route of naloxone administration. It is possible that this introduced selection bias.
2.	Was randomization concealed (blinded)?	No. The study was not randomized.
3.	Were patients analyzed in the groups to which they were randomized?	Yes. While the study was not randomized, patients were analyzed according to the route of naloxone administration initially used.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	No. Patients were similar with respect to age, gender, initial RR and GCS. However, there was a significantly higher rate of coingestion in the IV compared to the IN group (58.2% vs. 34.2%, p = 0.02) which could potentially bias the results in favor of the IN group.
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?	Yes. All outcomes were based on the EMS PCRs, so outcome data was available for all patients included in the analysis.
II.	**What are the results (answer the**	

<table>
<tr><td></td><td>questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>How large was the treatment effect?</td><td>

In the IV group: RR increased from 10 to 18 (p < 0.0001) for a median change of 6 (95% CI 4-10); GCS increased from 4 to 15 (p < 0.0001) for a median change of 4 (95% CI 3-8).
In the IN group: RR increased from 10 to 16 (p < 0.0001) for a median change of 4 (95% CI 2-6); GCS increased from 3 to 12 (p < 0.0001) for a median change of 3 (95% CI 0-5).

Table. Outcomes in IV vs. IN naloxone
<table>
<tr><td></td><td>IV naloxone</td><td>IN naloxone</td><td>p-value</td></tr>
<tr><td>Median final RR</td><td>18</td><td>16</td><td>0.001</td></tr>
<tr><td>Median final GCS</td><td>15</td><td>12</td><td>0.01</td></tr>
<tr><td>Naloxone redosing rate</td><td>20%</td><td>42%</td><td>0.02</td></tr>
</table>
Of the 16 IN patients to receive repeat naloxone dosing, 9 received the repeat dose IV at the decision of the paramedic. One patient in the IV group received 3 doses, and one patient in the IN group received 3 doses.
</td></tr>
<tr><td>2.</td><td>How precise was the estimate of the treatment effect?</td><td>See above.</td></tr>
<tr><td>III.</td><td>How can I apply the results to patient care (answer the questions posed below)?</td><td></td></tr>
<tr><td>1.</td><td>Were the study patients similar to my patient?</td><td>Likely yes. These were adult patients with confirmed opiate overdose requiring naloxone administration at EMS discretion.</td></tr>
<tr><td>2.</td><td>Were all clinically important outcomes considered?</td><td>No. The authors looked at changes in RR and GCS, without considering other patient or provider-important outcomes, such as complications (aspiration, pulmonary edema, needlestick injuries), incidence/duration of hypoxia, ED length of stay, or cost.</td></tr>
<tr><td>3.</td><td>Are the likely treatment</td><td>Uncertain. Based on this study, patients receiving IV</td></tr>
</table>

	benefits worth the potential harm and costs?	naloxone had significantly greater increases in RR and GCS, and were less likely to require additional doses of naloxone. While the clinical significance of the increased RR is questionable, the difference in median final GCS (15 vs. 12) is clinically significant, as is the need for additional doses of naloxone in 42% of patients receiving IN naloxone compared to 20% receiving IV naloxone. However, the use of IN naloxone is likely safe and noninvasive, and if its use reduced the need for IV placement or IM/SQ injection in a significant number of patients, it may worth using. Further information regarding cost would help in this assessment. This was a retrospective chart review subject to selection bias and performance bias. A randomized controlled trial would better answer the question of the effectiveness of IN naloxone in opiate overdose.

Limitations:

1) **The study was not randomized, and selection bias may have influenced the decision of which route of administration to use.**

2) **The higher rate of coingestion in the IV compared to the IN group (58.2% vs. 34.2%, p = 0.02) could potentially bias the results in favor of the IN group.**

3) **Authors did not specify reasons for redosing of naloxone.**

4) **There was no standardized time period over which the outcomes were measured. The final RR and GCS were considered as the first documented RR or GCS following naloxone administration.**

5) **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.**

6) **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.**

7) **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 demonstrated statistically significantly higher mean respiratory rates (18 vs. 16) and GCS scores (15 vs. 12) in the IV compared to the IN group, as well as significantly lower rates of naloxone redosing (20% vs. 42%). The study contained many methodological flaws, including the retrospective nature of the study with no defined timeframe for recording final RR or GCS score, no defined parameters for redosing naloxone, and failure to follow and document proper chart review procedures (Gilbert 1996, Worster 2004).