Capstone for Impact Submission | GY2021

Project Title: Safety, efficacy, and cost of 0.4 mg versus 2.0 mg intranasal naloxone for treatment of prehospital opioid overdose

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If this project can be continued by another UMMS student, please include your contact information or any other details you would like to share here: N/A

Summary (~250-500 words):

In the United States alone, opioid poisoning accounted for 197,970 emergency department visits and 47,600 fatalities during the most recent years for which data are available (1). Opioid reversal can be achieved by the administration of intravenous, intramuscular, or intranasal naloxone. Compared to intravenous and intramuscular routes, the bioavailability of intranasal naloxone is approximately 50% (2, 3). However, in the prehospital setting, the level of provider training and the availability of supplies and intravenous access often dictate an intranasal route of administration.

Despite the ubiquity of intranasal naloxone for treatment of prehospital opioid overdose, the optimal dose remains unclear. Higher doses have been associated with increased rates of pulmonary complication and carry a concern for precipitating opioid withdrawal (4). Opioid withdrawal is associated with catecholamine release, resulting in adverse effects ranging from agitation to overt aggression and combativeness (5). The American Heart Association has previously recommended using the "lowest effective dose" of naloxone to reduce the risk of adverse withdrawal effects including cardiac instability (6). However, the lowest effective dose of intranasal naloxone for treatment of opioid overdose is unclear, and recommendations for naloxone dosing vary as widely as an order of magnitude (7). The authors' review of the English-language medical literature did not reveal any studies comparing the clinical effect of intranasal naloxone at different doses -- a problem also noted in two recently published literature reviews and the most up to date evidence-based guidelines (8-10).

In order to investigate the safety, efficacy, and cost of various dosing protocols for intranasal naloxone in the treatment of prehospital opioid overdose, a retrospective analysis was performed of patient care records in two neighboring counties in Southeast Michigan, USA: one that used a 2.0 mg protocol and another that used a 0.4 mg protocol specially approved by the State of Michigan quality assurance committee. The goal of this investigation was to compare the safety, efficacy, and cost of 0.4 mg versus 2.0 mg intranasal naloxone for treatment of prehospital opioid overdose.

Methodology:

This was a retrospective, cross-sectional study of patients receiving intranasal naloxone for prehospital treatment of opioid overdose in either of two geographically adjacent counties in Southeast Michigan, USA. Oakland County (pop. 1,259,000) is served by multiple ground ambulance services, while Washtenaw County (pop. 345,000) is served by one. Both counties border the Detroit metropolitan area and include a similar mix

of urban, suburban, and rural communities. Their emergency medical services systems are overseen by independent medical control authorities with freedom to specify dosing protocols for prehospital medication administration. For prehospital opioid reversal with intranasal naloxone by Advanced Life Service (ALS) providers in adults, Oakland County ALS providers used an initial dose of 0.4 mg, while Washtenaw County ALS transporting providers used an initial dose of 2.0 mg. Under the lower dose protocol, naloxone was drawn up from a vial, while under the higher dose protocol naloxone was provided in a pre-filled syringe. Both protocols included the addition of an atomizer to the syringe for intranasal administration.

In order to compare these two protocols, records were collected for all adult patients receiving intranasal naloxone from ALS providers in either county during the study period of October 15, 2015, to March 6, 2017. The study protocol was reviewed by the authors' institutional review board and deemed exempt. Patient identifiers were removed prior to storage in a secure database.

All adults (age ≧ 18 years) receiving documented intranasal naloxone during the study period were included. The only criterion for exclusion was receipt of naloxone by another route prior to the first dose of intranasal naloxone. No patients met this criterion. The selection criteria yielded 94 patients in Oakland County and 124 in Washtenaw County.

For Oakland County, raw data were obtained as paper records collected from individual ALS agencies by the medical control authority. For Washtenaw County, raw data were obtained directly from a centralized electronic medical record system used by the transporting ALS agency, Stryker HealthEMS (Stryker Corporation, Redmond, WA, USA). Both datasets were digitized and further characterized by the authors via manual review and abstraction of narrative reports.

The primary outcomes were response to initial intranasal dose (as determined by manual chart review), requirement of additional dosing (as reported in medication administration records), and incidence of adverse effects (as determined by manual chart review).

Demographic data from patients in each county were compared in order to assess the equivalence of the populations and seek out any confounding factors prior to comparison with regard to treatment and response. Mean age, mean mass, mean initial intranasal dose, mean total number of doses by any route, and mean number of redoses by intranasal, intramuscular, and intravenous routes were each compared using unpooled, two-tailed, two-sample t-tests. Gender, proportion of known exposures identified as heroin, response to initial dose, proportion of patients requiring redosing, and rate of adverse effect were each compared using chi-squared tests for homogeneity. All tests were performed in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA). Statistical significance was defined as $p < 0.05$.

Results:

Ninety-four Oakland County patients were compared to 124 Washtenaw County patients, although some variables were inconsistently documented as noted in Table 1. There was no statistically significant difference between the two groups in age, mass, gender, or proportion of known exposures identified as heroin (Table 1).

Patients treated in Oakland County received intranasal naloxone at a mean initial dose of 0.48 mg (95% CI 0.42 - 0.54 mg), while those treated in Washtenaw County received a mean initial dose of 1.77 mg (95% CI 1.64 - 1.90 mg) ($p < 0.001$). There was no statistically significant difference in response to initial dose, proportion of patients requiring redosing, or total number of doses by any route. Patients in Oakland County were more likely to receive redosing by the intranasal route ($p < 0.001$), while patients in Washtenaw County were more likely to receive redosing by the intramuscular route ($p < 0.001$). There was no statistically significant difference in redosing by the intravenous route. The overall rate of adverse effect in Oakland County was 2.1%, while the overall rate in Washtenaw County was 29.0% ($p < 0.001$) (Table 1, Fig. 1).

Regarding cost, the lower dose protocol used a 0.4 mg/1 ml vial with separate syringe and needle, while the higher dose protocol used a 2 mg/2 ml pre-filled syringe (a pre-filled syringe is less costly than an improvised device when administering the higher dose). In total, the average wholesale price per dose under the lower dose protocol was $5.32 USD, while the average wholesale price per dose under the higher dose protocol was $24.75 USD. Given no observed difference in the rate of redosing, this translates directly to a cost savings of 79% in favor of the lower dose protocol.

Conclusion (~250-500 words):

This study cannot conclude whether the increased rate of adverse effect observed in patients treated under the higher dose protocol is due to the higher initial intranasal dose, the preference for intramuscular redosing in that county, or an unobserved confounding factor such as differences in reporting. However, the medical literature suggests that higher total doses of naloxone carry greater risk of adverse effect, as discussed above, and the results presented here indicate that the higher dose protocol was associated with a higher rate of adverse effects. With regard to efficacy, the equivalence in subjective response to the initial intranasal dose and equivalence in requirement of redosing support the conclusion that the lower dose protocol is equally effective during the prehospital period. The cost savings associated with the lower dose protocol may be especially important in vulnerable counties with low per capita income and high opioid burden (11). Although the need for redosing has been discussed in the literature before, the observed rate of redosing was considerably higher than rates published previously—conceivably reflecting the increasing national incidence of overdose involving strong synthetic opioids such as fentanyl and carfentanil (1, 12, 13).

Although statistical analysis revealed no statistically significant difference in age, mass, gender, or proportion of known exposures identified as heroin between Oakland and Washtenaw Counties, addressing all possible confounders in a non-randomized, observational study is not possible. As such, this study cannot conclude whether the observed difference in rate of adverse effects was due to the difference in initial dose or to an unobserved confounding factor such as differences in reporting. However, the observation that higher total doses of naloxone carry greater risk of adverse effects is supported by previous investigations. In addition, prehospital records are sparse by nature and the analysis was limited in some cases by incomplete documentation as noted in Table 1. Finally, patient records available for this study were limited to the prehospital period; thus, it was not possible to assess patient outcomes after arrival to the hospital.

In this study, treatment of prehospital opioid overdose using intranasal naloxone at an initial dose of 0.4 mg was equally effective during the prehospital period as treatment at an initial dose of 2.0 mg, was associated with a lower rate of adverse effects, and represented a substantial cost savings.

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Table 1. Demographics and Main Results, by County[a]

	Oakland County	Washtenaw County	p-value
Total number of patients	94	124	…[b]
Mean age, yr (n, S.D.)	38.2 (92, 14.9)	37.4 (124, 13.0)	0.70
Mean mass, kg (n, S.D.)	83.9 (19, 20.6)	76.1 (124, 18.7)	0.13
% male	70.2	64.5	0.38
% known exposures identified as heroin (n)	85.7 (35)	88.1 (67)	0.74
Mean initial intranasal dose, mg (n, S.D.)	0.48 (92, 0.28)	1.77 (121, 0.75)	**<0.001**
Subjective response to initial dose[c], %	Y: 39, N: 45, U: 16	Y: 54, N: 35, U: 11	0.10
% patients requiring redosing	58.5	54.8	0.59
Mean number of doses by any route (S.D.)	1.77 (0.74)	1.67 (0.70)	0.33
Mean number of intranasal redoses (S.D.)	0.51 (0.60)	0.17 (0.42)	**<0.001**
Mean number of intramuscular redoses (S.D.)	0.06 (0.29)	0.24 (0.43)	**<0.001**
Mean number of intravenous redoses (S.D.)	0.19 (0.47)	0.26 (0.49)	0.31
% patients with adverse effects	2.1	29.0	**<0.001**

[a] Data were available for 100% of patients unless otherwise noted. Statistically significant results ($p < 0.05$) are in bold.

[b] Not applicable.

[c] Categorized as "yes," "no," or "unclear."

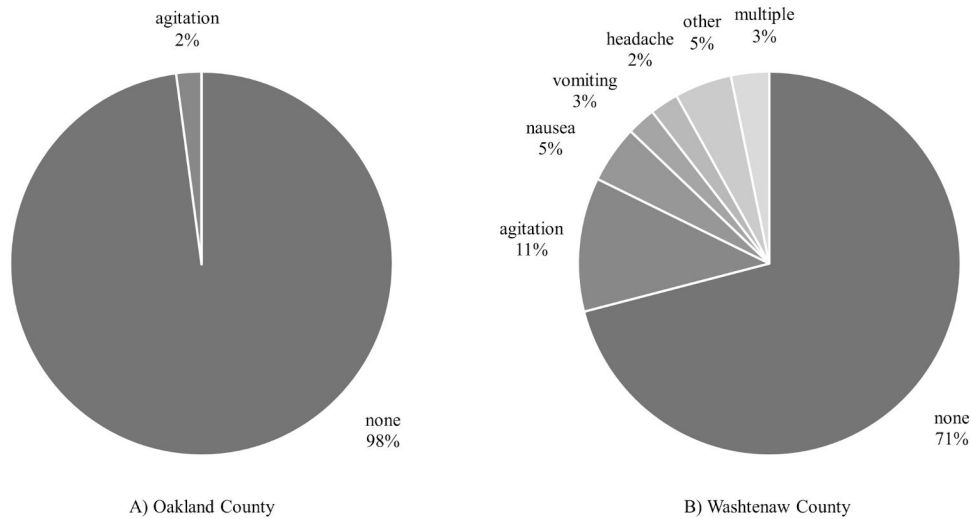**Figure 1. Adverse Effects, by County**

Fig. 1: Adverse effects observed in patients treated with intranasal naloxone in A) Oakland County, which used a 0.4 mg protocol, or B) Washtenaw County, which used a 2.0 mg protocol.

Reflection/Impact Statement:

This work was presented to the Washtenaw/Livingston Medical Control Authority for consideration and adoption into prehospital protocols (May 27, 2020). It has also been accepted for oral presentation at the National Association of EMS Physicians' Annual Meeting (January 15, 2021). By generating evidence to support optimal dosing of intranasal naloxone for prehospital opioid overdose, this work contributes directly to patient care at a systems level by limiting the incidence of adverse effects within the relevant population and protecting vulnerable counties with high opioid burden and low per capita income from unnecessary cost.