Author’s response to reviews

Title: Prehospital naloxone administration – what influences choice of dose and route of administration?

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Author’s response to reviews:

Dear Professor Wampler,

Thank you for reviewing this article and for the helpful and friendly comments from the reviewers and yourself. Please find enclosed the revised manuscript. You will find our responses and changes to the reviewers’ comments below.

Reviewer 1.

This is an observational study on the use of naloxone in Norway. The researchers presented evidence supporting the effectiveness of 0.4 to 0.8 mg of IM naloxone. They included a review of the national death registry to evaluate for safety.

Overall, I am impressed with this study. It is well written and, I believe it adds some interesting science to the field of Emergency Medical Services.

The manuscript could be published in its current state, but I would like to request that the authors add some additional information for a global audience.

First, I request that the authors describe the Oslo City Center EMS. Is this system comprised of ambulances only, or are there also non-transporting response vehicles? Are all personnel
paramedics, or are their individuals with advanced training (nurses or physicians) on the ambulances? How extensive is paramedic training?

Response: Thank you for this important comment and for the possibility to update the manuscript. We have added further details on the organization of Oslo City Center EMS to increase the paper’s value to international readers. The following sentences have been added in the methods section, under “setting” (page 7, lines 152-158):

During the study, Oslo City Center EMS were set up with ground ambulances only. Non-transporting response vehicles, physician manned rapid response unit, and other more specialized units were organized outside of the city center EMS but could assist the city center units as needed. The ground ambulances were staffed by personnel with competence ranging from emergency medical technicians (EMT) with two years of high school education followed by two years of clinical practice, to paramedics with a three-year bachelor’s degree.

I would also like amplifying information about the safe injection facilities. Do these facilities sell opioids? Do the sell or provide free injection equipment? What is the nature of the medical monitoring in the facilities, and how closely do they monitor their clients while using opioids?

Response: We have added more information on the safe injection facility in the methods section, under “setting” (page 7, lines 164-169):

Oslo had a public safe injection facility located in the center where drug users could inject illicit drugs provided by themselves. The facility provided the drug users with sterile equipment, information about safe drug injecting techniques, and presence of health care professionals. The facility staff monitored the users and called for professional assistance when needed. Staff were typically nurses or social workers trained in basic airway management.

I am intrigued by the relatively high non-transport rate. Is the EMS system designed to triage patients, and intentionally not transport patients determined to be stable, or do these all represent patients that refuse transport?

Response: The patients left on site in this study mainly represent patients that refuse transport to further care. The EMS staff are instructed to offer transport to further follow-up for all patients who have been treated for overdose, but a large proportion of the patients reject this offer. We have tried to clarify this as well as the criteria for leaving patients on site in the discussion section (page 16-17, lines 395-399):

A large proportion of the patients were left on site. All patients were offered transport to further care after naloxone treatment by the EMS, but many declined this offer. This is a recognized challenge worldwide(15, 16). The criteria for being left on site included having an appropriate level of consciousness and the capacity to give informed consent. No patients were transported against their will.
A few minor suggestions – The authors use the term 'transfer rates.' Perhaps I have a US bias, but I would prefer the term 'transport rates,' as we often consider the term 'transfer' to mean inter-facility transfer.

Response: Thank you for this comment, we have implemented this suggestion throughout the manuscript.

The effect of a missing national identity number is not clear. Was it not possible to track survival in all of these cases? Do the authors have any evidence to suggest that the survival rates in the group without a national identity number are the same as the group with the number? Clearly since this is a fairly large number of patients, if the group without identifiers has worse outcomes the outcome of the study could be quite different.

Response: We certainly understand this comment and thank you for the opportunity to clarify the matter. The group of cases with missing national identity number consists of two different subgroups. Due to a delay with approval from the Committee for Research Ethics, medical records were retrospectively collected for the period January 1st and June 1st, 2014. These 183 cases were consecutively and systematically collected without national identification. As these participants were not given information about the study and the opportunity to withdraw, they could only be registered anonymously. We do not believe that this group differs in mortality from the rest of the group as the lack of national identity number recording is unrelated to patient’s or EMS’ characteristics. The second group consists of 312 cases that were sporadically collected during the course of the study and where consists of individuals which did not disclose their national identity number to the EMS. We do not know how many individuals are represented among these cases, but there are indications that there are repeaters in this group, as it is in the rest of the material. This group could differ from the rest of the patients regarding mortality in either direction; better or worse. This is a limitation of the study which we have tried to further clarify in the limitations section, page 18, lines 431-439:

National identity numbers were not available in 22.3% of the cases. Some of these, 14.1% (n=312) of the total number of cases, consists of individuals who did not disclose their identification to EMS staff. There is a possibility that this group could have different outcomes, including mortality, than those with known national identification number. Furthermore, 8.2% (n=183) of the total number of cases were systematically collected retrospectively without national identification as ethical approval for using national identity numbers was pending in the first five months of the study period. We assume that they do not differ regarding outcomes from the cases with known identity.

I would also like a more detailed description of the consent process. Is consent obtained during the course of care by EMS?

Response: Thank you for this comment. We have tried to clarify by adding more information on this matter on page 8, lines 178-182.
The Committee for Research Ethics approved a procedure with waived consent with the opportunity to actively withdraw from the study. Patients received oral and written information about the study at the time of treatment by EMS. All patients were included except those who asked to be withdrawn from the study on site or contacted the study team later by phone.

On page 13 the authors mention the outcome of a patient in cardiac arrest, yet on page 7 they state that patients in cardiac arrest were not included in the study.

Response: According to the ERC guidelines and guidelines for Oslo City Center EMS patients with opioid-induced cardiac arrest are not treated with naloxone. However, one patient did receive naloxone during treatment of cardiac arrest. Since it was an observational study with the goal of documenting all EMS use of naloxone, the case was included in our material. We have tried to clarify the matter by adding additional information on this patient in several sections:

Page 7-8, lines 173-178: According to European resuscitation guidelines, treatment with naloxone were not recommended for patients with opioid-induced cardiac arrest, and this was also the guideline in the Oslo City Center EMS. However, one patient received naloxone prior to the recognition of cardiac arrest and since this was an observational study with the aim of documenting all EMS use of naloxone, the individual case was included in our material.

Page 13, lines 318-321: There was one death during EMS treatment of all the cases in our material. The patient was administered naloxone during advanced cardiac life support and died despite resuscitation efforts, hence not represented in either of the transport categories above.

Page 18, lines 443-445: Cases of opioid overdose presenting to EMS as cardiac arrest were excluded from this study as naloxone was not routinely administered in these cases.

The authors should consider moving the 'limitations and strengths' to the discussion section.

Response: We have revised the manuscript according to your suggestion and the section is now found on page 18.

Thanks for the opportunity to review this interesting manuscript, and congratulations on a job well done!

Reviewer 2.
This is a very interesting and well written study describing the use of naloxone be a single large EMS system in Norway.

I would be very interested in seeing additional details of the subjects that died. Were there differences in demographics, naloxone dose, transport rates, opioid of choice (PO opioids vs
injection/inhalation), safe injection site vs residence/public place? comorbidities (end-of-life care and palliative care was mentioned for some of these subjects).

Response: We have revised the manuscript and added more information on the subjects who died. The section “one-week mortality” (page 14-15) now reads:

Among the 1,720 episodes between June 1st, 2014 and December 31st, 2018 with a valid national identity number, there were 10 deaths within the first week after EMS treatment. The crude one-week mortality rate was 5.8 per 1000 episodes. Seven deaths were drug-related deaths, while three patients died from natural causes.

Among the seven cases of drug related deaths, six deaths were classified as unintended poisoning and one as suicide by intentional poisoning with heroin; five men and two women with median age of 45 years (min 37, max 60). All patients underwent autopsy and had heroin confirmed as their main opioid at time of death. None of the patients died on day they were provided with clinical assistance from EMS (day 0), three died on day 1, two died on day 2, and two died within the next five days (days 3 and 7). All had been left at the scene after the last known naloxone treatment prior to their death. The overall one-week mortality rate for drug-related deaths was 4.1 per 1000 episodes and 5.5 per 1000 episodes for patients left at the scene by the EMS.

Three patients died from natural causes: a 96-year-old nursing home patient, a 76-year-old patient in palliative care, and a 62-year-old complex medical patient in home care that died from chronic obstructive pulmonary disease and acute lower respiratory infection after five days of hospitalization.

We have also during the process had a “self-review” and have added updated information regarding the naloxone recommendations from FDA and a new reference in the “Introduction-section” (page 5, lines 105-109). We have also clarified the legend below table 3 and 4, and have revised a few grammatical errors throughout the text.

We hope that you will enjoy this revised manuscript and thank you once again for considering the manuscript. We are looking forward to your positive response.

Sincerely,

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