Author's response to reviews

Title: Pre-Hospital Treatment of Acute Poisonings in Oslo

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Version: 2 Date: 18 August 2008

Author's response to reviews: see over
Dear Dr Appleford

Thank you for this very thorough review. We have tried to accommodate the reviewers’ suggestions, and believe that the changes have improved our manuscript.

**Comments from more than one reviewer:**

*The transferred, but lost to follow-up:*

We agree that 385 transferred who were lost to follow-up is a large number (13%). A random check was made retrospectively to determine what happened to the lost to follow-ups, the results were originally presented in the legend of figure 1. This information is important, and we have therefore moved it to the method section (study sample) to make it more visible. We have also provided an explanation for the excess of hospitalized patients to the transferred.

As described, some of the patients were transferred for other reasons than the poisoning. Typically, the situation may change during the clinical course and treatment: the overdose situation may be the most important in the ambulance setting, while only a minor diagnosis after ambulance treatment (naloxone) and transfer. The inclusion criterion for this study was a main diagnosis of acute poisoning: patients may fulfill this criterion in the pre-hospital setting without fulfilling it at the next health care level. Since the inclusion was made prospectively, an additional retrospective inclusion based on medical records might bias the results. Besides, although technically possible (as done with the random check), the access to all these medical records in the hospitals, outpatient clinic and ambulance service is to some extent restricted and is very time-consuming, and a more thorough investigation is impractical to perform.

Most important is that the ambulance personnel have registered whether their patients were discharged after treatment or transferred to a higher health care level, and this makes the basis for the results that are presented.

*How were the hospital cases transported to hospital?*

Such information is described for the patient in the outpatient clinic. We are unfortunately not able to provide date for how all the hospital patients were transported – that was not part of the hospital registration form, and the hospital medical records do not provide consistent information regarding this. We are therefore unable to answer in detail.

Most of the hospitalized acutely poisoned patients arrive by ambulance: they were either registered in this study from an emergency response; only as a transport between two facilities (e.g. the outpatient clinic and one of the hospitals, hence not registered in the study); or with an unclear condition (poisoning not evident for ambulance personnel) leading to a missed inclusion in ambulance, but an inclusion in the hospital when the diagnosis is made. Some patients also arrive by other means of transportation (police, private cars etc), but we do not have these numbers.

*How often did the hospital or outpatient clinic determination of the most important substance differ from the assessment in the ambulance?*

This comment was very useful. We have performed a thorough investigation of the data set, and the results are provided in the methods section.
Possible long-acting opioids among the non-transferres

We do not know whether long acting opioids were common in those not transferred, because no toxicological testing was performed in the pre-hospital setting, and the study form was prefilled with the category “opioid” to make it simple to complete. More detailed categories would probably exceed the precision of the clinical diagnosis in this setting. But we agree that it would have been interesting to know.

Regarding the suggestion of using rapid response to naloxone as a definition of a heroin overdose, our experience is that due to frequent ingestion of multiple substances, the response to naloxone gives a rather imprecise determination of type of opioid, although a rapid response may indicate heroin in the street setting. We have not used this method as a way of excluding longer-acting opioids in our study.

Answer to Nick Buckley

1. “Reductionist approach”

Only one substance is recorded as responsible for the poisoning in the pre-hospital setting, although the majority of patients probably take more than one substance. We agree that this may weaken the data, but it was done as a compromise to minimize the study form used in the pre-hospital setting to ensure completeness of the registration. Besides, the unknown reliability of the determination of multiple additional agents in the pre-hospital setting was an argument for this “one-main-agent” strategy.

Although not toxicologist, ambulance officers in Oslo have traditionally been working quite independently regarding clinical evaluation and treatment, especially with emergencies related to opioid overdoses. Some more details of the Oslo pre-hospital system are provided in the method section.

“It is reassuring that no deaths were recorded against those triaged as primarily ingesting alcohol, but one can wonder to what extent these people had also ingested other drugs, and that failure to refer was inappropriate”.

Agreed, however, if another substance that should have led to referral was ingested in a patient not referred (that means a more toxic/dangerous substance than the one registered), the ambulance personnel did obviously fail to diagnose this – otherwise the most toxic drug should have been stated as the main agent. The study aims at describing the current practice of the evaluation, treatment and discharge vs the transfer in the pre-hospital setting – with or without possible failure to transfer – not to find the sensitivity of the agent determination (although both evaluation of possible failure to refer and diagnosing skills are important as such).

2. Lost to follow-up: see beginning of this letter.

3. Figure 1: Those 15 who died in ambulance should not exit from the discharged. If presented as a flowchart, this figure might be very complicated. However, we have tried to make a quite simple version, with explanations of the missing IDs and lost to follow-ups in the legend.

4. Statistics. We agree - the sentence is changed.

5. Ethics. We agree – the sentence is changed.

6. Results. 5.4/1000 is incidence: The rate of which new cases occur, but restricted to the first event for each patient with repetitions.
Postcode was not recorded.

7. We agree that many numbers are better expressed with a numerator, like \([x/y (z\%)]\), and have changed throughout the manuscript where we find it appropriate.

8. Long-acting opioids: see comment from more reviewers.

9. Table 4. Yes, there are many p-values in the tables, and it is a good idea to use odds ratios with 95% CI in this table.

Answer to Kent Olson

1. A more thorough description of the Oslo pre-hospital system is added in the method section.

2. Lost to follow-up: see beginning of this letter.

3. There was no toxicology testing in the pre-hospital setting. The aim was to record the diagnosis and determination of toxic agents made by the health care workers exactly as it is done in the every-day clinical life. A sentence in the classification paragraph in the method section is added to describe this.

4. Yes, hypotension is most often defined as systolic BP less than 90 mmHg – also in Norway. Our experience is however that many patients have a transient mild hypotension without any clinical consequences, and we wanted to record hypotension that was more clinically important. Besides, acutely poisoned patients are often young, with normal (or low) BP compared to other patient populations. For most of these patients 90 mmHg will be well tolerated, and for some a normal value.

5. Transport to hospital: see beginning of this letter.

6. We agree – the sentence is changed.

7. We do not know why you did not receive Figure 1.

Answer to Paul Dietze

1. Re-orienting the discussion to a system-wide focus rather than the opioid focus:
   We agree that the system-wide aspects represent a novel approach and some of the study’s strengths, and have added some points that highlight this aspect in the discussion section. A large part of the discussion focus on opioids, but opioid is the largest agent group discharged from the pre-hospital setting, representing the most controversial aspect of the pre-hospital discharge – hence this focus.

2. Provide more detail of the different patterns of case characteristics within agent type:
   We welcome this suggestion, although there is a risk of overwhelming the paper with more details. Some agent-specific results are already presented (e.g. fig 2). However, we have now additionally provided some key variables within each agent group at the end of the results section.

3. More thoroughgoing review of the literature:
   We have acknowledged some of the suggested related work in the discussion section.

4. Longer-acting vs short-acting opioids: see beginning of this letter.

5. Ambulance level diagnosis changed after referral: see beginning of this letter.
6. **Terminology**: We have used the term “poisoning” as the widest expression, “overdose” is a more narrow expression often related to drug abuse related or self-harm poisonings. “Intoxication” is not used in this revision. We have tried to be more consistent throughout the paper.

7. More information about analysis strategy regarding adjusted Odds Ratio is added in the statistics section.

8. **Redundancy in the presentation of the results**: We have edited, and hopefully removed some of the duplications between text and tables.

9. “do” is changed to “to”.

We hope these changes have improved the paper, and we look forward to hearing from you again.

Sincerely yours,

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