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Title: Paramedic assist-requiring hypoglycemia in adults in southwest Ontario, Canada: a population-based retrospective cohort study

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Reviewer 1: Dr. Ali Elbeddini

Institution: Winchester District memorial Hospital, Ottawa, Ont.

General comments (author response in bold)

1. In paramedic reporting system, the Diabetes associated- hypoglycemia is hard sometimes to investigate whether is due to being diabetic or high dose of insulin or something else not related to Non-diabetic source.

Thank you very much for your comments and noting the gap. We agree that from the data contained within the paramedic reporting system it is not possible to distinguish whether the cause of hypoglycemia is diabetes-related i.e. too much insulin/oral antihyperglycemic agents such as secretagogues vs. non-diabetes-related cause i.e. sepsis or severe liver failure in someone either with or without a known history diabetes. This was added to the Limitations paragraph of the Interpretation section on page 15. We did include “documented diagnosis of diabetes” as a baseline characteristic but this may not necessarily be accurate, for example in cases where a hypoglycemic patient is found unresponsive alone and unable to provide any history. Over 80% of calls did involve patients in whom a diabetes diagnosis was documented but this also does not necessarily rule out a non-diabetes-related cause.

Reviewer 2: Dr. Morgan Hillier

Institution: Sunnybrook Health Sciences Centre, Sunnybrook Center for Prehospital Medicine

General comments (author response in bold)

I think this is an important paper addressing a potential care gap for patients with sub-optimally controlled diabetes. There is potential to really highlight the importance of paramedics and a potential role for identifying these at-risk patients and providing information to their primary medical provider as well as paramedic initiated referral. Thank you for your work in this area. Fantastic to hear that you're working on a direct referral process for patients with SHG!!

Major Issues:

None

Thank you for your review and appreciate your acknowledgement of the importance of research in this area.

Minor Issues:

Abstract:

1. I would suggest slight caution in your interpretation of the results of your study. You state that physicians managing diabetes care ARE unaware of hypoglycaemic episodes because patients were not transported. I would suggest that physicians MAY not be aware both because patients may call their primary provider despite not being transported and because the primary provider may not be informed even if the patient is

transported to ED. I do however very much appreciate your messaging that paramedics should have the means to communicate these episodes to the appropriate care providers and this should be highlighted as much as possible.

Thank you for your comment. We agree, and have revised the Interpretation section of the Abstract to include the wording "...physicians managing diabetes care may be unaware..." on page 3.

Introduction:

2. I wonder if you might have the ability to expand slightly on paramedic scope of practice PCP vs PCPIV vs ACP as scope of practice varies by province. This becomes clear later in the paper but if possible, would be nice to have this clear to the average reader from the start.

Thank you. We have revised the Introduction to include the section on the paramedic scope of practice earlier, on pages 4-5.

Methods:

3. Page 5: The authors state that they included ACRs that were coded as paramedics providing treatment for hypoglycaemia as inclusion criteria. What is not addressed is calls for patients who were hypoglycaemic where treatment was not provided by paramedics (i.e. oral glucose by family or first aid provider). Was this data captured? I think this should be addressed as it may represent a larger number of patients having hypoglycaemic episodes.

Thank you for the comment. Yes, we agree that many patients with severe hypoglycemia may be treated by family or another first aid provider prior to paramedic arrival and thus subsequently are not treated by paramedics. However due to limitations of the ACR coding and available information, it was not possible to accurately identify these patients with certainty. We gave significant thought to all the options when designing the study.

There is no ACR problem code specifically for hypoglycemia, rather only a code for "diabetic emergency" (problem code 83), which includes both hypoglycemia and hyperglycemia. Thus, problem code 83 had to be combined with the initial capillary blood glucose (CBG) to distinguish hypoglycemia calls from hyperglycemia calls.

However, using the combination of problem code 83 and CBG < 4.0 mmol/L would miss calls where neither the primary and/or final primary problem code was a diabetic emergency but where treatment for hypoglycemia was also given. This may occur in calls with primary problem codes for i.e. altered level of consciousness or sepsis and importantly cases (such as in your comment) where patients were treated by family or others prior to paramedic arrival and thus the CBG may have been > 4.0 mmol/L when checked by paramedics. Therefore, there is no optimal threshold to distinguish between a code 83 call where a patient was hypoglycemic and treated by others prior to paramedic arrival vs. a code 83 call where someone was hyperglycemic.

We then considered using problem code 83 without treatment for hypoglycemia (to include those calls where patients may have been treated by others prior to paramedic arrival) or paramedic treatment for hypoglycemia, regardless of problem code as the inclusion criteria. This resulted in 11053 calls, as shown below:

a) paramedic treatment for hypoglycemia (regardless of problem code) (n=9361)
(these are the ones that were ultimately included in our study)

b) problem code 83 without paramedic treatment for hypoglycemia (n=1692) –
 which included the following calls:

	N=1692	
Initial CBG < 4.0 mmol/L	276 (16.3%)	hypoglycemic but not treated by paramedics
Initial CBG 4.0-14.9 mmol/L	885 (52.3%)	hyperglycemic OR hypoglycemic and treated by someone else (not treated by paramedics)
Initial CBG not documented	524 (31.0%)	
Initial CBG not available (error/no reading)	7 (0.4%)	

Data are N (%)

Initial CBG < 4.0 mmol/L – it is not clear why the patients in these 276 calls were not treated by paramedics, despite being hypoglycemic on arrival. (This would be in contradiction to the paramedic medical directive where the hypoglycemia treatment protocol would be required for this level of CBG). It is possible that family/other individuals treated the patient while in the presence of paramedics so the paramedics themselves did not administer any treatment.

Initial CBG 4.0–14.0 mmol/L or not documented or not available – it is not possible to distinguish whether these 1416 calls were for patients with hyperglycemia or with hypoglycemia that was treated (i.e. by family member/other individual) prior to paramedic arrival.

Thus, we ended up using the sole inclusion criterion of “paramedic treatment for hypoglycemia” (regardless of primary/final problem code) to ensure we only captured those calls for definite hypoglycemia. We recognize that this missed 276 calls where the patient was hypoglycemic but was not treated by paramedics including those calls where a patient was hypoglycemic and was treated by someone else prior to paramedic arrival and thus did not receive paramedic treatment.

Assuming all of the 1416 calls above were for hypoglycemia that was treated by others prior to paramedic arrival (instead of for hyperglycemia), if this number was added to the final 9185 calls included in our study they would represent a small proportion (13%) of the total study calls. Finally, we had to assume that those (still potentially serious low sugar calls) are by definition not paramedic assist-requiring hypoglycemia calls. We do appreciate this limitation and have added a more concise explanation of this in the *Limitations* paragraph in the Interpretation section on page 14.

4. Was there a difference in transport vs refusal when looking at glucagon vs IV D50? I always wonder with the onset time of glucagon being slower that the medics may have already initiated transport when the patient rouses. Is this something you looked at and on which you can comment?

We did not directly compare glucagon vs. IV D50 in those with and without transport refusal. We did include hypoglycemia treatment as a covariate in our univariate and multivariate regression models, categorized as i) oral glucose alone, ii) IV dextrose (alone or with oral glucose), iii) any IM glucagon (alone, with oral glucose or with IV dextrose), iv) all 3 (oral glucose, IV dextrose, IM glucagon) with oral glucose alone as the referent group. On univariate analyses, calls with the treatments IV dextrose (alone or with oral glucose), any IM glucagon (alone, with oral glucose or with IV dextrose) and all 3 (oral glucose, IV dextrose, IM

glucagon) were associated with higher odds of hospital transport vs. calls with oral glucose alone as treatment. However, on multivariate analyses, these associations were no longer significant.

5. Page 7: are you able to address why lower acuity CTAS was associated with a higher rate of hospital transport? This seems counterintuitive.

Thank you for the comment. This seemed counterintuitive to us also so the univariate and multivariate analyses were reviewed again more closely and an error was found and corrected, which subsequently affected the final results. We apologize for this error—during the coding process, we accidentally coded in reverse and mistakenly considered a numerically higher CTAS to be more acute (instead of less acute) but this was reviewed and corrected. The corrected results are more in keeping with what would be expected, i.e. higher acuity CTAS was associated with higher odds of transport.

For clarity (and word count limits), the text on page 7 was deleted and instead the results are presented in tabular form as odds ratios (95% CI) in new Table 3. On univariate analyses: age (years), documented diabetes diagnosis, OHA use, GCS <9, CTAS ≤ 3, “diabetic emergency” as final primary problem code, and IV dextrose (alone or with oral glucose), any IM glucagon, and all 3 (glucose, dextrose, glucagon) vs. oral glucose as referent group were significant positive predictors of hospital transport while male sex and capillary blood glucose (mmol/L) were significant negative predictors of transport. However, on multivariate analyses, CTAS ≤ 3 was the only significant independent positive predictor of hospital transport while documented diabetes diagnosis, capillary blood glucose and overnight calls (18:00 to 06:00) were significant independent negative predictors of hospital transport.

Minor Edits:

6. Page 5: ACR stands for “ambulance call report” not “ambulance call record” as defined in the MOH documentation standards.

Thank you for noting this oversight. This has been corrected in the Methods section, now on page 6.

7. Page 5 suggest should be “ACRs” plural not “ACR for all calls”

We have revised the manuscript so that the Methods section now contains the first use of the acronym ACR, and have revised it to be plural, as suggested, now on page 6.

8. Page 5: probably assumed by most but would clarify that glucagon is given IM to be clear

The route of administration for glucagon has been added, now on page 6, and also in Table 1 (and in the new Table 3).

9. Page 6: suggest adding “an”: There were 9185 paramedic calls in which treatment for hypoglycaemia to AN adult patient was provided during...

This change was made on page 8 (though further revisions were also made to the sentence).

10. Page 7: you have an extra period after "calls when transport to hospital was not refused. . A higher..."

The extra period was deleted (but then the sentence has now been omitted in the revised manuscript due to word count limitations).

11. Page 8: suggest changing "1" to "one" in second paragraph of interpretation.

The "1" was changed to "one" (but then the sentence was subsequently omitted in the revised manuscript).

12. Page 9: We would generally say "ACPs and PCPs" plural, rather than "ACP and PCP". This comes up numerous times on this page. Also to clarify (sorry being very specific here): All ACPs can administer D50 IV. It is only the PCPs with specialized training to do IVs that have the different scope of practice from normal PCP medics. Your statement implies that some ACPs are specially trained to give IV dextrose.

Thank you. The suggested changes were made (to add "s" to make plural as "ACPs" and "PCPs" throughout the manuscript. As well, the wording was revised on page 11 (moved ACPs after PCPs-IV) to clarify that only PCPs require specialized IV training to give IV dextrose while all ACPs can administer IV dextrose.

13. Page 12 Conclusion: I would strongly suggest highlighting the potential for the paramedic's role in identifying these at-risk patients and helping to facilitate referral to their primary provider!! I think that is a very important - perhaps the most important - conclusion of this study!!

Thank you. As per your suggestion, we have revised the Interpretation in the Abstract on page 3 and the Conclusion section in the manuscript on page 16 to highlight the potential role paramedics may play in identifying patients at high risk of recurrent paramedic assist-requiring hypoglycemia and communicating with their care providers

Reviewer 3: Prof. Heiner Berthold

Institution: Bielefeld Evangelical Hospital

General comments (author response in bold)

The present study is reporting a population-based retrospective cohort study from South West Ontario. The authors investigated the incidence and kind of severe hypoglycemic episodes (as consequence of diabetes treatment) using call protocols from paramedics.

Their hypothesis was that a proportion of patients with hypoglycemia requiring help do not present to the hospital. They found over a period of >6 years using 9185 data sets an estimated annual incidence rate of about 1 percent per patient year (in patients with DM), as compared to an incidence rate of 0.8 to 3.2. in the literature. Furthermore they found that in about one quarter (24.5 percent) patients "refused hospital transport". Their main conclusion is that due to this proportion treating physicians often are not aware of the occurrence of hypoglycemic episodes and that this represents a significant care gap.

The manuscript is clearly written, addresses an important health care issue, uses all in all good methodology and contributes important new insight into the research question. However, I have some concerns about their conclusions, which question the validity of the results.

I have 2 major concerns.

1. In their development of the hypothesis (page 4, 2nd para) they write, "If paramedics are called for a SHG event, patients may subsequently refuse hospital transport". According to their data, patients refused being hospitalized in about one quarter of the cases and they identified (using logistic regression analysis) parameters that determined the patients being hospitalized or not.

I assume that hospitalization was not in every case necessary and after paramedic deployment the cases were closed. Thus, the dichotomization between hospitalization and not due to refusal of the patient does not seem logical. There may be third or more options.

It would interest me in how many cases the paramedics decided that the medical problem was resolved and hospitalization was not further necessary. I just think that refusal by a patient of being hospitalized is not the only explanation of not taking him to the hospital. In this context, see also my concerns below about lack of information about the social situation.

During the time period of the study data (2008-2014), paramedic standard of care protocols in Ontario, Canada did not allow for paramedics to “treat and release” patients, i.e. paramedics were required to transport patients to hospital for assessment, although patients could sign a release form if they wished to refuse treatment or transport. More recently, as of June 2020, new models of paramedic care been approved in Ontario where paramedics have the option in low acuity cases to a) transport patients to a non-hospital publicly funded community health care facility for care (“alternate destination standard”) or b) treat the patient on scene then refer to a health care provider within the home or community (“treat and refer standard”). A “treat and release standard” is still currently under consideration and not yet approved. Thus, for the calls included in this study from 2008-2014, paramedics were mandated to transport patients to hospital and were not permitted to decide that transport was not necessary. We did note the reasons for non-transport in Table 2; although patient refusal was the main reason (92.4%) for non-transport, there are 4 other reasons for non-transport: patient in police custody, no patient found, patient deceased, transported by other ambulance. Given that hospital transport was mandated by paramedic standard of care at the time, and that patient refusal was the main reason for non-transport, we respectfully maintain that the dichotomy of “refusal of transport” and “no refusal of transport (i.e. includes transport as well as the 4 other reasons for non-transport) is reasonable.

2. There is hardly any information about the social aspects, most importantly patient's form of living (living alone, living with partner/family, living in assisted living situations or nursing home).

I believe the form of living (and therefore the caretaking of the patient before and after a hypoglycemic episode) plays one of the biggest roles in the decision to hospitalize a patient for further clinical surveillance or to leave him/her in his/her usual environment. Patients that live alone may have a higher likelihood being transported into the hospital than patients having partner/family.

Lack of these data poses a substantial bias to the interpretation of this cohort study. I am not sure if this bias can be resolved because they don't have these data. At least this aspect should be discussed in the limitations section.

Thank you for your comments. As noted in our reply above (Reviewer 3, comment #1), paramedics in Ontario were mandated to transport patients to hospital, i.e. paramedics did not have the ability to decide that transport was not necessary. However, we strongly agree with your comments regarding the importance of social context and its possible influence on the patient's decision to potentially refuse transport to hospital post-paramedic assist-requiring hypoglycemic event. Thus, as in our response to a similar comment by the Editors and Statisticians (comment 1c for Table 1 under Tables/Figures): the Ontario ambulance call reports do not have fields specifically for marital status or living arrangements. There is a field for "pick-up code" where 1 of 26 letter codes represent the pick-up location, and these locations include "long-term care" and "retirement home" as well as private dwellings (i.e. "apartment/condo building" and "house/townhouse") and indoor and outdoor public settings (i.e. "indoor shopping mall", "fairground/park"). However, we chose not to extract pick-up location data for this study as the pick-up location may not necessarily be the patient's residence but in retrospect, had we collected this data, it may still have provided some useful information. Mention of this was added to the *Limitations* paragraph of the Interpretation section on page 14. In any future studies, we will include data on social aspects as we agree that this context is very important.

Minor

1. Please also report glucose concentration units in mg/dl in brackets (many readers are used to that more than to SI units) [Editor's note: CMAJ Open style is to use SI units.] **Thank you. While we appreciate that many readers are used to reporting glucose in mg/dl, we have kept the units as mmol/L as per the preferred style of CMAJ Open.**

2. Please comment in more detail about the surprisingly high use rate of glucagon. **We revised and clarified the discussion on glucagon use on pages 11-12 of the Interpretation section to include more detail: our study had a high proportion (73.3%) of calls attended by PCP (who can administer glucagon but not IV dextrose). Also, compared to the Sinclair et al. study, our call patients may have been of higher overall acuity necessitating glucagon use. Finally, we did not have information if patients had been treated by others prior to paramedic arrival, but perhaps if they had been already treated with oral glucose prior to ambulance arrival but were still hypoglycemic, paramedics may be more inclined to use glucagon.**

STROBE cohort-reporting guidelines have been followed and declared.

Potential COI have been indicated.

Contributions and authorship have been declared.

Thank you for reviewing that the above requirements have been met.