Variability in the Treatment of Prehospital Hypoglycemia: A Structured Review of EMS Protocols in the United States

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VARIABILITY IN THE TREATMENT OF PREHOSPITAL HYPOGLYCEMIA: A STRUCTURED REVIEW OF EMS PROTOCOLS IN THE UNITED STATES

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ABSTRACT

Background: In many industries, limiting variability in process has been associated with a reduction in errors. Hypoglycemia is a common prehospital diabetic emergency for which most EMS systems have a treatment protocol.

Objective: To examine the treatment variability for prehospital hypoglycemia within EMS protocols in the U.S.

Methods: EMS protocols were reviewed in a structured fashion from 2 sources: the website www.emsprotocols.org and through manual identification from the 50 largest populated cities in the U.S. Data was abstracted by trained investigators regarding the concentration of glucose recommended for the parenteral reversal of hypoglycemia, clinical treatment thresholds, dose recommendations, follow-up care, and non-transport policies. Descriptive statistics were used to summarize the findings. We also reviewed these EMS protocols for the protocol’s effective date, the presence of a specific hypoglycemia patient non-transport policy, the use of dilutions of hypertonic dextrose for pediatric patients, glucagon use, and CBG or GCS for patient follow-up.

Results: Protocols were retrieved from 185 EMS agencies of a variety of sizes across the U.S. Seventy percent specified only D50 for the treatment of hypoglycemia in adult patients, 8% only D10, and 22% either D10 or D50. Most protocols (85%), which used D50, specified concentration dilutions for pediatric patients. The most frequently specified initial dose of glucose was 25 g of glucose for adults (73–78%), 0.5 g/kg for pediatric (70%), and 0.5 g/kg for neonates (45%). The median blood glucose level threshold for treatment was 60 mg/dl for patients of all ages, but the mean treatment threshold levels for adults, pediatric patients and neonates were statistically different (p < 0.0001). Nearly all protocols (97%) allowed for the use of glucagon in the absence of vascular access. Patient follow up with a repeat CBG was recommended in 32%, both CBG and GCS in 31%, GCS only in 4%, and no follow-up was specified in 33% of the protocols. A specific policy permitting the non-transport of select patients whose hypoglycemia had been corrected was noted in slightly less than half (49%) of the protocols.

Conclusions: In the U.S., EMS protocols for the treatment of hypoglycemia vary significantly. Further studies are warranted to determine the factors underlying this variability and effects on patient outcomes.

Key words: hypoglycemia; emergency medical services (EMS); variability; clinical practice variations

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INTRODUCTION

Diabetes affects over 6 million adults in the U.S. and its prevalence continues to increase. The current approach to management of diabetes mellitus calls for tight regulation of blood glucose levels through the use of dietary control, exercise programs, and medications. Two of the more commonly used medications, parenteral insulin and oral sulfonylureas, place patients at risk for the development of hypoglycemia, which is one of the more commonly encountered prehospital emergencies.1

Fifty milliliters of a 50% solution of glucose containing 25 g of glucose (also called an “amp of D50”) administered parenterally has been used for years to treat hypoglycemia emergently in the field. Although this dose is effective at correcting hypoglycemia, it also provides the patient with supraphysiologic levels of glucose. This D50 concentration is markedly hypertonic and associated with a risk of tissue necrosis in the event of extravasation. Furthermore, when used in children, the formulation must be diluted on-scene while attending the medical emergency, which places the pediatric patient at risk for dosing errors.

Glucose and dextrose are synonyms in common use for D-glucose. Throughout this paper, we will use the word “glucose” or the abbreviation of “D” along with a number representing % concentration, i.e., D50.

In the spring of 2013, our EMS system, as well as many others in the United States, were confronted with an acute shortage of D50 due to its lack of availability from commercial suppliers because of manufacturing delays and increased demand.2 3 Faced with this challenge, some EMS systems replaced the unavailable D50 with a D10 (10% glucose) concentration, which has
several desirable features and is used in a number of EMS systems around the world, including the U.K. and Singapore.

The purpose of this study was to examine the recommended concentration of hypertonic glucose solutions for the parenteral treatment of hypoglycemia within EMS protocols in the United States. We also investigated the initial and subsequent glucose doses, the recommended blood glucose threshold for treatment, routes of parenteral administration, the availability of glucagon to treat hypoglycemia in the event that vascular access was not obtainable, recommendations for post treatment patient monitoring, and non-transport policies for treated patients.

METHODS

Study Design

Study Population and Setting
Two convenience samples of EMS protocols: those with url links on the publicly accessible website http://www.emsprotocols.org4 and those from the 50 largest populated cities in the United States.5 Copies of the EMS protocols were obtained by downloading from the http://www.emsprotocols.org website, reviewing them on the Paramedic Protocol Provider app,6 downloading from the EMS agency website, or contacting the EMS agency or medical director.

Variables and Data Collection
Protocols were reviewed by the research team in a structured format using a standardized data collection tool for abstracted data elements (Table 1), which had been piloted and refined after the first 10 protocols. All of the protocols were abstracted or reviewed by the lead author.

Statistical Analysis
Descriptive statistics and chi-square were used to characterize findings. Means were compared with ANOVA (parametric) and the Kruskal-Wallis test (non-parametric).

Due to concerns that there might be a significant difference between EMS protocols from the 50 largest US cities and those listed on www.emsprotocols.org, the data were analyzed trichotomously as www.emsprotocols.org listing only, 50 largest U.S. cities only, or listed in both. We did not detect a significant difference between these groups in regard to the use of D50, D10 or both for adult patients. All further analyses were performed on the entire group of 185 EMS protocols.

Research Ethics Review
This study was reviewed and approved by the Oregon Institute of Technology (OIT) Institution Review Board (IRB).

RESULTS

We retrieved 185 sets of EMS protocols: from the 50 largest populated U.S. cities and 170 from www.emsprotocols.org; 35 were listed in both places.

We reviewed EMS protocols from 46 of the 50 US states and the District of Columbia (Figure 1). With regards to type, 11% appeared to be statewide protocols, 32% applied to a region, 38% to a county, 16% to a city, and 3% to a specific EMS agency. Almost all the EMS protocols were relatively recent with 68% having an effective date within the prior year and 96% within the prior 4 years.

The majority (70%) of the EMS protocols reviewed recommended use of only D50 for the treatment of adults with hypoglycemia. Only 8% called for the use of D10 exclusively. Either D50 or D10 use was allowed in 22% of the protocols; some specified that D10 was only to be used if D50 was not available and a few noted a preference for the use of D10.

An initial dose of 25 grams of glucose for adults was recommended in three-fourths of the EMS protocols for both D50 and D10 (Table 2). Other protocols recommended a smaller dose, usually 10-12.5 g or to titrate to effect. The subsequent adult dose was similar, although it was not specified more than one-third of the time. An initial dose of 0.5 g/kg of hypertonic glucose for pediatric patients was specified in more than two-thirds of the EMS protocols. Most of the rest called for a higher dose, up to 1 g/kg, with a few specifying a dose of less than 0.5 g/kg or not mentioning a specific dose. The most commonly specified dose for subsequent pediatric administration, if needed, was 0.5 g/kg, although a subsequent dose was noted in only one-quarter of the protocols. The most common initial dose for neonates was 0.5 g/kg in just less than half of the protocols. An initial neonatal dose was not listed in a quarter of the protocols and a subsequent neonatal dose was listed very infrequently.

The blood glucose level defining hypoglycemia requiring treatment varied from 30–120 mg/dl. The mean threshold levels for adults, for pediatric patients, and for neonates, were statistically different (Figure 2), although both the median and mode blood glucose thresholds for the treatment of hypoglycemia were 60 mg/dl for patients of all ages.

Of the 170 protocols calling for the use of D50, 85% specified dilution when treating children to D25 (25%
TABLE 1. Data elements abstracted from EMS protocols

- Protocol coverage location: state, region, county, city, agency
- Protocol effective date
- Concentration of hypertonic glucose specified for adult, pediatric, and neonatal patients
- Initial and subsequent doses of hypertonic glucose for adult, pediatric and neonatal patients
- Blood glucose treatment threshold for hypoglycemia in adult, pediatric and neonatal patients
- Presence of a glucagon protocol as an alternate treatment for hypoglycemia
- Parenteral route of hypertonic glucose administration: IV, IO (intraosseus) or both
- Follow-up criteria: CBG (capillary blood glucose) or mental status assessment such as GCS (Glasgow Coma Score)
- Presence of a specific EMS protocol allowing a patient treated for hypoglycemia to be released if appropriate conditions were met

A concentration of D10 or D12.5 for use in neonates was noted in almost two-thirds of the protocols with a quarter not specifying a concentration for neonates (Table 3). With regard to other specific information within these EMS hypoglycemia treatment protocols, intravenous (IV) or intraosseous (IO) administration of hypertonic glucose was permitted in two-thirds of the protocols, but IV use only in one-third. Glucagon use, if vascular access could not be readily obtained, was permitted in almost all of the EMS protocols reviewed. Patient monitoring after treatment using blood glucose levels (CBG) only was specified in one-third of the protocols, both CBG and patient mental status (or GCS) in almost one-third, only mental status (or GCS) in very few, and was not specified in one-third. A specific policy allowing for the non-transport of select patients whose hypoglycemia was corrected was noted in slightly less than half of the protocols.

**DISCUSSION**

The two most notable findings from this study are the predominance of D50 use for the treatment of hypoglycemia and the variability across EMS protocols in regards to the management of prehospital hypoglycemia in the U.S. Hypertonic glucose as a 50% concentration is a standard parenteral treatment for hypoglycemia.7 The continued recommendation for the use of D50 is surprising given the concerns about harmful effects of iatrogenic hyperglycemia, the extravasation risks of markedly hypertonic glucose solutions,8,9 and the safety concerns about dilution calculations for pediatric patients.10

The commonly recommended adult dose of D50 (25 g) and pediatric dose (0.5–1 g/kg following dilution to D25, D12.5, or D10) provide far more glucose than the body can utilize in a short time. Glucose is the primary brain fuel during normal activity with blood glucose levels maintained at about 100 mg/dl (5.5 mmole/L) through the action of number of hormones including, insulin, glucagon, and epinephrine.11 The blood content of a normal human is about 5 g in a 70 kg adult and 0.08–0.09 g/kg in a child. The use of “an amp of D50” in an adult provides about 5 times the amount of glucose in a normal adult’s blood; a commonly recommended pediatric dose12 of 0.5–1 g/kg of glucose (often at a more dilute concentration of D25, D12.5, or D10) provides 6–11 times the amount of glucose in a normal child’s blood. Basal glucose uptake is estimated to be 2.2 mg/kg/minute and can increase about three times this level (6.6 mg/kg/min)

![Figure 1. Distribution of EMS protocols collected.](image-url)
### TABLE 2. Hypertonic glucose dosages in U.S. EMS protocols

<table>
<thead>
<tr>
<th>Initial dose</th>
<th>Subsequent dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult D50</td>
<td></td>
</tr>
<tr>
<td>25 g</td>
<td>132 78% 58 34%</td>
</tr>
<tr>
<td>&lt;25 g</td>
<td>6 4% 4 2%</td>
</tr>
<tr>
<td>Titrate</td>
<td>32 19% 16 9%</td>
</tr>
<tr>
<td>Not listed</td>
<td>0 0% 92 54%</td>
</tr>
<tr>
<td>Adult D10</td>
<td></td>
</tr>
<tr>
<td>25 g</td>
<td>40 73% 20 36%</td>
</tr>
<tr>
<td>&lt;25 g</td>
<td>9 16% 9 16%</td>
</tr>
<tr>
<td>Titrate</td>
<td>4 7% 3 5%</td>
</tr>
<tr>
<td>0.1 g/kg</td>
<td>2 4% 2 4%</td>
</tr>
<tr>
<td>Not listed</td>
<td>0 0% 21 38%</td>
</tr>
<tr>
<td>Pediatric</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5–1 g/kg</td>
<td>39 21% 13 7%</td>
</tr>
<tr>
<td>0.5 g/kg</td>
<td>130 70% 32 17%</td>
</tr>
<tr>
<td>&lt;0.5 g/kg</td>
<td>6 3% 3 2%</td>
</tr>
<tr>
<td>Not listed</td>
<td>10 5% 137 74%</td>
</tr>
<tr>
<td>Neonatal</td>
<td></td>
</tr>
<tr>
<td>&gt;0.5–1 g/kg</td>
<td>17 9% 3 2%</td>
</tr>
<tr>
<td>0.5 g/kg</td>
<td>83 45% 7 4%</td>
</tr>
<tr>
<td>0.25–&lt;0.5 g/kg</td>
<td>10 5% 2 1%</td>
</tr>
<tr>
<td>&lt;0.25 g/kg</td>
<td>23 12% 6 3%</td>
</tr>
<tr>
<td>Not listed</td>
<td>52 28% 167 90%</td>
</tr>
</tbody>
</table>

*Percentages may not total 100% due to rounding.

Glucose uptake in adults has been noted to be as high as 23 mg/kg/min. The observation has been made that increased glucose concentration in blood perfusing the brain does not increase brain glucose levels. The intravascular administration over 1–3 minutes of “an amp of D50” provides an adult with 110–330 mg/kg/min of glucose and, at the commonly recommended pediatric dose of 0.5–1 g/kg, a child with 167–1,000 mg/kg/min of glucose. This approach to correcting symptomatic hypoglycemia in both adults and children provides much more glucose than the body can use during that time. Glucose may be similar to a number of other essential chemicals in the human body that can be harmful in excess, such as potassium, iron, water, and oxygen. Excessive glucose can cause post-treatment hyperglycemia complicating the care of the brittle diabetic patient. Furthermore, hyperglycemia has been shown to be a detrimental in several medical conditions including post-cardiac arrest and acute stroke.

When “an amp of D50” was first used to treat hypoglycemia in the middle of the last century, blood glucose measurements took hours or days. Now that nearly instant reading glucometers are standard equipment for most EMS agencies, it may be more desirable to titrate glucose administration to the patient’s condition, just as is now being recommended for the administration of oxygen and naloxone.

D10 (500 mOsm/L), one fifth as hypertonic as D50 (2,525 mOsm/L), while still hypertonic compared to blood plasma (285–295 mOsm/L), is less likely to cause extravasation necrosis and its use allows a single concentration of hypertonic glucose to be used for all age groups, thereby reducing the risk of dilution-associated medication calculation errors in the often challenging prehospital setting.

There is limited published data regarding the actual D10 use in EMS. An out-of-hospital randomized trial of hypoglycemic adults comparing treatment with either D50 or D10 in aliquots of 5 g of glucose reported a similar median time (8 minutes) for either concentration to return patients to a GCS of 15. This study also found that the use of D10 resulted in the administration of a lower total dose of glucose and less post-treatment hypoglycemia. More recently, a case series described the clinical course of 164 patients age 18 or greater treated with 10 g of glucose as D10 for symptomatic hypoglycemia. These authors found effective reversal of hypoglycemia with no adverse effects. In this series, one fifth of the patients required a 2nd dose of D10 and one patient required a 3rd dose.

### TABLE 3. Details of U.S. EMS hypoglycemia treatment protocols

<table>
<thead>
<tr>
<th></th>
<th>N</th>
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<tbody>
<tr>
<td>Neonatal</td>
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<td></td>
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<tr>
<td>concentration</td>
<td>D10</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>D12.5</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>D25</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>D50</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Not listed</td>
<td>48</td>
</tr>
<tr>
<td>Route of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration</td>
<td>IV</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>IV or IO</td>
<td>122</td>
</tr>
<tr>
<td>Glucagon protocol</td>
<td>Present</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>Not listed</td>
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</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
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<tr>
<td>assessment</td>
<td>CBG only</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>CBG and Mental status (GCS)</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Mental status (GCS) only</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Not listed</td>
<td>61</td>
</tr>
<tr>
<td>Non-transport protocol</td>
<td>Present</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Not listed</td>
<td>95</td>
</tr>
</tbody>
</table>

*Percentages may not total 100% due to rounding.
authors of a review of the limited literature comparing D50 and D10 concluded that both appear to be equally effective and that D10 was safer because of the reduction of risk of extravasation leading to tissue necrosis.21 In the U.K., for more than a decade, EMS protocols for the treatment of severe symptomatic hypoglycemia have specified the use D10 at a dose of 10 g of glucose in adults and 0.5 g/kg in children age 5 or less or weighing less than 40 kg.23

We also noted variability in U.S. EMS protocols for the management of hypoglycemia, including the blood glucose threshold for treatment, the initial and subsequent glucose doses, the potential routes of per- enteral hypertonic glucose administration (IV or IO), post treatment patient monitoring, and non-transport policies for treated patients. Although the median and mode glucose treatment thresholds were the same across all age groups, the means were significantly different with the range for neonates and higher for adults was lower. Glucagon use if intravascular access cannot be readily obtained was the one aspect of EMS hypoglycemia protocols for which was there was almost no variability. In at least one set of protocols, glucagon was not included because of the infrequency of use and the expense of the medication.

Variability has been noted in other studies that have looked at statewide EMS protocols,24 as well as EMS protocols for naloxone administration, pelvic binding,26 and blood glucose measurement in seizure patients which was associated with delayed seizure treatment.27 We believe that the frequently heard adage “If you’ve seen one EMS system, then you’ve seen one EMS system” applies to EMS protocols as well. As the body of pre-hospital and EMS knowledge and research expands and as EMS provider license reciprocity expands across the nation, EMS protocol standardization to reduce variability and reduce the risk of error is worthy of future consideration as has been suggested by the recently released NASEMSO Model EMS Guidelines.28

The NASEMSO Model EMS Guidelines for hypoglycemia call for a blood glucose treatment threshold of less than 60 mg/dL; 25 g of hypertonic glucose (in a concentration of 10–50%) in adults and 0.5–1 g/kg of hypertonic glucose (at a concentration of 10–25%) in pediatric patients; glucagon administration if vascular access is not readily obtained; post treatment monitoring with CBG and GCS; and a non-transport option if transport is refused, the patient has a post-treatment CBG of greater than 80 mg/dL, takes insulin and no oral medications to control blood glucose, returns to normal neurological status, can eat, and a reliable adult will be staying with the patient. Although the treatment threshold of 60 mg/dL is commonly used across current protocols, clinical symptoms may deserve consideration especially in patients with chronically elevated blood glucose levels. Somewhat problematic, these NASEMSO Model EMS Clinical Guidelines allow for variations in the hypertonic glucose concentration.

In many industries, limiting variability has been linked to a reduction in errors.29 As part of the effort to reduce errors in medicine,30 errors and safety in prehospital medicine have been investigated.31 Standardizing EMS protocols, in addition to standardizing medications,32 may be one way to reduce both variability and errors. EMS providers may relocate to different agencies or work in several different agencies and encounter different concentrations of glucose or hypoglycemia protocol differences that may not always be recognized in a timely fashion in the dynamic prehospital work environment. If there is no physiologic or scientific basis for protocol differences, treatment standardization may result in fewer errors and enhance patient safety.

In summary, given the supraphysiologic doses administered of D50 and the risks associated with the use of D50, future studies of EMS hypoglycemia treatment protocols in the U.S. should evaluate the possible transition to titrated D10 as an effective and safe option for all patients.

**Limitations**

There are several limitations to this descriptive survey, including sample selection, abstraction challenges, and the fact that we reviewed written protocols and not actual EMS practice.

We used 2 convenience samples of EMS protocols: one from a group of EMS agencies whose EMS protocols were internet-published and the other group from the 50 largest populated U.S. cities. We wanted to evaluate a spectrum of EMS protocols across the country and not focus on a specific region or size. The effective dates of the protocols suggest that most of them were recently reviewed or updated. This was a cross-sectional protocol study and we suspect that if we had conducted this study 5 years ago, very few agencies would have been using D10 and 5 years from now a greater proportion of EMS protocols will specify the use of D10.

As we abstracted EMS protocols to complete our data collection, we were able to determine many positive (Yes) answers, while negative (Not listed) answers could mean either not present or that we were unable to locate an answer. Some specific answers required interpretation, such as glucose doses or route of administration and may have had different answers in different places in one set of protocols. As examples, neurological monitoring might be mentioned as GCS or as mental status evaluations and diabetic-specific non-transport policy could be detailed or somewhat vague. The 185 EMS protocol sets reviewed displayed a variety...
of protocol styles in terms of format, topics and detail. We usually found specific medication protocols for hypertonic glucose and glucagon. Details of the treatment of hypoglycemia were found under the headings of hypoglycemia, diabetic emergencies, altered mental status, or loss of consciousness. The definition of children or pediatric patients was variable or not always specified. Neonatal or pediatric treatment protocols were sometimes combined with adult protocols, sometimes found in separate sections, and sometimes not present. In a given set of protocols, if a neonatal blood glucose treatment threshold was not found, then the pediatric threshold was used. Likewise, if a pediatric blood glucose treatment threshold was not found, then the adult threshold was used. We found inconsistency with regards to the route of parenteral glucose administration in a number of protocols from the same EMS agency, as glucose IV would be listed in one place and glucose IV or IO listed in another or different pediatric doses listed in the hypoglycemia treatment and glucose medication protocols. Policies regarding the non-transport of patients with hypoglycemia, when found, were under hypoglycemia, refusal, non-transport, or administrative headings.

Finally, written EMS protocols may differ from what actually transpires in practice.

CONCLUSION

In the U.S., EMS protocols for the treatment of hypoglycemia vary significantly. Further studies are required to determine the factors underlying this variability, the effects patient outcomes and the optimal EMS hypoglycemia treatment protocol.

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