ORIGINAL CONTRIBUTION
glucagon;
hypoglycemia, prehospital care

Glucagon: Prehospital Therapy for Hypoglycemia

Study objective: *This study evaluated the efficacy of glucagon for prehospital therapy of hypoglycemia in patients without IV access.*

Design: *Prospective clinical trial.*

Setting: *Prehospital in a busy, urban emergency medical services system.*

Type of participants: *Fifty consecutive patients presenting with documented hypoglycemia (ChemStrip BG® ≤ 80 mg/dL) and symptoms of decreased level of consciousness, syncope, or seizure were enrolled.*

Measures and main results: *Data collected included pretreatment (ChemStrip BG®) and post-treatment serum glucose (hospital assay) as well as assessment of level of consciousness by a quantitative measure, the Glasgow Coma Score, and by a qualitative scale (0 to 3). The mean pretreatment blood glucose of 33.2 ± 23.3 mg/dL increased after treatment to 133.3 ± 57.3 mg/dL. Qualitative level of consciousness increased from a mean of 1.26 ± .96 to 2.42 ± .94 and Glasgow Coma Score increased from a mean of 9.0 ± 4.19 to 13.04 ± 3.68. The mean time until response was 8.8 minutes in those who responded to both level of consciousness criteria 82% (41 of 50). Glucagon administered for hypoglycemia resulted in a glucose increase in 98% (49 of 50) with headache as the only side effect noted in 4% (two of 50) of patients (P < .0001).*

Conclusion: *Glucagon is safe and effective therapy for hypoglycemia in the prehospital setting. [Vukmir RB, Paris PM, Yealy DM: Glucagon: Prehospital therapy for hypoglycemia. Ann Emerg Med April 1991; 20:375-379.]*

Rade B Vukmir, MD*
Paul M Paris, MD, FACEP†
Donald M Yealy, MD, FACEP‡
Pittsburgh, Pennsylvania

From the Affiliated Residency in Emergency Medicine* and the Division of Emergency Medicine,† University of Pittsburgh; and the Center for Emergency Medicine of Western Pennsylvania,‡ Pittsburgh.

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Address for reprints: Rade B Vukmir, MD, University of Pittsburgh Affiliated Residency in Emergency Medicine, 230 McKee Place, Suite 500, Pittsburgh, Pennsylvania 15213.

INTRODUCTION

Treating patients with altered mental status due to hypoglycemia may be difficult. IV line access often cannot be obtained. The incidence of failed IV line access is minimal (4%; unpublished data, City of Pittsburgh Bureau of Emergency Medical Services [EMS]) in a random sample of patients encountered in this EMS system. However, it can be higher in the chronically ill who are predisposed to hypoglycemia. Venous cannulation is especially difficult in diabetics, who are prone to hypoglycemia because of peripheral scarring.[1]

A recent study established a minimum IV line insertion time of 2.71 minutes for medical patients.[2] Most studies have suggested longer times, especially for combative patients. Expeditious transport to a hospital is suggested in anticipation of central IV line access. However, central venous cannulation does carry a 10% complication rate.[3] Tenuous IV line access for D_{50} administration is not without hazard. D_{50} is hypertonic and acidic, resulting in tissue damage if extravasated.[4] Previous prehospital therapeutic options have included administration of Glucola, an oral agent used in glucose tolerance testing (75 g glucose); granulated sugar (4 g glucose); and Glutose, a gel-like supplement (35 g glucose for buccal administration) both with an aspiration risk; and D_{50} (25 g glucose) administered by nasogastric tube, with established procedural complications.[1,4,5] The efficacy of glucagon, a natural catabolic hormone, has been established for patients refractory to exogenous dextrose infusion but not documented in a systematic fashion for the prehospital population.

We examined the use of glucagon administered by IM or subcutaneous

routes for prehospital therapy of hypoglycemia.

MATERIALS AND METHODS

We conducted a prospective, nonrandomized trial of glucagon for prehospital therapy of hypoglycemia. Our study was approved by the medical director of the City of Pittsburgh Department of Public Safety using the doctrine of implied consent.[6] Fifty-four consecutive patients were enrolled during a six-month period. Inclusion criteria were symptoms of documented hypoglycemia and no IV line access. Exclusion criteria were known pheochromocytoma and pregnancy. Patients were administered glucagon in 1.0-mg doses for adults and 0.5-mg doses for children by subcutaneous or IM routes. Data included pretreatment glucose with an average of the range determined and post-treatment glucose (serum assay) recorded as an absolute value. Pretreatment serum glucose was not assessed in the patient population because IV line access could not be obtained by the paramedics in three attempts, a ten-minute time limit, or a clinical impression of poor likelihood of procedural success.

Response was measured as pretreatment and post-treatment level of consciousness (LOC) scores by paramedics in attendance and recorded by medic command personnel. LOC was assessed by a qualitative linear scale ranging from 0 to 3 with 3 being alert, 2 being responsive to verbal stimuli, 1 being responsive to painful stimuli, and 0 being unresponsive.

The patients also were assessed in a quantitative fashion using the Glasgow Coma Score ranging from 3 to 15. This means of assessment was well standardized and familiar to prehospital care providers but limited by its original design to assess mental status changes in patients with craniocerebral trauma. Retrospective analysis of hospital admission or emergency department records was performed to assess patient diagnosis and outcome.

Data analysis was performed with descriptive statistics, particularly mean ± SD, where appropriate. Comparisons between groups were performed with the Wilcoxon's two-tailed rank-sum test, Student's paired t test, and Fisher's exact test; α error was set at .05.

RESULTS

The survey population fulfilled standard altered response protocol with a decreased LOC in 82% of the patients (41 of 50), syncope in 10% (five of 50), and seizure in 8% (four of 50). The medical condition was hypoglycemia documented by ChemStrip BG® (Boehringer Mannheim, Indianapolis, Indiana) with 54% (27 of 50) having 0 to 40 mg/dL; 10% (five of 50) having 40 mg/dL; and 36% (18 of 50) having 40 to 80 mg/dL. The clinical setting was patients with difficult IV line access. Patients prone to hypoglycemia, including those with diabetes mellitus, alcohol or drug abuse, chronic renal failure, or congestive heart failure, made up 80% of those (40 of 50) with difficult IV line access in this study. Four patients were excluded for incomplete data; they improved enough clinically to refuse transport.

Analysis of patient demographics found that of those encountered, 52% (26 of 50) were female and 48% (24 of 50) were male with a mean age of 56.8 years and an age range of 4 months to 97 years; 49 of 50 were adults. A history of diabetes was found in 62% of the cases, with 29 of 50 patients using insulin, and two of 50 using oral hypoglycemic agents. The route of glucagon administration, which was determined arbitrarily, was IM in 46 of 50 and subcutaneous in four of 50.

Therapeutic intervention resulted in a significant mean increase in measured glucose of 100.1 mg/dL in patients given glucagon (Table 1). Clinical improvement was noted as a significant mean increase of 1.16 for qualitative and 4.04 for quantitative assessment of mental status ($P \leq .0001$; Table 1). This effect was noted at 8.85 ± 4.37 minutes in those responding to both LOC criteria (82%; 41 of 50). The only side effect noted was headache, which occurred in two of 50 patients.

Analysis of hospital records found that 35 of 50 patients had a primary diagnosis of hypoglycemia. They responded to treatment ("responders" group) with a significant increase of 1.4 for qualitative and 5.7 for quantitative mental status assessment (Table 2). The second group of patients (15) were those with a secondary diagnosis of hypoglycemia and extrinsic causes such as a cerebrovascular accident or sepsis accounting for their mental status change. This "nonresponders" group had an insignificant change of 0.40 for qualitative and 0.20 for quantitative mental status assessment (Table 2). However, measured glucose levels increased in 49 of 50 patients treated.

TABLE 1. *Effect of glucagon*

	Pretreatment	Post-Treatment
Glucose (mg/dL)	33.2 ± 23.3*	133.3 ± 57.3*
Mental Status		
Qualitative	1.26 ± 0.96*	2.42 ± 0.94*
Quantitative	9.00 ± 4.19*	13.04 ± 3.68*

*$P < .0001$.

TABLE 2. *Analysis of hospital diagnoses*

	Pretreatment	Post-Treatment
Responders (70%, 35/50)		
Qualitative	1.28 ± 0.98*	2.68 ± 0.50
Quantitative	8.48 ± 3.98*	14.05 ± 2.36
Nonresponders (30%, 15/50)		
Qualitative	1.33 ± 1.04	1.73 ± 1.27
Quantitative	10.13 ± 4.50	10.33 ± 4.50

*$P > .0001$.

DISCUSSION

Hypoglycemia is not a disease but a symptom complex associated with subnormal glucose levels that was first described by Claude Bernard in 1948.[6] Hypoglycemia is defined as serum glucose of 45 mg/dL or less; however, variation is noted and levels of 35 mg/dL are asymptomatic in certain populations, specifically, women and neonates.[7-10] Severity of symptoms is related to both the rate and extent of glucose decline.[11] Glucose decline is quantified as the "hypoglycemic index," enabling hypoglycemic symptoms to occur within a normoglycemic range.[12] This is the basis for the inclusion of ChemStrip BG® readings of 40 to 80 mg/dL in the hypoglycemic range for our present study. Hypoglycemia was found to be associated with decreased LOC, seizures, syncope, and focal neurologic deficits, and is the presenting complaint in 3% of ED visits.[13]

The majority of our patients (82%; 41 of 50) presented with altered LOC compared with a prospective study of

125 hypoglycemic patients in which 52% presented with coma, 30% with LOC, 7% with seizures, and 2% with hemiparesis, with an overall mortality rate of 11%. Syncope was attributed to a metabolic cause in 30.6% of patients of whom 14% had abnormal glucose tolerance testing, whereas seizures were associated with metabolic abnormalities in 10.1% to 16.5% of patients.[13-15] Hypoglycemia can also result in reversible, decorticate posturing or focal deficits, especially hemiplegia.[16,17] Coma was attributed to metabolic encephalopathy in 60% of the patients studied by Plum and Posner.[18]

We found that the population at risk for hypoglycemia accompanied by difficult IV access included those with diabetes mellitus (59.3%), drug (11.1%) or alcohol (14.8%) abuse, or chronic renal failure and congestive heart failure (16.6%). Patients with diabetes have an 8% (range, 4% to 30%) incidence of hypoglycemia with a 4% mortality rate.[19] Specifically, type I and, to a lesser extent, type II diabetics are predisposed to hypoglycemia because of insulin and oral hypoglycemic agent use or autonomic neuropathy blunting the response of counter-regulatory hormones.[20]

Hypoglycemia secondary to alcohol ingestion is the result of increased use of glycogen stores and decreased glucose synthesis as alcohol metabolism shifts the NADH-to-NAD ratio to its reduced form, increasing cyclic adenosine monophosphate (cAMP) to suppress the tricarboxylic acid cycle.[21-24] It has been suggested that alcoholics are refractory to glucagon therapy because of depleted glycogen reserves.[25] However, endogenous glucagon production is elevated in alcoholics.[26] This suggests that glucose homeostasis in alcoholics is glucagon dependent and that glucagon therapy may be preferable to dextrose infusion for refractory hypoglycemia in susceptible patients.[26] There were no patients with a history of alcohol abuse (14.8%) refractory to glucagon in this study.

Congestive heart failure is associated with hypoglycemia resulting from malabsorption due to passive intestinal congestion, liver dysfunction, and increased glucose use by ischemic tissue.[27] Patients with chronic renal failure have demonstrated hypoglycemia due to impaired renal glucogenesis, increased insulin sensitivity, and decreased glycogenolysis.[28]

The side effects of hypoglycemia are significant and include cardiac, neurologic, and psychiatric dysfunction.[29] Hypoglycemia is related to myocardial ischemia due to sympathoadrenal discharge resulting in increasing heart rate, contractility, and afterload[30] and manifests with premature atrial and ventricular contractions.[31] Early research examining hypoglycemic brain damage originated from insulin shock therapy for psychiatric dysfunction.[32] The study revealed selective neuronal destruction of the middle cerebral cortex and basal ganglia correlated with the duration of hypoglycemia, due to an endogenous "excitotoxin" related to decreased glutamine and increased aspartate as carbon skeletons are scavenged for gluconeogenesis.[32,33] Encephalopathy, cognitive dysfunction, and abnormal personality profiles have been reported as a result of prolonged hypoglycemic episodes.[34,35]

The severity of side effects of hypoglycemia may warrant aggressive therapy, assuming importance when considering diagnosis.[36] Serum glucose determined by autoanalyzer methodology is recognized as the testing standard. Prehospital determination of blood glucose was first accomplished using Dextrostix® (Ames Co, Inc, Elkhart, Indiana), a blood reagent strip based on the glucose oxidase test.[37] The most recent addition is Chemstrip BG®, using the glucose oxidase-peroxidase reaction. Glucose oxidase strips are free of systematic error at low glucose levels, replacing reduction testing, which often overestimated glucose by 20 mg/dL in 5% of patients.[37] Glucose oxidase strips are accurate in the glucose range of 40 to 400 mg/dL,[38] with clinical efficacy in the hypoglycemic range. Initial experience with DextroStix® found a 16% false-negative rate with glucose overestimated,[39] but ChemStrip BG® is the superior mode of testing with no cases of undiagnosed hypoglycemia in 62 subjects.[40]

Thus, because of a study design limited to patients without IV line access, thereby minimizing ethical considerations, comparisons of pre-treatment and post-treatment serum glucose were not performed. However, the accuracy of ChemStrip BG® in the hypoglycemic range provided a valid, semiqualitative approximation of serum glucose that allowed analysis of glucose trends in our study.

The physiological response to hypoglycemia is the release of endogenous counter-regulatory hormones resulting in a twofold to fourfold increase in glucagon and cortisol and a 20-fold increase in growth hormone and epinephrine.[41,42] Glucagon is the most important of the counter-regulatory hormones and is responsible for 75% of basal hepatic glucose production.[42-45]

Glucagon was first isolated as a hyperglycemic contaminant of porcine insulin, and the term was coined by Kimball and Murrow in 1923.[46] It is a natural hormone comprising 29 amino acids produced by the α-islet cells of the pancreas.[47,48] Immunoreactive glucagon comprises four discrete fragments with true glucagon (molecular weight, 3,500 kDa) and has the highest activity available as a 1.0-mg unit dose in a lactate-glycerin-phenol vehicle.[47-49]

The mechanism of glucagon is to counteract the effects of insulin. Glucose metabolism proceeds through the Embden-Meyeroff pathway and the hexose-monophosphate shunt; it is dependent on the ratio of insulin (anabolic) to glucagon (catabolic) hormones (normal value, 0.6).[45,50] The principal intracellular mediator of this response is cAMP, which responds to a glucagon infusion of 200 nmol/kg with a twofold increase in hepatic cAMP, and reaches a maximum level at 40 minutes.[43,49] The mechanism involves glucagon stimulating adenylate cyclase, cAMP, and protein kinase, which activates glycogen phosphorylase, thereby increasing glycogenolysis; inactivates glycogen synthase, thereby decreasing glycogenesis; and inactivates F-2,6-phosphorylase, thereby increasing gluconeogenesis.[51]

Glucagon increases serum glucose by its effects on hepatic, muscle, and adipose tissue. The liver undergoes an increase in glycogenolysis, resulting in a 70% to 80% glucose increase; gluconeogenesis results in a 20% to 25% glucose increase and a glycogenesis decrease.[8,29,52] Muscle undergoes a decrease in protein syn-

thesis and an increase in proteolysis, where alanine is converted to lactate and pyruvate.[8,29,52] Adipose tissue undergoes decreased lipogenesis and increased lipolysis and ketogenesis, where triglycerides are converted to free fatty acids and glycerol.[29,51,52]

The indications for glucagon use include insulin overdose, food bolus impaction, pancreatitis, as an inotropic agent, and in gastrointestinal radiology to enhance mucosal detail in double-contrast studies.[53] Endogenous glucagon production is 0.13 mg in 24 hours.[54] The dose of glucagon is 0.1 to 0.3 mg/kg, resulting in a 1.0- to 2.0-mg dose for adults and a 0.33- to 2.0-mg for pediatric patients.[39,48] A study of adult patients found similar efficacies for a 1.0- or 2.0-mg dose with decreased side effects with the recommended 1.0-mg dose.[55]

Onset of action is 15 minutes, as suggested by a study in which intraportal glucagon infusion tripled glucose output.[56] The route of administration includes IV with onset at five minutes, IM with onset by 15 minutes, subcutaneous with onset at 30 to 45 minutes, or nasal with 50% absorption of the other routes.[47,55,57] Thus, the preferable route of administration is IM or subcutaneous with equal increases in glucose at 20 minutes and sustained effect versus a peak action at five minutes for IV administration followed by rapid disposition of clinical effect.[58] Exogenous glucagon has a half-life of ten minutes with a 90-minute duration of effect, as degradation proceeds by hepatic and renal mechanisms.[59]

There are no absolute contraindications to glucagon administration. Relative contraindications include insulinoma associated with paradoxical hypoglycemia, pheochromocytoma with an incidence of 0.1% and a resultant release of catecholamines causing hypertension, and pregnancy where glucagon is a category B untested drug.[48,60] However, studies with pregnant rats found no damage using doses 90-fold to 120-fold that of the human dose.[48] Glucagon was administered to one pregnant woman in this study with a favorable result.

The side effects of glucagon are mild, transient, and approximated by placebo.[47] Reported symptoms include nausea (35.7%), dry mouth (21.4%), and headache (15.4%) compared with the single side effect of headache noted in 4% (two of 50) of our patients.[48] Headache is attributed to physiologic resistance to glucagon-increasing vascular reactivity to other hormones.[61] Less common reactions, including diarrhea, thrombophlebitis, erythema multiforme, and a generalized allergic reaction proportional to insulin contamination, are minimized in newer glucagon preparations.[48,53,62,63]

Prior experimental evidence for the efficacy of glucagon is sound, but clinical trials have been limited. The effect of glucagon is described in adults in whom glucose is increased from hypoglycemic levels to 119 mg/dL within 28 minutes with a duration of two hours compared with the increase to 133 mg/dL within 8.82 minutes in our study.[47] This effect is quantified as an increase in serum glucose of 45 mg/dL in adults and 132 mg/dL in pediatric patients.[64,65] Clinical evaluation of glucagon as sole therapy for hypoglycemia found this to be a successful treatment modality.[66,67] Comparison trials found glucagon to be equal to dextrose infusion and superior to oral glucose supplementation.[55,68]

Our study demonstrated a glucose increase of 100.2 mg/dL (range, 33 to 274 mg/dL) for glucagon compared with 166.0 mg/dL (range, 37 to 370 mg/dL) for D_{50} infusion demonstrated by Adler in a prospective study of normal patients.[69] Thus, this therapeutic intervention provides a predictable, stable improvement in serum glucose and, subsequently, mental status; over-correction and the deleterious effects of hyperglycemia are avoided.

CONCLUSION

It can be inferred that the prehospital use of glucagon for hypoglycemia allows expeditious transport in lieu of multiple IV line access attempts, is useful in combative patients, and is useful as adjunct therapy for insulin and oral hypoglycemic agent overdose. We conclude that glucagon is safe and effective therapy for hypoglycemia when IV line access is difficult, provides rapid onset of action and minimal side effects, and avoids the deleterious effects of prolonged hypoglycemia.

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