



**American
Red Cross**

ARC SAC Scientific Review Oral Glucose for Diabetic Emergencies

Scientific Advisory Council

Questions to be addressed:

Should lay rescuers be taught how and when to assist patients with administering glucose (sugar) during a diabetic emergency?

Additional questions addressed with this review:

What is the incidence of hypoglycemia in diabetics?

What is the mortality/morbidity associated with hypoglycemia?

What are the risks of treatment of hypoglycemia using oral agents?

What is the optimal method/amount for administration of oral glucose to an adult or pediatric diabetic experiencing signs or symptoms of hypoglycemia?

Review Process and Literature Search of Evidence

Search Strategy:

- Cochrane Database for systematic reviews.
- PubMed via OVID (UVA)
 - Key word search for (“hypoglycemia” OR “hypoglycaemia” OR ‘low blood sugar’) AND (“oral treatment” OR “oral therapy”); “diabetes” AND “hypoglycemia” or “hypoglycaemia”: 528
 - “hypoglycemia” AND “first aid”: 19
 - MESH headings, title or abstract search for “hypoglycemia/diet therapy” OR “hypoglycemia/oral therapy” OR “hypoglycemia/therapy”: 30
 - “hypoglycemia” AND “frequency” (Title/Abstract): 207
 - “hypoglycemia” AND “mortality”(MeSH Terms): 108
 - “hypoglycemia” AND “morbidity” (MeSH Terms): 148
 - “aspiration” AND “oral glucose” (MeSHkey words): 5
- Review of references from articles retrieved.
- Review of findings and recommendations from ARC/AHA International First Aid Science Advisory Committee Worksheet FA-1206A.R1, by Deanna L. Guy: Does administration of oral glucose to a diabetic experiencing signs of hypoglycemia improve outcome? (including optimal method and type of sugar). Submitted May 16, 2009

Inclusion and Exclusion Criteria:

English and humans only, links to full text, 2006 - 2012; Major review articles included in secondary search to assist with identifying studies not found in initial literature search. After elimination of duplicate references and screening for relevance (i.e., non-oral forms of treatment excluded, sepsis and hypoglycemia excluded), 16 articles were ultimately included.

Approved by ARC SAC January 2012

Scientific Foundation:

The 2006 ARCSAC Scientific Review reaffirmed the original 1999 Advisory Statement as follows:

The lay rescuer may give glucose or glucose rich substance to a patient when:

- 1. the patient is identified as a diabetic, and*
- 2. the patient says he or she needs some sugar or states that he or she is having a hypoglycemic reaction, and*
- 3. the patient is awake and able to swallow liquids (the patient might need assistance holding the glass if the patient is very shaky from the low blood sugar).*

The EMS should be activated for all patients.

For the last triennial review, a National Library of Medicine Medline database search was conducted for the period 1966 to April, 2006 using Mesh heading combinations of "hypoglycemia" or "insulin reaction" and "rescuer" or "lay rescuer" or "layperson." No citations were found. Consensus recommendations were based on standard medical reference textbooks.

This 2012 review again found no literature specifically looking at treatment of hypoglycemia by lay providers, lay rescuers, layperson or first aiders. A single article was found (Strote, 2008) comparing outcomes for patients with Type 1 Diabetes (T1D) and hypoglycemia treated without transportation using oral glucose by basic EMTs trained in glucosometry versus a similar cohort treated without transportation by paramedics (with IV or oral agents). In this study, 110 patients were treated by basic EMTs with oral glucose, and 93 by paramedics. Compared to the "gold standard" of treatment by paramedics, patients treated by EMTs with oral glucose had similar numbers of episodes of repeat hypoglycemia (8/7% versus 7/8%), repeat 911 calls (3/3% vs 5/5%) and hospital evaluations (9/8% vs 10/11%), and it was concluded that EMTs performed comparably with paramedics treating hypoglycemia (with oral glucose) without transport. The study suggests that assessment and treatment of hypoglycemia using oral glucose is within the scope of training and practice for basic EMTs. The study was limited in that it was not blinded, and the patient cohort treated by paramedics had a lower initial BG than those treated by EMTs, likely because of the nature of the 2-tier EMS.

This triennial review also discovered new literature examining the incidence of hypoglycemia in diabetics, and studies of oral treatment of hypoglycemia in children and adolescents with T1D.

Three specific questions were considered in this review to help answer the original scientific review question:

1. What is the frequency and risk of hypoglycemia in diabetics? Is lay rescuer intervention needed?

The true frequency of hypoglycemia can be difficult to estimate and varies with the type of

diabetes, the severity of the hypoglycemic event, and the definition used for mild, moderate or severe hypoglycemia. The frequency of *severe* hypoglycemic events ranges from <10 to >100 episodes per 100 patient years of diabetes exposure (DCCT Research Group 1997; Clarke 2008; Daneman 1989; Danne 2001). A 2011 Cochrane Database review (Hemmingsen, 2011) to assess the effects of targeting intensive versus conventional glycemic control in Type 2 Diabetic (T2D) patients found that targeting intensive glycemic control reduces the risk of microvascular complications while increasing the risk of both mild and severe hypoglycemia (61/1000 for intensive control vs. 30/1000 with conventional control). For this Cochrane review, hypoglycemia was defined as mild (controlled by patient), moderate (daily activities interrupted but self-managed), or severe (requiring assistance). Symptoms of mild episodes of hypoglycemia, such as tremor, palpitations, sweating and hunger, are often well tolerated by patients. Mild hypoglycemia often precedes severe hypoglycemia, resulting in more serious symptoms such as confusion, coma, or death (ADA Workgroup on Hypoglycemia 2005). Based on these definitions, lay rescuers are not likely to be needed for assistance to diabetics experiencing signs or symptoms of hypoglycemia unless the diabetic is progressing towards severe hypoglycemia and the patient is confused or unable to locate a source of sugar for him- or herself. In this scenario, common sense dictates that the assistance of a bystander or lay rescuer might prevent progression to more severe hypoglycemia with seizures, coma or death, although there are no studies showing this benefit.

In addition, a 2007 study by Tasker et al found the incidence of *mild* hypoglycemia in children and adolescents with T1D may be much greater than previously thought (up to 5.2 episodes/month in diabetics between 7 and 18 years of age).

As a rule of thumb, most individuals with T1D experience a hypoglycemic event on average at least once per week. Although mortality from hypoglycemia is very low, morbidity from acute and repetitive episodes of hypoglycemia include anxiety (fear of hypoglycemia and subsequent backing off from therapy targets), and acute/chronic mild cognitive dysfunction (Daneman 2010). ISPAD 2008 Clinical Practice Guidelines (Clarke 2008) for treatment of hypoglycemia in adults and children with diabetes recommend preventing hypoglycemia as it is often associated with significant psychosocial dysfunction and can lead to permanent long-term sequelae or be potentially life-threatening, and they recommend that a readily available source of rapid-acting glucose be carried by a child with diabetes.

2. Are there risks associated with treatment of hypoglycemia by lay rescuers?

A diabetic patient with hypoglycemia must be awake and able to swallow in order for the lay rescuer to provide assistance with oral forms of sugar, or there is theoretical risk of aspiration. There are no studies in the literature that describe the incidence of aspiration after oral medications are administered to patients who are not awake and who may not be able to swallow. On the other hand, giving sugar to someone who does not need it (i.e., a diabetic with symptoms or signs that suggest hypoglycemia but are not due to hypoglycemia) does no immediate real harm.

Family members of diabetics are often trained in the use of SC or IM glucagon for hypoglycemia. Use of glucagon and other alternatives to oral forms of sugar for treatment of

hypoglycemia were not evaluated by this review, as lay rescuers are generally not trained in the use of injectables.

3. What is the best form of sugar and amount that a lay rescuer should provide to a diabetic suspected of having hypoglycemia?

In light of intensive glycemic control for Type 2 diabetics, many endocrinologists prefer that treatment of hypoglycemia be tailored to avoid “overshooting” correction of blood glucose and rebound hyperglycemia.

Delahanty found in the Diabetes Control and Complications Trial that subjects with mild hypoglycemia who admitted to eating until they felt better had higher A1c’s compared to those that “never” overate. Several studies have looked at what form of sugar will correct hypoglycemia, the time frame needed for resolution of symptoms, and which forms of oral sugar are accepted in the pediatric population.

Brodows et al (1984) compared 20 grams of carbohydrate intake using milk, orange juice or D-glucose and 40 gm of orange juice to correct insulin-induced hypoglycemia in an inpatient setting. 20 gm of d-glucose tabs produced a faster and higher response to hypoglycemia than milk or 20 gm of orange juice, without rebound hyperglycemia. Forty (40) gm of orange juice produced a similar peak response to 20gm of D glucose tablets but with a delay in achieving the peak glucose and therefore makes this form of treatment less desirable. The glucose content of 40 gm of orange juice is equal to that of 20 gm of D-glucose, therefore the amount of glucose in 40 gm of orange juice and 20 gm of d-glucose is equivalent. This study also looked at isolated cases of spontaneous hypoglycemia and treated patients with D- glucose. All patients had a rise within 20 minutes of at least 20 mg/dl.

Slama et al (1990) studied 41 patients with Type 1 diabetes and IV insulin-induced hypoglycemia. Patients self-reported symptoms of hypoglycemia and were treated when they asked for treatment. Treatment compared 15 gms of seven different carbohydrates including glucose in tablets, gel, and solution (glucose tablet dissolved in 150 ml water); sucrose tablets and solution (dissolved in 150 ml water), and orange juice. Results suggested that 15 grams of carbohydrate in the form of sucrose and glucose in solution or tablets was effective at alleviating symptoms within 14 minutes +/- 0.8 minutes in patients with type 1 diabetes with induced hypoglycemia. The least effective carbohydrates in achieving rapid rise in glucose in the first 10 minutes were dextrose gel and orange juice (statistically significant). Sucrose achieved a statistically significant higher glucose level at 15 and 20 minutes as compared sucrose tablets dissolved in water. There was no difference between glucose tablets and glucose tablets in water.

Wiethop and Cryer (1993) performed a small study of 17 diabetics comparing oral glucose in 10 and 20 gm doses to subcutaneous glucagon and placebo. 10 gm of oral glucose provided a more rapid rise (30 minutes vs 45 minutes) in blood glucose but a lower peak as compared to 20 grams orally.

Clarke (2008), in the International Society for Pediatric and Adolescent Diabetes (ISPAD) Consensus Clinical Practice Guidelines, presents a review of hypoglycemia in children and

adolescents with T1D. Treatment of hypoglycemia in children is recommended with 5 – 15 gm of glucose or sucrose (glucose tablets, sugar lumps, or 100 ml of sweet drinks such as cola, glucose/sucrose drinks) repeated after 10 – 15 minutes if no or inadequate response. Severe hypoglycemia with loss of consciousness +/- convulsions should be treated with parenteral glucagon or IV glucose.

Chlup et al (2009) followed serial plasma glucose levels in 16 diabetics starting from fasting levels to 30 minutes after administering buccal glucose spray (not swallowed, 8.4 gm total), liquid sugar (jelly containing glucose 5.2gm/sucrose 5.2 gm/fructose 5.2 gm) and 1 tablet of dextrose (6gm). Liquid sugar and dextrose tablets raised plasma glucose within 10 minutes; The increase in plasma glucose at 30 minutes was greater with liquid sugar than for dextrose tablet; There was no significant increase in plasma glucose at 30 minutes following administration of buccal glucose.

Husband (2010) performed a randomized crossover design study in pediatric (5 – 15 years of age) Type 1 diabetics with 5 different hypoglycemia episodes using glucose (BD Glucose Tablets), sucrose (Skittles), and fructose (Fruit to Go). Outcome was defined by a blood glucose meter reading that was ≥ 4.0 mmol/L 15 min after treatment. Children <10 yrs received 10 gm of carbohydrate while those >10 received 15 gm, although Clinical Practice Guidelines published by the American and Canadian Diabetes Associations recommend a 15-g treatment, independent of age. They found no significant difference between treatment with glucose tablets and sucrose, but treatment effectiveness with fructose was significantly less than for glucose and sucrose. It was suggested that the fructose source is less effective for hypoglycemia because Fruit to Go contains soluble fiber, which can increase the viscosity of intestinal contents and delay the action of enzymes on the carbohydrate source. In addition, pre-study surveys found that treatment preferences were 36% glucose, 18% sucrose, and 33% fructose sources. Post study surveys found 52% of children preferred the same treatment that was effective (glucose or sucrose), while 35% of children changed their preference to an effective treatment (glucose or sucrose). The authors concluded that Skittles are as effective in treating hypoglycemia as more expensive BD Glucose Tablets in children with type 1 diabetes. Danneman 2010 noted in an editorial that there are many varieties of Skittles with varying amounts of carbohydrate, but that 12 Skittles of any variety should provide close to 15 gm of carbohydrate to treat a hypoglycemic episode (vs 2 -3 glucose tablets).

McTavish (2011) randomized treatment of 191 episodes of hypoglycemia in 39 children (8 – 12 years old) during a diabetes camp to glucose tablets, jellybeans (58% sucrose, 9% glucose, 7.6% fructose, 2.7% maltose, 22.7% starch), orange juice (47.3% fructose, 29% glucose, 23% sucrose), and sugar mints (Mentos dragees – 71% glucose and 29% oligosaccharides)) in equivalent carbohydrate doses for each patient for each treatment (0.3 g/kg) and performed serial glucose measurements over 15 minutes. Severe hypoglycemia (with impaired conscious state or seizure) was excluded. If hypoglycemia persisted at 13 minutes, the same treatment was repeated and glucose tested at 25 minutes. They found that jellybeans produced the slowest and lowest response. Glucose tablets, Mentos dragees and orange juice had similar efficacy although increase in blood glucose at 15 minutes was greatest following glucose tablets followed by Mentos and then orange juice. Jellybean protocol patients also showed a trend towards need for repeat treatment. The authors concluded that jellybeans are less effective treatment for

hypoglycemia in children than glucose tablets, Mentos dragees or orange juice. And that treatment with 0.3 g/kg of carbohydrate (excluding jellybeans) effectively resolved hypoglycemia in most children within 8-15 minutes. The authors suggest that resolution of hypoglycemia may be slow with jellybeans because they contain gelatin. They also suggest that waiting 10 – 15 minutes before repeat dosing may prevent unnecessary re-treatment and subsequent rebound hyperglycemia.

Recommendations and Strength:

Based on the frequency of hypoglycemic events in T1D adult and pediatric patients (once/week), the risk of progression to severe hypoglycemia with seizures or coma and associated morbidity such as chronic cognitive defects, it is recommended that lay rescuers be taught how and when to assist patients who are awake and able to swallow with administering oral carbohydrates containing glucose or sucrose (sugar) during a diabetic hypoglycemic emergency.

The available scientific evidence supports the position that assisting in the administration of oral glucose to a diabetic patient who is experiencing signs and symptoms of hypoglycemia plays a key role in preventing progression to severe hypoglycemia and in reducing morbidity.

Standards:

Guidelines:

1. The lay rescuer may give oral (swallowed) glucose or sucrose to a patient when:
 - a. the patient is identified as a diabetic, and
 - b. the patient says he or she needs some sugar or states that he or she is having a hypoglycemic reaction, and
 - c. the patient is awake and able to swallow.
2. The recommended amount of glucose or sucrose to ingest is 15 grams for children, 20 grams for adults, to be repeated if symptoms persist after 15 minutes.
3. Oral glucose tablets, 16 - 20 gm, are the preferred oral agents, and are usually available in 4 gm tablets. Sucrose-containing candies in an amount equivalent to ~15 grams are also effective in resolving hypoglycemia in children and adolescents.

Options:

Less effective methods (in priority of effectiveness) include dissolved (liquid) glucose, glucose gel, orange juice 12 oz, sugar cubes/granular table sugar. Buccal absorption of glucose is limited and is not recommended.

Summary of Key Articles/Literature Found and Level of Evidence

Citations

Brodows RG, Williams C, Amatruda JM: Treatment of insulin reactions in diabetics. JAMA. 1984 Dec 28;252(24):3378-81. PMID:6389915 (LOE 2a)

Abstract:

Using a modification of the glucose clamp technique, we have studied the efficacy of commonly used foods to correct hypoglycemia in insulin-dependent diabetics. After lowering the plasma glucose level to 55 mg/dL at a steady-state plasma free insulin concentration of about 50 microU/mL, patients were fed 20 g of carbohydrate as milk, orange juice, or D-glucose or 40 g of carbohydrate as orange juice. The data indicate that 20 g of carbohydrate as D-glucose corrects hypoglycemia without rebound hyperglycemia. In an outpatient setting, this treatment also proved effective in spontaneous episodes of hypoglycemia. We conclude that (1) the D-glucose content of the ingested carbohydrate is an important determinant of the glycemic response, and (2) at times of moderately severe hypoglycemia, ingestion of 20 g of D-glucose provides an effective glycemic response for periods of at least 40 minutes. In view of these data, a table is provided listing some common sources of 20 g of D-glucose.

Chlup R, Zapletalova J, Peterson K, Poljakova I, Lenhartova E, Tancred A, Perera R, Smital J: Impact of buccal glucose spray, liquid sugars and dextrose tablets on the evolution of plasma glucose concentration in healthy persons.

Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. **2009** Sep;153(3):205-9. PMID:19851433 (LOE 1a)

Abstract:

OBJECTIVES:

The purpose of this prospective controlled trial was to assess the efficacy of three commercially available glucose products, (1) buccal glucose spray, (2) liquid sugars, and (3) dextrose tablet, on the evolution of plasma glucose concentration (PG).

METHODS:

Sixteen healthy volunteers aged 21.8 +/- 0.78 y (mean +/- SE), BMI 23.5 +/- 0.84 kg/m(2), tested their PG over the course of 3 sets of 4 sessions (S) each: S(0)-control fasting, S(1)-buccal administration of 10 glucose spray-doses (0.84 g of glucose) without swallowing; S(2-) consumption of 1 sachet (13 ml) of liquid sugar (ca. 5.2 g glucose, 5.2 g fructose, 5.2 g sucrose); S(3-) consumption of one dextrose tablet (6 g). PG was tested in finger-prick capillary blood using a personal glucometer Linus at the start, and at 5, 10, 15, 20 and 30 min. The means of 3 respective sessions for each of the 16 subjects were analyzed.

RESULTS:

The Wilcoxon signed rank test revealed no significant differences between changes in the mean PG at the start vs. 5-minute interval either in control, or any intervention sessions. Analysis of regression coefficients after 30 min compared to the control session, demonstrated an increase in PG with the sachet of liquid sugars (0.068 mmol/l/min, p = 0.001) which was greater than a single dextrose tablet (0.052 mmol/l/min, p = 0.002), but no significant PG increase was found after buccal glucose spray.

CONCLUSION:

Liquid sugars or dextrose tablets, but not the buccal glucose spray, are effective means to increase PG within 10 minutes after ingestion.

Clarke W, Jones T, Rewers A, Dunger D, Klingensmith GJ: Assessment and management of hypoglycemia in children and adolescents with diabetes. ISPAD Clinical Practice Consensus Guidelines 2006 – 2007. Pediatric Diabetes 2008; 9: 165-174. PMID:18416698 (LOE 5)

A review of hypoglycemia in children/adolescents with T1D, describing epidemiology, signs/symptoms, definitions, consequences of hypoglycemia and treatment recommendations. For mild/moderate hypoglycemia, this guideline recommends treatment to restore blood glucose level to euglycemia by immediate carbohydrate intake. A dose for children given is 0.3 g/kg (extrapolated from Brodow, adult treatment of 20 g glucose raised BG by 2.5 mmol/L or 45 mg/dL.). One gram of glucose should raise BG by 3 mg/dL for the average adult. A dose of 5 – 15 gm glucose or sucrose is recommended, using glucose tablets, sugar lumps or 100 ml of sweet drink (glucose/sucrose drinks, cola, etc.) This is repeated after 10 – 15 minutes if no or inadequate response. Severe hypoglycemia with loss of consciousness +/- convulsions should be treated with injectable glucagon or IV glucose.

DCCT Research Group. Hypoglycemia in the Diabetes and Complications Trial. *Diabetes* 1997;46:271-286. (LOE 2a)

Abstract

A total of 1,441 patients with IDDM were randomly assigned to receive either intensive (n = 711) or conventional (n = 730) diabetes therapy in the Diabetes Control and Complications Trial (DCCT). The patients were followed for an average of 6.5 years. Subjects were instructed to report all episodes of suspected severe hypoglycemia to their health care team. In addition, at quarterly follow-up visits, each subject was asked about the occurrence of severe hypoglycemia. There were 3,788 episodes of severe hypoglycemia (requiring assistance); 1,027 of these episodes were associated with coma and/or seizure. A total of 65% percent of patients in the intensive group vs. 35% of patients in the conventional group had at least one episode of severe hypoglycemia by the study end; the overall rates of severe hypoglycemia were 61.2 per 100 patient-years vs. 18.7 per 100 patient-years in the intensive and conventional treatment groups, respectively, with a relative risk (RR) of 3.28. The relative risk for coma and/or seizure was 3.02 for intensive therapy. The increased risk with intensive treatment persisted over each of the 9 years of follow-up in the DCCT and over the calendar years 1984-1993 during which the study was conducted. When baseline patient characteristics were examined for effects on the risk of severe hypoglycemia, the relative risk of hypoglycemia for intensive versus conventional treatment was $> = 2$ for all subgroups. Several subgroups defined by baseline characteristics, including males, adolescents, and subjects with no residual C-peptide or with a prior history of hypoglycemia, had a particularly high risk of severe hypoglycemia in both treatment groups. Analyses of the cumulative incidence of successive episodes indicated that intensive treatment was also associated with an increased risk of multiple episodes within the same patient (e.g., 22% experienced five or more episodes of severe hypoglycemia within the first 5 years of follow-up vs. 4% in the conventional group). Within both treatment groups, patients who experienced severe hypoglycemia were at increased risk of subsequent episodes. Approximately 30% of patients in each group experienced a second episode within the 4 months following the first episode of severe hypoglycemia. Within each treatment group, the number of prior episodes of hypoglycemia was the strongest predictor of the risk of future episodes, followed closely by the current HbA1c value. After adjustment for the current quarterly HbA1c level, intensive treatment was still associated with a significantly increased risk of hypoglycemia, indicating that the increased risk with intensive treatment is not completely explained by differences in HbA1c values.

PMID: 9000705

Daneman D. Treating hypoglycemia in children with diabetes: A simple game of “skittles”? (editorial). *Pediatric Diabetes* 2010; 11:149-151 (LOE 5)

Editorial on use of skittles to treat hypoglycemia in kids, proposed actual number of Skittles to use for hypoglycemia.

Daneman D, Frank M, Perlman K, Tamm J, Ehrlich R: Severe hypoglycemia in children with insulin-dependent diabetes mellitus: frequency and predisposing factors. *J Pediatrics* 1989 Nov;115(5 Pt 1):681-5. (LOE 2C)

Abstract: We surveyed 311 children with insulin-dependent diabetes mellitus to evaluate the frequency and characteristics of those children experiencing severe hypoglycemia (defined by an episode of coma, convulsion, or both). The children and their parents completed a questionnaire, and we reviewed the hospital records to confirm reported episodes. Ninety-seven (31%) reported severe hypoglycemia, and a further 50 (16%) reported moderate hypoglycemia requiring the assistance of another person but not resulting in coma or convulsion. In 164 children (53%) there was no history of either moderate or severe hypoglycemia. Sixty-nine (22%) reported the occurrence of more than one severe hypoglycemic episode (range 2 to 20); 52 (16%) reported such an event in a single year. A total of 285 episodes were reported, 39% during sleep and 61% while awake. Children reporting such events tended to have diabetes of longer duration and be younger at the time of the first episode. Hemoglobin A1c concentration at the time closest to the severe episode was significantly lower than in children reporting no hypoglycemia. All families had been taught to use glucagon to reverse severe hypoglycemia at home, but it was available in only 80 of the 97 homes and used in only 30. These data suggest that severe hypoglycemia is common in children with insulin-dependent diabetes mellitus who are treated conventionally. Greater vigilance and education are required both to prevent and to treat severe hypoglycemia in children with insulin-dependent diabetes mellitus.

Danne T, Mortensen HB, Hougaard P, Lynggaard H, Aanstoot H-J, Charelli F, Daneman D, et al. Persistent center differences over 3 years in glycemic control and hypoglycemia in a study of 3,805 children and adolescents with type 1 diabetes from the Hvidovre Study Group. *Diabetes Care* 2001; 24:1342 – 1347. (LOE 2B)

Abstract

OBJECTIVE:

Twenty-one international pediatric diabetes centers from 17 countries investigated the effect of simple feedback about the grand mean HbA(1c) level of all centers and the average value of each center on changes in metabolic control, rate of severe hypoglycemia, and insulin therapy over a 3-year period.

RESEARCH DESIGN AND METHODS:

Clinical data collection and determination of HbA(1c) levels were conducted at a central location in 1995 (n = 2,780, age 0-18 years) and 1998 (n = 2,101, age 11-18 years).

RESULTS:

Striking differences in average HbA(1c) concentrations were found among centers; these differences remained after adjustment for the significant confounders of sex, age, and diabetes duration. They were apparent even in patients with short diabetes duration and remained stable 3 years later (mean adjusted HbA(1c) level: 8.62 +/- 0.03 vs. 8.67 +/- 0.04 [1995 vs. 1998, respectively]). Three centers had improved significantly, four centers had deteriorated significantly in their overall adjusted HbA(1c) levels, and 14 centers had not changed in glycemic control. During the observation period, there were increases in the adjusted insulin dose by 0.076

U/kg, the adjusted number of injections by 0.23 injections per day, and the adjusted BMI by 0.95 kg/m(2). The 1995 versus 1998 difference in glycemic control for the seven centers could not be explained by prevailing insulin regimens or rates of hypoglycemia.

CONCLUSIONS:

This study reveals significant outcome differences among large international pediatric diabetes centers. Feedback and comparison of HbA(1c) levels led to an intensification of insulin therapy in most centers, but improved glycemic control in only a few.

PMID:11473067

Delahanty LM, Halford BN. The role of diet behaviors in achieving improved glycemia control in intensively treated patients in the Diabetes Control and Complications Trial. *Diabetes Care*. 1993; 16: 1453 – 1458. (LOE 2C)

Abstract

OBJECTIVE:

To determine whether specific diet-related behaviors practiced by IDDM patients in the intensive treatment group of the Diabetes Control and Complications Trial were associated with lower HbA1c values.

RESEARCH DESIGN AND METHODS:

A questionnaire addressing various aspects of their dietary behavior during the previous year in the DCCT was completed by 623 DCCT intensive treatment group subjects. The association between self-reported diet behaviors and the subject's mean HbA1c during the previous year was evaluated using a linear rank test for trend. The goal of intensive treatment was to achieve blood glucose and HbA1c levels as close to the nondiabetic range as possible without hypoglycemia.

RESULTS:

Adherence to the prescribed meal plan and adjusting food and/or insulin in response to hyperglycemia were significantly associated with lower HbA1c levels. Over-treating hypoglycemia and consuming extra snacks beyond the meal plan were associated with higher HbA1c levels. Adjusting insulin dose for meal size and content and consistent consumption of an evening snack were associated, albeit to a lesser degree, with lower HbA1c.

CONCLUSIONS:

The average HbA1c among intensively managed patients who reported that they followed specific diet-related behaviors was 0.25 to 1.0 lower than among subjects who did not follow these behaviors. Health-care providers may wish to use these results to focus clinical care for intensively treated IDDM patients by emphasizing counseling on meal plans, prompt response to high blood glucose levels, appropriate treatment of hypoglycemia, and consistent snacking behaviors.

Gagliardi M. Neighbors M. Spears C. Byrd S. Snarr J. Emergencies in the school setting: are public school teachers adequately trained to respond? *Prehospital & Disaster Medicine*. 9(4):222-5, 1994 Oct-Dec. (LOE 2b)

Public school teachers represent a potentially effective first-response component during disasters and isolated emergencies in the school environment. Overall, most of public school teachers in this study were deficient in both training and knowledge of emergency care and BLS modalities. Lack of effective, formal emergency care training in teacher preparation programs coupled with no continuing education requirement is a possible explanation of these results. Emergency medical services providers should seek opportunities to help with first-responder training and continuing education in their schools.

Hemmingsen Bianca, Lund Søren S, Gluud Christian, Vaag Allan, Almdal Thomas, Hemmingsen Christina, Wetterslev Jørn. Targeting intensive glycaemic control versus targeting conventional glycaemic control for type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews*: Reviews 2011 Issue 6 John Wiley & Sons, Ltd Chichester, UK DOI: (LOE 1a)

Abstract

BACKGROUND:

Patients with type 2 diabetes mellitus (T2D) exhibit an increased risk of cardiovascular disease and mortality compared to the background population. Observational studies report a relationship between reduced blood glucose and reduced risk of both micro- and macrovascular complications in patients with T2D.

OBJECTIVES:

To assess the effects of targeting intensive versus conventional glycaemic control in T2D patients.

SEARCH STRATEGY:

Science Citation Index Expanded, LILACS, and CINAHL (until December 2010).

SELECTION CRITERIA:

We included randomised clinical trials that prespecified different targets of glycaemic control in adults with

T2D.

DATA COLLECTION AND ANALYSIS:

Two authors independently assessed the risk of bias and extracted data. Dichotomous outcomes were assessed by risk ratios (RR) and 95% confidence intervals (CI).

MAIN RESULTS:

Twenty trials randomised 16,106 T2D participants to intensive control and 13,880 T2D participants to conventional glycaemic control. The mean age of the participants was 62.1 years. The duration of the intervention ranged from three days to 12.5 years. The number of participants in the included trials ranged from 20 to 11,140. There was no significant difference between targeting intensive and conventional glycaemic control for all-cause mortality (RR 1.01, 95% CI 0.90 to 1.13; 29,731 participants, 18 trials) or cardiovascular mortality (RR 1.06, 95% CI 0.90 to 1.26; 29,731 participants, 18 trials). Trial sequential analysis (TSA) showed that a 10% RR reduction could be refuted for all-cause mortality. Targeting intensive glycaemic control did not show a significant effect on the risk of non-fatal myocardial infarction in the random-effects model but decreased the risk in the fixed-effect model (RR 0.86, 95% CI 0.78 to 0.96; $P = 0.006$; 29,174 participants, 12 trials). Targeting intensive glycaemic control reduced the risk of amputation (RR 0.64, 95% CI 0.43 to 0.95; $P = 0.03$; 6960 participants, 8 trials), the composite risk of microvascular disease (RR 0.89, 95% CI 0.83 to 0.95; $P = 0.0006$; 25,760 participants, 4 trials), retinopathy (RR 0.79, 95% CI 0.68 to 0.92; $P = 0.002$; 10,986 participants, 8 trials), retinal photocoagulation (RR 0.77, 95% CI 0.61 to 0.97; $P = 0.03$; 11,142 participants, 7 trials), and nephropathy (RR 0.78, 95% CI 0.61 to 0.99; $P = 0.04$; 27,929 participants, 9 trials). The risks of both mild and severe hypoglycaemia were increased with targeting intensive glycaemic control but substantial heterogeneity was present. The definition of severe hypoglycaemia varied among the included trials; severe hypoglycaemia was reported in 12 trials that included 28,127 participants. TSA showed that firm evidence was reached for a 30% RR increase in severe hypoglycaemia when targeting intensive glycaemic control. Subgroup analysis of trials exclusively dealing with glycaemic control in usual care settings showed a significant effect in favour of targeting intensive glycaemic control for non-fatal myocardial infarction. However, TSA showed more trials are needed before firm evidence is established.

AUTHORS' CONCLUSIONS:

The included trials did not show significant differences for all-cause mortality and cardiovascular mortality when targeting intensive glycaemic control compared with conventional glycaemic control. Targeting intensive glycaemic control reduced the risk of microvascular complications while increasing the risk of hypoglycaemia. Furthermore, intensive glycaemic control might reduce the risk of non-fatal myocardial infarction in trials exclusively dealing with glycaemic control in usual care settings.

PMID: 21678374

Husband AC, Crawford S, McCoy LA, Pacaud D: The effectiveness of glucose, sucrose, and fructose in treating hypoglycemia in children with type 1 diabetes. *Pediatr Diabetes*. 2010 May;11(3):154-8. Epub 2009 Aug 3. (LOE 1b)

Abstract

OBJECTIVE:

There is a lack of evidence regarding the most effective treatment option for managing naturally occurring hypoglycemia in children with type 1 diabetes. The objectives of this study were (i) to determine if sucrose and fructose are equally effective as glucose in the treatment of spontaneous hypoglycemia in children with type 1 diabetes; and (ii) to determine prestudy and poststudy hypoglycemia treatment preferences.

METHODS:

Thirty-three subjects [aged 5.4-15.5 yr and average duration of type 1 diabetes of 3.1 yr (SD = 2.3)] participated in a randomized, crossover design. The main outcome was the effectiveness of treatment as defined by a blood glucose meter reading that was ≥ 4.0 mmol/L 15 min after treatment. Each subject treated five hypoglycemic events with each treatment type: glucose (BD Glucose Tablets), sucrose (Skittles), and fructose (Fruit to Go).

RESULTS:

There was a significant difference between the effectiveness of the three treatments [Wilk's Lambda $F(2,28) = 8.64$, $p = 0.001$]. No significant difference between treatment with glucose and treatment with sucrose was noted, but the treatment effectiveness for fructose was significantly lower than sucrose [$F(1,29) = 16.09$, $p < 0.001$] and glucose [$F(1,29) = 15.64$, $p < 0.001$]. The preferred treatment choices before the study were as follows: 36% glucose, 18% sucrose, and 33% fructose sources. Poststudy, 52% of children preferred the same treatment, which was effective (glucose or sucrose), followed by 35% who changed their preference to an effective treatment.

CONCLUSION:

Skittles are as effective in treating hypoglycemia as more expensive BD Glucose Tablets in children with type 1 diabetes.

McTavish L, Wiltshire E: Effective treatment of hypoglycemia in children with type 1 diabetes: a randomized controlled clinical trial. *Pediatric Diabetes*. 2011 Jun;12(4 Pt 2):381-7. doi: 10.1111/j.1399-5448.2010.00725.x. Epub 2011 Mar 28. (LOE 1b)

Abstract

OBJECTIVE:

To determine the most effective of four oral treatments for hypoglycemia in children with type 1 diabetes using a weight-based protocol during diabetes camp.

METHODS:

During diabetes camp treatment of hypoglycemia was randomized to one of the four treatments, randomly assigned for each episode using a sealed envelope: glucose tablets, jellybeans, orange juice, and sugar mints (Mentos dragees®). An equivalent carbohydrate dose was calculated for each patient for each treatment (0.3 g carbohydrate/kg) and provided to camp leaders. Glucose was measured at 0, 2, 5, 10, and 15 min and symptoms recorded.

RESULTS:

A total of 191 episodes of hypoglycemia were recorded in 39 children (1-12 episodes per child), with 2 episodes excluded because of protocol violations. Fifty-two episodes were treated with glucose tablets, 45 with jellybeans, 44 with juice, and 48 with sugar mints. Change in glucose at 10 min ($p = 0.034$) and 15 min ($p = 0.005$) and glucose at 15 min ($p = 0.026$) were significantly different between treatment groups - jellybeans produced the lowest and slowest response. Glucose tablets did not differ significantly from juice or Mentos dragees. There was a trend for repeat treatment to be required more often with a single treatment 'dose' of jellybeans ($p = 0.058$). Symptoms occurred in 112 episodes, with a median time to symptom resolution of 12 min (interquartile range (IQR) 8-15 min).

CONCLUSIONS:

Jellybeans are less effective treatment for hypoglycemia than the other three treatments. Glucose tablets, Mentos dragees® and orange juice are of similar efficacy. Treatment with 0.3 g/kg of carbohydrate (excluding jellybeans) effectively resolved hypoglycemia in most children, with 15 min often required to normalize blood glucose.

Slama G, Traynard PY, Desplanque N, Pudar H, Dhunputh I, Letanoux M, Bornet FR, Tchobroutsky G: The search for an optimized treatment of hypoglycemia. Carbohydrates in tablets, solution, or gel for the correction of insulin reactions. *Archives of Internal Medicine*. 1990 Mar;150(3):589-93. PMID:2310277 (LOE 2b)

Abstract:

Recommendations for the treatment of insulin reactions are based more on habit than data. We investigated the efficacy in correcting blood glucose levels and alleviating clinical symptoms of hypoglycemia of seven orally administered carbohydrates--glucose in solution, tablets, and gel; sucrose in solution and tablets; a hydrolyzed polysaccharide solution; and orange juice--each of which provided 15 g of carbohydrate. Forty-one type I diabetic patients recently treated with insulin agreed to submit to artificially induced hypoglycemia by an intravenous injection of insulin. Corrective therapy was given when patients experienced symptoms and asked for treatment. Mean blood glucose levels 10 minutes after ingestion were found to be similar whether correction was dispensed with the tablets and the solutions of glucose, those of sucrose, or the polysaccharide preparation. However, almost no increment was obtained at this time point

with the gel or the fruit juice. Fifteen and 20 minutes after carbohydrate intake, blood glucose levels were higher with the tablet forms than with the solutions, although differences only became significant for sucrose. Glycemic responses were again consistently lower with the sucrose gel and the orange juice. Clinical symptoms were alleviated in 14.0 +/- 0.8 minutes (mean +/- SEM) with sucrose and glucose in solution or tablets. We conclude that in moderately severe hypoglycemia, ingestion of 15 g of carbohydrate in the form of glucose or sucrose tablets or as a solution provides an effective therapy; both sugars seem equivalent. Even if sucrose lumps are better recommended in terms of cost and availability, they may not be recommendable in terms of palatability. Glucose gel or orange juice cannot be recommended, at least in light of our experimental procedure and at the dosage used therein.

Strote J, Simons R, Eisenberg M: Emergency medical technician treatment of hypoglycemia without transport. American Journal of Emergency Medicine - March 2008 (Vol. 26, Issue 3, Pages 291-295, DOI: 10.1016/j.ajem.2007.05.030) (LOE 2b)

Abstract

Objectives

We examine the safety and efficacy of emergency medical technicians (EMTs) providing treatment to stable hypoglycemic patients without transport or paramedic involvement, which is currently beyond their scope of practice.

Methods

All hypoglycemic patients treated in the field without transport for 12 months were included. We used a patient follow-up survey to compare the outcomes of EMT and paramedic-treated patients on the occurrence of repeat hypoglycemic episodes, 911 calls, and/or in-hospital reevaluation within 48 hours; patients' adhering to the provided instructions; and patient satisfaction.

Results

Of 402 cases identified, we were able to contact and survey 203 (51%). There were no statistically significant differences for any of the outcome measures studied. Patients treated by EMTs (110) and paramedics (93) had 8 (7%) and 7 (8%) episodes of repeat hypoglycemia, 3 (3%) and 5 (5%) repeat 911 calls, and 9 (8%) and 10 (11%) hospital evaluations, respectively.

Conclusions

Emergency medical technicians performed comparably with paramedics treating hypoglycemia without transport.

Tasker, A. P., Gibson, L., Franklin, V., Gregor, P. and Greene, S. (2007), What is the frequency of symptomatic mild hypoglycemia in type 1 diabetes in the young?: assessment by novel mobile phone technology and computer-based interviewing. *Pediatric Diabetes*, 8: 15–20. doi: 10.1111/j.1399-5448.2006.00220. (LOE 2b)

Background: The prevalence of mild hypoglycemia is difficult to document, particularly, in young people with diabetes. The usual method is to ask for subject recall using written 'diaries'.

Objective: In 2004, we investigated if new technology could be used to ascertain an accurate prevalence of mild hypoglycemia, particularly self-treated. We compared the use of 'text messaging' and computer-based interviewing with the standard diary method.

Participants: Thirty-seven participants, aged 7–18 yr, with type 1 diabetes (T1D) for >1-yr duration.

Method: Open comparison of three systems to collect the data on frequency of hypos (all severity): diary, mobile phone and computer-based interview (CBI), with qualitative analysis of patient feedback.

Results: One hundred thirty-two hypos were found over 705 recorded days. All were graded mild or moderate and none severe. Calculated frequency was 5.2 hypos per month: 13.6% subjects had no recorded episode, 36.4% had 1–4, 31.8% 5–9 and 18.2% >10. Mean blood glucose level at the onset of hypoglycemia was 3.0 mmol/L (1.0–5.2). Response rate of occurrence of hypoglycemic episode recorded by three systems is as follows – diary: 24 (65%) of the 37 subjects reported episodes, mobile: 18 (95%) of 19 subjects and CBI: 16 (89%) of 18 subjects. Sixty-five percent of subjects preferred the mobile and 54% of subjects preferred CBI compared with the diary. Fifty-five percent and 30.8% of subjects found the mobile and the CBI, respectively, easiest to fit into their everyday life.

Conclusions: Mobile phone text messaging and CBI are alternatives to written diaries as methods of data collection. Each has its own strengths and weaknesses, but both have the advantage of daily reminders, rapid response and quick data analysis. Using this technology, it was found that the frequency of hypoglycemia was higher (>3 times) than that previously recognized.

Wiethop BV, Cryer PE: Alanine and terbutaline in treatment of hypoglycemia in IDDM. Diabetes Care. 1993 Aug;16(8):1131-6. PMID:8375243 (LOE 1b)

Abstract

OBJECTIVE:

To test the hypothesis that, in contrast to administration of glucose or glucagon, administration of the amino acid Ala or of the beta 2-adrenergic agonist terbutaline produces sustained glucose recovery from hypoglycemia.

RESEARCH DESIGN AND METHODS:

We developed a model of clinical hypoglycemia using subcutaneous injection of insulin (0.15 U/kg) in patients with IDDM. In comparison with nondiabetic subjects, patients with IDDM exhibited reduced glucagon (P = 0.0001), epinephrine (P = 0.0060), and pancreatic polypeptide (P = 0.0001) responses to hypoglycemia. In addition to placebos, the following were administered during hypoglycemia (2 h after insulin injection) in IDDM patients: oral glucose, 10 and 20 g; subcutaneous glucagon, 1.0 mg; oral Ala, 40 g; oral terbutaline, 5.0 mg; and subcutaneous terbutaline, 0.25 mg.

RESULTS:

Glucose (10 and 20 g) and glucagon raised plasma glucose (P = 0.0163, 0.0060, and 0.0001, respectively) from 3.0-3.3 mM to peaks of 5.4 +/- 0.4, 6.8 +/- 0.7, and 11.8 +/- 0.8 mM within 30, 45, and 60 min, respectively, but the responses were transient. Oral Ala raised glucose levels (P = 0.0401) to 4.0 +/- 0.4 mM within 30 min; glucose levels then rose gradually to a 6-h value of only 7.1 +/- 0.9 mM. Oral terbutaline raised glucose levels (P = 0.0294) to 4.3 +/- 0.3 mM within 30 min; glucose levels then rose substantially. In contrast, subcutaneous terbutaline raised glucose levels (P = 0.0249) to 3.7 +/- 0.1 mM within 15 min; the levels plateaued at 5.0 mM from approximately 60-150 min and then paralleled the placebo curve.

CONCLUSIONS:

Ala and terbutaline produce sustained glucose recovery from hypoglycemia in IDDM and are therefore potentially useful agents for the treatment of mild or moderate iatrogenic hypoglycemia, or the prevention of iatrogenic hypoglycemia, when food intake is not anticipated over the following several hours.

Level of Evidence	Definitions (See manuscript for full details)
Level 1a	Randomized clinical trials or meta-analyses of multiple clinical trials with substantial treatment effects
Level 1b	Randomized clinical trials with smaller or less significant treatment effects
Level 2a	<u>Prospective</u> , controlled, non-randomized, cohort studies
Level 2b	<u>Historic</u> , non-randomized, cohort or case-control studies
Level 2c	<u>Case series</u> : patients compiled in serial fashion, lacking a control group
Level 3	Animal studies or mechanical model studies
Level 4	Extrapolations from existing data collected for other purposes, theoretical analyses with limited correlation to current question
Level 5	Peer-reviewed, state of the art articles, review articles, editorials, or consensus statements
Level 6	Non-peer reviewed published opinions, such as textbook statements, official organizational publications, guidelines and policy statements and consensus statements
Level 7	Rational conjecture (common sense); common practices accepted before evidence-based guidelines
Level 1-6E	Extrapolations from existing data collected for other purposes, theoretical analyses which is on-point with question being asked. Modifier E applied because extrapolated but ranked based on type of study.