

QUESTION

Should buccal glucose compared with oral (swallowed) glucose be administered for hypoglycemia?

PROBLEM:	Routes of glucose administration for hypoglycemia
OPTION:	Buccal glucose administration
COMPARISON:	Oral (swallowed) glucose administration
MAIN OUTCOMES:	Resolution of symptoms; Blood/plasma glucose concentrations at 20 min (mg/dL) (Chlup 2009); Increased blood glucose at 20 min (Gunning 1976); Time to resolution of symptoms; Any adverse event; Resolution of hypoglycemia; Time to resolution of hypoglycemia; Ease of administration / administration delay;
SETTING:	First aid setting, healthy volunteers (adults)
PERSPECTIVE:	Perspective of both the hypoglycemia individual and first aid provider
BACKGROUND:	Hypoglycemia is a common problem worldwide. First aid is frequently provided by family, self and lay providers in the form of glucose via tablets or glucose-containing foods and beverages. Some commercial preparations of glucose are directed for use by buccal routes. This could be of benefit in part of the world where parenteral administration of glucose is not feasible, and when hypoglycemic individuals are unable to swallow.
CONFLICT OF INTEREST:	None

ASSESSMENT

Problem

Is the problem a priority?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know	<p>Hypoglycemia is common throughout the world, in both individuals with insulin-dependent and non-insulin dependent diabetes, (1) and is associated with a considerable cost and burden to the health service (2). There can also be substantial consequences for the individual, with an increased risk of morbidity and mortality from severe episodes [3–5].</p> <ol style="list-style-type: none"> 1. Edridge et al. Prevalence and Incidence of Hypoglycaemia in 532,542 People with Type 2 Diabetes on Oral Therapies and Insulin: A Systematic Review and Meta-Analysis of Population Based Studies. <i>PLoS One</i>. 2015; 10(6): e0126427. 2. Hex N, Bartlett C, Wright D, Taylor M, Varley D. Estimating the current and future costs of Type 1 and Type 2 diabetes in the UK, including direct health costs and indirect societal and productivity costs. <i>Diabetic medicine: a journal of the British Diabetic Association</i>. 2012;29(7):855–62. 3. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, et al. Severe Hypoglycemia and Cognitive Decline in Older People With Type 2 Diabetes: The Edinburgh Type 2 Diabetes Study. <i>Diabetes care</i>. 2014;37(2):507–15. doi: 10.2337/dc13-1384 4. Bloomfield HE, Greer N, Newman D, MacDonald R, Carlyle M, Fitzgerald P, et al. Predictors and Consequences of Severe Hypoglycemia in Adults with Diabetes—A Systematic Review of the Evidence. VA Evidence-based Synthesis Program Reports. Washington (DC)2012. 	<p>Hypoglycemia is common; prompt first aid management is needed; routes other than oral need to be explored.</p>

	5. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. <i>New England Journal of Medicine</i> . 2010;363(15):1410–8. doi: 10.1056	
--	---	--

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Trivial <input checked="" type="radio"/> Small <input type="radio"/> Moderate <input type="radio"/> Large <input type="radio"/> Varies <input type="radio"/> Don't know 	<p><u>Desirable effects:</u> There is very little evidence, but it would seem to favor oral administration of glucose (1, 2).</p> <p>We did not identify any evidence to address the critical outcomes of resolution of symptoms and time to resolution of symptoms, and the important outcomes of adverse events, resolution of hypoglycemia, time to resolution of hypoglycemia and treatment delay.</p> <p>Furthermore, the evidence for a significant rise in blood glucose is lacking. The comparison is with healthy volunteers, and the level of evidence is very low.</p> <ol style="list-style-type: none"> 1. 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. <i>Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub</i> 2009, 153(3):205-209 2. Gunning RR, Garber AJ. Bioactivity of Instant Glucose. Failure of Absorption through Oral Mucosa. <i>JAMA</i> 1978, 240:1611-1612 	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large <input type="radio"/> Moderate <input checked="" type="radio"/> Small <input type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p><u>Undesirable effects:</u> For the critical outcome of blood/plasma glucose concentration at 20 min (mg/dL), we identified harm from buccal glucose administration when compared with oral glucose administration (MD, -15; 95%CI, -24.20– -5.80 with an assumed within subjects correlation coefficient of 0.1; P < 0.01; MD, -15; 95%CI, -18.07– -11.93 with an assumed within subjects correlation coefficient of 0.9; P < 0.01) (1, 2).</p> <p>There were no adverse effects reported.</p> <ol style="list-style-type: none"> 1. 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. <i>Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub</i> 2009, 153(3):205-209 2. Gunning RR, Garber AJ. Bioactivity of Instant Glucose. Failure of Absorption through Oral Mucosa. <i>JAMA</i> 1978, 240:1611-1612 	

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT

- Very low
- Low
- Moderate
- High
- No included studies

RESEARCH EVIDENCE

Downgrading of evidence for serious risk of bias, indirectness and imprecision.

Outcomes	With oral (swallowed) glucose	With buccal glucose	Difference	Relative effect (95% CI)
resolution of symptoms - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-
Blood/plasma glucose concentrations at 20 min (mg/dL) (Chlup 2009)	The mean blood/plasma glucose concentrations at 20 min (mg/dL) (Chlup 2009) was 112 mg/dL	The mean blood/plasma glucose concentrations at 20 min (mg/dL) (Chlup 2009) in the intervention group was 15 mg/dL lower (0 to 0)	MD 15 mg/dL lower (0 to 0)	-
Increased blood glucose at 20 min (Gunning 1976)	1.000 per 1.000	0 per 1.000 (0 to 550)	1.000 fewer per 1.000 (1.000 fewer to 450 fewer)	RR 0.00 (0.00 to 0.55)
Time to resolution of symptoms - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-
Any adverse event - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per	-

ADDITIONAL CONSIDERATIONS

As much research includes healthy individuals or is about bioavailability and not clinical changes, it is difficult to determine if the effects demonstrated would impact on real-world outcomes.

				1.000 (0 fewer to 0 fewer)	
	Resolution of hypoglycemia - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-
	Time to resolution of hypoglycemia - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-
	Ease of administration / administration delay - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> Important uncertainty or variability <input type="radio"/> Possibly important uncertainty or variability <input checked="" type="radio"/> Probably no important uncertainty or variability <input type="radio"/> No important uncertainty or variability	There is only indirect evidence as most research on this topic is from less developed countries where there is little formal prehospital care and other resources are limited.	The Task Force agreed that the ability to quickly and effectively manage the individual in the out-of-hospital setting would be desirable and of value.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
-----------	-------------------	---------------------------

<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Based on the limited available data regarding buccal administration of glucose, the perceived, potential risk of accidental aspiration may outweigh the very low apparent benefit of buccal glucose.</p>	
---	---	--

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Large costs <input type="radio"/> Moderate costs <input checked="" type="radio"/> Negligible costs and savings <input type="radio"/> Moderate savings <input type="radio"/> Large savings <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>Swallowed glucose can be administered in multiple formats. Buccal glucose may require a gel and thus, increases the cost associated with care, with limited evidence to support improved outcomes.</p>	<p>Cost of glucose tablets is less than 50 cents per 15 gm dose, and for glucose gel is about \$3 per 15 gm dose (US).</p>

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
-----------	-------------------	---------------------------

<ul style="list-style-type: none"> <input type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input checked="" type="radio"/> No included studies 		
---	--	--

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Favors the comparison <input checked="" type="radio"/> Probably favors the comparison <input type="radio"/> Does not favor either the intervention or the comparison <input type="radio"/> Probably favors the intervention <input type="radio"/> Favors the intervention <input type="radio"/> Varies <input type="radio"/> No included studies 	<p>The cost effectiveness may favor oral glucose.</p>	<p>For the individual that is conscious and able to swallow, the cost would probably favor the oral route.</p>

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input type="radio"/> Reduced <input type="radio"/> Probably reduced <input checked="" type="radio"/> Probably no impact <input type="radio"/> Probably increased <input type="radio"/> Increased <input type="radio"/> Varies <input type="radio"/> Don't know 	<p>The impact on health equity is uncertain, however, access to a buccal source would be a concern. Glucose sources beyond tablets could be limited in certain parts of the world, thus there may be an increased impact.</p>	<p>There are plausible differences between buccal glucose and oral glucose where oral glucose appears to be less expensive.</p>

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input checked="" type="radio"/> Probably yes <input type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<input type="radio"/> No <input type="radio"/> Probably no <input type="radio"/> Probably yes <input checked="" type="radio"/> Yes <input type="radio"/> Varies <input type="radio"/> Don't know		Feasibility may depend on the form of glucose available for use.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies

JUDGEMENT							
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the option <input type="radio"/>	Conditional recommendation against the option <input checked="" type="radio"/>	Conditional recommendation for either the option or the comparison <input type="radio"/>	Conditional recommendation for the option <input type="radio"/>	Strong recommendation for the option <input type="radio"/>
---	--	---	--	---

CONCLUSIONS

Recommendation

We recommend against buccal mucosal glucose administration (the option; conditional recommendation) compared with oral glucose administration for individuals with suspected hypoglycemia.

Justification

Based on the evidence, buccal administration of glucose is not the preferred option in a person with suspected hypoglycemia who is conscious and able to swallow.

Subgroup considerations

Individuals with suspected hypoglycemia and altered mental status and inability to swallow will probably require advanced medical care.

Implementation considerations

None.

Monitoring and evaluation

Not required.

Research priorities

Current research regarding the administration of glucose via the buccal route compared with oral (swallowed) glucose tablets is limited both in terms of populations (pediatrics or adults) and in conditions (hypoglycemia associated with diabetes treatment or critical illness).

Randomized controlled trials or large cohort studies are needed to evaluate various outcomes include resolution of symptoms, adverse events and the impact on other health outcomes. These studies should include individuals with diabetes in addition to individuals with hypoglycemia from other causes (e.g. exercise induced, infection, etc).