

QUESTION

Should sublingual glucose compared with oral (swallowed) glucose be administered for hypoglycemia?	
PROBLEM:	Routes of glucose administration for hypoglycemia
OPTION:	Sublingual glucose administration
COMPARISON:	Oral (swallowed) glucose administration
MAIN OUTCOMES:	Resolution of symptoms; Blood/plasma glucose concentrations at 20 min (mg/dL); Time to resolution of symptoms; Any adverse event; Treatment failure rate (80 minutes); Early treatment failure rate (20 minutes); Time to resolution of hypoglycemia; Ease of administration / administration delay;
SETTING:	First aid setting, children with moderate clinical symptoms of acute malaria or moderate respiratory tract infections.
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 or sublingual 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"> 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>IPLoS One</i>. 2015; 10(6): e0126427. 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. 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 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. <i>VA Evidence-based Synthesis Program Reports</i>. Washington (DC)2012. 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 	<p>Hypoglycemia is common; prompt first aid management is needed; routes other than oral need to be explored.</p>

	<p>Hypoglycemia common in some parts of the world, for instance in Africa where children with malaria develop hypoglycemia and prognosis is poor in these cases. Many children die from hypoglycemia in that part of the world before they make it to medical care (English M, Wale S, Binns G, Mwangi I, Sauerwein H, Marsh K: Hypoglycaemia on and after admission in Kenyan children with severe malaria. QJM 1998, 91:191-197.). These children are often unable to swallow sugar and there are no resources for delivery of IV dextrose. Buccal delivery, if effective, would be potentially life-saving in these children.</p> <p>The sublingual route of administration may provide an alternative route of glucose administration and avoid the need to swallow.</p>	
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Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know 	<p><u>Desirable effects:</u></p> <p>For the critical outcome blood/plasma glucose concentrations at 20 min, we found a large effect in favor of sublingual group compared with oral group (MD 17 mg/dL higher: 4.38 higher to 29.62 higher). Single study included (69 individuals enrolled); level of evidence is very low (1).</p> <p>For the important outcome treatment failure rate at 80 min, no treatment failures were observed in the sublingual group (0/27) and 8/15 treatment failures were observed in the oral group (RR 0.03 - 0.00 to 0.54- p< 0.005) (1).</p> <p>For the important outcome treatment failure rate at 20 min, we identified a RR 0.28 (0.06 to 1.34) in favor of sublingual group (1).</p> <p>For the important outcome time to resolution of hypoglycemia, the results favor the sublingual group (MD 51.5 min lower [57.97 lower to 45.03 lower]) (1).</p> <p>For the important outcome of any adverse events, no adverse event was found at enrollment or during the follow up period of hypoglycemic children. The treatment seemed to be well tolerated.</p> <p>The other critical outcomes such as resolution of symptoms and time to resolution of symptoms were not reported.</p> <p>The important outcome ease of administration was not reported.</p> <p>1. Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E. Sublingual Sugar Administration as an Alternative to Intravenous Dextrose Administration to Correct Hypoglycemia Among Children in the Tropics. Pediatrics 2005, 116(5):e648-e653</p>	

Outcomes	With oral (swallowed) glucose	With sublingual 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)	The mean blood/plasma glucose concentrations at 20 min (mg/dL) was 76 mg/dL	The mean blood/plasma glucose concentrations at 20 min (mg/dL) in the intervention group was 17 mg/dL higher (4,38 higher to 29,62 higher)	MD 17 mg/dL higher (4.38 higher to 29.62 higher)	-
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	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	not estimable
Treatment failure rate (80 minutes)	533 per 1.000	16 per 1.000 (0 to 288)	517 fewer per 1.000 (533 fewer to 245 fewer)	RR 0.03 (0.00 to 0.54)
Early treatment failure rate (20 minutes)	267 per 1.000	75 per 1.000 (16 to 357)	192 fewer per	RR 0.28 (0.06 to 1.34)

				1.000 (251 fewer to 91 more)	
Time to resolution of hypoglycemia	The mean time to resolution of hypoglycemia was 80 min	The mean time to resolution of hypoglycemia in the intervention group was 51,5 min lower (57,97 lower to 45,03 lower)	MD 51.5 min lower (57.97 lower to 45.03 lower)	-	
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)	-	

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 type="radio"/> Small <input checked="" type="radio"/> Trivial <input type="radio"/> Varies <input type="radio"/> Don't know 	<p><u>Undesirable effects:</u> We identified a treatment failure rate of 0/27 for sublingual administration vs 8/15 for oral administration (1).</p> <p>We identified higher blood/plasma glucose concentrations at 20 minutes in the sublingual administration group compared with the oral group (1).</p> <p>No adverse events were reported. The undesirable effects may not have been identified with this review.</p> <p>The undesirable effects of sublingual are therefore trivial.</p> <p>1. Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E. Sublingual Sugar Administration as an Alternative to Intravenous Dextrose Administration to Correct Hypoglycemia Among Children in the Tropics. Pediatrics 2005, 116(5):e648-e653</p>	<p>There might be a small risk of aspiration in the poorly responsive or unconscious person. In these situations, the risk may be outweighed by the benefits of correcting hypoglycemia.</p>

Outcomes	With oral (swallowed) glucose	With sublingual 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)	The mean blood/plasma glucose concentrations at 20 min (mg/dL) was 76 mg/dL	The mean blood/plasma glucose concentrations at 20 min (mg/dL) in the intervention group was 17 mg/dL higher (4,38 higher to 29,62 higher)	MD 17 mg/dL higher (4,38 higher to 29,62 higher)	-
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	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	not estimable
Treatment failure rate (80 minutes)	533 per 1.000	16 per 1.000 (0 to 288)	517 fewer per 1.000 (533 fewer to 245 fewer)	RR 0.03 (0.00 to 0.54)

	Early treatment failure rate (20 minutes)	267 per 1.000	75 per 1.000 (16 to 357)	192 fewer per 1.000 (251 fewer to 91 more)	RR 0.28 (0.06 to 1.34)
	Time to resolution of hypoglycemia	The mean time to resolution of hypoglycemia was 80 min	The mean time to resolution of hypoglycemia in the intervention group was 51,5 min lower (57,97 lower to 45,03 lower)	MD 51.5 min lower (57.97 lower to 45.03 lower)	-
	Ease of administration/treatment delay - not reported	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	-

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> <input checked="" type="radio"/> Very low <input type="radio"/> Low <input type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>There was a serious risk of bias (unclear randomization and allocation concealment and lack of blinding), indirectness (indirect population: children with malaria), and imprecision due to limited sample size or low number of events and large confidence intervals.</p>	

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability 	There is probably no important uncertainty or variability.	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"> ○ 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 	<p>For severe hypoglycemia with inability to swallow, the benefit of sublingual glucose may outweigh the risk of trying to administer oral (swallowed) glucose.</p> <p>For hypoglycemia in awake individuals with the ability to swallow, the benefit of sublingual glucose may outperform oral glucose.</p> <p>The balance between desirable and undesirable effects may favor sublingual administration (intervention).</p>	

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
<ul style="list-style-type: none"> ○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know 	Administration of sublingual glucose in awake individuals is simple and safe. The resources necessary to implement this technique are limited.	

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 checked="" type="radio"/> Moderate <input type="radio"/> High <input type="radio"/> No included studies 	<p>The cost is limited for both the oral and sublingual routes. This technique may prevent hospitalization or emergency health care visits.</p>	
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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>We did not identify any studies directly studying the cost effectiveness of sublingual administration, but there may be benefit of treating hypoglycemia in the prehospital setting.</p>	<p>The cost will depend on the type of sublingual glucose administered.</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>In studies examining infants, sublingual administration sources appear to be granulated sugar, moistened with a few drops of water and placed under the tongue. This is unlikely to have an impact on health equity (1).</p> <p>(1) Graz B, et al. Sublingual sugar for hypoglycaemia in children with severe malaria: a pilot clinical study. Malar J. 2008 Nov 23;7:242. doi: 10.1186/1475-2875-7-242.</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	Oral glucose is in wide use currently but sublingual glucose appears feasible.	The key stakeholders - individuals, families, healthcare providers - will likely have varying acceptance of an intervention such as sublingual or oral glucose for individuals with hypoglycemia due to concerns about potential aspiration or recurrent hypoglycemia.

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	The time to glucose administration is similar between oral administration and sublingual administration.	Feasibility and acceptance will likely vary widely based on local adoption patterns and financial considerations.

SUMMARY OF JUDGEMENTS

PROBLEM	JUDGEMENT						
	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 type="radio"/>	Conditional recommendation for either the option or the comparison <input type="radio"/>	Conditional recommendation for the option <input checked="" type="radio"/>	Strong recommendation for the option <input type="radio"/>
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CONCLUSIONS

Recommendation

We recommend the use of either sublingual glucose administration (the option) or oral glucose administration (the comparison) for individuals with suspected hypoglycemia (conditional recommendation).

Justification

The evidence favors the use sublingual administration in this specific population of patients 1 to 15 years old with moderate symptoms of malaria or respiratory illness. However, given the limited study population, the Task Force were uncertain as to the effectiveness of this route in the general population. As a result, oral glucose should also be considered the method of choice for individuals with suspected hypoglycemia.

Subgroup considerations

In making these recommendations, we recognize that the available evidence suggests a benefit in favor of sublingual administration. However, this was demonstrated in a single study in only one specific population (awake children with moderate symptoms of malaria or respiratory illness). How these two routes compare in other populations, is unknown.

Implementation considerations

The recommendation should be considered a conditional recommendation in favor of sublingual administration of glucose, but only in awake children between 1 and 15 years old with suspected hypoglycemia and with moderate clinical symptoms of acute malaria or moderate respiratory tract infections.

Monitoring and evaluation

Research priorities

Current research regarding the administration of glucose via the sublingual route in adult populations compared with oral (swallowed) glucose tablets is limited. 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).