Question

Should oral + buccal glucose (glucose gel) compared with oral (swallowed) glucose be administered for hypoglycemia?	
PROBLEM:	Routes of glucose administration for hypoglycemia
OPTION:	Combined oral and buccal glucose administration (glucose gel)
COMPARISON:	Oral (swallowed) glucose administration
MAIN OUTCOMES:	Resolution of symptoms within 10 min; Resolution of symptoms within 15 min; Resolution of symptoms within 20 min; Resolution of symptoms after 20 min; Blood/plasma glucose concentrations at 20 min; Time to resolution of symptoms; Any adverse events; Resolution of hypoglycemia; Time to resolution of hypoglycemia; Ease of administration/administration delay;
SETTING:	Out of hospital, adults with insulin dependent diabetes
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
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	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]. 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. IPLoS One. 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. Diabetic medicine: a journal of the British Diabetic Association. 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. Diabetes care. 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. 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. New England Journal of Medicine. 2010;363(15):1410–8. doi: 10.1056	

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● Small ○ Moderate ○ Large ○ Varies ○ Don't know	Desirable effects: For the critical outcome resolution of symptoms within 10, 15 or 20 minutes, we did not find a difference between the groups (oral + buccal glucose compared with oral glucose) (1). For the critical outcome resolution of symptoms after 20 minutes, we found a greater relative effect for oral+ buccal glucose compared with oral glucose (1). 1. Slama G, Traynard P, Desplanque N, Pudar H, Dhunputh I, Letanoux M, Bornet FRJ, Tchobroutsky G. The Search for an Optimized Treatment of Hypoglycemia. Carbohydrates in Tablets, Solution, or Gel for the Correction of Insulin Reactions. Arch Intern Med 1990, 150:589-593	

Outcomes	With oral (swallowed) glucose	With oral + buccal glucose (glucose gel)	Difference	Relative effect (95% CI)
Resolution of symptoms within 10 min	250 per 1.000	**168 per 1.000** (23 to 1.000)	**82 fewer per 1.000** (228 fewer to 1.033 more)	**RR 0.67** (0.09 to 5.13)
Resolution of symptoms within 15 min	750 per 1.000	**330 per 1.000** (105 to 1.000)	**420 fewer per 1.000** (645 fewer to 330 more)	**RR 0.44** (0.14 to 1.44)
Resolution of symptoms within 20 min	917 per 1.000	**330 per 1.000** (110 to 1.000)	**587 fewer per 1.000** (807 fewer to 128 more)	**RR 0.36** (0.12 to 1.14)
Resolution of symptoms after 20 min	83 per 1.000	**667 per 1.000** (94 to 1.000)	**583 more per 1.000**	**RR 8.00** (1.13

			(11 more to 4.649 more)	to 56.79)
Blood/plasma glucose concentrations at 20 min	The mean blood/plasma glucose concentrations at 20 min was **77** mg/dL	The mean blood/plasma glucose concentrations at 20 min in the intervention group was 16 mg/dL lower (34,32 lower to 2,32 higher)	MD **16 mg/dL lower** (34.32 lower to 2.32 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 events - not reported	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 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)	-

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ● Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Undesirable effects: Research favors the oral route with a faster and more complete resolution of symptoms Adverse events were not reported (1). 1. Slama G, Traynard P, Desplanque N, Pudar H, Dhunputh I, Letanoux M, Bornet FRJ, Tchobroutsky G. The Search for an Optimized Treatment of Hypoglycemia. Carbohydrates in Tablets, Solution, or Gel for the Correction of Insulin Reactions. Arch Intern Med 1990, 150:589-593	Failure to resolve symptoms or a slower resolution is undesirable therefore the undesirable effect of oral + buccal glucose (glucose gel) is moderate.

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Blood/plasma glucose concentrations at 20 min	The mean blood/plasma glucose concentrations at 20 min was **77** mg/dL	The mean blood/plasma glucose concentrations at 20 min in the intervention group was 16 mg/dL lower (34,32 lower to 2,32 higher)	MD **16 mg/dL lower** (34.32 lower to 2.32 higher)	-
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Any adverse events - not reported	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 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)	-

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	Due to limitations in the study design there is resultant imprecision.	Most research with oral + buccal glucose (glucose gel) is in the neonate/infant population. This may not be generalizable to the pediatric and adult population.

Values

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● Probably no important uncertainty or variability ○ No important uncertainty or variability	There is value in the improved individual clinical outcomes in those experiencing hypoglycemia.	The Task Force agreed that the ability to quickly and effectively manage the individual with hypoglycemia 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
○ 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	Oral + buccal provided a greater resolution of symptoms after 20 minutes (one study) but no difference within 20 minutes.	In the individual who is able to safely swallow, oral glucose may be preferred.

Resources required

How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ○ Moderate costs ● Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	We were unable to find formal cost-effectiveness studies. Oral (swallowed) glucose can be administered in multiple formats.	

Certainty of evidence of required resources

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● No included studies	We did not identify any relevant studies.	

Cost effectiveness

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

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ 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	This study evaluated the same intervention materials administered by different routes. This may minimize the impact on cost effectiveness however, no formal cost-effective analysis was performed.	Commercial oral + buccal glucose (glucose gel) may be more costly than the oral tabs, although all are less expensive than a hospital visit.

Equity

What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	This is uncertain, however, access to an oral + buccal source such as glucose gel would be of concern. Glucose sources beyond tablets could be limited in certain parts of the world, thus there may be an increased impact due to cost.	If the recommendation is to give commercial oral + buccal glucose (glucose gel) then the cost of these commercial products could prevent first aid providers of low socioeconomic status from being able to purchase them.

Acceptability

Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Oral glucose is in wide use currently, but the exact form may vary from country to country depending on resources.	

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Both glucose administration routes are similarly effective.	Swallowing of buccally administered glucose gel may contribute to similar effectiveness

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**
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	Conditional recommendation against the option	**Conditional recommendation for either the option or the comparison**	Conditional recommendation for the option	Strong recommendation for the option
○	○	●	○	○

CONCLUSIONS

Recommendation

We recommend either oral administration or a combined oral + buccal route of administration of glucose for individuals with suspected hypoglycemia.

Justification

When reviewing the evidence, we did not find a difference in most outcomes between the two groups, suggesting clinical equipoise. Only one outcome (blood glucose levels after 20 min) favored the combined (oral + buccal) administration. When reviewing the Evidence to Decision table and examining the cost and ease of access of oral glucose, the task force considered the balance may favor the oral route (the comparison) in awake individuals, however, if oral glucose is not available, the combined oral + buccal option may be considered.

Subgroup considerations

We recognize that in some parts of the world, glucose gels may not be available.

Implementation considerations

Commercial preparations of glucose gel are not widely available.

Monitoring and evaluation

Research priorities

Current research regarding the administration of glucose via the oral + buccal 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).

In addition, more research is needed examining the bioavailability of oral + buccal administration in various populations and the availability of the various forms of glucose available worldwide.