Recommendations- Treatment

Question 21. What is the target blood glucose range for babies diagnosed with neonatal hypoglycaemia?

PICO: Should higher or lower minimum target blood glucose concentration vs. the most common minimum target during treatment (2.6 mmol/L) be used for babies being treated for neonatal hypoglycaemia?

Recommendation 21:

A target blood glucose of ≥2.6 mmol/L should be used for treating neonatal hypoglycaemia within the first 72 hours after birth. [Conditional recommendation]

A target blood glucose of ≥3.4 mmol/L should be used for treating neonatal hypoglycaemia after the first 72 hours after birth.

Justification: There is some evidence supporting the most common target for treatment of ≥2.6 mmol/L and a lack of evidence to justify changing it.

Very low certainty evidence shows that using a lower threshold than 2.6 mmol/L has little to no effect on neurodevelopmental outcomes at 18 months. Low certainty evidence shows use of lower thresholds may result in a large increase in moderate hypoglycaemia (2.0 – 2.6 mmol/L), and a moderate increase in severe hypoglycaemia (<2.0 mmol/L).

Most guidelines recommend a target of ≥2.6 mmol/L for hypoglycaemia in babies, but some advocate for a higher target threshold in older babies. This is because severe and prolonged hypoglycaemia can sometimes indicate congenital hyperinsulinism, which is associated with a high risk of neurodevelopmental impairment.

A blood glucose concentration of 3.3 mmol/L is the threshold for onset of autonomic symptoms in adults experiencing hypoglycaemia, and is the lower target recommended by some for babies with persistent hypoglycaemia (1). It was estimated that this would apply to approximately 4 per 1000 babies so would not have a large impact on feasibility or costs.

Implementation considerations: Consider additional investigations (see recommendation 18) and consultation with an paediatric endocrinologist if hypoglycaemia persists after 72 hours of age.

There are no data on resources required, but with a higher threshold, longer treatment would most likely be necessary.

Monitoring and evaluation: Blood glucose concentrations should be monitored regularly while babies are being treated for hypoglycaemia and for at least 12 hours after treatment stops and the baby is feeding adequately.

Research priorities:

Studies are needed on:

Outcomes of using the target of ≥2.6 mmol/L compared to lower or higher targets.

Health Equity: The impact on health equity is not clear.

Evidence to decision table: refer to Appendix G

Question 22. What are the benefits and risks of buccal dextrose gel for babies diagnosed with neonatal hypoglycaemia?

PICO: Should buccal dextrose gel vs. placebo gel or no gel be used for babies with neonatal hypoglycaemia?

Recommendation 22:

Babies diagnosed with neonatal hypoglycaemia should be treated with 40% oral dextrose gel. [Conditional recommendation]

Justification: Moderate certainty evidence shows that buccal dextrose gel results in a large increase in correction of hypoglycaemia, moderate reduction in admission to NICU and large reduction in separation of mother and baby for treatment of hypoglycaemia. No adverse effects were reported.

Treatment is feasible as it is already being used, and acceptable to caregivers and whānau.

Gel is inexpensive, cost effective, and can be used in any care setting.

Conditional recommendation because there is no information on babies born before 34 weeks' gestation, or effect of different doses and different timings of administration.

Implementation considerations: If baby is clinically stable and able to feed, administer 0.5 ml/kg (200 mg/kg) 40% dextrose gel.

Draw up the prescribed dose in an enteral syringe. Dry the buccal mucosa using a gauze swab. Apply gel to the buccal mucosa in small aliquots using a gloved finger, and massage it in gently. Offer the baby a feed immediately after administering the gel.

If the blood glucose concentration is <2.0mmol/L, dextrose gel alone is unlikely to be sufficient treatment. Administer dextrose gel while arranging transfer to a facility where IV infusion is available.

Dextrose gel can be given to a baby while having skin-to-skin care.

Monitoring and evaluation: Repeat blood glucose concentration testing 30-60 minutes after administering dextrose gel and beginning the feed.

If the repeat blood glucose is < 2.6 mmol/L, repeat the dextrose gel and offer a feed, then test again 30-60 minutes after administering the second dose.

Continue clinical observations. If any subsequent blood glucose concentration is < 2.6 mmol/L, the clinical condition of the baby should be reviewed and referral considered for further investigation and treatment.

Research priorities:

Studies are needed on:

1. The effect of buccal dextrose gel for treatment of neonatal hypoglycaemia on long-term neurodevelopmental impairment.

2. The effect of buccal dextrose gel for treatment of babies born <34 weeks' gestation.

3. The most effective dose, frequency and mode of administration of buccal dextrose gel.

Health Equity: Severe or symptomatic hypoglycaemia is a medical emergency. Not all babies at risk of neonatal hypoglycaemia can be identified before birth, and hypoglycaemia can occur in babies without risk factors. Dextrose gel and capacity accurately to measure blood glucose concentrations should therefore be available as standard emergency equipment wherever newborns are cared for, including in community settings. Carers need appropriate education and resourcing for this.

Provide whānau with information on health benefits and potential adverse effects of dextrose gel treatment. Whānau should also be provided with resources that align with their cultural values. Provide whānau with information on dextrose treatment in multiple mediums (e.g., written, oral, visual).

Evidence to decision table: refer to Appendix G

Question 23. Should formula vs. control be used for treating neonatal hypoglycaemia?

Recommendation 23:

Formula may be considered as a treatment option for babies diagnosed with neonatal hypoglycaemia. [Conditional recommendation]

Justification: Low to very low certainty of evidence shows large to moderate effect of formula on the correction of neonatal hypoglycaemia, and reduction in recurrent hypoglycaemia.

The cost of formula for treatment of hypoglycaemia is likely comparable to that of dextrose gel and significantly lower than intravenous dextrose. Formula is widely available, but acceptability varies among different populations.

Use of formula as a treatment option for neonatal hypoglycaemia could help reduce the need for intravenous dextrose, which is more invasive, costly, and commonly involves NICU admission, with associated economic, emotional and social costs.

Implementation considerations: Consider giving formula 5 to 7 ml/kg as an alternative to intravenous dextrose for babies whose hypoglycaemia persists after two doses of dextrose gel plus breastfeeding.

Whānau should be fully informed about the risks and benefits of both treatment options and be involved in joint decision making.

Ensure that formula is readily available in clinical settings with appropriate protocols to manage the supply and administration of formula as a treatment option for neonatal hypoglycaemia (2, 3).

Carers should ensure that formula use does not undermine breastfeeding efforts, offering guidance to mothers on how to maintain or transition back to breastfeeding after the hypoglycaemia is corrected. Encourage mothers to express breast milk when formula is given as treatment to maintain breast milk supply.

Monitoring and evaluation: Repeat blood glucose concentration testing 60 minutes after administering the formula. Do not repeat formula if blood glucose concentration is ≥2.6 mmol/L. If the repeat blood glucose concentration is <2.6 mmol/L, prompt referral is required for consideration of intravenous dextrose.

Research priorities:

Studies are needed on:

1. Effect of formula compared to intravenous dextrose or donor human milk on correcting neonatal hypoglycaemia, NICU admission rates, and breastfeeding at hospital discharge.
2. The cultural acceptability to whānau of using formula for the treatment of neonatal hypoglycaemia.
3. The optimal amount of formula to be given for the treatment of neonatal hypoglycaemia.
4. The long-term neurological effects on infants treated with formula for neonatal hypoglycaemia.

Health Equity: Communication strategies should be adapted to align with the cultural values and preferences of whānau, particularly in communities where breastfeeding is strongly

preferred. Whānau should be fully informed about the advantages and disadvantages of using formula as a treatment for hypoglycaemia.

Evidence to decision table: refer to Appendix G

Question 24. Should intravenous dextrose vs. other treatment or no treatment be used for treatment of neonatal hypoglycaemia?

Recommendation 24:

Intravenous (IV) dextrose should be given if blood glucose concentration remains < 2.6 mmol/L despite treatment with increased feeding and buccal dextrose gel. Do not give an initial bolus of IV dextrose *routinely*. [Conditional recommendation]

Justification: Using IV dextrose is typically reserved for cases where oral treatment options have been exhausted, but there is very little evidence of benefits and harms.

There is some evidence that treatment of hypoglycaemic babies with an IV bolus is associated with more rapid change in blood glucose concentrations, including increased incidence of high glucose concentrations, and that these are associated with adverse neurodevelopmental outcomes.

One before-and-after study showed that tailoring the dose of IV dextrose and use of an initial bolus depending on the glucose concentration resulted in similar time to resolution of hypoglycaemia but shorter NICU stay and reduced costs.

While IV dextrose itself is inexpensive, the costs associated with NICU care, including administration and staffing, can be significant.

The panel considered that evidence from randomised trials of IV dextrose compared to oral sucrose were not relevant when formulating this recommendation.

Implementation considerations: Start treatment with 30-60ml/kg/d 10% dextrose. Continue feeding if possible.

Consider an initial bolus of 1-2ml/kg of 10% dextrose over 10min only if the initial blood glucose concentration is very low (< 1 mmol/L) or the baby has severe symptomatic hypoglycaemia (seizures or reduced consciousness).

It is important to have an open and honest discussion with parents about the uncertainty regarding the benefits of IV dextrose.

Monitoring and evaluation: Check blood glucose concentration after 1 hour and adjust infusion rate as necessary.

Continue regular monitoring of blood glucose concentrations during IV treatment.

Research priorities:

Studies are needed on:

1. The effects of IV dextrose bolus administration on short and longterm outcomes.

2. The optimal dosage and methods for administering IV dextrose

3. The optimal strategies for weaning babies off IV dextrose and onto full oral feeds.

Health Equity: IV treatment may not be available at all healthcare facilities, so may worsen inequities for those with limited access. Ensure that all babies at risk of neonatal hypoglycaemia and their whānau have prompt access to facilities that can provide IV treatment if needed.

Evidence to decision table: refer to Appendix G

Question 25. Should diazoxide vs. placebo be used for treating neonatal hypoglycaemia?

Recommendation 25:

Consider use of diazoxide if hypoglycaemia persists despite treatment with intravenous dextrose and is severe (<1.5 mmol/L) or unstable. [Conditional recommendation]

Justification: One randomised trial found that a low dose of diazoxide (3 mg/kg/day) for early management of severe or recurrent neonatal transitional hypoglycaemia may result in

a large increase in the correction of hypoglycaemia after completing the loading dose (5 mg/kg). However, diazoxide did not reduce the time to resolution of hypoglycaemia.

One randomised trial conducted in India did not report on critical or important outcomes related to diazoxide use.

Evidence from five observational studies indicated that 71% of babies responded to diazoxide.

Diazoxide may be associated with serious side effects, including pulmonary hypertension, congestive heart failure, oedema, hypertrichosis (excessive hair growth), and necrotising enterocolitis. Most side effects resolve upon discontinuation of the drug, although hypertrichosis may persist for several weeks.

The cost of liquid diazoxide is moderate to high, at $620 per bottle, but costs are much lower (<$1) if prepared by a hospital pharmacy from tablets.

Oral administration of diazoxide may be preferable to parents compared to intravenous administration.

Implementation considerations: Diazoxide is not recommended as a first-line treatment due to significant potential adverse effects.

Discussions with whānau should include detailed information on dosing and possible side effects.

Input from endocrinology specialists is recommended for decision-making, and if hyperinsulinaemic hypoglycaemia is suspected.

Monitoring and evaluation: Plasma insulin concentration should be measured before starting diazoxide.

Babies should be monitored carefully for possible side effects of diazoxide.

Research priorities:

Studies are need on:

1. The long-term effect diazoxide

2. The optimal dosage of diazoxide to minimise the risk of side effects.

Health Equity: Whānau need to be fully informed of the health benefits and potential adverse effects of diazoxide. Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question 26. Should glucagon vs. control be used for neonatal hypoglycaemia?

Recommendation 26:

Consider use of intramuscular glucagon for short-term management of neonatal hypoglycaemia until IV access can be established. [Conditional recommendation]

Justification: Three non-randomised studies showed a large effect in correcting hypoglycaemia, with a large increase in blood glucose concentrations.

The safety of glucagon for treatment of hypoglycaemia has been established in adults, and there is no evidence of differing safety in babies.

Nausea is reported by some adults using glucagon, but it is uncertain whether babies may experience this.

The cost of glucagon was considered moderate to negligible.

Long-term outcomes and safety in babies remain uncertain, necessitating comprehensive information sharing with families for informed decision-making.

Implementation considerations: Severe or symptomatic hypoglycaemia is an emergency. If there is difficulty or delay in starting IV glucose, give glucagon 0.2 mg/kg as an intramuscular injection. Establish an IV infusion as soon as possible. Intramuscular glucagon may not be effective in situations outside of hyperinsulinism, and IV glucose may still be necessary.

The increase in glucose concentration usually occurs within 5-20 minutes. The dose can be repeated after 1 hour if IV access remains problematic, but there may be a smaller increase in glucose concentration in response to the second dose.

In refractory hypoglycaemia, glucagon infusion 5-20 microgram/kg/h may be considered (4).

Monitoring and evaluation: Measuring blood glucose concentration 30 minutes after giving IM glucagon.

Research priorities:

Studies are needed on:

The benefits, adverse effects and long-term outcomes of glucagon use in babies, including optimal dose and route of administration.

Health Equity: Whānau need to be fully informed of the health benefits and potential adverse effects of glucagon. Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

Question 27. What care settings are appropriate?

PICO: Should secondary or tertiary level care settings vs. primary care setting be used for monitoring babies with neonatal hypoglycaemia?

Recommendation 27:

Consider caring for babies who require monitoring for neonatal hypoglycaemia at a primary care setting if timely and accurate blood glucose monitoring is possible, treatment can be initiated if required, e.g. with buccal dextrose gel, and the baby can be transferred promptly to a secondary or tertiary facility if necessary. [Conditional recommendation for either option]

Justification: Based on a UK study, the panel considered that even if all babies were cared for in a tertiary care unit, not all cases of hypoglycaemia would be detected.

Primary care settings are associated with better breastfeeding outcomes, while quicker access to hypoglycaemia treatment in secondary or tertiary settings may lead to improved outcomes.

However, the costs associated with transferring to secondary or tertiary care are considered moderate to high.

There is considerable variability in parental preferences, with some preferring a secondary or tertiary care setting regardless of distance, while others may prioritise proximity to home

Implementation considerations: Other considerations, including maternal health and stability of diabetes management, may play a role in the decision about place of birth.

All babies at risk of hypoglycaemia should have access to accurate blood glucose monitoring. Prompt treatment of hypoglycaemia is essential, so initial treatment such as dextrose gel should be available immediately.

If the blood glucose concentration is <2.0mmol/L, dextrose gel alone is unlikely to be sufficient treatment. Administer dextrose gel while arranging transfer to a facility where IV infusion is available.

Ensure that appropriate glucose analysers and dextrose gel for treatment of neonatal hypoglycaemia are available in all settings where newborn babies are cared for, including in primary units, to avoid potentially widening health inequities.

Monitoring and evaluation: Nil.

Research priorities: Nil.

Health Equity: Refer to health equity summary on Page 32.

Evidence to decision table: refer to Appendix G

References

1. Thornton PS, Stanley CA, De Leon DD, Harris D, Haymond MW, Hussain K, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. The Journal of Pediatrics. 2015;167(2):238-45.
2. Te Whatu Ora – Health New Zealand. Cronobacter species invasive disease, Part of the Communicable Disease Control Manual Wellington: Te Whatu Ora – Health New Zealand; 2024 [cited 2024 December 18]. Available from: https://www.tewhatuora.govt.nz/for-health-professionals/clinical-guidance/communicable-disease-control-manual/cronobacter-species-invasive-disease

3. Word Health Organization (WHO) in collaboration with Food and Agriculture Organization of the United Nations. Safe preparation, storage and handling of powdered infant formula: guidelines: World Health Organization; 2012 [cited 2024 December 18]. Available from: https://www.who.int/publications/i/item/9789241595414
4. Australian Nursing and Midwifery Federation. Glucagon: Guidelines for practice (Version 2.0). Australian Nursing and Midwifery Federation. ; 2020 [cited 2024 December 18]. Available from: https://www.anmfonline.org/wp-content/uploads/2021/06/glucagon-15122020-2.0.pdf