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# Prophylactic Oral Dextrose Gel and Neurosensory Impairment at 2-Year Follow-up of Participants in the hPOD Randomized Trial

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**IMPORTANCE** Prophylactic oral dextrose gel reduces neonatal hypoglycemia, but later benefits or harms remain unclear.

**OBJECTIVE** To assess the effects on later development of prophylactic dextrose gel for infants born at risk of neonatal hypoglycemia.

**DESIGN, SETTING, AND PARTICIPANTS** Prospective follow-up of a multicenter randomized clinical trial conducted in 18 Australian and New Zealand hospitals from January 2015 to May 2019. Participants were late preterm or term at-risk infants; those randomized in 9 New Zealand centers (n = 1359) were included and followed up between January 2017 and July 2021.

**INTERVENTIONS** Infants were randomized to prophylactic 40% dextrose (n = 681) or placebo (n = 678) gel, 0.5 mL/kg, massaged into the buccal mucosa 1 hour after birth.

**MAIN OUTCOMES AND MEASURES** The primary outcome of this follow-up study was neurosensory impairment at 2 years' corrected age. There were 44 secondary outcomes, including cognitive, language, and motor composite Bayley-III scores (mean [SD], 100 [15]; higher scores indicate better performance).

**RESULTS** Of eligible infants, 1197 (91%) were assessed (581 females [49%]). Neurosensory impairment was not significantly different between the dextrose and placebo gel groups (20.8% vs 18.7%; unadjusted risk difference [RD], 2.09% [95% CI, −2.43% to 6.60%]; adjusted risk ratio [aRR], 1.13 [95% CI, 0.90 to 1.41]). The risk of cognitive and language delay was not significantly different between the dextrose and placebo groups (cognitive: 7.6% vs 5.3%; RD, 2.32% [95% CI, −0.46% to 5.11%]; aRR, 1.40 [95% CI, 0.91 to 2.17]; language: 17.0% vs 14.7%; RD, 2.35% [95% CI, −1.80% to 6.50%]; aRR, 1.19 [95% CI, 0.92 to 1.54]). However, the dextrose gel group had a significantly higher risk of motor delay (2.5% vs 0.7%; RD, 1.81% [95% CI, 0.40% to 3.23%]; aRR, 3.79 [95% CI, 1.27 to 11.32]) and significantly lower composite scores for cognitive (adjusted mean difference [aMD], −1.30 [95% CI, −2.55 to −0.05]), language (aMD, −2.16 [95% CI, −3.86 to −0.46]), and motor (aMD, −1.40 [95% CI, −2.60 to −0.20]) performance. There were no significant differences between groups in the other 27 secondary outcomes.

**CONCLUSIONS AND RELEVANCE** Among late preterm and term infants born at risk of neonatal hypoglycemia, prophylactic oral 40% dextrose gel at 1 hour of age, compared with placebo, resulted in no significant difference in the risk of neurosensory impairment at 2 years' corrected age. However, the study may have been underpowered to detect a small but potentially clinically important increase in risk, and further research including longer-term follow-up is required.

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Neonatal hypoglycemia is common in newborns,[1] especially those born preterm, small, or large or to mothers with diabetes.[2] These infants are commonly screened and treated for hypoglycemia, initially with increased feeding or oral dextrose gel,[3-6] and admitted to neonatal intensive care units (NICUs) if hypoglycemia is persistent or severe.[7,8] However, this approach is expensive, separates mother and infant, and interferes with breastfeeding.

Even episodes of hypoglycemia that are clinically undetected, or detected and treated, are associated with adverse childhood outcomes.[9,10] Hence, even the most effective treatment may not be enough to improve outcomes, and prophylaxis should be considered. The Hypoglycemia Prevention With Oral Dextrose (pre-hPOD)[11] dose-finding randomized clinical trial and hPOD[12] randomized clinical trial showed that prophylactic oral 40% dextrose gel reduced hypoglycemia without adverse effects. However, because approximately 30% of all births are considered at risk for hypoglycemia and potentially eligible for prophylaxis, it is essential to assess longer-term benefits and risks before implementation is recommended.

In the follow-up of the dose-finding study (n = 360), the co-primary outcomes of neurosensory impairment and executive function at 2 years were not significantly different between the prophylactic dextrose and placebo groups.[13] There were possible improvements in executive function, language, and motor development, but the study was underpowered to detect clinically meaningful effects.

This study assessed children in the larger trial at 2 years' corrected age to further determine the effect of prophylactic buccal 40% dextrose gel given to infants born at risk of neonatal hypoglycemia on later development, which was a prespecified secondary outcome of the original trial. The hypothesis was that there would be no differences in neurocognitive, health, and growth outcomes between infants randomized to dextrose vs placebo gel.

### Key Points

**Question** Among late preterm and term infants born at risk of neonatal hypoglycemia, does prophylactic oral 40% dextrose gel 1 hour after birth alter the risk of neurosensory impairment at 2 years' corrected age?

**Findings** In this prospective follow-up of a subset of 1321 participants enrolled in a randomized clinical trial, the prevalence of neurosensory impairment was 21% among those randomized to prophylactic oral dextrose gel and 19% among those randomized to placebo gel, a difference that was not statistically significant.

**Meaning** Administration of prophylactic oral dextrose gel to at-risk late preterm and term infants, compared with placebo, resulted in no significant difference in the risk of neurosensory impairment at 2 years' corrected age, although the study may have been underpowered to detect a small but potentially clinically important difference in risk.

## Methods

### Study Design and Participants

Ethics approval was obtained from the New Zealand Health and Disability Ethics Committee. Written informed consent was given by the child's caregiver. The study protocol/statistical analysis plan is available in Supplement 1.

Details of this multicenter, double-blind, placebo-controlled randomized clinical trial have been published.[12,14] In brief, inclusion criteria were 1 or more risk factors for hypoglycemia (mother with diabetes, small [birthweight <2.5 kg or <10th centile], large [birthweight >4.5 kg or >90th centile], or preterm [35 to 36 weeks' gestation]), less than 1 hour after birth, birthweight of 2.2 kg or greater, gestation of 35 weeks or more, no apparent indication for NICU admission, and maternal intention to breastfeed. Randomization was computer-generated with fixed block size of 4, stratified by study site and reason for risk of hypoglycemia. The primary outcome was admission to the NICU.

The trial randomized infants from 18 hospitals in New Zealand and Australia between January 2015 and May 2019 to 40% dextrose or placebo gel, 0.5 mL/kg, massaged into the buccal mucosa 1 hour after birth, followed by a breastfeeding. Blood glucose concentrations were measured at 2 hours and then according to hospital protocol. Dextrose gel did not reduce NICU admission but did reduce hypoglycemia, with a number needed to treat of 21.[12] NICU admission for hypoglycemia, breastfeeding at discharge, and receipt of formula before discharge and at 6 weeks were similar between groups. There were no adverse effects of dextrose gel, and no hyperglycemia.

Families of surviving infants randomized in New Zealand who gave consent for future contact were approached when the child was 2 years old, corrected for preterm birth, to participate in this follow-up study, conducted between January 2017 and July 2021. For logistic reasons, including COVID-19 pandemic restrictions, follow-up of infants randomized in Australia was not possible.

### Procedures

Families, investigators, study staff, and outcome assessors were blinded to treatment allocation. Physicians and trained developmental assessors assessed children in a research clinic or at home, including neurologic examination, parent-reported medical questionnaire, Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III),[15] performance-based executive function,[16] Behavior Rating Inventory of Executive Function–Preschool Version,[17] motion coherence thresholds,[18] growth, and body composition.

Bayley-III assesses cognitive, language, and motor development and parent-reported socioemotional and adaptive behavior.[15] Composite scores have a mean of 100 and SD of 15. Higher scores indicate better performance. A child unable to complete the assessment because of severe delay was assigned a score of 49.

Performance-based executive function was assessed using 4 tasks to quantify simple inhibition (Snack Delay), complex inhibition (Fruit Stroop and Reverse Categorization), and attentional flexibility (Multisearch/Multilocation).[16] Up to 6 points were allocated per task and summed to give a maximum score of 24. Higher scores indicate better performance. Low performance for each task was defined as 2 or less.



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Questionnaire-based executive function was assessed using the Behavior Rating Inventory of Executive Function–Preschool Version, which produces a Global Executive Composite T score with mean (SD) of 50 (10). Lower scores indicate better performance. Low performance was defined as a T score of 65 or greater.

Visual processing was measured using motion coherence thresholds.[18] Children's eye movements were recorded while they watched random dot kinetograms of various coherence (100%, 80%, 60%, 40%, 20%). Two assessors independently determined the lowest coherence at which optokinetic reflex responses were visible on the video, with a third assessor used if there was disagreement. Data were considered missing when video quality was poor or assessors disagreed on the threshold.

Weight was measured by electronic scales to the nearest 0.1 kg, standing height by stadiometer to the last complete 0.1 cm, and head and mid-arm circumference by loop tape to the nearest 0.1 cm. Triceps and subscapular skinfold thickness were measured by Harpenden calipers to the nearest 0.2 cm. The mean of 2 or, if they differed by more than 0.6 mm, the median of 3 measurements was used. Data were converted to *z* scores using World Health Organization growth charts.[19] Abdominal circumference (measured in centimeters) was adjusted for height. Whole-body fat and lean mass were estimated using bioimpedance analysis (ImpediMed Imp SFB7, ImpediMed Inc).

Socioeconomic decile was categorized using the New Zealand Index of Deprivation, where 1 is the lowest and 10 is the highest deprivation decile.[20] Child ethnicity was reported by the caregiver using standard categories and prioritized using Ethnicity New Zealand Standard Classification.[21] Reporting of ethnicity is required in New Zealand.

## Outcomes

All outcomes were prespecified before completion of data collection, analysis, or unblinding (Supplement 1).

The primary outcome (a prespecified secondary outcome in the original trial protocol) was neurosensory impairment, defined as any of the following: blindness (visual acuity <3/60 or >1.3 logMAR), hearing impairment requiring aids, cerebral palsy, developmental delay (Bayley-III cognitive, language, or motor composite score <85), or performance-based executive function total score more than 1.5 SD below the cohort mean.

Secondary outcomes were components of the primary outcome and severity, above-average development, socioemotional and adaptive behavior (Bayley-III composite scores), low visual processing (motion coherence threshold ≥80%), questionnaire-based executive function, history of seizures, allergic and infectious diseases, growth, and body composition.

Cerebral palsy was defined as none, mild (walking), and moderate or severe (not walking but eventually would or permanently nonambulant). Developmental delay was defined as none (Bayley-III cognitive, language, and motor composite scores ≥85), mild (Bayley-III cognitive, language, or motor composite score of 70 to 84), and moderate or severe (Bayley-III cognitive, language, or motor composite score <70). Above-average development was defined by a Bayley-III cognitive, language, or motor composite score greater than 115.

Medical history was collected from parental questionnaire and history taken by the examining physician. Allergic disease was any physician-diagnosed and -treated asthma, eczema, hay fever, or food allergy. Infectious disease was any infection requiring antibiotics, including pneumonia, ear infection, urinary tract infection, tonsillitis, cellulitis, or skin abscess.

## Statistical Analysis

The cohort size was limited by the inception cohort. Based on the previous study,[13] if at least 1162 infants (581 per group) were assessed (85% follow-up), there would be 90% power to detect a 7% absolute difference in the primary outcome between groups, a difference likely to be clinically important (2-sided Fisher exact test, $\alpha = .05$).

All analyses were prespecified unless otherwise stated. Categorical outcomes were compared between groups using $\chi^2$ or Fisher exact tests and log-binomial generalized linear regression. Risk differences (RDs) were estimated using generalized linear regression with a binary distribution and the identity link function. Ordinal outcomes were analyzed using generalized cumulative logit models. For cerebral palsy and developmental delay, none vs mild and none vs moderate or severe were compared using log-binomial generalized linear regression. Continuous outcomes were analyzed using independent sample *t* tests or Wilcoxon rank-sum tests and identity-normal generalized linear regression.

When models failed to converge, the analysis algorithm was optimized by choosing the model with the smallest Akaike Information Criteria from other algorithms for optimization techniques and increasing maximum number of iterations.[22] Models were adjusted for study site, primary reason for risk of hypoglycemia, socioeconomic decile, and multiple births. Body composition analyses were also adjusted for prioritized ethnicity.

Subgroup analyses explored interactions between risk factors for hypoglycemia (maternal diabetes vs others) and sex and the effect of dextrose vs placebo gel on selected neurosensory outcomes using generalized linear models.

Sensitivity analyses excluded infants with a post-neonatal-acquired morbidity or diagnosed congenital or genetic condition likely to influence the outcome and infants who did not receive the assigned study gel (per-protocol analysis). Additional post hoc sensitivity analyses excluded infants whose first language was not English because assessment materials were in English, and infants assessed outside the intended assessment window of 23 to 25 months' corrected age.

All analyses were carried out in SAS version 9.4 (SAS Institute Inc). Infants were analyzed according to their randomization group, excluding infants randomized in error and those randomized in Australia. As prespecified, mode imputation was performed when data were missing for 1 or more components of the performance-based executive function assessment. No other missing data were imputed because it was assumed missing not at random, and children with missing data for a given outcome were excluded from analysis of that outcome.

Unadjusted RDs and unadjusted and adjusted mean differences (MDs) and relative risks (RRs) with 95% CIs are presented. Two-sided tests with 95% CIs were used, with $P < .05$ considered significant. There was no adjustment for multiplicity. Because of the potential for type I error due to multiple



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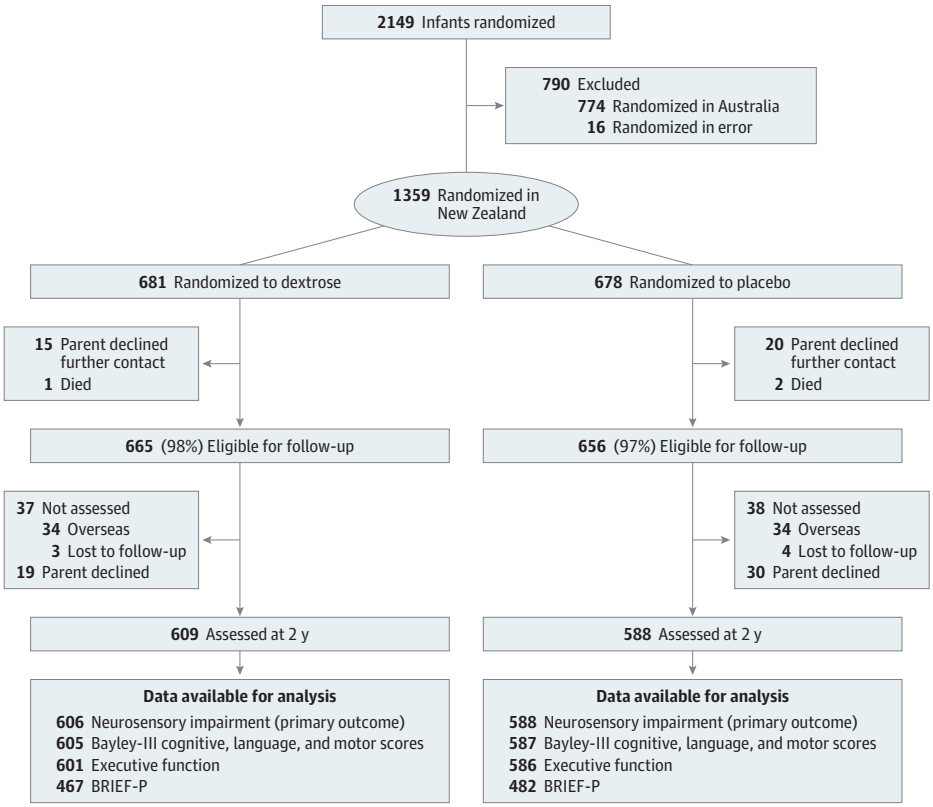
Figure. Study Flow of Recruitment to Assessment at 2 Years




BRIEF-P indicates Behavior Rating Inventory of Executive Function–Preschool Version.

comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

## Results

Of 2149 infants randomized, 16 randomized in error and 774 randomized in Australia were excluded, leaving 1359 infants randomized in New Zealand (**Figure**). Three died after the neonatal period and 35 families declined contact consent. Of 1321 children (97%) eligible for follow-up, 49 families declined, 68 were overseas, 7 were lost to follow-up, and 1197 were assessed at a mean of 24 months' corrected age (91% of eligible and 88% of those randomized): 609 of 665 (92%) randomized to dextrose and 588 of 656 (90%) randomized to placebo gel. Primary outcome data were available for 1194 children. Maternal and infant characteristics were similar between those assessed and not assessed and between randomized groups (**Table 1**).

### Primary Analyses

Neurosensory impairment occurred in 19.8% (236 of 1194); 20.8% (126 of 606) of infants randomized to dextrose gel and 18.7% (110 of 588) of infants randomized to placebo gel (RD, 2.09% [95% CI, −2.43% to 6.60%]; aRR, 1.13 [95% CI, 0.90 to 1.41]) (**Table 2**).

Rates of cognitive and language delays were not significantly different between groups, but the dextrose gel group had significantly higher risk of motor delay (15 of 601 [2.5%] vs 4 of 587 [0.7%]; RD, 1.81% [95% CI, 0.40% to 3.23%]; aRR, 3.79 [95% CI, 1.27 to 11.32]). Infants randomized to dextrose gel had significantly lower Bayley-III composite scores for cognitive (mean [SD], 97.9 [11.6] vs 99.2 [10.8]; aMD, −1.30 [95% CI, −2.55 to −0.05]), language (mean [SD], 97.5 [15.5] vs 99.6 [15.2]; aMD, −2.16 [95% CI, −3.86 to −0.46]), and motor (103.4 [11.1] vs 104.8 [10.1]; aMD, −1.40 [95% CI, −2.60 to −0.20]) performance.

There were no significant differences between groups in low performance-based overall executive function. Infants randomized to dextrose gel had significantly higher risk of low performance for Snack Delay (464 of 601 [77.2%] vs 421 of 586 [71.8%]; RD, 5.36% [95% CI, 0.41% to 10.32%]; aRR, 1.08 [95% CI, 1.01 to 1.15]) but not the other tasks (**Table 3**).

There were no significant differences between groups in moderate or severe neurosensory impairment, hearing impairment, cerebral palsy, developmental delay, above-average development, socioemotional and adaptive behavior, questionnaire-based executive function, low visual processing, history of seizures, allergic and infectious diseases, growth, and body composition. Two infants randomized to placebo gel were blind (Tables 2 and 3; eTable 1 in Supplement 2).

### Secondary Analyses

The effect of dextrose gel on the risk of neurosensory impairment (mild, moderate, or severe) and cognitive, language, motor, and executive function scores did not differ significantly between infants of mothers with diabetes and those with other



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Table 1. Maternal and Infant Characteristics of Children Assessed and Not Assessed at 2 Years

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Assessed | | |
| | Dextrose | Placebo | Not assessed |
| **Mothers**[a] | | | |
| No. | 601 | 582 | 161 |
| Age, mean (SD) [No. of mothers], y | 32.4 (5.4) | 32.4 (5.3) [n = 580] | 31.5 (6.0) |
| Prioritized ethnicity[b] | n = 599 | | n = 153 |
| Asian | 91 (15.2) | 96 (16.5) | 31 (20.3) |
| European | 241 (40.3) | 220 (37.7) | 43 (28.1) |
| Indian | 84 (14.0) | 72 (12.4) | 22 (14.4) |
| Maori | 102 (17.0) | 111 (19.1) | 34 (22.1) |
| Pacific | 52 (8.7) | 51 (8.8) | 18 (11.8) |
| Other | 29 (4.8) | 32 (5.5) | 5 (3.3) |
| Cesarean delivery | 261 (43.4) | 247 (42.4) | 66/159 (41.3) |
| Maternal diabetes | 465 (77.4) | 443 (76.1) | 118/160 (73.3) |
| **Infants** | | | |
| No. | 609 | 588 | 162 |
| Sex | | n = 587 | n = 159 |
| Female | 282 (46.3) | 299 (50.9) | 80 (50.3) |
| Male | 327 (53.7) | 288 (49.1) | 79 (49.7) |
| Gestation, mean (SD) [No. of children], wk | 38.0 (1.2) | 38.0 (1.1) [n = 587] | 38.0 (1.2) [n = 159] |
| Birthweight, mean (SD) [No. of children], g | 3357.3 (662.9) | 3312.9 (630.7) [n = 587] | 3283 (636.1) [n = 159] |
| Birthweight *z* score, mean (SD) | 0.31 (1.2) | 0.25 (1.2) | 0.18 (1.2) |
| One of twins | 52 (8.5) | 44 (7.5) | 8 (5.0) [n = 160] |
| Socioeconomic decile[c] | | | |
| 1-2 (least deprived) | 92 (15.2) | 87 (14.9) | |
| 3-4 | 116 (19.1) | 112 (19.1) | |
| 5-6 | 125 (20.6) | 127 (21.7) | |
| 7-8 | 146 (24.1) | 135 (23.0) | |
| 9-10 (most deprived) | 127 (21.0) | 125 (21.3) | |
| Primary risk factor[d] | | | |
| Infant of mother with diabetes | 461 (75.7) | 442 (75.2) | 118 (72.8) |
| Preterm | 49 (8.1) | 54 (9.2) | 13 (8.0) |
| Small | 61 (10.0) | 61 (10.4) | 19 (11.7) |
| Large | 38 (6.2) | 31 (5.2) | 12 (7.4) |
| Any episodes of hypoglycemia[e] | 232 (38.2) | 258 (44.0) | 59/157 (37.6) |
| ≥3 episodes of hypoglycemia[e] | 29 (4.8) | 34 (5.8) | 7/157 (4.5) |
| Any episodes of severe hypoglycemia[f] | 53 (8.7) | 54 (9.2) | 16/157 (10.2) |
| First blood glucose concentration, mean (SD) [No. of children], mg/dL[g] | 57.4 (13.8) [n = 605] | 54.1 (12.2) [n = 586] | 55.4 (13.2) [n = 156] |

SI conversion factor: To convert glucose to mmol/L, multiply by 0.0555.

[a] Mothers included once per pregnancy per treatment group because there were mothers with more than 1 infant and more than 1 pregnancy in this cohort.

[b] Self-reported maternal ethnicity at birth prioritized according to the New Zealand Ministry of Health classifications. Other maternal ethnicity includes 4 each of African, Middle Eastern, Nepalese, and South African ethnicity; 3 each of Latin American and Malaysian ethnicity; 2 of Indonesian ethnicity; 1 each of Canadian/Brazilian, Colombian, Fijian, Hawaiian, Kurdish, Lebanese, Malaysian Indian, Mauritian, and Somali ethnicity; and 25 who did not further specify.

[c] New Zealand Socioeconomic Deprivation Profile. Decile 1 is least deprived and decile 10 is most deprived. No data were available for infants not assessed.

[d] Primary risk factors are reported in prioritized order because an infant can have more than 1 primary risk factor.

[e] Hypoglycemia is any blood glucose concentration of less than 47 mg/dL in the first 48 hours.

[f] Severe hypoglycemia is any blood glucose concentration of less than 36 mg/dL in the first 48 hours.

[g] Measured 2 hours after birth.

risk factors for hypoglycemia, or between boys and girls (eTables 2 and 3 in Supplement 2).

Sensitivity analyses excluding 9 infants with postneonatal diagnoses likely to affect outcome (dextrose: 6 of 609 [1%] vs placebo: 3 of 588 [1%]) and 13 infants who did not receive the assigned study gel (dextrose: 10 of 609 [2%] vs placebo: 3 of 588 [1%]) did not alter the findings (eTables 4 and 5 in Supplement 2). Post hoc analyses excluding 426 infants whose first language was not English (dextrose: 210 of 609 [34%] vs placebo: 216 of 588 [37%]) and 202 infants assessed outside the



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Table 2. Primary Outcome and Neurocognitive Secondary Outcomes in Children Randomized to Dextrose or Placebo Gel[a]

| Outcome | No./total (%) | | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| | Dextrose (n = 609) | Placebo (n = 588) | | | | |
| **Primary outcome** | | | | | | |
| Neurosensory impairment[b] | 126/606 (20.8) | 110/588 (18.7) | 2.09 (−2.43 to 6.60) | 1.11 (0.88 to 1.40) | 1.13 (0.90 to 1.41) | .29 |
| **Secondary outcomes** | | | | | | |
| Moderate or severe neurosensory impairment[b] | 24/606 (4.0) | 16/588 (2.7) | 1.24 (−0.80 to 3.28) | 1.46 (0.78 to 2.71) | 1.51 (0.81 to 2.80) | .20 |
| Blind | 0/605 | 2/587 (0.3) | −0.34 (NE) | NE | NE | NE |
| Hearing impairment | 1/605 (0.2) | 2/587 (0.3) | −0.18 (−0.75 to 0.40) | 0.49 (0.04 to 5.35) | 0.51 (0.05 to 5.63) | .58 |
| Cerebral palsy | 1/601 (0.2) | 2/583 (0.3) | −0.18 (−0.75 to 0.40) | 0.49 (0.04 to 5.35) | 0.57 (0.05 to 6.41) | .65 |
| None | 600/601 (99.8) | 581/583 (99.7) | 0.18 (−0.40 to 0.75) | | | .85 |
| Mild | 1/601 (0.2) | 0/583 | 0.17 (NE) | NE | NE | |
| Moderate or severe | 0/601 | 2/583 (0.3) | −0.34 (NE) | NE | NE | |
| Developmental delay[c] | 114/601 (19.0) | 94/586 (16.0) | 2.85 (−1.49 to 7.18) | 1.18 (0.92 to 1.52) | 1.21 (0.94 to 1.54) | .13 |
| None ≥85 | 487/601 (81.0) | 492/586 (84.0) | −3.36 (−7.67 to 0.95) | | | .11 |
| Mild 70 to 84 | 91/601 (15.2) | 82/586 (14.0) | 1.15 (−2.87 to 5.17) | 1.10 (0.84 to 1.45) | 1.14 (0.87 to 1.49) | |
| Moderate or severe <70 | 23/601 (3.8) | 12/586 (2.0) | 1.78 (−0.14 to 3.70) | 1.89 (0.95 to 3.77) | 1.89 (0.95 to 3.75) | |
| Cognitive delay[c] | 46/605 (7.6) | 31/587 (5.3) | 2.32 (−0.46 to 5.11) | 1.44 (0.93 to 2.24) | 1.40 (0.91 to 2.17) | .13 |
| None ≥85 | 559/605 (92.4) | 556/587 (94.7) | −2.32 (−5.11 to 0.46) | | | .07 |
| Mild 70 to 84 | 37/605 (6.1) | 30/587 (5.1) | 1.01 (−1.61 to 3.62) | 1.21 (0.76 to 1.94) | 1.18 (0.74 to 1.86) | |
| Moderate or severe <70 | 9/605 (1.5) | 1/587 (0.2) | 1.32 (0.30 to 2.34) | 8.83 (1.12 to 69.59) | 9.36 (1.20 to 72.73) | |
| Language delay[c] | 103/605 (17.0) | 86/586 (14.7) | 2.35 (−1.80 to 6.50) | 1.16 (0.89 to 1.51) | 1.19 (0.92 to 1.54) | .19 |
| None ≥85 | 502/605 (83.0) | 500/586 (85.3) | −2.35 (−6.50 to 1.80) | | | .29 |
| Mild 70 to 84 | 84/605 (13.9) | 74/586 (12.6) | 1.26 (−2.60 to 5.11) | 1.11 (0.83 to 1.49) | 1.15 (0.86 to 1.53) | |
| Moderate or severe <70 | 19/605 (3.1) | 12/586 (2.1) | 1.09 (−0.71 to 2.90) | 1.56 (0.76 to 3.17) | 1.57 (0.77 to 3.18) | |
| Motor delay[c] | 15/601 (2.5) | 4/587 (0.7) | 1.81 (0.40 to 3.23) | 3.66 (1.22 to 10.98) | 3.79 (1.27 to 11.32) | .02 |
| None ≥85 | 586/601 (97.5) | 583/587 (99.3) | −1.81 (−3.23 to −0.40) | | | .15 |
| Mild 70 to 84 | 11/601 (1.8) | 4/587 (0.7) | 1.15 (−0.11 to 2.41) | 2.70 (0.86 to 8.45) | 2.82 (0.90 to 8.77) | |
| Moderate or severe <70 | 4/601 (0.7) | 0/587 | 0.67 (NE) | NE | NE | |
| Above-average development[c] | 113/601 (18.8) | 123/586 (21.0) | −2.19 (−6.73 to 2.36) | 0.90 (0.71 to 1.13) | 0.90 (0.72 to 1.13) | .37 |
| Cognitive score >115 | 17/605 (2.8) | 26/587 (4.4) | −1.62 (−3.74 to 0.51) | 0.63 (0.35 to 1.16) | 0.67 (0.37 to 1.22) | .19 |
| Language score >115 | 67/605 (11.1) | 77/586 (13.1) | −2.07 (−5.78 to 1.64) | 0.84 (0.62 to 1.15) | 0.84 (0.62 to 1.14) | .26 |
| Motor score >115 | 61/601 (10.1) | 62/587 (10.6) | −0.41 (−3.88 to 3.06) | 0.96 (0.69 to 1.34) | 0.96 (0.69 to 1.35) | .82 |

(continued)



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Table 2. Primary Outcome and Neurocognitive Secondary Outcomes in Children Randomized to Dextrose or Placebo Gel[a] (continued)

| Outcome | No./total (%) | | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| | Dextrose (n = 609) | Placebo (n = 588) | | | | |
| Bayley-III, mean (SD) [No. of children][c] | | | | | | |
| Cognitive score | 97.9 (11.6) [n = 605] | 99.2 (10.8) [n = 587] | −1.31 (−2.59 to −0.03) | | −1.30 (−2.55 to −0.05) | .04 |
| Language score | 97.5 (15.5) [n = 605] | 99.6 (15.2) [n = 586] | −2.14 (−3.88 to −0.40) | | −2.16 (−3.86 to −0.46) | .01 |
| Motor score | 103.4 (11.1) [n = 601] | 104.8 (10.1) [n = 587] | −1.37 (−2.57 to −0.16) | | −1.40 (−2.60 to −0.20) | .02 |
| Social-emotional behavior score | 105.8 (15.9) [n = 235] | 107.2 (17.0) [n = 243] | −1.48 (−4.43 to 1.48) | | −1.52 (−4.49 to 1.44) | .31 |
| Adaptive behavior score | 99.8 (15.6) [n = 235] | 100.5 (16.5) [n = 245] | −0.67 (−3.56 to 2.21) | | −0.81 (−3.73 to 2.12) | .59 |

Abbreviations: MD, mean difference; NE, not estimable; RD, risk difference; RR, risk ratio.

[a] See eTables 4-7 in Supplement 2 for sensitivity analyses.

[b] Neurosensory impairment includes blindness, deafness, cerebral palsy, developmental delay (Bayley-III cognitive, language, or motor composite score <85), or performance-based executive function total score more than 1.5 SD below the cohort mean. Moderate or severe neurosensory impairment is blindness, deafness, moderate or severe cerebral palsy, or moderate or severe developmental delay (Bayley-III cognitive, language, or motor composite scores <70).

[c] Composite scores: mean (SD), 100 (15); range, 40-160, with higher scores indicating better performance. One child included in the dextrose group was assigned a score of 49 for the Bayley-III scales due to a severe delay. As noted in the Methods section, this child was the only one to have an assigned score.

intended window of 23 to 25 months (dextrose: 111 of 609 [18%] vs placebo: 91 of 588 [15%]) also did not alter the findings (eTables 6 and 7 in Supplement 2).

## Discussion

In late preterm and term infants born at risk of neonatal hypoglycemia, prophylactic oral 40% dextrose gel at 1 hour of age, compared with placebo, resulted in no significant difference in the risk of neurosensory impairment at 2 years' corrected age.

This finding is consistent with previous reports on the safety of oral dextrose gel used to treat and prevent hypoglycemia.[13,23] However, the 95% CI for the primary outcome suggests up to a 7% increase in neurosensory impairment with dextrose gel vs placebo; an absolute difference of 7% in the primary outcome may be clinically important. There were small differences in some components of the Bayley-III scales, but Bayley-III scales have only modest predictive value for later cognitive[24] and motor[25,26] function. In addition, the findings were consistent across different domains and in the different subgroup and sensitivity analyses. Therefore, caution is warranted before using prophylactic dextrose gel. Further follow-up of this trial cohort at school age will help clarify whether prophylactic dextrose gel is associated with any later benefits or harms.

In contrast, 2-year follow-up of the dose-finding trial reported possible benefits of dextrose gel prophylaxis in many of the same developmental domains.[13] Specifically, higher dextrose doses were associated with improved Bayley-III composite language scores and executive function, and any dose was associated with higher motor scores (MD, 2.7 [95% CI, 0.04 to 5.37]), although this was no longer significant after adjustment.[13]

The reason for these conflicting findings is unclear. It is possible the dose is important. This trial used a single dose of 200 mg/kg of dextrose gel, selected from previous findings as having the greatest efficacy for preventing hypoglycemia with the fewest limitations, whereas in the dose-finding trial better outcomes were seen at 2 years with greater cumulative doses (200, 400, 600, and 1000 mg/kg).[13] However, there were no differences between dosage groups in the lowest blood glucose concentration or the number of hypoglycemic episodes to suggest that these may have contributed to better outcomes.

There are several other differences between the trial cohorts. The dose-finding trial participants were recruited from 2 hospitals that used the same guideline for management of hypoglycemia, consistently used high-quality methods for blood glucose measurements, 75% were infants of mothers with diabetes, and the overall rate of hypoglycemia was 45%. In contrast, this trial recruited from 9 New Zealand hospitals using several different guidelines, 17% of glucose measurements were done using less accurate cot-side glucometers, 80% were infants of mothers with diabetes, and the rate of hypoglycemia was 40%. Nevertheless, the prevalence of neurodevelopmental impairment at 2 years was similar in both cohorts (19% in the dose-finding trial, 20% in this trial) and it is difficult to understand why dextrose gel prophylaxis might have opposite effects in view of these small differences between trials. These outcome differences may simply reflect



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Table 3. Additional Neurocognitive and Health Secondary Outcomes in Children Randomized to Dextrose or Placebo Gel[a]

| Outcome | No./total (%) | | RD/MD (95% CI) | RR (95% CI) | Adjusted RR/MD (95% CI) | *P* value |
|---|---|---|---|---|---|---|
| | Dextrose (n = 609) | Placebo (n = 588) | | | | |
| Poor executive function[b] | 34/601 (5.7) | 35/586 (6.0) | −0.32 (−2.98 to 2.35) | 0.95 (0.60 to 1.50) | 0.94 (0.59 to 1.47) | .77 |
| Executive function composite score, mean (SD) [No. of children][b] | 10.4 (4.4) [n = 601] | 10.6 (4.5) [n = 586] | −0.24 (−0.75 to 0.27) | | −0.27 (−0.76 to 0.23) | .29 |
| Simple inhibition (Snack Delay task) score ≤2[c] | 464/601 (77.2) | 421/586 (71.8) | 5.36 (0.41 to 10.32) | 1.07 (1.01 to 1.15) | 1.08 (1.01 to 1.15) | .03 |
| Complex inhibition (Fruit Stroop task) score ≤2[c] | 305/597 (51.1) | 284/585 (48.5) | 2.54 (−3.16 to 8.25) | 1.05 (0.94 to 1.18) | 1.05 (0.94 to 1.17) | .41 |
| Complex inhibition (Reverse Categorisation task) score ≤2[c] | 468/598 (78.3) | 450/585 (76.9) | 1.34 (−3.42 to 6.10) | 1.02 (0.96 to 1.08) | 1.00 (0.94 to 1.06) | .98 |
| Attentional flexibility (Multisearch/Multilocation Task) score ≤2[c] | 86/597 (14.4) | 108/586 (18.4) | −4.03 (−8.25 to 0.20) | 0.78 (0.60 to 1.01) | 0.79 (0.61 to 1.02) | .07 |
| BRIEF GEC T score ≥65[d] | 60/467 (12.8) | 62/482 (12.9) | −0.02 (−4.28 to 4.25) | 1.00 (0.72 to 1.39) | 1.00 (0.72 to 1.39) | .99 |
| BRIEF GEC T score, mean (SD) [No. of children][d] | 49.4 (12.4) [n = 467] | 49.8 (12.8) [n = 482] | −0.33 (−1.94 to 1.28) | | −0.27 (−1.88 to 1.34) | .74 |
| Motion coherence threshold ≥80%[e] | 55/302 (18.2) | 49/308 (15.9) | 2.30 (−3.68 to 8.28) | 1.14 (0.81 to 1.63) | 1.15 (0.81 to 1.63) | .43 |
| Any seizures | 21/605 (3.5) | 21/587 (3.6) | −0.11 (−2.20 to 1.99) | 0.97 (0.54 to 1.76) | 0.95 (0.53 to 1.72) | .86 |
| Afebrile | 5/605 (0.8) | 5/587 (0.9) | −0.03 (−1.06 to 1.01) | 0.97 (0.28 to 3.34) | 1.00 (0.29 to 3.43) | .99 |
| Febrile | 17/605 (2.8) | 17/587 (2.9) | −0.09 (−1.98 to 1.81) | 0.97 (0.50 to 1.88) | 0.96 (0.50 to 1.86) | .91 |
| Allergic disease | 207/605 (34.2) | 212/587 (36.1) | −1.90 (−7.33 to 3.53) | 0.95 (0.81 to 1.11) | 0.95 (0.82 to 1.11) | .53 |
| Infectious disease | 370/605 (61.2) | 349/587 (59.5) | 1.70 (−3.86 to 7.26) | 1.03 (0.94 to 1.13) | 1.01 (0.92 to 1.11) | .83 |

Abbreviations: BRIEF GEC, Behavior Rating Inventory of Executive Function–Global Executive Composite Score; MD, mean difference; RD, risk difference; RR, risk ratio.

[a] Adjustments are for study site, primary reason for risk of hypoglycemia, socioeconomic decile at birth, and multiple births. Refer to eTables 4-7 in Supplement 2 for sensitivity analyses of executive function outcomes.

[b] Poor executive function is defined as an executive function total composite score more than 1.5 SD below the mean. Composite score range, 0-24, with higher scores indicating better performance.

[c] Task scores range, 0-6, with higher scores indicating better performance.

[d] Parent-reported executive function: mean (SD) score of 50 (10), with lower scores indicating better performance; poor performance = T score of 65 or greater.

[e] Motion coherence thresholds, a measure of visual processing, range from 0% to 100%, with lower thresholds indicating better performance; poor performance = threshold of 80% or greater.

chance, or there may be other unmeasured differences between groups despite randomization, emphasizing the importance of follow-up and replication in determining the likely effect of clinical interventions.

High and unstable glucose concentrations, particularly immediately after hypoglycemia, have been associated with neurosensory impairment,[27] possibly due to oxidative stress with glucose reperfusion injury.[28] However, it is extremely unlikely that the dose of dextrose gel used in this trial resulted in high or unstable glucose concentrations. A rapid rise in glucose concentrations after hypoglycemia was previously seen among infants who received intravenous dextrose but not among those who received 200-mg/kg dextrose gel.[29] Further, in the dose-finding trial, continuous glucose monitoring showed that prophylactic dextrose gel increased rather than decreased glycemic stability[30] and there was no hyperglycemia detected in either the dose-finding trial or this trial.

It is also possible that the reduction in early hypoglycemia after prophylactic dextrose gel may have led to less monitoring and potentially to underdiagnosis or delayed treatment of late-onset hypoglycemia contributing to worse outcomes. However, the number of blood tests and the proportion of infants treated for hypoglycemia were not different between randomized groups, making this explanation unlikely.[12]

This study had several strengths. The cohort derived from a randomized clinical trial with a high follow-up rate that was adequately powered to detect clinically meaningful differences in outcomes at 2 years. The comprehensive assessment included standardized measures[15,17] and assessments designed for infants born at risk of hypoglycemia.[16,18]

### Limitations

This study had limitations. First, it may have been underpowered to detect small but potentially clinically relevant differences in neurosensory impairment between groups. Second, generalizability may be limited because most participants were infants of mothers with diabetes.

## Conclusions

Among late preterm and term infants born at risk of neonatal hypoglycemia, prophylactic oral 40% dextrose gel at 1 hour of age, compared with placebo, resulted in no significant difference in the risk of neurosensory impairment at 2 years' corrected age. However, the study may have been underpowered to detect a small but potentially clinically important increase in risk, and further research including longer-term follow-up is required.



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## ARTICLE INFORMATION

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