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# Delivery room dextrose gel for preterm hypoglycaemia (the GEHPPI study): a randomised placebo-controlled trial

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## ABSTRACT

**Objective** Early hypoglycaemia at the time of neonatal intensive care unit (NICU) admission is common in very/extreme preterm infants. This study aimed to determine whether buccal dextrose gel in the delivery room (DR) would improve rates of early hypoglycaemia in this population.

**Design** Randomised, blinded, placebo-controlled trial.

**Setting** Four level-3 and one level-2 neonatal units.

**Patients** Inborn infants≤32+0 weeks gestational age (GA).

**Interventions** Infants were randomised to 40% dextrose or placebo gel in the DR (≤29+0 GA: 0.5 mL gel, ≥29+1 GA: 1 mL gel).

**Main outcome measure** Hypoglycaemia (<1.8 mmol/L) measured at the time of first intravenous access at NICU admission.

**Results** Between November 2020 and August 2022, the recruitment rate was slow (impacted by the requirement for antenatal consent). This fact, coupled with finite research resources, led to a decision to end recruitment early. Data analysis of 169 newborns (33% of target sample size) showed no significant difference in the frequency of the primary outcome between dextrose 24/84 (29%) and placebo 25/85 (29%) groups (OR 0.95; 95% CI 0.49 to 1.86; p=0.88). A post-hoc analysis indicated that the trial had a low (47% conditional power) chance of detecting a statistically significant benefit from the intervention (had the target sample been achieved).

**Conclusions** This study showed no evidence of benefit of 40% dextrose gel on rates of hypoglycaemia at NICU admission. Management of these vulnerable newborns should continue to focus on vascular access and commencement of dextrose-containing intravenous fluids as early as possible.

**Trial registration number** NCT04353713.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Very/extreme preterm newborns are often hypoglycaemic prior to achieving vascular access and commencing dextrose infusions in the neonatal intensive care unit (NICU). In clinical practice buccal dextrose gel is commonly used as a treatment of hypoglycaemia in late-preterm/term newborns.

### WHAT THIS STUDY ADDS

⇒ Giving 40% dextrose gel to very/extreme preterm newborns in the delivery room did not show benefit (compared with placebo) on rates of hypoglycaemia (<1.8 mmol/L) measured at the time of initial vascular access in the NICU.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ As our study did not show benefit, and in the absence of high-quality evidence in the literature showing benefit of dextrose gel, we suggest that management of this very/extreme preterm population should continue to focus on vascular access and early commencement of dextrose containing intravenous fluids.

## INTRODUCTION

It is known that severe hypoglycaemia (symptomatic/prolonged) occurring in term infants is associated with pathological cerebral MRI changes[1 2] and impaired neurodevelopment function.[1–3] Similarly, in preterm infants, severe or recurrent hypoglycaemia is associated with a neurodevelopmental delay at 3.5–5 years.[4 5] However, the effect of less severe hypoglycaemia (moderate/intermittent) on neurodevelopmental outcomes is less certain. In term infants (or late-preterm) exposed to less severe hypoglycaemia, no increased neurodevelopmental delay at either 2[6] or 9 years[7] is reported. For moderately preterm (or younger) infants exposed to less severe hypoglycaemia the evidence is conflicting: some preterm studies report increased neurodevelopment delays at 18 months[8] and lower academic achievement scores at 10 years[9]; while other studies report no increased risk of neurodevelopment delay at 2 and 15 years[10 11] or no deficits in cognitive/academic scores up to 18 years.[12] While avoiding more severe hypoglycaemia in these preterm infants is commonly agreed upon, given the evidence, it seems prudent to also avoid episodes of less severe hypoglycaemia in this vulnerable population.

From birth, very/extreme preterm newborns have high glucose utilisation rates, limited glycogen stores, delayed induction of enzymes of gluconeogenesis and limited lipid stores. As such, hypoglycaemia is almost unavoidable in the first few hours

after birth if exogenous glucose is not administered.[4 13 14] Early establishment of nutrition and exogenous glucose delivery are critical interventions, during the golden first hour of postnatal life, for both very low birth weight and extremely low birth weight infants.[15] Despite improvements in delivery room (golden hour) management, early hypoglycaemia occurs in approximately 20–40% of very preterm infants.[12 16 17] It is these infants who often receive rescue intravenous dextrose boluses[18] on establishment of intravenous access. Recently a systematic review of the literature, regarding delivery room exogenous glucose delivery to improve rates of early/admission hypoglycaemia, indicated that there are few studies that address this issue, and that it is unclear whether the included interventions impacted on rates of early hypoglycaemia in these preterm newborns.[19]

Over the last 10 years, the use of buccal dextrose gel to 'treat' hypoglycaemia in late-preterm or term infants has resulted in fewer admissions to the neonatal intensive care unit (NICU) for hypoglycaemia.[20–24] In more recent years studies have examined buccal dextrose gel as 'prophylaxis' of hypoglycaemia in late-preterm or term infants, with results showing reduced hypoglycaemia, but no significant difference in the proportion of newborns admitted to NICU for hypoglycaemia.[25–27] To date, very preterm newborns have not been included in studies of either treatment or prophylaxis of hypoglycaemia using dextrose gel.[28 29] In this study, it was hypothesised that buccal dextrose gel may have a direct benefit to normoglycaemia in the non-feeding very preterm newborn, specifically during the early period of the fetal to neonatal transition (delivery room), prior to admission to NICU and definitive intravenous access being established. Our primary hypothesis was that buccal dextrose gel, given in the delivery room, would decrease rates of early hypoglycaemia in newborn infants born≤32+0 weeks gestational age (GA).

## METHODS

### Trial design

This was a multicentre, randomised, placebo-controlled trial that compared dextrose versus placebo buccal gel for the prevention of early postnatal hypoglycaemia in newborn infants born≤32+0 weeks GA. The study protocol was registered on ClinicalTrials.gov prior to the first participant enrolment.

### Blood glucose measurement

In this study, we examined two thresholds of early hypoglycaemia: blood glucose<1.8 mmol/L and blood glucose<2.6 mmol/L. The study protocol dictated that blood glucose measurement for the primary study outcome consisted of either a glucose oxidase enzymatic, amperometric method (blood gas analyser or equivalent), or plasma (laboratory) glucose measurement. A blood glucose value of 'un-recordable' (in the setting of hypoglycaemia) was assigned the absolute value of 0.1 mmol/L below the lower limit of clinical quantification of the individual gas machine in the study site (lower limit range: 0.2–1.1 mmol/L for the various gas machines across sites). For secondary study outcomes, any method of blood glucose measurement (bedside glucometer/gas analyser/laboratory) was accepted.

### Eligibility and exclusions

Eligibility criteria included being inborn in a study centre at a gestation of≤32+0 weeks GA. This included newborns of singleton or multiple pregnancies. Antenatal signed informed consent was required, and no deferred/waiver of consent was permitted. Mothers on medications potentially impacting neonatal glycaemia were included (see list in table 1). Exclusion criteria consisted of any infant with an antenatal diagnosis of a major congenital anomaly, chromosomal abnormality or known terminal condition (postnatal palliative care).

**Table 1** Characteristics of intention-to-treat population

| Variable | Dextrose (n=84) n (%)* | Placebo (n=85) n (%)* |
|---|---|---|
| **Maternal** | | |
| Antenatal steroids† | | |
| Complete | 67 (80) | 64 (75) |
| Incomplete | 16 (19) | 20 (24) |
| None | 1 (1) | 1 (1) |
| Magnesium sulfate | 73 (87) | 79 (93) |
| Chorioamnionitis | 8 (10) | 8 (9) |
| PET/hypertension | 17 (20) | 17 (20) |
| Diabetes | | |
| Pre-pregnancy | 2 (2) | 2 (2) |
| Gestational | 7 (8) | 10 (12) |
| None | 75 (90) | 73 (86) |
| On medication potentially impacting neonatal glycaemia‡ | 20 (24) | 20 (23) |
| Race/ethnicity | | |
| White | 75 (90) | 72 (85) |
| African | 2 (2) | 4 (5) |
| Asian | 6 (7) | 6 (7) |
| Hispanic | 1 (1) | 3 (3) |
| Mode of delivery | | |
| Caesarean section | 67 (80) | 64 (75) |
| Vaginal | 17 (20) | 21 (25) |
| **Neonatal** | | |
| Female sex | 41 (49) | 42 (49) |
| Infant of multiple pregnancy | 29 (35) | 24 (28) |
| Gestational cohort | | |
| 29+1 to 32+0 | 45 (54) | 48 (56) |
| ≤29+0 | 39 (46) | 37 (44) |
| Birth weight (g)—mean (SD) | | |
| 29+1 to 32+0 | 1399 (308) | 1473 (387) |
| ≤29+0 | 898 (273) | 895 (310) |
| Apgar score—median (IQR)§ | | |
| 1 min | 7 (4) | 7 (3) |
| 5 min | 9 (1) | 9 (1) |
| Arterial cord pH (mmol/L)—mean (SD)¶ | 7.30 (0.09) | 7.29 (0.10) |
| Age at admission temperature (min)—median (IQR) | 24 (11) | 24 (15) |
| Admission temperature (Celsius)—mean (SD) | 36.9 (0.58) | 36.9 (0.55) |
| **Intervention related** | | |
| Age at gel (min)—mean (SD)** | 14.0 (7) | 12.7 (7) |
| Gel spill** | | |
| None | 38 (46) | 51 (60) |
| Small | 37 (45) | 29 (34) |
| Medium | 7 (8) | 5 (6) |
| Large | 1 (1) | 0 (0) |
| Age at primary outcome (min)—median (IQR) | 54 (29) | 52 (28) |
| Primary outcome measurement method | | |
| Amperometric | 73 (87) | 78 (92) |
| Photometric | 11 (13) | 7 (8) |

*Unless otherwise stated.
†Vermont Oxford Network definition of variables (unless otherwise indicated).
‡Mothers receiving (within 48 hours of delivery) medications that have known potential to impact neonatal glycaemic control (insulin, oral hypoglycaemic agents, beta-blockers, indomethacin, calcium channel blockers).
§84 in the placebo group and 83 in the dextrose group.
¶62 in the placebo group and 58 in the dextrose group.
**85 in the placebo group and 83 in the dextrose group.
PET, pre-eclampsia toxaemia.

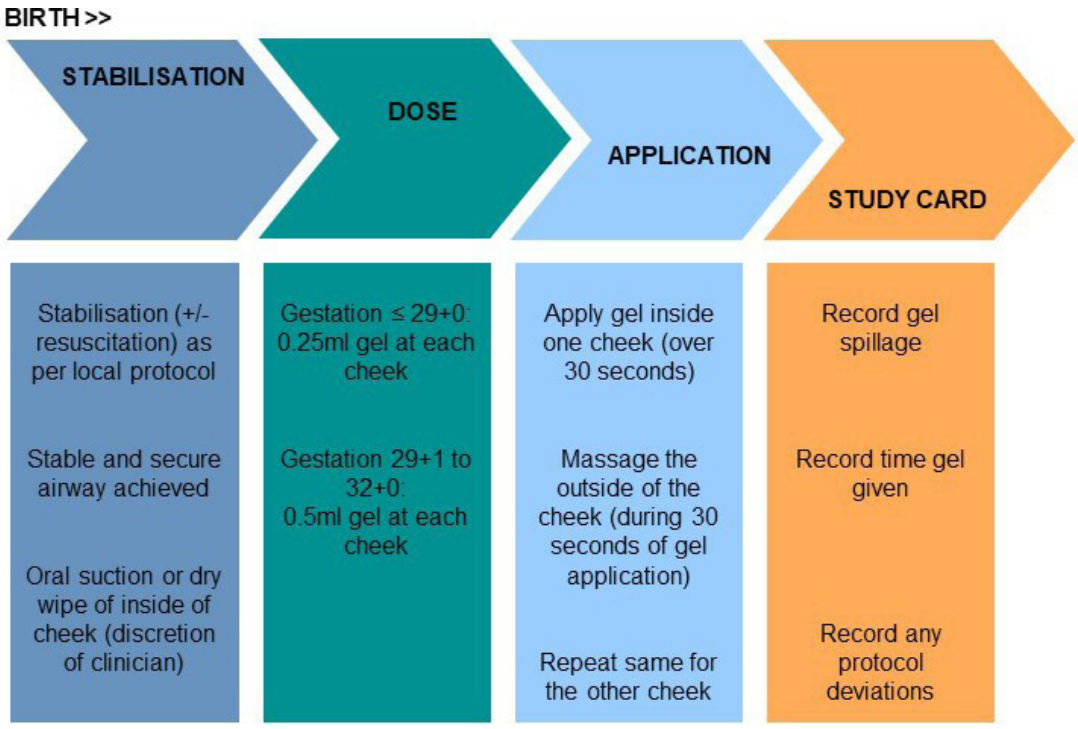


**Figure 1** Study intervention steps.

## Study intervention

The study intervention consisted of 40% dextrose buccal gel. For newborns≤29+0 weeks GA a total dose of 0.5 mL of gel was administered, while for newborns≥29+1 weeks GA a total dose of 1 mL of gel was administered (dosing background information in online supplemental material). In the minutes prior to birth the attending clinician selected the next sequential study envelope from the study fridge. Study gel was produced by Biomed (Auckland, New Zealand) which had previously provided the study gel for the Sugar Babies[24] and hPOD[26] trials. The allocated study envelope contained a single pre-packaged syringe of 40% dextrose gel (constituents=dextrose, carboxymethylcellulose, citric acid (excipient for acid-base balance) and water) or identical-appearing 2% carboxymethylcellulose placebo gel (constituents=carboxymethylcellulose and water).

The study gel was applied immediately following newborn stabilisation (and/or resuscitation) in the delivery room (figure 1). The newborn required a secure airway (defined as: self-ventilating, or on nasal continuous positive airway pressure (nCPAP), or intubated) prior to applying the study intervention. Over 30 s, half the dose of gel was gently squeezed from the syringe and directed (by the clinician's finger located at the corner of the newborn's mouth) onto the inside surface of one cheek. During these same 30 s external massage of that cheek occurred. This procedure was repeated for the other cheek (figure 1). The team member recorded buccal gel spillage (small=few drops; moderate=half of volume administered; large=nearly all of volume administered).

## Randomisation and blinding

Randomisation was stratified by study site and gestational age (≤29+0, and 29+1 to 32+0 weeks GA). Newborns from multiple births were randomised independently. Newborns were randomly assigned in a 1:1 ratio in blocks of six. Group allocation was based on the newborn receiving the next sequential numbered envelope (study syringe inside) from either of two boxes (based on the two gestational age cohorts) in the study fridge at each study site. Randomisation was prepared by the trial pharmacist, who was not involved with perinatal delivery room management or study gel application. Further, the company producing the gel syringes provided a coded list ('A' vs 'B') to allow the trial pharmacist to prepare randomisation while remaining blinded to the final group allocation. Families, clinical staff, data collectors and data analysts were all blinded to the allocations.

## Outcome assessment

The primary outcome was hypoglycaemia<1.8 mmol/L measured at the time of first intravenous access in the NICU. Hypoglycaemia<1.8 mmol/L was chosen as this value lies mid-way between the lower and higher operational thresholds (asymptomatic or symptomatic, respectively) defined by the American Academy of Pediatrics[30] and British Association of Perinatal Medicine guidelines.[31] Secondary outcomes included were as listed in table 2 (and defined in online supplemental material).

## Sample size and statistical analysis

In a pilot study (unpublished/local data) hypoglycaemia<1.8 mmol/L at NICU admission occurred in 33% of this population. The sample size was therefore calculated assuming that the proportion of infants receiving a placebo and experiencing the primary outcome would be 33%. As the desired difference was to detect a reduction to 22% (type I error(α) 0.05, with power 80%), the required sample size was 508 infants (254 per group). Categorical variables were described using frequency and percentage (%), and continuous variables were described using mean (and SD) when the variable was normally distributed or the median (and IQR) when the variable was non-normally distributed. Logistic mixed-effects and Poisson mixed-effects regression were used for the comparison of binary and frequency

**Table 2** Primary and secondary outcomes

| | Dextrose (n=84) n (%)* | Placebo (n=85) n (%)* | OR (95% CI)† | P value† |
|---|---|---|---|---|
| **Primary outcome** | | | | |
| Admission hypoglycaemia (<1.8 mmol/L) | 24 (29) | 25 (29) | 0.95 (0.49 to 1.86) | 0.88 |
| **Secondary outcomes** | | | | |
| Admission hypoglycaemia (<2.6 mmol/L) | 47 (56) | 42 (49) | 1.36 (0.71 to 2.59) | 0.35 |
| Further hypoglycaemia (<1.8 mmol/L)‡ | 5 (6) | 4 (5) | 1.23 (0.31 to 4.85) | 0.77 |
| Hypoglycaemia (<2.6 mmol/L)‡ | | | 1.22 (0.86 to 1.75) | 0.27§¶ |
| None | 36 | 42 | | |
| 1 | 33 | 36 | | |
| 2 | 12 | 4 | | |
| 3 | 3 | 2 | | |
| 5 | 0 | 1 | | |
| Hyperglycaemia (>10.0 mmol/L)‡ | 5 (6) | 6 (7) | 0.60 (0.00 to 246) | 0.87 |
| Received intravenous dextrose bolus‡ | 17 (20) | 19 (22) | 0.86 (0.37 to 1.96) | 0.71 |
| Death (<12 postnatal hours) | 0 (0) | 1 (1) | 0.00 (0.00 to ∞) | 0.99 |
| Death before discharge | 7 (8) | 7 (8) | 0.91 (0.26 to 3.20) | 0.88 |
| Early onset sepsis/meningitis | 2 (2) | 4 (5) | 0.45 (0.08 to 2.68) | 0.38 |
| IVH**†† | | | 0.41 (0.17 to 0.96) | 0.04§ |
| None | 72 | 65 | | |
| Grade 1 | 7 | 13 | | |
| Grade 2 | 3 | 1 | | |
| Grade 3 | 0 | 2 | | |
| Grade 4 | 1 | 3 | | |
| NEC‡‡§§ | 1 (1) | 3 (4) | 0.27 (0.00 to 96,451) | 0.84 |
| FIP‡‡§§ | 2 (2) | 2 (2) | 1.02 (0.13 to 8.08) | 0.98 |
| ROP‡‡ | 3 (4) | 2 (2) | 1.53 (0.00 to ∞) | 0.99 |
| PVL‡‡§§ | 2 (2) | 1 (1) | 1.94 (0.003 to 1182) | 0.93 |

*Unless otherwise stated.
†From logistic mixed-effects regression analysis unless otherwise stated.
‡Within the first 24 postnatal hours.
§Poisson mixed-effects regression analysis.
¶No cases of symptomatic hypoglycaemia were documented.
**Highest grade of IVH from any cranial ultrasound up to postnatal day 28.
††84 in the placebo and 83 in the dextrose group.
‡‡83 in the placebo and 82 in the dextrose group.
§§Vermont Oxford Network definition of variables.
FIP, focal intestinal perforation; IVH, intraventricular haemorrhage; NEC, necrotising enterocolitis; PVL, cystic periventricular leucomalacia; ROP, retinopathy of prematurity.

outcomes, respectively, between groups. Group and randomisation stratification variables (study centre, and gestational cohort) were entered as fixed effects. To account for the non-independence of multiple births, the birth set (maternal identifier) was entered as a random effect. Adjusted ORs and CIs are given. Exploratory sensitivity analyses for the primary outcome included assessment of; those who received the assigned intervention; those whose admission glucose was measured using the glucose oxidase amperometric method; and those who had no gel spillage. All statistical analysis was performed using Jamovi V.2.3.21 (The Jamovi Project, 2022).[32]

## RESULTS

### Study conduct

Recruitment took place across five study sites (four in Ireland and one in Czech Republic) between November 2020 and August 2022. During the recruitment period a total of 462 infants (born≤32+0 weeks GA) were born and 169 infants were randomised. A major factor impacting recruitment was the requirement for antenatal consent (see figure 2). Based on the slow rate of recruitment, and due to finite funding and research resources/personnel, a prolonged recruitment period was not feasible and as such a decision was made to end the study at that time.

The Consolidated Standards of Reporting Trials diagram (figure 2) indicates the reasons for exclusion (293 infants). All infants randomised were included in the intention-to-treat (ITT) analysis. The dextrose group (ITT n=84) and placebo group (ITT n=85) included two and eight infants, respectively, who were randomised but did not receive the allocated intervention (reasons as per figure 2). Table 1 shows the baseline participant characteristics. There was a difference in spillage between groups but this was predominantly due to 'small' spillage.

### Results of primary and secondary outcomes

There was no significant difference in the frequency of the primary outcome between groups (table 2). Of the secondary study outcomes (table 2), only counts of intraventricular haemorrhage were significantly lower in the dextrose group (OR 0.41 (95% CI 0.17 to 0.96), p=0.04). There were no recorded cases of 'symptomatic' hypoglycaemia, likely reflecting clinicians' uncertainty whether a very/extreme preterm infant is symptomatic.

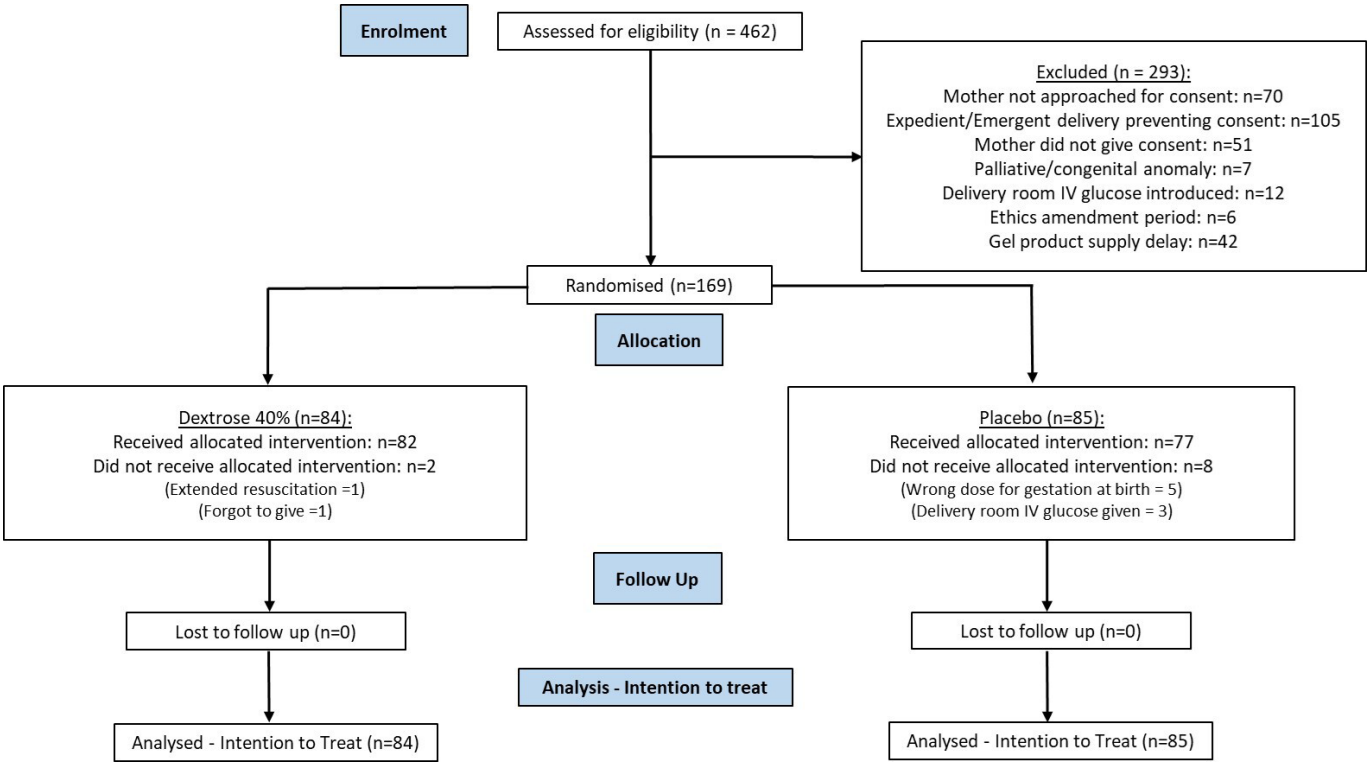


**Figure 2** Consolidated Standards of Reporting Trials diagram demonstrating the enrolment of subjects, their allocation to treatment, disposition status and how they are analysed in the trial. IV, intravenous.

Exploratory sensitivity analyses for the primary outcome (table 3) did not show any significant differences between groups when including only newborns who received the assigned intervention or had their admission blood glucose measured using only the glucose oxidase amperometric (gas machine) method. As gel spill ('small' spill mainly) occurred more frequently in the intervention (dextrose) group, a further sensitivity analysis (table 3) did not show significance for the primary outcome when including only those infants with no spillage.

### Conditional power analysis

A post-hoc conditional power analysis (details in online supplemental material) for the primary outcome showed that even if the trial had recruited the planned sample size, and under the most optimistic assumptions of treatment benefit (projected difference in proportion remaining at the original estimate), the trial only had a 47% chance of demonstrating a statistically significant benefit from the intervention. This value is considerably lower than the planned 80% power and suggests likely futility should the trial have continued further.

## DISCUSSION

### Consideration of relevant evidence

The results of our study question whether buccal dextrose gel is absorbed in preterm infants. To date, while there are no published data on the efficacy of buccal dextrose absorption in humans, dextrose gel has been considered effective in treating hypoglycaemia in adults,[33] children[34] and late-preterm/term infants.[20–24] Results from recent large randomised controlled trials in late-preterm/term infants, using dextrose gel as prophylaxis, have shown a significant reduction in hypoglycaemia (<2.6 mmol/L).[25 26] Newborns in these studies received prophylactic dextrose gel followed by a feed.

Only one study (contemporaneous to our study) has reported giving dextrose gel to preterm infants (born<34 weeks GA).[35] In their quality improvement (before–after) single-centre study clinicians adopted the routine practice of giving 40% dextrose gel in the delivery room.[35] The incidence of hypoglycaemia (<2.0 mmol/L) significantly reduced from 38% (before-group, n=150) to 27% (after-group, n=150) over 2 years (p<0.05).[35] This constitutes a relative risk reduction of 30% which contrasts with the minimal effect seen in our study. Important

**Table 3** Exploratory sensitivity analyses—admission hypoglycaemia<1.8 mmol/L (primary outcome)

| | Dextrose | Placebo | OR (95% CI)* | P value* |
|---|---|---|---|---|
| Including only infants who received the assigned intervention | 24/82 (29%) | 22/77 (29%) | 1.06 (0.53 to 2.11) | 0.88 |
| Including only glucose oxidase amperometric measurements | 21/73 (29%) | 24/78 (31%) | 0.89 (0.44 to 1.80) | 0.74 |
| Including only infants who both received the assigned intervention and had glucose oxidase amperometric measurements | 21/71 (30%) | 21/70 (30%) | 0.99 (0.48 to 2.07) | 0.99 |
| Including only infants who had no gel spillage | 8/38 (21%) | 18/51 (35%) | 0.46 (0.17 to 1.25) | 0.13 |

*From logistic mixed-effects regression analysis unless otherwise stated.

methodological differences exist between this recent study[35] and our study. First, infants in their study received approximately double the total dose (compared with our study) of 40% dextrose gel (estimated fetal weight 500–1000 g received 1 mL, while estimated fetal weight>1000 g received 2 mL) given in two divided doses.[35] The authors do not comment on spillage of these multiple divided doses[35] (in our study approximately 47% of infants had some spillage).

A recognised important methodological difference between our study and other studies of dextrose gel[24–27 35] concerns the act of rubbing the gel on buccal mucosa. In our study, gel was directed (by the clinician's finger located at the corner of the newborn's mouth) onto the inside surface of one cheek while, at the same time, massaging the outside of the cheek (to facilitate in-direct distribution of the gel on the buccal mucosa between the gum and cheek). It was felt that fitting a gloved adult finger into an extremely preterm newborn's mouth would prove physically tight/difficult and would potentially be associated with a loss of positive end expiratory pressure (for preterm infants on nCPAP) while the mouth remained open. In contrast, researchers in this other preterm study used a gloved finger to massage gel inside the mouth and, despite approximately 90% of their infants receiving some ventilatory support at stabilisation (intubation/nCPAP/high-flow), did not report any complications of their method of gel application.[35] Lastly, these authors report that infants in their study were statistically significantly more premature and smaller (birth weight) in their after-group (dextrose) group compared with their before-group.[35] A post-hoc analysis in our study has shown a small statistically significant relationship between lower birth weight and higher admission blood glucose (online supplemental figure 1) independent of the study intervention group (multiple linear regression: $R^2=0.05$, $F(1,166)=7.82$, standardised coefficient=−0.21 (95% CI −0.36 to −0.06), $p<0.006$). This may perhaps be a reflection of some smaller preterm infants being sicker/stressed. As such the younger smaller infants in their after-group might have contributed towards the increase in admission blood glucose in their before-after study.[35]

### Strengths and limitations

Our study was a multicentre, randomised, blinded, placebo-controlled trial that achieved the successful randomisation of 169 participants in just under 2 years. We recorded a detailed list of baseline characteristics, and these were equally distributed between groups. Infants of diabetic mothers and mothers on medications effecting glycaemia were included. Study gels used did not contain preservatives (used in commercial gels) and as such allowed us to avoid their effect on study outcomes. It is known that the accuracy of blood glucose measurement varies with the method of measurement used and that point-of-care testing systems have a greater error range than laboratory systems based on glucose oxidase methods.[36] In our study 151 (90%) of infants had primary outcomes measured using a consistent (glucose oxidase amperometric) method.

Obtaining written informed antenatal consent proved challenging. During the recruitment period 105 infants were born in expedient/emergent deliveries (inappropriate to approach guardian for antenatal consent) and another 70 infants were born to mothers who were never approached (out of hours and due to study resources/manpower) (figure 2). Added together these 175 missed infants approximate the rate of recruitment during the same period. Even though rates of the primary outcome (29% for dextrose and control groups) were similar to the predicated rate for the population (estimated 33%), there is a real risk that our study enrolled a non-representative population (the 175 missed infants may have been sicker and may have benefited most from the intervention). Any future trials could consider the option of waiving consent. Waived consent has been used in neonatal trials where the interventions being studied are deemed to be minimal risk and obtaining antenatal consent prior to the intervention is not possible/practical.[37] At the time of our study design, there were no studies in the literature reporting the administration of dextrose gel to very preterm newborns. This fact, coupled with the fact that multiple hospital research ethics committees' approvals were needed, led us to believe that a waiver of consent was not feasible at the time we designed the GEHPPI study.

## CONCLUSION

The requirement for antenatal consent greatly impacted this delivery room trial. While acknowledging this impact, our results did not find evidence of the benefit of 40% dextrose gel on rates of early hypoglycaemia (at the time of first vascular access in the NICU). As our study did not show benefit, and in the absence of high-quality evidence in the literature showing the benefit of dextrose gel, we suggest that management of this very/extreme preterm population should continue to focus on vascular access and early commencement of dextrose-containing intravenous fluids.

**X** Jean James @Jean James Paris

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**Contributors** All authors made substantial contributions to the conception and/or design of the work: GK and JK conceptualised, designed and oversaw the study. JM, JJan, JRP, MM and JBL ensured realisation of the project in their respective participating sites. PD managed the trial product, and the randomisation process. GK, JK, JS, SD, SM, JBL and AK contributed to database collection and organisation. GK, JK, AO'S, NOC, SD, SM, JRP, CM, JJam, JBL, KT and AK performed recruitment. GK and JK performed the data analysis (blinded) and interpretation of data for the work. GK drafted the first draft of the manuscript. All authors critically reviewed the manuscript for important intellectual content. All authors provided final approval of the version published. JK is the guarantor of this work and takes full responsibility for the work and conduct of the study, had access to the data and controlled the decision to publish.

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**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study was approved by the research ethics committees of the Coombe Hospital, Ireland (ref: No.6/2019 (03/08/2019)), Rotunda Hospital, Ireland (ref: REC-2021-006 (01/03/2021)), National Maternity Hospital, Ireland (ref: EC46.2020 (31/03/2021)), University Hospital Galway, Ireland (ref: 113/12 (12/05/2021)) and Motol University Hospital, Czech Republic (ref: EK-410/21 (21/04/2021)). Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. The data sets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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## REFERENCES

1 Burns CM, Rutherford MA, Boardman JP, *et al*. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. *Pediatrics* 2008;122:65–74.
2 Filan PM, Inder TE, Cameron FJ, *et al*. Neonatal hypoglycemia and occipital cerebral injury. *J Pediatr* 2006;148:552–5.
3 Edwards T, Alsweiler JM, Crowther CA, *et al*. Prophylactic Oral Dextrose Gel and Neurosensory Impairment at 2-Year Follow-up of Participants in the hPOD Randomized Trial. *JAMA* 2022;327:1149–57.
4 Duvanel CB, Fawer CL, Cotting J, *et al*. Long-term effects of neonatal hypoglycemia on brain growth and psychomotor development in small-for-gestational-age preterm infants. *J Pediatr* 1999;134:492–8.
5 Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, *et al*. Neonatal morbidities and developmental delay in moderately preterm-born children. *Pediatrics* 2012;130:e265–72.
6 McKinlay CJD, Alsweiler JM, Ansell JM, *et al*. Neonatal Glycemia and Neurodevelopmental Outcomes at 2 Years. *N Engl J Med* 2015;373:1507–18.
7 Shah R, Dai DWT, Alsweiler JM, *et al*. Association of Neonatal Hypoglycemia With Academic Performance in Mid-Childhood. *JAMA* 2022;327:1158–70.
8 Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. *BMJ* 1988;297:1304–8.
9 Kaiser JR, Bai S, Gibson N, *et al*. Association Between Transient Newborn Hypoglycemia and Fourth-Grade Achievement Test Proficiency: A Population-Based Study. *JAMA Pediatr* 2015;169:913–21.
10 Tin W, Brunskill G, Kelly T, *et al*. 15-year follow-up of recurrent "hypoglycemia" in preterm infants. *Pediatrics* 2012;130:e1497–503.
11 Tottman AC, Alsweiler JM, Bloomfield FH, *et al*. Relationship between Measures of Neonatal Glycemia, Neonatal Illness, and 2-Year Outcomes in Very Preterm Infants. *J Pediatr* 2017;188:115–21.
12 Goode RH, Rettiganti M, Li J, *et al*. Developmental Outcomes of Preterm Infants With Neonatal Hypoglycemia. *Pediatrics* 2016;138:e20161424.
13 Hay WW. Recent observations on the regulation of fetal metabolism by glucose. *J Physiol* 2006;572:17–24.
14 Mitanchez D. Glucose regulation in preterm newborn infants. *Horm Res* 2007;68:265–71.
15 Sharma D. Golden 60 minutes of newborn's life: Part 1: Preterm neonate. *J Matern Fetal Neonatal Med* 2017;30:2716–27.
16 Koolen MR, van Kempen AA, Maaskant JM, *et al*. Incidence and risk factors for early hypoglycemia in very preterm infants: The hyporisk study. *Clin Nutr ESPEN* 2023;56:67–72.
17 Mitchell NA, Grimbly C, Rosolowsky ET, *et al*. Incidence and Risk Factors for Hypoglycemia During Fetal-to-Neonatal Transition in Premature Infants. *Front Pediatr* 2020;8:34.
18 Lilien LD, Pildes RS, Srinivasan G, *et al*. Treatment of neonatal hypoglycemia with minibolus and intraveous glucose infusion. *J Pediatr* 1980;97:295–8.
19 King G, Tabery K, Hall M, *et al*. Delivery room glucose to reduce the risk of admission hypoglycemia in preterm infants: a systematic literature review. *J Matern Fetal Neonatal Med* 2023;36:2183466.
20 Gregory K, Turner D, Benjamin CN, *et al*. Incorporating dextrose gel and feeding in the treatment of neonatal hypoglycaemia. *Arch Dis Child Fetal Neonatal Ed* 2020;105:45–9.
21 Gupta K, Amboiram P, Balakrishnan U, *et al*. Dextrose Gel for Neonates at Risk With Asymptomatic Hypoglycemia: A Randomized Clinical Trial. *Pediatrics* 2022;149:e2021050733.
22 Makker K, Alissa R, Dudek C, *et al*. Glucose Gel in Infants at Risk for Transitional Neonatal Hypoglycemia. *Am J Perinatol* 2018;35:1050–6.
23 Rawat M, Chandrasekharan P, Turkovich S, *et al*. Oral Dextrose Gel Reduces the Need for Intravenous Dextrose Therapy in Neonatal Hypoglycemia. *Bio Hub* 2016;1:448511:1–9:.
24 Harris DL, Weston PJ, Signal M, *et al*. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. *The Lancet* 2013;382:2077–83.
25 Hegarty JE, Harding JE, Gamble GD, *et al*. Prophylactic Oral Dextrose Gel for Newborn Babies at Risk of Neonatal Hypoglycaemia: A Randomised Controlled Dose-Finding Trial (the Pre-hPOD Study). *PLoS Med* 2016;13:e1002155.
26 Harding JE, Hegarty JE, Crowther CA, *et al*. Evaluation of oral dextrose gel for prevention of neonatal hypoglycemia (hPOD): A multicenter, double-blind randomized controlled trial. *PLoS Med* 2021;18:e1003411.
27 Coors SM, Cousin JJ, Hagan JL, *et al*. Prophylactic Dextrose Gel Does Not Prevent Neonatal Hypoglycemia: A Quasi-Experimental Pilot Study. *J Pediatr* 2018;198:156–61.
28 Edwards T, Liu G, Battin M, *et al*. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. *Cochrane Database Syst Rev* 2022;3:CD011027.
29 Roberts L, Lin L, Alsweiler J, *et al*. Oral dextrose gel to prevent hypoglycaemia in at-risk neonates. *Cochrane Database Syst Rev* 2023;11:CD012152.
30 Adamkin DH. Neonatal hypoglycemia. *Semin Fetal Neonatal Med* 2017;22:36–41.
31 British Association of Perinatal Medicine. Identification and management of neonatal hypoglycaemia in the full term infant (2017). 2017. Available: https://www.bapm.org/resources/40-identification-and-management-of-neonatal-hypoglycaemia-in-the-full-term-infant-2017 [Accessed 01 Jan 2024].
32 Jamovi. The jamovi project (2022). 2022.
33 American Diabetes Association. Standards of medical care in diabetes--2013. *Diabetes Care* 2013;36 Suppl 1:S11–66.
34 Abraham MB, Karges B, Dovc K, *et al*. ISPAD Clinical Practice Consensus Guidelines 2022: Assessment and management of hypoglycemia in children and adolescents with diabetes. *Pediatr Diabetes* 2022;23:1322–40.
35 Carr CP, MacMillan H, Reynolds PR. Routine buccal glucose reduces admission hypoglycaemia in premature newborns: A quality improvement project. *Acta Paediatr* 2022;111:1709–11.
36 Beardsall K. Measurement of glucose levels in the newborn. *Early Hum Dev* 2010;86:263–7.
37 Rich WD, Katheria AC. Waived Consent in Perinatal/Neonatal Research-When Is It Appropriate? *Front Pediatr* 2019;7:493.