ORIGINAL ARTICLE

Lower versus Traditional Treatment Threshold for Neonatal Hypoglycemia

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ABSTRACT

BACKGROUND

Worldwide, many newborns who are preterm, small or large for gestational age, or born to mothers with diabetes are screened for hypoglycemia, with a goal of preventing brain injury. However, there is no consensus on a treatment threshold that is safe but also avoids overtreatment.

METHODS

In a multicenter, randomized, noninferiority trial involving 689 otherwise healthy newborns born at 35 weeks of gestation or later and identified as being at risk for hypoglycemia, we compared two threshold values for treatment of asymptomatic moderate hypoglycemia. We sought to determine whether a management strategy that used a lower threshold (treatment administered at a glucose concentration of <36 mg per deciliter [2.0 mmol per liter]) would be noninferior to a traditional threshold (treatment at a glucose concentration of <47 mg per deciliter [2.6 mmol per liter]) with respect to psychomotor development at 18 months, assessed with the Bayley Scales of Infant and Toddler Development, third edition, Dutch version (Bayley-III-NL; scores range from 50 to 150 [mean {±SD}, 100±15]), with higher scores indicating more advanced development and 7.5 points (one half the SD) representing a clinically important difference). The lower threshold would be considered noninferior if scores were less than 7.5 points lower than scores in the traditional-threshold group.

RESULTS

Bayley-III-NL scores were assessed in 287 of the 348 children (82.5%) in the lower-threshold group and in 295 of the 341 children (86.5%) in the traditional-threshold group. Cognitive and motor outcome scores were similar in the two groups (mean scores [±SE], 102.9±0.7 [cognitive] and 104.6±0.7 [motor] in the lower-threshold group and 102.2±0.7 [cognitive] and 104.9±0.7 [motor] in the traditional-threshold group). The prespecified inferiority limit was not crossed. The mean glucose concentration was 57±0.4 mg per deciliter (3.2±0.02 mmol per liter) in the lower-threshold group and 61±0.5 mg per deciliter (3.4±0.03 mmol per liter) in the traditional-threshold group. Fewer and less severe hypoglycemic episodes occurred in the traditional-threshold group, but that group had more invasive diagnostic and treatment interventions. Serious adverse events in the lower-threshold group included convulsions (during normoglycemia) in one newborn and one death.

CONCLUSIONS

In otherwise healthy newborns with asymptomatic moderate hypoglycemia, a lower glucose treatment threshold (36 mg per deciliter) was noninferior to a traditional threshold (47 mg per deciliter) with regard to psychomotor development at 18 months. (Funded by the Netherlands Organization for Health Research and Development; HypoEXIT Current Controlled Trials number, ISRCTN79705768.)

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Hypoglycemia is the most common metabolic problem in newborns and may lead to persistent brain injury.[1,2] Because neonatal hypoglycemia often is asymptomatic, up to 30% of all newborns are routinely monitored for hypoglycemia for 12 to 36 hours after birth when current guidelines are followed.[3-6] However, there is no consensus regarding the threshold glucose concentration at which treatment for asymptomatic neonatal hypoglycemia should be initiated.[1,7,8] On the basis of expert opinion, a concept of operational thresholds was developed that considered glucose concentrations between 36 mg per deciliter (2.0 mmol per liter) and 47 mg per deciliter (2.6 mmol per liter) to be acceptable for short periods of time.[9-12]

To date, studies on developmental outcome after neonatal hypoglycemia have been observational, comparing newborns who have had hypoglycemia with newborns who have not had hypoglycemia, and have shown contradictory results.[1,8,13-20] In the absence of robust evidence, screening and treatment protocols differ considerably among hospitals.[21,22] Both overtreatment and undertreatment can occur, with negative effects on the newborns' health, the budding mother–child relationship, and health care costs.[23] Since the 1990s, experts have called for well-designed trials to devise the appropriate treatment strategies.[8,11,12,23-25]

We now report the results of a randomized trial that compared two accepted threshold glucose values (as yet unsupported by evidence) for treatment of asymptomatic moderate hypoglycemia (defined as plasma glucose concentrations of 36 to 46 mg per deciliter [2.0 to 2.5 mmol per liter]) in four high-risk subgroups of otherwise healthy newborns.

METHODS

TRIAL DESIGN AND OVERSIGHT

The HypoEXIT (Hypoglycemia–Expectant Monitoring versus Intensive Treatment) trial was a multicenter, randomized, controlled, noninferiority trial. The trial protocol is available with the full text of this article at NEJM.org.

The trial was registered prospectively, as described in the protocol. The institutional review board at the Academic Medical Center, Amsterdam, and the medical ethics committee at each participating institution reviewed and approved the trial. The trial was conducted in accordance with the principles of the Declaration of Helsinki. Parents of enrolled infants provided written informed consent. Information on the data and safety monitoring board is provided in Section S2.1 in the Supplementary Appendix, available at NEJM.org.

The study steering group designed the trial. The site collaborators were responsible for patient inclusion, data collection, and registration. Nine of the authors analyzed the data and prepared the manuscript. All the authors reviewed the manuscript and vouch for the accuracy and completeness of the data and analyses and for the fidelity of the trial to the protocol and made the decision to submit the paper for publication. Because this was a publicly funded trial, no agreements concerning confidentiality of the data were made between the sponsor and the authors or institutions involved in the trial.

PARTICIPANTS

From October 2007 through April 2011, newborns at 17 academic or teaching hospitals were eligible for inclusion in the trial if they were born at 35 weeks or more of gestation, had a birth weight of 2000 g or more, and had an indication for routine screening for hypoglycemia. The participants were newborns in four subgroups at high risk for hypoglycemia — late-preterm infants (gestational age from 35 to 37 weeks), newborns who were small (below the 10th percentile) or large (above the 90th percentile) for gestational age, and infants of mothers with diabetes. The participants were all otherwise healthy newborns without initial severe hypoglycemia (defined as plasma glucose concentrations of ≤35 mg per deciliter [1.9 mmol per liter]). (A full list of inclusion and exclusion criteria is provided in Section S2.2.)

RANDOMIZATION AND TREATMENT STRATEGIES

We compared two threshold values for treatment of neonatal hypoglycemia. Newborns found to have asymptomatic moderate hypoglycemia between 3 and 24 hours after birth were randomly assigned in a 1:1 ratio (with the use of Web-based block randomization) to receive treatment when the glucose concentration was lower than 36 mg per deciliter (lower-threshold group) or to receive treatment when the glucose concentration was lower than 47 mg per deciliter (traditional-threshold group); participants were stratified according to study center and prespeci-

fied high-risk subgroup. (Details regarding the trial methods are provided in Sections S2.3 through S2.5.)

In the lower-threshold group, the aim was to maintain the infants' glucose concentration at 36 mg per deciliter or greater. In the traditional-threshold group, the aim was to attain a glucose concentration of 47 mg per deciliter or greater and then maintain that level. If an infant's glucose concentration fell below the prespecified threshold, the carbohydrate intake was increased by 1 to 2 mg per kilogram of body weight per minute. The glucose concentration was checked 1 hour after each increase, and, if necessary, the infant's carbohydrate intake was further adjusted.

Treatment interventions, which were similar in the two groups, were supplemental oral feeding, tube feeding, or intravenous glucose administration. To reflect daily clinical practice, these management decisions were not based on a single glucose measurement but were tailored to the course of glucose concentrations and the clinical condition of the individual newborn.

PRIMARY OUTCOME

The primary outcome was psychomotor development at 18 months, as measured by the Bayley Scales of Infant and Toddler Development, third edition, Dutch version (Bayley-III-NL) (Section S2.6 and Table S1). In this trial, we used Bayley-III-NL scores to measure cognitive and motor development; scores range from 50 to 150 (mean [±SD], 100±15), with higher scores indicating more advanced development and 7.5 points (one half the SD) representing a clinically important difference.[26,27] For preterm infants, age was corrected for prematurity. The examiners who administered the Bayley-III-NL were unaware of the treatment assignments. The trial was designed as a noninferiority trial to determine whether — within statistical variability — psychomotor development was less than 7.5 points (one half the standard deviation of 15 for the normative mean in the Bayley-III-NL) lower after treatment according to a management strategy based on a lower threshold (treatment started at a glucose concentration of <36 mg per deciliter) than after treatment according to a traditional threshold strategy (treatment started at a glucose concentration of <47 mg per deciliter).

SECONDARY OUTCOMES

Secondary outcomes were related to burden, efficacy, and use of health care resources. The secondary outcomes related to burden included the number of glucose measurements; treatment of hypoglycemia with supplemental oral feeding, tube feeding, or intravenous glucose; and duration of breast-feeding. The secondary outcomes related to efficacy included glucose concentrations and episodes of hypoglycemia after randomization, and the secondary outcomes related to the use of health care resources included the duration of hospital stay and health care costs within 18 months after randomization.

STATISTICAL ANALYSIS

Sample sizes were calculated separately for each of the four prespecified subgroups (Section S2.7). We used the absolute difference between the two groups in the Bayley-III-NL score (normative mean, 100±15) to estimate the sample size according to the principles and methods of sample-size calculation for noninferiority trials. The noninferiority margin was set at minus one half the standard deviation of 15 for the normative value (i.e., –7.5 points), reflecting a 1-month delay in development.[26] We estimated that with 200 newborns in each of the four subgroups, the study would have 90% power to determine the noninferiority of the lower threshold to the traditional threshold, at a one-sided alpha level of 0.025, assuming that 15% of the participants would be withdrawn.

Because the clinical management decisions had to be tailored to the individual newborn, deviations from the assigned treatment strategy could not be classified simply as crossovers. This made a per-protocol analysis difficult; hence only an intention-to-treat analysis was performed. To evaluate whether the treatment strategies in the two groups were substantially different, we compared the glucose concentrations, frequency of hypoglycemia episodes, and treatment interventions in the two groups.

For the primary outcome, we considered that noninferiority of the lower threshold strategy to the traditional threshold strategy would be shown if the lower limit of the confidence interval for the absolute between-group difference in the observed Bayley-III-NL scores did not cross the prespecified limit of –7.5 points. We performed

post hoc Bonferroni correction for the primary (cognitive and motor) outcome by providing 97.5% confidence intervals instead of 95% confidence intervals to account for multiplicity. For the secondary outcomes, unadjusted 95% confidence intervals are provided for the differences between the groups; hence they cannot be used to infer effects.

Post hoc, we performed sensitivity analyses for the prespecified primary outcome after multiple imputation by chained equations to account for missing data. Data presented are derived from the imputed data set. (Additional details on the statistical methods are provided in Sections S2.8 through S2.11 and Table S2.)

RESULTS

PATIENTS AND FOLLOW-UP

Of the 2024 eligible newborns whose parents provided informed consent, 722 (35.7%) had moderate hypoglycemia; of those, 689 infants (born to 682 mothers) were included in the trial (Fig. 1 and Section S3.1). Clinical characteristics were similar in the two groups (Table 1 and Table S3). The Bayley-III-NL was administered to 582 of the 689 children (84.5%) (Fig. 1 and Tables S4 and S5).

PSYCHOMOTOR DEVELOPMENT

Bayley-III-NL scores at 18 months of age were similar in the lower-threshold and traditional-threshold groups (Table 2). The prespecified inferiority limit of −7.5 points was not crossed (Fig. 2). After sensitivity analyses were performed for missing data, our conclusions remained the same (Section S3.2 and Tables S6 and S7). The proportion of children with Bayley-III-NL scores below −1 or −2 SD was similar in the two trial groups. Bayley-III-NL scores were not correlated with the number or severity of hypoglycemic episodes. Linear regression analysis showed no differences among centers in the effect of treatment assignment on the Bayley-III-NL scores (details provided in Sections S3.3 and S3.4 and Tables S8 and S9).

SECONDARY OUTCOMES

Results for secondary outcomes are shown in Table 3 (see also Section S3.5). Fewer glucose measurements were performed in the lower-threshold group than in the traditional-threshold group (mean difference of −0.7 measurements, or 9% less), and fewer newborns in the lower-threshold group received treatments for hypoglycemia. The number needed to treat to save 1 newborn from intravenous glucose administration was 7, to save 1 newborn from tube feeding was 12, and to save 1 newborn from supplemental oral feeding was 5. After randomization, episodes of hypoglycemia (plasma glucose ≤46 mg per deciliter) occurred in 57% of the newborns in the lower-threshold group and in 47% in the traditional-threshold group (mean difference, 10 percentage points [95% confidence interval, 2 to 17]). The episodes of hypoglycemia were managed according to the trial protocol. None of the infants with hypoglycemia had any clinical signs or symptoms of hypoglycemia. The durations of hospital stay of the newborns and of their mothers were similar in the two groups, as were health care costs (Tables S10 and S11). Serious adverse events were reported in two infants in the lower-threshold group; one newborn with signs of hypoxic–ischemic brain injury on magnetic resonance imaging had convulsions during normoglycemia, and one infant died from a severe respiratory infection after the neonatal period. (Serious and common adverse events are described in Section S3.6 and Tables S12 through S14.)

DISCUSSION

In the present trial involving otherwise healthy newborns born at 35 weeks of gestation or later and weighing 2000 g or more, a management strategy that used a lower glucose threshold value to start treatment for asymptomatic moderate hypoglycemia did not lead to worse psychomotor development at 18 months than a strategy that used a traditional (higher) threshold. In fact, allowing glucose concentrations of 36 mg per deciliter or higher in the first 48 hours after birth was associated with developmental outcomes that were similar to those observed when glucose concentrations of 47 mg per deciliter or higher were targeted. Furthermore, there were fewer diagnostic interventions, including 9% fewer glucose measurements, and fewer therapeutic interventions in the lower-threshold group than in the traditional-threshold group. The durations of hospital stay of the newborns and of their

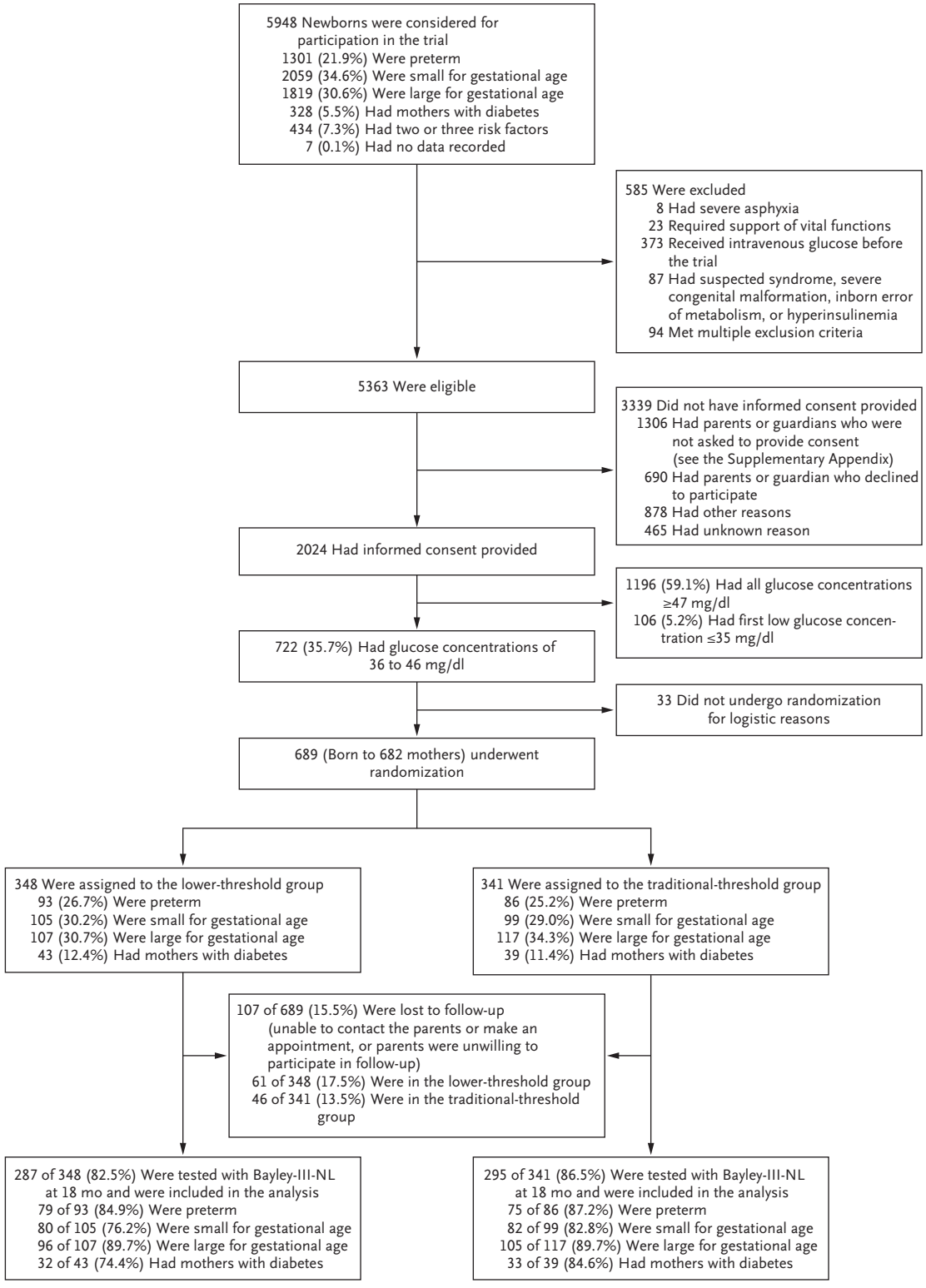

Figure 1. Screening, Randomization, Treatment, and Follow-up.

Bayley-III-NL denotes Bayley Scales of Infant and Toddler Development, third edition, Dutch version.

Table 1. Characteristics of Participants at Baseline.*

Characteristic	Lower-Threshold Group	Traditional-Threshold Group
Newborns — no.	348	341
Gestational age — wk	38.6±0.1	38.7±0.1
Birth weight — g	3316±47	3354±46
Male sex — no. (%)	202 (58)	185 (54)
Singleton birth — no. (%)	324 (93)	324 (95)
Apgar score at 5 min	9.6±0.04	9.6±0.04
Age at randomization — hr	6.4±0.2	6.9±0.2
Glucose at randomization — mg/dl	41.4±0.2	41.2±0.2
Missing data — no. (%)	3 (0.9)	4 (1)
Mothers — no.†	345	337
Age — yr	31.5±0.3	31.3±0.3
Missing data — no. (%)	7 (2)	14 (4)
Parity	0.7±0.05	0.8±0.06
Nonsmoking — no. (%)	285 (83)	274 (81)
Missing data — no. (%)	32 (9)	29 (9)
Pregnancy complications — no. (%)	95 (28)	94 (28)
Missing data — no. (%)	2 (0.6)	
Socioeconomic status score‡	−0.01±0.07	−0.11±0.08
Missing data — no. (%)	2 (0.6)	1 (0.3)

* Plus–minus values are means ±SE. Data are pooled results from analyses after imputation of missing data. There were no significant differences in the clinical characteristics between the lower-threshold and traditional-threshold groups. Additional data, including data for subgroups, are provided in Table S3. To convert the values for plasma glucose to millimoles per liter, multiply by 0.0555.

† The number of mothers (682) is lower than the number of newborns (689) because there were seven sets of twins, and both infants in each set underwent randomization.

‡ Socioeconomic status scores refer to the socioeconomic status of a postal code area, calculated from the education, income, and job positions of the people living there, and are based on data from the Social and Cultural Planning Office of the Netherlands (www.scp.nl). The mean score is 0, with higher scores indicating higher socioeconomic status.

mothers were similar in the two groups, as were health care costs.

Our trial supports earlier expert opinion[9-12] and current guidelines[4-6] that recommend a treatment threshold value of 36 mg per deciliter and provides additional data for the development of guidelines for the large group of newborns — late-preterm infants, infants born small or large for gestational age, and infants of mothers with diabetes — who have a high incidence (50%) of neonatal hypoglycemia.[28] Before such guidelines can be developed, several issues need to be addressed.

First, discussion of the definition of neonatal hypoglycemia is ongoing and has intensified in recent years since several observational cohort studies comparing the outcomes of newborns with and those without hypoglycemia have shown contradictory results regarding the safety of using a threshold of 45 to 47 mg per deciliter (2.5 to 2.6 mmol per liter) for treatment.[1,13-20] A limitation of observational cohort studies is the lack of control for intrinsic factors — such as the presence of alternative fuels such as lactate and ketone bodies — and other prognostic characteristics that may affect neurologic outcome.[29] Furthermore, although observational studies may result in a treatment threshold being identified retrospectively, clinical practice demands management of prospective series of glucose concentrations that have an unpredictable course over time. Therefore, agreement on treatment strategy rather than on a single glucose concentration seems a more suitable approach to guide clinical practice. By comparing two treatment threshold values that are currently in use, our pragmatic

Table 2. Bayley-III-NL Outcome Scores at 18 Months of Corrected Age.*

Group	Lower-Threshold Group	Traditional-Threshold Group	Mean Difference (97.5% CI)
Total trial population tested — no./total no. (%)	287/348 (82.5)	295/341 (86.5)	
Bayley-III-NL cognitive score	102.9±0.7	102.2±0.7	0.7 (–1.5 to 2.9)
Missing data — no. (%)	61 (18)	46 (13)	
Bayley-III-NL motor score	104.6±0.7	104.9±0.7	–0.3 (–2.4 to 1.8)
Missing data — no. (%)	64 (18)	51 (15)	
Preterm infants — no./total no. (%)	79/93 (84.9)	75/86 (87.2)	
Bayley-III-NL cognitive score	104.3±1.2	103.9±1.2	0.3 (–3.5 to 4.2)
Missing data — no. (%)	14 (15)	11 (13)	
Bayley-III-NL motor score	105.0±1.3	106.5±1.3	–1.5 (–5.7 to 2.6)
Missing data — no. (%)	15 (16)	11 (13)	
Infants small for gestational age — no./total no. (%)†	80/105 (76.2)	82/99 (82.8)	
Bayley-III-NL cognitive score	97.5±1.3	98.5±1.3	–1.0 (–5.1 to 3.2)
Missing data — no. (%)	25 (24)	17 (17)	
Bayley-III-NL motor score	102.4±1.3	102.5±1.4	–0.1 (–4.4 to 4.3)
Missing data — no. (%)	26 (25)	20 (20)	
Infants large for gestational age — no./total no. (%)‡	96/107 (89.7)	105/117 (89.7)	
Bayley-III-NL cognitive score	105.4±1.3	103.7±1.1	1.7 (–2.1 to 5.5)
Missing data — no. (%)	11 (10)	12 (10)	
Bayley-III-NL motor score	106.0±1.2	106.0±0.9	–0.1 (–3.4 to 3.2)
Missing data — no. (%)	12 (11)	13 (11)	
Infants of mothers with diabetes — no./total no. (%)	32/43 (74.4)	33/39 (84.6)	
Bayley-III-NL cognitive score	106.5±1.8	103.1±2.3	3.4 (–3.2 to 10.0)
Missing data — no. (%)	11 (26)	6 (15)	
Bayley-III-NL motor score	105.7±1.5	104.2±2.0	1.4 (–4.1 to 7.0)
Missing data — no. (%)	11 (26)	7 (18)	

* Plus–minus values are means ±SE. Data are pooled results from analyses after imputation of missing data. Bayley-III-NL denotes Bayley Scales of Infant and Toddler Development, third edition, Dutch version, and CI confidence interval.
† Small for gestational age indicates birth weight below the 10th percentile.
‡ Large for gestational age indicates birth weight above the 90th percentile.

trial was designed to identify the superior management strategy while controlling for other factors that can influence psychomotor development.

Second, because the neonatal hypoglycemia experience cannot be defined by a single numerical value, and long-term psychomotor development depends on multiple factors, a management strategy with a threshold value of 36 mg per deciliter should not be regarded as safe under all circumstances. Treatment begun at a higher glucose concentration of 47 mg per deciliter prevented infants from having frequently recurrent (≥4 episodes after randomization) and severe episodes of hypoglycemia in our trial. Although we did not find that the number of hypoglycemic episodes affected the psychomotor outcome, the number of newborns with recurrent hypoglycemia was too low to exclude an effect with certainty. We therefore would advise that frequent episodes of moderate hypoglycemia should not be accepted; instead, additional investigations for underlying causes should be considered alongside adequate treatment for hypoglycemia.

Third, although the difference in the inter-

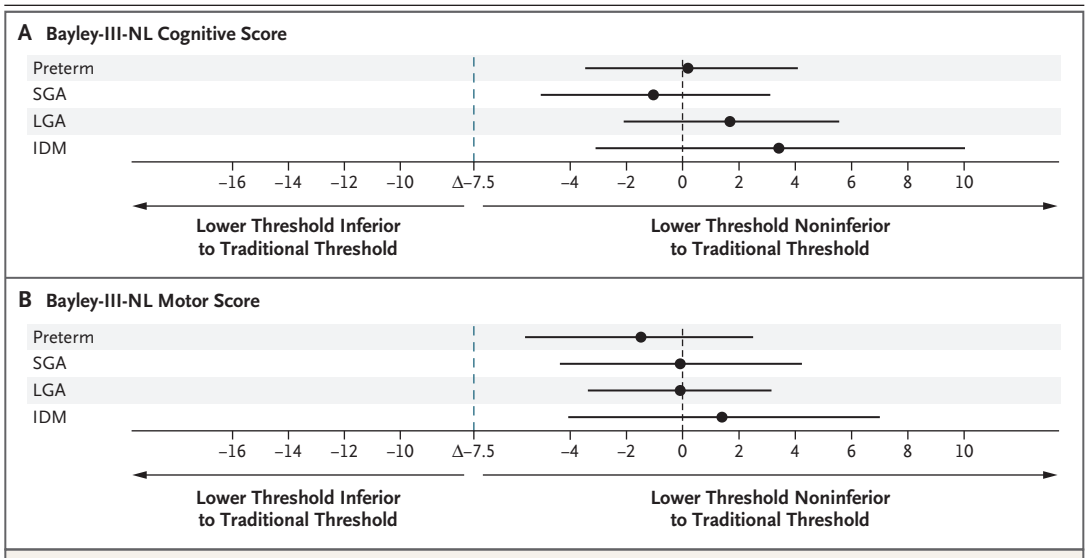

Figure 2. Effect Sizes in Relation to the Noninferiority Margin.

Shown are mean absolute differences between newborns assigned to the lower-threshold group and those assigned to the traditional-threshold group with respect to cognitive scores (Panel A) and motor scores (Panel B) on the Bayley-III-NL, in relation to the prespecified noninferiority margin of –7.5 points, indicated by a vertical dashed line. Horizontal bars show 97.5% confidence intervals. IDM denotes infants of mothers with diabetes mellitus, LGA large for gestational age, and SGA small for gestational age.

vention thresholds for our treatment strategies was rather small, this difference is considered — both in daily practice[4-6] and in the literature[11,12,23] — to be important. With the prespecified glucose thresholds for the treatment groups (36 mg vs. 47 mg per deciliter), large differences in the glucose concentrations or hypoglycemic episodes could not be expected. Therefore, we think that the observed differences reflect a reasonable contrast between the treatment groups. In addition, we believe that from the perspective of the patient, the differences in the need for painful and invasive procedures will be regarded as clinically relevant.

Finally, our conclusions should not be extrapolated to hypoglycemia that persists after the first 2 postnatal days or to newborns who are born at less than 35 weeks of gestation, have a birth weight of less than 2000 g, or are sick. Such infants are already at an increased risk for impaired developmental outcome, which makes a lower treatment threshold less desirable. In addition, we emphasize the need for a higher target glucose concentration in newborns who have persistent hypoglycemia due to endocrine or metabolic disorders.[30]

Our trial had certain limitations. The originally planned number of infants of mothers with diabetes was not reached because infants in this subgroup were less prevalent than expected. No certain conclusions can be made for this subgroup. The overall percentage of participants lost to follow-up was 16%, despite great efforts to trace all participants at 18 months. Although the number of infants who completed the trial was slightly lower than planned in the subgroups of late-preterm newborns and newborns small for gestational age, we believe that our conclusions for these subgroups remain valid, because the differences in psychomotor outcomes between the management groups were small and confidence intervals were narrow. To control for differences in feeding protocols, glucose measurement methods, and unknown variations in local clinical practice, we stratified the newborns according to hospital. With this pragmatic design, we believe that our trial bridges the gap between daily practice and a robust scientific approach.

Dextrose gel is increasingly used to treat neonatal hypoglycemia; however, randomized trials have provided scarce evidence of its effectiveness

Table 3. Secondary Outcomes.*

Variable	Lower-Threshold Group (N=348)	Traditional-Threshold Group (N=341)	Mean Difference (95% CI)
No. of glucose measurements	6.4±0.1	7.0±0.2	–0.7 (–1.0 to –0.3)
Missing data — no. (%)	3 (0.9)	4 (1.2)	
Glucose concentration — mg/dl†	57±0.4	61±0.5	–4.4 (–5.6 to –3.1)
Missing data — no. (%)	3 (0.9)	4 (1.2)	
Infants with hypoglycemic episodes after randomization — no. (%)	197 (57)	160 (47)	9.7 (2.2 to 17.0)‡
No. of hypoglycemic episodes — no. (%)			
0 or 1	244 (70)	280 (82)	–12.0 (–18.2 to –5.6)‡
2 or 3	73 (21)	54 (16)	5.1 (–0.7 to 10.9)‡
4 or more	31 (9)	7 (2)	6.9 (3.5 to 10.5)‡
Severity of hypoglycemia — no. (%)§			
No hypoglycemia	151 (43)	181 (53)	–9.7 (–17.0 to –2.2)‡
Moderate	164 (47)	142 (42)	5.5 (–1.9 to 12.8)‡
Severe or both moderate and severe¶	33 (10)	18 (5)	4.2 (0.3 to 8.2)‡
Infants who received supplemental oral feeding — no. (%)	275 (79)	332 (97)	–18.3 (–23.1 to –13.8)‡
Missing data — no. (%)	5 (1.4)	4 (1.2)	
No. of supplemental oral feedings	5±0.2	7±0.2	–2.2 (–2.8 to –1.7)
Missing data — no. (%)	10 (3)	7 (2)	
Volume of supplemental oral feeding — ml	86±5	157±6	–71 (–86 to –56)
Missing data — no. (%)	10 (3)	7 (2)	
Tube feeding — no. (%)	17 (5)	44 (13)	–8.0 (–12.4 to –3.8)‡
Missing data — no. (%)	3 (0.9)	3 (0.9)	
Continuous IV glucose — no. (%)	21 (6)	70 (21)	–14.5 (–19.5 to –9.5)‡
Missing data — no. (%)	2 (0.6)	2 (0.6)	
Bolus glucose IV — no. (%)	6 (1.8)	12 (3.4)	–1.8 (–4.5 to 0.7)‡
Missing data — no. (%)	2 (0.6)	2 (0.6)	
Hospital stay for newborn — days	4.6±0.2	4.7±0.2	–0.1 (–0.6 to 0.4)
Missing data — no. (%)	2 (0.6)	1 (0.3)	
Hospital stay for mother — days	3.8±0.1	4.0±0.1	–0.2 (–0.5 to 0.02)
Missing data — no. (%)	2 (0.6)	1 (0.3)	
Duration of breast-feeding — no. (%)			
Never or <2 wk	96 (28)	75 (22)	5.6 (–0.9 to 12.0)‡
2 wk to <3 mo	98 (28)	101 (30)	–1.5 (–8.2 to 5.3)‡
≥3 mo	74 (21)	99 (29)	–7.8 (–14.2 to –1.3)‡
Missing data	80 (23)‖	66 (19)**	

* Plus–minus values are means ±SE. Data are pooled results from analyses after imputation of missing data. Difference in proportions with 95% confidence intervals were calculated with a calculation tool (http://vassarstats.net/prop2_ind.html). Percentages may not total 100 because of rounding.

† To convert the values for plasma glucose to millimoles per liter, multiply by 0.0555.

‡ Values for mean difference are percentage points.

§ Moderate hypoglycemia is defined as plasma glucose concentration of 36 to 46 mg per deciliter. Severe hypoglycemia is defined as plasma glucose concentration of 35 mg per deciliter or less.

¶ This subgroup includes newborns with severe hypoglycemia and newborns who had episodes of both moderate and severe hypoglycemia.

‖ Of 80 infants with missing data, 18 were preterm, 20 were small for gestational age, 30 were large for gestational age, and 12 were infants of mothers with diabetes.

** Of 66 infants with missing data, 21 were preterm, 20 were small for gestational age, 19 were large for gestational age, and 6 were infants of mothers with diabetes.

and so far show neither a decrease in the need for intravenous glucose nor improved neurodevelopmental outcome.[31-33] In our trial, we evaluated two glucose treatment thresholds, using similar treatment interventions in the two trial groups. We consider it unlikely that the use of dextrose gel would have affected the results of our trial, because according to our trial design, dextrose gel would have been available to both groups.

We used the Bayley-III-NL test with population-specific reference values for Dutch children to minimize overestimation or underestimation of neurodevelopment.[34] It is important to note that although we found no between-group differences in the Bayley-III-NL scores for cognitive and motor functioning at 18 months of age, this evaluation was performed early in life. Many important and sophisticated facets of cognitive and social functioning, such as executive functioning, language comprehension, speech, and more complex visual–motor integration — functions that may be especially important after a neonate has had hypoglycemia — emerge after the age at which the children in our trial were tested. Although the Bayley-III-NL test has been shown to correlate with intelligence tests at various ages up to 10 years,[35,36] a follow-up trial is required because outcome studies of neonatal therapies have described changes in cognitive performance when children are retested in greater detail after 18 months of age.[1,14,17,37]

In this randomized trial involving otherwise healthy newborns, born at 35 weeks or more of gestation and at a birth weight of 2000 g or more, who had asymptomatic moderate hypoglycemia, a management strategy of starting treatment at a glucose concentration threshold of 36 mg per deciliter proved noninferior to a strategy that used a threshold of 47 mg per deciliter with regard to the infants' psychomotor development at 18 months.

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No potential conflict of interest relevant to this article was reported.

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APPENDIX

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REFERENCES

1. Shah R, Harding J, Brown J, McKinlay C. Neonatal glycaemia and neurodevelopmental outcomes: a systematic review and meta-analysis. Neonatology 2019;115:116-26.
2. Caksen H, Güven AS, Yilmaz C, et al. Clinical outcome and magnetic resonance imaging findings in infants with hypoglycemia. J Child Neurol 2011;26:25-30.
3. Queensland Clinical Guidelines. Newborn hypoglycaemia. Brisbane, QLD, Australia: Queensland Health, August 2013. (Guideline no. MN13.8–V5–R18) (https://www.health.qld.gov.au/__data/assets/pdf_file/0019/142156/g-hypogly.pdf).
4. Aziz K, Dancey P. Screening guidelines for newborns at risk for low blood glucose. Paediatr Child Health 2004;9:723-40.

5. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics 2011;127:575-9.
6. Diabetes in pregnancy: management from preconception to the postnatal period. NICE guideline (NG3). London: National Institute for Health and Care Excellence, February 2015 (https://www.nice.org.uk/guidance/ng3).
7. Rozance PJ, Hay WW Jr. Describing hypoglycemia — definition or operational threshold? Early Hum Dev 2010;86:275-80.
8. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia: a systematic review and design of an optimal future study. Pediatrics 2006;117:2231-43.
9. Adamkin DH. Metabolic screening and postnatal glucose homeostasis in the newborn. Pediatr Clin North Am 2015;62:385-409.
10. Tin W. Defining neonatal hypoglycaemia: a continuing debate. Semin Fetal Neonatal Med 2014;19:27-32.
11. Hawdon JM. Definition of neonatal hypoglycaemia: time for a rethink? Arch Dis Child Fetal Neonatal Ed 2013;98:F382-F383.
12. Cornblath M, Hawdon JM, Williams AF, et al. Controversies regarding definition of neonatal hypoglycemia: suggested operational thresholds. Pediatrics 2000;105:1141-5.
13. Mahajan G, Mukhopadhyay K, Attri S, Kumar P. Neurodevelopmental outcome of asymptomatic hypoglycemia compared with symptomatic hypoglycemia and euglycemia in high-risk neonates. Pediatr Neurol 2017;74:74-9.
14. McKinlay CJD, Alsweiler JM, Anstice NS, et al. Association of neonatal glycemia with neurodevelopmental outcomes at 4.5 years. JAMA Pediatr 2017;171:972-83.
15. Goode RH, Rettiganti M, Li J, et al. Developmental outcomes of preterm infants with neonatal hypoglycemia. Pediatrics 2016;138(6):e20161424.
16. 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.
17. McKinlay CJD, Alsweiler JM, Ansell JM, et al. Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015;373:1507-18.
18. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, Reijneveld SA, Bos AF. Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 2012;130(2):e265-e272.
19. Tin W, Brunskill G, Kelly T, Fritz S. 15-Year follow-up of recurrent "hypoglycemia" in preterm infants. Pediatrics 2012;130(6):e1497-e1503.
20. Tam EW, Haeusslein LA, Bonifacio SL, et al. Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy. J Pediatr 2012;161:88-93.
21. Dixon KC, Ferris RL, Marikar D, et al. Definition and monitoring of neonatal hypoglycaemia: a nationwide survey of NHS England Neonatal Units. Arch Dis Child Fetal Neonatal Ed 2017;102:F92-F93.
22. Harris DL, Weston PJ, Battin MR, Harding JE. A survey of the management of neonatal hypoglycaemia within the Australian and New Zealand Neonatal Network. J Paediatr Child Health 2014;50(10):E55-E62.
23. Rozance PJ. Update on neonatal hypoglycemia. Curr Opin Endocrinol Diabetes Obes 2014;21:45-50.
24. Harding JE, Harris DL, Hegarty JE, Alsweiler JM, McKinlay CJ. An emerging evidence base for the management of neonatal hypoglycaemia. Early Hum Dev 2017;104:51-6.
25. Hay WW Jr, Raju TN, Higgins RD, Kalhan SC, Devaskar SU. Knowledge gaps and research needs for understanding and treating neonatal hypoglycemia: workshop report from Eunice Kennedy Shriver National Institute of Child Health and Human Development. J Pediatr 2009;155:612-7.
26. Bayley N. Bayley scales of infant and toddler development. 3rd ed. San Antonio, TX: Harcourt Assessments, 2006.
27. Van Baar AL, Steenis LJP, Verhoeven M, Hessen DJ. Bayley-III-NL: Bayley scales of infant and toddler development. 3rd ed., Dutch version. Technical manual. Amsterdam: Pearson Assessment and Information B.V., 2014.
28. Harris DL, Weston PJ, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr 2012;161:787-91.
29. Vetter TR, Mascha EJ. Bias, confounding, and interaction: lions and tigers, and bears, oh my! Anesth Analg 2017;125:1042-8.
30. Thornton PS, Stanley CA, De Leon DD, et al. Recommendations from the Pediatric Endocrine Society for evaluation and management of persistent hypoglycemia in neonates, infants, and children. J Pediatr 2015;167:238-45.
31. Harris DL, Gamble GD, Weston PJ, Harding JE. What happens to blood glucose concentrations after oral treatment for neonatal hypoglycemia? J Pediatr 2017;190:136-41.
32. Harris DL, Alsweiler JM, Ansell JM, et al. Outcome at 2 years after dextrose gel treatment for neonatal hypoglycemia: follow-up of a randomized trial. J Pediatr 2016;170:54-59.e1-2.
33. Weston PJ, Harris DL, Battin M, Brown J, Hegarty JE, Harding JE. Oral dextrose gel for the treatment of hypoglycaemia in newborn infants. Cochrane Database Syst Rev 2016;5:CD011027.
34. Steenis LJ, Verhoeven M, Hessen DJ, van Baar AL. Performance of Dutch children on the Bayley III: a comparison study of US and Dutch norms. PLoS One 2015;10(8):e0132871.
35. Bode MM, D'Eugenio DB, Mettelman BB, Gross SJ. Predictive validity of the Bayley, Third Edition at 2 years for intelligence quotient at 4 years in preterm infants. J Dev Behav Pediatr 2014;35:570-5.
36. Van Baar AL, Ultee K, Gunning WB, Soepatmi S, de Leeuw R. Developmental course of very preterm children in relation to school outcome. J Dev Phys Disabil 2006;18:273-93 (https://doi.org/10.1007/s10882-006-9016-6).
37. Schmidt B, Anderson PJ, Doyle LW, et al. Survival without disability to age 5 years after neonatal caffeine therapy for apnea of prematurity. JAMA 2012;307:275-82.