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Cost Analysis of Treating Neonatal Hypoglycemia with Dextrose Gel

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Abstract

Objective—To evaluate the costs of using dextrose gel as a primary treatment for neonatal hypoglycemia in the first 48 hours after birth compared with standard care.

Study design—We used a decision tree to model overall costs, including those specific to hypoglycemia monitoring and treatment and those related to the infant's length of stay on the postnatal ward or neonatal intensive care unit, comparing the use of dextrose gel for treatment of neonatal hypoglycemia with placebo, using data from the Sugar Babies randomized trial. Sensitivity analyses assessed the impact of dextrose gel cost, neonatal intensive care cost, cesarean delivery rate and costs of glucose monitoring.

Results—In the primary analysis, treating neonatal hypoglycemia using dextrose gel had an overall cost of NZ\$6,863.81 and standard care (placebo) cost NZ\$8,178.25; a saving of NZ \$1,314.44 per infant treated. Sensitivity analyses showed that dextrose gel remained cost saving with wide variations in dextrose gel costs, neonatal intensive care unit costs, cesarean delivery rates and costs of monitoring.

Conclusions—Use of buccal dextrose gel reduces hospital costs for management of neonatal hypoglycemia. Because it is also non-invasive, well tolerated, safe and associated with improved breast-feeding, buccal dextrose gel should be routinely utilized for initial treatment of neonatal hypoglycemia.

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Keywords

Health Economics

Neonatal hypoglycemia is a metabolic condition that occurs in approximately 5–15% of healthy infants, and up to 50% in those with risk factors.¹ It is widespread in developing countries, where access to resources for treatment or monitoring may be limited.^{2, 3} Neonatal hypoglycemia is frequently asymptomatic and even in the absence of symptoms can be associated with brain injury and poor neurodevelopmental outcomes^{4, 5}, including cognitive impairment, sensory disability, developmental delay, cerebral palsy, and seizures.⁶ Direct costs attributable to the acute management of neonatal hypoglycemia can be large, particularly if the infant is admitted to the neonatal intensive care unit (NICU). Although prompt, early treatment that effectively maintains the blood glucose concentrations >47 mg/dL (2.6 mmol/L) is associated with an absence of developmental impairment at 2 years of age,⁷ hypoglycemia may be associated with delays in aspects of development that do not manifest until later, such as executive function and visual-motor performance at 4.5 years⁸ and literacy and mathematics achievement at 10 years.⁹ Thus, long term financial and societal costs may accrue from the requirement for ongoing management and support if initial treatment is inadequate, or if covert disease is missed or diagnosed late.

Initial management of neonatal hypoglycemia focuses on increased blood glucose concentration monitoring and the administration of supplemental carbohydrate, traditionally by increased feeding. Admission to NICU for intravenous dextrose is indicated if oral feeding is not tolerated or if the infant does not respond adequately to initial therapy. Both supplemental oral and intravenous administration of carbohydrate may interrupt initiation of breastfeeding¹⁰, and the latter may also result in separation of the mother and infant.¹¹ More recently, dextrose gel has been shown to be well tolerated as a treatment for neonatal hypoglycemia in the first 48 hours after birth, and resulted in fewer instances of treatment failure, and fewer admissions to the neonatal intensive care unit for hypoglycemia, than feeding alone.¹² However, the overall costs of dextrose gel treatment versus other treatments for neonatal hypoglycemia have not been calculated.

We undertook a cost analysis using a decision tree, comparing the use of dextrose gel for treatment of neonatal hypoglycemia with placebo, with a time horizon limited to the duration of the infants' postnatal hospital stay.

Methods

A decision tree model was constructed that covered the initial postnatal hospital stay using raw data from the Sugar Babies Study (Australian New Zealand Clinical Trials Registry: ACTRN12608000623392).¹² The Sugar Babies Study was a randomized, double-blind trial comparing 40% dextrose gel with placebo for the treatment of neonatal hypoglycemia in the first 48 h after birth. Participants were infants at risk of neonatal hypoglycemia (infant of a diabetic mother, late preterm (35 or 36 weeks' gestation), small (birthweight < 2500 g or $< 10^{\text{th}}$ centile) or large (birthweight > 4500 g or $> 90^{\text{th}}$ centile) or with other risk factors such as poor feeding). Infants who developed hypoglycemia were randomized to a treatment pack

containing syringes of either 40% dextrose gel or 2% carboxymethyl cellulose placebo. Of 514 infants enrolled, 242 became hypoglycemic and were randomized, 119 to placebo gel and 118 to dextrose gel. Gel administration (0.5ml/kg rubbed into the buccal mucosa) was followed by a feed, and, if feeding was poor, infants received supplemental expressed breastmilk or formula. Thus, the comparison between dextrose and placebo gel groups is effectively a comparison between treatment with dextrose gel and treatment solely with increased feeding. If the infant remained hypoglycemic 30 minutes after treatment, or if hypoglycemia recurred at a later time, the trial protocol allowed for further gel administration from the allocated pack, up to a total of 6 doses over 48 hours. Recurrent hypoglycemia was defined as an infant having a further episode of hypoglycemia after successful treatment, within 48 h after birth.¹² The primary outcome of treatment failure (blood glucose concentration < 47 mg/dL (2.6 mmol/L) after two treatment attempts) was observed less frequently in the dextrose gel group (relative risk 0.57, 95% confidence intervals 0.33–0.98, $p = 0.04$)¹². Infants who met the criteria for treatment failure were then treated according to local clinical protocols, which could include administration of formula, open label dextrose gel and admission to NICU for intravenous dextrose.

For this cost analysis, infants who developed neonatal hypoglycemia were allocated into 8 groups, based on whether they were randomized to receive dextrose gel or placebo, whether their hypoglycemia was a single episode or recurrent and whether they were admitted to NICU or not, regardless of the reason for admission (Figure 1). A decision tree modelling approach was selected as each clinical event or disease state forming the branches of the tree are either present or absent, are mutually exclusive at each node in the tree, and occur relatively closely together.¹³ The evaluation was undertaken from the perspective of the hospital (postnatal ward +/- NICU) during the infant's initial hospital stay. The raw data from the Sugar Babies Study¹² was used to model the proportions of infants who fell into each of the categories represented in the decision tree (Figure 1), their length of stay on the postnatal ward and NICU, and monitoring and treatment specific to the management of hypoglycemia.

Resource Utilization and Costs

The costs included in the analysis span four main categories: postnatal ward costs, NICU costs, hypoglycemia screening and monitoring costs, and costs of therapy. As the perspective chosen relates to the costs attributable to the infant's hospital encounter, the costs related to the mother's antenatal care were excluded, and the costs associated with the postnatal ward bed occupied by the mother were considered only from the infant's date of birth. These costs were calculated using the New Zealand Ministry of Health's Weighted Inlier Equivalent Separations 2016 (WIESNZ16)¹⁴ which includes the stay of both the mother and the infant together, taking into account whether the birth of the infant was by vaginal delivery or cesarean section.

If the infant was admitted to NICU, those costs accrue in parallel to the cost of the postnatal ward bed, which is held until the mother's discharge (often delayed if the infant is in NICU). The total cost is therefore the sum of: WIESNZ16-calculated postnatal ward costs starting at the birth of the infant and concluding at the infant's discharge from the postnatal ward or the

mother's discharge if the infant was in NICU at the time the mother was discharged, the NICU costs calculated as the product of the length of stay and an overall *per diem* rate, which includes all treatment costs during this period and the treatment and monitoring costs, including the cost of all dextrose gel administered (trial gel and open label gel) and of measuring blood glucose concentrations.

A bootstrap approach was utilized by drawing 10,000 samples in Microsoft Excel with replacement from the original dataset of 237 hypoglycemic infants to estimate the standard deviation (SD) of the average costs of hospital stay per infant in each patient group. The sum of the products of the proportions in each group and their average costs of hospital stay yields the overall cost per treatment option.

For the base analysis, NICU was assumed to be Level II, and the average cost was taken to be NZ\$2200 per day (personal communication). Admissions of a duration shorter than one day were rounded up to one whole day. Costs of blood glucose concentration testing include those undertaken on the postnatal ward and those in NICU. For postnatal wards, the cost per test (inclusive of staff time) of bedside glucometers using a glucose oxidase reaction has been calculated as NZ\$11.49. For infants admitted to NICU, it was assumed that blood glucose concentration would be measured using a blood gas analyser, with an overall cost per test of NZ\$33.36.

Dextrose gel is supplied commercially as either a multi-dose container (100mL costing NZ \$ 86.00), or single-dose 2.5mL syringes. In the base analysis, a conservative approach was employed, assuming the use of single-dose syringes, priced at NZ\$15.00 each (Biomed Ltd., Auckland, NZ).

Participants in this study were enrolled from 11/13/2008–11/26/2010. Costs were collected and recorded in New Zealand dollars (US\$1 = NZ\$1.38), with base year of 2016/17.

Sensitivity Analyses

Sensitivity analyses were undertaken by running the bootstrap sampling process with altered cost input variables. The possible range of dextrose gel cost was varied from a scenario where a 100mL multi-dose container yields 66 1.5mL doses (based on 0.5 ml/kg and an average birth weight of 3000g),¹² to a scenario where a 100mL multi-dose container yields only a single dose within its shelf-life.

The rate of cesarean delivery in the Sugar Babies Study population was 38%, which is higher than the overall rate in New Zealand (25.9% in 2014).¹⁵ A sensitivity analysis was therefore also performed via the bootstrap approach, modelling a different proportion of deliveries by cesarean delivery, and constraining sampling to reflect the specified ratio of cesarean deliveries to normal vaginal deliveries.

The impact of daily NICU cost was examined by varying that variable from \$1,100 (half of the base case value) to a \$3,200 (an estimated value for level III NICU admissions).

The impact of blood glucose concentration tests was varied to first exclude those tests undertaken in NICU, to take into account the fact that glucose is often only one of many

analytes obtained on a single blood sample, and thus represents only a very small incremental cost that is difficult to quantify. Second, we excluded the costs of blood glucose concentration monitoring in both the postnatal ward and NICU, to reflect the assumption that the costs of blood glucose monitoring are already included in the per diem costs for these services.

Results

In the base analysis, the average cost for management of an infant with neonatal hypoglycemia treated with dextrose gel was NZ\$6,863.81, and in the placebo group was NZ\$8,178.25, a difference of NZ\$1,314.44 per infant treated (Table I). Within the bootstrapped sample, dextrose gel cost less than placebo in 99.18% of the 10,000 resampled runs.

Sensitivity Analyses

If the cesarean delivery rate was reduced to 20%, the average postnatal cost of an infant with neonatal hypoglycemia treated with either dextrose or placebo gel would decrease, but the difference between the two treatment options would increase to NZ\$1,587.67 per infant treated (Table 2). In general, reducing the cesarean delivery rate increased the difference in cost between the dextrose and placebo arms, and increasing the cesarean delivery rate reduced the difference, although treatment using dextrose gel remained cost saving even at a hypothetical 100% cesarean delivery rate.

The impact of a reduction in the cost per dose of dextrose gel to NZ\$1.29 per dose (maximum number of doses from a single container) was minimal (Table 2). Increasing the price of dextrose gel to a theoretical maximum of NZ\$86.00 per dose (a single dose per container) reduced the difference between the two treatment options by 8%, with treatment with dextrose gel remaining the less costly option.

The cost difference between dextrose gel and placebo halved when the cost per day of a NICU stay was reduced to NZ\$1,100, and increased by 47% when the cost per day was increased to NZ\$3,200 (Table 2). Again, treatment with dextrose remained the less costly option.

The effect of varying the method of calculating the costs of blood glucose concentration monitoring to exclude monitoring performed in the NICU, and to exclude monitoring performed in either the postnatal ward or NICU, was small. Treatment with dextrose remained the less costly option, with the difference between the two treatment options falling by 3.40% and 3.46% respectively.

Discussion

We have performed a cost analysis comparing the use of 40% dextrose gel and placebo gel in conjunction with usual care for treating neonatal hypoglycemia in term and late preterm infants. Use of dextrose gel resulted in cost savings compared with usual care.

Although the Sugar Babies Study found that NICU admission rates were not statistically different between the treatment groups, infants who received dextrose gel were less likely to

be admitted to NICU for hypoglycemia, less likely to receive additional dextrose, and less likely to experience treatment failure.¹² In our analysis, most of the difference in the overall costs between the two treatment arms arises from those infants admitted to NICU for hypoglycemia. The additional cost of hypoglycemia-specific treatment and monitoring contributes a only small proportion to overall costs, with the majority of the variance arising from the product of the numbers admitted to NICU and their average length of stay.

The observation that treatment with dextrose gel costs less than feeding alone remains valid for scenarios involving a lower cesarean delivery rate. The overall costs of a hospital stay for both groups is reduced with a lower modelled cesarean delivery rate, presumably due to the lower proportion of infants admitted to NICU for other indications, but the difference in costs between treatment with dextrose gel and feeding alone increases as the cesarean delivery rate decreases.

The cost of dextrose gel depends on the mode of packaging (pre-loaded syringes versus multi-dose container) and the rate of wastage, which is a function of the rate at which it is used relative to its shelf life. In our base case analysis, we presumed single-dose syringes were used. Our sensitivity analysis compared the scenarios where a multi-dose container was used with maximum efficiency, to a scenario where only a single dose was used before the container exceeded its shelf life. However, dextrose gel contributes only a small proportion of the total costs of care, and hence its use remains the less costly treatment option under both extremes.

The estimation of the costs of the hospital stay per infant excluded any complications experienced by, or additional costs incurred specifically by, the mother. The cost of a bed on a postnatal ward used in our model was based on the New Zealand Ministry of Health's WIESNZ tables, which is a simplified and generalized representation of costs in this population and includes the costs of the infant staying with the mother. Costs of a NICU admission were added to the costs of a postnatal bed, as they accrue in parallel. The base case analysis shows that the rate of NICU admission for infants with neonatal hypoglycemia is a significant contributor to the overall cost and cost difference for the two treatment groups. However, across a wide range of possible costs, from a halving of the base case cost to an extreme scenario where all NICU admissions were to a level III unit for the full duration of NICU stay, dextrose gel treatment remains cost saving, and the extent of that cost saving increases with any increase in NICU daily cost.

This analysis is based on data from a large cohort managed at a single institution. Thus, the transition probabilities incorporated into the decision tree model are a good representation of the proportions of infants experiencing each of the outcomes modelled, but caution must be employed if extrapolating to other institutions where the population characteristics and treatment protocols may differ. Some management criteria, such as the threshold for admission to NICU, may result in different overall costs from those in our model.

Ideally we would have compared costs in groups of babies who were or were not treated with dextrose gel. However, in the Sugar Babies Study, open label dextrose gel was available as a treatment option for infants who met the study criteria for treatment failure. This may

have improved blood glucose concentrations in some infants in the placebo group who would otherwise have required NICU admission, thus biasing our analysis to lower costs in this group. Our findings may therefore represent an underestimation of the true cost savings associated with use of dextrose gel.

Dextrose gel is effective, well tolerated by infants, easy to administer including by parents, and is inexpensive.¹² Further, it is a treatment option that is less likely to interrupt the initiation of breastfeeding, and less likely to involve mother-infant separation.¹⁶ For these reasons it has been recommended as a first-line treatment of late preterm and term infants who develop hypoglycemia in the first 48 h after birth.¹² We have now shown that in addition to these advantages, dextrose gel is also cost saving when used to treat neonatal hypoglycemia in late preterm and term infants.

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Abbreviations

NICU neonatal intensive care unit

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Appendix

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Figure.
Decision tree for treatment of neonatal hypoglycemia

Table 1

Average cost of treatment for hypoglycemia per infant

Treatment (number)	Hypoglycemia (number)	Encounter cost per infant	Average encounter cost per infant
Dextrose gel (118)	Single episode, admitted to NICU (25)	\$12,033.91 (\$1,394.16)	\$6,863.81 (\$345.11)
	Recurrent episodes, admitted to NICU (20)	\$9,680.17 (\$801.16)	
	Single episode, no NICU admission (51)	\$4,585.82 (\$249.31)	
	Recurrent episodes, no NICU admission (22)	\$4,963.91 (\$365.77)	
Placebo (119)	Single episode, admitted to NICU (32)	\$10,709.04 (\$801.03)	\$8,178.25 (\$411.82)
	Recurrent episodes, admitted to NICU (20)	\$12,884.16 (\$1,913.33)	
	Single episode, no NICU admission (44)	\$4,683.59 (\$326.52)	
	Recurrent episodes, no NICU admission (23)	\$5,233.69 (\$369.12)	

Values are mean (SD) in New Zealand dollars.

Table 2

Base case analysis and sensitivity analyses

Scenario	Dextrose Gel	Placebo	Difference
Base case	6,863.81 (\$345.11)	\$8,178.25 (\$411.82)	\$1,314.44 (\$535.55)
Caesarean section rate reduced to 20%	\$6,125.94 (\$317.39)	\$7,713.61 (\$431.83)	\$1,587.67 (\$538.25)
Caesarean section rate increased to 100%	\$9,363.68 (\$362.73)	\$9,840.30 (\$254.64)	\$476.62 (\$445.07)
Dextrose gel dose cost reduced to \$1.29	6,803.52 (\$347.58)	\$8,156.28 (\$406.40)	\$1,352.76 (\$539.90)
Dextrose gel dose cost increased to \$86.00	\$6,974.40 (\$347.29)	\$8,178.83 (\$408.92)	\$1,204.44 (\$539.06)
NICU cost per day decreased to \$1,100	\$5,798.89 (\$229.13)	\$6,464.85 (\$254.92)	\$665.96 (\$344.41)
NICU cost per day increased to \$3,200	\$7,767.24 (\$460.66)	\$9,698.74 (\$568.32)	\$1,931.50 (\$725.40)
Monitoring costs excluded for NICU	\$6,670.74 (\$336.64)	\$7,940.48 (\$409.80)	\$1269.74 (\$529.99)
All monitoring costs excluded (assumed to be included in per diem costs)	\$6,586.55 (\$337.12)	\$7,855.57 (\$409.84)	\$1269.02 (\$530.90)

Values are mean (SD) in New Zealand dollars.