CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

Hypoglycemia in low-risk term newborns

PROTOCOLS

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Background

Clinically important neonatal hypoglycemia is a significant health issue, with potential to cause neurodevelopmental impairment.[1] Prolonged or extremely low blood glucose values have uncertain prognosis while symptomatic hypoglycemia has been linked to a range of brain lesions on MRI.[2] There is still poor understanding of the factors that increase risk of hypoglycemic brain damage, although studies suggest that some newborns, particularly those with hyperinsulinism, cannot access alternative brain energy substrates when milk intake is low in the first few days of life. In any case, prompt treatment would minimize duration of low glucose and symptoms, which in turn should reduce risk of a poor outcome.[3] Monitoring recommendations, such as those published by the Canadian Paediatric Society (CPS) in 2004,[4] are used for early detection of low blood glucose in high-risk term newborns, including those with acute illness, infants of diabetic mothers and those who are macrosomic or growth restricted. In monitored newborns, the vast majority of hypoglycemic events are asymptomatic, while in unmonitored newborns, symptoms may be the sole trigger to obtain a glucose level. Thus, although hypoglycemia is far less common in newborns with no pre-identified risk factors, this small group may be at particularly high risk of a poor outcome, because of the inevitable delay in treatment.

It is not appropriate practice to monitor blood glucose in all term newborns, since as many as 14% of infants have a transient self-corrected hypoglycemia that does not appear to be deleterious.[5,6] Since the research team was not aware of population studies, a review of cases was done at an academic centre in Ontario to obtain an estimate of the prevalence of hypoglycemia amongst newborns who did not have

pre-identified risk factors. Using a pragmatic case definition, i.e., blood glucose <2 mmol/L and requiring IV dextrose, eight hypoglycemic infants were identified in a population of 6272 term newborns. Four of the newborns were just below the 10th centile for weight and one infant had Down syndrome, leaving three cases where no risk factor or underlying diagnosis was apparent. Most of the cases were tested because of either inadequate feeding or symptoms suggestive of hypoglycemia. All had jitteriness and one had a seizure with very low glucose level at diagnosis. Four mothers were hypertensive, one was obese and one mother was both obese and hypertensive.[7]

It is not known why apparently well newborns develop clinically significant hypoglycemia. The study will allow exploration for unrecognized or under-appreciated risk factors. For example, routine monitoring is not carried out on infants of hypertensive mothers, especially if birth weight is normal. The poorly defined entity of perinatal stress hyperinsulinism may be a factor in hypertensive mothers. Similarly, newborns of overweight/obese mothers are not screened unless there is gestational diabetes or macrosomia in the baby. Missed late pregnancy hyperglycemia may increase the risk of neonatal hyperinsulinism and hypoglycemia, while not increasing fetal size.[8] If high body mass index and excessive weight gain are over-represented in the study, this may have important public health implications. The Canadian Health Measures Survey, 2007–2009, showed that 25% of teenage girls were either overweight or obese.[9]

Study results will highlight the extent of the problem and inform future studies and subsequent recommendations for monitoring.

Methods

Through the established methodology of the CPSP, over 2500 paediatricians and paediatric subspecialists, including neonatologists, will be actively surveyed on a monthly basis for all new cases of hypoglycemia in low-risk term newborns. For each case reported on the monthly form, participants will complete a detailed questionnaire seeking non-nominal demographic and clinical information to ensure that the case definition is met.

Case definition

Report any otherwise healthy neonate less than 96 hours (4 days) old with **all** of the following:

- Term gestation: 37–42 weeks
- Birth weight: 2500–3999 grams
- Hypoglycemia, defined as whole blood or serum glucose <2.0 mmol/L
- Hypoglycemia treated with IV dextrose

Exclusion criteria

Neonate being monitored for hypoglycemia because of known risk factors, i.e., maternal diabetes (gestational or pre-gestational), growth restriction, macrosomia or important neonatal illness

Objectives

1) Estimate the national incidence of significant neonatal hypoglycemia amongst full term infants who do not meet criteria for current screening guidelines.
2) Obtain details on presentation, short-term morbidity/outcomes amongst these hypoglycemic newborns.
3) Describe maternal characteristics and neonatal history of these hypoglycemic newborns in order to identify potential risk factors for future study.

Duration

April 2014 to March 2016

Expected number of cases

There is no incidence data available in Canada. Extrapolating from regional data, we estimate that in Canada, 140 cases per year will meet inclusion criteria.

Ethical approval

Health Sciences Research Ethics Board, Queen's University

Analysis

An interim analysis of data collected will be completed annually. Total annual Canadian live births from Statistics Canada will be used as the denominator to calculate annual national incidence. Data will be analyzed using Statistical Package for the Social Sciences. Continuous variables will be compared using Student's t-test or the Mann-Whitney U-test and chi-squared or Fisher's exact test will be used to compare categorical variables. Logistic regression will be used to examine relationships between outcome variables, such as seizures or abnormal brain imaging and one or more predictor variables, such as age or glucose level at presentation.

Study results will be presented at national and international meetings and submitted for publication in scientific peer-reviewed journals.

References

1. Boardman JP, Wusthoff CJ, Cowan FM. Hypoglycaemia and neonatal brain injury. Arch Dis Child Educ Pract Ed 2013;98(1):2-6
2. Alkalay AL, Flores-Sarnat L, Sarnat HB, Moser FG, Simmons CF. Brain imaging findings in neonatal hypoglycemia: case report and review of 23 cases. Clin Pediatr 2005;44(9):783-90
3. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: Features associated with adverse outcomes. Biol Neonate 2006;90(2):74-86
4. Aziz K, Dancey P. Canadian Pediatric Society, Fetus and Newborn Committee (position statement). Screening guidelines for newborns at risk for low blood glucose. Paediatr Child Health 2004;9(10):723-9
5. Srinivasan G, Pildes RS, Cattamanchi G, Voora S, Lilien LD. Plasma glucose values in normal neonates: A new look. J Pediatr 1986;109(1):114-7
6. Nicholl R. What is the normal range of blood glucose concentrations in healthy term newborns? Arch Dis Child 2003;88(3):238-9
7. Hu L, Grewal K, Flavin M. Hypoglycemia in full-term infants with no pre-identified risk factors. 36th Annual Eastern Canada Perinatal Investigators Meeting, Toronto, November 2012 (poster)
8. Sosenko JM, Kitzmiller JL, Fluckiger R, Loo SW, Younger DM, Gabbay KH. Umbilical cord glycosylated hemoglobin in infants of diabetic mothers: relationships to neonatal hypoglycemia, macrosomia, and cord serum C-peptide. Diabetes Care 1982;5(6):566-70
9. Statistics Canada. Canadian health measures survey: Body composition and fitness, 2007–2009. www.statcan.gc.ca/daily-quotidien/100113/dq100113a-eng.htm (accessed February 21, 2014)