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Management of Neonatal Hyperglycaemia in Sweden—A Survey Study

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ABSTRACT

Aim: Neonatal hyperglycaemia is associated with a multitude of adverse outcomes, including mortality and impaired neurological development. The aim of this study was to characterise the current management of neonatal hyperglycaemia in Swedish neonatal units.

Methods: A digital survey was sent to 27 Swedish neonatal units providing care to preterm infants born before 32 completed gestational weeks.

Results: Sixty-eight responses were collected from 21 different units. Thirty-two percent (22/68) of clinicians reported having a local treatment guideline for neonatal hyperglycaemia. Hyperglycaemia was defined as a glucose concentration above a value in the range of 8.0–10.0 mmol/L by 62.5% of clinicians, while 16.7% and 21.8% used a definition between 10.1 and 12.0 mmol/L and > 12 mmol/L, respectively. Intravenous glucose reduction was initiated at higher glucose concentrations by clinicians working at university hospital units ($p = 0.006$). Glucose concentration threshold for initiation of insulin treatment varied between 8 and 30 mmol/L. Three clinicians (3/35 (8.5%)) reported having experienced problems with frequent hypoglycaemia during ongoing insulin treatment.

Conclusions: This study demonstrates extensive differences in clinical practice regarding neonatal hyperglycaemia both within and between neonatal units in Sweden. Randomised controlled trials are needed to provide evidence for clinical guidelines and to improve and standardise the care of these infants.

1 | Background

In Sweden, 5.5% of all births occur before gestational week 37, with 0.3% representing births before gestational week 28 (extremely preterm) [1]. Neonatal hyperglycaemia is a clinical condition scarcely researched despite being a common occurrence among preterm and low birth weight infants [2–13]. Previous studies have shown that hyperglycaemia is associated with a multitude of adverse outcomes, including increased risk for mortality and morbidities such as impaired neurological development [2, 3, 14–23]. Treatment options are a topic of debate among clinicians, as neither a common definition of neonatal hyperglycaemia nor a consensus regarding its causes has been reached. Several studies have linked low gestational age, low birth weight, and intrauterine growth restriction to neonatal hyperglycaemia [3–7, 24–29]. Furthermore, correlation

Abbreviations: DOL, Day of life; ESPGHAN, European Society for Paediatric Gastroenterology, Hepatology and Nutrition; LIGHT, Very low birthweight infants—glucose and hormonal profiles over time; NICU, Neonatal intensive care unit; UH, University hospital unit.

Summary

- Glucose concentration threshold values for definition and subsequent action regarding neonatal hyperglycaemia differed widely among clinicians.
- Only one in three clinicians reported having a local treatment guideline for neonatal hyperglycaemia.
- Few clinicians reported hypoglycaemic events during insulin treatment.

between hyperglycaemia, nutrition intakes, and sepsis has been reported [9].

Current treatment options for hyperglycaemia in preterm infants in Sweden consist of a reduction of intravenously administered glucose and intravenous insulin therapy. A systematic review of insulin treatment in preterm neonates did not find evidence for a beneficial effect on mortality, severe intraventricular haemorrhage, late-onset sepsis, or chronic lung disease when treating neonatal hyperglycaemia with insulin [30]. Alsweiler, Kuschel, Bloomfield have previously reviewed the management of neonatal hyperglycaemia in Australasia, showing that treatment approaches differed widely between neonatal units [31].

The aim of this study was to investigate the current management of neonatal hyperglycaemia in Swedish neonatal units. Our hypothesis was that a wide range of thresholds for the definition of hyperglycaemia and treatment initiation would be found both within and between different neonatal units in Sweden.

2 | Methods

Through the Swedish Society for Neonatology, contact details for all Swedish neonatology units with the capability of providing care for newborns born before 32 completed gestational weeks were acquired. A total of 27 neonatal units were identified. A digital survey with a total of 32 questions was created using SurveyMonkey (SurveyMonkey Inc., San Mateo, California, USA, www.surveymoneky.com) (see Appendix S1). The survey was sent to the clinical directors of the 27 neonatal units, and the directors were asked to forward the survey to physicians employed in their respective units. Responses were collected between 12th November 2021 and 28th January 2022.

Data was analysed using SPSS (IBM SPSS Statistics version 29.0 for Windows, Armonk, New York). Responses were analysed collectively and were subsequently divided into two groups—university hospital units (UH; including 6 units treating extremely preterm infants) and non-university hospital units (non-UH; including 15 units treating infants born after 28 completed gestational weeks). The reason for this being the variation in patients cared for, as all extremely preterm infants born in Sweden are initially treated at an UH until they are stable and mature enough to be transferred back to their local hospital (usually at 28–32 weeks postmenstrual age), if applicable. UHs are usually well staffed with experienced neonatologists and nursing staff, regularly caring for extremely preterm infants and other severely ill neonates. Non-UH treating neonates born after 28 gestational weeks vary in staff composition, some having both neonatologists and general paediatricians among their staff and some only having general paediatricians.

Responses including a range were recategorised using the more proactive value given. For example, a response that insulin therapy would be initiated at glucose values of 12–15 mmol/L was recoded to a single value of 12.0 mmol/L, as this would be the first potential point of action according to the range given.

The study was approved by the Swedish ethical review authority. The study was exempted from the informed consent requirement.

3 | Results

Out of 27 contacted units, 21 (77.8%) replied with 68 individual respondents (32 from UH vs. 36 from non-UH). Among the 68 respondents, 36 (53%) were neonatologists with more than 5 years of experience (22 from UH, 14 from non-UH); 15 (22%) were neonatologists with 0–5 years of experience (4 from UH, 11 from non-UH); and 17 (25%) were paediatricians (5 from UH, 12 from non-UH). Paediatricians training to become neonatologists were categorised as paediatricians.

Twenty-two (22/68 (32%)) respondents reported that they had a local guideline for treatment of neonatal hyperglycaemia in place. Out of these, 16 (73%) were employed at a UH.

Twenty-four clinicians (24/68 (35%)) specified a definition of hyperglycaemia (Table 1). The definition of neonatal hyperglycaemia varied between a single glucose concentration > 8–15 mmol/L and repeated glucose measurements > 8–13 mmol/L. Considering UH

TABLE 1 | Glucose concentration thresholds used in Swedish neonatal units. Data shown as a percentage of responses from the entire cohort, from university units (UH) and from non-university units (non-UH).

		Glucose concentration threshold (mmol/L)		
		≤10	10.1–12.0	>12.0
Definition of neonatal hyperglycaemia	All	62.5	16.7	21.8
	UH	58.3	16.7	25.0
	Non-UH	66.6	16.7	16.7
Reduction of intravenous glucose infusion	All	45.6	34.8	19.6
	UH	21.7	52.2	26.1
	Non-UH	69.6	17.4	13.0
Insulin therapy	All	15.2	36.3	48.5
	UH:	5.8	47.1	47.1
	Non-UH:	25.0	25.0	50.0

and non-UH separately, the widest range of definitions of neonatal hyperglycaemia within a single unit was 10–15 mmol/L for UH and 8–12 mmol/L for non-UH.

Forty-six clinicians (46/68 (68%)) reported a threshold value for reduction of intravenous glucose (Table 1). Glucose concentration threshold for reduction of intravenous glucose varied between 6 and 15 mmol/L in the entire cohort. Considering UH and non-UH separately, the widest range of thresholds within a single unit was 8–15 mmol/L for UH and 7–12 mmol/L for non-UH. Glucose reduction was initiated at lower glucose concentrations by clinicians employed at non-UH (UH: median 12.0 mmol/L (IQR = 10.1 to 12.1), non-UH: median 10.0 mmol/L (IQR = 8.0 to 11.1), $u = 139.5$, $p = 0.006$). Twenty-one (31%) clinicians reported having a threshold for minimal glucose infusion rate, with all but one referring to levels between 4 and 6 mg/kg/min.

Thirty-seven clinicians (37/68 (54%)) reported a threshold value for initiation of insulin therapy. Glucose concentration threshold for initiation of insulin treatment varied between 8 and 30 mmol/L in the entire cohort (Figure 1). Considering UH and non-UH separately, the widest range of thresholds within a single unit was from 25 mmol/L to "never" for UH and 7–12 mmol/L for non-UH. The most common starting dose of insulin was 0.05 U/kg/h (14/37 (38%)). Twenty-six clinicians (70%) used ≤ 10 mmol/L as an upper glucose target range level during ongoing insulin treatment. Three clinicians (3/35 (8.5%)) reported experience of frequent hypoglycaemic episodes during insulin treatment (Table 2).

Thirty-five (35/68 (51%)) responses were collected regarding nutrition. Parenteral nutrition was started as soon as possible after birth, with 31 (31/35 (89%)) of the respondents reporting prescribing parenteral amino acids on the first day of life (DOL 0), and 27 (27/35 (77%)) and 34 (34/35 (97%)) initiating lipid and glucose solutions on DOL 0, respectively. Thirty-four (34/35 (97%)) clinicians reported initiating some form of enteral nutrition on DOL 0. Mean (+-SD) target day for reaching full nutritional intake (estimated at 120 kcal/kg/day and 3.5 g/kg/day of protein) was 4.5 (1.74) days and varied between DOL 2 and 9 with no significant differences between UH and non-UH ($p = 0.25$). Twenty-three (23/35 (66%)) of the clinicians who reported a set target day for reaching full nutritional intake reported calculating energy and protein intakes daily, with the remaining 12 (12/35 (34%)) of respondents not specifying if nutritional intakes were calculated. Glucose

TABLE 2 | List of responding units in alphabetical order.

University units	Non-university units
Karolinska (Solna & Huddinge)	Borås
Linköping	Falun
Lund	Gävle
Umeå	Halmstad
Uppsala	Jönköping
Örebro	Kalmar
	Karlstad
	Kristianstad
	Norrköping
	Sunderbyn (Luleå)
	Sundsvall
	Södersjukhuset (Stockholm)
	Trollhättan
	Västervik
	Växjö

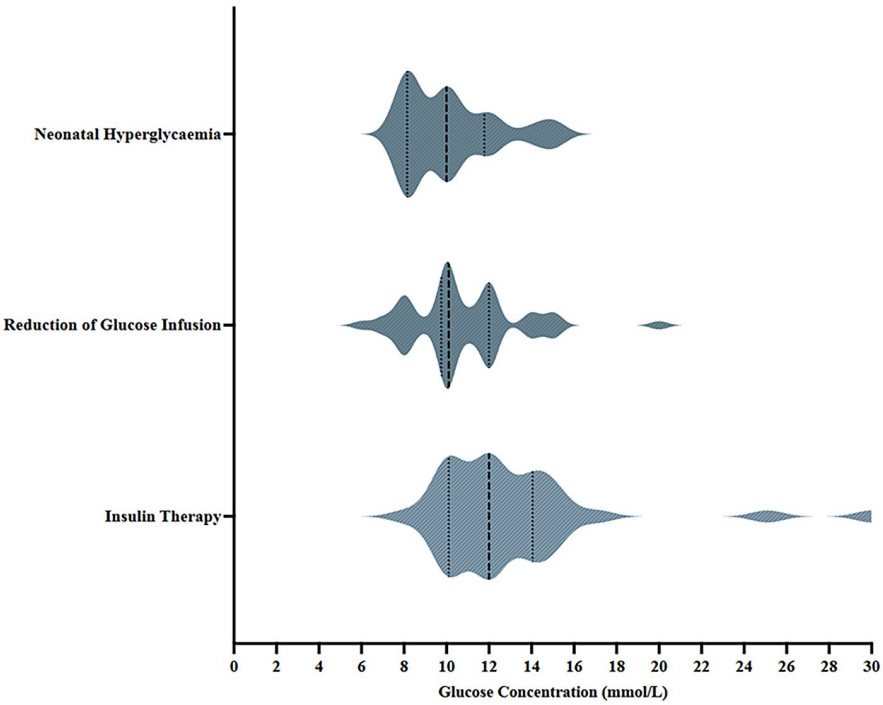

FIGURE 1 | Variation of glucose concentration thresholds used in Swedish neonatal units. Violin plot representation of all collected responses regarding the definition of hyperglycaemia, reduction in glucose infusion, and initiation of insulin treatment. Including quartiles representing the 25th, 50th and 75th percentiles.

concentration monitoring routines varied both within and between units, commonly with more frequent blood sampling initially, followed by a gradual reduction in frequency.

4 | Discussion

The findings of this study reveal extensive differences in clinical practice regarding neonatal hyperglycaemia both within and between different neonatal units in Sweden. The differences observed can be seen across most studied factors, including definition and thresholds for treatment initiation.

The definition of neonatal hyperglycaemia varied between 8 and 15 mmol/L, indicating both a large intra- and inter-unit difference. The lack of evidence for long-term health benefits of different treatment strategies is likely to be contributing to the large variation observed. The variation observed might have a negative impact on communication and decision-making regarding interventions, as the interpretation of the condition can vary between involved clinicians and units. Reduction of intravenous glucose infusion was generally seen as the first line of action, in accordance with previous results published by Alsweiler, Kuschel, Bloomfield [31]. Interestingly, a reduction of glucose infusion rates at lower glucose concentrations was noted among clinicians employed in non-UH. The reason for this is currently not known. However, a higher frequency of extremely preterm infants with more severe comorbidities treated at UH could be a plausible explanation for allowing higher glucose concentrations before intervening. Only 31% of respondents reported a limit for minimum glucose infusion, a rather low figure. Of those, all but one reported levels between 4 and 6 mg/kg/min, in accordance with the 2018 ESPGHAN guidelines on paediatric parenteral nutrition: carbohydrates [32]. Even though only 32% reported having a local treatment guideline, many of the clinicians employed in non-UH referred to guidelines issued by the UH in their region.

The threshold for initiation of insulin treatment varied between 8 and 30 mmol/L, indicating a varying approach to insulin treatment initiation. A systematic review conducted in 2021 showed that preterm neonates (< 32 weeks or < 1500 g) with hyperglycaemia ≥ 10 mmol/L had increased odds for mortality, and prolonged hyperglycaemia was associated with adverse outcomes, including retinopathy of prematurity, severe intraventricular haemorrhage, and poor growth and psychomotor development at 1–2.5 years [15]. A dose-response correlation between prolonged hyperglycaemia and worse neurodevelopmental outcomes in extremely preterm infants at age 6.5 years has also been reported [14]. A systematic review assessing the use of insulin treatment in neonatal hyperglycaemia did not find clear evidence for positive health outcomes associated with insulin treatment [30]. The reasons for this remain unknown but might imply that insulin resistance could be a contributing factor to hyperglycaemia in preterm neonates [13], thus rendering insulin treatment ineffective. Further research is needed to confirm these speculations and explore possible treatment methods.

Traditionally, hypoglycaemia during insulin treatment has been seen as a major concern, possibly impacting the decision to initiate treatment. It is thus worth considering that only three clinicians reported experiencing frequent hypoglycaemic episodes during ongoing insulin treatment. These findings are in line with recently published results from the prospective LIGHT study, where only a single glucose concentration < 4 mmol/L during ongoing insulin infusions was registered, and no glucose concentrations < 2.6 mmol/L were noted [13].

Even though a large difference in threshold for insulin treatment initiation could be seen, the most common reported starting dose of 0.05 U/kg/h (0.01–0.1 U/kg/h) and the upper target glucose concentration level of ≤ 10 mmol/L during ongoing treatment were much the same across units. Further research is needed to determine the optimal threshold values for treatment initiation. Wide clinical differences might increase the risk of confusion and emotional dissatisfaction among patients and their families. This is especially true in cases of intra-unit differences, which might lead to frequent changes in patient care. Efforts to standardise definitions and treatment recommendations are needed. A coherent treatment approach as more evidence becomes available would likely benefit both patients and clinicians.

This study collected responses from most neonatal units treating infants born before 32 completed gestational weeks in Sweden, although no responses were received from one UH. The responses also represent a variation of both neonatologists with different degrees of clinical experience and general paediatricians involved in the care of preterm infants. More responses from different clinicians within each unit could have benefitted our results further. Most UH were represented by several clinicians responding, whereas most non-UH were represented by one or two respondents. The respondents have answered the questionnaire to a varying degree, resulting in the missing responses seen in Appendix S1 as well as different denominators in reported data. However, to the best of our knowledge, it is the largest survey study of its kind regarding neonatal hyperglycaemia, and only the second of its kind following Alsweiler, Kuschel, Bloomfield [31].

In conclusion, this study demonstrates extensive differences in clinical practice regarding neonatal hyperglycaemia among neonatologists and general paediatricians across Sweden. The same treatment strategies, reduction of glucose infusion and insulin treatment, are used, but the definition and threshold values for initiating treatment differ widely. The evidence for adverse outcomes in preterm neonates with hyperglycaemia is mounting, with a shortage in clear evidence for beneficial treatment options. This leaves an evidence gap likely contributing to such wide differences in treatment approaches as can be seen in our study. Randomised controlled trials are needed to provide evidence for clinical guidelines and thus improve and standardise the care of these preterm infants.

Author Contributions

Ludvig Henriksson Frithiof: writing – original draft, formal analysis, data curation. **Magnus Domellöf:** conceptualization, methodology, writing – review and editing, supervision. **Itay Nilsson Zamir:** supervision, conceptualization, writing – review and editing, methodology, data curation, funding acquisition, project administration.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.