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Is Insulin the Safest Approach to Treat Hyperglycemia in Preterm Infants under 37 weeks GA? Evidence-based Approach to a Clinical Question for the Postgraduate Child Health Diploma's EBM Module

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Abstract: ***This comprehensive review explores the management of hyperglycemia in preterm neonates, focusing on the use of insulin therapy and its impact on long-term outcomes. Two relevant observational studies and a randomized controlled trial are analyzed to assess the safety and effectiveness of insulin treatment in hyperglycemic preterm infants. The review also delves into the critical appraisal of these studies, discussing their methodology, statistical significance, and limitations. Key outcomes include the frequency of hypoglycemic episodes and the neurodevelopmental impact of hyperglycemia in these neonates. While the studies show that insulin infusion for hyperglycemia appears safe with no significant effects on morbidity and mortality, questions remain regarding its impact on long-term neurodevelopment. This review sheds light on the complex issue of hyperglycemia management in preterm neonates, providing valuable insights for healthcare professionals and researchers in neonatology.***

Keywords: Preterm neonates, hyperglycemia, insulin therapy, long-term outcomes, hypoglycemic episodes

1. Scenario

- 29 weeks GA baby with a BW of 1.5 kg was born via emergency C/S to a pre-eclamptic mother with uncontrolled BP readings, due to reduced fetal movements.

The baby was born in relatively good condition requiring minimal respiratory support in form of nasal CPAP and was progressing very well in the neonatal unit. On day 3 of life, baby's blood glucose levels were raising to 13-15 mmol/L for which Insulin was commenced with better control over glucose level. PN wasn't reduced. In fact, it was enhanced according to daily requirements of age and weight. However,the baby started experiencing many hypoglycemia episodes some which require more than singlecorrection bolus to normalize glucose levels.

- Another Scenario: 30-week GA baby with a BW of 1.75 kg, born spontaneously via normal vaginal delivery due to premature rupture of membrane.

At2 days of life glucose levels were as high as 14mmol/L, so glucose rate, and therefore PN rate was reduced which affect overall calorie intake of this baby and collectively reflected as poor weight gain until discharged.

PICO Question:

P: sick preterm babies born before 37 weeks of age who would develop hyperglycemia (defines as Blood glucose levels >12 mmol/l +glycosuria ++

I: starting insulin infusion when hyperglycemic definition fulfilled.
C: to compare with other control group of preterm neonates who fulfill similar hyperglycemic criteria, but carbohydrate was cut from PN/fluids rather than starting insulin infusion:
O: Primary Outcome:the neurodevelopment impact of hypoglycemia in these neonates{ indicated by the Head growth rate to 40 weeks' postmenstrual age or at discharge + Cranial US scan results}. A secondary outcome is the number of hypoglycemic episodes (Where glucose level is <2).

Search Process:
Secondary sources used: Cochrane:
5 studies→2 which are relevant:

1) Hyperglycemia in Extremely Preterm Infants-Insulin Treatment, Mortality and Nutrient Intakes
2) Insulin treated hyperglycemia, hyperalimentation and growth in very preterm infants receiving parenteral nutrition: a randomized controlled trial

Summary search: (Insulin) and 'hyperglycemic treatment' + {'preterm infant or preterm babies} using title,abstract keywords with no limitations otherwise.

Primary sources: Ovid Medline& Embase:

Summary search: 'hyperglyc?emia Management/treatment' AND 'preterm/ premature babies, neonates or ' → 172 results. Manual filtering seized options to 2 results based on their relevance. Unfortunately, no SR nor MA, but 2 observational studies.

2. Concluded Studies

Article title	Study type	Study group	Outcome	Key Results	comments	Citation
Insulin infusion for hyperglycemia in very preterm infants appears safe with no effect on morbidity, mortality and long-term neurodevelopmental outcome.	Retrospective observational study	97 infants born < 29 weeks GA 17 received Insulin therapy	Episodes of hypoglycemic attacks were infrequent. Mortality No significant difference in 12 months neurodevelopmental and anthropometric outcome detected in infants receiving Insulin	1.3 % with 95% CI (0.5 to 2.9) 1.2% with CI(0.29-5.0)	Critical appraisal details as below. Less number of cases studied. 1st study to examine long-term neurodevelopment outcome in Insulin treated group around neonatal period.	Heald A, Abdel-Latif J Maternal-Fetal Neonatal Med. 2012 Nov;25(11):2415-8.
Hyperglycemia in Extremely Preterm Infants-Insulin Treatment, Mortality and Nutrient Intakes	Cohort observational study gathered from previous Sweden perspective study, where some data were precluded retrospectively	580 infants born< 27 weeks were involved in the study, 9850 glucose measurements were obtained, Insulin treatment was the reference standard in the study.	In logistic regression model, Insulin treated group was associated with less 28- and 70-day mortality when given to infants with hyperglycemia, irrespective of the duration of the hyperglycemic episodes (P v. <0.05)	Less mortality in Insulin treated infants' group	Despite being relevant to its population, the study's control group consisted of infants who didn't take insulin rather than those whose PN had lower glucose concentrations. The clinical choice to modify glucose intake in accordance with the plasma glucose levels may have brought confounder bias into the results, which could account for the findings. Adjusted logistic regression was used as the analytic strategy of the study giving validity to the results.	Zamir I, -. J Pediatric. 2018 Sep;200:104-110.e1
Insulin treated hyperglycemia, hyperalimentation and growth in very preterm infants receiving parenteral nutrition.	Randomized Controlled trial	150 infants were targeted from previous study of SCAMP: standardized concentrated additional macronutrients in neonatal Parenteral nutrition, were 63 (Insulin treated infants) and 76 (control non-Insulin treated group) were sub-stratified from that study, and 1 infant was excluded. Insulin therapy was the standard reference.	Insulin treated hyperglycemic group shown better growth in form of weekly HC and weight gain when compared to the control group; (Glucose reduction from PN) group	14 mm Vs 11 mm change in HC with P value of 003 137 Vs 109 grams weight gain with P value of 0.25	Derived from a previous RCT study. Strong internal validity: Focused PICO question Statistical significance is not clear. Extremely externally valid	Morgan C, Archives of disease in childhood, 2014, 99, A39

3. Critical Appraisal:

Regarding the article, "Insulin infusion for hyperglycemia in very preterm infants appears safe with no effect on morbidity, mortality and long-term neurodevelopmental outcome.":

Given that they were primarily chosen from the same demographic, the two groups of neonates—those who received insulin treatment and those who did not—seem to be rather comparable: Extremely preterm infants born at 29 weeks or earlier, however those given insulin had lower birth weights and poorer developmental maturity.

As the unit guideline for starting insulin included a BGL 10-12 mmol/L and substantial glycosuria on 10% dextrose parenteral nutrition, the exposures (hyperglycemic newborn group) were measured similarly in a valid and reliable manner to assign neonates to both exposed and unexposed groups.

Multiple logistic regression was used to control variable confounding factors that were clearly defined and mentioned

in a demographic table at the start of the study, by employing stepwise exclusions based on likelihood ratio. Using two-tailed comparisons, the level of statistical significance for each analysis was set at p 0.05.

The newborn group that wasn't exposed didn't experience the outcome that ensued when the study first began. The study's findings, which included assessments of neurodevelopment and hypoglycemia episodes, were very clearly characterized in a valid and dependable manner from the outset.

The reported follow-up period was sufficient and long enough for results, such as neurodevelopmental evaluation or hypoglycemia episodes, to materialize.

77 of the original 97 infants in the study—the ones that survived—were tracked down. For that reason, follow-up failed to conclude, and the causes of lost follow-up weren't explained and investigated.

Utilizing Predictive Analytics SoftWare (PASW) statistics, the statistical analysis was adequate. Information is displayed as a percentage (%) or median (interquartile range, IQR). Fisher exact testing, Mann-Whitney, and $\chi 2$ were employed.

The study's limitation—that fewer infants received insulin than in prior studies—is strengthened by the long-term data that is now available. This study's power is diminished by its retrospective nature and it may be constrained by a variety of biases, including clinician prejudice. Even if some confounders were taken into account, the results could have been affected by others.

4. Commentary

All the studies listed in this review properly addressed the relevant targeted PICO question of the effect of insulin on extremely preterm hyperglycemic newborns. Some of the studies that were cited had issues with the conclusions. These studies nearly all used case-control or cohort groups that were relatively similar (good randomization in the RCT study, though not blinded due to study nature), with practically comparable forecasting outcomes to look at (hypoglycemic episodes, and some long-term neurodevelopmental follow up).

Even though confounding variables were effectively removed from all of the studies described by properly correcting for them beforehand, and patient were followed up to a great extent, statistical significance was not always clearly derived in all studies, making it difficult to precisely estimate their importance.

At 12 months corrected age, no statistically significant difference between neonates who received insulin and those who did not. While mortality ate significantly dropped in Insulin treated group.

Bottom line:

- Insulin is generally a safe medicine used to treat hyperglycemia in extremely preterm neonates when compared to traditional methods of diet restriction.
- Although hypoglycemic episodes brought on by insulin therapy may be a concerning side effect, the cited studies found that they were largely eliminated by working in a secure environment where normoglycemia was not the target.
- More research is required to highlight the significance of insulin and shed light on other long-term consequences of insulin therapy, such as neurodevelopmental issues.

5. Conclusion

In conclusion, the management of hyperglycemia in preterm neonates remains a nuanced and challenging aspect of neonatal care. The reviewed studies suggest that insulin therapy for hyperglycemia is safe and does not significantly affect morbidity or mortality in extremely preterm infants. However, questions persist regarding its impact on long-term neurodevelopmental outcomes. While these studies provide valuable insights, further research is needed to comprehensively assess the potential benefits and risks of insulin treatment in this vulnerable population. Clinicians should carefully consider the individual needs of preterm neonates and monitor them closely to ensure optimal glucose control while minimizing the risk of hypoglycemic episodes.