

EDITORIAL

Call for a randomized controlled trial: early glyceemic control in the development of retinopathy of prematurity

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In this edition of the *Journal of Perinatology*, Mohsen *et al.*¹ present the first prospective study on the effect of elevated glucose on the development of retinopathy of prematurity (ROP). While the correlation between elevated glucose and ROP has been well delineated by several retrospective studies, Mohsen *et al.*¹ are the first to conduct a prospective study and are able to confirm that elevated average neonatal glucose concentrations in the first week of life are independently associated with the development of ROP.

Concerns about the impact of exogenous insulin as an independent risk factor for ROP have confounded the discussions on the correlation of hyperglycemia with ROP. Mohsen *et al.*'s¹ elegant avoidance of insulin use allowed for the conclusion that the effects of elevated glucose are linked to ROP and not exogenous insulin infusions, which other studies had not been able to exclude.

Another clever design decision was the use of only regularly scheduled glucose tests in the analysis. This approach nullified the known effect of abnormal glucose results leading to more testing and more abnormal results. If all glucose results had been used, episodes of hyper- and hypoglycemia would have received exaggerated weight due to the more frequent testing around the events with the result of a distorted or skewed picture. As only the regularly scheduled (every 8 h for the duration of a week) glucose laboratory tests were used, there was no need to apply the computationally expensive area-under-the-curve methodology (time-weighted) used by Chavez-Valdez *et al.*²

What are the determining factors of today's understanding that ROP is correlated to early glyceemic state? In part, the answer is serendipity. In 1998, attending a dinner with a lecture on adult diabetes as a guest of an invited family medicine physician, the talk had little relevance for me as a neonatology fellow. At one point, the lecturer discussed the complications of diabetes including 'neo-proliferative eye disease'. Having heard of 'neo-proliferative eye disease' before, but in conjunction with premature infants' ROP, the remainder of the evening allowed the formulation of a novel question: Could the development of ROP also have a connection to neonatal glucose levels?

A literature search in the next few months discovered indirect evidence for a connection between elevated glucose and ROP. Events in the early life of premature infants that are usually associated with elevated glucose levels such as candida sepsis or the use of steroids had already been connected to the development of ROP. Absence of hypoglycemia also had been identified as a risk factor for ROP. Obviously, at that time the association of an important player in metabolism—oxygen—had been long established and oxygen was already administered in a controlled manner to reduce ROP risk.

A quick 'sanity check' that involved the review of the charts of five infants with severe ROP suggested evidence of a link to elevated glucose. However, distracted by a fellowship in Clinical Informatics, the plan to explore the role of glucose in ROP went

into the 'ideas to pursue one day' file until in 2001, a pediatric resident requested a project for her research rotation. Dr Garg's determination and extraordinary work led in 2003 to the publication of the first retrospective study—also in the *Journal of Perinatology*—correlating glucose levels in the first month of life to the development of ROP.³

From the first serendipitous notion that glucose may be linked to ROP and from the first published study, 16 years and 11 years have passed respectively until today's publication of the first prospective study. Distractions may be to blame for the first 5-year delay, but the evidence has now been published and available for more than 10 years.³ Unfortunately, today we are not much closer to putting this knowledge into use in the prevention of ROP. Awareness of the correlation between glucose and ROP has not made it in the minds of the public. The current entry for ROP on Wikipedia does not include glucose as a risk factor.⁴

To date, the correlation between ROP and glucose has also not achieved the deserved attention by neonatologists. Glucose in newborn intensive care units is currently not managed with the intention to prevent ROP. No clinical trials have been conducted to evaluate approaches, safety and outcomes on ROP of tighter glucose control in the newborn intensive care unit in the first month of life, despite the evidence that glyceemic protocols can be implemented safely in adult intensive care units⁵ and in neonatal intensive care units.⁶

In the 1950s, ROP was a disease considered extinct until new technologies and treatments permitted the survival of ever smaller and more premature infants. With the improved survival came an increase in the incidence ROP. In the history of this disease, the enormous time delay between recognition of disease correlation and clinical trials translates into tremendous opportunity loss. Time is of the essence! We need clinical trials on the management of acute hyperglycemia and exposure to prolonged elevated glucose levels in neonates with ROP as an outcome measure. It is time to develop and test new measures and approaches that will allow neonatologists to reduce the risk of blindness and loss of vision in their tiny patients.

CONFLICT OF INTEREST

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