Glutamine Supplementation in Neonates: Is There a Future?

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Over the past couple of decades, glutamine (GLN) has emerged as an important metabolic intermediate signaling molecule and nutrient that becomes rapidly depleted and therefore critically important during stress. In very low-birthweight infants, a population of patients in whom supplementation of GLN should provide major benefits, GLN is provided in subnutritional quantities because standard parenteral nutrition solutions do not contain GLN, and most of these babies do not receive full enteral feedings until several weeks after birth. Results of efficacy on a limited number of outcomes have been mixed, but there is controversy regarding the validity and interpretation of these trials [1]. Some authors suggest that further study in this area is no longer warranted [2]. The use of GLN supplementation in very low-birthweight infants has therefore not become routine.

However, in premature infants there is a strong theoretical rationale for supplementation with GLN. Premature birth leads to a sudden cessation of a special combination of nutrients, including GLN, specifically suited for the rapidly developing fetus [3]. In the first weeks of life, these infants frequently derive most of their nutrition from the parenteral route, which contains no GLN, and are deprived of luminal nutrients, which contain GLN, because of the reluctance of neonatologists to use the enteral route. Furthermore, these infants are highly stressed and have an increased utilization of GLN during their first several weeks of life [4].

There are several inherent dilemmas common to trials of GLN supplementation (and perhaps many other types of nutritional supplementation studies):

1. Should isonitrogenous controls be used?
2. How long should the GLN supplementation last, and what is the correct amount that should be supplemented?
3. Is it better to supply GLN via the enteral or the parenteral route?
4. What outcomes should be evaluated in future studies? The primary outcome in many of the studies was sepsis. Is hospital-acquired sepsis a good outcome to evaluate in multicenter trials?

In conclusion, there is a recent reluctance to continue research on GLN-mediated amelioration of morbidity in premature infants. Based on the large body of evidence available from studies in animals and adults, as well as several of the recent studies in preterm infants, the notion that additional GLN research in premature infants should not be a priority is probably injudicious. As with the studies in adults, trials encompassing a large variety of premature infants with an array of problems may dilute effects. A variety of dosages have never been evaluated. If one extrapolates the dosages used in studies of enteral GLN administration in adults normalized to total protein requirements, the dosages used in the infant studies were relatively low. The route of administration (enteral vs. parenteral) may be critical. Downregulation of intestine-derived inflammation, apoptosis and stabilization of heat shock responses would theoretically occur to a greater degree with direct enteral application than if administered by the intravenous route, and this has not been investigated in preterms. The use of dipeptides of GLN also provides new avenues of research where the dosages can be increased and absorption improved. A thoughtful reevaluation of future applications and trials of GLN in premature infants is warranted.

References