

Relationship between Oxytocin and Growth in Premature Infants

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Abstract

Infants born extremely premature (less than 29 weeks gestation) are at high-risk for inadequate growth because of the effects of acute illness. Researchers have demonstrated that these infants are often discharged from the neonatal intensive care unit (NICU) with weights below the 10th percentile. It is important to identify factors that promote growth. One promising factor is oxytocin. Limited findings from animal models suggest that there is a relationship between weight gain and oxytocin levels. This relationship is not well understood and has not been examined in premature infants. The purpose of this exploratory study was to examine the relationship between oxytocin and weight gain in extremely premature infants. The study hypothesis was that higher oxytocin levels would be associated with better weight gain. The sample was comprised of 25 premature infants in the NICU born between 25-28^{6/7} weeks of gestation who were followed until 34 weeks gestation. Urine was collected at two weeks of life and then weekly until 34 weeks gestation to measure oxytocin. Weekly weights were also recorded from the medical record. After completion of data analysis, no significant relationship was found between oxytocin levels and growth velocity. However, this study serves as a foundation for further investigation.

Introduction

Prematurity remains a significant problem in the United States. In 2013, approximately 447,000 infants were born premature. Of those, 28,000 were extremely premature (less than 29 weeks gestation) (NVSS, 2015). These infants are at high risk for a number of complications. Fortunately, survival rates are significantly improving. However, it is now necessary to begin to focus on improving overall health outcomes for these infants. Growth is one area receiving increased attention because of its relationship to long-term outcomes (Sammallahti et al., 2015). Although the majority of premature infants are born at an appropriate weight (10th-90th percentile) for their gestational age and sex, many will develop extrauterine growth retardation (EUGR) and will be discharged from the neonatal intensive care unit (NICU) with growth measurements at or below the 10th percentile (Ehrenkranz, 2014). This suggests that growth in the NICU is inadequate and ways to promote growth throughout the hospital stay need to be further investigated given the significant length of stay for many premature infants.

While much of the research effort is focused on the relationship between nutritional management and growth, one area worth exploring is the impact of the stressful NICU environment on growth. Premature infants are exposed to frequent handling and a variety of painful procedures, especially during the first few days of life when infants are acutely ill, that are stressful to these vulnerable infants. Limited evidence shows an inverse relationship between the number of painful procedures a premature infant experiences in the NICU and subsequent weight gain (Vinall et al., 2012). This suggests that examining the effects of stress on growth in premature infants will allow for the development of strategies to decrease stress and support growth. There may be a biobehavioral contribution to a

premature infant's growth. Limited findings from animal models have suggested that at certain physiologic levels, oxytocin dampens the stress response, as well as promotes weight gain through the release of growth hormone (Björkstrand, Hulting, Uvnäs-Moberg, 1997). This relationship is still not well understood and has not yet been studied in premature infants.

Purpose of Study

The purpose of this exploratory study was to determine the relationship between oxytocin and weight gain in premature infants.

Review of Literature

Importance of Growth in Neonates

Promoting growth in the NICU has been a well-known challenge throughout the years. By discharge, many premature infants, especially extremely premature infants, will develop extrauterine growth retardation (EUGR). Extrauterine growth retardation is typically defined as a growth measurement (weight, length, or head circumference) that is below the 10th percentile of the expected intrauterine growth for the postmenstrual age (PMA) (Ehrenkranz, 2014). Stoll et al. (2010), in their study, demonstrated that 79% of extremely premature infants had attained weights less than the 10th percentile by 36 weeks PMA. A significant number of extremely premature infants exhibit a decrease in standard deviation scores by discharge (Franz et al., 2009). These findings are further supported by the findings from Frondas-Chauty and colleagues (2014). In a large cohort study, these researchers demonstrated that 66% of premature infants experienced a decrease in the z-score for weight of at least -0.51 between birth and discharge from the NICU. The findings from these studies provide evidence that EUGR is an important problem for premature

infants. Due to the increased survival rates of premature infants, it is essential to also focus on improving growth in order to improve long-term outcomes (Steward, 2012). EUGR can place these infants at risk for many complications and most importantly impact their neurodevelopment.

Relationship between Neonatal Pain and Growth

Unfortunately, pain is a crucial component of life-saving care in the NICU. However, it has also been proposed that painful procedures is a significant contributor to the stress experienced by premature infants. Researchers have demonstrated that premature infants experience, on average, 12 painful or stressful procedures per day (Carbajal et al., 2008; Roofthoof, Simons, Anand, Tibboel, & van Dijk, 2014). Importantly, the stress surrounding pain is hypothesized to be a factor directly impacting growth and development. The minimal evidence available suggests that there is an important relationship between procedural pain and growth in premature infants. According to a study by Vinall et al., (2012), neonatal procedural pain was associated with delayed post-natal body and head growth in the NICU, independent of other medical confounders. These researchers also demonstrated that the influence of procedural pain on postnatal weight gain may be limited to the first few weeks of life (Vinall et al.). Importantly, this is the same time period when the infant undergoes the highest number of painful procedures (Carbajal et al.). This suggests that successful growth may depend more on adversities encountered in the early weeks of life, rather than the severity of a premature infant's illness at birth. Vinall et al. concluded that the necessity and frequency of skin-breaking procedures performed needs to be evaluated, with the goal of reducing unnecessary pain exposure.

Relationship between Oxytocin and Growth in Animal Studies

Oxytocin has been found to play a central role in increasing levels of social interaction, maternal/infant bonding, and anti-stress effects (Uvnäs-Moberg, Handlin, & Petersson, 2015). It also has been shown to influence the secretion of many pituitary hormones, including growth hormone. Björkstrand, Hulting, and Uvnäs-Moberg (1997), using an animal model, explored the effects of administration of variable doses of oxytocin on the release of growth hormone. Findings from the study demonstrated that oxytocin can have an inhibitory or stimulatory effect on growth hormone secretion. In low doses of oxytocin, release of growth hormone is stimulated. In contrast, higher doses of oxytocin resulted in inhibiting secretion of growth hormone. Early work by Uvnäs-Moberg (1997) demonstrated that daily injections of oxytocin for a period of five days to rats resulted in clear anti-stress behavior patterns. Further, female rats, in particular, also showed an increase in body weight following the five-day administration of oxytocin.

Summary

Premature infants, especially those born extremely premature, experience growth difficulties while in the NICU. By discharge, a significant number of these infants have attained weights below the 10th percentile. Inadequate growth is most likely as a result of several interacting factors. An important contributing factor may be the number of painful procedures that the infant experiences. The stressful nature surrounding these procedures may impact growth. Oxytocin, an affiliative hormone, may reduce stress and promote growth.

Methods

This longitudinal, descriptive study was part of a larger study focused on the role of oxytocin in the neurodevelopment of extremely premature infants in the NICU. The study

received prior IRB approval. Premature infants were recruited from three Level III NICUs in central Ohio. Urinary oxytocin samples collected on Day of Life 14 and then weekly thereafter until the infant achieves 34 weeks corrected gestational age. Oxytocin levels determined using a commercially available ELISA assay kit (Enzo Life Sciences). Weekly weights recorded at the time of oxytocin sample collection and used to calculate growth velocity.

The inclusion criteria included: Gestational age: 25-28 ^{6/7} and free of major congenital or chromosomal abnormality, grade 3 or 4 intraventricular hemorrhage, hypoxic ischemic encephalopathy, metabolic disorders involving the adrenal system, and necrotizing enterocolitis requiring surgical intervention.

Results

Twenty-five extremely premature infants comprised the sample. The average birthweight was 989.79 ± 263.30 grams. Their average gestational age was 26.67 ± 1.13 weeks. The growth velocity average was 27.87 ± 7.61 grams. After analyzing all lab data, we were able to find average oxytocin levels in the urine at 30 and 34. At 30 weeks, the average level was 8909.00 ± 9925.41 pg/ml, while at 34 weeks it was $12,739 \pm 13,414.69$ pg/ml. No significant relationships were found between oxytocin levels and growth velocity.

Discussion

Our results showed no significant correlation between growth and oxytocin levels. The large variability in oxytocin levels, along with the small sample size, hindered detecting any significant relationships. However, fortunately, the majority of premature infants in this study had attained weights above the 10th percentile. Facilitating the growth of

extremely premature infants remains a challenge within the stressful environment of the NICU. Identifying the factors that promote and hinder growth will require continued research in premature infants. We recommend oxytocin's role in promoting growth be further studied with a larger sample. If a positive correlation is found, additional research should also include growth hormone levels, nutritional intake, and measures of stress in the NICU.

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