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A Higher Incidence of Intermittent Hypoxemic Episodes is Associated with Severe Retinopathy of Prematurity

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Abstract

Objective—Retinopathy of prematurity (ROP), a vasoproliferative disorder of the retina in preterm infants, has been associated with multiple factors including levels of oxygenation. As intermittent hypoxemic events are common in preterm infants, this study investigates their association with the development of ROP.

Study Design—Oxygen desaturation events were quantified in 79 preterm infants (gestational age 24–27 6/7wks) during the first 8 weeks of life. Infants were classified as requiring laser treatment for ROP (LaserROP) versus less severe or no ROP. A linear mixed model was used to study the association between the incidence of intermittent hypoxia and LaserROP, controlling for gestational age, gender, race, multiple births and initial severity of illness.

Results—For all infants, there was an increase in hypoxemic events with increasing postnatal age ($p<0.001$). Controlling for all covariates, a higher incidence of oxygen desaturation events was found in the LaserROP infants ($p<0.001$), males ($p<0.02$) and infants of younger gestational age ($p<0.003$).

Conclusion—This study demonstrated a higher incidence of hypoxemic events in infants with ROP requiring laser therapy. Therapeutic strategies to optimize baseline oxygenation in preterm infants should include minimization of desaturation episodes, which may in turn decrease serious morbidity in this high risk population.

Keywords

Intermittent hypoxia; oxygen saturation; retinopathy of prematurity; infant

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Background

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the retina that can produce significant loss of vision in preterm infants. ROP is the result of perturbations of retinal vascular development triggered by several factors, including levels of oxygenation. These disturbances of vascular development begin with a phase of delayed retinal vascular growth and/ or vascular regression[1]. During this first phase, it has been widely proposed that hyperoxia suppresses vascular endothelial growth factor (VEGF) which in turn inhibits normal vascularization. The second phase of ROP consists of vascular over-proliferation initiated by hypoxia-induced elevated levels of VEGF and other growth factors which, in turn, results in pathological retinal neovascularization. Thus, both hyperoxia and hypoxia may play a role in the development of ROP.

The controlled use of supplemental oxygen and a corresponding reduction in baseline oxygen saturation levels in neonates have had some success in reducing the incidence of ROP[2–5]. Yet, this vision-threatening disease continues to be a significant problem for premature infants. Previous studies have suggested that an increased magnitude and variability of fluctuations in oxygenation may also be implicated in the development of ROP[6–8]. However, these studies employed intermittent sampling of oxygenation and were therefore unable to address the frequency and time course of oxygen desaturation events in relation to the development of ROP. The purpose of our study was to employ continuous non-invasive monitoring of oxygen saturation via pulse oximetry to: 1) document the incidence of intermittent oxygen desaturation events in preterm infants during the first 8 weeks of life; and 2) investigate the association of these events with the development of ROP.

Methods

This is a sample of convenience from a study characterizing the incidence and long term consequences of intermittent hypoxemic events in preterm infants. The study population included 79 preterm infants with a gestational age of 24 to 27 6/7 weeks admitted to Rainbow Babies & Children's Hospital, Cleveland Ohio, from 2005 to 2009. Infants with no congenital malformations were eligible for enrollment regardless of the need for ventilatory support or supplemental O_2. Patient care consisted of a target oxygen saturation of 85–95% with a neonatal-care algorithm for response to desaturation events as follows: 1) for an infant with an oxygen saturation of 80–84% or 96–99% for more than 1 minute, the FiO_2 was adjusted by 2%; 2) for an infant with an oxygen saturation of 70–79% or 100% for more than 1 minute, the FiO_2 was adjusted by 4–5%; and 3) for an infant with an oxygen saturation of <70% for more than 30 seconds, the FiO_2 was adjusted by 5%.

Intermittent hypoxia and hyperoxia were documented using high resolution pulse oximetry data continuously recorded from day 1 to 8 weeks postnatal age. Data were acquired using a Masimo Radical pulse oximeter with 2 second averaging and a 2 second sample rate. Desaturation events were identified using customized software (RTI, Research Triangle, North Carolina) and defined as a fall in SaO_2 of ≤80% for ≥10sec and ≤3 minutes duration. Hyperoxemic events were defined as an increase in SaO_2 >95% for ≥10 seconds and were

included during both room air and supplemental oxygen. For each infant, the number of hypoxemic and hyperoxemic events was calculated for each week of postnatal age.

To minimize disparities in diagnosis of less severe forms of ROP, infants were classified as 1) those requiring laser treatment for ROP (LaserROP) or 2) those with either no ROP or mild ROP not severe enough to require laser therapy (NoLaserROP). The guidelines of the Early Treatment for Retinopathy of Prematurity Cooperative Trial were used to determine the need for laser treatment[9]. Differences in severity of systemic illness between ROP infants requiring and not requiring laser treatment were assessed by calculating a SNAPPE-II score for each infant[10]. This score was calculated during the first 12 hours of life and included the following: blood pressure, urine output, lowest temperature, birth weight , PO_2/FiO_2 ratio, lowest serum pH, and the presence of an Apgar at 5min <7, multiple seizures, and small size for gestational age. The number of days of mechanical ventilation, supplemental oxygen therapy and caffeine administration were also recorded.

A two sample t-test and Fisher's exact test were used to compare differences in clinical and demographic variables between groups treated and not treated with laser therapy. A linear mixed model for repeated measures analysis was used to assess the time course of both hypoxemic and hyperoxemic events for all infants and to identify the association between the number of events and ROP requiring laser treatment, adjusting for gestational age, race, gender, multiple births, and SNAPPE-II score. As birth weight is included in the calculation of the SNAPPE-II score, birth weight was excluded, due to redundancy, as an additional covariate. The square root of weekly hypoxemic and hyperoxemic episodes was modeled to better meet normality assumptions of the mixed model. Estimates of weekly means from the model were back-transformed to the original scale when plotted. Institutional Review Board approval was obtained for this study.

Results

There were 63 infants with mild or no ROP (NoLaserROP) and 16 infants requiring laser treatment for ROP (LaserROP). Study characteristics showed that LaserROP infants were of lower birth weight ($p<0.01$), lower gestational age ($p<0.001$) and had a higher percentage of male infants ($p<0.05$) compared with NoLaserROP infants, (Table 1). There were no statistical differences between infant groups for multiple births or race. LaserROP infants were significantly more ill during the first day of life, as defined by a higher SNAPPE-II score ($p<0.01$), and required longer periods of supplemental oxygen therapy (<0.001) and ventilatory support (<0.001). Lastly, LaserROP infants had fewer days on caffeine ($p<0.01$) compared with NoLaserROP infants.

For all infants, there was a change in intermittent hypoxemic events over time ($p<0.0001$), with relatively few hypoxemic episodes during the first week of life (94 events, 95% confidence interval 77–112), a progressive increase over weeks 2 through 4 (628 events, 95% confidence interval 517–751), followed by a decrease in weeks 6 through 8 (Figure 1). Figure 2 shows a graphical representation of the model-based estimate of hypoxemic episodes in LaserROP and NoLaserROP infants, controlling for gestational age, race, gender, multiple births and SNAPPE-II score. After controlling for these covariates, a

likelihood ratio test found that the mean profiles of intermittent hypoxemic events between LaserROP and NoLaserROP groups differed significantly ($p<0.001$). Post hoc analysis by week found a significantly higher incidence of hypoxemic events in the LaserROP infants ($p<0.05$) at 5, 7 and 8 weeks of age. The model-based estimate also revealed a higher incidence of hypoxemic events in males ($p<0.02$) and in infants of younger gestational age ($p<0.003$).

Controlling for all covariates, there was an increase in hyperoxemic events over the first eight weeks of life in both infant groups ($P<0.005$). A likelihood ratio test found that the mean profiles of intermittent hyperoxemic events between LaserROP and NoLaserROP groups differed significantly ($p=0.005$, Figure 3). Post hoc analysis by week found a significantly lower incidence of hyperoxemic events in the LaserROP group at 2 and 4 through 8 weeks of age (all $p<0.05$). The model based estimate revealed a lower incidence of hyperoxemic events significantly associated with a higher SNAPPE-II score ($p=0.01$).

Discussion

This study represents the first use of high resolution pulse oximetry technology to document the occurrence of intermittent hypoxemic events over a prolonged period in preterm infants and demonstrates that morbidity is associated with these events. Our investigation revealed an increase in the incidence of hypoxemic events in preterm infants, of 24–27 6/7 weeks gestation, during the first 8 weeks of life. In addition, these data demonstrate a higher frequency of hypoxemic episodes in infants who develop ROP requiring laser therapy, regardless of gestational age, race, multiple births, sex or severity of early systemic illness. These findings are consistent with the concept that intermittent hypoxia may precipitate retinal neovascularization during the second phase of ROP development.

Clinical and randomized controlled trial pulse oximeter settings are commonly set at prolonged averaging times (10–16 seconds) and low sample rates (10 seconds) in order to decrease false alarms due to motion artifact. Although excessive alarms have been minimized with new generation pulse oximeters[11,12] the continued use of these monitor settings decreases the ability to detect desaturation events[13]. We employed a minimum duration threshold of 10 seconds to correspond with the commonly used clinical alarm threshold and a 3 minute maximum threshold was established to distinguish intermittent hypoxia from prolonged changes in baseline SaO_2. With the use of these monitor settings and duration thresholds we have been able to document the high frequency of hypoxemic events over time in this infant population, and relate these events to ROP, a serious cause of morbidity in the preterm population.

Early publications have proposed a relationship between apnea requiring bag and mask ventilation with oxygen and the development of ROP[14]. It was assumed that the hyperoxemic resuscitation was the risk factor for ROP. Intermittent sampling of oxygenation has also suggested that increased magnitude and variability of fluctuations of oxygenation are related to the development of ROP in infants[6–8]. More recent data have demonstrated a decrease in the incidence of severe ROP[15] and duration of respiratory support and supplemental oxygen[16] with caffeine administration for apnea of prematurity. This is

consistent with our findings of a higher incidence of caffeine use, and decreased duration of mechanical ventilation and supplemental oxygen in the NoLaser infants.

With a high resolution continuous monitoring protocol, we have been able to show a statistically significant association between the frequency of the hypoxemic events and the development of severe ROP. These results are consistent with animal models showing a link between fluctuations in oxygenation and ROP[17–20]. Animal studies have demonstrated that patterns of intermittent hypoxia are important for the progression of this retinal disorder. Recent data from an oxygen-induced rat model of retinopathy have revealed that clustered episodes of hypoxia result in a more severe form of ROP than hypoxemic episodes that are more equally distributed over time[19]. Rat pups exposed to clustered hypoxemic events also exhibited the highest systemic and ocular levels of VEGF. Future studies may identify patterns of intermittent hypoxia and their association with ROP in the human preterm infant population.

Preterm infants who developed ROP requiring laser treatment were found to be of lower gestational age, birth weight, and more likely to be male. Risk factors previously found to be associated with ROP include race[21], gender[21–23], early gestational age[21], birth weight[21], severity of illness[24,25] and multiple births[21]. Our inability to detect a significant association between race and multiple births may have been limited by the sample size in this study. In agreement with previous studies, severity of illness (SNAPPE-II) was found to be higher in LaserROP infants, but after adjustment for other covariates, SNAPPE-II scores did not enhance the assessment of risk for ROP[24–25]. Additional longer term measurements of severity of illness such as BPD and duration of hospital stay, among others, were not included in the statistical model as the focus of this study was to identify an early and possibly preventable precursor of severe ROP.

Hypoxemic episodes are widely attributed to respiratory pauses or apnea in spontaneously breathing preterm infants. However, intermittent hypoxia is also a consequence of ineffective ventilation of intubated, mechanically ventilated infants[26,27]. Baseline levels of oxygen saturation may also influence the number of desaturation events[28]. Our data revealed that infants requiring laser treatment for ROP needed longer periods of supplemental oxygen and ventilatory support. As baseline SaO_2 and the need for assisted ventilation and supplemental oxygen changed on a day-to-day basis in many infants, these potential confounding factors could not be included in the statistical analysis. Hypercarbia can accompany apnea and has also been shown to be a risk factor for ROP in rats[29]. Although this has not been replicated in human studies[30] we cannot exclude the possibility that hypercarbia accompanying intermittent hypoxemic events may have played a role in our findings. In addition, recent data have shown that a decrease in the rate of weekly weight gain is a predictor of ROP[31]. It is unclear whether this is a causal relationship or a marker of severity of illness.

Hyperoxia is the most common risk factor for ROP. Interestingly, this study has shown a higher incidence of intermittent hyperoxemic events in the NoLaserROP infants. Intermittent hyperoxia may occur spontaneously or due to excessive supplemental oxygen therapy. Infants in room air commonly exhibit oxygen saturation values oscillating around

94–100% which would meet the hyperoxemic event threshold criteria of >95%. As the NoLaser infants spent more days in room air this may explain the higher incidence of hyperoxemic events in this infant group. Excessive additional supplemental oxygen therapy in response to a hypoxemic event could also play a role in both infant groups. However, the vast majority of intermittent hypoxia events did not meet the criteria for intervention by the clinical staff minimizing the occurrence of overshoot hyperoxia. We recognize that variability commonly exists in clinical staff responses to fluctuations in O_2. Without documentation of each adjustment of supplemental O_2 and corresponding SaO_2 it was not possible to confirm the implementation of the neonatal-care guidelines. There are other types of alterations in oxygenation that may also play a role in the development of ROP including the magnitude of alterations in oxygenation among others. However, our analysis was not designed to detect these additional parameters and their association with the development of ROP. Lastly, due to the inability to record the corresponding plethysmographic waveform to identify periods of motion artifact, all SaO_2 data have been included in the data analysis. As the Masimo signal extraction technology has been shown to minimize the occurrence of artifact based low values[32] this should not significantly affect the results of this study.

In summary, this study demonstrates an increase in the frequency of hypoxemic episodes during the first 8 weeks of life in preterm infants, with a higher incidence of hypoxemic events associated with severe ROP requiring laser therapy. The findings of our investigation are timely as there is great interest in ongoing protocols designed to optimize baseline levels of oxygenation in preterm infants, and new instrumentation designed for automated control of inspired oxygen concentration[33,34]. As the automated control of oxygenation could significantly impact the pattern of intermittent hypoxemic episodes, our investigation suggests that this technology may have a beneficial effect in reducing the incidence of severe, potentially blinding retinopathy of prematurity.

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Abbreviations

ROP Retinopathy of Prematurity

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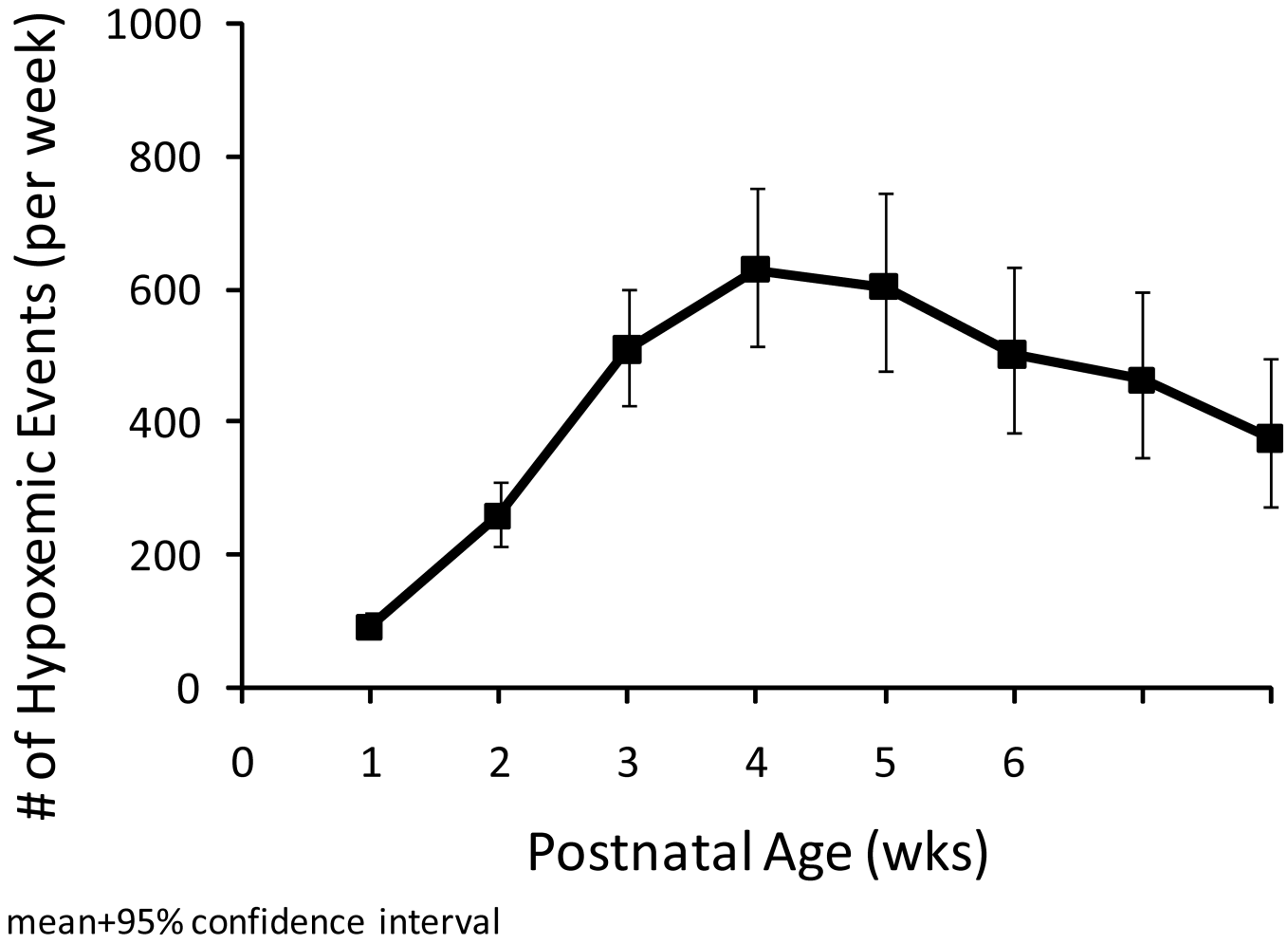

Figure 1.

The model-based estimate of intermittent hypoxemic events for all infants. There was a change in the incidence of hypoxemic events with increasing postnatal age ($p<0.0001$), with relatively few desaturation episodes during the first week of age, a progressive increase over weeks 2 through 4, followed by a decrease in weeks 6 through 8.

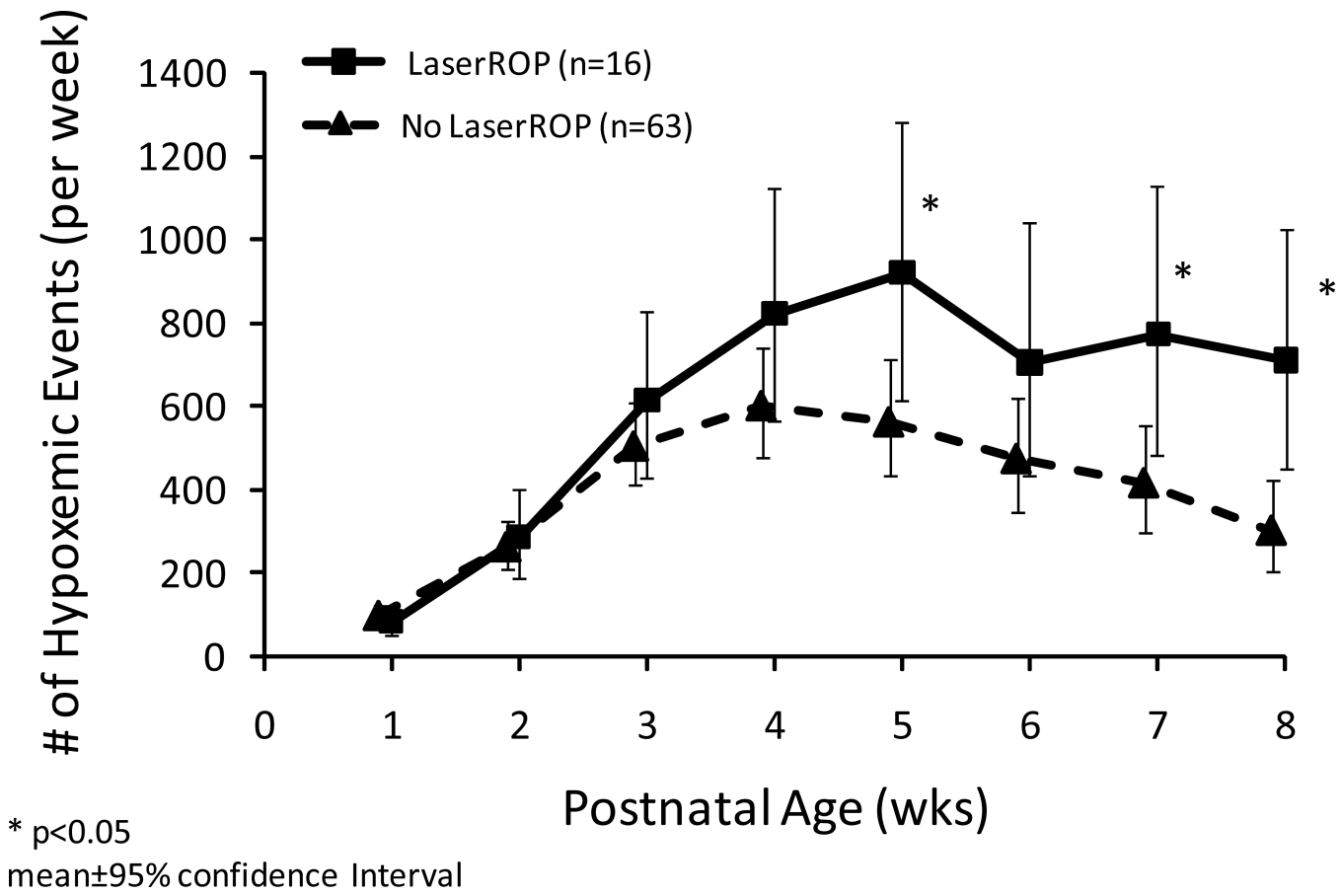

Figure 2.

The model-based estimate of intermittent hypoxemic events in infants requiring laser treatment for ROP (LaserROP) and those with either no ROP or ROP not severe enough to require laser therapy (NoLaserROP) controlling for gestational age, race, gender, multiple births and SNAPPE-II score. There was an overall higher incidence of hypoxemic events in LaserROP infants ($p<0.001$) with significant differences at 5, 7 and 8 weeks of age (*$p<0.05$).

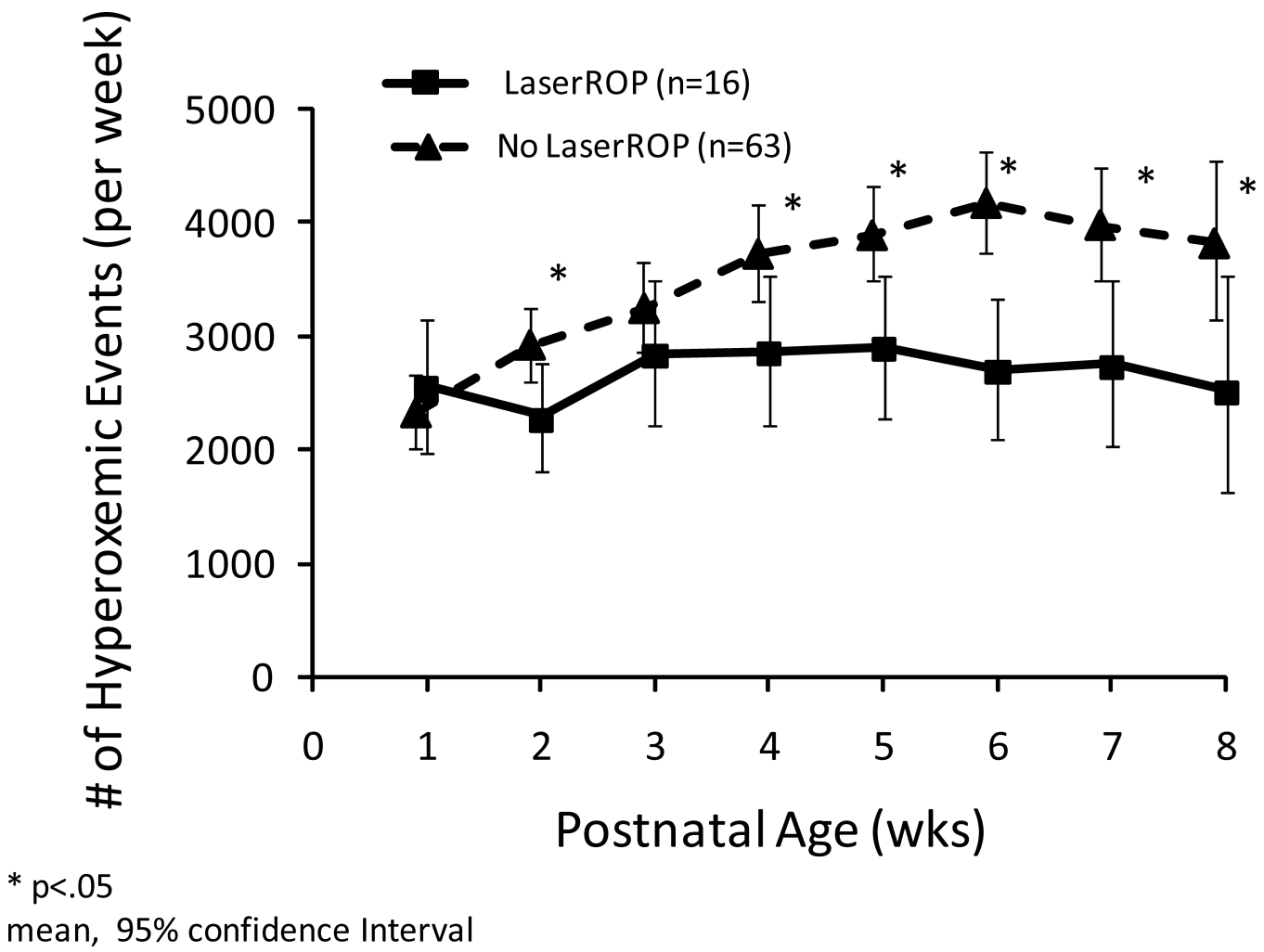

Figure 3.

The model based estimate for hyperoxemic (>95%) events in infants requiring laser treatment for ROP (LaserROP) and those with either no ROP or ROP not severe enough to require laser therapy (NoLaserROP). There was a higher incidence of hyperoxemic events in the NoLaserROP group (p=0.005) with significant differences at 2 and 4 through 8 weeks of age (p<0.05).

Table

Study Population Characteristics

	LaserROP (n=16)	No LaserROP (n=63)	P value
Birth weight (gm)	730±156	863±180	<.01
Gestational Age (wks)	25.5±0.7	26.4±1.2	<.001
Race (caucasian)	10 (63%)	26 (41%)	NS
Sex (male)	11 (69%)	22 (36%)	<.05
Multiple Births	4 (25%)	13 (21%)	NS
SNAPPE-Il score	55±15	40±20	<.01
Supplemental O_2 (days)	51±12	34±20	<.001
Caffeine (days)	34±16	44±12	<.01
Mechanical Ventilation (days)	40±18	14±15	<.001

Mean ± SD