The Incidence and Risk Factors of Apnea in Premature Infants underwent General Anesthesia for Cryotherapy or Laser Photocoagulation for Treatment of Retinopathy of Prematurity at Queen Sirikit National Institute of Child Health

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Objective: *To determine the incidence and risk factors of postoperative apnea in premature infants who received general anesthesia for cryotherapy or laser photocoagulation for treatment of retinopathy of prematurity (ROP) at Queen Sirikit National Institute of Child Health.*

Material and Method: *A retrospective cohort study was performed by reviewing medical records of premature infants with ROP who underwent general anesthesia for cryotherapy or laser photocoagulation during January 2008 and December 2010 at Queen Sirikit National Institute of Child Health. The incidence and risk factors of postoperative apnea were analyzed.*

Results: *Forty of 167 (24%) premature infants had apnea after general anesthesia for treatment of ROP. The risk factors were post-conceptual age and history of apnea. The risk of apnea in patients with post-conceptual age less than 35 weeks was 5.7 times higher than in patients with post-conceptual age more than 37 weeks (95%CI 1.59-20.45). Patients with a prior history of apnea had a 6.42 times greater risk of postoperative apnea compared to patients without a prior history of apnea (95%CI 2.01-20.50). No other serious complications were reported during the study period.*

Conclusion: *The incidence of apnea after general anesthesia in infants with ROP treated with cryotherapy or laser photocoagulation was 24%. The risk factors of postoperative apnea were post-conceptual age less than 35 weeks and prior history of apnea. Patients with risk factors should be closely monitored.*

Keywords: *Anesthesia, Apnea, Cryotherapy, Laser photocoagulation, Premature infants, Retinopathy of prematurity*

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Retinopathy of prematurity (ROP) is a disease that affects immature vasculature in the eyes of premature babies. It can be mild with no visual defects, or it may become aggressive with new blood vessel formation (neovascularization) and progress to retinal detachment and blindness. As smaller and younger babies are surviving, the incidence of ROP has increased and ROP becomes the significant cause of blindness globally. In Thailand the incidence of ROP in premature babies is14.12 to 15.9%[1,2]. Cryotherapy or laser photocoagulation is the mode of treatment, aiming to ablate areas of avascular retina thereby inducing involution of widespread intravitreous neovascularization[3]. The babies frequently need general anesthesia or sedation for these procedures that can be a cause of major concern. Postoperative apnea, a life threatening condition, is a common complication associated with anesthesia in former premature babies. Many studies have reported that postoperative apnea and bradycardia are two common complications after cryotherapy for ROP in premature infants[4-7]. One study showed the incidence of ventilatory support due to postoperative apnea after cryotherapy for ROP was 72.58%[7] and the most predictive factor for successful or unsuccessful extubation was body weight at the time of operation. Other studies in former premature infants having other kinds of operations or procedures have reported additional predictive factors for postoperative apnea such as post-conceptual age less than 44 weeks[8-11],

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small body weight at the time of operation[7,12], history of apnea[8-10], anemia[8,10,14], receiving opioid[8-10], hypothermia[10] and general anesthesia[8]. These are important data in the care of former premature infants who have survived critical events at birth, yet still at risk because of immaturity and its sequelae. Well planned perioperative care will improve the outcome of surgery without adding more problems to the patients.

Nowadays, premature babies have a higher survival rate. Smaller babies are being treated for ROP. Patient characteristics have changed. Medicine has also changed; new technology and drugs are being introduced into practice. Therefore, the risk factors and incidence of postoperative apnea after cryotherapy or laser photocoagulation for ROP may also have changed from what was concluded by earlier studies. In this study the authors, facing the task of providing anesthetic care to these patients in a major referral eye center, did a retrospective cohort review of the medical records of the former premature infants who received general anesthesia for cryotherapy or laser photocoagulation for treatment of ROP at Queen Sirikit National Institute of Child Health from 2008 to 2010. The objective was to determine the incidence and risk factors of postoperative apnea in this study group.

Material and Method

A retrospective cohort study was performed after obtaining approval by the Queen Sirikit National Institute of Child Health ethics committee. Data collection was done by reviewing medical records of ROP patients receiving cryotherapy or laser photocoagulation and general anesthesia between 2008 and 2010. The exclusion criteria were patients who were already intubated at the time of surgery and patients who were transferred to another hospital post-operatively. Parents or guardians gave their consent to the study.

All patients underwent similar type of general anesthesia which consisted of sevoflurane induction, intubation with atracurium 0.5-0.6 mg/kg or cisatracurium 0.1-0.15 mg/kg intravenously, maintenance with 1.0-1.5% isoflurane in mixture of air and O_2 at FiO_2 0.3-0.35 followed by neuromuscular blocking agent reversal at the end of procedure. Monitoring consisted of electrocardiography, non-invasive blood pressure, pulse oximetry, end tidal carbondioxide and body temperature throughout the procedure. All patients were observed in a post anesthetic care unit (PACU) and extubated when all extubation criteria were met, which were normal cardiovascular parameter, adequate spontaneous respiration without apnea, appropriate protective airway reflex e.g. coughing and gagging, adequate motor power and normothermia.

Demographic data, age, sex, birth weight, gestational age (GA) at birth, post-conceptual age (PCA) at the time of procedure and body weight were recorded. In addition, American Society of Anesthesiologists (ASA) classifications of physical status, history of apnea, co-existing morbidity (IVH, NEC, RDS, BPD), anemia, pre-existing hypothermia, metabolic derangement (acidosis, hypocalcemia, hypoglycemia), duration of surgery, anesthetic agents, vital signs during surgery and postoperative apnea were recorded. Postoperative apnea was defined as an episode of apnea for at least 20 seconds or less than 20 seconds but associated with bradycardia or desaturation. Percentile, mean, median and standard deviation were used to describe descriptive data. Risk factors for postoperative apnea were analyzed by univariate analysis (using independent t-test, Chi-square test, and Fisher exact test) and multivariate logistic regression. Missing data were omitted for the analysis of risk factors in each category. Statistical significance was defined as p-value <0.05 at 95% confidence interval. Statistical analysis was done using SPSS version 16.

Results

A total of 194 patients met the present study criteria, but only 167 parents consented to it. Demographic data are shown in Table 1. Of all the patients, 141 (84.40%) were extubated in PACU. All patients underwent laser photocoagulation, except for two who had cryotherapy. Postoperative apnea was found in 40 patients (24%), of which 27 were male and 13 were female. Univariate analysis showed that preoperative body weight, PCA at time of surgery, ASA classification of physical status and history of apnea were risk factors for postoperative apnea ($p<0.05$) (Table 2). Results from multivariate logistic regression analysis using significant risk factors from univariate analysis are shown in Table 3. Patients with PCA less than 35 weeks at the time of surgery were 5.7 times more likely to have postoperative apnea than patients with PCA more than 37 weeks (OR_{adj} 5.70, 95%CI 1.59-20.45). Patients with prior history of apnea were 6.42 times more likely to have postoperative apnea than patients without history of apnea (OR_{adj} 6.42, 95%CI 2.01-20.50).

The onset of apnea was between 5-840

Table 1. Demographic data (n = 167)

Patient data	Value
Sex (male: female)	100:67 (59.9:40.1%)
GA at birth (weeks)	29.28 (±2.22)
Birth weight (g)	1,328.29 (±315.28)
Pre-op body weight (g)	2,148.67 (±533.97)
PCA (weeks)	36.76 (±2.77)
ASA II:III	157:10 (94:6%)
Hct (n = 164)	36.39 (±6.43)
Coexisting disease	
IVH (n = 166)	6 (3.6%)
BPD (n = 165)	37 (22.2%)
NEC (n = 165)	3 (1.8%)
History of apnea (n = 157)	28 (16.8%)
Duration of surgery (min)	67.83 (±22.31)
Muscle relaxant used:	
Atracurium: cisatracurium	165:2 (98.8:1.2%)

Data shown as mean ± SD or n (%)
GA = gestational age; PCA = postconceptual age; ASA = American Society of Anesthesiologists physical status; IVH = intraventricular hemorrhage; BPD = bronchopulmonary dysplasia; NEC = necrotizing enterocolitis

minutes (median of 50 minutes) after the procedure. Most of the patients (n = 24, 60%) had onset of apneic episode within 1 hour postoperatively (Fig. 1).

Discussion

In the present study the incidence of postoperative apnea after general anesthesia in former preterm infants with ROP treated with cryotherapy or laser photocoagulation was 24%. One hundred and forty one (84.40%) patients were successfully extubated in PACU. TH Shih et al did a similar study in Taiwan and reported that 72.58% of their patients did not meet the criteria for extubation and required mechanical ventilation in the NICU[7]. They postulated that postoperative apnea and respiratory outcomes seem to be due to poor lung function in these infants who mostly had history of dyspnea and needed intubation at birth. Interestingly, there were many differences between the studies. First, all their patients underwent cryotherapy for treatment of ROP while in the present study all but two patients underwent laser photocoagulation. Duration of the procedure was 151.4±44.9 minutes in the cryotherapy group compared to 67.83±22.31 minutes in the laser photocoagulation group. Second, their patients seemed to be smaller and younger with lower mean GA (26.4±2.3 vs. 29.28±2.22), birth weight (914.8±208.5 vs. 1,328±315.28) and body weight at operation (1,970.0±447.0 vs. 2,148.67±533.97). Furthermore, the anesthetic techniques used were different. The authors used only inhalation induction while TH Shih et al used intravenous induction with ketamine or propofol. N_2O was not used in the present study. Thus, differences in patient characteristics and other variables may account for the difference in incidence of postoperative apnea in former preterm infants. Similarly, the incidence of postoperative apnea in former preterm infants who underwent inguinal hernia repair ranged from 4.7% to 80%[12,14,15]. The method and duration of monitoring for apneic episode may also contribute to the wide range in the incidence of postoperative apnea. In the present study, the infants were continuously monitored with pulse oximeter so all apneic episodes that caused desaturation and bradycardia were detected. This was practical and clinically important.

Despite varying incidences, most studies on postoperative apnea in former preterm infants have found similar risk factors. They include small GA, post-conceptual age less than 44 weeks, small body weight at the time of operation, prior history of apnea, anemia, receiving opioid, hypothermia, coexisting morbidities and general anesthesia[7-12]. In the present study, risk factors were post-conceptual age, body weight at the time of operation, prior history of apnea and ASA classification of physical status. After multivariate logistic regression analysis, only post-conceptual age and prior history of apnea were found to be independent risk factors. Patients with PCA less than 35 weeks at the time of surgery were 5.7 times more likely to have apnea than patients with PCA more than 37 weeks. As post-conceptual age decreased, postoperative apnea increased. There were seven patients aged more than 37 weeks, the oldest being 40 weeks, who had apnea episodes. This supports the recommendation from Welborn LG et al that former preterm infants up to 44 weeks PCA should be monitored for apnea after general anesthesia[15]. Malviya S also found that ex-preterm infants younger than 44 weeks PCA were at risk for post anesthetic apnea but recommended that all ex-preterm infants younger than 50 weeks PCA should be monitored overnight as inpatients even after minor procedures under general anesthesia to prevent discharging home these infants at risk of post anesthetic apnea in the unlikely event that PCA may have been overestimated[16].

Considering history of apnea, the present study found that patients with prior history of apnea were 6.42 times more likely to have apnea rather than

Table 2. Univariate analysis of risk factors

Variable	Apnea n = 40 (%)	No apnea n = 127 (%)	*p*-value
Sex			
Male	27 (27.0)	73 (73)	0.26
Female	13 (19.4)	54 (80.6)	
GA (week)			
>30	10 (21.3)	37 (78.7)	0.62*
26-30	29 (24.6)	89 (75.4)	
<26	1 (50.0)	1 (50.0)	
Birth weight (g)			
>1,500	9 (18.4)	40 (81.6)	0.52
1,000-1,500	20 (21.7)	72 (78.3)	
<1,000	11 (42.3)	15 (57.7)	
Preoperative weight (g)			
>2,500	2 (5.7)	33 (94.3)	<0.001
2,001-2,500	8 (15.7)	43 (84.3)	
1,500-2,000	24 (33.3)	48 (66.7)	
<1,500	6 (66.7)	3 (33.3)	
Post conceptual age (week)			
>37	10 (12.2)	72 (87.8)	<0.001
35-37	11 (22.9)	37 (77.1)	
<35	19 (51.4)	18 (48.6)	
ASA			
Class 2	34 (21.7)	123 (78.3)	0.01*
Class 3	6 (60.0)	4 (40.0)	
Hct (n = 164)			
<30%	1 (5.9)	16 (94.1)	0.07
>30%	39 (26.5)	108 (73.5)	
IVH (n = 166)			
Yes	2 (33.3)	4 (66.7)	0.63*
No	37 (23.1)	123 (76.9)	
BPD (n = 165)			
Yes	8 (21.6)	29 (78.4)	0.74
No	31 (24.2)	97 (75.8)	
NEC (n = 165)			
Yes	1 (33.3)	2 (66.7)	0.56*
No	38 (23.5)	124 (76.5)	
History of apnea (n = 157)			
Yes	15 (53.6)	13 (46.4)	<0.001
No	17 (13.2)	112 (86.8)	

**p*-value for Fisher's exact test; GA = gestational age; PCA = post conceptual age; ASA = American Society of Anesthesiologists physical status; IVH = intraventricular hemorrhage; BPD = bronchopulmonary dysplasia; NEC = necrotizing enterocolitis

patients without history of apnea. This is consistent with previous studies by Murphy JJ and Cote et al, which also reported history of apnea was a significant risk factor in their studies[9,12].

Small numbers of the infants in the present study had coexisting morbidities (IVH, BPD, NEC and anemia). They were in stable, well controlled condition. The authors could not demonstrate significant correlation between these conditions with postoperative apnea in preterm infants after general anesthesia. This could be due to the small numbers of these cases in the present study and inadequate data.

In previous studies the first episode of post anesthetic apnea occurred within 12 hours after discontinuation of anesthesia[16-18]. In the present study, the first episode occurred within 14 hours but

Table 3. Multivariate logistic regression analysis

Variable	Apnea n = 32 (%)	No apnea n = 125 (%)	OR_{crude}	95%CI	OR_{adjust}	95%CI	*p*-value
Preoperative weight (g)							
>2,500	1 (3)	32 (97)	1		1		
2,001-2,500	5 (10.6)	42 (89.4)	3.07	0.61-15.43	1.97	0.23-19.08	0.560
1,500-2,000	21 (30.4)	48 (69.6)	8.25	1.82-37.31	4.17	0.47-37.10	0.200
<1,500	5 (62.5)	3 (37.5)	33	4.51-241.28	10.83	0.80-147.57	0.074
PCA (weeks)							
>37	7 (9.1)	70 (90.9)	1		1		
35-37	11 (22.9)	37 (77.1)	2.14	0.83-5.50	2.55	0.74-8.74	0.137
<35	14 (43.8)	18 (56.2)	7.6	3.02-19.14	5.70	1.59-20.45	0.008
ASA							
Class 2	27 (18.2)	121 (81.8)	1				
Class 3	5 (55.6)	4 (44.4)	5.43	1.45-20.30	0.56	0.09-3.43	0.530
History of apnea (n = 157)							
No	17 (13.2)	112 (86.8)	1				
Yes	15 (53.6)	13 (46.4)	7.6	3.09-18.71	6.42	2.01-20.50	0.002

All variables in the table included in the model. OR = odds ratio

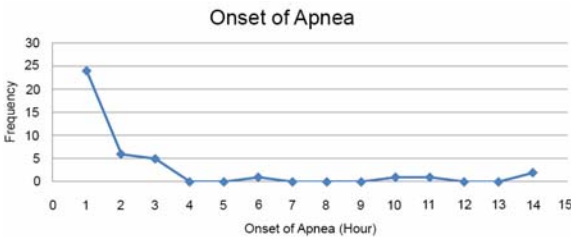

Fig. 1 Onset of apnea.

60% occurred within 1 hour. There was one infant, 38 weeks PCA with a prior history of apnea who experienced apnea episode for 4 days, postoperatively. Only one infant needed reintubation while the rest of the patients with apnea were treated by stimulation and aminophylline. Malviya S recommended all former preterm infants younger than 44 weeks PCA be monitored for apnea overnight and discharged home the morning after if they were apnea free for at least 12 hours[16].

Cryotherapy and laser photocoagulation have been the preferred methods of treatment of ROP since 1988. Many infants who developed ROP subsequently became myopic. It was later confirmed that less myopia occurred in laser treated eyes. At present, laser photocoagulation is considered mainstay of treatment for ROP[19]. Another advantage of laser over cryotherapy is that it can be done under topical anesthesia. This makes it possible for infants with ROP in the hospitals that cannot provide neonatal anesthesia care to receive timely treatment to prevent blindness. However, there have been reports that preterm infants undergoing treatment for ROP under local anesthesia have more severe and protracted cardiorespiratory complications compared to those given general anesthesia via intubation[5,20,21]. At Queen Sirikit National Institute of Child Health, all former preterm infants with ROP undergoing treatment by laser photocoagulation are put under general anesthesia, intubated, with standard monitoring. The procedure is usually best done with the OR light being turned off. Operative field is shared between ophthalmologist and anesthesiologist since the face is so small. This method provides suitable condition for ophthalmologists to do adequate and effective delicate procedure for tiny eyes. This also provides safe and controllable condition. The airway is protected. Vital signs can be maintained. Time can be adjusted for longer procedure. Then postoperative care is tailored according to patient condition and problems.

In conclusion, the incidence of apnea in former preterm infants underwent general anesthesia for ROP treatment by cryotherapy or laser photocoagulation was 24%. The risk factors of postoperative apnea were PCA less than 35 weeks and prior history of apnea. No other serious complications were seen. Patients with risk factors should be identified and well planned perioperative care by all subspecialties involved can

prevent adverse events and improve outcomes.

Potential conflicts of interest

None.

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อุบัติการณ์และปัจจัยเสี่ยงต่อการเกิดภาวะหยุดหายใจในทารกคลอดก่อนกำหนดหลังได้รับการระงับความรู้สึกแบบทั่วไปเพื่อการรักษาโดยการจี้เย็นหรือ laser photocoagulation ในผู้ป่วยทารกคลอดก่อนกำหนดที่มีจอประสาทตาผิดปกติในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

อัญชลี อัตชู, เดือนเพ็ญ ห่อรัตนาเรือง, วนิดา จงอรุณงามแสง, สุดา เลาห์สัฒนะ

วัตถุประสงค์: เพื่อศึกษาอุบัติการณ์และปัจจัยเสี่ยงต่อการเกิดภาวะหยุดหายใจในทารกคลอดก่อนกำหนด หลังได้รับการระงับความรู้สึกแบบทั่วไปเพื่อการรักษาโดยวิธีการจี้เย็น (cryotherapy) หรือ laser photocoagulation ในผู้ป่วยทารกคลอดก่อนกำหนดที่มีจอประสาทตาผิดปกติ (Retinopathy of prematurity (ROP)) ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี

วัสดุและวิธีการ: เป็นการศึกษาแบบเก็บข้อมูลย้อนหลัง (retrospective cohort study) เก็บข้อมูลจากเวชระเบียนของผู้ป่วย ROP ที่มารับการรักษาโดยวิธีจี้เย็น (cryotherapy) หรือ laser photocoagulation ภายใต้การระงับความรู้สึกแบบทั่วไปตั้งแต่ 1 มกราคม พ.ศ. 2551 ถึง 31 ธันวาคม พ.ศ. 2553 ในสถาบันสุขภาพเด็กแห่งชาติมหาราชินี โดยศึกษาถึงอุบัติการณ์และปัจจัยเสี่ยงที่ส่งผลต่อการเกิดภาวะหยุดหายใจ

ผลการศึกษา: ทารกคลอดก่อนกำหนด 164 คนพบภาวะหยุดหายใจภายหลังได้รับการระงับความรู้สึกแบบทั่วไปเพื่อการรักษา ROP จำนวน 40 คน (24%) โดยมีปัจจัยเสี่ยงคือ อายุครรภ์บวกอายุหลังคลอด (post conceptual age (PCA)) และผู้ป่วยที่มีประวัติเคยหยุดหายใจมาก่อนโดย PCA น้อยกว่า 35 สัปดาห์ลงไป มีโอกาสเสี่ยงต่อการเกิดภาวะหยุดหายใจหลังการระงับความรู้สึกมากกว่าผู้ป่วยที่มี PCA มากกว่า 37 สัปดาห์ 5.7 เท่า (95%CI = 1.59-20.45) ผู้ป่วยที่มีประวัติเคยหยุดหายใจมาก่อนมีโอกาสเสี่ยงต่อการเกิดภาวะหยุดหายใจหลังการระงับความรู้สึกมากกว่าผู้ป่วยที่ไม่มีประวัติหยุดหายใจมาก่อน 6.42 เท่า (95%CI = 2.01-20.50) ผู้ป่วยในการศึกษาไม่มีรายใดเกิดภาวะแทรกซ้อนที่รุนแรง

สรุป: ภาวะหยุดหายใจหลังได้รับการระงับความรู้สึกแบบทั่วไปในผู้ป่วย ROP ที่มารับการรักษาโดยวิธี cryotherapy หรือ laser photocoagulation มีอุบัติการณ์เกิด 24% โดยปัจจัยเสี่ยงคือ PCA น้อยกว่า 35 สัปดาห์และมีประวัติเคยหยุดหายใจมาก่อน ดังนั้นควรมีการเฝ้าระวังอย่างใกล้ชิดในทารกที่มีปัจจัยเสี่ยงเหล่านี้