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Our General Anesthesia Experiences in Premature Patients Undergoing Laser Photocoagulation in Retinopathy Treatment: A Retrospective Evaluation

Retinopati Tedavisinde Lazer Fotokoagülasyon Uygulanan Prematürelerde Genel Anestezi Deneyimlerimiz: Retrospektif Değerlendirme

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ÖZET

Amaç: Neonatal yoğun bakım ünitelerinin yaygınlaşması prematürelerde mortaliteyi azaltırken prematüre retinopatisi gibi pek çok morbiditenin artmasına neden olmuştur. Prematüre retinopatisi özel takip ve tedavi gerektiren bir klinik durumdur. Lazer fotokoagülasyon en sık uygulanan tedavi yöntemi olup işlem sırasında seçilecek anestezi yöntemi ve ilaçlar üzerinde ise tam bir fikir birliği yoktur.
Yöntemler: Yerel etik kurul onayı alındıktan sonra Ocak 2010-Eylül 2021 tarihleri arasında retinopati nedeniyle lazer fotokoagülasyon uygulanan 166 olgunun kayıtları retrospektif olarak incelendi.
Bulgular: 166 olgunun tamamına genel anestezi uygulaması yapılmış olup 163 olgu (%98.2) entübe edilirken 3 olguya (%1.8) 1.5 numara laringeal mask airway takıldı. Hipnotik amaçla en sık tercih edilen ajanlar sevoflurane (%100) ve propofol (%32.5) idi. Analjezik amaçla en sık tercih edilen ajanlar fentanil (%46.4) ve remifentanil (%53.6) idi. Kas gevşetici olarak tek tercih edilen ajan ise rokuronyum (%98.2) idi. 92 olgu (%55.4) 1 saatten daha kısa sürede ekstübe edilirken sadece 1 olgunun (%0.6) ekstübasyon süresinin 24 saatten uzun olduğu tespit edildi. İntraoperatif 20 olguda (%12) bradikardi gelişirken postoperatif 8 olguda (%4.8) apne, 2 olguda (%1.2) desatürasyon geliştiği tespit edildi. İntraoperatif ve postoperatif komplikasyon gelişen olguların tamamı düşük doğum ağırlığına sahipti (p=0.009, p=0.015). İntraoperatif bradikardi gelişen olguların tamamında operasyon süresinin 1 saatten uzun olduğu tespit edildi (p<0.001).
Sonuç: Multidisipliner yaklaşım ve uygun bir postoperatif bakım ile genel anestezi uygulanması bu özellikli hasta grubunda retinopati cerrahisi için konforlu ve güvenli bir yöntemdir.

Anahtar Kelimeler: İnfant, prematüre retinopatisi, genel anestezi

ABSTRACT

Objective: While the spread of neonatal intensive care units decreased mortality in premature patients, it caused an increase in many morbidities, such as retinopathy. Retinopathy of prematurity is a clinical condition that requires special follow-up and treatment. Laser photocoagulation is the most common treatment method and there is no consensus on the anesthesia method and drugs to be selected during the procedure.
Methods: After obtaining the approval of the local ethics committee, the records of 166 patients who underwent laser photocoagulation for retinopathy between January 2010 and September 2021 were retrospectively examined.
Results: General anesthesia was applied to all 166 patients and 163 patients (98.2%) were intubated, while three patients (1.8%) had laryngeal mask airway number 1.5. Sevoflurane (100%) and propofol (32.5%) were the most commonly preferred agents for hypnotic purposes. The most commonly preferred analgesic agents were fentanyl (46.4%) and remifentanyl (53.6%). The only preferred muscle relaxant was rocuronium (98.2%). While 92 cases (55.4%) were extubated in less than one hour, only one case (0.6%) was found to have an extubation time longer than 24 hours. Intraoperative bradycardia developed in 20 cases (12%), postoperative apnea developed in eight cases (4.8%) and desaturation developed in two cases (1.2%). All cases with intraoperative and postoperative complications had low birth weight (p=0.009, p=0.015). In all cases with intraoperative bradycardia, the duration of operation was found to be longer than one hour (p<0.001).
Conclusion: The application of general anesthesia with a multidisciplinary approach and appropriate postoperative care is a comfortable and safe method for retinopathy surgery in this specific patient group.

Key words: Infant, retinopathy of prematurity, general anesthesia

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INTRODUCTION

Infants born before the 37th week of pregnancy are defined as premature. In recent years, the mortality of infants in this group has decreased considerably with the widespread use of neonatal intensive care units (ICU). However, decreased mortality results in increased morbidity (1). One of the clinical conditions that require follow-up and treatment in premature patients is premature retinopathy (ROP). Indirect laser photocoagulation or cryotherapy is used for treatment. These babies, who require anesthesia for the diagnosis and treatment of retinopathy, carry a high risk because they are premature (2). In the anesthesia applications of premature infants, it is important to regulate the doses of anesthetic agents, to maintain hemodynamic balance, to prevent bradycardia caused by the oculocardiac reflex, and to avoid hyperoxia and hypothermia. Due to the high frequency of apnea in premature patients, respiratory support and intensive care may be required after general anesthesia (3). The anesthesia methods and drugs to be selected during these procedures vary depending on the preferences and experiences of the anesthesiologist.

In this study, the file records of pediatric patients who underwent general anesthesia for ROP were retrospectively scanned and the patient profile, preferred anesthetic drugs and developing complications, and the relationship between complications and patient characteristics were investigated. We believe that the results of the study will contribute to the issues that should be considered in the practice of general anesthesia in ROP cases.

METHODS

The study was carried out by retrospectively screening the file records of pediatric patients who underwent general anesthesia for laser photocoagulation between January 2010 and September 2021 after the approval of the local ethics committee (Decision No: 2021/3469). In accordance with the routine procedure we apply, all patients are evaluated preoperatively, the American Society of Anesthesiologists (ASA) risk classification is made and anesthesia consent forms are obtained from the parents of the patients. In addition, parents are advised to stop the intake of clear liquid two hours before, breast milk four hours before, and food and solid food six hours before the operation. Some of the patients are intubated in the neonatal ICU and some of them come to the operating room without intubation. Electrocardiogram, pulse oximeter and noninvasive blood pressure monitoring, which are routine monitoring applications, are performed on all infants. It is applied by selecting the appropriate general anesthesia agents considering the additional diseases, general conditions and weight of the babies. At the end of the surgery, the patients are often intubated and transferred to the neonatal ICU and extubated in a controlled manner in the relevant ICU. In the study, demographic data such as sex, gestational age, birth weight, postconceptional age, weight, ASA scores, presence of additional disease and anomaly, how the airway is ensured, anesthetic agents used, duration of operation, presence of intraoperative complications (bronchospasm, bradycardia, desaturation, hypotension, arrest, etc.), presence of postoperative complications (apnea, convulsion, arrhythmia, desaturation, etc.) and extubation time were determined from the file records of pediatric patients who underwent laser photocoagulation treatment due to ROP under this procedure.

Statistical Analysis

The data obtained in the study were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 23.0 (IBM SPSS 23.0 for Windows, Armonk, New York, United States). Demographic data and categorical variables of the patients were expressed in percentage and mean ± standard deviation. Chi-Square and Fisher's Exact tests were used to determine the effect of categorical variables. $P<0.05$ was considered statistically significant.

RESULTS

The files of 166 patients were retrospectively reviewed within the scope of the study. A total of 49.4%(82) of the cases were male, and 50.6%(84) were female. The demographic characteristics of the cases are shown in Table I.

When the preoperative risk factors for the cases were examined, 150(90.4%) patients had respiratory distress syndrome (RDS), and 143(86.1%) patients had low birth weight (LBW). Eighty-nine (53.6%) of the cases were ASA III. The most common cardiac anomaly was patent ductus arteriosus (PDA), which was detected in 30 cases. The preoperative risk factors for the cases are shown in Table II.

General anesthesia was applied to all 166 cases and 163 cases (98.2%) were intubated, while three cases (1.8%) had laryngeal mask airway (LMA) number 1.5. The preferred airway equipment and anesthetic agents in general anesthesia application are shown in Table III.

While 48(28.9%) of the cases were intubated in the neonatal ICU, 118(71.1%) were intubated or inserted LMA in the operating room. While 150(90.4%) patients were

Table 1. Demographic characteristics of the cases

	n:166 (%, mean±SD)
Sex (male/female)	82(49.4%)/84(50.6%)
Gestational age (weeks)	27.66±2.47
Birth weight (grams)	1058.61±378.44
Postconceptional age (weeks)	37.46±3.82
Body weight (grams)	2278.18±796.43

SD: Standart deviation

Table 2. Preoperative risk factors for the cases.

	n(%)
LBW	143(86.1)
RDS	150(90.4)
BPD	13(7.8)
O_2 treatment	136(31.9)
CPAP	120(72.3)
Mechanical ventilation	126(75.9)
Apnea	114(68.7)
Sepsis	57(34.5)
Cardiac anomaly	35(21.1)
Anemia	57(34.3)
Intraventricular hemorrhage	9(5.4)
Abnormal ABG	62(37.3)
TPN	109(65.7)
Phototherapy	140(84.3)
ASA (I/II/III/IV)	3(1.8)/71(42.8)/89(53.6)/3(1.8)

LBW: Low birth weight, RDS: Respiratory distress syndrome, BPD: Bronchopulmonary dysplasia, O_2: Oxygen, CPAP: Continuous positive airway pressure, ABG: Arterial blood gas, TPN: Total parenteral nutrition, ASA: American Society of Anesthesiologists

Table 3. Preferences in general anesthesia application

		n(%)
Endotracheal intubation	No: 2	4(2.4%)
	No: 2.5	39(23.5%)
	No: 3	85(51.2%)
	No: 3.5	30(18.1%)
	No: 4	5(3%)
Laryngeal mask airway		3(1.8%)
Propofol		54(32.5%)
Sevoflurane		166(100%)
Remifentanil		89(53.6%)
Fentanyl		77(46.4%)
Rocuronium		163(98.2%)

Table 4. Extubation time of the cases

	n(%)
<1 hour	92(55.4%)
2-12 hours	52(31.3%)
12-24 hours	21(12.7%)
>24 hours	1(0.6%)

transferred to the ICU as intubated, 16(9.6%) were extubated and transferred to the intensive care unit. The extubation times of the cases are shown in Table IV.

The mean operation time was 67.35±33.1 minutes. While complications developed in 20 cases (12%) intraoperatively, all of them were detected as bradycardia. All patients who developed bradycardia were born at less than 32 weeks old, lasted more than 60 minutes and were diagnosed with RDS and bronchopulmonary dysplasia (BPD). At the same time, more than 50% of the patients who developed bradycardia were born with a birth weight below 1500 g, had preoperative oxygen (O_2) treatment, continuous positive airway pressure (CPAP) treatment, mechanical ventilation (MV) treatment, total parenteral nutrition (TPN) treatment, apnea history, and ASA III and above. Complications were detected in 10 (6%) postoperative cases. While desaturation was observed in two cases (1.2%), apnea was detected in eight (4.8%) cases. All of these cases were born at less than 32 weeks old, had birth weights below 1500 g and were diagnosed with RDS. More than 50% of these cases had preoperative O_2 treatment, CPAP treatment, MV treatment, TPN treatment, apnea history, ASA

Table 5. The relationship of developing complications and extubation times with preoperative patient characteristics

	Postoperative Complication (n=10)			Intraoperative Complication (n=20)		Extubation Time (n=166)				
	Desaturation	Apnea	P	Bradycardia	P	<1 h	2-12 h	12-24h	>24 h	P
GA < 32 weeks	2	8	0.336	20	0.153	84	48	19	1	0.945
GA >32 weeks	0	0		0	8	4	2	0		
BW <1000 gr	2	8	0.015	17	0.009	53	31	12	1	0.452
BW=1001-1500 gr	0	0		3	28	14	9	0		
BW=1501-2500 gr	0	0		0	11	7	0	0		
DoO<1 hour	1	6	0.530	0	0.000	64	28	12	0	0.530
DoO>1 hour	1	2		20	28	24	9	1		
ASA I-II	0	2	0.210	5	0.100	42	23	8	1	0.816
ASA III-IV	2	6		15	50	29	13	0		
RDS	2	8	0.301	20	0.115	83	46	20	1	0.628
O_2 treatment	2	7	0.566	15	0.280	72	45	18	1	0.212
MV treatment	2	7	0.023	19	0.336	72	37	16	1	0.687
CPAP treatment	1	7	0.434	14	0.497	57	45	17	1	0.005
TPN treatment	2	8	0.022	18	0.010	58	32	18	1	0.103
History of apnea	2	6	0.534	16	0.184	60	37	16	1	0.218

GA: Gestational age, BW: Birth weight, DoO: Duration of operation, ASA: American Anesthesiologists' Association, RDS: Respiratory distress syndrome, O_2: Oxygen, MV: Mechanical ventilation, CPAP: Continuous positive airway pressure, TPN: Total parenteral nutrition

III and above. The effect of preoperative patient characteristics on developing complications and extubation times is shown in Table V.

DISCUSSION

Infants with a gestational age of 37 weeks or less are defined as premature regardless of body weight and all infants with a birth weight below 2500 grams regardless of gestational age are defined as LBW infants (4). ROP, which is a disease of premature and LBW infants, is an increasing common health problem with increasing survival rates of premature babies. ROP, in which many different etiological factors are accused, should be treated within 72 hours when it is contracted at a stage III and above (5). Indirect laser photocoagulation or cryotherapy is used for treatment. Although the anesthesia method used during treatment is often general anesthesia, different options, such as sedoanalgesia and local anesthesia are also preferred. However, there is no clear consensus on the ideal anesthesia method.

One of the critical factors in the success of ROP surgery is the infant's inactivity and adequate analgesia. Primitive pain pathways develop at 23-25 weeks, and interventions under insufficient analgesia can lead to poor motor and cognitive outcomes in infants (6). The anesthesia methods used for treatment of ROP differ significantly between centers. The experiences of physicians, safety concerns and resource limitations, as well as the clinical condition of the baby and the multidisciplinary approach are the causes of these differences. In studies investigating the most frequently used anesthesia methods, general anesthesia was frequently preferred. Local anesthesia alone, the combination of local anesthesia and sedoanalgesia, or sedoanalgesia alone were also preferred methods (7). In a survey conducted in Turkey, 72.7% of ophthalmologists preferred general anesthesia, while 20.5% used intravenous sedation and topical anesthesia together (8). In recent years, the tendency toward sedoanalgesia applications where spontaneous breathing is preserved has increased. This can be attributed to the belief that this approach can be beneficial for the baby in the postoperative period in terms of respiratory mechanics of premature babies (9). However, general anesthesia is still more preferred in terms of providing optimum conditions to the surgeon by ensuring the immobility of the premature baby and ensuring the full safety of the airway very close to the surgical site. Our practice in our clinic is general anesthesia that provides complete surgical inactivity and we consider it the safest method for airway and ventilation in premature infants.

The major disadvantages of general anesthesia are that it requires endotracheal intubation and undoubtedly the requires an anesthesiologist experienced in premature infants. Most of the organs of premature babies are completely dysfunctional. In addition, these infants have life-threatening morbidities such as RDS, BPD, cardiac anomalies, especially PDA, and intraventricular hemorrhage. Premature infants are at higher risk for hemodynamic and respiratory changes than term infants due to improved ocular cardiac reflexes (10). Serious complications such as desaturation, bradycardia, apnea and cardiopulmonary arrest may occur during anesthesia. Risks such as changes in drug pharmacokinetics, a possible development of hypoxia, hypotension or the possibility of acidosis reopening the ductus arteriosus make special the anesthesia method to be applied. With adequate anesthesia, changes in heart rate and blood pressure can be prevented and significant morbidity can be reduced (11). Evaluation of the clinical condition of the baby and ASA scoring with a preoperative multidisciplinary approach are important for the intraoperative roadmap, and the ASA score has been associated with postoperative complications in preterm and term newborns (12). In our study, 55.4% of the infants had ASA III and above risk scores. Although not statistically significant, we found that most of the infants who developed intraoperative and postoperative complications had ASA III and above risk scores. Similar to ASA, LBW has been reported as a risk factor for the development of complications (13). We found that LBW was a risk factor for the development of both intraoperative and postoperative complications. A total of 86.1% of the infants in our study and all of the infants who developed complications had LBW.

There is no consensus on the drugs and doses to be used in anesthesia, such as the type of anesthesia to be applied. Many different hypnotic and analgesic agents can be used safely (14). Optimizing the drug dose required for anesthesia depth and hemodynamic stability is critical for the prevention of complications in premature infants. In the general anesthesia applications, the selection of sevoflurane, one of the inhalation anesthetics, for balanced anesthesia often provides an advantage in rapid control of anesthesia depth, is not irritant to the airways and has no prolonged effect when anesthesia is discontinued (15). However, sevoflurane may be the cause of hypotension and postextubation apnea. In a study involving 72 infants who received inhalation sedation and topical anesthesia combination, Ferrer et al. concluded that inhalation gases could be safely used in this patient group (16). Other hypnotically preferred agents are ketamine and propofol, which are intravenous anesthetics. Although its use in infants younger than one month is controversial, it has been successfully used in premature infants, including those undergoing laser treatment for anesthesia ROP with propofol (17). Since ketamine does not suppress spontaneous breathing, it is especially preferred in sedoanalgesia protocols. However, it should not be ignored that it may increase intracranial and intraocular pressure and cause an increase in

secretion (18). When we examined our hypnotic preferences, we found that we induced propofol in 54 infants (32.5%) and used sevoflurane in maintenance, while we used sevoflurane in both induction and maintenance in 112 infants (67.5%). Since we frequently perform endotracheal intubation in our general anesthesia protocol, we found that we do not prefer ketamine because we do not aim to protect spontaneous breathing and because of its potential side effects.

Opioids and muscle relaxants are associated with a risk of postoperative apnea and hypoventilation. However, it is almost impossible to stay away from these two groups of agents in general anesthesia applications where effective analgesia is desired and endotracheal intubation is performed. Fentanyl, which has a potency 50 times that of morphine, is a synthetic opioid with a rapid onset of action and a short duration of action (19). Örge et al. have demonstrated that fentanyl is safer in infants undergoing laser photocoagulation than morphine (20). Remifentanil is one of the most preferred opioids due to its short duration of action, organ-independent breakdown and effective suppressive properties of the stress response to surgery (21). It also provides an advantage for early recovery in newborns (22). In our practical application, we found that we preferred these two most preferred opioids at close rates (fentanyl 46.4%, remifentanil 53.6%). We preferred rocuronium as a muscle relaxant in all 163 infants with endotracheal intubation. Apart from postoperative apnea and hypoventilation, one of the reservations about the use of opioids and muscle relaxants is prolonged intubation times. In a study in which all infants were intubated with sevoflurane, opioids and muscle relaxants, only 19.4% of the infants could be extubated at the end of the procedure and 40.3% continued mechanical ventilation after 24 hours (23). In 71 cases reported by Nath, LMA was placed in all infants using only sevoflurane and only one infant needed postoperative ventilation, and two infants developed postoperative apnea and bradycardia (24). In our clinic, general anesthesia is applied as a procedure in which hypnotic, opioid and muscle relaxants are used together and babies are followed up in a mechanical ventilator during the procedure and postoperatively, they are often intubated and transferred to the neonatal ICU. In the study, eight (4.8%) infants developed postoperative apnea, and two (1.2%) infants developed desaturation. Twenty-two (13.3%) infants were extubated for more than 12 hours. We believe that these rates are considerably lower than the rates presented in the literature and are acceptable for a patient group with such a high risk. In addition, since not only the analgesic agents used but also the perioperative characteristics of the infants are effective on postoperative complications and extubation times, we believe that the balanced anesthesia procedure we apply is a safe option to be used for treatment of ROP.

Apnea is a pathological indicator of anatomical and physiological immaturity. It can be triggered by many factors associated with surgery and anesthesia, including hypoxia, hypoglycemia, hypo/hyperthermia, anemia, sedative drugs, neurohormonal response to surgery, and postoperative pain (2). Premature infants are expected to be susceptible to postoperative apnea and the incidence of apnea increases to 30% after general anesthesia (3). The fact that the postconceptional age is less than 60 weeks, LBW, inability to feed the baby perorally and general anesthesia are the factors that increase the risk of postoperative apnea. Litman et al. investigated the risk of apnea after general anesthesia in full-term and premature infants and showed that the risk of apnea was correlated with body weight, ASA score and apnea history (12). Postoperative apnea usually occurs within the first four hours, but this period may extend up to 12 hours; therefore, babies with a postconceptional age less than 60 weeks should be followed up in the hospital regardless of the anesthesia approach after any surgical procedure. Due to the risk of developing postoperative apnea, it is recommended to avoid muscle relaxants and opioids as much as possible and to use a general anesthesia technique based on inhaled anesthetics (3). In the study, all infants were followed up in the neonatal ICU for at least 24 hours postoperatively. Postoperative apnea was detected in eight infants. Considering the relationship between apnea and perioperative characteristics, LBW, preoperative MV treatment history and TPN treatment history were determined to be risk factors in accordance with the literature. Although an anesthesia protocol without opioids and muscle relaxants was recommended in this patient group to minimize the risk of postoperative apnea, the incidence of apnea in our protocol was found to be as low as 4.8% compared to the literature. The follow-up of premature infants in the ICU for the first 24 hours postoperatively reduces complications. Depending on comorbidities, gestational age, and risk of apnea, many infants may be safely extubated, although some are likely to require postoperative ventilator support. For this reason, although opioids and muscle relaxants are used, we believe that a balanced anesthesia application and intubation of postoperative infants in the intensive care unit and controlled extubation may reduce the incidence of postoperative apnea.

Ophthalmic surgery can stimulate a strong oculocardiac reflex, resulting in deep bradycardia. This reflex is caused by pressure on the sphere or traction of extraocular muscles and mediates trigeminal afferent and vagal efferent pathways. It is more common in children due to high vagal tone. The oculocardiac reflex is also well developed in premature infants and they are more sensitive to apnea and bradycardia with increased cardiorespiratory instability (25). If bradycardia develops, it can be treated with adrenaline due to both inotropic and chronotropic activity. The study found that 20 infants (12%) developed intraoperative bradycardia and

all were treated with adrenaline. Total parenteral nutrition treatment and LBW history were detected as perioperative risk factors in infants who developed bradycardia. The duration of anesthesia increases the risks in preterm and LBW infants (26). The study also showed that operation time was over one hour in all infants who developed bradycardia. Therefore, we believe that it is important to keep the operation time as short as possible, especially to reduce the risk of developing intraoperative bradycardia in ROP surgery.

CONCLUSION

Premature retinopathy surgery is a frequently encountered condition in premature infants. The safety of the anesthesia method to be applied in this specific patient group is very important. A general anesthesia application, in which hypnotic, opioid and muscle relaxant agents are used in a balanced manner and endotracheal intubation is preferred in institutions where a multidisciplinary approach and adequate postoperative care is provided, enables safe and comfortable surgery.

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