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Original Article

Anesthetic management of argon laser photocoagulation in patients with premature retinopathy: Single center three-years experience of 178 cases

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Abstract

Aim: The better survival rate of extremely low birth weight preterm infants results in retinopathy of prematurity (ROP). Blindness due to ROP can be prevented with urgent treatment started within 72 hours. A preterm infant always presents a great challenge to the anesthetists. Laser photocoagulation treatment under general anesthesia possesses extreme risks due to sharing the limited area with the surgeon. We aimed to present our experience of anesthetic management of premature infants receiving general anesthesia during laser photocoagulation treatment of ROP.

Materials and Methods: Data belonging to a total of 159 former preterm infants that had 178 laser photocoagulation under general anesthesia between January 1st, 2013, and December 31st, 2015 were evaluated retrospectively in a period of three-years. Demographic and medical data were recorded from pre-anesthetic assessment sheets. Anesthesia induction technique, airway and pain management, peri/post operative adverse events, need for intubation were also recorded from anesthesia charts.

Results: There was no significant difference between the stage of ROP and gender. Among 159 infants 13 of them were from twin-births and 5 of them were from triplet-births. Number of infants, who previously had general anesthesia for a surgical procedure other than laser photocoagulation, was 10 (%5.6). Most common surgical operation performed was explorative laparotomy for ileus (%2.8). Mean duration of anesthesia was 78.12±34.8 min (min-max 20-210). Mean birth weight of the infants was 1334±398g (min-max 480-2330). Mean gestational age at birth was 29.37±2.5 w (min-max 23-35 w).

Conclusion: In the light of our results, with an experienced anesthetic and neonatal team, general anesthesia with sevoflurane can be performed safely to perform an immediate return to their preoperative hemodynamic and consciousness state at the end of the procedure. The need for further prospective data regarding the management of this vulnerable patient group is still evident.

Keywords: General anesthesia; premature; retinopathy of prematurity

INTRODUCTION

There is a significant decrease in mortality rates of preterm births due to both wider availability and advances in neonatal care facilities. The better survival rate of extremely low birth weight preterm infants results in retinopathy of prematurity (ROP), a hard to handle complication. Aggressive cases of ROP can rapidly progress to total retinal detachment in 1-2 weeks according to the International Committee for the Classification of Retinopathy of Prematurity (1)

Blindness due to ROP can be prevented with urgent treatment started within 72 hours (2). There are guidelines to ensure the optimal treatment to avoid delays, however, they do not clearly guide the anesthetists to manage preterm infants during laser treatment (3).

A preterm infant always presents a great challenge to the anesthetists in any kind of surgery, because of their specific physiology and anatomy during the first 6 months of age. Laser photocoagulation treatment under general anesthesia possesses extreme risks due to sharing the limited area with the surgeon.

There is a scarcity of data in the literature for the management of this vulnerable patient population confined to limited cases series.

We aimed to present our experience of anesthetic management of premature infants receiving general anesthesia during laser photocoagulation treatment of ROP in terms of demographics, treatment and complications of pre-operative, intra-operative and postoperative period.

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MATERIALS and METHODS

Infants, who are diagnosed with ROP and received laser photocoagulation therapy under general anesthesia in Gaziantep Cengiz Gökçek Maternity and Children's Hospital, were enrolled to the study. Approval of the Gaziantep University Clinical Investigations Ethical Committee (ethical committee approval number: 2019/168) was obtained. Data were retrospectively obtained from the patients' files between January 1st, 2013 and December 31st, 2015. Data regarding patients' age, gender, weight, ASA physical status, medical history including cardiac, pulmonary, vascular, neurologic disorders, extremity anomalies, routine biochemical and hematologic laboratory data, grade of ROP (4), effected eye (one or both), were all obtained and recorded from preanesthetic assessment sheets. Also, the anesthesia induction technique, airway and pain management, perioperative adverse events (laryngospasm, bronchospasm, desaturation, hypoxia, hypo/hypertension, bradycardia, apnea), any need for postoperative ICU management or intubation were also recorded from anesthesia charts.

Same experienced anesthesiologists and surgeons performed surgery and anesthesia of all cases in the study period. In our hospital, preterm infants that have surgery under general anesthesia are routinely monitored with ECG, SpO_2, noninvasive blood pressure, oral temperature, $EtCO_2$ and heart rate. The anesthetic induction is performed via sevoflurane 8% MAC with 0.5 mcg/kg intravenous fentanyl in order to alleviate the sympathetic stimulation during laryngoscopy in the study period. If needed, muscle relaxation is obtained with 0.5 mg/kg intravenous atracurium only to perform laryngoscopy then no repeated doses are applied. Maintenance of anesthesia is ensured with sevoflurane 2-3% MAC and maintaining doses of atracurium and fentanyl if needed. We used non-rebreathing breathing circuits among extremely low actual weight prematures and ventilated manually with a tidal volume of 4-6 ml/kg with the respiratory rate of 30-60/min to keep $EtCO_2$ between 35-45 mmHg. Infants who were >2.5 kg of actual weight are ventilated with closed breathing circuits with the same values mentioned above. Our aim was to keep the SpO_2 between 90-96% because of the risk of ROP persists until about 8 months of age (1). We usually do not need muscle relaxation for premature newborns for laryngoscopy. The reversal of the muscle relaxants -if used- is ensured with 0.04-0.06 mg/kg intravenous neostigmine with 0.02 mg/kg intravenous atropine in order to treat bradycardia caused by neostigmine.

The routine temperature management protocol of premature infants in our hospital is as follows: The temperature of the operating room reserved for premature infants was kept between 23°C -24 °C. The rectal body temperature of all infants are monitored. All infants were heated with radiant heaters and all of their extremities were covered with cotton sheets in order to avoid heat loss. Warm air blankets were used to maintain normothermia. Prematures are always transferred in an incubator. Intravenous fluids are kept in room temperature and heated. We used balanced crystalloids (1/3 İZODEKS® -dextrose 3.33%, sodium chloride 0.3% solution) for fluid management with 4 ml/kg/h infusion rate. If there are signs of dehydration, assessed with skin turgor, roughly evaluating the fingertips to capillary refill time, fullness quality of anterior fontanels, Hb, urea and electrolyte values, estimation of need of the premature with insensible losses, the infusion rate of the intravenous fluids is increased.

For the management of postoperative pain, 10-15 mg/kg rectal or intravenous paracetamol is used.

Statistical analysis

The normality of distribution of numerical variables was tested by Shapiro-Wilk test. Mann-Whitney U test was used for the non-normally distributed numerical variables in the comparison of the two groups. Relationships between categorical variables were tested with chi-square test; Spearman rank correlation coefficient is used to test for relationships between numerical variables. SPSS 22.0 Windows version package program was used in the analysis (A p value <0.05 was considered as significant).

RESULTS

Data belonging to a total of 159 former preterm infants who had 178 laser photocoagulation under general anesthesia were evaluated retrospectively in a period of three-years. There were 14 infants that had recurrent laser therapy. Nine infants underwent surgery twice and five infants underwent surgery thrice. Details of anesthetic management were tabulated separately (178 general anesthesia exposures). Patient demographics are given in Table 1.

Table 1. Patient demographics (n=178 cases)

		n	%
Gender	Female	73	41.0
	Male	105	59.0
Gestational age at birth (weeks)	24-31	127	71.3
	32-36	51	28.7
Age at surgery (months)	0-3	55	30.9
	3-6	119	66.9
	6-9	4	2.2
Birth weight (g)	<1000	51	28.7
	1000-1500	77	43.3
	1501-2500	50	28.1
Weight at surgery (g)	<1500	13	7.3
	1500-2500	115	64.6
	>2500	50	28.1
ASA physical status	I	4	2.2
	II	107	6.1
	III	67	37.7
Operation side	Unilateral	36	20.2
	Bilateral	142	79.8

Stage of ROP	I	1	0.6
	II	170	95.5
	III	7	3.9
Surgery history other than ROP	Ileus	5	2.8
	Shunt	1	0.6
	Hernia	1	0.6
	other	3	1.7
Intubation history prior laser treatment		133	76
Intubated cases at admission		13	7.3
Supplemental O_2 therapy at admission		30	16.9
Induction agent	Sevoflurane	168	94.4
	Propofol+ketamine	10	5.6

There was no significant difference between the stage of ROP and gender.Preoperative laboratory values of the infants are presented at Table 2.

Table 2. Preoperative laboratory values

	N	Min	Max	Mean	Std. Deviation
Hb	178	6.40	16.40	10.02	2.01
Htc	178	14.70	47.40	29.59	5.70
Wbc	178	2.88	95.10	10.14	8.00
Plt	178	65.00	848.00	371.21	140.59
ALT	178	6.00	248.00	28.38	33.91
AST	178	31.00	262.00	44.72	37.03
Urea	178	2.00	81.00	13.64	8.31
Creatinine	178	0.02	2.30	0.35	1.84

Among 159 infants 13 of them were from twin births and 5 of them were from triplet births. Number of infants, who previously had general anesthesia for a surgical procedure other than laser photocoagulation, was 10 (%5.6). Most common surgical operation performed was explorative laparotomy for ileus (%2.8). Mean duration of anesthesia was 78.12±34.8 min (min-max 20-210).

Mean birth weight of the infants was 1334±398g (min-max 480-2330). Mean gestational age at birth was 29.37±2.5 w (min-max 23-35 w).

The number of infants, who had co-existing diseases, was 73 (41%). The most common co-existing disease was cardiac disorder with a rate of 14.6% (n=26). This was followed by bronchopulmonary dysplasia (BPD) with a rate of 10.1% (n=18) and respiratory distress syndrome (RDS) with a rate of 9.6% (n=17).

Co-existing diseases according to the age and weight at surgery are tabulated at Table 3 and 4, respectively.

Table 3. Co-existing diseases according to the age at surgery

	Age At Surgery						
	0-3		3-6		6-9		
Co-existing disease	n	%	n	%	n	%	p
RDS	9	16.4	8	6.8	0	0.0	0.108
Cardiac pathologies	5	9.1	21	17.6	0	0.0	0.164
BPD	8	14.5	10	8.4	0	0.0	0.314
NEC	2	3.6	1	0.8	0	0.0	0.424
Sepsis	2	3.6	2	1.7	0	0.0	0.677
Convulsion	4	7.3	4	3.4	0	0.0	0.450
Pulmonary infection	2	3.6	4	3.4	1	25.0	0.311
Anemia	2	3.6	5	4.2	0	0.0	0.837

RDS; Respiratory Distress Syndrome, BPD; Broncho Pulmonary Dysplasia, NEC; Necrotizing Entero Colitis. *p <0.05 considered significant

Table 4. Co-existing diseases according to the weight at surgery

	Weight At Surgery						
	<1500		1500-2500		>2500		
Co-existing disease	n	%	n	%	n	%	p
RDS	6	46.2	9	7.9	2	4.0	0.001*
Cardiac pathologies	1	7.7	20	17.4	5	10.0	0.332
BPD	1	7.7	17	14.8	0	0.0	0.001*
NEC	1	7.7	2	1.7	0	0.0	0.199
Sepsis	0	0.0	3	2.6	1	2.0	0.715
Convulsion	2	15.4	3	2.6	3	6.0	0.164
Pulmonary infection	0	0.0	3	2.6	4	8.0	0.188
Anemia	0	0.0	5	4.3	2	4.0	0.579

RDS; Respiratory Distress Syndrome, BPD; Broncho Pulmonary Dysplasia, NEC; Necrotizing Entero Colitis. *p <0.05 considered significant

In 165 cases airway management were done by endotracheal intubation and 13 cases (7,3%) were managed by laryngeal mask airway (LMA). The duration of anesthesia was significantly longer in patients with endotracheal intubation. (p=0.001).

There was a history of previous intubation for any reason before laser photocoagulation therapy in 133 infants (76%). The number of infants who were intubated at admission was 13 (7.3%) and the number of infants transferred to the NICU as intubated was 28 (15.7%).

The bradycardia in two cases was due to excessive vagal stimulation and was managed by interrupting extraocular pressure and intravenous atropine injection.

Adverse events according to age at surgery are given at Table 5.

Table 5. Adverse events according to age at surgery

	Age At Surgery						
	0-3		3-6		6-9		
Adverse events	n	%	n	%	n	%	p
Laryngospasm	2	3.6	6	5.0	0	0.0	0.760
Bronchospasm	8	14.5	11	9.2	0	0.0	0.376
Intubation difficulty	1	1.8	10	8.4	0	0.0	0.143
Transfer to ICU intubated	15	27.3	13	10.9	0	0.0	0.015*
Apnea	2	3.6	0	0.0	0	0.0	0.093
Bradycardia	2	3.6	2	1.7	0	0.0	0.677

Adverse events according to weight at surgery are given at Table 6.

At intraoperative period, an average of 2.32 ± 0.91 (min 1- max 5) mcg dose of fentanyl was used in 94.4% of infants in anesthesia induction. No additional doses were required for maintaining intraoperative analgesia.

As a standard analgesic regimen, rectal paracetamol of 10-15 mg/kg applied to all of the patients at the end of the anesthesia for postoperative pain management.

Table 6. Adverse events according to weight at surgery

	Weight At Surgery						
	<1500		1500-2500		>2500		
Adverse events	n	%	n	%	n	%	p
Laryngospasm	1	7.7	5	4.3	2	4.0	0.864
Bronchospasm	1	7.7	15	13.0	3	6.0	0.378
Intubation difficulty	0	0.0	7	6.1	4	8.0	0.382
Transfer to ICU intubated	7	53.8	18	15.7	3	6.0	0.001*
Apnea	0	0.0	2	1.7	0	0.0	0.415
Bradycardia	1	7.7	2	1.7	1	2.0	0.536

DISCUSSION

The incidence of ROP among different countries offers wide variations linked to the socio-economic circumstances and the standard accessibility of premature health care (5). Since it is first described as a cause of blindness in children in 1940 (6), this 'man-made disease' influenced more than 50.000 children worldwide (7). While the rate of premature newborns increased, on the other hand, the mortality rate of premature infants is decreased due to the development of neonatal healthcare facilities. However, there is a scarcity of uniform quality of neonatal healthcare facilities among different institutes and so delays in diagnosis caused to increase rates of ROP blindness. According to a study in 2010, it is estimated that 20 million infants per year are born globally with low birth weight (<2500 g) (8). And also this study stated that the prevalence of SGA births in Turkey is 16%. Among ten countries including China, India, Brazil, Indonesia, Iran, Russian Federation, USA, Mexico, Thailand, and Turkey, approximately two- thirds of all SGA births had influenced by ROP (9).

In our study all the patients had low birth weight less than 2500 g. 43.3% of the patients were between1000-1500 g and 28.7% of the patients were under 1500 g at birth. Most of the patients were between 1500-2500 g at the time of the surgery.

According to the guidelines, these cases with high-risk retinopathy would benefit from early treatment commence within 72 h of diagnosis (10). The majority of our cases were type 1 eyes, which would get benefit from early treatment. The emergent indication for laser photocoagulation in this patient population poses many risks of being unprepared for anesthesia. The most consistent risk factor for ROP is prematurity. Low birth weight and low gestational age are directly proportional to the risk of ROP. All the patients in our study had low birth weight. Actual weight of 71.9% of the patients was under 2500 g even at operation time. In a recent retrospective cohort study performed in one-year period among 267 cases stated that low body weight was a predictor for both bradycardia and postoperative desaturation.

The observational analysis of postextubation complications published in 2019 pointed out that careful consideration of postoperative ventilation and monitoring strategy must be given in this vulnerable population. According to this study in 707 cases of 607 patients, 81 adverse events were reported. Among these events, 64 of them were stated as major. 0.8 % (6 out of 707 cases) of these patients needed postoperative reintubation at recovery in the postanesthesia care unit (12).

In our study it was observed that the majority of patients (76%) were intubated at different times for different reasons preoperatively. The number of intubated patients at admission to the operating room was 13(7.3%), and 28 patients (15.7%) were transferred from the operating room to intensive care as intubated. A higher percentage of postoperative reintubation may be due to the less experienced post-anesthesia care unit staff than this study. The number of unsuccessful extubation was statistically significant in infants whose current weight was below 2500 g ($p < 0.05$). The study mentioned above recommends careful consideration of postoperative ventilation strategy to the patients under 1.58 kg birth weight and under 41 weeks of postmenstrual age at the time of the surgery(12). Another study among 61 infants of 72 laser treatment cases reported similar results with our study. Postextubation apnea occurred in 21 procedures and 58 cases remained intubated. And 29 of these, needed mechanical ventilation for more than 24 hours (13).

This study emphasized that the postoperative extubation of these infants is associated with a high risk of apnea and bradycardia.

According to our results, intensive care duration was found to be significantly higher in patients with systemic disease and in patients who were transferred from the operating room with intubation (p=0.001). No significant relationship between intensive care duration, number of repeated ROPs and other surgical procedures was detected.

Laser photocoagulation became the standard of care for the treatment of ROP (14). However, the optimal choice of anesthesia in this vulnerable patient group is still debatable. According to a UK survey, 50% of the neonates required intubation and general anesthesia as the 'gold' standard, and the rest of the participants found this method an 'old fashioned' choice in the United Kingdom in the laser treatment of ROP (15).

Another survey performed in the US, 351 practitioners responded and 60% of the responders preferred intravenous sedation, 19% preferred general anesthesia in NICU, and 26% preferred general anesthesia in the operating theatre. In the same study, 58% of the respondents reported endotracheal intubation for ROP laser treatment as a part of the routine procedure (16).

In our clinic, the majority of anesthetic choice of anesthesia for laser photocoagulation is general anesthesia performed in the operation theatre to achieve surgical immobility with maximum safety in airway and ventilation. It is a well-known factor that many patients are transferred to different hospitals to have laser treatment with many risk factors. We agree that general anesthesia with endotracheal intubation may be a risky alternative for those who are transferred to another healthcare center. And bedside sedation and local anesthetic methods may be safe alternatives. However, there is still a tendency towards general anesthesia with endotracheal intubation in the literature today although many authors advocate that local anesthesia methods with sedation may be safe alternatives. Our study may contribute to the literature with a relatively large case series of management of laser photocoagulation performed under general anesthesia via endotracheal intubation.

Local anesthetic methods may be preferred to avoid intubation. Nevertheless, it has been accepted to be insufficient for surgery because of higher rates of life-threatening cardiorespiratory events (17). An alternative anesthetic approach may be propofol and fentanyl sedation. In this pilot study, researchers achieved a satisfactory level of anesthesia and analgesia and succeeded in ventilating with a laryngeal mask. However, to date, propofol is not recommended by the Food and Drug Administration under 3 years of age. Furthermore, the immature enzymatic system of this population may lead to undesirable pharmacokinetic and pharmacodynamic metabolism.

Sevoflurane is an advantageous volatile anesthetic, which ensures rapid control of the depth of anesthesia and does not have a prolonged residual effect. In our clinic, we prefer sevoflurane anesthesia because of relatively safe properties in prematures. On the other hand, some authors state that increasing the rate of premature infants who require laser treatment at younger ages, especially the ones who need for repeated treatments, confront the risk of higher systemic complications and difficulty in weaning from ventilation (18). Therefore safer alternatives to general anesthesia must be considered.

Although the retrospective design of our study, homogeneity of the cases, and the relatively large number of case series may be assumed to be the superiority of this paper.

It may be speculated that besides the advantages of local anesthesia and sedation, these methods may not maintain adequate analgesia and surgical immobilization. Treatment with argon laser photocoagulation of the eye for ROP is a very stressful and painful procedure. Although it is known to be a painful and uncomfortable procedure, pain management during these interventions is inadequate. There is no consensus on pain management during the ROP interventions. Studies concerning anesthesia and pain management of premature infants in literature are lacking and have small sample sizes. Further studies are still needed to ensure a consensus on the needs of premature infants during laser photocoagulation.

Some authors advocated that topical anesthetic pretreatment may

reduce the pain response in most cases, but not completely at all (19). Even for simple examinations of the eye, topical anesthetic applications only, may not ensure adequate pain management. Premature infants in a study of Haigh et al, who are treated with only topical local anesthetic eye drops before cryotherapy suffered from severe and recurrent cardiorespiratory complications. However, the infants who were treated under general anesthesia or sedation with controlled ventilation had significantly fewer complications (18)

Currently, to the best of our knowledge premature infants are capable of feeling pain. Repeated and significantly painful stimuli can cause significant morbidity because of long bradycardic and apneic episodes (20).

Exposures to repeated painful stimuli for several interventions may cause exaggerated affective and behavioral changes in their further lives (21).

Regardless of the targeted level of sedation, a premature infant may get through from sedation to loss of consciousness with the loss of protective reflexes (22).

Thus, it is a common concern of many anesthesiologists to secure the airway in a region shared with the surgeon. Despite healthy neonates are tolerable to very low doses of sedatives and analgesics, higher doses are needed for laser photocoagulation for low birth weight premature infants which may soon result in respiratory depression and airway obstruction. The fact that the surgeon operating on the eyes restrains the need for closer observation and securing the airway of infants. Therefore it can be stated that neonates should be intubated and ventilated electively before laser photocoagulation. A balanced anesthetic technique using sedation, analgesia, and muscle relaxation in lower doses may be a reasonable choice, which has reduced side effects. However, there are many animal and human studies concerning the long-term impact on the neonatal brain which is already immature. Especially in the first 7 days of life, it is observed that diffuse apoptotic neurodegeneration with learning and memory impairments (23). Many studies performed to date in humans to assess the long-term effect of anesthesia. In 2017, the FDA statement warned that ‘exposure to anesthetics for lengthy periods of time or over multiple surgeries or procedures may negatively affect brain development in children younger than 3 years’(24). Life and/or sight-threatening pathologies frequently require early and often repetitive interventions. If possible, surgery can be delayed to older ages (25).

To perform an immediate return to their preoperative hemodynamic and consciousness state at the end of the procedure and according to the current global anesthetic management trends on ROP, the choice of volatile anesthetics such as sevoflurane was the common choice of our anesthetic team.

CONCLUSION

ROP, which is a result of the struggle with prematurity is sometimes inevitable.

In the light of our results, with an experienced anesthetic and neonatal team, general anesthesia with sevoflurane can be performed safely. Although we have described our experience in a significant number of infants, the need for further prospective data regarding the management of this vulnerable patient group is evident.

Conflict of interest : The authors declare that they have no competing interest.

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