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Decreasing the need for mechanical ventilation after surgery for retinopathy of prematurity: sedoanalgesia vs. general anesthesia

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Background/aim: Premature infants experience more respiratory problems after surgical procedures. We aimed to compare general anesthesia with sedation regarding the need for postoperative mechanical ventilation in infants undergoing retinopathy of prematurity (ROP) surgery.

Materials and methods: Sixty patients who underwent laser surgery for ROP were included in this study. This study was performed between October 2010 and December 2012. The sedation group (Group S, n = 30) received 1 mg/kg ketamine and 1 mg/kg propofol as a bolus for induction. The patients then received an infusion of 100–150 μg kg^{-1} min^{-1} propofol and 0.25 mg kg^{-1} h^{-1} ketamine for maintenance. In the general anesthesia group (Group G, n = 30), anesthesia was induced using 8% sevoflurane by inhalation with 50% nitrous oxide in oxygen. Anesthesia was maintained with sevoflurane (2%) and 50% nitrous oxide in oxygen.

Results: There was no difference in gestational age, birth weight, current age, or current body weight between the two groups. Preoperative medical histories of the groups were similar. Two patients in Group S and 11 patients in Group G required postoperative mechanical ventilation (P = 0.010). Blood pressures and heart rates were similar.

Conclusion: In premature infants, sedoanalgesia administration reduced the need for postoperative mechanical ventilation after surgery for ROP.

Key words: Prematurity, retinopathy, propofol, ketamine, sedation

1. Introduction:

Retinopathy of prematurity (ROP) is a vasoproliferative disorder affecting the premature retina. Laser treatment is a surgical procedure to treat threshold ROP in order to prevent its progression to visual impairment and blindness (1). Premature infants tend to be more unstable than full-term infants of the same postnatal age and more susceptible to episodes of apnea (2). Significant systemic complications occurring during and after ROP treatment have been reported (3,4). Most babies are thus self-ventilating with supplemental oxygen or nasal continuous positive airway pressure around the time at which acute ROP develops (5). If these babies are intubated for ROP surgery, it could cause a challenging period.

General anesthesia in premature neonates can be associated with a high risk of morbidity, especially when intraventricular hemorrhage, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), a history of mechanical ventilation, or bronchopulmonary dysplasia (BPD) are also present (6). BDP has classically been described as including inflammation, architectural disruption, fibrosis, and disordered/delayed development of the infant lung (7). The cardiorespiratory system is fragile in these babies. Any intervention can aggravate cardiorespiratory instability. These patients are sensitive to airway infections and inserting a foreign object into the trachea will increase the risk of both respiratory infection and bronchospastic episodes (8). For these reasons, sedoanalgesia and avoidance of endotracheal intubation would be a good anesthetic technique in this fragile population.

In this study, we hypothesized that patients taken for ROP operation under sedoanalgesia would require less postoperative mechanical ventilation support than patients taken for operation under general anesthesia. We therefore aimed to compare the effects of general anesthesia and

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sedoanalgesia on the postoperative need of mechanical ventilation; our secondary goal was to compare these two anesthetic methods on hemodynamic changes in the ROP surgery.

2. Materials and methods

This study was approved by the Erciyes University Institutional Review Board and Ethics Committee (Project no: 2010/145). The clinical trial was also registered with the clinical trial registry in the United States (www.clinicaltrial.gov); the registration number for this trial is NCT01955135. Written informed consent was obtained from the parents of all included patients. This study was performed between October 2010 and December 2012.

2.1. Study design

Sixty infants aged 32–40 weeks who were scheduled to undergo laser surgery for the treatment of ROP were enrolled in this prospective controlled clinical study. Patients were randomized by drawing names from a sealed envelope. The exclusion criteria were patients requiring inotropic support, the need for mechanical ventilation or intubation in the 3 days prior to operation, known allergy or hypersensitivity reaction to ketamine and propofol, and age of >40 weeks. The procedure was the first operation in all patients. Pupils were dilated with eye drops containing 2.5% phenylephrine and 0.5% cyclopentolate administered 60 min before treatment. Noninvasive blood pressure, peripheral oxygen saturation (SpO_2), electrocardiography, and invasive and noninvasive end tidal carbon dioxide ($ETCO_2$; invasively in intubated patients (AMS 200) and noninvasively in the sedation group; Capnotrue-CO_2/SpO_2 Monitor, Selmsdorf, Germany) were monitored throughout the procedure. Gestational age at delivery, gestational age at ROP surgery, birth weight, body weight at ROP surgery, duration of anesthesia, body temperature, preoperative clinical history, and the clinical risk index for babies (9) were recorded.

After a fasting period of 4–6 h, patients were admitted to the operating room. The sedation group (Group S, n = 30) received 1 mg/kg ketamine and 1 mg/kg propofol as a bolus for induction. The patients then received an infusion of 100–150 μg kg^{-1} min^{-1} propofol (5 mg/mL in 5% dextrose) and 0.25 mg kg^{-1} h^{-1} ketamine (0.5 mg/mL in isotonic sodium chloride) for maintenance. Propofol was injected within 30–60 s. In addition, 0.5 mg/kg propofol was given over 30 s until the infant's neonatal infant pain scale score was ≤1 (Table 1). If hypotension or apnea developed, the infusion rate of propofol was decreased by 20%. If the period of apnea was prolonged and required mask ventilation for more than 10 min, endotracheal

Table 1. Neonatal infant pain scale.

Variable	Finding	Points
Facial expression	Relaxed (restful face, neutral expression)	0
	Grimace (tight facial muscles, furrowed brow, chin, jaw)	1
Crying	No crying (quiet, not crying)	0
	Whimpering (mild moaning, intermittent)	1
	Vigorous crying (loud scream, shrill, continuous); if infant is intubated, score silent cry based on facial movement	2
Breathing pattern	Relaxed (usual pattern for this infant)	0
	Change in breathing (irregular, faster than usual, gagging, breath holding)	1
Arms	Relaxed (no muscular rigidity, occasional random movements of arms)	0
	Flexed/extended (tense, straight arms, rigid and/or rapid extension, flexion)	1
Legs	Relaxed (no muscular rigidity, occasional random leg movements)	0
	Flexed/extended (tense, straight legs, rigid and/or rapid extension, flexion)	1
State of arousal	Sleeping/awake (quiet, peaceful, sleeping or alert and settled)	0
	Fussy (alert, restless and thrashing)	1
Heart rate	Within 10% of baseline	0
	11%–20% of baseline	1
	>20% of baseline	2
O_2 saturation	No additional O_2 needed to maintain O_2 saturation	0
	Additional O_2 required to maintain O_2 saturation	1

intubation was planned. In cases where an additional sedative was needed, it was planned that propofol would be administered at 0.5 mg/kg in 30 s. In the general anesthesia group (Group G, n = 30), anesthesia was induced using 8% sevoflurane by inhalation with 50% nitrous oxide in oxygen for 3–5 min; endotracheal intubation was performed without the use of a neuromuscular blocking agent. Anesthesia was maintained with sevoflurane (2%, end tidal concentration) and 50% nitrous oxide in oxygen. Anesthetic agents were stopped when the procedure ended in the general anesthesia group and patients were subsequently ventilated with 80% oxygen and 20% air. The infants were extubated if Bett's signs (10) (signs that the infant could be safely extubated, such as flexing the hip and knees to hold the feet off the bed) and other parameters, including normal airway protective reflexes, hemodynamic stability, and adequate peripheral arterial oxygen saturation, were present. The patients were observed until their Steward recovery scores (11) (Table 2) became 6, and then they were transferred to the neonatal intensive care unit. If the infant could not breathe sufficiently 1 h after the inhalation agent was stopped, or extubation was performed but laryngospasm/bronchospasm occurred and reintubation was required, the patient was transferred to the neonatal intensive care unit as intubated. All patients were transferred to the neonatal intensive care unit after the ROP surgery.

Apnea was defined as the cessation of breathing lasting >20 s, or <20 s in combination with bradycardia, cyanosis, or pallor. Bradycardia was defined as heart rate lower than the 2nd percentile (12). Hypotension was defined as a mean arterial pressure lower than the reference values of the 10th percentile (13). Infusion of the anesthetic agent was stopped after the operation ended in the sedation group and recovery times were recorded.

Table 2. Recovery scoring system*.

Consciousness	
Awake	3
Responds to verbal stimuli	2
Responds to tactile stimuli	1
Not responding	0
Airway	
Coughs on command or cries	2
Maintains good airway	1
Requires airway assistance	0
Motor	
Moves limbs purposefully	2
Nonpurposefully	1
Not moving	0

*Modified from Steward (11).

Cardiorespiratory stability scores (CRSSs) for infants in both groups were recorded 1 day before the operation, during surgery, during the postoperative period, and 1 day after the operation (Table 3).

Body temperatures were measured rectally during the operation and awakening period; external heaters were used to help maintain body temperature. The surgeon's satisfaction was given as bad, moderate, or excellent.

2.2. Statistical analysis

After studying 10 patients in each group, it was determined that a minimum of 29 patients in each group were needed and a power analysis ($\alpha = 0.05$, $\beta = 0.20$; $p = 0.05$) was conducted based on the expected postoperative intubation rate of 40% of the patients in Group G and 10% in Group S. Statistical analyses were performed using SPSS 15.0 (SPSS Inc., USA). The statistical analysis of differences between the two groups with respect to age, weight, duration of procedure, recovery time, heart rate, systolic arterial pressure, diastolic arterial pressure, SpO_2, and $ETCO_2$ were performed using unpaired Student's t-tests. The data regarding sex, aminophylline use, asphyxia, sepsis, NEC, ventricular septal defect, and hydrocephalus were analyzed by chi-square (Fisher's exact) test. The RSD, surfactant use, BPD, and history of mechanical ventilation data were analyzed by chi-square (continuity correction) test. Binary logistic regression analyses were used to evaluate the effects of comorbid diseases on the need for postoperative mechanical ventilation. The sedation scores, clinical risk indexes, and CRSSs were analyzed using a Mann–Whitney U-test. A P-value of less than 0.05 was considered statistically significant.

3. Results

Thirty patients each in Group S and Group G completed the study. The demographic characteristics and preoperative medical history of the infants are shown in Table 4. The data about the medical histories of the patients were obtained from their medical records.

Only two infants needed postoperative mechanical ventilation in Group S after ROP surgery, but eleven infants needed postoperative mechanical ventilation in Group G (P = 0.01) (Table 5). In Group S, six infants developed intraoperative apnea; one infant recovered with tactile stimuli and the other five infants developed bradycardia and required mask ventilation and a 20% reduction in the rate of propofol infusion. Four of these five infants needed endotracheal intubation at minutes 18, 27, 43, and 58 due to the need for respiratory support exceeding 10 min. Of these infants, two were successfully extubated at the end of the operation. Two infants were transferred to the neonatal intensive care unit and intubated. One of these patients was extubated again after 13 h and the other after 8 h; there were no other problems during the postoperative period.

Table 3. Cardiorespiratory stability score.

Score 0	Improved from baseline. Decreased oxygen requirement (>20% relative change in FiO_2).
Score 1	No change from baseline.
Score 2	Mild instability. Increased oxygen requirement (20%–50% relative change in FiO_2), more apnea and/or bradycardia responding to gentle stimulation.#
Score 3	Marked instability. Increased oxygen requirement (>50% relative change in FiO_2), more apnea and/or bradycardia responding to vigorous stimulation*, higher ventilation requirements.
Score 4	Life-threatening events. Requiring emergency resuscitation (e.g., intubation, suction/bag and mask oxygen, or cardiac massage).

#: Such as touching a hand.
*: Such as firmly rubbing a limb.
FiO_2: Fraction of inspired oxygen.

Table 4. The weights, ages, clinical risk indexes, hemoglobin values, and preoperative medical histories of the groups.

	Group S (n = 30)	Group G (n = 30)	P-value
Sex (M / F)	14 / 16	12 / 18	0.706[a]
Birth weight (g)	1159 ± 275	1222 ± 286	0.393[b]
Body weight at ROP surgery (g)	1984 ± 470	1967 ± 450	0.983[b]
Gestational age at delivery (weeks)	28.56 ± 2.45	28.43 ± 2.04	0.604[b]
Gestational age at ROP surgery (weeks)	36.46 ± 2.11	35.60 ± 2.40	0.143[b]
Clinical risk index	5.36 ± 2.22	5.80 ± 1.76	0.298[c]
Hemoglobin values (g/dL)	10.26	11.10	0.105[b]
Respiratory distress syndrome	14	13	0.940[d]
Aminophylline use	4	5	0.918[a]
Surfactant use	10	11	0.938
Bronchopulmonary dysplasia	17	19	0.702[d]
Asphyxia	3	3	1.00[a]
Mechanical ventilation	19	18	0.939[d]
Sepsis	4	2	0.433[a]
NEC	1	0	0.333[a]
PDA	2	4	0.486[a]
VSD	0	1	0.551[a]
Hydrocephalus	2	2	1.000[a]

ROP: Retinopathy of prematurity. NEC: Necrotizing enterocolitis. PDA: Patent ductus arteriosus. VSD: Ventricular septal defect. a: Chi-square (Fisher's exact) test. b: unpaired Student's t-test. c: Mann–Whitney U test. d: Chi-square (continuity correction) test.

Table 5. End tidal CO_2 measurements, procedural durations and recovery times, and need for mechanical ventilation of the groups.

	Group S (n = 30)	Group G (n = 30)	P-value
End tidal CO_2.10.min (mmHg)	18.43 ± 1.33	21.86 ± 1.35	<0.001
End tidal CO_2.40.min (mmHg)	16.83 ± 1.31	22.50 ± 2.09	<0.001
End tidal CO_2.70.min (mmHg)	17.60 ± 1.92	23.56 ± 1.63	<0.001
End tidal CO_2.100.min (mmHg)	16.66 ± 0.88	23.93 ± 1.43	<0.001
Duration of the procedure (min)	95.96 ± 22.73	104.36 ± 24.24	0.172
Recovery time of the groups (min)	16.40 ± 7.06	15.96 ± 7.97	0.824
Need for mechanical ventilation postoperatively (number of patients)	2	11	0.010
Bradycardia	5	4	0.720
CRSS 1 day before surgery	1 (0–1)	1 (0–1)	0.690
CRSS Perioperative/during extubation	1 (1–4)	3 (2–4)	<0.001
CRSS 1 day after surgery	1 (0–1)	2 (1–4)	<0.001

CRSS: Cardiorespiratory stability score. CO_2: Carbon dioxide.

Six of the eleven infants in Group G requiring postoperative mechanical ventilation during the postoperative period had insufficient muscular strength and respiratory depth so that extubation could not be performed. In five of these eleven infants, extubation was performed but reintubation was needed because of laryngospasm/bronchospasm and/or insufficient respiration. In the postoperative period, one infant needed postoperative mechanical ventilation treatment for 5 days, and another patient needed mechanical ventilation treatment for 3 days. The other nine infants were extubated after intubation periods of 15–27 h.

When the effects of body weight at ROP surgery, gestational weight, gestational age, age at surgery, NEC, bronchopulmonary dysplasia, PDA, and anesthesia technique were evaluated for the need for postoperative mechanical ventilation, only the anesthesia technique was found to be effective (8.105 (1.602–40.766), P = 0.001).

Bradycardia developed during the extubation period in four infants in Group G.

Blood pressures in both groups were similar (Figure). The cardiorespiratory stability score was significantly higher in the general anesthesia group during and 1 day after surgery. $ETCO_2$ values are given in Table 5. Operation times and recovery times are given in Table 5.

Surgeon satisfaction was excellent in both groups. The mean number of burns per eye was 2134 in the sedation group and 2270 in the general anesthesia group.

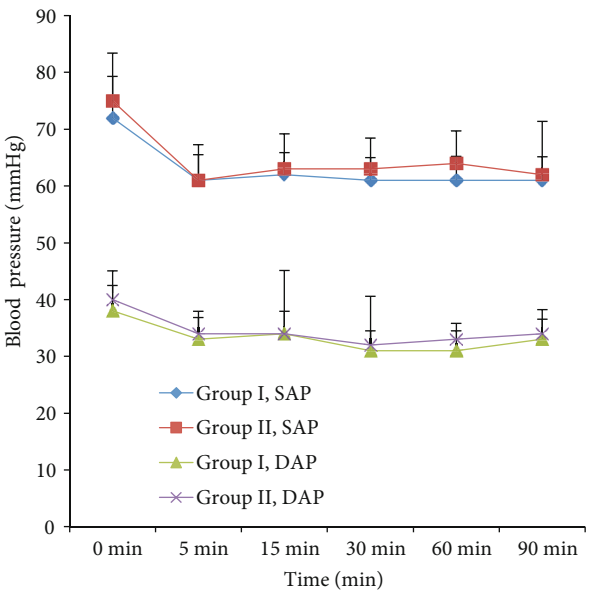

Figure. Systolic and diastolic arterial pressures of the groups.

4. Discussion

The results of this study show that the administration of deep sedation reduces the need for postoperative mechanical ventilation when compared to general anesthesia in premature infants undergoing ROP surgery.

A variety of methods of anesthesia are used during ROP treatment. General anesthesia is the most common method for laser treatment of ROP, but in this fragile population general anesthesia has some disadvantages

(14). Sub-Tenon's local anesthesia, intravenous sedation, oral sedation combined with topical anesthesia, rectal chloral hydrate and acetaminophen combined with topical anesthesia, and topical anesthesia alone have all been used as alternatives to general anesthesia (8,15,16).

The use of topical anesthesia alone is associated with an increased incidence of potentially life-threatening cardiorespiratory events. Haigh et al. (15) compared topical anesthesia, general anesthesia, and sedoanalgesia in ROP surgery and showed that life-threatening complications developed at a rate of 33% in the topical anesthesia group and 16% in the general anesthesia group; however, no serious complications developed in any patients in the sedoanalgesia group.

Physicians supporting administration of general anesthesia for ROP surgery suggest that these infants might experience cardiovascular depression even with low-dose sedatives and thus controlled intubation and ventilation are better (16). However, infants undergoing treatment are frequently unwell and suffering from other complications of preterm delivery. There is a real risk that a general anesthetic at this critical time may destabilize the infant again. Most of these infants suffer from chronic lung disease. Manipulation of the endotracheal tube paves the way for severe complications such as respiratory tract infection or bronchospasm, and these infants have many multisystemic problems. They have an irritable airway and commonly during extubation period they need emergency reintubation because of bronchospasms and laryngospasms in the postoperative period (17). In our study, we needed to reintubate five infants under emergency conditions due to laryngospasms. As a result, some infants who had recently finalized care and had been weaned from mechanical ventilation required mechanical ventilation again following surgery.

Woodhead et al. (5) used endotracheal intubation in 23 neonatal infants and a nasopharyngeal prong in 24 neonatal infants in order to avoid the complications of endotracheal intubation in this patient group. They reported that all of the infants in the intubated group remained intubated for the first postoperative day, whereas only one of those not intubated for surgery was intubated in the postoperative period. Fifty percent of the intubated infants were still intubated at postoperative day 3. It was concluded that it would be advantageous to avoid intubation as much as possible in these patient groups.

Lönnqvist (18) stated that avoiding intubation in this sensitive population would be advantageous and used a laryngeal mask airway (LMA) in administration of cryotherapy for the treatment of ROP in seven infants whose weights varied between 1.3 and 2.3 kg; this was successful in all cases except for one infant who developed abdominal distension. Gunenc et al. (19) performed a retrospective study that included 80 babies and reported that LMA is safe and useful. However, in pediatric patients, the success rate of correct placement of LMA on the first attempt varies between 67% and 90% (20), so multiple attempts could be required during LMA placement. LMA placement is less invasive than endotracheal intubation but most babies with ROP have bronchopulmonary dysplasia and even minimal airway manipulation could cause severe laryngospasm and bronchospasm. At that time, urgent endotracheal intubation could be required. By applying sedoanalgesia, we aimed to protect the patients from the complications mentioned above.

Premature babies have a very poor respiratory drive and can be very difficult to wean off the ventilator after intubation for general anesthesia. This increases morbidity and may unnecessarily prolong their stay in the neonatal intensive care unit after laser treatment. Several conditions in newborns are associated with postoperative respiratory complications. Anemia is defined as hemoglobin of less than 10 g/dL and predisposes the infant to postoperative apnea. Neurological diseases are accompanied by apneic attacks. The concentration and duration of supplemental oxygen are indicators of the severity of chronic lung disease. Days on mechanical ventilation continuous positive airway pressure are indicators, too (21). All of these conditions affect the postoperative outcome of the babies (22). In our study, only anesthetic technique was found to have an effect on the need for postoperative mechanical ventilation.

In our study, 36% of the infants who received general anesthesia either could not be extubated or required reintubation under emergency conditions after surgery. At this critical time, if there is a failure to reintubate, infants could experience hypoxia since they commonly develop severe laryngospasms/bronchospasms, which does not allow mask ventilation to be performed. In our sedation group, no patients developed laryngospasms/bronchospasms, and it was much easier to manage the respiratory system than in the general anesthesia group. In our study, in the general anesthesia group, the CRSS was higher in the operation period and on postoperative day 1. In this fragile population, high CRSSs are related to negative outcomes.

In a retrospective study, sedoanalgesia was administered with morphine to 109 infants undergoing ROP surgery. Morphine administration was started at 10 $\mu g\ kg^{-1}\ h^{-1}$ for 6 h preoperatively and was increased to 20 $\mu g\ kg^{-1}\ h^{-1}$ during the procedure. Only 5.5% of these infants needed intubation. The authors reported that morphine sedoanalgesia provided the possibility for treatment without causing any major complications (23). Another sedoanalgesia study was performed with ketamine; 11 babies were involved, 3 of which had intraoperative

complications, but resolved spontaneously. Overall, 27.3% of them had postoperative complications requiring additional ventilation. Significant patient movement was reported in three cases and it was concluded that ketamine administration provided sufficient conditions for these patients (24). These authors thought that it would be advantageous for the infants to avoid general anesthesia. In our study, we combined ketamine with propofol to avoid its side effects. The ketamine dosage was less than the routine sedation dosage. It is known that high-dose ketamine leads to increased secretion and emesis, and prolongs the recovery period. Propofol has antiemetic and bronchodilator effects and blunts the hemodynamic response while providing good conditions when combined with ketamine (25).

Blood pressure was in the normal range in the general anesthesia and sedation groups. The hypotensive effect of propofol is known; however, we combined it with ketamine, which elevates blood pressure, and performed our bolus administrations slowly. Thus, we did not observe any problems with hypotension. Bradycardia was observed in both groups after hypoxia. The problem was quickly solved with rapid mask ventilation in the sedation group and there was no need for atropine administration. Mask ventilation was easy and possible in this group because the only problem was prolonged apnea. However, since postoperative desaturation was observed due to laryngospasm and bronchospasm in the awakening period in the general anesthesia group, we accomplished our intervention with atropine until it was rectified with mask ventilation or reintubation (because of laryngospasm, hypoxia continued and bradycardia persisted and needed atropine treatment).

The recovery times were similar in both groups. We did not experience any other complications such as agitation, convulsions, nausea, or vomiting.

We showed that sedoanalgesia administration was a very effective method for reducing postoperative respiratory complications. Only 6.6% of patients in the sedation group received postoperative mechanical ventilation treatment. This rate was one-fifth the rate of our patients who had general anesthesia and is of high importance in terms of positive prognosis. At the same time, sedoanalgesia provided good conditions for the surgery, as the infants did not develop any complications associated with sedoanalgesia.

In conclusion, premature infants commonly need intervention for ROP. In this fragile population, sedoanalgesia provides good conditions for laser surgery, provides hemodynamic stability, and reduces the requirement for postoperative mechanical ventilation.

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