TÜBİTAK

Original Article

Turk J Med Sci
2012; 42 (4): 573-579
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E-mail: medsci@tubitak.gov.tr
doi:10.3906/sag-1103-74

Comparison of anesthesia with sevoflurane-N_2O and midazolam-remifentanil in low-birth-weight premature infants undergoing diode laser photocoagulation

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Aim: The present study aimed to compare anesthesia with sevoflurane-N_2O and midazolam-remifentanil in terms of hemodynamic parameters and safety in low-birth-weight (LBW) premature infants undergoing diode laser photocoagulation (DLP) for retinopathy of prematurity (ROP).

Materials and methods: A total of 91 infants undergoing DLP for ROP were enrolled in this study. All of the infants were established with LBW (<2000 g) and were preterm (gestational age of <32 weeks; age range: 0-28 days). The infants were intubated in the neonatal intensive care unit (NICU) and were randomly divided into 2 groups. For Group 1 (n = 47), anesthesia was induced with 45% O_2 + 55% N_2O + 3%-5% sevoflurane to which 1 μg kg^{-1} fentanyl was added, and it was then maintained with 45% O_2 + 55% N_2O + 1%-3% sevoflurane. For Group 2 (n = 44), anesthesia was induced with 0.1 mg kg^{-1} midazolam + 2 μg kg^{-1} remifentanil, and it was then maintained with a concomitant infusion of 0.1-0.2 mg kg^{-1} h^{-1} midazolam + 0.125-0.2 μg kg^{-1} min^{-1} remifentanil. Hemodynamic data, perioperative complications, and extubation time were recorded. The patients were transported to the NICU in the postoperative period without being extubated.

Results: No significant differences were observed between the groups in terms of demographic data, perioperative complications, and extubation time. Heart rate values were significantly lower in both groups at different measurement times with respect to baseline values. Mean arterial pressure values were significantly higher in Group 1 only at 60 min in comparison to Group 2.

Conclusion: Anesthesia with sevoflurane + O_2 + N_2O and with remifentanil + midazolam were established to be safe anesthetic approaches for LBW premature infants.

Key words: Retinopathy of prematurity, sevoflurane, midazolam, remifentanil

Diod lazer fotokoagülasyon uygulanan düşük doğum ağırlıklı prematürelerde sevofluran-N_2O ve midazolam-remifentanil anestezisinin karşılaştırılması

Amaç: Bu çalışmada premature retinopatisi (ROP) nedeniyle diod lazer fotokoagülasyon (DLP) uygulanacak düşük doğum ağırlıklı premature yenidoğanlarda; sevofluran-N_2O ve midazolam-remifentanil anestezisinin hemodinamik parametreler ve güvenlik açısından karşılaştırılması amaçlanmıştır.

Yöntem ve gereç: Çalışmaya ROP nedeniyle DLP uygulanacak yaşları 0-28 gün arasında olan, ağırlığı 2000 g'ın altında ve gestasyonel yaşı 32 haftadan az olan 91 yenidoğan dahil edildi. Hastalar; Neonatal Yoğun Bakım Ünitesinde (NYBÜ) elektif şartlarda deneyimli pediyatri uzmanları tarafından entübe edildikten sonra ameliyathaneye alındılar ve rasgele yöntemle iki gruba ayrıldılar. Grup 1'de (n = 47) anestezi indüksiyonu; % 45 O_2 + % 55 N_2O + % 3-5 sevofluran ile

Received: 31.03.2011 – Accepted: 29.09.2011

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gerçekleştirildi ve 1 μg kg^{-1} fentanil eklendi. Anestezi idamesi % 45 O_2 + % 55 N_2O + % 1-3 sevofluran ile sağlandı. Grup 2'de (n = 44) anestezi indüksiyonu 0.1 mg kg^{-1} midazolam + 2 μg kg^{-1} remifentanil ile gerçekleştirildi ve anestezi idamesi 0.1-0.2 mg kg^{-1} h^{-1} midazolam + 0.125-0.2 μg kg^{-1} min^{-1} remifentanil ile sağlandı. Hemodinamik veriler, perioperatif komplikasyonlar ve ekstübasyon süreleri kaydedildi. Tüm olgular operasyon sonunda entübe olarak NYBÜ'ye nakledildi.

Bulgular: Her iki grup arasında demografik veriler, peroperatif gelişen komplikasyon sayıları ve ekstübasyon süreleri açısından istatistiksel olarak fark saptanmadı. Kalp hızı değerlerinde her iki grupta da giriş değerlerine göre farklı ölçüm zamanlarında düşüşler gözlendi. Gruplar arası değerlendirmede; ortalama arter basıncı sadece 60. dakikada Grup 1'de Grup 2'ye göre yüksek saptandı.

Sonuç: Düşük doğum ağırlıklı premature yenidoğanların anestezisinde sevofluran + O_2 + N_2O ve remifentanil + midazolam tekniklerinin her ikisinin de güvenle kullanılabileceği kanısındayız.

Anahtar sözcükler: Prematüre retinopatisi, sevofluran, midazolam, remifentanil

Introduction

Retinopathy of prematurity (ROP) is one of the leading causes of childhood blindness, requiring immediate surgical intervention. A number of factors have been associated with ROP, such as gestational age, sepsis, hypotension, hypoxia, apnea requiring ventilation, and hypercapnia/hypocapnia. However, the most important factor has been reported to be incomplete retinal maturation. While the incidence of ROP in premature infants was reported to be 5%-6.4% in developed countries, it is as high as 19%-65.8% in developing countries. The increase in ROP surgery has been associated with advances in neonatal care and improved survival rates of premature infants (1-4).

Currently, cryotherapy and diode laser photocoagulation (DLP) are the 2 approaches utilized in the treatment of ROP. Analgesia and immobility have critical roles in the success of surgery. The extremely sensitive nature of newborn anatomy and physiology warrant particular care during anesthesia and surgery. Moreover, prematurity and low birth weight (LBW) further complicate the issue. There is an increased likelihood of life-threatening complications such as oxygen desaturation, apnea, severe bradycardia, or cardiovascular arrest in the perioperative stage of LBW infants. However, no consensus has been reached so far regarding the ideal anesthetic approach to be employed for infants (4-6).

The aim of the present study was to compare anesthesia with sevoflurane-N_2O and midazolam-remifentanil in terms of hemodynamic parameters and safety in LBW premature infants undergoing DLP for ROP.

Materials and methods

Following the approval of the ethics committee, we enrolled 91 premature infants designated to undergo DLP for ROP between 2008 and 2010. All of the premature infants were established with LBW (<2000 g) and were preterm (gestational age of <32 weeks; age range: 0-28 days). Neonates were excluded from the study if they had congenital heart disease, hemodynamic instability before intubation, or symptomatic central nervous system disease. The premature infants were followed up with in our newborn intensive care unit (NICU). They were evaluated preoperatively and informed consent was obtained from their families.

The premature infants were administered 0.1 mg kg^{-1} midazolam and intubated by experienced pediatricians before being taken to the operating room in the NICU.

Anesthesia monitoring included electrocardiography (ECG), pulse oximetric saturation (SpO_2), heart rate (HR), and mean arterial blood pressure (MAP). The patients were randomly allocated into Group 1 (n = 47) or Group 2 (n = 44) using a random number table. The drugs were prepared by a team member not involved in data recording. Anesthesia was induced with 45% O_2 + 55% N_2O + 3%-5% sevoflurane to which 1 μg kg^{-1} fentanyl was added, and then it was maintained with 45% O_2 + 55% N_2O + 1%-3% sevoflurane for Group 1. For Group 2, anesthesia was induced with 0.1 mg kg^{-1} midazolam + 2 μg kg^{-1} remifentanil, and then it was maintained with concomitant infusion of 0.1-0.2 mg kg^{-1} h^{-1} midazolam + 0.125-0.2 μg kg^{-1} min^{-1} remifentanil and 45% O_2 + 55% air. In both groups, the dosage

of agents used during the maintenance of anesthesia was applied between the concentrations mentioned above based on the anesthetic depth required to achieve immobility considering the intraoperative hemodynamic parameters.

The body temperature of the premature infants and the operating room temperature were maintained by peripheral heaters. The fluid management in the patients was standardized by heated mix fluids at 5-10 mL h^{-1}.

SpO_2, HR, and MAP values were recorded at 5-min intervals intraoperatively and at elapsed time intervals from the discontinuation of anesthetic to the time of extubation. The weight of the infants, gestational age, American Society of Anesthesiologists (ASA) physical status scores, and the operation time were all recorded, as well.

Complications such as bradycardia, desaturation, hypotension, and endotracheal tube malposition and their occurrences were noted. Bradycardia was defined as HR < 90 beats/min, desaturation as SpO_2 < 90%, and hypotension as systolic blood pressure < 45 mmHg. Bradycardia was treated by the administration of atropine (0.015 mg kg^{-1}), desaturation by increasing the inspired O_2 concentration, and hypotension by decreasing the anesthetic drug concentration.

After the surgical procedure, the anesthetic agents were discontinued and the patients were transferred, without being extubated, to the NICU accompanied by anesthesiologists, and mechanical ventilation was initiated and adjusted. Extubation was performed when the patient met the adequate ventilatory parameters in the NICU, and the extubation time was recorded.

Statistical analyses were performed using SPSS 17.0 (SPSS Inc., Chicago, IL, USA). The results were expressed as mean ± standard deviation (SD). Student's t-test was used for the comparisons between the groups. The paired samples t-test was performed on the hemodynamic parameters for repeated measures. Pearson's correlation analysis was used to demonstrate the correlation between the duration of the operation and the time to extubation. $P < 0.05$ was considered statistically significant for all analyses.

Results

The demographic data and the time to extubation for both groups are given in Table 1. No significant differences were observed between the groups.

The following perioperative complications were observed: bradycardia in 5 patients in Group 1 and 4 patients in Group 2, bradycardia + hypotension in 3 patients in Group 1 and 3 patients in Group 2, and transient desaturation in 3 patients in Group 1 and 4 patients in Group 2. Malposition in endotracheal intubation was seen in one patient due to the change of the position of the patient's head by the surgeon, and the patient was reentubated. No differences were observed between the groups in terms of perioperative complications (Table 2).

Table 1. Demographic data and extubation time.

	Group 1 (n = 47)	Group 2 (n = 44)
Gestational age (weeks)	28.26 ± 2.15	28.77 ± 2.42
Birth weight (g)	1182.7 ± 329.7	1235.2 ± 338.4
ASA status	2.32 ± 0.6	2.36 ± 0.6
Operation time (min)	74.7 ± 10.7	77.8 ± 10.8
Extubation time (h)	9.44 ± 3.62	10.13 ± 3.32

Note: Data are means ± SDs.

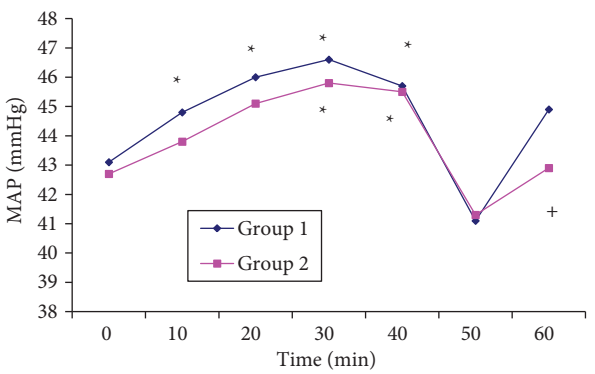
Table 2. Intraoperative complications.

	Group 1 (n = 47)	Group 2 (n = 44)
Bradycardia (n)	5	4
Temporary desaturation (n)	3	4
Bradycardia + hypotension (n)	3	3

Intraoperative changes in HR, MAP, and SpO_2 are shown in Figures 1-3.

MAP values were significantly higher in Group 1 at 10, 20, 30, and 40 min and in Group 2 at 30 and 40 min in comparison to the baseline value ($P < 0.05$). MAP values were significantly higher in Group 1 only at 60 min in comparison to Group 2. HR values were significantly lower in Group 1 at all of the measurement times and in Group 2 at 20, 30, 40, 50, and 60 min in comparison with the baseline value ($P < 0.05$). No significant changes in HR values were observed between the groups. A significant difference was observed in the SpO2 value at 30 min, which was lower in Group 2 when compared with that observed in Group 1.

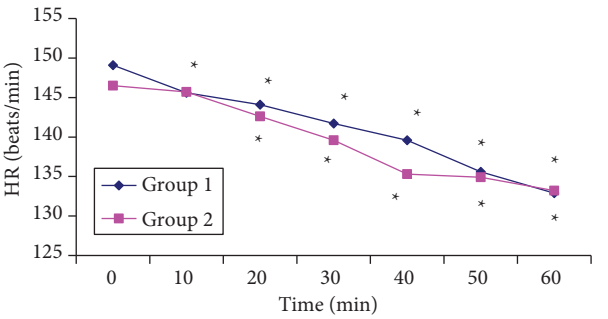
The 2 groups were similar in terms of extubation time. There was no correlation between the duration of operation and extubation time.



* P < 0.05; compared with baseline value

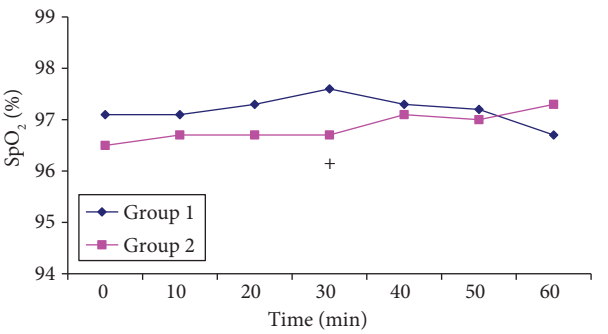
+ P < 0.05; between groups

Figure 1. Mean arterial pressure (MAP).



* P < 0.05; compared with baseline value

Figure 2. Heart rate (HR).



+ P < 0.05; between groups

Figure 3. Pulse oximetric saturation (SpO_2).

Discussion

In this study, we observed similar hemodynamics, intraoperative complications, and extubation times with both the sevoflurane-N_2O and midazolam-remifentanil methods during this type of surgery. Both of these anesthetic methods can be used safely in this type of operation by taking into consideration the anatomic and physiologic properties of the patients.

The early diagnosis and treatment of ROP plays a critical role in preventing blindness, and, contrary to common belief, treatment procedures are painful. It has been well established that premature infants feel pain. Therefore, immobility and analgesia are of major importance in increasing the success of surgery (7,8).

A number of methods, such as topical anesthesia, sedation, or general anesthesia, can be utilized during ROP surgery. It is recommended that infants be intubated and ventilated under elective conditions before laser treatment so as to control their airways and avoid surgical stress (8,9). That is why, in the current study, the patients were intubated before entering the operation room, and then general anesthesia was maintained and controlled mechanical ventilation was initiated.

The evaluation of preoperative systemic functions, birth weight, and gestational age, as well as the determination of ASA classification before general anesthesia, are critical in terms of the establishment of intraoperative strategies (6). Litman et al. (10) reported that although postoperative complications were directly associated with ASA scores and body weight in preterm and term neonates, no correlation was established with gestational age. Preoperative evaluation of ASA scores and body weight in the present study revealed increased likelihood of intraoperative complications. However, the number of intraoperative complications observed in our patients was within the acceptable range. The duration of anesthesia increases the existing risks in preterm and LBW infants, as well. In the current study, the mean duration of operation was 74.7 ± 10.7 min in Group 1 and 77.8 ± 10.8 min in Group 2 as all patients underwent DLP, and these findings were consistent with those observed in similar studies in the literature (11).

Optimizing the drug dosage required for anesthetic depth and hemodynamic stability during anesthesia is of critical importance in terms of avoiding complications in premature infants. Frequent problems during anesthesia for infants are LBW, hypothermia, concomitant pulmonary diseases, metabolic problems, immature receptors, and alterations in the cerebral blood flow. Maintaining hemodynamic stability during anesthesia is also critical, as tachycardia, hypotension, or hypertension can lead to elevated perioperative cardiac morbidity (12). It has to be remembered that inadequate depth of anesthesia will lead to a marked increase in the stress response of the infant to surgical trauma. A number of studies have been carried out to investigate different kinds of combinations of agents for general anesthesia in LBW infants. In a study including 72 infants who were administered a combination of inhalatory sedation and topical anesthesia, Ferrer Novella et al. (13) concluded that inhalatory gases could be safely used in this patient group. Yavaşcaoğlu et al. (14) reported that the retrospective evaluation of patients treated with laser photocoagulation for ROP revealed no significant differences in terms of hemodynamic parameters and complications in groups administered different agents, such as sevoflurane, ketamine, and fentanyl, for the induction and maintenance of anesthesia. Davis et al. (15) reported that the combination of remifentanil with N_2O and O_2 could be used safely in infants under 2 months of age, as well as in infants who are to be extubated in the postoperative period. The results of the present study were consistent with the data reported in those studies. However, to the best of our knowledge, the current study presents the largest study sample among similar studies comparing inhaled and intravenous anesthetic agents in LBW infants.

In newborn anesthesia, intravenous agents are used in conjunction with inhalation agents. The intravenous use of ketamine, benzodiazepines, alpha-2 agonists, and opioids reduce the requirement for inhalation anesthetics (12).

Remifentanil has become a popular agent in recent years because of its short effecting time, organ-free breakdown, and suppressive effects on the hemodynamic response. The ideal infusion rate to maintain hemodynamic stability in infants was reported as 0.25 $\mu g\ kg^{-1}\ min^{-1}$ (15,16).

Midazolam is another agent that has been used in infants for sedation and anesthesia (17,18). Sammartino et al. (18) induced anesthesia with 0.20 mg kg^{-1} midazolam and followed up with 3-5 $\mu g\ kg^{-1}\ min^{-1}$ remifentanil infusion in preterm infants undergoing DLP for ROP. They reported the technique to be safe. In the current study, we

observed similar results in our patients in Group 2 and achieved the required hemodynamic target.

In a retrospective study conducted by Yavaşcaoğlu et al. (14), patients undergoing laser treatment for ROP were administered ketamine, fentanyl, sevoflurane, and mivacurium or rocuronium as a myorelaxant for endotracheal intubation. In their sample of 32 patients, they reported the most common complication to be apnea (7 cases, 17.5%), followed by convulsion (2 cases, 5%), desaturation (2 cases, 5%), and bradyarrhythmias (1 case, 2.5%). Litman et al. (10) investigated the risk of apnea following general anesthesia in term and preterm infants and showed that the risk was correlated with body weight, ASA status, and apnea history. Aoyama et al. (11) used fentanyl and sevoflurane anesthesia in DLP treatment and reported only one patient with upper airway obstruction leading to pulmonary edema. They emphasized that despite the associated high risks, anesthesia could be managed successfully in these patients by planning the anesthesia thoroughly, taking the necessary precautions, and intervening promptly when complications arose. The evaluation of the complication incidences in the present study revealed that our results were consistent with those observed in similar studies in the literature.

In our study, times to extubation in both groups were similar. Anesthetic protocol is an important factor for time to extubation in these patients; however, extubation times are even more dependent on the preclinical conditions of the infants (19). On the other hand, we did not find a positive correlation between duration of operation and time to extubation.

In conclusion, comparing the sevoflurane-N_2O and the midazolam-remifentanil anesthesia in LBW premature infants undergoing DLP for ROP, we found that the hemodynamic responses, intraoperative complications, and extubation times in both groups were similar and clinically acceptable. We suggest that both of these techniques can be used safely for LBW premature infants.

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