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SHORT REPORT

Propofol and fentanyl sedation for laser treatment of retinopathy of prematurity to avoid intubation

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ABSTRACT

Background: Despite the optimization of neonatal assistance, severe retinopathy of prematurity (ROP, stage III–IV) remains a common condition among preterm infants. Laser photocoagulation usually requires general anesthesia and intubation, but extubation can be difficult and these infants often affected by chronic lung disease. We retrospectively evaluated the clinical charts of 13 neonates that were sedated with propofol in association with fentanyl for the laser treatment of ROP. This protocol was introduced in our unit to avoid intubation and minimize side effects of anesthesia and ventilation.

Methods: Propofol 5% followed by a bolus of fentanyl was administered as sedation during laser therapy to 13 preterm infants, affected by ROP stage III–IV. Propofol was initially infused as a slow bolus of 2–4 mg/kg and then continuously during the entire procedure, at 4 mg/kg/hour, increasing the dosage to 6 mg/kg/hour if sedation was not achieved. A laryngeal mask was placed and patients were ventilated with a flow-inflating resuscitation bag.

Results: Thirteen neonates were treated allowing to perform surgery without intubation. Only 4/13 (30.8%) of infants required minimal respiratory support during and/or after surgery. Heart rate after the intervention was higher than that at the beginning while remaining in the range of normal values. Blood pressures before, during and after surgery were similar. No episodes of bradycardia nor hypotension were recorded. Laser treatment was always successful.

Conclusion: The good level of anesthesia and analgesia achieved sustains the efficacy of sedation with propofol during laser photocoagulation to avoid intubation and mechanical ventilation during and after the procedure.

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Intubation; laser photocoagulation; neonates; propofol; retinopathy of prematurity; spontaneous breathing

Introduction

Despite the optimization of oxygen administration, ventilatory assistance and blood gas monitoring, severe retinopathy of prematurity [1] (retinopathy of prematurity (ROP), stage III–IV) remains a frequent condition among preterm infants, with an incidence of ~20% among neonates with birth weight (BW) between 500 and 1000 g and 33% among neonates with BW between 500 and 600 g [2].

Severe ROP requires surgery, which in turn requires the transfer of the neonate in the operating room to perform general anesthesia and intubation. Extubation at the end of the procedure is sometimes difficult in these delicate infants who often present chronic lung disease.

A variety of anesthesiology techniques have been used to try managing the neonate in the neonatal intensive care unit (NICU) setting, to avoid transportation to the operating room and therefore lower the risk of hypothermia. Furthermore, in the NICU setting, the neonate can be handled by the anesthesiologist in collaboration with the neonatologist, who better knows the needs of these delicate patients. Fentanyl, remifentanil and morphine have been used for this purpose, but whereas this kind of anesthesia allows to handle the neonate in the NICU, the necessity of tracheal intubation and mechanical ventilation persists, as these agents do not allow spontaneous breathing. Topical anesthesia has been used to avoid intubation, but it has been proven to be insufficient for surgical treatment as it is associated with an increased incidence of potentially life-threatening cardiorespiratory events.

Propofol is a short-acting hypnotic agent that is already largely used for induction in general

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anesthesia. It has no analgesic effect; therefore, it has to be given in conjunction with an analgesic agent for painful procedures. Because of its fast induction and functional recovery time, it is also widely used for procedural sedation in the pediatric population, as it allows to perform short procedures in spontaneous breathing [3]. Our aim was to evaluate the effectiveness of propofol sedation associated with fentanyl analgesia in avoiding intubation and mechanical ventilation during and immediately after the laser photocoagulation treatment for ROP in preterm born neonates.

Materials and methods

In 2015 in the Department of Neonatology of the Bambino Gesù Children's Hospital, in Rome, Italy, we started a new anesthesiology protocol to treat neonates in spontaneous breathing requiring laser therapy for severe ROP. Prior to procedure, informed consent was obtained by the parents of all neonates. Patients were sedated with propofol and fentanyl to avoid intubation during the procedure. Thirteen neonates were treated with the new protocol. We performed a retrospective analysis of the clinical data of these neonates to assess effectiveness of the new procedure to avoid intubation and mechanical ventilation.

The following data were recorded: gestational age (GA) at birth, birth weight, age and weight at the time of procedure, baseline ventilation status before surgery and rate of complications, including temperature instability, apneic events, bradycardia episodes, desaturations and changes in ventilation status during surgery. Medical records included a complete NICU standardized sedation flow sheet, which included documentation of vital signs (heart rate, oxygen saturation, blood pressure and temperature) at 3-minute intervals by NICU staff and documentation of any complications.

During the procedure, the patients were handled by both the caring neonatologist and an anesthesiologist. At study entry, a laryngeal mask was placed and patients were ventilated with a flow-inflating resuscitation bag. Pulse oximetry (SpO_2), respiratory rate (RR) and heart rate (HR) were continuously recorded, and noninvasive blood pressure (BP) was recorded every 5 minutes. A peripheral line was inserted before the beginning of the surgical procedure and used exclusively for propofol infusion. Propofol 5% was administered as a slow bolus, with a dosage of 2 mg/kg. If sedation was not achieved, dosage was increased to a maximum of 4 mg/kg. After the achievement of sedation and before the positioning of the laryngeal mask, a bolus of fentanyl 1 μg/kg was administered to provide analgesia. No local anesthesia was given. Subsequently, propofol was infused at a dosage of 4 mg/kg/hour continuously. If sedation was not properly maintained, considering hemodynamic and respiratory changes or spontaneous movements, the dosage was increased to a maximum of 6 mg/kg/hour continuously. At the end of the surgical procedure, propofol infusion was discontinued and the laryngeal mask was removed. A blood gas analysis was performed at the end of the procedure.

Statistical analysis

Preliminarily, the Kolmogorov–Smirnov test was used to assess the distribution of the continuous variables that was not different from the normal distribution. The mean ± standard deviation (SD) was calculated for these normally distributed data. Comparisons were conducted using paired Student's *t*-test and ANOVA with SPSS 21.0 software (Statistical Package for Social Science (SPSS) Company, Chicago, IL). Differences were considered statistically significant at a p value $\leq .05$.

Because this is a report on a series of cases who were treated with a new anesthetic technique, comparisons were made among the relevant variables recorded before and after the sedation. The calculation of the power of the study was therefore not performed.

Results

Thirteen neonates (9 males and 4 females; mean GA 25.9 ± 1.3 weeks; mean age at surgery 85.2 ± 22.9 days; mean BW 876.5 ± 205.3 g; mean weight at surgery 2235.4 ± 751.6 g) were treated with propofol sedation, allowing to perform surgery without intubation and without side effects related to propofol administration. Eleven patients (84%) presented chronic lung disease at the time of surgery, but only one required nasal continuous positive airway pressure (nCPAP) and oxygen supplementation despite spontaneous breath. Further baseline characteristics of the patients are shown in Table 1.

The mean operative time was 45.8 ± 16.6 minutes (ranging 21–90 min). During the procedure, two

Table 1. Clinical characteristics of the 13 patients who underwent laser treatment for ROP.

Clinical characteristics	Mean ± SD (range)
Gestational age at birth (weeks)	26 ± 1.3 (24–28)
Birth weight (g)	876 ± 205 (540–1100)
Age at procedure (days)	85 ± 23 (60–120)
Weight at procedure (g)	2235 ± 751 (1250–4150)

neonates presented with some episodes of apnea and fall in the peripheral oxygen saturation (minimum value SpO_2 85%) with prompt resolution of the desaturation after being assisted with the flow-inflating resuscitation bag and oxygen. During the first hour after the end of the procedure, these two infants needed support with nCPAP for 2 hours to relieve apnea spells and two other infants presented with apnea and desaturation requiring a bolus of 10 mg/kg of caffeine. In total, 2/13 infants (15.4%) needed a minimal ventilatory support, without ever requiring endotracheal intubation nor mechanical ventilation.

We observed no episodes of bradycardia nor hypotension. The mean HR at the end of the intervention was significantly higher than that of the beginning (144.6 ± 14.5 versus 135.8 ± 16.7 beats per minute; CI 4–13.6; $p = .02$) while remaining in the normal range for the age. Regarding BP values, there was a slight decrease in the BP in four patients (30%), without any significant difference between BP at the end of the intervention (55.38 ± 13.0; 95%CI 47.5–63.2, range 45–94) compared with the mean BP value before the sedation (55.92 ± 10.1; 95%CI 52.7–65.0, range 45–84) ($p = .69$). None of the treated neonates required tracheal intubation for mechanical ventilation. The blood gas analysis performed at the end of surgery did not show any significant increase in the CO_2 level. The laryngeal mask was always successfully removed at the end of the procedure. Laser treatment was successful in all treated neonates and the surgeon was satisfied with the grade of sedation achieved.

Discussion

Laser treatment is widely recognized as an acceptable treatment method for severe ROP as it requires less manipulation and causes less trauma than cryotherapy [4]. Hence, some form of anesthetic support is still necessary with laser use, but there is still no consensus on the best anesthetic approach to use [5].

In the present pilot study, we treated a group of very preterm neonates at birth with propofol and fentanyl during laser treatment, avoiding tracheal intubation for mechanical ventilation. No serious adverse events were registered and surgery was always successful. The use of propofol for procedural sedation in neonates has been studied only in one open-label randomized controlled trial of 63 patients. Propofol reduced time to complete procedure and time of recovery; however, due to the small number of newborns studied, no practice recommendation could be issued regarding its safety [6].

Nevertheless, propofol seems to be a promising drug for procedural sedation in the neonate, although poor information is currently available concerning its use in the first months of life. It acts by increasing the activity of the GABA-related inhibitory synapses, which leads to the inhibition of its uptake. It is mainly metabolized in the liver by glucuronidation, mediated by the phase II enzyme UDP-glucuronosyltransferase. Glucuronidation produces water-soluble metabolites which are excreted by renal pathways. Due to the immature enzymatic system typical of the first life periods, leading to different pharmacokinetic and pharmacodynamic properties, propofol distribution and clearance are notably different in neonates and infants compared to older children. In fact during the first month of life, the phase I and II hepatic metabolism shows an important ontogeny of isoenzymes. In particular, phase II reactions seem to be the most affected by the intrinsic immaturity of the liver. In an interesting study investigating urinary metabolites, Allegaert observed that during the neonatal period, the decreased ability for glucuronidation diverts propofol metabolism toward the prevalence of hydroxylation catalyzed CYP 2B6 enzymes [7]. In addition, a considerable interindividual variability in propofol metabolism was observed during the neonatal period [8]. The dosage for anesthesia induction is higher in neonates compared to older infants and its clearance is longer in neonates than in older children. This is the reason why in the case of repeated boluses or continuous infusion over 24 hours, the so-called propofol infusion syndrome, a syndrome characterized by acute cardiac failure, myopathy, hyperkalemia and metabolic acidosis, may develop more frequently in the neonatal period [9].

To date, the Food and Drug Administration does not recommend the use of propofol in children younger than 3 years old. In fact, the few experiences reported in the scientific literature relate to small samples and are often contrasting: effective use of propofol has been reported among full-term neonates and infants, with only a few cases of mild, irrelevant hypotension [10–13]. Contrariwise, other authors found many cases of severe hypotension in neonates who were induced with propofol [14–16]. Given the results of the present study, the use of propofol seems to represent a valid alternative to the use of anesthetic agents for ROP surgery.

Previous studies have examined the use of topical anesthetics, general anesthesia and combinations of sedation and analgesia during surgical treatment of ROP. Haigh et al. [17] found that premature infants undergoing cryotherapy for ROP who were treated

using topical anesthesia alone had more severe and protracted cardiorespiratory complications than with general anesthesia or sedation/analgesia, although the performance of the procedure was comparable. Even the use of tenon anesthesia combined with sedation was associated with cardiorespiratory instability and excessive head mobility [18]. General anesthesia is therefore preferred for ROP treatment by laser; however, there is still wide variation in the type of anesthetic used.

Over the last decade, morphine and fentanyl have been the most commonly used opioids for ROP treatment in the NICU setting [19–21]. Recently, remifentanil has been suggested as an alternative choice to these opioids [22]. The authors showed few respiratory complications with remifentanil; nevertheless, all infants required intubation during the procedure. Our goal was to avoid intubation, as reintubating premature neonates is not ideal considering the frequent difficulty we have weaning them off ventilation and considering also that premature infants are at greater risk of adverse events from intubation [23].

Ketamine, a short-acting "dissociative" anesthetic with a potent analgesic effect, has also been recently used for pediatric and neonatal sedation [24]. It provides analgesia but does not require intubation, as it preserves airway patency and respiratory function. Lyon et al. [25] used ketamine to treat 11 neonates in the NICU setting; they recorded few respiratory complications, and despite significant movement in three cases, all procedures could be completed. Nevertheless, recent studies raise concerns on its use in preterm infants as it can be associated with neurotoxicity [26].

In conclusion, our analysis showed that propofol sedation associated with fentanyl analgesia was effective in this short-lasting surgery and presented no side effects, thus putting the base for a randomized study to assess propofol safety.

Disclosure statement

The authors state no conflict of interest.

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