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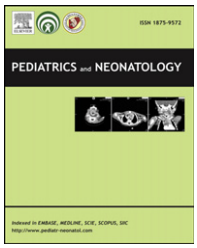

CASE REPORT

Experience of Remifentanil in Extremely Low-birth-weight Babies Undergoing Laparotomy

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Premature babies experience pain and require adequate analgesia for any painful procedure. Fentanyl and morphine resulted in safe and effective anesthesia in the past; however, their pharmacokinetics may be impaired in preterm babies with multiorgan failure. Remifentanil, despite the absence of available pharmacokinetic data in preterm infants and few reports in newborns, demonstrated its advantages in children undergoing either major surgery or minor painful procedures and has been shown to be useful even in neonates, because its elimination is independent of organ function. We report two cases of babies born at 26 weeks' and 27 weeks' gestation, weighing 580 g and 400 g, respectively, undergoing laparotomy for necrotizing enterocolitis. Both received midazolam bolus and remifentanil infusion at high doses. This technique seems to be an advantageous alternative even in extremely low-birth-weight prematures. Furthermore, it becomes a technique of choice in these babies because the available ventilators are often not equipped with halogenated vaporizers. Particularly in intensive care, where there are no scavenger systems, it could allow to operate without moving out the preterm babies and avoiding stress and hypothermia.

1. Introduction

It is now accepted that premature babies experience pain; therefore, adequate analgesia should be provided for any painful procedure.[1] Anand and Sippell[2] report that babies

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who undergo surgical procedures without effective analgesia show a pronounced increase in stress hormone concentrations, and these changes may adversely influence outcome. Neonates are known to be relatively sensitive to hypotension induced by volatile agents in comparison with older children.[3]

It should be considered that very-low-birth-weight premature babies are often ventilated by high-frequency oscillatory ventilation (HFOV) to reduce barotrauma associated with conventional ventilation.[4] These ventilators are not equipped with halogenated vaporizers, and total intravenous anesthesia is mandatory.

Several opioid agents have been used for this purpose: fentanyl anesthesia has been shown to be safe and effective, but the pharmacokinetics of this drug may be impaired in premature babies with multiorgan failure.[5] Morphine alleviates prolonged pain, reduces behavioral and hormonal stress responses, and improves ventilator synchrony and sedation among ventilated preterm neonates.[6] However, it is unclear whether it provides adequate analgesia for the acute pain caused by invasive procedures in ventilated preterm neonates.

Remifentanil is widely used in children,[7] but literature shows limited reports in infants,[8] shortage regarding preterms,[9] and no evidence in extremely low-birth-weight (ELBW) infants. However, it may be a useful opioid for preterm infants because its elimination is independent of hepatic and renal functions. For this reason, it has been used in neonatal intensive care unit (NICU) for brief ophthalmic procedures[10] and for long-term sedation in preterms needing mechanical ventilation.[11]

Encouraged by these sporadic experiences and by its unique pharmacokinetic and pharmacodynamic characteristics, we decided to use this opioid for two very small preterms undergoing surgery for necrotizing enterocolitis.

We do believe that our cases are the youngest patients reported until now, and for this reason, written informed consent to publish these data was obtained from both families. Because the survival of ELBW prematures, such as the possibility for them to undergo surgery is always more frequent, we expect this report to be helpful as an alternative anesthesia technique.

2. Case Report

2.1. Case 1

The baby was born by caesarean section at 26 weeks' gestation, weighing 580 g. Immediately after birth, he was intubated, admitted to NICU, and connected to mechanical ventilator (Babylog 8000 ventilator; Dräger, Lübeck, Germany) in HFOV.

The following day, because of the diagnosis of enterocolitis, he underwent laparotomy. Before leaving the NICU, a dopamine infusion (4 mcg/kg/min) was started to control the hypotension caused by the septic state. On arrival to the operating theater, the baby was moved from the incubator to the operating table, where a forced air warming device (Bair Hugger, Augustine Medical Inc., Eden Prairie, MN, USA) was previously prepared. During all the procedures, HFOV parameters were as follows: mean airway pressure, 10 cmH_20; frequency, 8 Hz; amplitude, 70%; and FiO_2, 0.25. In this way, we could obtain regular respiratory pattern performed by O_2 percutaneous saturation (SaO_2) between 88% and 96% and a value of final expiratory CO_2 ($EtCO_2$) between 31 mmHg and 35 mmHg. The hemodynamic and respiratory parameters are shown in Table 1.

Midazolam 0.5 mg bolus was administered and remifentanil infusion (RI) 0.25 mcg/kg/min was started and increased in 15 minutes up to 3 mcg/kg/min. Because of a desaturation episode (from 94% to 86%), FiO_2 was temporarily increased to 0.35, and the oxygen saturation was restored to 95%. Then RI was increased step by step up to 7.2 mcg/kg/min and was maintained during the entire operation. After 30 minutes, the mean arterial pressure decreased at 26 mmHg, and it was treated by increasing dopamine infusion (6 mcg/kg/min) and by starting blood administration (5 mL). As blood pressure was restored to normal values, dopamine infusion was decreased to initial rate (4 mcg/kg/min).

The surgery lasted for 1 hour, and no other episodes of hypotension or desaturation were observed. In the last 15 minutes, RI was gradually decreased to 0.1 mcg/kg/min and was maintained at the same rate until the baby was transferred back to the NICU. In the postoperative period, RI was

Table 1 Hemodynamic (HR and MAP) and respiratory (SaO_2 and $EtCO_2$) parameters

Cases	Baseline	Minutes of surgery										
		5'	10'	15'	20'	25'	30'	35'	40'	45'	50'	55'
First case												
HR	142	125	135	138	140	150	151	149	147	145	148	149
MAP	34	30	31	31	33	32	26	28	33	36	34	34
SaO_2	95	94	95	95	86	95	93	95	96	94	95	94
$EtCO_2$	34	33	35	33	32	34	28	29	30	32	33	32
Second case												
HR	138	127	136	143	140	135	132	133	135	134	137	
MAP	27	26	25	26	28	27	26	25	26	27	28	
SaO_2	93	93	92	91	92	90	88	90	91	93	92	
$EtCO_2$	33	35	33	32	33	33	32	34	31	34	33	

HR = heart rate; MAP = mean arterial pressure; SaO_2 = O_2 percutaneous saturation; $EtCO_2$ = final expiratory CO_2.

maintained at 0.05-mcg/kg/min to 0.1-mcg/kg/min range to achieve a good sedation for mechanical ventilation. The condition of the baby was stable for the following week, after which it was possible to extubate him.

2.2. Case 2

The baby was born by caesarian section at 27 weeks and 4 days' gestation, weighing 340 g. Apgar at the first minute was 3 and after 5 minutes was 8. He was intubated and transferred to NICU where he was connected to a mechanical ventilator (Babylog 8000 Plus). The heart rate was 140/min and SaO_2 was 96%, with FiO_2 of 0.21.

In the second day of life, epinephrine, red cells, and frozen plasma were administered for a massive lung hemorrhage. The following day, he was again hypotensive. A chest X-ray was performed, and it showed severe bilateral opacities: an improvement of SaO_2 and a reduction of FiO_2 were achieved by surfactant therapy. Clinical conditions became more stable. In the seventh day of life, a distended abdomen was observed: an abdominal X-ray confirmed the presence of air trapping. The baby was receiving albumin, a total parenteral nutrition, so that at the moment of surgery he weighed 400 g.

He was transferred to the operating theater with a remifentanil sedation at 0.08-mcg/kg/min rate. HFOV parameters were as follows: mean airway pressure, 8 cmH_20; frequency, 8—9 Hz; amplitude, 70%; and FiO_2, 0.21.

For anesthesia induction, midazolam 0.4 mg was administered, and RI was increased up to 0.25 mcg/kg/min. During the procedure, remifentanil rate achieved a maximum of 3 mcg/kg/min. Oxygen saturation remained stable ranging between 88% and 93%, with FiO_2 of 0.21. Hemodynamic parameters were stable, and there was no evidence of hypotension and tachycardia (Table 1). At the end of surgery, RI was gradually decreased to 0.25 mcg/kg/min and maintained until the baby was transferred to the NICU. Surgery was well tolerated, as reported in the clinical chart by neonatologists, but 3 days after surgery, the baby developed severe metabolic acidosis and hypotension and rapidly became decompensated. An immediate therapy with bicarbonates, fluids, dopamine, and dobutamine was started, but the following night, clear signs of shock were observed, and the baby died as a result of cardiac collapsus.

3. Discussion

In our cases, it was not possible to use inhalation anesthesia. In fact, in our NICU, HFOV is preferred to conventional ventilation because of the protective role against barotrauma in ELBW, and this kind of ventilator does not allow the use of halogenated agents. We chose to administer a single bolus of midazolam for the induction of anesthesia. Soriano and Anand[12] have showed that prolonged administration of anesthetic drugs, including midazolam, produces increased neurodegeneration in 7-day-old rat pups. Although these studies question the applicability of the data to the anesthetic management of neonates,[12] our patients received a single high dose of midazolam to provide anesthesia and to avoid the use of muscle relaxants to monitor the possible motor response to pain. Furthermore, several studies by Anand[13] demonstrated that preterm babies build up a substantial stress response to surgery if opioids are not administered.

Consequently, infants undergoing anesthetics without opioids develop clinical complications because of skeletal muscle breakdown associated with weight loss and poor clinical conditions. Preterm babies are not, as widely accepted, capable of localizing pain because of the lack of myelinization in the central nervous system and cannot interpret it because they are not able to memorize previous painful experiences. However, these studies noted a very early pain perception mediated by brain regions (sensory motor cortex, thalamus, and others) particularly involved during painful procedures.[14]

As preterm infants have immature hepatic and renal functions, variations in opioid metabolism may often occur. Compared with both older children and adults, they have a reduced clearance, an increased half-life, and a greater volume of distribution.[15] These variations in clearance and elimination are likely because of the age-related maturation of hepatic microsomial enzyme activity and/or the age-related distribution of hepatic blood flow.[16]

In our two cases, classic opioid side effects, such as bradycardia, rigidity, and severe hypotension, were not observed. We did not modify the oscillatory ventilation parameters except a transient modification of FiO_2, and hemodynamic stability was a witness of adequate anesthesia. Because it is not possible in ELBW infants to predict the pharmacokinetics of other opioids, such as fentanyl and morphine, the risk of side effects and inadequate anesthesia is high. Moreover, fentanyl can induce hypotension not easily reversible. In this context, remifentanil appears to be very useful as its unique pharmacokinetic profile results in rapid metabolism by nonspecific plasma and tissue esterases independent of hepatic and renal functions[15] and in fast offset.

As a potent opioid, it can be titrated to allow different levels of sedation and analgesia or deep anesthesia.[17] Because of the lack of validated monitoring devices, we were obliged to titrate RI based on our previous experiences[10] and on hemodynamic responses.

In the present cases, we observed an intraoperative hemodynamic stability using remifentanil at high doses. In the first case, a mild transient hypotension was observed, but it was not associated with bradycardia, and we assumed that it did not depend on remifentanil dose.

According to its pharmacokinetics, the remifentanil context-sensitive half-life does not vary with duration of infusion. Clinical effects rapidly disappear on discontinuation of the drug without prolonged recovery and long-lasting ventilatory complications even in these delicate and tiny patients.[18] Considering the difficulties in performing pharmacokinetic studies in such microprimies, clinical reports are still the major source of knowledgeable information in this issue.

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