



ORIGINAL ARTICLE

Pharmacologic pain management in a high-complexity neonatal intensive care unit: real-world patterns of analgesic and sedative use in neonates



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Abstract

Introduction: Effective pain management in neonates remains a major challenge, with limited real-world data on the pharmacologic strategies used in NICUs. Untreated pain and suboptimal sedation in the neonatal period has been associated with adverse neurodevelopmental outcomes. The aim of this study was to describe real-world patterns of systemic sedatives and analgesics use in a level III NICU.

Methods: We conducted a 13-month retrospective observational study, including inborn infants admitted to the NICU for more than 24 hours. We analyzed drug selection, administered doses, cumulative doses, route of administration, adverse events and management of drug withdrawal.

Results: During the study period, 423 newborn infants were admitted to the NICU, of whom 357 met the inclusion criteria. Among them, 53.2% (n = 190) required sedation or analgesia. The median (IQR) duration of sedation/analgesia was 4.5 (2–11) days. Sedation was significantly more frequent among patients requiring mechanical ventilation (92.7% vs 35.9%, $P < .005$). Eighty-two infants received continuous opioid infusion, with fentanyl as the first choice (96.3%). Sixty-eight received dexmedetomidine, often in combination with midazolam (severe cases requiring deep sedation). Neuromuscular blockers were used in only five patients, primarily for extracorporeal membrane oxygenation or major surgeries. Adverse events, mainly hypotension or bradycardia occurred in 9.2% of the patients.

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Conclusions: Our findings underscore the need for standardized, evidence-based protocols for analgesia and sedation in NICUs. Detailed documentation of real-world prescribing practices (including prescribed individual and cumulative doses) and safety outcomes may support safer pain management in vulnerable neonatal populations.

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PALABRAS CLAVE

Dolor neonatal;
Analgesia;
Sedación;
Seguridad en el uso
de medicamentos;
Unidad de Cuidados
Intensivos Neonatales

Tratamiento farmacológico del dolor en una Unidad de Cuidados Intensivos Neonatales de alta complejidad: uso en vida real de analgésicos y sedantes en neonatos

Resumen

Introducción: El manejo eficaz del dolor en neonatos sigue siendo un desafío importante, con datos limitados sobre las estrategias farmacológicas utilizadas en unidades de cuidados intensivos neonatales (UCIN) en la práctica clínica real. La exposición neonatal al dolor no tratado y a una sedación subóptima se ha asociado con efectos adversos en el neurodesarrollo. El objetivo de este estudio fue describir los patrones reales de uso de fármacos sedantes y analgésicos en una UCIN de alta complejidad.

Métodos: Se realizó un estudio observacional retrospectivo de 13 meses que incluyó a los neonatos nacidos en el hospital e ingresados en la UCIN durante más de 24 horas. Se analizaron la selección de fármacos, las dosis administradas y acumuladas, la vía de administración, los eventos adversos y el manejo del síndrome de abstinencia.

Resultados: Durante el periodo de estudio se ingresaron 423 neonatos, de los cuales 357 cumplieron los criterios de inclusión. Entre ellos, el 53,2 % (n = 190) requirió sedación o analgesia. La mediana de duración del tratamiento sedoanalgésico fue de 4,5 días (RIC: 2-11). Los pacientes que requirieron ventilación mecánica presentaron tasas significativamente más altas de sedación (92,7 % frente a 35,9 %, p < 0,005). La infusión continua de opioides se utilizó en 82 neonatos, siendo el fentanilo el fármaco de primera elección (96,3 %). La dexmedetomidina se empleó en 68 pacientes, a menudo en combinación con midazolam en casos graves que requerían sedación profunda. Los bloqueantes neuromusculares se utilizaron únicamente en cinco pacientes, principalmente en contexto de oxigenación por membrana extracorpórea o cirugías mayores. Los eventos adversos (principalmente hipotensión o bradicardia) se presentaron en el 9,2 % de los pacientes.

Conclusiones: Nuestros hallazgos refuerzan la necesidad de establecer protocolos estandarizados y basados en la evidencia para la analgesia y sedación en UCIN. La documentación detallada de la práctica clínica real, incluyendo las dosis administradas y dosis acumuladas y los resultados de seguridad, puede contribuir a un manejo más seguro del dolor en la población neonatal vulnerable.

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Introduction

Pain management in hospitalized neonates is a critical concern and has historically been undertreated.¹ During their stay, these patients undergo numerous painful procedures, such as blood sampling, vascular access placement, intubation, and lumbar punctures. Studies estimate that NICU patients experience an average of up to 16 daily procedures.^{2,3}

Pain management in preterm infants is particularly important, as inadequate treatment has been found to have a negative impact on neurodevelopment.⁴ Specifically, greater exposure to pain during the neonatal period in preterm infants has been associated with poorer cog-

nitive, motor, and behavioral outcomes in childhood.⁵⁻⁷ While untreated pain and inadequate sedation can be harmful, the pharmacologic management of pain and stress in neonates is not without risks. Analgesics and sedatives may cause adverse effects such as cardiorespiratory depression, hypotension, delayed gastric motility, tolerance, and withdrawal syndrome, and there is growing concern about their potential long-term impact on neurodevelopment.⁸

Both pharmacologic and nonpharmacologic approaches are used for neonatal pain management. Some non-pharmacologic interventions have proven effective for certain procedures.⁹ However, there is no standardized pharmacologic approach to neonatal sedation and pain management.¹⁰ Currently, each NICU must develop an in-

house treatment protocol based on the available evidence.¹¹ In our hospital, pain management is standardized. However, in Europe, most of the commonly used drugs have no approved indication for use in preterm infants, and only a few have an approved indication for use in term neonates. Furthermore, the summary of product characteristics for certain drugs, such as methadone and midazolam, explicitly contraindicates use in newborns.¹²

Due to the lack of approved therapeutic options, dosing in neonates is often extrapolated from pharmacokinetic data from pediatric and adult populations. Such extrapolation is frequently not supported by robust studies demonstrating its safety and efficacy, particularly in preterm infants. Additionally, advanced techniques, such as extracorporeal membrane oxygenation and therapeutic active hypothermia, alter drug pharmacokinetics, although their impact on clinical practice has not yet been adequately characterized.^{13,14} This uncertainty underscores the need for real-world studies to evaluate the use of these treatments and their potential adverse effects.

Although there have been large-scale studies on neonatal pain medication, the cumulative exposure to these treatments during the stay in the NICU has not been analyzed in depth. Much of the previous evidence comes from surveys or registries that do not provide detailed information on aspects like treatment duration or the administered doses.¹⁰ This lack of detailed information is a critical limitation for prescribers, affecting clinical decision-making and safety assessments.

In this context, we designed a study with the primary objective of conducting a detailed analysis of the drugs used for neonatal pain management, including their indications, doses and durations. We also evaluated treatment safety in order to contribute key evidence to help optimize prescribing practices and improve pain management in this vulnerable population.

Methods

Study design

We conducted a single-center retrospective descriptive study in the level III Q3 NICU of a hospital that manages approximately 4200 births per year, including 110 preterm births of infants weighing less than 1500 g. The study period spanned 13 months, from April 2023 to April 2024.

The inclusion criteria was admission to the NICU with a stay longer than 24 hours. Outborn infants were excluded.

To assess the use of sedation and analgesia in the unit, we reviewed prescribing records. Prescriptions were entered using an electronic prescribing system integrated into the patient data management system of the NICU (IntelliSpace Critical Care and Anesthesia). We included all prescriptions for sedatives or analgesics for systemic use in the analysis, including neuromuscular blockers: paracetamol, metamizole, morphine, fentanyl, remifentanyl, dexmedetomidine, lorazepam, midazolam, clonidine, methadone, ketamine, rocuronium, and cisatracurium.

Pain and stress assessment

In our NICU, pain and stress assessment is performed according to an institutional protocol based on the European Standards of Care for Newborn Health, which outlines a stepwise multimodal strategy for prevention and treatment (see Supplemental material, Appendix A). This protocol includes the routine use of validated clinical scales: the Premature Infant Pain Profile-Revised (PIPP-R) for acute pain (validated in infants born at or after 25 weeks of gestation aged up to two months), the CRIES scale (Crying, Requiring oxygen, Increased vital signs, facial Expression, and Sleeplessness) for postoperative pain in term neonates (validated for postoperative pain assessment in infants born at or after 32 weeks of gestation), and the COMFORTneo scale for prolonged pain and for sedation assessment (validated for neonates born preterm from 24 weeks of gestation).

Definition of variables

For all included patients in whom any pharmacologic treatment had been prescribed, we reviewed the health records to determine the indication for treatment and whether any adverse events occurred. For the purpose of the study, "adverse events" were those adverse events attributed to the pharmacologic treatment documented in the health record by the attending physician.

For each patient, we collected data on the following demographic from the database: gestational age, birth weight, reason for admission, sex, five-minute APGAR score, need for resuscitation at birth and type of resuscitation, diagnosis of intrauterine growth restriction, administration of prenatal corticosteroids, and mode of delivery. Additionally, we obtained data on the highest level of respiratory support used during the stay and the days of invasive mechanical ventilation to assess severity. We also classified patients according to the use of ECMO, therapeutic hypothermia or surgery during the stay.

In relation to pharmacologic treatment, for each systemic sedative, systemic analgesic or neuromuscular blocking agents used during the stay, we collected the following data: indication for use, route of administration, maximum dose, minimum dose, and cumulative dose over the entire stay. For intermittent medication, we documented the administered dose, the dose per kilogram of body weight, and the number of administered doses. For medications delivered via continuous intravenous infusion, we recorded the infusion time, prescribed and cumulative doses, and the number of days the patient received the drug.

Statistical analyses

In the descriptive analysis of the characteristics of the sample, we summarized quantitative data using the median (IQR), as the data did not follow a normal distribution (Kolmogorov-Smirnov test). We summarized qualitative data as absolute and relative frequencies (counts and percentages). To test for differences between the phases or intervention groups for each characteristic, we used the Mann-Whitney *U* test the χ^2 test as applicable. All the analyses were performed with the software Intercooled Stata for

Table 1 Demographic and clinical characteristics of the cohort.

	Patients (n = 357)
Female sex, n (%)	146 (40.9%)
Gestational age, median (IQR)	35 (31–39)
<28 weeks, n (%)	34 (9.5%)
28–32 weeks, n (%)	101 (28.3%)
33–37 weeks, n (%)	85 (23.8%)
>37 weeks, n (%)	137 (38.4%)
Birth weight in g, median (IQR)	2300 (1390–3100)
<1000 g, n (%)	50 (14%)
1000–1500 g, n (%)	58 (16.3%)
>1500–2500 g, n (%)	85 (23.8%)
>2500 g, n (%)	164 (45.9%)
5-min APGAR	(n = 356)
0–4	16 (4.5%)
5–7	54 (15.2%)
8–10	286 (80.3%)
Prenatal corticosteroids (PT < 34 wk), n (%)	138/168 (82.1%)
Intrauterine growth restriction, n (%)	52 (14.6%)
Surgery during admission, n (%)	48 (13.4%)
ECMO, n (%)	3 (0.8%)
HIE with therapeutic hypothermia, n (%)	6 (1.7%)
Deaths, n (%)	12 (3.4%)
Days of mechanical ventilation, median (IQR)	0 (0–1)
NICU stay in days, median (IQR)	7 (3–19)

Abbreviations: ECMO, extracorporeal membrane oxygenation; HIE, hypoxic-ischemic encephalopathy; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit; PT < 34 wk, preterm infant born before 34 weeks' gestation.

Windows, version 16 (StataCorp LLC; College Station, TX, USA), setting the significance level at 5%.

Ethical aspects

The study was evaluated and approved by the Research Ethics Committee of the Hospital Universitario 12 de Octubre (code 24/503). The study adhered to the General Data Protection Regulation and the principles of the Declaration of Helsinki.

Results

During the study period, 423 patients were admitted to the NICU. Of this total, 357 met the inclusion criteria; 48 patients were excluded because they were outborn and 18 because they stayed less than 24 hours in the NICU. **Table 1** presents the demographic characteristics of the patients admitted to the NICU during the study period.

Of the patient admitted to the NICU, 53.22% (n = 190) required treatment with some sedative or analgesic drug. Considering only those requiring a higher level of analgesia beyond paracetamol, the percentage who received analgesics or sedatives decreased to 31.37% (n = 112) in the overall sample and 33.88% (n = 41) in infants born preterm

Table 2 Proportion of patients who received sedation/analgesia based on their baseline characteristics.

	Patients who received sedation/analgesia
Gestational age	
<28 weeks	88.1%; 30/34
28–32 weeks	45.4%; 46/101
33–37 weeks	41.2%; 35/85
>37 weeks	57.7%; 79/137
Birth weight	
<1000 g	80%; 40/50
1000–1500 g	53.4%; 31/58
>1500–2500 g	32.9%; 28/85
>2500 g	55.5%; 91/164
Prenatal corticosteroids	54%; 87/161
Intrauterine growth restriction	65.4%; 34/52
Cesarean delivery	56.4%; 106/188
APGAR 5	
0–4	87.5%; 14/16
5–7	68.4%; 37/54
8–10	48.2%; 138/286
Maximum level of respiratory support during stay	
No respiratory support	27.6%; 16/58
Noninvasive mechanical ventilation	38%; 73/192
Conventional mechanical ventilation	93.3%; 84/90
High-frequency ventilation	100%; 17/17
Surgery during stay	100%; 48/48
ECMO	100%; 3/3
HIE with therapeutic hypothermia	100%; 6/6
Death	100%; 12/12

Abbreviations: ECMO, extracorporeal membrane oxygenation; HIE, hypoxic-ischemic encephalopathy.

before 32 weeks of gestation or with birth weights of less than 1500 g. **Table 2** shows the proportion of patients who received sedation or analgesia based on their baseline characteristics. Among patients who received sedoanalgesia, 42.1% were female, with a median (IQR) gestational age of 36 (29–39) weeks and birth weight of 2365 (1145–3190) grams. The median (IQR) duration of mechanical ventilation was 1 (0–3) day and the median (IQR) length of stay in the NICU was 14 (6–34) days.

We found a statistically significant difference in sedation and analgesia use between patients born before 32 weeks or with birth weights under 1500 g and those born after 32 weeks with weights of greater than 1500 g (61.15% [74/121] vs 49.15% [116/236]; $P = .0041$). Additionally, 92.7% (101/109) of patients who required mechanical ventilation received sedation/analgesia, compared to 35.9% (89/248) of those who did not require mechanical ventilation ($P < .005$).

The median (IQR) duration of sedation or analgesia in patients who received one or both was 4.5 (2–11) days.

Table 3 lists the drugs prescribed for pain management and sedation during the study period, in addition to the indications for which they were used. The same drug may have been administered to a patient for more than one indication. It is important to note that our protocol does not contemplate the routine use of opioids or neuromuscular blockers

Table 3 Drugs used for sedative analgesia and indications for which they were used.

Drug and number of patients receiving it	Indication	Number of patients receiving it	
Enteral paracetamol (n = 134)	Severe respiratory/hemodynamic compromise	42	
	Postoperative analgesia	36	
	Agitation/irritability	34	
	Extravasation injury	15	
	Skin injuries (bruises/wounds)	12	
	Postprocedural	9	
	Diaper dermatitis	6	
	Fever	5	
	ECMO	2	
	Therapeutic hypothermia	2	
	Chest tube drainage	1	
	Intravenous paracetamol (n = 118)	Severe respiratory/hemodynamic compromise	80
		Postoperative	44
Agitation/irritability		15	
Postprocedural		8	
Others (ventricular reservoir puncture, fever, bruises, anal fissure)		4	
ECMO		3	
Extravasation injury		2	
Lumbar puncture		1	
Intravenous fentanyl (n = 81)		Respiratory/hemodynamic severity	50
		Postoperative	24
	Vascular catheter insertion	15	
	Intraocular injection	10	
	Atrial septostomy	8	
	Intubation	7	
	Others (ultrasonography, secretion aspiration, catheter treatment, ventricular reservoir puncture, drainage placement)	5	
	Therapeutic active hypothermia	5	
	Laser photocoagulation	4	
	Postcatheterization	3	
	Abdominal wall defect repair	3	
	ECMO	2	
	Chest tube drainage	1	
	End-of-life care	1	
	Hyaluronidase administration for the treatment of extravasations	1	
	Embolization	1	
	Bronchoscopy	1	
	Paracentesis	1	
	Lumbar puncture	1	
	Intranasal fentanyl (n = 45)	Vascular catheter insertion	30
Hyaluronidase administration for the treatment of extravasations		8	
Severe respiratory/hemodynamic compromise		6	
Intubation		2	
Intraocular injection		1	
Ileostomy cure		1	
Blood sampling		1	
Atrial septostomy		1	
Drain removal		1	
Morphine (n = 20)	Severe respiratory/hemodynamic compromise	16	
	Postoperative	4	
	ECMO	2	
	Vascular catheter insertion	1	
	Abdominal wall defect repair	1	
	Lumbar puncture	1	

Table 3 (Continued)

Drug and number of patients receiving it	Indication	Number of patients receiving it
Remifentanyl (n = 15)	Severe respiratory/hemodynamic compromise	1
	Intubation	14
Dexmedetomidine (n = 68)	Severe respiratory/hemodynamic compromise	54
	Therapeutic hypothermia	5
	ECMO	3
	Postoperative	14
	Vascular catheter insertion	6
	Intraocular injection	7
	Postcatheterization	2
	Laser photocoagulation	3
	Atrial septostomy	4
	Bronchoscopy	1
Intranasal dexmedetomidine (n = 4)	Intraocular injection	2
	Severe respiratory/hemodynamic compromise	1
Midazolam (n = 34)	Vascular access	1
	Severe respiratory/hemodynamic compromise	21
	Postoperative	8
	Vascular catheter insertion	8
	Atrial septostomy	4
	ECMO	2
	Intraocular injection	2
	Chest tube drainage	2
	Abdominal wall defect repair	2
	Therapeutic active hypothermia	1
	Intubation	1
	Chest tube placement	1
	Laser photocoagulation	1
	Intranasal midazolam (n = 7)	Severe respiratory/hemodynamic compromise
Vascular access		2
Intraocular injection		2
Intravenous ketamine (n = 15)	Vascular access	10
	ECMO	2
	Severe respiratory/hemodynamic compromise	1
	Intraocular injection	1
	Fiberoptic bronchoscopy	1
	Abdominal wall defect repair	1
	Atrial septostomy	1
Intramuscular ketamine (n = 2)	Severe respiratory/hemodynamic compromise	1
	Vascular catheter insertion	1
Intranasal ketamine (n = 1)	Vascular catheter insertion	1
Cisatracurium (n = 10)	Severe respiratory/hemodynamic compromise	7
	ECMO	3
	Postoperative	2
	Vascular catheter insertion <i>in hemodynamically unstable patient</i>	2
Rocuronium (n = 36)	Omphalocele treatment	1
	Intubation	27
	Vascular catheter insertion <i>in hemodynamically unstable patient</i>	6
	Intraocular injection	5
	Severe respiratory/hemodynamic compromise	4
	Laser photocoagulation	2
	Surgical procedures (loop reduction, omphalocele cure)	2
	ECMO	1
	Chest tube drainage <i>in hemodynamically unstable patient</i>	1
	Ultrasonography <i>in hemodynamically unstable patient</i>	1
	Atrial septostomy	1

Table 4 Doses administered for each drug and route of administration.

Drug	Route of administration	Patients (n)	Minimum median dose/weight (RI)	Median maximum dose/weight (RI)	Number of doses received (RI)	Continuous infusion (RI) hours	Median cumulative dose during admission (RI)
Paracetamol	Enteral	134	9.8 ± 0.4 mg/kg	10 ± 0.8 mg/kg	6 (2–16)	NA	119.9 (45–324) mg
	Intravenous	118	9.1 ± 1.9 mg/kg	10.1 ± 3.5 mg/kg	7 (3–21.7)	NA	145.2 (62.1–499.8) mg
Fentanyl	IV (continuous infusion)	62	0.8 (0.5–1) µg/kg/h	2 (1.3–2.6) µg/kg/h	NA	130 (38.5–259)	249.4 (59.7–647.9) µg
	IV (bolus)	76	0.9 ± 0.3 µg/kg	1.2 ± 0.4 µg/kg	5.5 (2–19.2)	NA	11 (4–40.5) µg
Morphine	Intranasal	45	1 ± 0.2 µg/kg	1 ± 0.2 µg/kg	1 (1–3)	NA	3.8 (2.9–7.1) µg
	IV (continuous infusion)	18	12.3 (7.4–15.1) µg/kg	25 (20.7–57.5) µg/kg	NA	167 (90.2–278.7)	3204.4 (1518.4–9632.2) µg
Remifentanyl	IV (bolus)	19	10.2 (10–10.7) µg/kg	10 (9.9–10.3) µg/kg	11 (5.5–24)	NA	109.5 (69.3–520.2) µg
	IV (bolus)	15	1 (1–1.1) µg/kg	1 (1–1.1) µg/kg	1 (1–1)	NA	3 (1–3,4) µg
Dexmedetomidine	IV (continuous infusion)	68	0.2 (0.2–0.2) µg/kg	0.65 (0.4–0.92) µg/kg	NA	74 (26.5–266.75)	56.48 (19.48–205.42) µg
	Intranasal	4	0.5 (0.048–0.5) µg/kg	0.5 (0.048–0.5) µg/kg	2 (1–3.5)	NA	3.25 (1.33–4.96) µg
Midazolam	IV (continuous infusion)	19	0.05 (0.05–0.08) mg/kg/h	0.2 (0.1–0.27) mg/kg/h	NA	167 (49.5–274.5)	65.1 (12.4–137.1) mg
	IV (bolus)	32	0.05 (0.05–0.09) mg/kg	0.1 (0.09–0.11) mg/kg	5 (2–16)	NA	1.34 (0.55–5.4) mg
Ketamine	Intranasal	7	0.09 ± 0.006 mg/kg	0.09 ± 0.006 mg/kg	1 (1–1)	NA	0.3 (0.2–0.3) mg
	Intravenous	15	0.52 (0.5–0.83) mg/kg	0.53 (0.5–0.97) mg/kg	2 (1–3)	NA	4 (1.9–6) mg
Cisatracurium	Intramuscular	2	1.9 (1.92–1.97) mg/kg	1.9 (1.92–1.97) mg/kg	1 (1–1)	NA	5.62 (4.31–5.93) mg
	Intranasal	1	3 mg/kg	3 mg/kg	1	NA	12 mg
Rocuronium	IV (continuous infusion)	5	1 (1–1) µg/kg/min	3.5 (1–4) µg/kg/min	NA	391 (25–484)	3583.3 (77.5–4530.66) µg
	IV (bolus)	9	100 (100–100) µg/kg	100 (100–100) µg/kg	3 (1–48)	NA	606 (310–11190.75) µg
Rocuronium	IV (continuous infusion)	1	5 µg/kg/min	8 µg/kg/min	NA	157	4119.2 µg
	IV (bolus)	36	591.3 (300–600) µg/kg	600 (593.67–600) µg/kg	1 (1–2)	NA	1800 (862–2313.75) µg

for noninvasive procedures, such as ultrasound scans. The recorded bolus doses administered for imaging tests correspond to critically ill patients who were already unstable and frequently on mechanical ventilation. In these cases, additional boluses were administered to optimize hemodynamic and respiratory stability during the procedure, rather than as an analgesic or sedative requirement for the imaging itself. Table 4 shows the minimum and maximum doses used for each drug and the median cumulative dose during the stay of patients in the sample.

Paracetamol was the drug of choice for non-opioid analgesics. During the study period, more than half the patients received paracetamol at some point. Metamizole was used exclusively as an antipyretic and never as an analgesic.

Fentanyl and morphine were administered as continuous infusion for maintenance pain management in 82 patients. Ninety-six percent ($n = 79$) of the patients initially received fentanyl, with 18.9% ($n = 15$) transitioning to morphine. Morphine was initially used in three patients, two of whom were hemodynamically stable. Remifentanyl was used only in intermittent doses in 93.3% ($n = 14$) of patients who required intubation during the procedure.

Regarding sedation, 68 patients received continuous dexmedetomidine infusions. Nineteen patients also received midazolam in critical situations requiring deep sedation. The median (IQR) corrected gestational age was 39 (35–40) weeks in patients who received midazolam and 37 (27–39) weeks in those who received dexmedetomidine.

Cisatracurium and rocuronium were the drugs used for muscle relaxation. Continuous infusions were administered only during ECMO treatment and in the critical and postoperative period of two patients with congenital diaphragmatic hernia, always in patients on mechanical ventilation ($n = 5$). Single doses were administered for all other procedures in which muscle relaxants were used.

Five patients underwent therapeutic hypothermia, and all received fentanyl for analgesia during cooling. The dose was similar to the doses used in other patients; none received a dose higher than $2 \mu\text{g}/\text{kg}/\text{hour}$, and the median (IQR) maximum dose was $1.5 \mu\text{g}/\text{kg}/\text{hour}$ (1–2). All patients received dexmedetomidine as a sedative, and two also received midazolam.

As for the adverse events associated with the use of these drugs, there was one case of paracetamol poisoning during the study period that required treatment with N-acetylcysteine. Due to an administration error, the patient received a $75 \text{ mg}/\text{kg}$ dose instead of $7.5 \text{ mg}/\text{kg}$. The patient was 27⁺⁴ weeks of corrected gestational age and weighed 850 g. Four hours after drug administration, the serum paracetamol level in the patient was $49.5 \mu\text{g}/\text{mL}$. The paracetamol levels subsequently normalized to undetectable levels, and the patient did not exhibit any associated clinical manifestations.

Furthermore, 8.8% (6/68) of patients treated with dexmedetomidine required a dose reduction or temporary discontinuation due to hypotension or bradycardia. In regard to drug withdrawal, 50.7% (34/67) of the patients treated with benzodiazepines or opioids received some form of replacement therapy for prophylaxis or treatment for withdrawal syndrome. Among the patients who received continuous opioid infusion, 53.1% (34/64) received methadone. Additionally, some patients (32.3%,

22/68) required treatment with clonidine or lorazepam as a substitute for sedative therapy (dexmedetomidine or midazolam).

Discussion

Our study provides a detailed overview of sedation and analgesia use in a high-acuity NICU, highlighting both the frequency of their use and their dosage. In this sample, 53.2% of the patients required sedation. This percentage is higher compared to the 34% reported in the EUROPAIN study cohort, in which fewer patients appeared to require sedation.¹⁰ However, comparing data for patients born before 32 weeks of gestation in the Swedish cohort, the percentage of patients requiring intravenous sedation and analgesia was similar (38.5% in the Swedish cohort vs. 33.8% in our study).¹⁵ Previous studies have shown that attitudes toward analgesia in neonates can vary depending on the cultural context and national treatment guidelines.¹⁶ The high proportion of sedation and analgesia in our cohort suggests a greater sensitivity to neonatal pain management in our setting, as well as awareness/knowledge among our professionals that pain in early life has significant long-term effects on health outcomes persisting into childhood and even adulthood.

The results show that fentanyl was the first-line opioid in most cases, with subsequent switching to morphine in patients with prolonged or more severe conditions. Remifentanyl was used almost exclusively for orotracheal intubation, which was consistent with the previous literature.¹⁷ Sedation was primarily based on dexmedetomidine, with midazolam reserved for patients in more critical situations requiring deep sedation. This approach was consistent with previous evidence suggesting that dexmedetomidine may be a safer alternative to benzodiazepines, given its potential neuroprotective effect and the adverse effects on neurodevelopment associated with benzodiazepines.^{18,19} The use of muscle relaxants was exceptional and limited to particular situations, such as ECMO or major surgery.

When we compared our results with those of the EUROPAIN study, we found that 82% of ventilated neonates in that study received some form of sedation and analgesia,¹⁰ compared to 92.7% of ventilated neonates in our cohort. With respect to opioids, the EUROPAIN cohort primarily received morphine, whereas fentanyl was the most commonly prescribed opioid in our unit. Furthermore, 25% of neonates in the EUROPAIN cohort received midazolam, whereas, in our cohort, dexmedetomidine was the primary sedative, with less frequent use of midazolam. Notably, the use of neuromuscular blockers in continuous infusion in ventilated patients was significantly more frequent in the EUROPAIN study (7% compared to 4.6% in our study). We also found a critical difference in the use of drugs for treating or preventing withdrawal syndrome. In the EUROPAIN study, 8.1% of patients treated with opioids or benzodiazepines received such drugs, compared to 50.7% in our cohort. This discrepancy may be due to changes in withdrawal management practices in recent years, as the EUROPAIN study was published ten years ago. In our unit, the decision to initiate methadone is not based on predefined cumulative dose thresholds but rather on the duration of opioid exposure,

the presence of clinical signs suggestive of withdrawal, and the judgment of the care team.

Another relevant finding of our study was the extensive use of paracetamol in various clinical settings. Its role as a first-line agent for management of postoperative pain is well established and supported by robust evidence.²⁰ However, in critically ill neonates, paracetamol was also used alongside opioid therapy to achieve an opioid-sparing effect and improve safety.²¹ In cases of mild pain, such as skin injuries, diaper rash, or minor procedures, paracetamol was often used as the primary systemic analgesic. While this approach is consistent with paracetamol's profile as a safe and well-tolerated drug, nonpharmacologic measures should be reinforced in these situations to minimize unnecessary drug exposure. These findings emphasize the need to optimize protocols, consolidate the role of paracetamol in postoperative pain and promote its use as an adjuvant in selected critically ill patients. They also encourage rational prescribing in cases of mild pain.

Regarding the cumulative doses administered during the stay, to our knowledge, our study is the first one to collect and analyze this information, so we were unable to compare it these with data from previous studies.

In respect to therapeutic hypothermia, all patients who underwent cooling received analgesia with fentanyl and sedation with dexmedetomidine or midazolam. This contrasts with the results of a survey on the medication used in these patients in Italian NICUs, where 71.4% of patients were treated with monotherapy, for which fentanyl (58.6%) was the most commonly used drug.²² A systematic review comparing sedation and analgesia strategies during therapeutic hypothermia revealed that morphine was the most widely used drug, often as monotherapy, with a dose range of 8 to 60 $\mu\text{g}/\text{kg}/\text{hour}$ for morphine and 1 to 5 $\mu\text{g}/\text{kg}/\text{hour}$ for fentanyl.²³ Adding dexmedetomidine to opioids may reduce the required opioid dose and the time to extubation or resumption of feeding.²⁴ The combination with dexmedetomidine in our cohort could have allowed for a reduction in opioid doses, and the maximum dose administered was 2 $\mu\text{g}/\text{kg}/\text{hour}$.

Sedation and analgesia in neonates with hypoxic-ischemic encephalopathy (HIE) undergoing therapeutic hypothermia is an area of growing interest and ongoing debate. In our center, as in many clinical protocols, routine sedation/analgesia is administered to these patients, based on the ethical principle of preventing pain and stress in this highly vulnerable population. Preclinical evidence suggests that pain and stress may counteract the neuroprotective benefits of hypothermia.²⁵ Clinical data are also emerging: in a retrospective study of neonates with HIE, opioid treatment was associated with reduced brain injury on neuroimaging and improved long-term neurological outcomes.²⁶ In a European multicenter randomized trial of therapeutic hypothermia, a greater treatment efficacy was observed compared to earlier studies (number needed to treat 4 vs 6–9), a finding attributed to the fact that all cooled infants also received morphine or an equivalent fentanyl dose.²⁷ However, other studies have reported neutral findings: in a secondary analysis of the National Institute of Child Health and Human Development (NICHD) hypothermia randomized trial, use of sedation/analgesia was not associated with either better or poorer long-term neurodevelopmental

outcomes.²⁸ These results highlight that, although sedation/analgesia can mitigate pain and stress, the potential risks should also be considered. These include interference with neurological and neurophysiological monitoring, prolonged mechanical ventilation, hemodynamic instability, and altered drug pharmacokinetics during hypothermia, potentially leading to increased drug exposure. In line with this, Róka et al reported higher serum morphine concentrations between 24 and 72 hours of life in cooled neonates compared with normothermic infants receiving equivalent doses.²⁹ Although our observational study included a limited number of patients with HIE, it contributes valuable real-world information regarding the routine use of sedation/analgesia and the absence of observed adverse effects in this subset of infants.

A relevant finding in our study was the use of the intranasal route for administration of sedative or analgesic drugs. Fentanyl and dexmedetomidine were administered intranasally in specific procedures, such as venous catheter insertion and intraocular injection, offering a noninvasive alternative that facilitates analgesia in situations where the intravenous route is unavailable or less convenient. The intranasal route appears to be an effective and safe option in neonates, although its use has not yet been standardized across neonatal units. Including this route in analgesia protocols could improve neonatal care.³⁰

Our study, which is based on real-world clinical practice data, contributes to the evidence on the use of sedation and analgesia in critically ill neonates. Real-world data and evidence are crucial tools for improving drug development and safety in neonatal care.³¹ In this context, the implementation of electronic prescription systems, like the one used in our study, offers an opportunity to improve the safety of neonatal pharmacotherapy.³² Electronic prescriptions facilitate the structured collection of clinical and therapeutic data and enable detailed recording of administered doses.³³

This study has several limitations. Due to its retrospective nature, the identification of adverse events may have been limited by the quality of the health records. Furthermore, the efficacy of the treatments was not assessed because the analysis did not include the scores in the pain assessment scales applied during treatment. However, the study also has strengths, including the large sample size, the follow-up of patients through hospital discharge, and the exhaustive recording of administered doses. This stands in contrast with other large-scale studies on pain management in neonates, such as the EUROPAIN study, in which there were no data on the indications and doses.¹⁰

Our study contributes to the knowledge of sedation and analgesia practices in the NICU, emphasizing the role of fentanyl as the first-line opioid, the widespread use of dexmedetomidine as a first-line sedative, and the need for strategies to reduce opioid withdrawal syndrome. We provide information on the doses used for all drugs, as well as their cumulative doses, which have been poorly described in previous studies. Incorporating electronic prescription systems and analyzing real-world data could be key tools for improving the safety and efficacy of sedation and analgesia in these patients.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.anpede.2026.504134>.

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