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ORIGINAL ARTICLE

Use of dexmedetomidine during mechanical ventilation in extremely preterm and extremely low birth weight neonates receiving morphine: A single-center retrospective study

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Abstract

Analgesia and sedation are often provided during mechanical ventilation in extremely preterm neonates. Opioids and benzodiazepines are the most frequently used agents but can have adverse effects. Dexmedetomidine, an alpha-2 agonist, might be interesting to spare opioid and benzodiazepine use. The objective of this study was to describe a cohort of mechanically ventilated extremely, preterm infants treated with morphine with or without dexmedetomidine. This was a retrospective, observational, single-center study in the neonatal intensive care unit of Creteil. We included preterm neonates born before 28 weeks of gestation and/or weighting less than 1000 g hospitalized between July 2017 and June 2020, on mechanical ventilation for at least 72 h and who received morphine with or without dexmedetomidine as a second- or third-line treatment. We described morphine and midazolam exposure, respiratory, and digestive outcomes for patients who received dexmedetomidine and those who did not. Twenty nine preterm infants received morphine and dexmedetomidine, and 44 received morphine without dexmedetomidine. Dexmedetomidine was used in patients of 25.7 [25.1–26.7] weeks, 680 [600–750] g and significantly more often in patients with vascular complications during pregnancy ($p=0.008$), intrauterine growth restriction ($p=0.01$) and in patients who received higher cumulative doses of morphine ($p=0.01$). Morphine and midazolam doses tended to decrease after the introduction of dexmedetomidine. Dexmedetomidine was never discontinued because of side effects. In this study, dexmedetomidine, used as a second or third-line treatment during mechanical ventilation, was associated with a decrease in morphine and midazolam doses after introduction. Dexmedetomidine was used in a specific population of extremely preterm infants, with severe respiratory disease, who required prolonged mechanical ventilation and high morphine doses. This study highlights the need for pharmacokinetic/pharmacodynamic studies in this population, followed by randomized controlled trials and studies on the long-term effects of dexmedetomidine to determine its place in analgosedation of ventilated preterm infants.

KEYWORDS
analgesia, dexmedetomidine, mechanical ventilation, preterm, sedation

1 | INTRODUCTION

It is now well established that premature neonates detect and respond to painful stimuli and that such stimuli can impair their brain development.[1,2] Mechanical ventilation is considered a common cause of prolonged pain or discomfort in these infants, which justifies pharmacological treatments.[3] Opioids, such as morphine, and midazolam are thus frequently used in ventilated premature neonates.[4,5] However, prolonged mechanical ventilation is challenging regarding analgesia and sedation because prolonged opioid treatment can lead to both tolerance and withdrawal syndrome.[6] In addition, morphine can impair digestion,[7] depress the respiratory drive[8] and thus increase the risk of extubation failure in premature infants. Midazolam can also cause adverse effects, such as hypotension, and possibly has neurotoxic effect.[9,10] Some studies also reported a possible association between prolonged treatment with opioids, midazolam, or their combination, and impaired neurodevelopmental outcome.[11] These data support the search for alternative drugs to reduce the dose and/or duration of opioid or midazolam exposure while maintaining proper comfort and pain management.

Dexmedetomidine is a selective alpha-2 receptor agonist with both sedative and analgesic effects and is increasingly used in the adult, pediatric, and neonatal intensive care unit.[12–14] Over the last decades, dexmedetomidine has been suggested as a useful strategy to spare opioid use and prevent opioid withdrawal syndrome.[13–15] In neonates, dexmedetomidine seems to have no or little effect on digestive motility or respiratory drive.[18] Several animal studies also suggested a possible neuroprotective effect of this molecule.[19,20] In a phase II/III study, dexmedetomidine was well tolerated in 42 neonates born after 28 weeks of gestation.[21] However, clinical data in extremely premature neonates are currently very limited.[22,23]

The objective of this study was to describe the use and the tolerance of dexmedetomidine as a 2nd or 3rd line analgo sedative agent in a cohort of ventilated extremely premature neonates already treated with morphine +/− midazolam. A control group of ventilated neonates treated with morphine +/− midazolam was used to compare baseline characteristics, analgo sedative drugs' use and outcomes. Due to the indication bias related to our treatment protocol, we hypothesized that neonates treated with morphine and dexmedetomidine would have a more severe respiratory course and clinical outcomes than the control group but that dexmedetomidine would be well tolerated.

2 | MATERIALS AND METHODS

2.1 | Type of study and population

This study was an observational, retrospective, single-center study in the neonatal intensive care unit (NICU) of Créteil, France, between July 2017 and June 2020. The study population included neonates born before 28 weeks of gestation and/or with a birth weight less than 1000 g, under mechanical ventilation for more than 72 h and who received morphine for at least 72 h. The dexmedetomidine group included infants who received dexmedetomidine as a 2nd or 3rd line agent, meaning that they could be already receiving midazolam (dexmedetomidine as a 3rd line agent) or not (dexmedetomidine as second line agent). The control group included infants who received morphine only or morphine and midazolam, but no dexmedetomidine. Since some infants had more than one period of mechanical ventilation, we chose to study the first period of mechanical ventilation with dexmedetomidine in the dexmedetomidine group and the longest period of mechanical ventilation in the control group.

The starting date of the study corresponded to the start date of use of the Logipren® neonatal prescription software,[24] and the end date was a convenient date corresponding to the initiation of the study. The Logipren software is used for standardized prescriptions of drugs with reference to a database of regularly updated therapeutic protocols. Patients in palliative care or who died before discharge from hospital were excluded from the study because of a different use of analgesics and sedatives in this context with possibly higher doses used. Patients who had a period of mechanical ventilation in another hospital before their local NICU admission were excluded because of the difficulty to obtain baseline characteristics regarding previous analgo-sedation use.

2.2 | Ethics

Parents of patients were informed on admission in the NICU of the possibility of anonymously using the data related to the hospitalization of their children. The data were collected in a pseudonymized database. The local ethics committee of the Centre Hospitalier Intercommunal of Créteil approved this study in February 2021 (Approval number no. 2021-02-02).

2.3 | Administration of sedation and analgesia

A protocol for the use of sedation and analgesia during mechanical ventilation was available and recommended in the NICU during the study (Appendix 1). Briefly, if mechanical ventilation was expected to last longer than 12 h and the neonate presented signs of pain or discomfort, continuous infusion of morphine was recommended. If the neonate remained agitated or uncomfortable continuous infusion of midazolam could be introduced in the absence of hemodynamic compromise. Midazolam use as a single agent was discouraged. When morphine +/− midazolam did not achieve enough comfort for the patient, dexmedetomidine could be added.

The contraindications to the introduction of this treatment and indications to discontinue treatment were bradycardia <120/min or hemodynamic disorders. Dexmedetomidine was introduced with a loading dose of 0.05 μg/kg over 30 min followed by a maintenance dose of 0.05 μg/kg.[21] Doses were titrated in increments of 0.05 μg/kg/h every 12 h with a maximum of 0.4 μg/kg/h.

If possible, morphine treatment was stopped at least 6 h before extubation and extubation could only take place if the spontaneous ventilation of the child, as assessed by triggering of the ventilator, was satisfactory. The treatment with midazolam, if introduced, was also stopped before extubation.

2.4 | Data collection

We collected baseline data on pregnancy, birth, and early neonatal history.

We extracted data on duration of treatment and doses prescribed from the Logipren® prescriptions software for dexmedetomidine, morphine, and midazolam. For these treatments, the studied period started at intubation and ended 48 h after dexmedetomidine discontinuation in the dexmedetomidine group and 48 h after morphine discontinuation in the control group. The cumulative doses (μg/kg) for each medication were calculated by summing all maintenance doses (μg/kg/h) x the number of hours of treatment. We collected dexmedetomidine's interruption due to adverse events. When a treatment is stopped in this software, the prescriber must specify the cause of this interruption, which makes it possible to determine whether a treatment has been stopped for an adverse effect or for another reason.

In the dexmedetomidine group, we retrieved doses of morphine, midazolam, and dexmedetomidine from 3 days before the introduction of dexmedetomidine to 5 days after the introduction of the treatment to describe the evolution of morphine and midazolam doses before and after the introduction of dexmedetomidine.

The following outcomes were collected:

1. Respiratory outcomes: bronchopulmonary dysplasia at 36 weeks of corrected gestational age (according to Walsh criteria[25]), total duration of mechanical ventilation (days), total duration of noninvasive ventilation (NIV, days), and extubation failure corresponding to reintubation within 48 h after extubation;
2. Neurological outcomes: grade III or IV intraventricular hemorrhage (IVH) according to Papile's classification[26] at 36 weeks of corrected gestational age.
3. Digestive outcomes: age at full enteral feed corresponding to the postnatal age at removal of central line.

2.5 | Statistical analysis

Results were reported using the median and interquartile range (IQR) for quantitative data and the number and percentage for qualitative data. Comparison between the two groups (with or without dexmedetomidine) were made using Chi2 tests or Fisher's tests for categorical variables and Student's *t*-tests for continuous variables. A *p*-value <0.05 was considered statistically significant. Statistics were performed on the R software, version 4.0.5. There was no missing data for the outcomes.

3 | RESULTS

3.1 | Population

Between July 2017 and June 2020, 212 neonates weighing less than 1000 g and/or less than 28 weeks of gestation were hospitalized in neonatal intensive care at Créteil's NICU.

Of these, 139 were excluded (Figure 1), yielding to a cohort of 29 neonates who received both morphine and dexmedetomidine (dexmedetomidine group) and 44 who received morphine without dexmedetomidine (control group).

3.2 | Description of patients' characteristics

The baseline characteristics of patients from both groups are in Table 1. The group treated with dexmedetomidine, as compared to the control group, had a significantly higher rate of vascular complications during pregnancy (59% vs. 25%, $p=0.008$) and of intrauterine growth restriction (45% vs. 16%, $p=0.01$). There was no significant difference for other baseline characteristics (Table 1).

3.3 | Characteristics of dexmedetomidine use

Dexmedetomidine was introduced at a median [IQR] postnatal age of 25 days [19–32] (Table 2). All neonates received a loading dose of 0.05 μg/kg over 30 min before initiating an initial maintenance dose with a median [IQR] dose of 0.05 μg/kg/h [0.05–0.05]. Thereafter, doses were increased to a maximum dose of 0.4 μg/kg/h, with a median [IQR] dose of 0.25 [0.2–0.3] μg/k/h. All our patients were monitored for cardiac rate and blood pressure, and dexmedetomidine treatment was never discontinued due to the occurrence of bradycardia or hypotension. The cumulative morphine dose was higher before than after the introduction of dexmedetomidine with a median [IQR] of 5114 [2921–6818] μg/kg and 1850 [907–5482] μg/kg, respectively. Of the 29 patients who received dexmedetomidine, 27 (93%) were extubated on dexmedetomidine. Dexmedetomidine was usually weaned off every 12–24 h.

3.4 | Morphine, midazolam, and dexmedetomidine doses over time

The evolution of morphine, midazolam, and dexmedetomidine doses over time before and after dexmedetomidine introduction

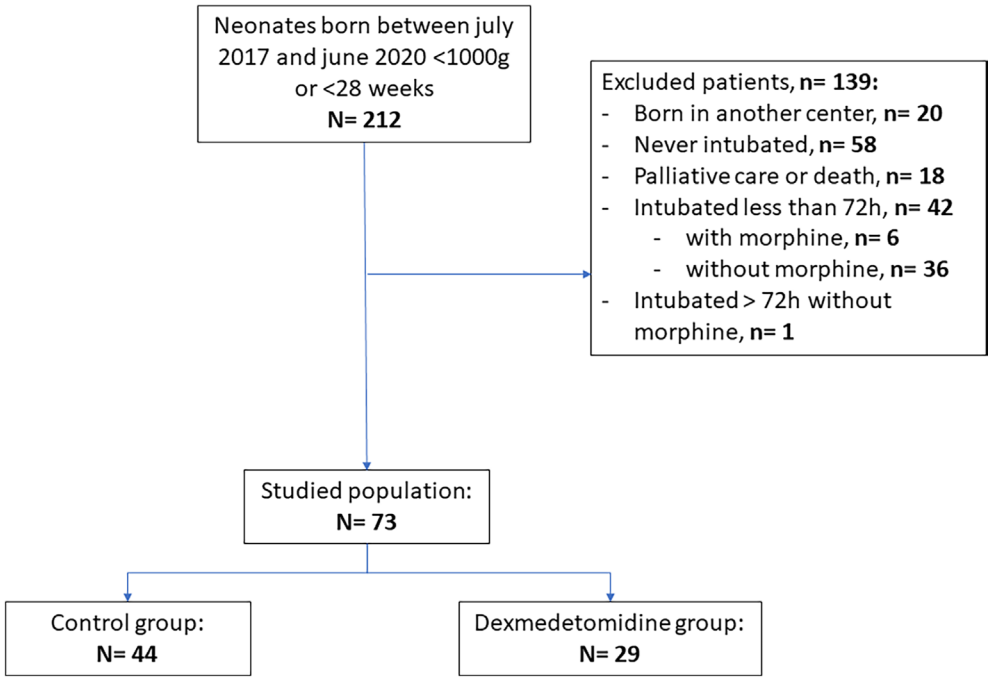

FIGURE 1 Population flow chart.

are in Figure 2. Morphine doses tended to increase before the introduction of dexmedetomidine and decreased after the start of dexmedetomidine. Midazolam doses tended to increase before the introduction of dexmedetomidine. These doses were reduced at the time of dexmedetomidine introduction and continued to decrease over time afterwards.

3.5 | Morphine and midazolam use in the dexmedetomidine and control groups

A comparison of doses and duration of treatment for morphine and midazolam is displayed in Table 3. The dexmedetomidine group had significantly higher morphine cumulated doses and longer morphine exposure than the control group during the whole studied episode and also before and after extubation. When cumulative doses were adjusted on the duration of treatment by calculating mean daily doses of morphine, the difference between the two groups was reduced but still significantly different: median [IQR] 335 [232–447] μg/kg/d in the dexmedetomidine group versus 225 [164–350] μg/kg/d in the control group, $p=0.01$. There was no significant difference in the cumulated midazolam doses or duration of midazolam use between groups.

3.6 | Outcomes

A comparison of clinical outcomes for the two groups is shown in Table 4. Total durations of mechanical ventilation and noninvasive ventilation during hospital stay were significantly longer in the dexmedetomidine group than in the control group (16.8 [10.2–24.7] vs. 11.6 [7–18.2] days, $p=0.03$ and 45.2 [33.8–58.7] vs. 40.7 [33.3–49.9] days, $p=0.03$, respectively). Extubation failure rates at 48 h were 17% and 9% in the dexmedetomidine and control groups, respectively ($p=0.47$). There was more bronchopulmonary dysplasia at 36 weeks in the group receiving both dexmedetomidine and morphine (79% vs. 41%, $p<0.001$) but there was no significant difference on other outcomes, especially on age to full enteral feed.

4 | DISCUSSION

This study reporting the use of dexmedetomidine in a specific population of ventilated extremely premature infants receiving continuous morphine, provides useful information on doses and shows a good tolerance of the drug. Specifically, no treatment interruption was observed due to adverse effects and dexmedetomidine could be continued after extubation, supporting its absent or negligible respiratory-depressive effect in this population. The introduction of dexmedetomidine in this cohort of patients largely exposed to morphine was accompanied with progressive reduction of morphine and midazolam dose over time.

Due to the local protocol, we could not control for indication bias between the dexmedetomidine and the control group, resulting in differences at baseline and in outcomes. Infants in the dexmedetomidine group had a higher rate of IUGR at birth, received more cumulated doses and a longer duration of morphine, and had a higher rate of BPD. Nevertheless, cumulated midazolam doses, extubation failure rate, and severe IVH were not significantly different from those observed in the control and less severe group. These results

TABLE 1 Characteristics of patients.

	Dexmedetomidine group, $n=29$	Control group, $n=44$	p-Value*
Obstetrical characteristics			
Cause of preterm birth			
Vascular disorders	17 (59%)	11 (25%)	**0.008**
Preterm labor	9 (31%)	24 (55%)	0.08
PROM	6 (21%)	16 (36%)	0.24
Prenatal steroids	26 (90%)	40 (90%)	1
Cesarean section	17 (59%)	20 (45%)	0.39
Neonatal characteristics			
Gender (female)	18 (62%)	23 (53%)	0.56
Gestational age at birth	25.7 [25.1–26.7]	25.6 [24.9–26.4]	0.21
Birth weight (g)	680 [600–750]	710 [642,5–791]	0.13
IUGR[a]	13 (45%)	7 (16%)	**0.01**
5 min APGAR score	9 [6–10]	9 [8–10]	0.07
Early neonatal course			
Surfactant therapy	28 (96%)	37 (84%)	0.2
Early Low-Dose Hydrocortisone Therapy	18 (62%)	33 (75%)	0.36
Early onset sepsis	1 (3%)	5 (11%)	0.39
Studied period of mechanical ventilation	2 [1–2]	2 [1–2]	0.14
PMA at the start of studied period of mechanical ventilation (weeks)	26.7 [25.9–29]	27.1 [25.6–28.8]	0.78
Inotropic agents	18 (62%)	27 (61%)	1
Volume expansion	7 (24%)	5 (11%)	0.2
Persistent ductus arteriosus requiring treatment	21 (72%)	30 (68%)	0.9
Pharmacological (acetaminophen)	13 (45%)	19 (43%)	1
Surgical ligation	8 (28%)	11 (25%)	1
Treatments			
Age at introduction of morphine (d)	9 [2–27]	8 [2–15]	0.26
PMA at introduction of morphine (weeks)	27.1 [26–29]	27.3 [25.9–29.4]	0.3
Age at introduction of dexmedetomidine (d)	25 [19–32]		
PMA at introduction of dexmedetomidine (weeks)	29.4 [28.3–30.7]		

[a]Defined by an AUDIPOG score ≤ 10th percentile at birth.[33]

*Chi2 or Fisher test for categorical variables and Student's t tests for continuous variables.

Note: Results are presented as N (%) or median [IQR], as appropriate. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: IUGR, intra-uterine growth restriction; PMA, post menstrual age; PROM, premature rupture of membranes >12 h.

must be interpreted cautiously because of the small sample size but are not in favor of a major toxicity of dexmedetomidine in the short-term.

Our study highlights the existence in NICUs of a population largely exposed to opioids due to the need of prolonged mechanical ventilation for severe respiratory disease, and for whom appropriate sedation and analgesia can be an issue during their stay. Similarly, a recent large observational cohort study reported that neonates exposed to dexmedetomidine were born more immature, had a lower birth weight, longer length of hospitalization, more opioid exposure, and more days of mechanical ventilation.[27] This cohort reported an increased use of dexmedetomidine from 2010 to 2020 and a decrease in opioid exposure.

The spice III study in adults[28] shows that the younger and sicker the patient, the higher the mortality. However, we know that studies carried out in adults, notably because of their totally different pharmacodynamics and pharmacokinetics, cannot be extrapolated to children, and even less so to neonates. To date only a few other studies reported the use of dexmedetomidine in a population comparable to ours.[20,21] In the other cohorts described in the literature, populations differed from ours. In the retrospective study by Dersch-Mills et al.[16] the cohort included 38 neonates, 17 of whom were born before 37 weeks' gestation with mainly surgical patients (79%). In the retrospective study by O'Mara et al, 19 patients were term born and dexmedetomidine was used in the context of hypothermia for neonatal encephalopathy.[30] The only safety and efficacy study performed in neonates included neonates from 28 weeks of gestation.[21] O'Mara et al. also conducted a retrospective case–control study comparing dexmedetomidine ($n=24$) versus fentanyl ($n=24$) in extremely premature infants before 48 h of life. They reported no significant adverse events and a drastic decrease in the duration of invasive ventilation in the dexmedetomidine-treated group.[23] A retrospective study by Nakauchi et al.[29] showed no significant differences for death at the age of three between the use of fentanyl versus dexmedetomidine. An originality of our study was to describe the possible use of dexmedetomidine in extremely premature neonates born <28 weeks and extremely low birth weight on prolonged mechanical ventilation and prolonged opioid exposition, which provides

TABLE 2 Description of doses and durations of dexmedetomidine treatment in the dexmedetomidine group ($n = 29$).

Characteristics of dexmedetomidine treatment	Median [interquartile range]
Postnatal age at introduction (d)	25 [19–32]
Postmenstrual age at introduction (weeks)	29.6 [28.4–30.4]
Loading dose (μg/kg)	0.05 [0.05–0.05]
Cumulative dose before extubation (μg/kg)	5.3 [1.4–19.4]
Cumulative dose before extubation (μg/kg/d)	1.06 [0.67–2.15]
Cumulative dose after extubation (μg/kg)	17 [8.2–27.3]
Cumulative dose after extubation (μg/kg/d)	0.22 [0.05–0.89]
Cumulative dose over the study period[a] (μg /kg)	23.9 [15.7–51.5]
Cumulative dose over the study period (μg/kg/d)	0.71 [0.34–1.38]
Initial maintenance dose (μg /kg/h)	0.05 [0.05–0.05]
Maximum maintenance dose (μg/kg/h)	0.25 [0.2–0.3]
Duration of treatment after extubation (d)	3.8 [2.8–5.2]
Duration of treatment over the study period (d)[a]	6 [4.9–8.9]
Duration of ventilation before dexmedetomidine introduction (d)	6 [9.5–24.5]
Cumulative dose of morphine before dexmedetomidine introduction (μg/kg)	5114 [2921–6818]
Cumulative dose of morphine after dexmedetomidine introduction (μg/kg)	1850 [907–5482]

[a]The study period started at intubation and ended after 48 h of drug discontinuation.

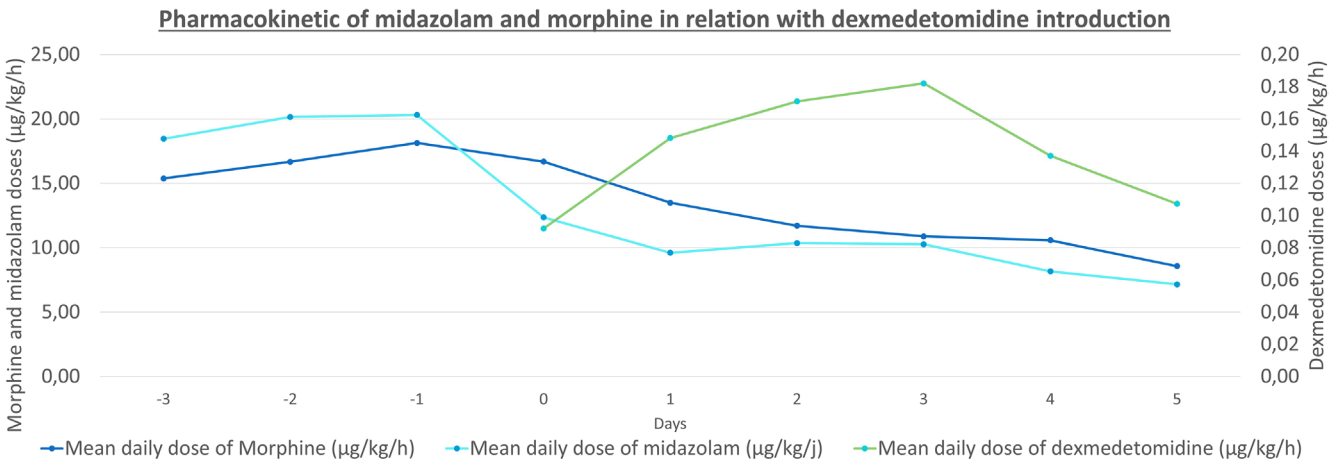

FIGURE 2 Mean maintenance doses of morphine, midazolam and dexmedetomidine over time. Day 0 corresponds to dexmedetomidine introduction.

additional information. Concerning doses used, cohorts in the literature reported different dosing regimen.[18,23,31] The initial dose was 0.2 to 0.3 μg/kg/h and then increasing in steps of 0.1 μg/kg/h up to maximum doses of 0.5 to 1 μg/kg/h according to the cohorts. At these doses, bradycardia and hypotension were described but a reduction in dose was sufficient to resolve these haemodynamic effects. In contrast, in the phase II/III study by Chrysostomou et al., which is one of[21,32] the only pharmacokinetic study so far involving 42 neonates from 28 to 44 weeks of gestation, the doses ranged from 0.05 μg/kg/h to 0.2 μg/kg/h. With these doses, the tolerance of dexmedetomidine treatment was good. In another pharmacokinetic study involving neonates born between 34 and 40 weeks, a dose of 0.4 μg/kg/h resulted in adequate exposure in treated neonates.[32] In our cohort, the initial dose was of 0.05 μg/kg/h after a 0.05 loading dose, rising to a maximum of 0.4 μg/kg/h. Similarly, the treatment was well tolerated in our patients. The maximum dose and the need for a loading dose in a population of extremely preterm infants are not known to date and pharmacokinetic/pharmacodynamic studies are necessary to determine the optimal doses according to gestational age and postnatal age.

In the literature, dexmedetomidine was mainly used in mechanically ventilated neonates and very rarely in noninvasive ventilation.[16] In our study, the cumulative postextubation dose and duration of dexmedetomidine use was greater than the cumulative preextubation dose, with median (IQR) postextubation doses of 17 μg/kg (8.2–27.3) and preextubation doses of 5.3 μg/kg (1.4–19.4), respectively.

TABLE 3 Comparison of morphine and midazolam doses and duration of treatment.

Drugs	Doses and duration	Dexmedetomidine group, *N* = 29	Control group, *N* = 44	*p*-Value*
Morphine	Duration of use over the study period[a] (days)	20.3 [14.5–36.4]	11.2 [4.9–19.8]	**<0.001**
	Duration of use postextubation (days)	6.4 [2–10]	0.4 [0–3.8]	**<0.001**
	Cumulative dose over the study period[a] (μg/kg)	7699 [4240–9009]	1835 [953–5350]	**0.003**
	Mean daily dose over the study period[a] (μg/kg/d)	335 [232–447]	225 [164–350]	**0.01**
	Cumulative preextubation dose (μg/kg)	5604 [3678–7800]	1835 [953–5165]	**0.01**
	Mean daily preextubation dose (μg/kg/d)	325 [255–486]	211 [117–349]	**0.002**
	Cumulative postextubation dose (μg/kg)	733 [90–2071]	0 [0–324]	**0.006**
	Mean daily postextubation dose (μg/kg/d)	144 [61–215]	0 [0–94]	**0.01**
Midazolam	Duration of use over the study period[a] (days)	9 [3.5–15.7]	5.35 [2.98–10.7]	0.15
	Cumulative dose over the study period[a] (μg/kg)	2611 [935.5–6441.5]	1965 [699–3782]	0.42
	Mean daily dose over the study period[a] (μg/kg/d)	357 [272–447]	341 [233–494]	0.8

*Chi2 or Fisher test for categorical variables and Student's *t* tests for continuous variables.

[a]The study period started at intubation and ended after 48 h of drug discontinuation.

Note: Number (percentage) for qualitative data, Median [interquartile] for quantitative data. Bold values denote statistical significance at the $p < 0.05$ level.

TABLE 4 Comparison of clinical outcomes between the dexmedetomidine and control groups.

		Dexmedetomidine group, *N* = 29	Control group, *N* = 44	*p*-Value*
Respiratory	Total duration of mechanical ventilation over the study period[a] (days)	16.8 [10.2–24.7]	11.6 [7–18.2]	**0.03**
	Failed extubation for the studied episode[b]	5 (17%)	4 (9%)	0.47
	Total NIV duration during hospital stay (days)	45.2 [33.8–58.7]	40.7 [33.3–49.9]	**0.03**
	BPD at 36 weeks postmenstrual age	23 (79%)	18 (41%)	**<0.001**
Digestive	Age at full enteral feed (days)	44 [35.7–52.5]	46 [36.5–53]	0.65
Neurology	IVH (≥grade III) at 36 weeks postmenstrual age	3 (10%)	1 (2%)	0.29

[a]The study period started at intubation and ended after 48 h of drug discontinuation.

[b]Defined as reintubation within 48 h of extubation.

*Chi2 or Fisher test for categorical variables and Student's *t* tests for continuous variables.

Note: Number (percentage) for qualitative data, Median [interquartile] for quantitative data. Bold values denote statistical significance at the $p < 0.05$ level.

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intra ventricular hemorrhage; NIV, Noninvasive ventilation.

This was in favor of the possible use of dexmedetomidine in noninvasive ventilation patients and therefore in agreement with the data in the literature which described the absence of respiratory depressant effects in contrast to morphine.[32]

Some studies have suggested an opioid-sparing effect of dexmedetomidine and a decreased number of days to full enteral feeding.[17,18,23] We could not evaluate these effects in our cohort because of an indication bias with patients on dexmedetomidine already receiving much more morphine before dexmedetomidine introduction. Our study was not designed to demonstrate a reduction in opioids and benzodiazepines use but to describe a practice. However, morphine and midazolam doses decreased at the start of dexmedetomidine in our cohort. Concerning digestive outcomes in our cohort, even though morphine doses were much higher in the dexmedetomidine group, there was no difference in time to full enteral feeds between both groups. This result was encouraging even though not sufficient to conclude on a positive effect of dexmedetomidine use on digestive outcomes. Also, patients

received a significantly higher cumulative dose of morphine after extubation in the dexmedetomidine group. This could have led to a higher risk of extubation failure in this group, which was not the case in our comparison. Similarly, literature data seem to suggest the absence of an effect of dexmedetomidine on respiratory drive at doses used in neonates.[17,18]

Our study had several limitations. First, it was limited by the fact that we could not compare the dexmedetomidine/morphine group to the control group due to indication bias in our cohort. A historical cohort might have provided a comparable control group, but we did not have the detailed treatment data available until July 2017. Also, we did not have data on indication of mechanical ventilation to further compare the characteristics of our groups. Another limitation is the lack of data on pain and withdrawal assessment. Finally, we have described the use of dexmedetomidine in a relatively small cohort (29 patients). Our groups were too small to do more than a simple comparison analysis. However, there is little use of dexmedetomidine reported in the literature to date in extremely preterm infants.

5 | CONCLUSION

This study reported the possibility of using dexmedetomidine in extremely preterm infants born below 28 weeks of gestation with good tolerance. The population treated in this study was a specific population of patients with severe respiratory pathology, requiring prolonged mechanical ventilation, and high doses of morphine. Our study found low extubation failure rates and proved the feasibility of dexmedetomidine use during noninvasive ventilation, supporting the limited or absent respiratory depressive effect of this drug. Our results also suggested a decrease of morphine and midazolam doses after initiation of dexmedetomidine treatment. There is no clear consensus to date on the best alternative to opioids and benzodiazepines use during invasive ventilation in NICUs. Further studies, including pharmacokinetic/pharmacodynamic studies and data on short-term safety and long-term neurodevelopment, followed by randomized controlled trials, are needed to determine the place of dexmedetomidine in the sedation-analgesia of preterm neonates.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest related to this study to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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APPENDIX 1

DEXDOR (Dexmedetomidine) protocol
Dexmedetomidine: α 2 agonist
Indication: Exceptional situation of addiction, tachyphylaxis or contraindication to morphine and/or benzodiazepines, after collegial discussion and information of the parents: Trade name: Dexdor®, vial of 2 mL = 200 µg
Contraindications: Bradycardia <120/min, hemodynamic disorders, hepatic cytolysis >2 N
Loading dose: 0.05 µg/kg over 15 min
Proposed starting dose: 0.05 µg/kg/hr continuous IV
Dosage adjustment according to behavioral scores. Dose change increments are 0.05 µg/kg/h to a maximum dose of 0.4 µg/kg/h Discontinue if bradycardia <100/min or hypotension occurs.