Association of Continuous Opioids and/or Midazolam During Early Mechanical Ventilation with Survival and Sensorimotor Outcomes at Age 2 Years in Premature Infants: Results from the French Prospective National EPIPAGE 2 Cohort

Marie-Amélie de Tristan, MD, MSc[1], Laetitia Martin-Marchand, MSc[1], Jean-Michel Roué, MD, PhD[2], Kanwaljeet J. S. Anand, MBBS, D.Phil[3], Véronique Pierrat, MD, PhD[1,4], Pierre Tourneux, MD, PhD[5], Pierre Kuhn, MD, PhD[6], Christophe Milesi, MD[7], Valérie Benhammou, PhD[1], Pierre-Yves Ancel, MD, PhD[1], Ricardo Carbajal, MD, PhD[1,8,9], and Xavier Durrmeyer, MD, PhD[1,10,11]

Objective To evaluate the association of early continuous infusions of opioids and/or midazolam with survival and sensorimotor outcomes at age 2 years in very premature infants who were ventilated.

Study design This national observational study included premature infants born before 32 weeks of gestation intubated within 1 hour after birth and still intubated at 24 hours from the French EPIPAGE 2 cohort. Infants only treated with bolus were excluded. Treated infants received continuous opioid and/or midazolam infusion started before 7 days of life and before the first extubation. Naive infants did not receive these treatments before the first extubation, or received them after the first week of life, or never received them. This study compared treated (n = 450) vs naive (n = 472) infants by using inverse probability of treatment weighting after multiple imputation in chained equations. The primary outcomes were survival and survival without moderate or severe neuromotor or sensory impairment at age 2 years.

Results Survival at age 2 years was significantly higher in the treated group (92.5% vs 87.9%, risk difference, 4.7%; 95% CI, 0.3-9.1; *P* = .037), but treated and naive infants did not significantly differ for survival without moderate or severe neuromotor or sensory impairment (86.6% vs 81.3%; risk difference, 5.3%; 95% CI –0.3 to 11.0; *P* = .063). These results were confirmed by sensitivity analyses using 5 alternative models.

Conclusions Continuous opioid and/or midazolam infusions in very premature infants during initial mechanical ventilation that continued past 24 hours of life were associated with improved survival without any difference in moderate or severe sensorimotor impairments at age 2 years. *(J Pediatr 2021;232:38-47)*.

No sedation" strategies in adults receiving mechanical ventilation usually include intermittent analgesia because mechanical ventilation causes discomfort.[1] Because of widespread concerns about developmental neurotoxicity, however, many neonates receive mechanical ventilation without any sedation or analgesia.[2] A European cohort study in 2012-2013 of 2142 neonates undergoing invasive ventilation reported that 18% received no analgesic, sedative-hypnotic, or anesthetic treatment.[3] The current evidence does not support the routine use of opioids or midazolam in neonates undergoing mechanical ventilation.[4,5] In 2019, however, clinical guidelines recommended continuous opioids for premature infants undergoing prolonged mechanical ventilation, based on a moderate level of evidence.[6] The limited evidence of the risk/benefit ratio for opioid and sedative use indicates that current practices are heterogeneous.[3] Analgesia/sedation is justified for ethical reasons and by the poorer long-term neurodevelopmental outcomes associated with repeated or prolonged painful experiences in the neonatal period.[7] In contrast, follow-up studies of randomized controlled trials comparing opioids with placebo in ventilated neonates and observational studies of neonatal opioid or sedative exposure provide conflicting results about their effects on neurodevelopment.[8-17]

This study was conducted to assess the risk of long-term neurotoxicity associated with start analgesia and/or sedation with continuous opioids/midazolam in the early course of a ventilated infant. Therefore, we analyzed the association be-

IPTW	Inverse probability of treatment weighting

From the [1]Center of Research in Epidemiology and Statistics, University of Paris, CRESS, INSERM, INRA, Paris; [2]Neonatal Intensive Care Unit, University Hospital of Brest, Brest, France; [3]Department of Pediatrics, Anesthesiology, Perioperative & Pain Medicine, Stanford University School of Medicine, Stanford, CA; [4]Department of Neonatal Medicine, Jeanne de Flandre Hospital, Lille University Hospital, Lille; [5]Neonatal Intensive Care Unit, CHU Amiens – University of Picardie Jules Verne, Amiens; [6]Neonatal Intensive Care Unit, CHU Strasbourg, France, University of Strasbourg, INSERM, Institute of Cellular and Integrative Neurosciences, Strasbourg; [7]Pediatric and Neonatal Intensive Care Unit, University Hospital of Montpellier, Montpellier; [8]Pediatric Emergency Department, Assistance Publique des Hôpitaux de Paris, Armand Trousseau Hospital, Paris; [9]Sorbonne University, Faculty of Medecine, Paris; [10]Neonatal Intensive Care Unit, Hospital Center Intercommunal Créteil, Créteil, France; and [11]University of Paris East Créteil, Faculty of Medecine, Mondor Biomedical Research Institute, Cardiovascular and Respiratory Manifestations of Acute Lung Injury and Sepsis Clinical Research Group, Créteil, France

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tween treatment with continuous opioids and/or midazolam during early mechanical ventilation and survival and sensorimotor outcomes at age 2 years among very premature infants still intubated after 24 hours of life. We hypothesized that infants treated with opioids and/or midazolam would have survival rates and sensorimotor outcomes similar to those of infants who were not treated, after adjustment for the probability of treatment.

Methods

The Etude éPIdémiologique sur les Petits Ages GEstationnels 2 (EPIPAGE 2) study is a nationwide, prospective, observational, longitudinal birth-cohort study that recruited premature infants from March through December 2011.[18,19] Infants born at 22-26 weeks of gestation were recruited over 8 months, those born at 27-31 weeks of gestation over 6 months, and those born at 32-34 weeks of gestation during a 5-week period.[18] All survivors were enrolled for longitudinal follow-up and included in the study at 2 years' corrected age if parents consented.[20] Infants eligible for this study were born between 23 and $31^{6/7}$ weeks of gestation, were intubated in the delivery room or within the first hour of life, and remained intubated for >24 hours after birth. They were excluded if born with major congenital abnormalities or if the start date for opioid and/or midazolam treatment was missing.[21] Acknowledging that continuous analgesia and/or sedation were the preferred modalities in France and that boluses of opioids or midazolam were at risk of adverse events, we excluded infants treated with boluses only.[3,22-24] However, add on boluses during continuous opioids and/or midazolam administration were possible. Infants with a decision to limit or withhold care in the first week of life were also excluded because midazolam and/or opioids use in these infants was possibly part of palliative care, which was outside the scope of the present study.

Treated infants were those who received a continuous infusion of opioids and/or midazolam at some point during this first intubation period, before the age of 7 days. The naive group comprised those infants who did not receive a continuous infusion of opioids and/or midazolam during this first intubation; or who received these treatments only after the age of 7 days or after their first extubation (whichever came first); or never received these treatments. The treated and naive populations were defined using these criterions to mimic an interventional trial, that is, without knowing possible later exposure to the studied drugs during the patient's clinical course.

This study focused on the first episode of invasive ventilation after birth because, although guidelines recommend and current practices corroborate early extubation of intubated infants rapidly after birth, a common clinical question is whether to start analgesic and/or sedative treatment when extubation has not occurred soon after birth.[6,25,26] In addition, we deemed this approach necessary for our data to be comparable with those from randomized controlled trials on this topic, which included intubated neonates in their first hours or days after birth.[27,28]

Outcomes

The 2 primary outcomes were death before corrected age 2 years and survival at this age without moderate or severe neuromotor or sensory disabilities, as previously defined.[20] Data for cerebral palsy, vision, and hearing were obtained from medical reports available at the age 2 examination. Cerebral palsy was defined according to the diagnostic criteria of the Surveillance of Cerebral Palsy in Europe network, and motor ability was graded with the 5-level Gross Motor Function Classification System.[29,30] Sensory disability was defined by deafness or blindness, and was considered to be moderate (unilateral) or severe (bilateral). Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment. Children without severe or moderate neuromotor or sensory disabilities had either no or minor neuromotor or sensory disabilities.

Secondary outcomes included outcomes at hospital discharge: survival without severe morbidities, severe brain abnormalities on brain ultrasound before discharge (defined as grade III or IV intraventricular hemorrhage and/or periventricular leukomalacia), cumulative mechanical ventilation duration, and length of hospitalization for infants surviving to discharge.[19] They also included 2 outcomes at 2 years' corrected age: cerebral palsy and an Ages and Stages Questionnaire score below threshold defined as a score of <2 SDs below the mean on any of the 5 domains (communication abilities, gross and fine motor skills, problem solving abilities, and personal-social skills).[31]

Statistical Analyses

A propensity score approach was used to control for the nonrandom assignment of patients to the treated or naive groups. The propensity score was defined as the infant's probability of exposure to continuous opioids and/or midazolam based on his/her individual observed covariates and estimated with a logistic regression model. In this model, opioid and/or midazolam treatment was the dependent variable and was studied in relation to the baseline characteristics clinically or statistically associated with the exposure and/or the outcome. The propensity score included the following covariates: gestational age; sex; intrauterine growth restriction (birth weight <10th percentile for gestational age and sex, based on the French "EPOPé" intrauterine growth curves); cause of prematurity in 4 classes: preterm premature rupture of membranes, preterm labor, hypertensive disorders, and other causes (eg, placental abruption, triplet or quadruplet births); antenatal steroid use; prenatal magnesium sulfate use; delayed cord clamping; inborn status; mode of delivery (cesarean or vaginal); maternal anesthesia (general, epidural, or no anesthesia); birth asphyxia defined

as a 5-minute Apgar score of <7 or base deficit of <7 in the first 12 hours of life; number of doses of surfactant received (0, 1, or ≥2); caffeine treatment in the first 2 days of life; maternal age (<25, 25-35 or >35 years); mother's country of birth (France or elsewhere); parity; number of children (singleton or multiple); and family socioeconomic status, defined as the highest occupational status of the mother and father, or the mother only if she was a single parent, divided into 4 categories: management jobs, public and administrative jobs, workers, or no job declared.[32] We also included in the model the volume of activity of the unit where the infant was born, defined by the number of infants included in the EPIPAGE 2 study in the unit, divided into terciles.

The main analysis used inverse probability of treatment weighting (IPTW) to attribute different weights to children according to their propensity score, that is, their probability of assignment to receive opioid and/or midazolam treatment. By this weighting, we created a synthetic sample (IPTW sample) in which treatment assignment was independent of measured baseline covariates.[33,34] Balance in the observed baseline covariates between treated and naive patients in the initial and IPTW samples was assessed by examining standardized differences. A standardized difference of <10% is considered an acceptable imbalance between groups.[35]

In the initial sample, all percentages were weighted to take differences in the recruitment periods into account for infants born at 24-26 weeks and 27-31 weeks. Comparisons between groups for treatment exposure through hospital discharge used the Rao–Scott F-adjusted χ^2 test.

Differences in outcomes between groups were expressed as risk differences calculated with a generalized estimating equation regression analysis to take the center effect into account. Survival in both groups was estimated by Kaplan-Meier survival curves and compared with Cox models in the IPTW sample. All tests were 2-sided and P values of <05 were considered significant.

Missing data were handled with multiple imputations using chained equations with the R package 'mice.' Imputation model variables included exposure to continuous opioids and/or midazolam, propensity score variables, and outcomes. Categorical variables were imputed by using logistic or multinomial regression and continuous variables by a linear regression model. We generated 50 independent imputed datasets with 30 iterations each, pooled according to the Rubin rule.[36]

All analyses were performed with R (version 3.6.1; The R Foundation) and SAS (version 9.4; SAS Institute) software packages.

Six sensitivity analyses, primarily intended to reduce the effect of extreme weights within the propensity score, were conducted by (a) symmetric trimming of weights, (b) asymmetric trimming of weights, (c) overlap weighting, (d) stabilized weights, (e) propensity score matching, and (f) negative control; that is, an outcome that is not expected to be different between groups such as the proportion of children with a weight inferior to the 10th percentile of the World Health Organization curve at the 2-year visit.[37-42]

We performed exploratory analyses similar to the main analysis in these subgroups defined a priori: (1) infants born before 29 weeks of gestation, (2) infants treated only with opioids in the treated group, (3) infants treated with midazolam in the treated group, and (4) only infants who never received continuous opioids and/or midazolam at any time in the naive group. A new propensity score was calculated in each of these specific populations.

Ethics

EPIPAGE 2 received approval from the National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés (CNIL) n°911009) and from 2 ethics committees: the consultative committee on the treatment of information on personal health data for research purposes (approval granted November 18, 2010, reference 10.626) and the committee for the protection of people participating in biomedical research (approval granted March 18, 2011, reference Comité de Protection des Personnes SC-2873).

Results

Population

The study included 922 of the 981 eligible infants born before 32 weeks of gestation and still intubated at 24 hours after birth (**Figure 1**). Baseline characteristics of the treated (n = 450) and naive (n = 472) groups before imputation are summarized in **Table I** (available at www.jpeds.com). **Table II** and **Figure 2** (available at www.jpeds.com) show the standardized differences between treated and naive groups in the initial and IPTW samples. Standardized differences ranged from 0.6 to 35.5 in the initial sample and were below 0.10 for all covariates after IPTW. Distributions of propensity scores and of weights are illustrated in **Figure 3**, A and B (available at www.jpeds.com), respectively, and show a substantial overlap.

Throughout their hospitalization, infants in the treated group were significantly more frequently exposed to the studied drugs than infants from the naive group (**Table III**) because 290 infants (63.7%) in the naive group never received continuous opioids or midazolam. In the first week after birth and before their first extubation, infants in the treated group received the following drugs, alone or in combination, by continuous infusion: sufentanil (n = 241); midazolam (n = 161), which was the only sedative used; morphine (n = 125); and fentanyl (n = 69). Among the 161 infants treated with midazolam, 34 received it alone and 127 received an association of midazolam and opioids. Some infants in the treated group also received continuous opioids and/or midazolam after day 7 or their first extubation but less frequently than those in the naive group (**Table III**). After their first extubation or after the

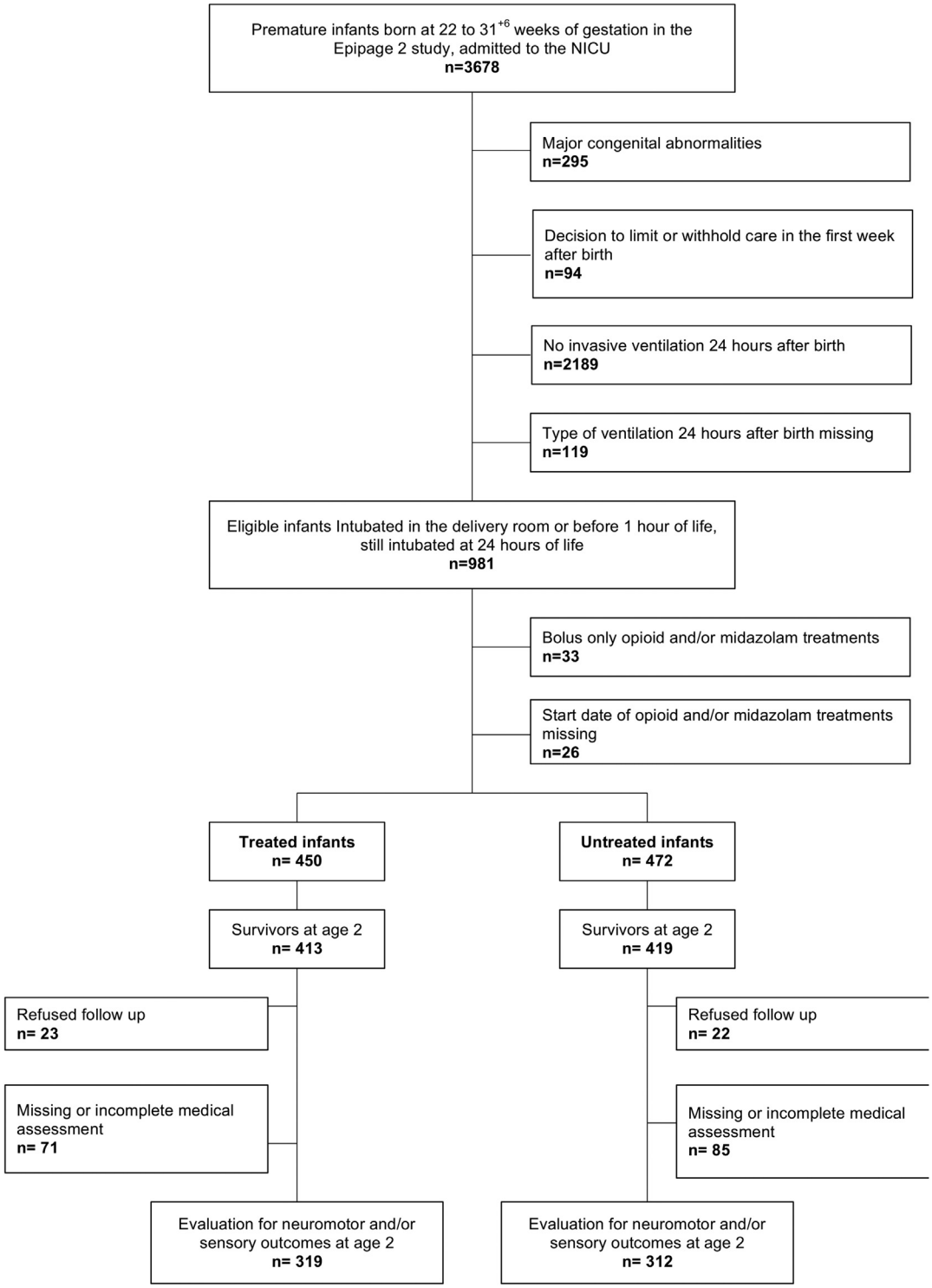

Figure 1. Population flow chart.

age of 7 days, 182 infants in the naive group received the following drugs alone or in combination: midazolam (n = 113), sufentanil (n = 97), morphine (n = 77), and fentanyl (n = 24) (**Table III**). Neuromotor and/or sensory status were imputed for 94 infants in the treated and 107 in the naive group.

Primary Outcomes

At 2 years' corrected age, survival was significantly higher in the treated group: 92.5% vs 87.9% in the naive group (adjusted risk difference, 4.7; 95% CI, 0.3-9.1; P = .037) (**Table IV**). Survival without moderate or severe neuromotor or sensory disabilities at that age was 86.6% in

Table II. Baseline characteristics of initial and IPTW samples and standardized differences between groups after imputation

	Samples after imputation and weighting					
	Initial sample, No. (%)*			IPTW sample, %†		
Clinical characteristics	Treated (n = 450)	Naive (n = 472)	SD, %	Treated (n = 450)	Naive (n = 472)	SD, %
Gestational age (wk)						
23	1 (0.2)	2 (0.3)	10.0	0.6	0.4	6.4
24	24 (4.4)	26 (4.5)		5.9	5.6	
25	68 (12.5)	69 (12.1)		14.2	15.1	
26	90 (16.6)	86 (15)		18.3	18.3	
27	68 (16.9)	84 (19.8)		16.5	16.4	
28	67 (16.6)	75 (17.6)		15.9	15.5	
29	59 (14.6)	59 (13.9)		12.1	12.8	
30	42 (10.4)	39 (9.2)		8.9	9.3	
31	31 (7.7)	32 (7.5)		7.7	6.6	
Small for gestational age‡	124 (28.3)	144 (31.0)	6.0	28.7	29.0	0.6
Boy	236 (52.7)	241 (51.6)	2.3	51.7	51.7	0.1
Birth asphyxia§	241 (53.3)	229 (47.4)	12.1	50.8	50.9	0.1
Vaginal delivery	165 (35.0)	166 (33.5)	2.9	35.5	36.2	1.4
Inborn status	361 (80.0)	399 (84.0)	10.3	81.3	82.0	1.9
Multiple birth	135 (29.2)	163 (34.6)	11.7	32.3	31.5	1.7
Antenatal steroids	269 (60.4)	301 (63.6)	6.8	60.9	59.9	2.0
Antenatal magnesium sulfate	26 (5.9)	35 (7.7)	7.4	6.8	6.8	0.1
Delayed cord clamping	6 (1.5)	33 (7.0)	27.6	4.6	4.2	1.6
Number of doses of surfactant						
None	12 (3.0)	24 (5.6)	29.6	4.1	4.0	1.4
1	242 (53.9)	304 (64.9)		57.8	57.3	
≥2	195 (43.0)	142 (29.5)		38.1	38.7	
Caffeine treatment in the first 2 days of life	204 (46.8)	296 (64.2)	35.5	53.5	53.8	0.6
Cause of prematurity						
Preterm labor	201 (43.7)	192 (40.6)	14.5	42.5	42.8	2.3
PROM	108 (23.5)	111 (22.4)		23.5	22.9	
Hypertensive disorders	111 (26.1)	117 (26.2)		24.4	25.2	
Other	30 (6.7)	52 (10.7)		9.5	9.1	
Maternal age (y)						
<25	111 (24.9)	116 (24.1)	2.1	25.4	24.3	2.4
25-35	266 (58.6)	277 (59)		59.2	60.0	
>35	73 (16.5)	79 (16.9)		15.5	15.6	
Primiparous	223 (48.8)	243 (51.6)	5.4	50.8	51.7	1.8
Maternal general anesthesia	79 (18.1)	86 (18.3)	0.6	17.8	18.2	1.0
Family socioeconomic status						
Executive jobs	103 (22.5)	75 (16)	19.4	19.5	20.1	1.6
Public and administrative jobs	189 (42.7)	238 (50.6)		46.5	46.2	
Workers	139 (31.2)	141 (29.8)		30.1	29.8	
No job declared	17 (3.6)	17 (3.6)		4.0	3.9	
Mother born in France	332 (73.5)	371 (79.0)	13.0	75.1	75.6	1.3
Volume of activity of the unit						
<55 infants	126 (28.6)	170 (36.0)	17.1	31.4	30.9	1.2
55-75 infants	146 (32.0)	146 (31.2)		31.5	31.6	
≥75 infants	178 (39.5)	156 (32.9)		37.0	37.5	

PROM, premature rupture of membranes.
For each variable, percentages might not sum up to 100%, owing to rounding.
*Data are presented as numbers (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take into account the differences in recruitment periods between gestational age groups.
†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.
‡Small for gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves (Ego 2016).
§Defined as a 5-minute Apgar score of <7 or a base deficit of <7 in the first 12 hours of life.

the treated group vs 81.3% in the naive group (adjusted risk difference, 5.3%; 95% CI, −0.3 to 11.0; $P = .063$) (Table IV).

Secondary Outcomes

At hospital discharge, survival without severe morbidity, severe brain abnormalities on brain ultrasound examination, duration of mechanical ventilation, and length of hospitalization did not differ significantly between the treated and naive groups (Table IV). Similarly, rates of cerebral palsy and Ages and Stages Questionnaire below threshold were not significantly different between the groups at age 2 years (Table IV).

Figure 4 (available at www.jpeds.com) presents the Kaplan-Meier mortality curves over the first 150 days in both groups. Over time, cumulative mortality was lower in the treated group (log rank test $P = .035$). In-hospital causes of death for the initial cohort are reported in Table V (available at www.jpeds.com).

Table III. Treatments with continuous opioids and/or midazolam through hospital discharge in the treated and naive groups

Drugs	No. (%)* Treated group (n = 450)	Naive group (n = 472)	*P* value†
No opioids or midazolam infusion	0 (0)	290 (63.7)	–
Sufentanil			
Total No. of treated patients	269 (59.4)	97 (19.0)	<.001
No. treated before first extubation or day 7	241 (55.2)	0	–
No. treated after first extubation or day 7	28 (5.5)	97 (19.0)	<.001
Median [IQR] age at treatment initiation, days	0 [0-1]	14 [8-24]	–
Cumulative duration of treatment			
No. with data available	264 (98.1)	96 (99.0)	–
Median [IQR], days	4 [2-10]	6 [2-13]	–
Morphine			
Total No. of treated patients	171 (37.3)	77 (14.9)	<.001
No. treated before first extubation or day 7	125 (27.7)	0	–
No. treated after first extubation or day 7	46 (9.6)	77 (14.9)	.013
Median [IQR] age at treatment initiation, day	0 [0-5]	19 [13-30]	–
Cumulative duration of treatment			
No. with data available	169 (98.8)	75 (97.4)	–
Median [IQR], day	8 [3-25]	9 [5-17]	–
Fentanyl			
Total No. of treated patients	74 (16.1)	24 (4.7)	<.001
No. treated before first extubation or day 7	69 (15.0)	0	–
No. treated after first extubation or day 7	5 (1.1)	24 (4.7)	.001
Median [IQR] age at treatment initiation, days	1 [0-2]	16 [8-28]	–
Cumulative duration of treatment			
No. with data available	73 (98.6)	24 (100)	–
Median [IQR], days	3 [1-10]	3 [2-9]	–
Midazolam			
Total No. of treated patients	239 (51.9)	113 (22.4)	<.001
No. treated before first extubation or day 7	161 (36.4)	0	–
No. treated after first extubation or day 7	78 (15.5)	113 (22.4)	.006
Median age [IQR] at treatment initiation, days	1 [0-11]	15 [12-25]	–
Cumulative duration of treatment			
No. with data available	234 (97.9)	113 (100)	–
Median [IQR], days	4 [2-10]	4 [2-11]	–

*Except for number of patients with data available, all percentages are weighted to take into account the differences in recruitment periods between gestational age groups. For each variable, percentages might not sum up to 100% owing to rounding.
†Rao-Scott F-adjusted χ^2.

Sensitivity and Subgroup Analyses

The survival rate at 2 years' corrected age was significantly higher in the treated group when symmetric or asymmetric trimming of weights and stabilized weights were used, but the difference between the groups did not reach statistical significance with overlap weighting or a propensity score-matched cohort (**Table VI**; available at www.jpeds.com). Survival without moderate or severe neuromotor or sensory disabilities at this age did not differ significantly between the groups in any sensitivity analyses (**Table VI**). The result with negative control showed that the proportion of infants with a weight below the 10th percentile of the World Health Organization curve was not significantly different between groups (32.5% in the treated vs 30.0% in the naive group; $P = .49$).[42]

The results of the exploratory subgroup analyses were consistent with the main analysis among infants born before 29 weeks' gestation (**Table VII**; available at www.jpeds.com), in the analysis including infants who received only continuous opioids in the treated group (**Table VIII**; available at www.jpeds.com), in the analysis including infants who received continuous midazolam in the treated group (**Table IX**; available at www.jpeds.com), and that including infants who never received continuous opioids and/or midazolam in the naive group (**Table X**; available at www.jpeds.com).

Discussion

In this nationwide comparative effectiveness study, continuous opioid and/or midazolam infusions during a first episode of invasive ventilation that started on day 1 were significantly associated with higher survival rates. Furthermore, no harmful effect on survival without moderate or severe sensorimotor impairment was observed at 2 years' corrected age.

Previous randomized trials in intubated premature infants reported that death rates did not differ significantly between morphine- and placebo-treated infants.[27,28,43] Hypotheses potentially explaining the better survival include the use of continuous infusion as opposed to boluses, the type of opioids used, or chance. In the NEOPAIN trial, morphine

Table IV. Results for primary and secondary exploratory outcomes in the initial and IPTW samples after imputation

Outcomes	Frequency or duration of events					
	Initial sample, No. (%)*			IPTW sample, %†		
	Treated group (n = 450)	Naive group (n = 472)	Risk or mean differences: Treated group *minus* naive group (95% CI)‡	Treated group (n = 450)	Naive group (n = 472)	Risk or mean differences: Treated group minus naive group (95% CI)‡
Primary outcomes						
Survival at 2 years	413 (92.3)	419 (89.7)	2.6 [–1.2 to 6.5]	92.5	87.9	4.7 [0.3 to 9.1]
Survival at 2 years without moderate or severe neuromotor or sensory disabilities§	385 (86.2)	390 (83.7)	2.6 [–2.3 to 7.4]	86.6	81.3	5.3 [–0.3 to 11.0]
Secondary exploratory outcomes						
Survival at discharge without severe neonatal morbidity¶	292 (66.7)	295 (64.8)	1.9 [–5.5 to 9.3]	66.2	59.9	6.4 [–1.9 to 14.6]
Outcomes at discharge						
Cumulative duration of mechanical ventilation (day)						
Median [IQR]	8 [3 to 21]	5 [2 to 16]	–	8 [3 to 22]	6 [2 to 21]	–
Mean (SD)	13.7 (13.9)	11.5 (14.3)	2.2 [–0.7 to 5.1]	14.4 (14.5)	13.0 (14.9)	1.3 [–2.1 to 4.8]
Duration of hospital stay, days						
Median [IQR]	80 [61 to 98]	76 [61 to 99]	–	81 [62 to 101]	79 [62 to 101]	–
Mean (SD)	83.0 (30.7)	81.4 (29.9)	1.6 [–3.4 to 6.6]	84.1 (31.0)	85.1 (31.4)	1.0 [–4.7 to 6.8]
Outcomes at age 2 among survivors						
Cerebral palsy**	26 (6.7)	35 (8.3)	−1.6 [–5.7 to 2.5]	6.6	8.8	−2.3 [–7.1 to 2.5]
ASQ below threshold††	207 (49.3)	214 (50.7)	−1.4 [–9.8 to 6.9]	51.1	51.4	−0.3 [–9.1 to 8.6]

ASQ, Ages and Stages Questionnaires.

*Data are presented as number (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take into account the differences in recruitment periods between gestational age groups.

†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.

‡Risk differences and mean differences were calculated with a generalized estimation equation regression analysis to take into account a potential center effect.

§Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.

¶Severe morbidity was defined as severe bronchopulmonary dysplasia, severe necrotizing enterocolitis, or severe retinopathy (stage 3 or treatment needed) or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage with ventricular dilatation (grade III intraventricular hemorrhage) or intraparenchymal hemorrhage, or cystic periventricular leukomalacia.

**According to the criteria of the Surveillance of Cerebral Palsy in Europe.

††An Ages and Stages Questionnaire score below threshold was defined as a score lower than 2 SDs below the mean on any of the 5 domains.

boluses were suspected of having adverse effects in hypotensive extremely immature infants, but continuous infusion of morphine was not an independent risk factor for high-grade intraventricular hemorrhage in logistic regression models.[22,28] Despite the limited literature about sufentanil in neonates, it was the opioid most frequently used in the present study.[44-47]

Whether all opioids have similar effects on human neurodevelopment is unknown, although an animal study suggested that sufentanil, but not fentanyl, might protect the developing brain from injury.[48] However, considering the potential deleterious effects of continuous fentanyl, a molecule close to sufentanil, on long-term outcomes in preterm neonates, cautious use of sufentanil should be recommended.[10]

Follow-up studies of randomized controlled trials comparing sensorimotor outcomes in ventilated infants who received morphine or placebo in the first week of life have yielded conflicting results. Neonates from a multicenter trial from 2000 to 2002 who were randomized to morphine vs placebo had significantly lower scores on the visual analysis IQ subtest at age 5 years.[8] However, the next follow-up study from the same trial found no deleterious effect and possible positive effects of morphine on executive function and pain sensitivity at age 8-9 years.[11,49] Currently, the largest randomized controlled trial comparing morphine with placebo recruited 898 neonates, but the assessment of only 19 of them at the age 5 year follow-up precludes any conclusions.[9,28]

Prospective cohort studies have reported neonatal morphine exposure is associated with impaired cerebellar growth, regional diminution of cortical volumes, and short-term behavioral impairments in very preterm neonates.[13,14] However, these studies neither adjusted for such potential confounders as obstetric or parental factors nor attempted to decrease bias by a propensity score approach, as here.[13,14] Nevertheless, considering the potential deleterious dose-dependent effect of opioids, assumptions on administered doses in the present study can be made.[13] In the 2 randomized controlled trials conducted at the beginning of the twenty-first century, morphine was used with an initial bolus of 100 μg/kg followed by infusions of ≥10 μg/kg/h.[27,28] Since the second decade of the twenty-first century, lower doses have been recommended for morphine starting at 5 μg/kg/h, with even lower doses (2.5 $\mu g/kg^{1.5}/h$ for infants aged <10 days) in a clinical trial assessing the efficacy of paracetamol for postoperative analgesia in neonates.[6,50,51] Although large cohort studies do not report data on analgesic or sedatives doses used, we can speculate, based on the previous comments

and personal practices, that opioids and midazolam were administered in the present study with the goal of using the minimal effective dose.[3,47,52] We can also speculate that these treatments were used based on clinical indications, and not as a routine procedure as in an interventional trial. However, we had no information on unit's protocols to support this assumption. The differences in outcomes observed between the present study and the previously published randomized controlled trials could thus be attributable to a dose effect and/or to a more appropriate selection of treated infants.[27,28]

A Cochrane review of midazolam included only 3 studies published between 1994 and 2001 and concluded that further research is needed about its effectiveness and safety in ventilated neonates.[5] An observational study reported an association between midazolam and impaired development at 18 months.[17] Although reported data have not supported the use of midazolam in the neonate, this drug is still commonly used in the neonatal intensive care unit worldwide as illustrated by several large cohort studies: 18% of infants with very low birthweight received midazolam in Germany in 2010, 25% of ventilated neonates received midazolam in European neonatal intensive care units in 2012-2013, 17% of preterm infants born at <33 weeks of gestation received midazolam or other sedatives in Canadian neonatal intensive care units between 2010 and 2014, and in 2012 in the US, 24% of ventilated very preterm infants participating in the Pediatrix Medical Group Data Warehouse received benzodiazepines.[3,5,52-54] The present results do not support any sensorimotor toxicity of midazolam, keeping in mind the unknown doses used and the difficulty in identifying midazolam's specific toxicity owing to its frequent use in combination with other drugs such as opioids.

Nevertheless, decreasing the use of opioids and benzodiazepines in premature neonates seems desirable and future studies should more carefully assess the risk/benefit ratio of other drugs such as paracetamol or dexmedetomidine.[55]

The strengths of this study include its population-based cohort design and the prospective enrollment of very preterm infants in France in 2011. The data collected reflect daily bedside practices and enabled the inclusion of a broad nonselected sample, as opposed to a randomized trial requiring perinatal consent and perhaps with a risk of selection bias affecting outcomes regardless of the allocated arm.[56] This study also has a much larger population than any previous analgesia/sedation study with a 2-year follow-up. Standardized definitions of outcomes following international recommendations and systematic and prospective data collection increase its external validity and comparability with previous studies. Because French practices in this area do not differ greatly from those in many other European countries, these results may be applicable elsewhere.[3,52] The numerous sensitivity analyses, generally consistent with the main analysis, support the robustness of the results.

Limitations

First, infants who had been intubated between 1 and 24 hours after birth or extubated before 24 hours were not included in this study; we sought to exclude infants intubated for surfactant administration and rapid extubation and those with very short-term ventilation. The current findings, therefore, apply to the majority of preterm infants with prolonged (>24 hours) primary respiratory failure owing to lung immaturity. It might not apply in settings where invasive ventilation is delayed in favor of noninvasive ventilation. Second, the naive group as defined in the study's design included infants who received midazolam and/or opioids after their first episode of mechanical ventilation, which could be considered as a confounding factor. In addition, no information was available on the indication for these latter treatments. We can not rule out that these infants received these late treatments because of prolonged mechanical ventilation or complications such as necrotizing enterocolitis or sepsis. However, survival without neonatal morbidity and cumulated durations of invasive ventilation were not statistically different between the treated and naive groups, which does not support this hypothesis. As stated in the Methods, we aimed to assess an early sedation/analgesia strategy for ventilated infants, regardless of future sedation or analgesia drugs use, as would be the case in an interventional trial. Moreover, the subgroup analysis among infants who never received the studied drugs showed no difference with the treated group for the main outcomes. Third, no information was available about the opioid or midazolam doses used or the existence of local protocols or policies within each unit. Enormous variability has been observed in clinical practices, with up to 100-fold differences in opioid doses in ventilated children.[57] This point is critical, as cumulative neurotoxic effects have been suggested for both morphine and midazolam in very premature infants.[13,17] Fourth, sensorimotor outcomes were assessed at 2 years of age; these outcomes are not always consistent with later school-age outcomes. Nonetheless, assessment at age 2 years is usually considered a good safety indicator.[58] An analysis of neurodevelopmental outcomes at age 5 within the EPIPAGE 2 cohort is planned. Fifth, pain was not assessed in this study; this information together with the opioid and/or midazolam doses would have been useful for assessing their association with our predefined outcomes. Sixth, all analyses were based on a propensity score, which can only control for the known confounders it includes.[34] As in any propensity-score based study, we cannot rule out potential confounders that were not taken into account. Seventh, the analyses were performed post hoc.

The clinical practice of continuous opioid and/or midazolam infusions in very premature infants during an initial episode of mechanical ventilation continued after 24 hours of age was associated with improved survival without any increase in the likelihood of moderate or severe neuromotor or sensory impairments at a corrected age of 2 years. These results suggest that the current use of continuous opioids and/or midazolam, not including bolus only use, does not seem to have a major sensorimotor neurotoxic effect in this population. This finding might help reduce barriers to the

use of such treatments in mechanically ventilated preterm neonates and thus contribute to their more humane care. ■

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Reprint requests: Xavier Durrmeyer, MD, PhD, Neonatal Intensive Care Unit, CHI Créteil, 40 avenue de Verdun, 94000, Créteil, France. E-mail: xavier.durrmeyer@chicreteil.fr

Data statement

Data sharing statement available at www.jpeds.com.

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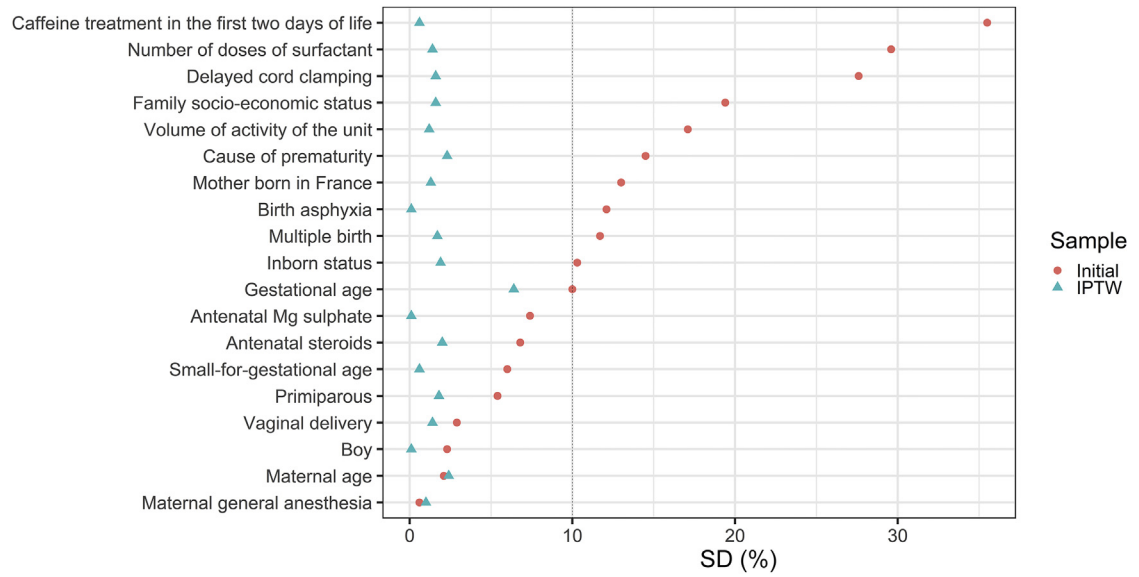

Figure 2. SDs in the initial and IPTW samples after imputation. SDs are represented on the *x* axis. Each covariate included in the propensity score is on the *y* axis. *Red dots* represent values for the initial sample after weighting to take into account the difference in recruitment periods between gestational age groups and after imputation. *Blue triangles* illustrate values for the IPTW sample. The *dotted line* represents the 10% standardized difference, which is usually considered as the threshold for balance in a propensity score.

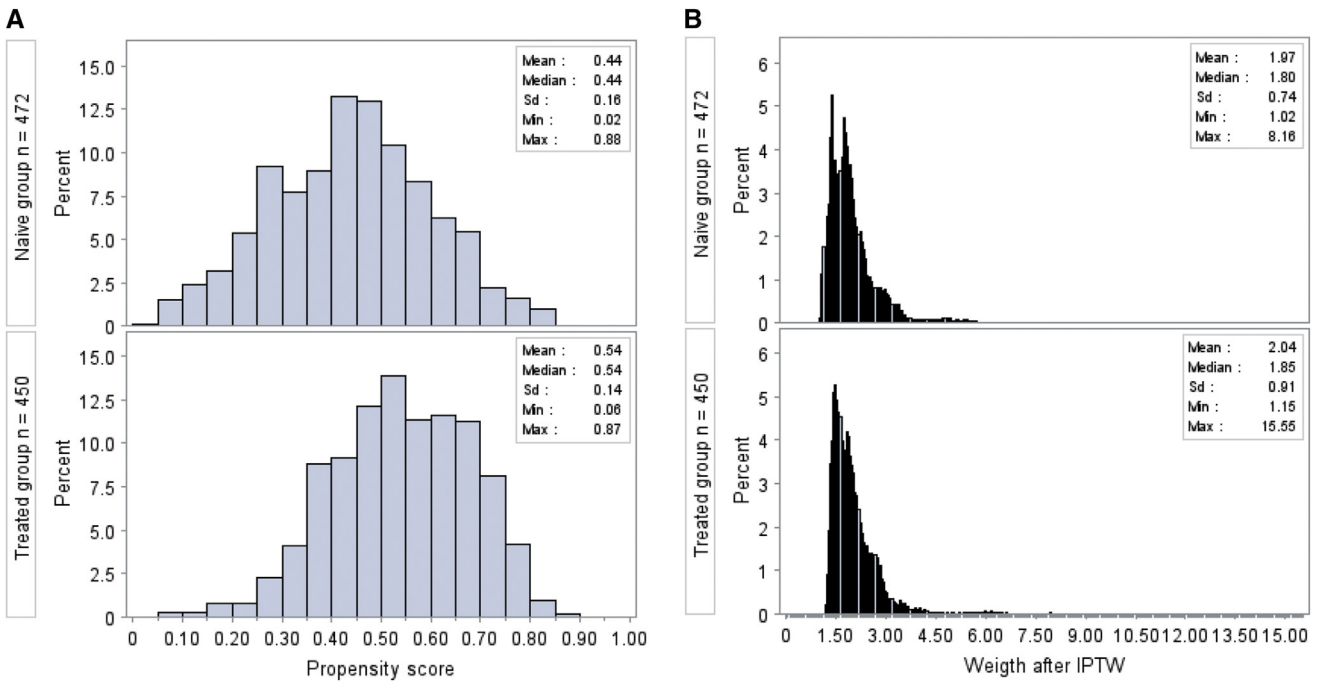

Figure 3. Distributions of **A,** propensity scores and **B,** weights in the IPTW sample.

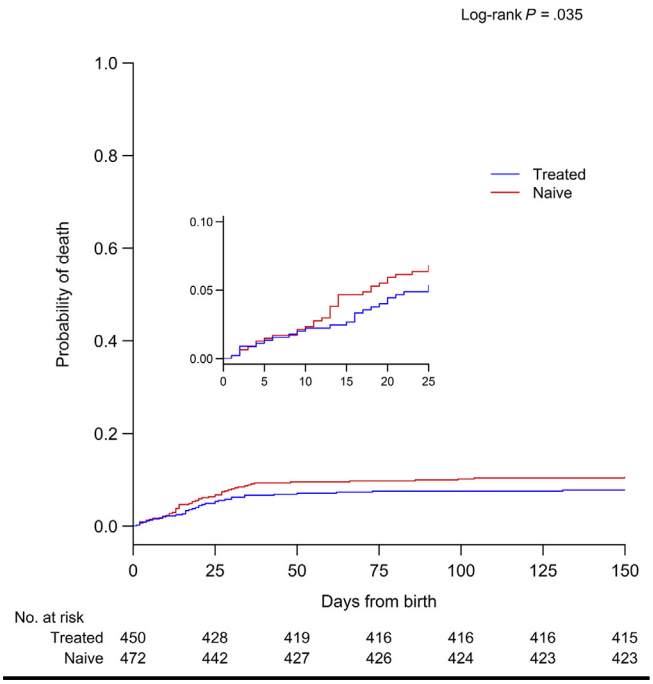

Figure 4. Cumulative probability of death in the first 150 days after birth in the IPTW sample.

Table I. Baseline characteristics of the population before imputation

Characteristics	No. (%) Treated (n = 450)	Naive (n = 472)
Gestational age (weeks)		
No. with data available	450 (100)	472 (100)
23	1 (0.2)	2 (0.3)
24	24 (4.4)	26 (4.5)
25	68 (12.5)	69 (12.1)
26	90 (16.6)	86 (15.0)
27	68 (16.9)	84 (19.8)
28	67 (16.6)	75 (17.6)
29	59 (14.6)	59 (13.9)
30	42 (10.4)	39 (9.2)
31	31 (7.7)	32 (7.5)
Small for gestational age*		
No. with data available	450 (100)	472 (100)
Yes	124 (28.3)	144 (31)
Sex		
No. with data available	450 (100)	472 (100)
Boy	236 (52.7)	241 (51.6)
Birth asphyxia†		
No. with data available	446 (99.1)	464 (98.3)
Yes	207 (53.2)	199 (47.1)
Delivery route		
No. with data available	446 (99.1)	464 (98.3)
Vaginal	163 (34.7)	161 (33.1)
Inborn status		
No. with data available	450 (100)	472 (100)
Yes	361 (80.0)	399 (84.0)
Multiple birth	135/450 (29.2)	163/472 (34.6)
No. with data available	450 (100)	472 (100)
Yes	135 (29.2)	163 (34.6)
Antenatal steroids		
No. with data available	437 (97.1)	455 (96.4)
Yes	264 (60.9)	291 (63.7)
Antenatal magnesium sulfate		
No. with data available	444 (98.7)	465 (98.5)
Yes	26 (5.8)	35 (7.8)
Delayed cord clamping		
No. with data available	434 (96.4)	443 (93.9)
Yes	5 (1.2)	28 (6.4)
No. of doses of surfactant		
No. with data available	435 (96.7)	459 (97.2)
None	12 (3.1)	24 (5.6)
1	234 (53.9)	297 (65.0)
≥2	189 (43.0)	138 (29.3)
Caffeine treatment in the first 2 days of life		
No. with data available	446 (99.5)	467 (98.9)
Yes	202 (46.6)	293 (64.1)
Cause of prematurity		
No. with data available	450 (100)	472 (100)
Preterm labor	201 (43.7)	192 (40.6)
PROM	108 (23.5)	111 (22.4)
Hypertensive disorders	111 (26.1)	117 (26.2)
Other	30 (6.7)	52 (10.7)
Maternal age		
No. with data available	450 (100)	472 (100)
<25 years	111 (24.9)	116 (24.1)
25-35 years	266 (58.6)	277 (59)
>35 years	73 (16.5)	79 (16.9)
Parity		
No. with data available	443 (98.4)	466 (98.7)
Primiparous	220 (48.8)	240 (51.5)
Type of maternal anesthesia		
No. with data available	422 (93.8)	448 (94.9)
General anesthesia	74 (18.0)	83 (18.5)
Family socioeconomic status		
No. with data available	421 (93.5)	436 (92.4)
Management jobs	98 (22.8)	67 (15.5)
Public and administrative jobs	177 (42.6)	222 (51.1)
Workers	130 (31.1)	132 (30.1)
No job declared	16 (3.5)	15 (3.4)
Mother born in France		
No. with data available	442 (98.2)	460 (97.5)
Yes	326 (73.4)	362 (79.0)
Volume of activity of the unit		
No. with data available	450 (100)	472 (100)
<55 infants	126 (28.6)	170 (36.0)
55-75 infants	146 (32.0)	146 (31.2)
≥75 infants	178 (39.5)	156 (32.9)

PROM, premature rupture of membranes.

Except for No. of patients with data available, all percentages are weighted to take into account the differences in recruitment periods between gestational age groups. For each variable, percentages might not sum up to 100%, owing to rounding.

*Small for gestational age was defined as birth weight less than the 10th percentile for gestational age and sex based on French intrauterine growth curves (Ego 2016).

†Defined as a 5-minute Apgar score of <7 or a base deficit of <−7 in the first 12 hours of life.

Table V. Causes of in-hospital deaths among treated and naive infants with continuous opioids and/or midazolam during early mechanical ventilation (no imputation)

Causes of death	In-hospital deaths, No. (%) Treated group (n = 35)	Naive group (n = 50)
Respiratory distress syndrome	12 (34)	17 (34)
Necrotizing enterocolitis	4 (11)	3 (6)
Infection	6 (17)	11 (22)
Central nervous system injury	6 (17)	12 (24)
Other	6 (17)	6 (12)
Unknown	1 (3)	1 (2)

Table VI. Primary outcomes assessed by using different models for sensitivity analysis after multiple imputation

Models used for sensitivity analysis	Frequency of events (%)		
	Treated group sample	Naive group sample	Risk differences: Treated group minus naive group (95% CI)
IPTW and symmetric trimming*	Average n = 450	Average n = 466	
Survival at 2 years' corrected age	92.4	87.9	4.6 [0.1 to 0.9]†
Survival at 2 years' corrected age without moderate or severe neuromotor or sensory disabilities‡	86.5	81.2	5.2 [–0.4 to 10.9]†
IPTW and asymmetric trimming§	Average n = 446	Average n = 468	
Survival at 2 years' corrected age	92.5	87.9	4.7 [0.2 to 9.1]†
Survival at 2 years' corrected age without moderate or severe neuromotor or sensory disabilities‡	86.6	81.2	5.3 [–0.3 to 11.0]†
IPTW and overlap weighting¶	n = 450	n = 472	
Survival at 2 years' corrected age	92.1	87.6	4.5 [–0.0 to 9.1]†
Survival at 2 years' corrected age without moderate or severe neuromotor or sensory disabilities‡	86.2	81.0	5.2 [–0.5 to 10.8]†
IPTW and stabilized weights**	n = 450	n = 472	
Survival at 2 years' corrected age	92.5	87.9	4.7 [0.3 to 9.1]†
Survival at 2 years' corrected age without moderate or severe neuromotor or sensory disabilities‡	86.6	81.3	5.3 [–0.3 to 11.0]†
Propensity score matched cohorts††	Average n = 374	Average n = 374	
Survival at 2 years corrected age	92.2	88.5	4.0 [–0.5 to 8.6]‡‡
Survival at 2 years corrected age without moderate or severe neuromotor or sensory disabilities‡	86.3	82.1	4.6 [–1.1 to 10.3]‡‡

*Excluding infants with propensity scores of <0.1 and >0.9.
†Risk differences were calculated with a generalized estimation equation regression analysis to take into account a potential center effect.
‡Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.
§Selection of a common propensity score range formed by treated and naive infants and exclusion of infants with cut-points corresponding to the 1st and 99th percentiles of propensity score distribution.
¶Weighting with 1 – propensity score for treated infants and with the propensity score for naive infants.
**Weights were multiplied by the marginal probability of the treatment actually received.
††This analysis used a 1:1 matching algorithm without replacement to match treated and naive infants on the propensity score with a caliper width measuring 0.2 of the SD of the score's logit.
‡‡Risk differences were calculated with a generalized estimation equation regression analysis to take paired data into account.

Table VII. Exploratory subgroup analyses among infants born before 29 weeks: Primary and secondary outcomes in the initial and IPTW samples after multiple imputation

Outcomes	Frequency or duration of events					
	Initial sample, No. (%)*			IPTW sample, %†		
	Treated group (n = 318)	Naive group (n = 342)	Risk or mean differences: Treated group minus naive group (95% CI)‡	Treated group (n = 318)	Naive group (n = 342)	Risk or mean differences: Treated group minus naive group (95% CI)‡
Primary outcomes						
Survival at 2 years,	285 (90.1)	291 (85.8)	4.3 [–1.3 to 9.8]	90.4	83.9	6.5 [0.4 to 12.6]
Survival at 2 years without moderate or severe neuromotor or sensory disabilities§	263 (83.3)	273 (81.1)	2.2 [–4.5 to 9.0]	83.8	78.0	5.9 [–1.9 to 13.6]
Secondary exploratory outcomes						
Survival at discharge without severe neonatal morbidity¶	185 (59.7)	189 (57.2)	2.5 [–6.9 to 11.9]	60.3	51.6	8.7 [–1.3 to 18.7]
Severe cerebral abnormalities at discharge¶	50 (15.6)	43 (12.6)	3.0 [–1.8 to 7.7]	14.6	13.6	1.0 [–4.1 to 6.2]
Outcomes at discharge						
Cumulative duration of mechanical ventilation (day)						
Median [IQR]	12 [5 to 27]	9 [3 to 24]	–	12 [5 to 30]	12 [4 to 26]	–
Mean (SD)	17.7 (15.1)	15.3 (15.9)	2.4 [−1.3 to 6.1]	18.0 (15.6)	17.2 (16.4)	0.8 [–3.5 to 5.1]
Duration of hospital stay (day)						
Median [IQR]	90 [76 to 107]	90 [72 to 106]	–	90 [76 to 111]	93 [75 to 107]	–
Mean (SD)	95.0 (27.1)	93.0 (27.8)	1.9 [–2.8 to 6.7]	95.9 (27.7)	96.1 (28.5)	−0.3 [–5.8 to 5.3]
Outcomes at age 2 among survivors						
Cerebral palsy**	20 (7.4)	24 (8.1)	−0.6 [–5.7 to 4.4]	7.3	9.2	−1.9 [–8.2 to 4.3]
ASQ below threshold††	155 (53.9)	151 (51.2)	2.7 [–7.5 to 12.9]	55.9	52.8	3.1 [–7.6 to 13.7]

ASQ, Ages and Stages Questionnaires.

*Data are presented as number (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take the differences in recruitment periods between gestational age groups into account.

†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.

‡Risk differences and mean difference were calculated with a generalized estimation equation regression analysis to take a potential center effect into account.

§Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.

¶Severe morbidity was defined as severe bronchopulmonary dysplasia, severe necrotizing enterocolitis, or severe retinopathy (stage 3 or treatment needed) or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage with ventricular dilatation (grade III intraventricular hemorrhage) or intraparenchymal hemorrhage (IPH), or cystic periventricular leukomalacia.

**According to the criteria of the Surveillance of Cerebral Palsy in Europe.

††An ASQ score below threshold was defined as a score lower than 2 SDs below the mean on any of the 5 domains.

Table VIII. Exploratory subgroup analyses among infants exclusively treated with opioids in the treated groups: Primary and secondary outcomes in the initial and IPTW samples after multiple imputation

	Frequency or duration of events					
	Initial sample, No. (%)*			IPTW sample, %†		
Outcomes	Treated group (n = 289)	Naive group (n = 472)	Risk or mean differences: Treated group minus naive group (95% CI)‡	Treated group (n = 289)	Naive group (n = 472)	Risk or mean differences: Treated group minus naive group (95% CI)‡
Primary outcomes						
Survival at 2 years,	270 (94.1)	419 (89.7)	4.4 [0.6 to 8.1]	94.2	88.2	6.0 [1.8 to 10.2]
Survival at 2 years without moderate or severe neuromotor or sensory disabilities§	253 (88.1)	390 (83.7)	4.4 [–0.6 to 9.5]	88.7	81.6	7.1 [1.3 to 12.8]
Secondary exploratory outcomes						
Survival at discharge without severe neonatal morbidity¶	193 (68.7)	295 (64.8)	3.8 [–4.8 to 12.5]	68.8	60.2	8.6 [–1.1 to 18.2]
Severe cerebral abnormalities at discharge¶	32 (10.6)	55 (11.4)	−0.8 [–5.1 to 3.5]	9.8	12.3	−2.5 [–7.2 to 2.2]
Outcomes at discharge						
Cumulative duration of mechanical ventilation (day)						
Median [IQR]	8 [3 to 21]	5 [2 to 16]	–	8 [3 to 22]	6 [2 to 21]	–
Mean (SD)	14.7 (14.7)	11.5 (14.3)	3.2 [0.0 to 6.3]	14.8 (14.9)	13.1 (15.0)	1.7 [–2.0 to 5.4]
Duration of hospital stay (day)						
Median [IQR]	80 [61 to 99]	76 [61 to 99]	–	81 [62 to 101]	79 [63 to 101]	–
Mean (SD)	85.8 (32.3)	81.4 (29.9)	4.5 [–1.5 to 10.4]	86.8 (32.8)	84.4 (30.9)	2.3 [–4.5 to 9.2]
Outcomes at age 2 among survivors						
Cerebral palsy**	18 (7.4)	35 (8.3)	−0.9 [–5.5 to 3.7]	6.9	8.9	−2.1 [–7.2 to 3.1]
ASQ below threshold††	135 (48.9)	214 (50.7)	−1.8 [–11.1 to 7.4]	50.6	51.6	−1.0 [–11.1 to 9.0]

*Data are presented as number (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take the differences in recruitment periods between gestational age groups into account.

†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.

‡Risk differences and mean difference were calculated with a generalized estimation equation regression analysis to take a potential center effect into account.

§Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.

¶Severe morbidity was defined as severe bronchopulmonary dysplasia, severe necrotizing enterocolitis, or severe retinopathy (stage 3 or treatment needed) or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage with ventricular dilatation (grade III intraventricular hemorrhage) or intraparenchymal hemorrhage (IPH), or cystic periventricular leukomalacia.

**According to the criteria of the Surveillance of Cerebral Palsy in Europe.

††An ASQ score below threshold was defined as a score lower than 2 SDs below the mean on any of the 5 domains.

Table IX. Exploratory subgroup analyses among infants treated with midazolam in the treated groups: primary and secondary outcomes in the initial and IPTW samples after multiple imputation

	Frequency or duration of events					
	Initial sample, No. (%)*			IPTW sample, %†		
Outcomes	Treated group (n = 161)	Naive group (n = 472)	Risk or mean differences: Treated group minus naive group (95% CI)‡	Treated group (n = 161)	Naive group (n = 472)	Risk or mean differences: Treated group minus naive group (95% CI)‡
Primary outcomes						
Survival at 2 years,	143 (89.3)	419 (89.7)	−0.4 [−5.8 to 5.0]	89.6	88.2	1.4 [−4.4 to 7.2]
Survival at 2 years without moderate or severe neuromotor or sensory disabilities§	132 (83.0)	390 (83.7)	−0.7 [−7.4 to 5.9]	83.2	82.1	1.1 [−8.1 to 10.6]
Secondary exploratory outcomes						
Survival at discharge without severe neonatal morbidity¶	99 (63.3)	295 (64.8)	−1.6 [−11.3 to 8.1]	63.9	61.9	1.7 [−9.8 to 13.2]
Severe cerebral abnormalities at discharge¶	32 (19.9)	55 (11.4)	8.5 [1.8 to 15.2]	18.1	12.0	6.1 [−1.2 to 13.4]
Outcomes at discharge						
Cumulative duration of mechanical ventilation (day)						
Median [IQR]	8 [4 to 15]	5 [2 to 16]	–	8 [2 to 20]	6 [2 to 17]	–
Mean (SD)	12.0 (12.2)	11.5 (14.3)	0.4 [−2.7 to 3.6]	13.0 (13.4)	12.5 (14.7)	0.6 [−3.1 to 4.3]
Duration of hospital stay (day)						
Median [IQR]	75 [59 to 92]	76 [61 to 99]	–	81 [60 to 95]	78 [62 to 101]	–
Mean (SD)	77.8 (26.8)	81.4 (29.9)	−3.6 [−9.3 to 2.1]	81.3 (27.6)	83.2 (30.6)	−1.9 [−8.5 to 4.6]
Outcomes at age 2 among survivors						
Cerebral palsy**	8 (5.5)	35 (8.3)	−2.8 [−8.0 to 2.3]	5.5	8.4	−2.9 [−11.2 to 5.4]
ASQ below threshold††	72 (50.0)	214 (50.7)	−0.7 [−11.9 to 10.4]	48.1	50.8	−2.7 [−16.1 to 10.6]

*Data are presented as number (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take the differences in recruitment periods between gestational age groups into account.

†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.

‡Risk differences and mean difference were calculated with a generalized estimation equation regression analysis to take a potential center effect into account.

§Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.

¶Severe morbidity was defined as severe bronchopulmonary dysplasia, severe necrotizing enterocolitis, or severe retinopathy (stage 3 or treatment needed) or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage with ventricular dilatation (grade III intraventricular hemorrhage) or intraparenchymal hemorrhage (IPH), or cystic periventricular leukomalacia.

**According to the criteria of the Surveillance of Cerebral Palsy in Europe.

††An ASQ score below threshold was defined as a score lower than 2 SDs below the mean on any of the 5 domains.

Table X. Exploratory subgroup analyses among infants who never received continuous opioids or midazolam in the naive group: primary and secondary outcomes in the initial and IPTW samples after multiple imputation

Outcomes	Frequency or duration of events					
	Initial sample, No. (%)*			IPTW sample, %†		
	Treated group (n = 450)	Naive group (n = 290)	Risk or mean differences: Treated group minus naive group (95% CI)‡	Treated group (n = 450)	Naive group (n = 290)	Risk or mean differences: Treated group minus naive group (95% CI)‡
Primary outcomes						
Survival at 2 years,	413 (92.3)	277 (95.9)	−3.5 [−7.2 to 0.2]	93.0	92.8	0.2 [−6.8 to 7.2]
Survival at 2 years without moderate or severe neuromotor or sensory disabilities§	385 (86.2)	259 (89.8)	−3.5 [−8.6 to 1.6]	87.3	87.2	0.1 [−7.5 to 7.7]
Secondary exploratory outcomes						
Survival at discharge without severe neonatal morbidity¶	292 (66.7)	222 (77.6)	−10.9 [−22.2 to 0.4]	68.5	70.3	−1.8 [−17.0 to 13.4]
Severe cerebral abnormalities at discharge¶	64 (14.0)	21 (7.5)	6.5 [2.2 to 10.7]	13.0	8.5	4.5 [−0.9 to 9.9]
Outcomes at discharge						
Cumulative duration of mechanical ventilation (day)						
Median [IQR]	8 [3 to 21]	3[2 to 7]	–	8 [3 to 19]	5 [2 to 12]	–
Mean (SD)	13.7 (13.9)	7.2 (10.2)	6.5 [2.6 to 10.4]	13.2 (13.7)	10.2 (12.9)	3.0 [−3.2 to 9.2]
Duration of hospital stay (day)						
Median [IQR]	80 [61 to 98]	69 [55 to 82]	–	79 [60 to 97]	76 [76 to 92]	–
Mean (SD)	83.0 (30.7)	71.5 (22.1)	11.5 [5.3 to 17.6]	81.8 (30.5)	76.7 (23.6)	5.1 [−2.7 to 12.8]
Outcomes at age 2 among survivors						
Cerebral palsy**	26 (6.7)	22 (7.7)	−1.0 [−5.4 to 3.4]	6.4	6.7	−0.3 [−5.0 to 4.5]
ASQ below threshold††	207 (49.3)	129 (46.6)	2.6 [−6.3 to 11.6]	49.7	49.1	0.5 [−9.6 to 10.7]

*Data are presented as number (percentages) of patients unless otherwise indicated. Percentages and risk difference are weighted to take the differences in recruitment periods between gestational age groups into account.

†Data are presented as percentages only unless otherwise indicated since numerators are not relevant for the IPTW sample.

‡Risk differences and mean difference were calculated with a generalized estimation equation regression analysis to take a potential center effect into account.

§Severe neuromotor or sensory disabilities included any of Gross Motor Function Classification System level 3-5 cerebral palsy or severe visual or auditory impairment; moderate disability included Gross Motor Function Classification System level 2 cerebral palsy and/or moderate visual or auditory impairment.

¶Severe morbidity was defined as severe bronchopulmonary dysplasia, severe necrotizing enterocolitis, or severe retinopathy (stage 3 or treatment needed) or any of the following severe cerebral abnormalities on cranial ultrasonography: intraventricular hemorrhage with ventricular dilatation (grade III intraventricular hemorrhage) or intraparenchymal hemorrhage, or cystic periventricular leukomalacia.

**According to the criteria of the Surveillance of Cerebral Palsy in Europe.

††An ASQ score below threshold was defined as a score lower than 2 SDs below the mean on any of the 5 domains.