



Exposures of Neonates in the NICU to Opioid Analgesic and Sedative Agents



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Introduction

Neurotoxicity from prolonged or repeated exposures to sedative and anesthetic agents in the developing brain is well documented in preclinical studies, but the risks of adverse neurodevelopmental outcome in neonates with such exposures remain unknown.

Preterm neonates with developing brains may be particularly vulnerable to such exposures. The goal of the present study is to characterize exposures to opioid analgesic and sedative agents in neonates and preterm infants using the PHIS database.

Methods

This study was approved by Columbia University IRB. Data are NICU discharges from 2012 to 2023 in PHIS database. Preterm infants (according to gestational age (GA) included

EP (extreme preterm neonates): <28 weeks GA

VP (very preterm neonates): 28-31 weeks GA

LP (late preterm): 32-36 weeks GA.

Data were analyzed by ANOVA (continuous), Chi-square tests (categorical). Poisson regression analyses assessed GA groups and the outcome variables of interest. R was used for all analyses.

Table 1: Patient Demographic Characteristics

	ALL (n=374,018)	PRETERM INFANTS (n=185,293)			FULL TERM INFANTS (n=188,725)	
		≤ 36 weeks (n=185,293)	< 28 wks (n=28,537)	28-31 wks (n=34,191)		32-36 wks (n=122,565)
Birthweight (grams) Mean ± SD	2,612 ± 978	1,916 ± 783	791 ± 242	1,386 ± 368	2,326 ± 578	3,294 ± 592
Race n (%)	(n=367,903)					
Non-Hispanic White	172,170 (46.8)	82,075 (45.1)	9,834 (35.1)	14,571 (43.4)	57,670 (47.9)	90,095 (48.5)
Non-Hispanic Black	61,928 (16.8)	36,115 (19.8)	8,406 (30.0)	7,638 (22.7)	20,071 (16.7)	25,813 (13.9)
Hispanic	62,775 (17.1)	30,166 (16.6)	4,597 (17.5)	5,588 (16.6)	19,671 (16.3)	32,609 (17.5)
Asian	13,584 (3.7)	5,890 (3.2)	851 (3.0)	1,017 (3.0)	4,022 (3.3)	7,694 (4.1)
Multiracial	6,507 (1.8)	3,053 (1.7)	436 (1.6)	544 (1.6)	2,073 (1.7)	3,454 (1.9)
Other	26,388 (7.2)	12,559 (6.9)	1,929 (7.0)	2,361 (7.0)	8,269 (6.9)	13,829 (7.4)
Unknown	24,551 (6.7)	12,211 (6.7)	1,647 (6.9)	1,890 (5.6)	8,674 (7.2)	12,340 (6.6)
Payor n (%)	(n=367,903)					
Commercial	149,638 (40.7)	71,990 (39.5)	9,509 (33.9)	12,676 (37.7)	49,805 (41.3)	77,648 (41.8)
Government: Medicaid	189,639 (51.5)	96,287 (52.9)	16,065 (57.4)	18,428 (54.8)	61,794 (51.3)	93,352 (50.2)
Government: Other	12,703 (3.5)	6,366 (3.5)	1,020 (3.6)	1,207 (3.6)	4,139 (3.4)	6,337 (3.4)
Self-pay	6,738 (1.8)	2,821 (1.5)	386 (1.4)	392 (1.2)	2,043 (1.7)	3,917 (2.1)
Other payor	6,717 (1.8)	3,415 (1.9)	897 (3.2)	675 (2.0)	1,843 (1.5)	3,302 (1.8)
Unknown	2,468 (0.7)	1,190 (0.7)	133 (0.5)	231 (0.7)	826 (0.7)	1,278 (0.7)

Table 2: Patient Clinical Characteristics

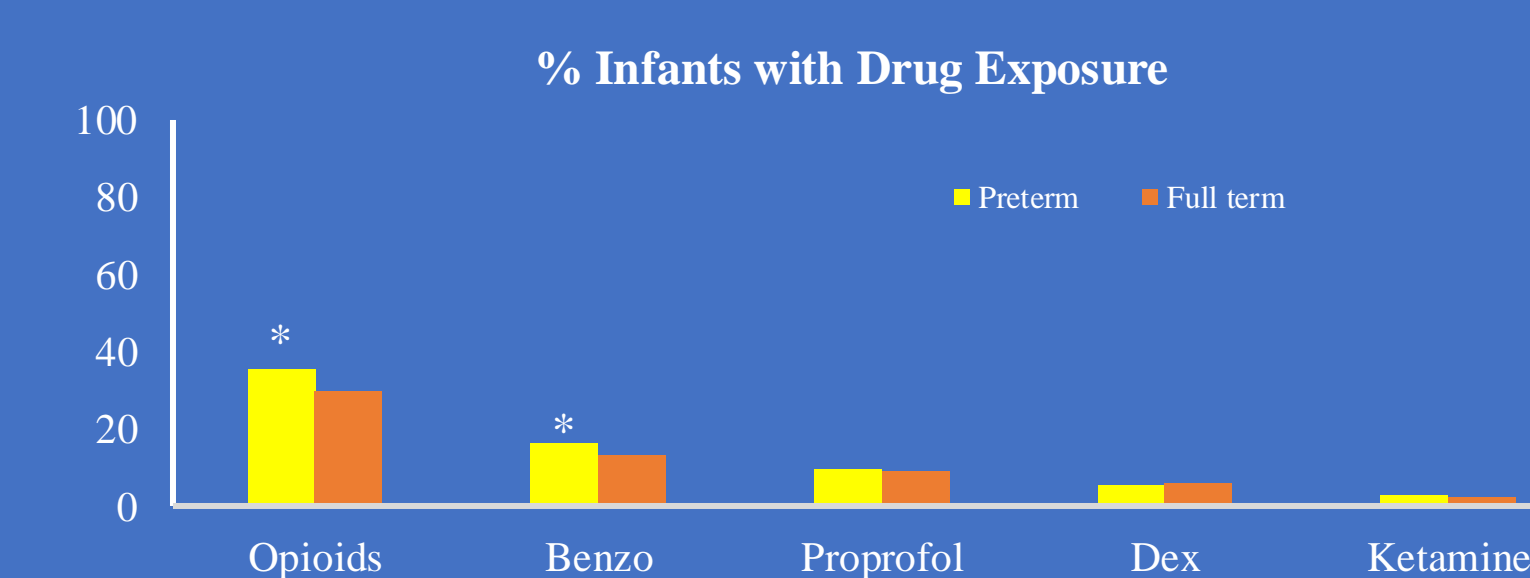
	All (n=374,018)	≤ 36 weeks (n=185,293)	> 36 weeks (n=188,725)			
			< 28 wks (n=28,537)	28-31 wks (n=34,191)	32-36 wks (n=122,565)	
Length of stay (days) Mean ± SD	23.8 ± 35.6	36.3 ± 42.9	84.0 ± 63.7	52.2 ± 35.6	20.8 ± 25.4	11.5 ± 19.9
Complex chronic condition, n (%)	174,418 (46.6)	90,588 (48.9)	26,939 (94.4)	19,451 (56.9)	44,198 (36.1)	83,830 (44.4)
Mechanical ventilation n (%)	131,148 (35.1)	84,862 (45.8)	25,690 (90.0)	20,523 (60.0)	38,649 (31.5)	46,286 (24.5)

Table 3: Total Number and Types of Drugs Exposure

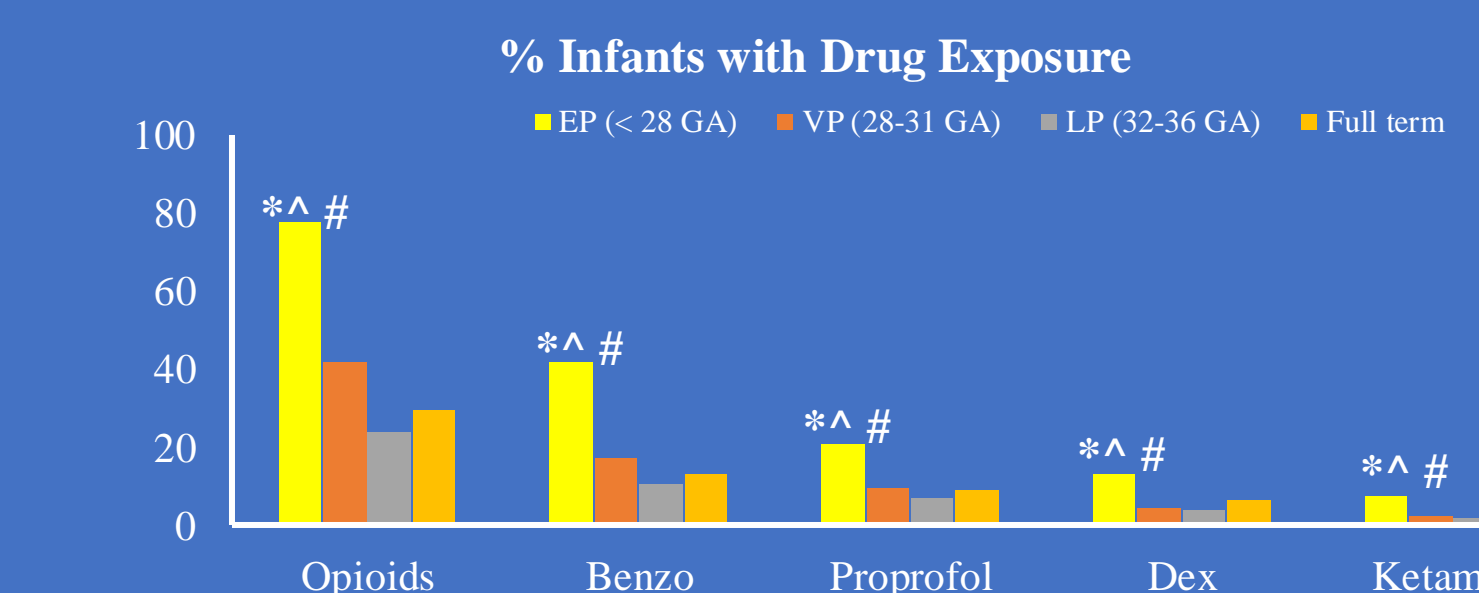
	All Neonates (NEO)	PRETERM INFANTS (PREMIES) < 36 WEEKS						FULL TERM INFANTS > 36 WEEKS				
		≤ 36 weeks (185,293)		< 28 wks (28,537)		28-31 wks (34,191)			32-36 wks (122,565)			
TOTAL # DRUGS OF EXPOSURE		n	%	n	%	n	%	n	%	n	%	
0	238,806	63.8	114,146	61.6	3,284	18.5	18,452	54.0	90,410	73.8	124,660	66.1
1	54,318	14.5	30,550	16.5	9,524	33.4	8,956	26.1	15,122	12.3	25,788	12.6
2	46,645	12.5	23,922	12.9	9,243	32.4	4,901	14.3	11,514	9.4	23,725	11.6
3	22,197	5.9	10,913	5.9	3,674	12.9	1,597	4.4	4,192	3.4	11,284	6.0
≥ 4	12,052	3.2	6,762	3.6	709	2.5	259	0.8	752	0.6	5,290	2.8
TYPES OF DRUGS OF EXPOSURE												
Opioid	122,009	32.6	65,809	35.3	22,185	77.7	14,302	41.8	29,352	23.9	17,422	9.2
Benzodiazepine	55,539	14.9	30,547	16.5	11,558	40.5	5,996	17.2	13,993	10.7	25,292	13.4
Propofol	35,517	9.5	18,173	9.8	5,986	21	3,273	9.6	8,914	7.3	17,344	9.2
Dexmedetomidine	22,175	5.9	10,360	5.5	3,726	13.1	1,624	4.7	4,910	4.0	11,915	6.3
Ketamine	9,682	2.6	5,328	2.9	2,139	7.5	814	2.4	2,375	1.9	4,554	2.3

Results

Prevalence of Types of Drugs of Exposure

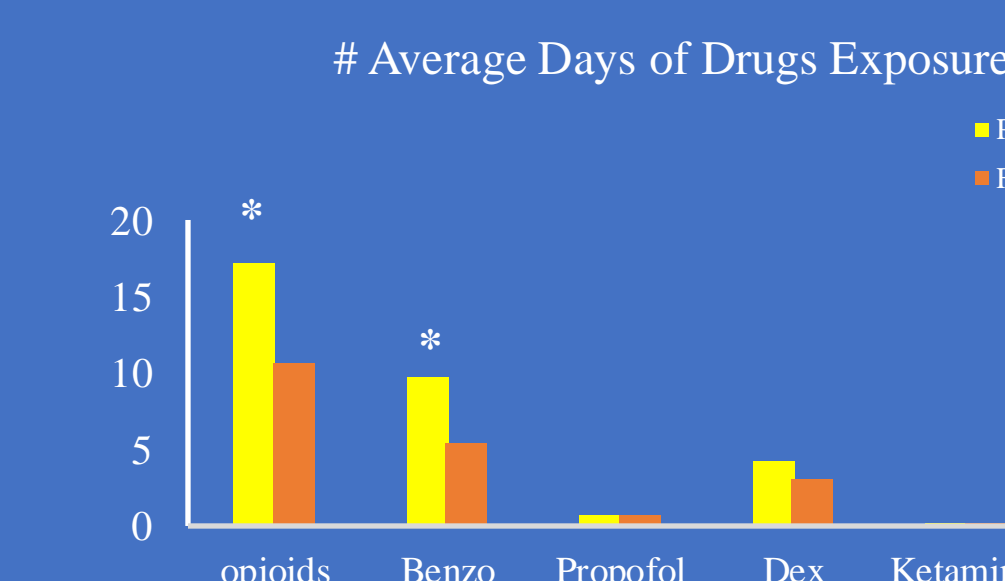


The prevalence of types of drug exposure in terms of % infants receiving the drug was: opioids>benzodiazepines (benzo)>propofol>dexmedetomidine (dex)>ketamine. Preterm infants received significantly more opioids and benzodiazepines compared to full term infants, but not the other types of drugs. * indicates p<0.05

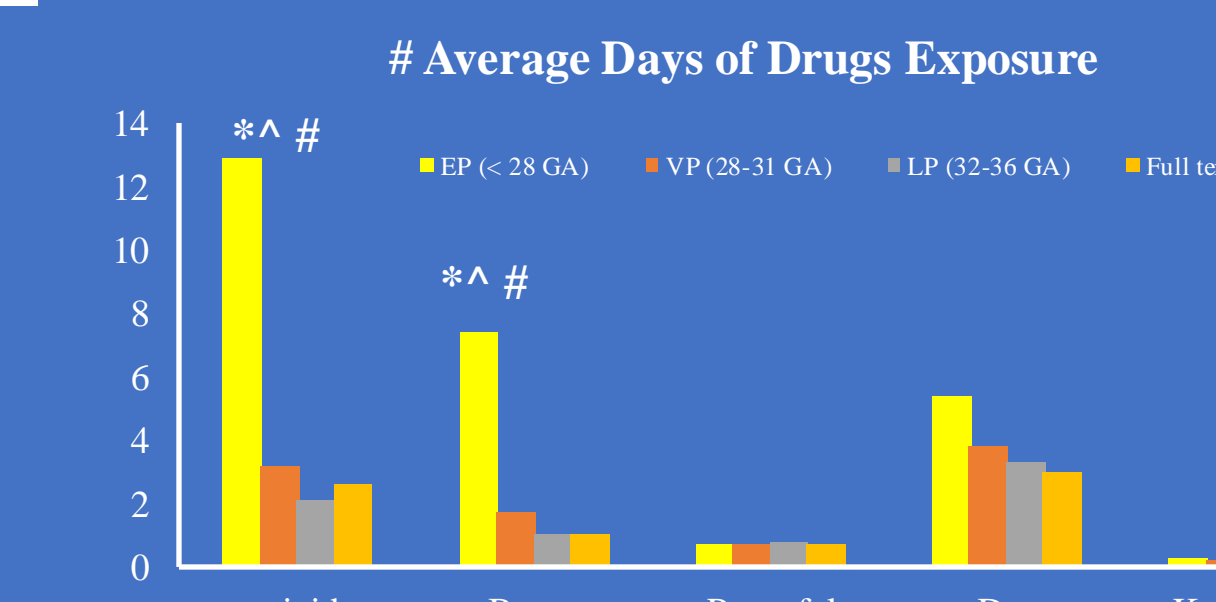


In EP (<28 weeks GA), 77.7% received opioids, 41% received benzodiazepines, and 21%, 13% and 7.5% received propofol, dexmedetomidine and ketamine, respectively. In VP (28-31 weeks GA), it was 42%, 17%, 9.6%, 4.7% and 2.4% for opioids, benzos, propofol, dex and ketamine, respectively. In LP, it was 24%, 10.7%, 7.3%, 4% and 2% for for opioids, benzos, propofol, dex and ketamine, respectively. * indicates p<0.05 vs full term, ^ p<0.05 vs VP, # p<0.05 vs LP

Durations of Drugs Exposures



Preterm infants had significantly longer exposure to opioids (17.3±29.6 days) and benzodiazepines (9.7±27.4 days) than full term infants (opioids=10.6±21.1 days, Benzos=5.4±18.4 days), but were comparable for other drugs. * indicates p<0.05.



Durations of exposures in EP for opioids (23.3±35 days), benzos (13.5±32.9 days) were significantly longer compared to VP, LP and full term (FT) infants. Opioids were 14.2±26.7, 13.3±24.1 and 10.6±21.1 days of exposure for VP, LP and FT, respectively. Benzos were 7.9±24.1, 7.1±22.6, 5.4±18.4 days for VP, LP and FT, respectively. Dex durations of exposures were 5.4± 21.8, 3.8±18.2, 3.3±14.9, 3.0±13.2 days for EP, VP, LP and FT, respectively. Propofol exposures were 0.7±1, 0.7±1, 0.8± 1.2, 0.7±1 for EP, VP, LP and FT, respectively. For ketamine, it was 0.3±1.7, 0.2±1.1, 0.3±1.5 and 0.2±1.2 for EP, VP, LP and FT, respectively. * indicates p<0.05 vs full term, ^ p<0.05 vs VP, # p<0.05 vs LP

Conclusions

- Preterm Infants have significantly greater exposure to opioid analgesic and sedative agents compared to full term infants. The drug exposure in preterm infants is gestational age-dependent, with those at younger gestational age receiving more analgesic and sedative agents than those at older gestational age.
- Preterm infants have longer durations of exposure to opioids and benzodiazepines than full term infants, and the duration of exposure is also gestational age dependent.
- Thus, those infants who had the most immature brains had more and longer exposures. These results can contribute to design of future studies examining the neurodevelopmental risks associated with exposure of preterm infants to analgesic and sedative agents.

References

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Jansen, L., et al., Longitudinal Follow-Up of Children Born Preterm: Neurodevelopment From 2 to 10 Years of Age. *Front Pediatr*, 2021, 9: p. 674221.