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# Analgesia and Sedation Medication Use in Infants with Congenital Diaphragmatic Hernia is Associated with Adverse Outcome

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## Background

Congenital diaphragmatic hernia (CDH) occurs in 1/3000 live births and is associated with mortality in nearly 30% of affected infants.

Infants with CDH are often treated with analgesia and sedation medications despite their use being associated with negative effects on the developing brain. There is little guidance in published literature, and it is unknown how these medications are being used in the CDH population.

Better understanding of the variation in use of analgesia and sedation for these infants may allow for more targeted therapy to improve outcomes and reduce resource utilization.

## Objective

To describe the use and variation of sedation and analgesic medications as well as short-term clinical outcomes in infants with CDH.

## Materials & Methods

Retrospective cohort analysis (2010-16) of 19 Level IV tertiary referral NICUs participating in the Children's Hospitals Neonatal Database (CHND).

Infants were excluded if database records were not complete, diaphragmatic repair occurred prior to referral, previously discharged home, death/discharge occurred at <3 days of life, or if there were surgical co-morbidities.

Medication use was captured using patient-record linkage to data in the Pediatric Health Information Systems (PHIS) dataset.

Participating centers were excluded if total number of CDH infants was ≤10 over the study period, or PHIS linkage unavailable.

Descriptive measures and variability among participating centers are reported.

Usage was stratified by use of extracorporeal membrane oxygenation (ECMO) and survival.

Primary outcomes were use, duration, and inter-center variation (ICV) in analgesic and sedative medications.

Association between prolonged, concurrent use of opioids and benzodiazepines was determined by regression analysis.

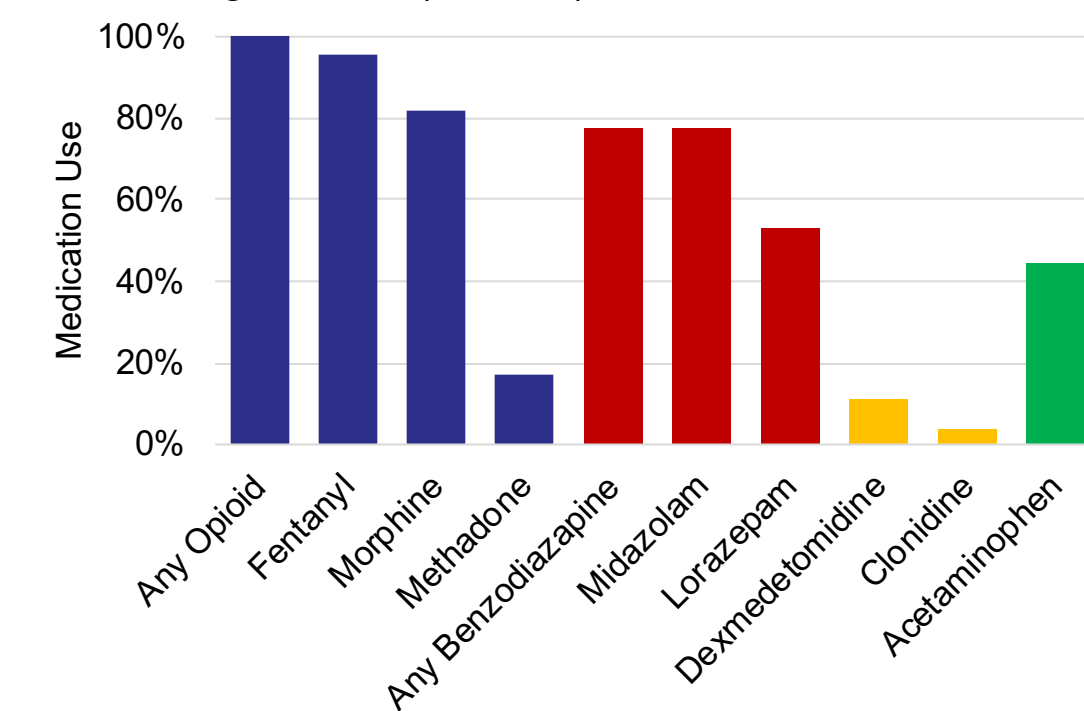
## Results

**Table 1:** Demographic data and clinical outcomes for CDH patients, stratified by survival to NICU discharge and use of ECMO.

Variable	All CDH	By Survival			By ECMO Use		
		Survived to Discharge	Non-Survivors*	p	NO ECMO	ECMO	p
Number of CDH patients	1063	776	287		748	315	
Median GA in weeks [IQR] at birth	38 [37, 39]	38 [37, 39]	38 [36, 39]	0.000	38 [37, 39]	38 [37, 39]	0.293
Median BW in grams [IQR] at birth	3055 [2700, 3398]	3125.5 [2775, 3420]	2824.5 [2500, 3225]	0.000	3090 [2700, 3420]	3000 [2695, 3280]	0.066
Born <34 weeks gestation (n,%)	113 (10.63)	64 (8.25)	30 (14.85)	0.005	75 (10.03)	38 (12.06)	0.325
Admission pH	7.3 [7.2, 7.4]	7.3 [7.2, 7.4]	7.2 [7, 7.3]	0.000	7.3 [7.2, 7.4]	7.2 [7.1, 7.3]	0.000
APGAR at 10 min ≤5	58 (5.46)	23 (2.96)	26 (12.87)	0.000	23 (3.07)	35 (11.11)	0.000
Left CDH (n,%)	858 (80.71)	625 (80.54)	166 (82.18)	0.598	611 (81.68)	247 (78.41)	0.217
Repair type							
Primary	434 (40.83)	391 (50.39)	13 (6.44)	0.000	386 (51.6)	48 (15.24)	0.000
Patch	495 (46.57)	366 (47.16)	88 (43.56)		304 (40.64)	191 (60.63)	
Hospital LOS [median, IQR]	36 [20, 69]	39 [22, 73]	19.5 [12, 36]	0.000	32 [20, 58]	50 [20, 98]	0.000
Total vent days [median, IQR]	16 [8, 29]	14 [8, 26]	20 [12, 35]	0.000	12 [7, 20]	28 [19, 49]	0.000
ECMO (n,%)	315 (29.63)	130 (16.75)	158 (78.22)	0.000	-	315 (100)	0.000
Days on ECMO (median, IQR)	11.3 [6.6, 17.8]	8.9 [6.1, 15]	14.3 [7.8, 20.7]	0.000	-	11.3 [6.6, 17.8]	0.000
CDH repair (n,%)	948 (89.18)	772 (99.48)	101 (50)	0.000	703 (93.98)	245 (77.78)	0.000
Cardiac catheterization (n,%)	56 (5.27)	22 (2.84)	25 (12.38)	0.000	15 (2.01)	41 (13.02)	0.000
Tracheostomy (n,%)	28 (2.63)	13 (1.68)	5 (2.48)	0.451	14 (1.87)	14 (4.44)	0.017
Gastrostomy tube placement (n,%)	142 (13.36)	120 (15.46)	7 (3.47)	0.000	92 (12.3)	50 (15.87)	0.118
Thoracostomy tube placement (n,%)	408 (38.38)	285 (36.73)	90 (44.55)	0.042	240 (32.09)	168 (53.33)	0.000

\* 85 transferred out of NICU to other unit

**Figure 1:** Frequency of analgesia and sedation medication use among all CDH (n=1063).

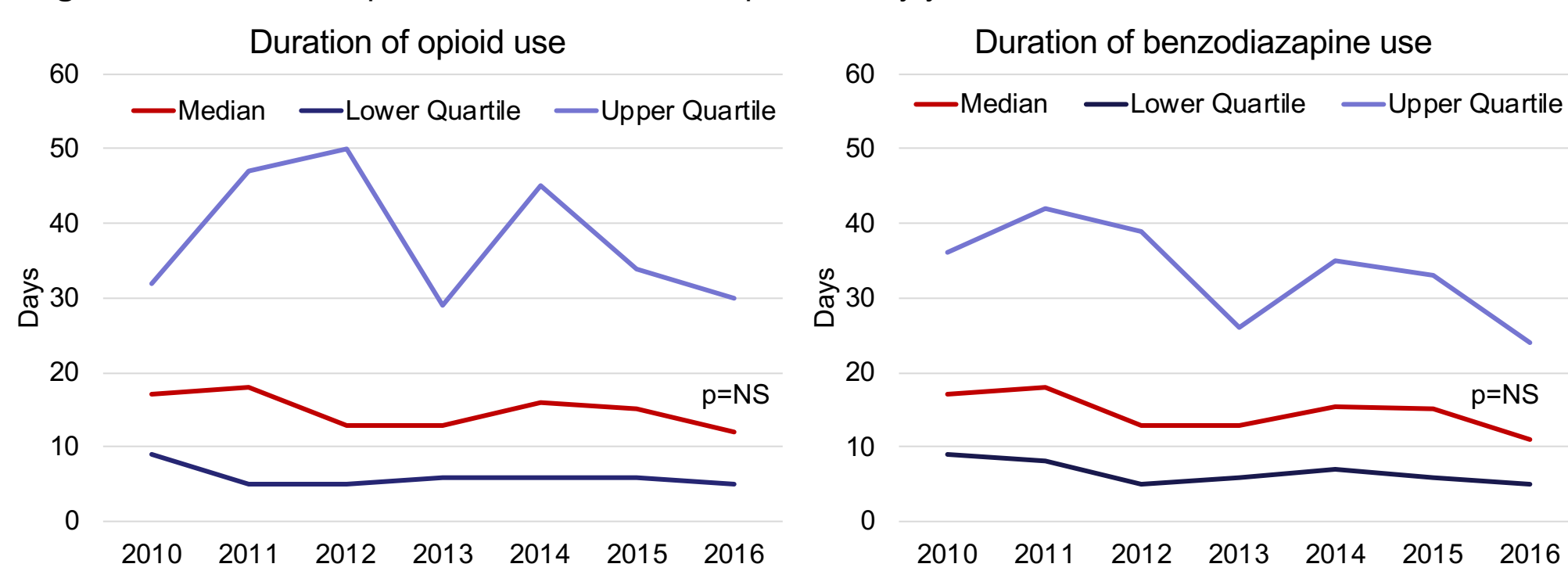


**Table 2:** Frequency and duration of analgesia and sedation among CDH patients stratified by ECMO use.

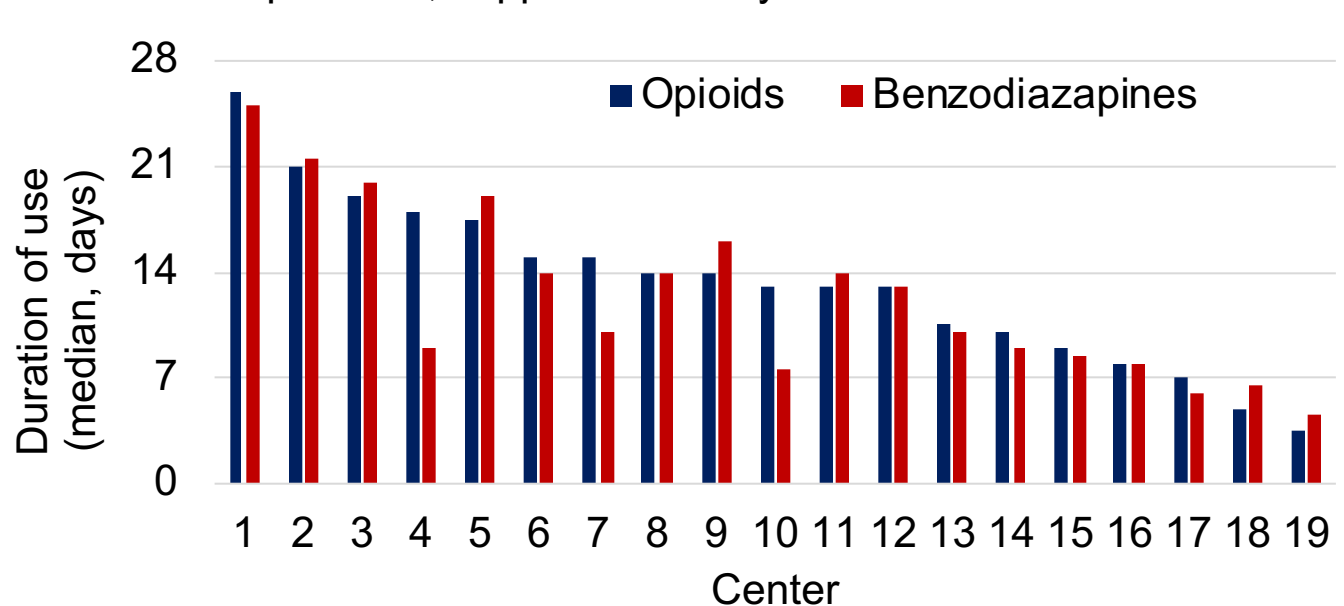
Medication	All CDH (n=1063)		No ECMO (n=748)		ECMO (n=315)	
	Frequency (n, %)	Duration (d, median [IQR])	Frequency (n, %)	Duration (d, median [IQR])	Frequency (n, %)	Duration (d, median [IQR])
Fentanyl	1016 (95.6)	4 [2,10]	708 (94.7)	3 [1,9]	308 (97.8)	6 [3,18]
Morphine	873 (82.1)	13 [5,27]	604 (80.7)	10 [4,21]	269 (85.4)	23 [12,40]
Methadone	185 (17.4)	29 [14,57]	95 (12.7)	22 [13,49]	90 (28.6)	39 [17,66]
Midazolam	825 (77.6)	11 [4,23]	453 (60.6)	7 [3,16]	282 (89.5)	21 [10,44]
Lorazepam	565 (53.2)	11 [4,27]	358 (47.9)	8 [4,19]	207 (65.7)	19 [8,42]
Dexmedetomidine	118 (11.1)	8 [2,19]	59 (7.9)	4 [1,12]	59 (18.7)	12 [6,26]
Clonidine	39 (3.7)	16 [4,40]	19 (2.5)	12 [4,21]	20 (6.3)	19 [11,62]
Acetaminophen	474 (44.6)	4 [2,7]	362 (48.4)	4 [2,7]	112 (35.6)	4 [1,8.5]

Survivors (opioids 775/776, 99.9%, benzodiazepines 592/776, 76.3%) and non-survivors (opioids 202/202, 100%, benzodiazepines 167/202, 82.7%) received medications frequently.

**Figure 2:** Duration of opioid use and benzodiazepine use by year, 2010-2016.

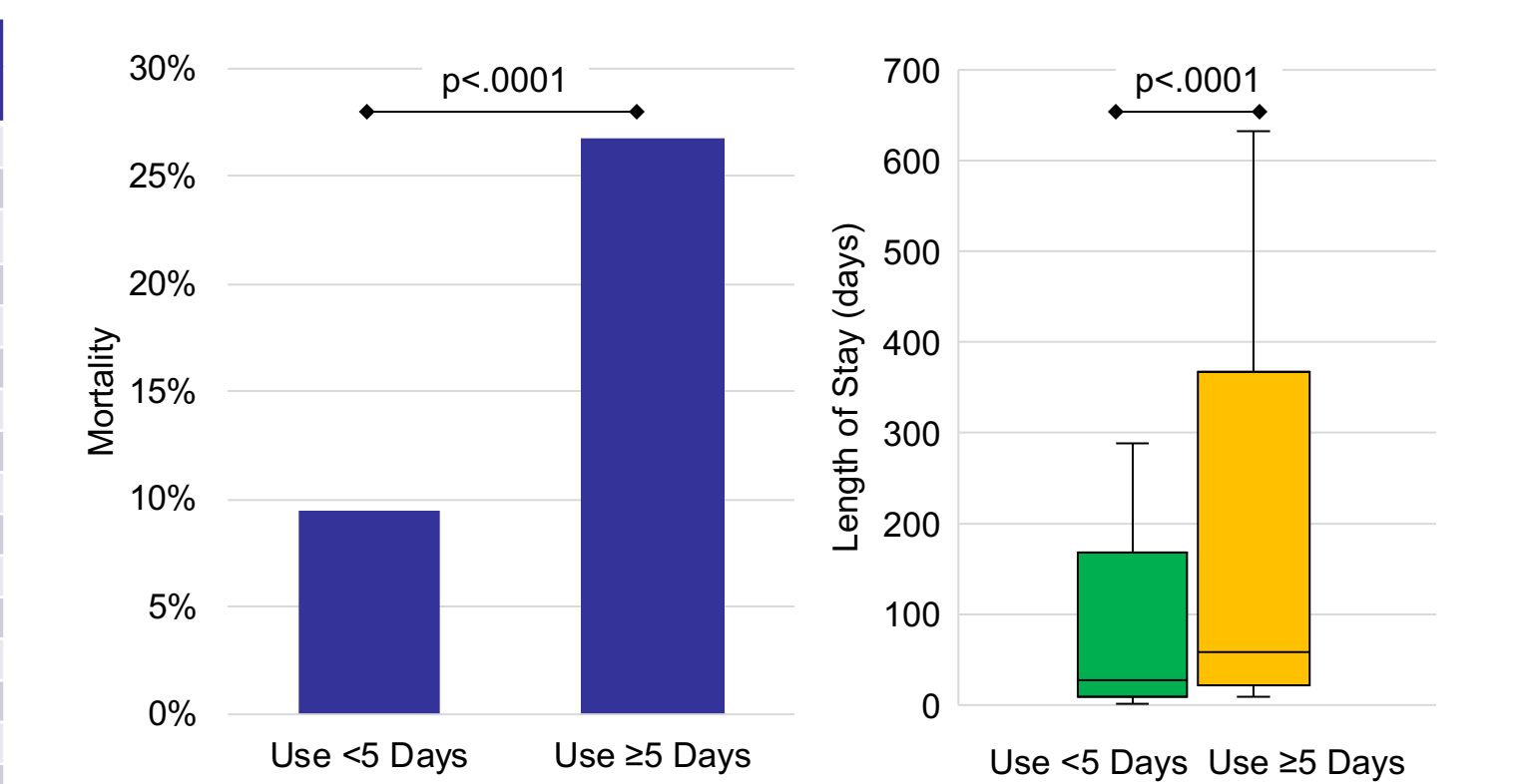


**Figure 3:** Inter-center variability for duration of opioid and benzodiazepine use, capped at 60 days.



3.5-fold variation in benzodiazepine duration (12.4 d, range 6-21.5 d; p<0.0001). 7-fold variation in opioid duration (13.2 d, range 3.5-26 d, p<.0001). Acetaminophen (n=474, 44.6%) use and duration also varied between centers (median 4 [2,7] d).

**Figure 4:** Concurrent use of analgesia and sedation.



Concurrent use of opioids (1062/1063, 99.9%) and benzodiazepines (825/1063, 77.6%) for ≥5 days was associated with mortality (26.2% vs 9.5%; p<.0001) and longer LOS (58.5 vs 27 d; p<.0001)

## Summary

CDH patients treated with ECMO were:

- More frequently treated with any benzodiazepine, methadone, dexmedetomidine, or clonidine.
- Had longer duration of use of analgesia and sedation medications.

Inter-center variation in use was marked, demonstrating 7-fold (opioids) and 3.5-fold (benzodiazepines) difference in duration.

36% of CDH patients had concurrent use of both opioids and benzodiazepines for at least 5 days. This was associated with:

- Longer length of hospital stay.
- Higher mortality.

## Conclusions

Analgesia and sedation medication use is frequent with a variable pattern of utilization across centers in infants with CDH, particularly those treated with ECMO.

Though unmeasured markers of illness severity persist, concurrent use of medications appears to be associated with adverse short-term outcomes.

## Acknowledgments

