Efficacy of Clonidine versus Phenobarbital in reducing Neonatal Morphine Sulfate therapy days for Neonatal Abstinence Syndrome. A Prospective Randomized Clinical Trial

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BACKGROUND

- Neonatal abstinence syndrome (NAS) affects 55-94% of infants exposed to intrauterine opioids
- Infants with moderate to severe NAS often require hospitalization and pharmacotherapy to reduce symptoms and prevent complications (death, poor weight gain, seizures, distress/discomfort)
- Treatment with opioid and an adjunctive agent has been shown to be useful in reducing the length of stay and caregiver demand
  - Phenobarbital, a barbiturate has been classically used for this purpose
  - Recent literature has raised concerns of neurocognitive and behavioral adverse effects with phenobarbital exposure.
  - Clonidine, an α-2 adrenergic agonist is emerging as a safe and effective alternative
- There have been no direct comparison of clonidine and phenobarbital as adjunctive therapies

OBJECTIVE

- To compare the efficacy of Clonidine versus Phenobarbital as an adjunct to Neonatal Morphine Sulfate (NMS) for treatment of NAS

METHODS

- Prospective, non-blinded, randomized, clinical trial conducted at a single Level III NICU at Baystate Children's Hospital from June 2010-June 2012
- Eligible infant were 0 to 15 days of age, had prenatal opioid exposure, developed moderate to severe NAS (defined as Modified Finnegan Scores persistently ≥ 8) and were medically stable
- Infants were excluded if gestational age <35 weeks; intrauterine growth retardation, congenital anomalies, exposure to benzodiazepines in utero or medically unstable
- Infants were block randomized and stratified based on maternal drug history of single vs. polydrug use to either NMS/C or NMS/P arm
- The medications were started based on the Modified Finnegan Scores (MFS) as per the unit protocol
- After an initial 48h period of MFS <8, NMS was weaned by 10% of absolute dose if scores remained below 8 in preceding 24 hours. Wean held if >8 x 2 in 24 hours and escalated if >10 x 2 in 24 hours
- For NMS/C arm, once off NMS, Clonidine was weaned in a stepwise fashion and discontinued prior to discharge home
- For NMS/P arm, infants were observed for at least 24h period before discharge home, with Phenobarbital to be weaned as outpatient

TABLE 1: Baseline Cohort Characteristics

Characteristic	Phenobarbital (*n = 34*)		Clonidine (*n=32*)		p-value
	mean	*(sd)*	*mean*	*(sd)*	
Gestational age, *wks*	38.6	(1.7)	39.2	(1.4)	0.11
Birth weight, *gms*	3,075.0	(476.0)	3,217.8	(488.0)	0.23
Head circumference, *cm*	33.5	(1.8)	33.8	(1.8)	0.58
Apgar at 5 min	8.8	(0.4	8.7	(0.6)	0.38
Maternal age	28.1	(4.6)	28.2	(4.8)	0.91
Gravida	3.4	(2.5)	3.6	(2.2)	0.76
Age at diagnosis, *mo*	2.3	(1.6)	1.8	(0.9)	0.17
Finn score	11.9	(2.1)	13.4	(3.2)	0.03
	median	*(min, max)*	*median*	*(min, max)*	
Methadone dose [1]	110.0	(5, 243)	112.5	(75, 188)	0.51
Buprenorphine dose [2]	8.0	(2, 24)	8.0	(2, 20)	0.42
Oxycodone dose [3]	27.5	(10, 40)	90	(40, 125)	0.03
	%	*(n)*	*%*	*(n)*	
Male gender	52.9	(18)	46.9	(15)	0.81
Breast Milk	26.5	(9)	25.0	(8)	> 0.99
Formula	94.1	(32)	96.9	(31)	> 0.99
Alcohol use	2.9	(1)	3.1	(1)	> 0.99
Smoker	55.9	(19)	56.3	(18)	> 0.99
Vaginal delivery	67.6	(23)	75.0	(24)	0.59
Methadone use	47.1	(16)	31.3	(10)	0.22
Buprenorphine use	32.4	(11)	53.1	(17)	0.14
Oxycodone use	23.5	(8)	25.0	(8)	> 0.99
Poly-drug use	41.2	(14)	40.6	(13)	> 0.99

Notes: 1 Phenobarbital: n = 16; Clonidine: n = 10
2 Phenobarbital: n = 11; Clonidine: n = 14
3 Phenobarbital: n = 6; Clonidine: n = 3

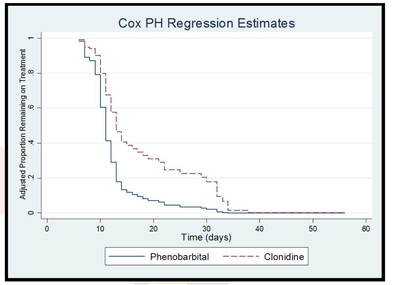
RESULTS

- 82 infants met inclusion criteria of which 68 consented and were randomized, with 34 infants in each arm of the study. 2 infants withdrew from Clonidine group for unrelated issues
- Our maternal cohort was notable for older, multigravid women, of which 41% were known to have polydrug use
- Almost 65% were in rehabilitation and on maintenance therapy due to prescription oxycodone abuse
- The baseline characteristics were similar for the two study groups as shown in Table 1
- Average treatment days on NMS showed a clinically non-significant difference in favor of Phenobarbital group by 4.6 days (Table 2)
- The average total dose of neonatal morphine sulfate between the two groups was similar (1.1 mg/kg, 95%CI: -0.1, 2.4; p=0.07)
- There were no adverse events noted for the Clonidine group
- In the Phenobarbital group oversedation was noted in 3 infants, with supratherapeutic serum levels requiring downward titration of the dose, but this was not statistically significant
- Post discharge phenobarbital was continued for an average of 3.8 months (range 1 to 8 months)
- For both the groups there was no inpatient mortality or re-admission within 1 week post discharge

TABLE 2: Regression Outcomes for Variables

Outcome	Univariable (n = 66)		Multivariable (n = 64)	
	Estimate (95% CI)	p	Estimate (95% CI)	p
Average NMS treatment days				
Phenobarbital	12.4 (10.1, 14.7)		13.6 (11.0, 16.1)	
Clonidine	19.5 (15.7, 23.2)		18.2 (14.9, 21.5)	
Difference	7.1 (2.7, 11.4)	0.001	4.6 (0.3, 8.9)	0.037
Total NMS treatment dose *(mg/kg)*				
Phenobarbital	3.8 (2.9, 4.7)		4.6 (3.8, 5.4)	
Clonidine	6.7 (5.1, 8.3)		5.7 (4.7, 6.8)	
Difference	2.9 (1.1, 4.7)	0.002	1.1 (-0.1, 2.4)	0.069

FIGURE 1
Rate of treatment completion for the two groups



CONCLUSIONS

- Phenobarbital when compared to Clonidine as an adjunct had a clinically non-significant shorter duration of treatment with NMS
- There was no difference in the total NMS used during the treatment phase
- However, Clonidine had an overall shorter NAS therapy time as no continued outpatient treatment was required
- Clonidine was safe with no adverse effects noted

FUTURE AIMS

- To implement the clinical use of Clonidine as an adjunct to neonatal morphine sulfate for treatment of NAS
- To compare the long term neurocognitive and behavioral outcomes for the two study groups

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