The Effects of Clonidine on Neonatal Abstinence Syndrome Patient Outcomes

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Abstract

Neonatal abstinence syndrome (NAS) is one of the most common diagnoses in Neonatal Intensive Care Units today due to the unprecedented number of women taking opioids during pregnancy. After becoming physically dependent on the drug in utero, infants with NAS are born suffering severe withdrawal symptoms and neurological instability. Morphine sulfate (MS) is the most common drug of choice used to treat opioid withdrawal, but it poses a high risk to vulnerable infants as it causes oversedation and respiratory depression. Current research shows that incorporating clonidine, an antihypertensive medication, into the drug regimen reduces withdrawal symptoms without severe side effects. East Tennessee Children's Hospital's (ETCH) NICU has recently changed its treatment protocol for NAS. Providers are now administering clonidine as an adjunctive therapy sooner in the treatment of NAS at lower doses of morphine. Therefore, the purpose of this study was to investigate whether the new protocol produces better neonatal outcomes based on a reduction in the overall duration of stay, height of MS required, need for phenobarbital, and number of rescue doses used. Designed as a quasi-experimental retrospective case study, 208 patient charts were divided into two groups based on the new protocol (clonidine introduced when MS < 140 mcg) and old protocol (clonidine introduced when MS > 140 mcg). T-tests and chi-square analyses were conducted to compare variables between groups. The results supported the hypothesis that administering clonidine earlier at lower doses of MS decreases the length of stay in NICU, total height of MS administered, and need for phenobarbital. However, the difference in the number of rescue doses was non-significant between groups. These findings suggest that the new treatment protocol at ETCH is effective and should continue to be implemented in order to maintain more efficient and safe treatment of NAS.

The Effects of Clonidine on Neonatal Abstinence Syndrome Patient Outcomes

Today, in the midst of the opioid epidemic, the prevalence of neonatal abstinence syndrome (NAS) has reached an unprecedented height as women take illicit substances during pregnancy which results in chronic fetal drug exposure. The infant may then experience severe withdrawal symptoms after birth when suddenly removed from the maternal drug source, resulting in a diagnosis of neonatal abstinence syndrome (NAS). From 2000 to 2016, the national prevalence of maternal opioid use increased exponentially causing a six-fold parallel increase in NAS diagnoses (Batra et al., 2020). It is now estimated that an infant is born with NAS every 25 minutes in the United States, meaning further investigation into both the prevention and treatment of this syndrome is becoming increasingly important (Miller, 2019).

Neonatal Abstinence Syndrome

Infants diagnosed with NAS have hyperexcitable central and autonomic nervous systems after birth because their bodies are no longer under the depressant effects of opioids in the womb (Sanlorenzo et al., 2018). Opioids, stimulants, benzodiazepines, and hallucinogens readily pass from maternal to fetal blood flow through the placenta with heroin and methadone being the most common causes of NAS (Siu & Robinson, 2014). These drugs act on opioid receptors throughout the body in the central/peripheral nervous system and gastrointestinal tract, affecting nearly every organ system in the body.

Unregulated neural activity leads to a vast array of symptoms with the most common being excessive irritability, difficulty feeding, and gastrointestinal upset (Kocherlakota, 2016). More serious reactions such as seizures, muscle rigidity, tachycardia, hypertension, and hypothermia require constant monitoring in the Neonatal Intensive Care Unit (NICU) (Kocherlakota, 2016; Streetz et al., 2016). These changes to vital signs occur because the body

has developed mechanisms to heighten the normal ranges of heart rate, blood pressure, and respiration rate in order to maintain homeostasis despite the depressant influence of opioids (Kolcherlota, 2016; Streetx et al., 2016). Given the acuity of this condition, 60-80% of patients with NAS require pharmacological treatment in critical care settings (Siu & Robinson, 2014).

According to multiple studies, a diagnosis of NAS in infancy has long lasting effects on early childhood and adolescent development (Bada et al., 2015; Miller, 2019; Siu & Robinson, 2014). Children with a history of NAS are more likely to suffer from neurodevelopmental disorders; over 20% are diagnosed with learning disorders, language delays, and cognitive difficulties by age ten (Miller, 2019). A diagnosis of NAS in infancy was significantly predictive of abnormal behavioral development such as attention deficit hyperactivity disorder and oppositional defiant disorder later in childhood (Miller, 2019). Therefore, the impact of antepartum drug use extends well-beyond development into the womb to physical symptoms in infancy and psychological challenges in adolescence.

Clonidine as a Treatment Option

Mirroring other substance-use and withdrawal disorders, the major cause of concern for patients with NAS is the sudden change from dependence on a drug in utero to cessation after birth. The standard of care for NAS treatment includes using progressively smaller doses of the opioid agonist morphine sulfate (MS) until the patient's body is physiologically stable without it. MS successfully lessens the severity of withdrawal symptoms, but like all opioids, it greatly increases the risk of over-sedation and respiratory depression in an already vulnerable infant (Siu & Robinson, 2014). In addition, MS was found to significantly prolong the duration of treatment in the NICU and be less efficient than other pharmacological options at treating NAS (Kocherlakota, 2016; Disher et al., 2019).

In recent years, research has been conducted to identify alternative treatments for NAS which have less adverse reactions than MS. One drug that shows promise is clonidine. Clonidine has been used as both a primary and adjunctive therapy with MS to effectively treat NAS with a favorable side effect profile (Broom & So, 2011; Streetz et al., 2016). Clonidine is marketed as an antihypertensive medication because it is an alpha-adrenergic receptor agonist that inhibits the release of norepinephrine throughout the body (Broome & So, 2011). While decreasing blood pressure and heart rate, this biological mechanism also lessens the hyperexcitability of neurons (Agathe, 2009). Therefore, it was approved by the Federal Drug Association (FDA) in 2010 as a treatment alternative to amphetamines for attention deficit and hyperactivity disorder (ADHD) in children (Saabadabi & Yasei, 2019).

Using the same philosophy, the drug is now used off-label as a treatment for NAS. By binding to adrenergic receptors, overactive neural impulses are inhibited and withdrawal symptoms are prevented. Patients treated with clonidine have improved outcomes when compared to those that did not receive the drug as evidenced by more stable heart and respiration rates in addition to reduced symptoms of irritability, tremors, and gastrointestinal upset (Streetz et al., 2016). Clonidine is minimally addictive and has few adverse reactions besides the need to monitor for hypotension. It has a shorter half-life than opioids which reduces the risk of oversedation, making it a safer option than MS (Streetz et al., 2016).

Literature Review

Before conducting this study, a systematic review of the literature was done to provide a foundation of knowledge while also identifying limitations in current research. The earliest article presenting clonidine as an effective NAS treatment was published in 2009, around the time that it was used in clinical trials as an ADHD medication (Agathe, 2009; Saabadabi &

Yasei, 2019). Clonidine was first introduced as a secondary treatment, but more recent studies show it is even effective as a monotherapy without necessitating any opioid administration (Bada et al., 2015).

In an experimental study with a randomized double-blind design, Agthe et al. (2009) hypothesized that clonidine would reduce the opioid detoxification time for infants with NAS when used in combination with diluted tincture of opium (DTO). A convenience sample of 80 patients diagnosed with NAS and treated with DTO were randomly assigned either clonidine or a placebo as an adjunctive therapy using a standardized algorithm. The duration of hospital stay was used as the primary outcome as a means to quantify detoxification time. The clonidine group had a significantly shorter length of therapy (11 days) than the placebo (15 days). Higher daily doses of opium were required by 40% of the placebo group whereas only 20% of the clonidine group. When used with DTO, clonidine stabilized and detoxified infants with NAS faster than DTO alone. Agthe et al. (2009) recommend further research using a larger trial to determine long-term safety of using clonidine as an NAS treatment.

Broome and So (2011) compared length of NICU stay between groups of infants diagnosed with NAS treated with clonidine or MS. Using a systematic review of the literature, they found that the clonidine group had a significantly shorter duration of hospital stay than the MS group. In addition, clonidine was shown to be effective at treating NAS through analysis of the group's Finnegan Scores before and after therapy. The Finnegan Neonatal Abstinence Scoring System is used to assess newborns for symptoms of withdrawals based on 21 subjective signs; higher scores on the scale indicate a more severe case of NAS. Within four hours of clonidine administration, the infants' Finnegan Scores decreased significantly from 6.4 to 1.9. A Finnegan Score of 1.9 means that infants only demonstrated one more severe or two lesser NAS

symptoms after clonidine (See Appendix A for Finnegan Scoring Chart). They also compared the total amount of diluted tincture of opium (DTO) required when clonidine was used as an adjunctive therapy compared to a placebo. Significantly less DTO/kg was required for the clonidine group which shows that clonidine is effective at reducing the total amount of opioids needed to treat NAS. Overall, clonidine treatment resulted in shorter length of stays, less opioid use, and less respiratory depression in patients with NAS. The only identified limitation of this study is the outdated use of Finnegan Scoring as a means of measurement, being that the most recent methodology is the "Eat, Sleep, Console" model (See Appendix B for "Eat, Sleep, Console" Model).

Through a meta-analysis of pharmacological treatments for NAS, Disher et al. (2019) compared buprenorphine, MS, clonidine, DTO, methadone, and phenobarbital. MS and phenobarbital were consistently ranked the lowest in terms of length of stay and duration of treatment. Buprenorphine was identified as the optimal drug being that it produced the shortest length of stay by 12.75 days compared to MS and only 2.19 days compared to clonidine. Because MS is the standard of care for patients with NAS, Disher et al. recommend further investigation into other treatment options which produce better patient outcomes. Clonidine ranked closely to buprenorphine in every outcome, and the investigators mention that it may be an even more favorable treatment option because it is not a narcotic.

Because most research focused on the use of clonidine as a secondary drug, Bada et al. (2015) questioned its effect on NAS symptoms as a monotherapy. A double blind, randomized trial of 31 newborns diagnosed with NAS without other major medical conditions was used. When compared with MS, clonidine produced significantly less detoxification time in neonates: 26 versus 13.5 days. Upon assessment of the two groups, the clonidine group showed improved

scores for attention and handling whereas the MS group did not. The results indicate that clonidine may be more effective and efficient than MS alone in treating NAS. Limitations of the study include a small sample size and lack of long term follow-up.

Overwhelmingly, the literature demonstrates that clonidine is a prime alternative or adjunct treatment to other opioids, barbiturates, or benzodiazepine therapies. It produces better patient outcomes with significantly less lengths of stay in the NICU, duration of treatment, and adverse events.

Purpose

Current drug regimens for NAS must continue to be evaluated in order to determine the most effective and safest option for infants experiencing opioid withdrawal. East Tennessee Children's Hospital's (ETCH) NICU has recently changed its treatment protocol for NAS. According to the protocol, the initial height of MS is increased until a dose is found at which NAS symptoms are managed. Then, MS is slowly weaned as Finnegan Scores improve until the infant can remain stable without any intervention. In the old protocol, clonidine was introduced when MS doses reached 200 micrograms (mcg). The new treatment protocol indicates that clonidine should be administered sooner in the escalation of MS at 140 mcg.

Therefore, the purpose of this research is to investigate whether clonidine is more effective as an adjunctive treatment for NAS at a lower dose of MS as evidenced by better patient outcomes. Ideally, early introduction of clonidine in the drug regimen should stop the MS escalation and reduce the amount of opioids administered. Four outcomes will be compared between the new protocol and old protocol groups with the primary being length of stay in the NICU and others being the need for phenobarbital, height of morphine required, and the number of rescue doses administered in each case. It is hypothesized that using clonidine earlier in the

treatment of neonatal abstinence syndrome alongside lower doses of morphine sulfate (<140 mcg) will:

1. Decrease the length of stay in the NICU
2. Decrease the height of morphine sulfate required
3. Decrease the number of phenobarbital doses administered
4. Decrease the number of rescue doses used

when compared with introducing it later in the protocol at higher doses of morphine sulfate (>140 mcg).

Methods

A quasi-experimental posttest retrospective design was used to conduct a chart review of 208 patients treated for NAS at East Tennessee Children's Hospital (ETCH). The intervention evaluated is the new NAS treatment protocol in which clonidine is introduced at lower doses of MS. For the purposes of this study, the term "old protocol" refers to the group of patients given clonidine when MS doses were greater than 140 mcg. The term "new protocol" refers to the group of patients given clonidine when MS doses were less than or equal to 140 mcg. The four outcomes measured are length of stay, height of MS, number of phenobarbital doses, and number of rescue doses.

While the intervention is the use of clonidine, no manipulation of the variables or patient interaction was required by the primary investigator since it is a posttest design. All patients included in the study had previously signed a general informed consent form for the hospital as a whole which allowed the use of their data in medical research. No additional consent was required for the purposes of this project. The study gained Institutional Review Board (IRB)

approval from ETCH, and a confidentiality contract through the National Institute of Health was signed by all involved parties in April 2022 (See Appendix C & D).

After being assigned access to a select number of applicable NAS patient charts, the primary investigator gathered all data points by sorting through electronic medical records (EMR). Patient confidentiality was maintained throughout the process by removing all identifiable information and assigning patients anonymous numbers (1-208). Demographic data and variables were then logged under each patient number into an Excel spreadsheet on an encrypted, password-protected flash drive. The reliability of data transfer and transcription was established by triple checking for accuracy before analyzing results. It was assumed that information documented in the EMR was a valid indicator of the care received by infants at ETCH.

Sampling

On behalf of ETCH, a neonatologist (Dr. Malinda Harris) and neonatal nurse practitioner (Kyle Cooke, NNP) granted the primary investigator access to a given number of applicable medical records for the purposes of this study. Convenience sampling was then used to identify 208 patient charts from the accessible population - neonates with a sole diagnosis of NAS that have been treated at ETCH's NICU using a combination of MS and clonidine. The charts were divided into the "old protocol" group (n=88) and "new protocol" group (n=120) based on when clonidine was administered in the treatment protocol. The sample size was determined based on the greatest number of patient charts accessible by the primary investigator and also usable in the study according to the criteria detailed below. Power analysis was calculated using sample size, significance level, and effect size. Based on the analysis, the sample size of 208 is sufficient to determine the effect of the intervention at a significant level.

Inclusion criteria for the sample are ‘neonates that have been diagnosed with NAS, treated at ETCH’s NICU, and administered clonidine as an adjunctive therapy to MS. Exclusion criteria include not completing the treatment at ETCH or having a disease/diagnosis in addition to NAS that requires significant treatment that would likely impact the outcome being evaluated. The neonatologist was responsible for identifying neonates to be excluded from the study. For example, infants with cerebral palsy or Down Syndrome in addition to NAS would be excluded from the study since their length of stay may be determined by their other diagnoses and would not be an accurate representation of NAS treatment. Because convenience sampling is used, there is a potential for sampling bias being that the included participants are based on those who are eligible and available.

Measures

Variables to be collected are the length of stay, highest dose of MS administered, number of phenobarbital doses, and number of rescue doses. Previous and current research on NAS consistently uses these outcomes as valid determinants of effective treatment. Overall, shorter treatment time and less opioid use indicate better patient outcomes for those with NAS.

Length of stay (“LOS”) is the number of days spent in the NICU from admission to discharge. The highest dose of MS (“high MS”) is quantified as the most morphine given in one single dose throughout treatment measured in micrograms. The number of phenobarbital doses (“phen”) is the number of times phenobarbital was used as a tertiary drug treatment. The number of rescue doses (“rescue”) signifies the amount of times an emergency dose of MS was required in addition to the prescribed treatment protocol to keep the infant at a physiological stable state.

In addition to these outcomes, demographic data was also collected to compare the old and new protocol groups. Data to be collected are each infant's sex (male, female), gestational age (in days), birth weight (in grams), and feeding type (breast, bottle, both).

Data Analysis

The extracted data was analyzed post-intervention using a retrospective review. Descriptive statistics were first conducted for the demographic data. Frequencies and distributions were used to describe the sex, gestational age, birth weight, and feed type. Means and standard deviation were used to describe gestational age and birth weight. In order to mitigate the possibility of a history threat to internal validity, t-tests and chi-square analyses were conducted to determine equivalency (i.e., there was no significant difference) of the demographics between groups (See Table 1).

The hypothesis is that introducing clonidine at lower doses of MS will reduce the LOS, decrease the amount of MS administered, decrease the need for phenobarbital, and decrease the number of rescue doses. Paired independent samples t-tests were used to compare the old protocol and new protocol groups based on each of the four outcomes. Descriptive statistics were then used to compare the identified outcome variables for each group.

Demographic Data in Descriptive Statistics

To better understand the population at hand, demographics were analyzed with descriptive statistics. For the nominal data points, gestational age and birth weight, ranges were provided along with the mean and standard deviation (Table 1). Bar graphs were then used to depict frequency distributions for these two demographics (Figure 1 & 2).

Table 1

T-test for Equality of Means Based Gestational Age and Birth Weight

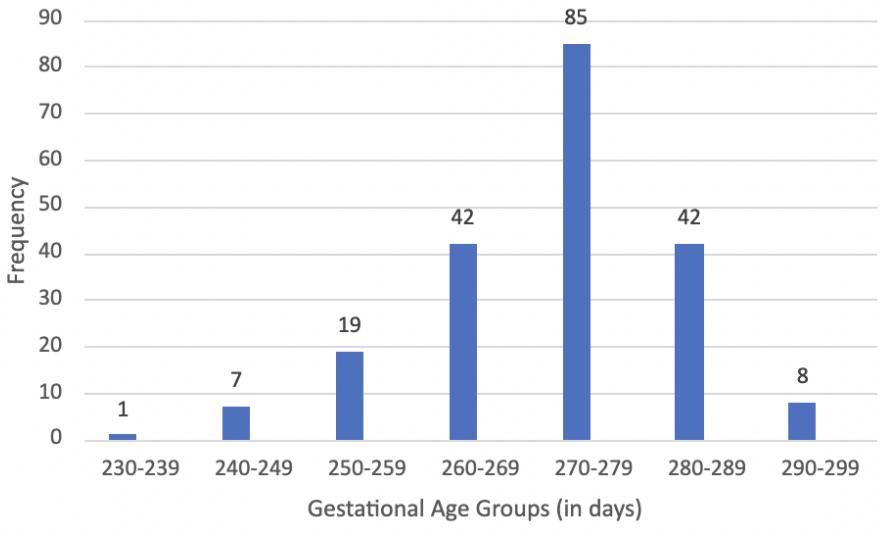
	M	SD	Min	Max	t	*df*	SE	*p*
Gestational Age	272.33	13.93	237	532	-1.316	111.697	3.628	0.191
Birth Weight	3095.66	447.856	2059	4200	-8.83	94.81	60.643	0.75

Note. Mean parameter values and frequencies are shown for gestational age and birth weight for the sample as a whole. The results of paired *t* tests (equal variances not assumed) are also included to show that no significant difference exists between groups based on these demographics.

Gestational age ranged from 237 to 532 days with an average of about 272 days (M = 272.33; SD = 13.93). The sample was divided into age groups by every 10 days of gestation. Figure 1 depicts a normal bell-curve distribution pattern between these age groups with 40.8% of infants (n=85) between 38.5-39.5 weeks (270-279 days) gestation while 20.2% (n=42) were either 37-38.5 weeks or 40-41 weeks (260-269; 280-289 days, respectively). Only 12% of infants (n=25) were considered premature with less than 258 or less days gestation (Figure 1). Three outliers were identified within the data at 373, 379, and 532 days gestation; these data points are not included on Figure 1 since they were too high to be accounted for with the given scale.

Figure 1

Bar Graph Depicting Frequency Distribution of Gestational Age

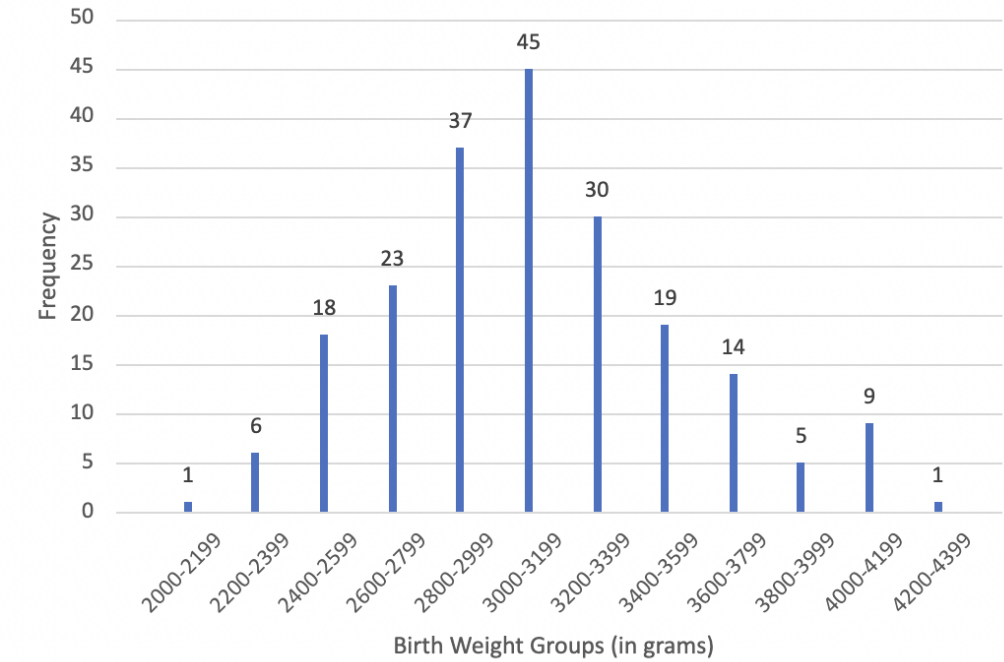


Note. The sample was divided into age groups by 10 days gestation. Three outliers were too high to be included on the bar graph: 373, 379, 532.

Birth weight ranged from 2059 to 4200 grams, with an average of around 3096 grams (M=3095.66; SD = 447.856). Figure 2 shows the normal distribution of the sample based on weight classes, each separated by 200 grams. Most infants (n=45; 21.6%) weighed between 3000-3199 grams. Only 7.2% of infants (n = 15) were considered low birth weight at less than 2500 grams (Figure 2). This strengthens the validity of the research as neither prematurity nor low birth weight were prevalent problems in the neonatal sample at hand, maintaining the integrity of the tested outcomes.

Figure 2

Bar Graph Depicting Frequency Distribution of Birth Weight



Note. The sample was divided into weight groups by every 200 grams.

Table 2 describes sex and feed type in frequencies and percentages. The population was fairly equally distributed by sex with 56.7% male (n=118) and 48.1% female (n=90). The feed type was also investigated as to whether the infants were given formula, breast milk or both. The vast majority of 90.4% (n=188) were bottle fed, while only 9.6% (n=20) received both breast and formula. Not a single infant was exclusively breastfed.

Table 2

Frequencies and Percentages in Sex and Feed Type

Sample Statistic	n	%
Sex		
Male	118	56.7
Female	90	48.1
Feed Type		
Breast	0	0
Bottle	188	90.4
Both	20	9.6

To ensure the validity of research, the equivalency of means was analyzed between the New Protocol and Old Protocol groups using demographic data. A paired t-test was conducted for gestational age and birth weight (Table 1). Both gestational age ($t = -1.316$, $df = 111.697$, $p = 0.191$) and birth weight ($t = -8.83$, $df = 94.81$, $p = 0.75$) were *not* significantly different between groups. A chi-square analysis was done for the ordinal data and revealed that *neither* sex *nor* feed type were significantly different between groups. Table 2 demonstrates that for sex ($X^2 = 2.068$, $df = 1$, $p = 0.15$) and for feed type ($X^2 = 0.484$, $df = 1$, $p = 0.487$). In all of these tests, $p > 0.05$. Therefore, it can be assumed that there is *no* significant difference, and groups are equal based on demographic factors.

Table 2

Chi-Square Analysis Conducted on Sex and Feed Type

	X^2	*df*	Fisher's Exact Test	*p*
Sex (male = 0, female = 1)	2.068	1	0.16	0.15
Feed Type (breast = 0, bottle = 1, both = 2)	0.484	1	0.635	0.487

Note. When this information was originally gathered from the EMR, each ordinal data point was

assigned a numerical value in order to conduct chi-square analyses. These numbers are listed in parentheses beside the demographic they represent for clarification (i.e. male = 0).

Analysis of Variables

In order to test the hypothesis, paired t-tests were conducted on each of the four variable outcomes to determine whether there was a significant difference between the old and new protocol regarding the length of stay, height of MS, use of phenobarbital, and need for rescue doses. The results of these statistical analyses are outlined in Table 3. Table 4 provides statistics about the demographic and outcome variables represented by each group separately so that the data can be further compared between groups.

The average height of MS when clonidine was introduced to the old protocol group (all infants received it at MS > 140 mcg) was 196.25 mcg (SD = 25.878) compared to the new protocol group (all infants received it at MS < 140 mcg) which had an average of 75.33 mcg (SD = 52.866). This represents a mean difference of 120.92 mcg of MS when clonidine was used in NAS treatment.

Table 3

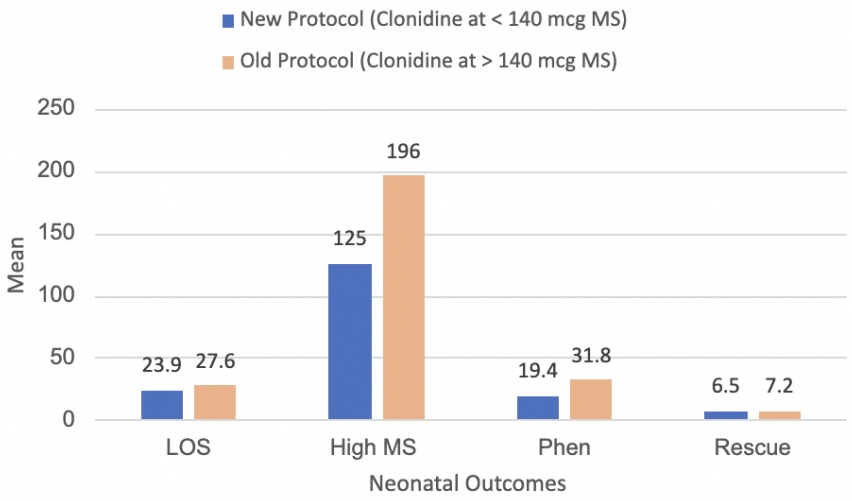
Results of Paired T-test for Equality of Means Between New and Old Protocol Groups

	New Protocol		Old Protocol					
	M	SD	M	SD	t	*df*	SE	*p*
Length of Stay	23.86	7.633	27.61	5.974	-3.633	120.496	1.031	<0.001*
Highest MS Dose	124.96	63.963	196	34.234	-8.83	94.81	8.045	<0.001*
Phenobarbital Doses	19.37	36.63	31.78	39.626	-2.265	157.968	5.478	<0.001*
Number of Rescue Doses	6.52	3.489	7.16	3.507	-1.252	148.373	0.508	0.213

Note. Mean parameter values are shown for the New Protocol group (n=73) and Old Protocol group (n=135) as well as the results of *t* tests (equal variances not assumed) comparing the parameter estimates between the two groups.

Figure 3

Comparison of Means Between New and Old Protocol Groups Based on Neonatal Outcomes



Note. Meaning of the abbreviations for neonatal outcome variables are explained in the Measures section.

Length of stay (LOS) was the primary outcome tested as this is the best determinate of the efficiency and effectiveness of a treatment protocol. The new protocol group had a mean LOS of 23.86 days (SD = 7.633) compared to the old protocol group's mean of 27.61 (SD =5.974) (Table 3). The new protocol group had a significantly shorter LOS than the old protocol group by a difference of 3.7 days (Figure 3). The t-value was -3.633 with 120.496 degrees of freedom and a significance level of $p < 0.001$. This means that infants with NAS treated with clonidine earlier in the treatment protocol are discharged from the NICU sooner.

The highest dose of morphine sulfate administered throughout NAS treatment was also significantly less in the new protocol group as compared to the old protocol group. The t-test shows a mean difference of 71 mcg between groups (t-value = -8.83, df = 94.81, $p < 0.001$). Table 4 shows that the new protocol had an average highest dose of 124.96 mcg (SD = 63.936),

while the old protocol group's was 196.00 mcg (SD = 34.234). Therefore, smaller doses of MS overall were used to treat infants from the new protocol group.

Table 4

Mean Parameters of Demographic and Variable Data by Group

	N	M	SD
New Protocol Group			
Demographics			
Sex	73	0.48	0.501
Gest Age	73	0.501	13.93
Birth Weight	73	3095.66	447.856
Feed Type	73	0.22	0.624
Outcomes			
LOS	73	23.86	7.633
High MS	73	124.96	63.936
Phen	73	19.37	36.63
Rescue	73	6.52	3.489
Old Protocol Group			
Demographics			
Sex	135	0.38	0.487
Gest Age	135	277.1	31.855
Birth Weight	135	3114.98	418.687
Feed Type	135	0.16	0.544
Outcomes			
LOS	135	27.61	5.974
High MS	135	196	34.234
Phen	135	31.78	39.626
Rescue	135	7.16	3.489

The difference in the number of phenobarbital doses given to patients was significantly different between groups. When clonidine was introduced earlier in treatment, infants received 12.41 less doses than those treated with the old protocol (Table 3; Figure 3). The t-value is -2.265 with 157.968 degrees of freedom and a significance of $p < 0.001$. Looking at each group's individual mean for phenobarbital, the new protocol had 19.37 doses (SD = 36.63) and the old

protocol had 31.78 (SD = 39.626) (Table 4). Infants treated with the new protocol did not require tertiary drug therapy in the form of phenobarbital as often as those treated with the old protocol.

Lastly, the number of rescue doses of morphine sulfate was evaluated using a t-test. Table 3 shows that the difference of only 0.7 dose between the new and old protocol groups was nonsignificant (t-value = -1.252, df = 148.373, p = 0.213). The new protocol group had a mean of 6.52 doses (SD = 3.489) compared to the old protocol group's 7.16 (SD = 3.489). Because p > 0.05, the null hypothesis is supported. It can not be concluded that introducing clonidine earlier in the treatment of NAS has any correlation with how often rescue doses are administered.

Discussion

The purpose of this study was to determine whether a new treatment protocol put in place at East Tennessee Children's Hospital was effective at producing better outcomes in patients diagnosed with neonatal abstinence syndrome.The findings detailed above indicate that three out of four of the hypotheses were supported. Using clonidine earlier in the treatment of neonatal abstinence syndrome alongside lower doses of morphine sulfate (<140 mcg):

1. Decrease the length of stay in the NICU
2. Decrease the height of morphine sulfate required
3. Decrease the number of phenobarbital doses administered

These three variables are valid determinants of health because they show that treatment duration is shorter and less pharmaceutical intervention is required overall when patients are treated with the new treatment protocol.

There was, however, one hypothesis which was not supported by this study: The number of rescue doses administered throughout the treatment of infants diagnosed with NAS was *not* significantly different between new and old protocol groups.

Significant Findings

A significant reduction in LOS is correlated with more efficient and effective medical management of NAS. Infants treated with the new protocol are discharged home nearly four days sooner, because they do not require medications or monitoring for as long as the old protocol group. This positively impacts patients by enhancing the opportunity for parent-child bonding at home and reducing the stress associated with a hospital stay. Infants are discharged from the hospital and able to begin bonding with their families at home sooner. The formation of a secure attachment with a parent or guardian is important for infants with NAS since they often exhibit excessive fussiness and irritability. In fact, studies show that supportive measures such as swaddling, cuddling, and rocking the infant in a quiet, calm environment should be included in the care of all patients diagnosed with NAS (Siu & Robinson, 2014). A shorter stay is not only beneficial for the social and emotional well-being of the patient and their families, but it is also cost effective for the hospital corporation by reducing the occupancy and staffing required in the NICU.

Infants in the new protocol group required 71 mcg less MS in the highest dose administered throughout treatment. This is an incredibly significant finding as it means infants are less at risk for the oversedation and respiratory depression caused by MS, especially in high doses and lengthy treatments. Clonidine is a safer drug choice being that it has very few associated adverse reactions and has a short half-life which allows the body to metabolize it quicker than opioids. Therefore, alongside the current literature, the results of this study support the transition to using clonidine earlier and more strategically in the treatment of NAS.

When less drugs are required to manage symptoms, the treatment is considered more effective. The new protocol group required 12.41 less doses of phenobarbital. This indicates that

the introduction of clonidine at less than 140 mcg of MS was sufficient at managing symptoms and does not require tertiary drug use as often as the old protocol. Less phenobarbital may also be associated with shorter length of stay and duration of treatment according to Disher et al. (2019) whose study showed phenobarbital and MS are the lowest ranked in these health outcomes.

Nonsignificant Findings

Although the new protocol group required less rescue doses during treatment than the old protocol group (M = 6.5, M = 7.2 respectively), the difference was non-significant. Therefore, the null hypothesis was supported, and early introduction of clonidine can not be correlated with less rescue doses of MS. Rescue doses are administered when the patient's NAS symptoms are not well managed at the current dosage of MS and require a supplemental MS dose to maintain stability. Therefore, the findings imply that infants treated with both the new and old protocol experience a similar amount of declines requiring additional treatment.

The researchers conclude that the non significant difference in rescue doses may be caused by the limitations of the study related to how rescue doses were documented. Every provider documented orders for them in a different section of the EMR, making it difficult to calculate totals. In addition, it was reported by both a Neonatal Nurse Practitioner and RN who work at ETCH that the administration of rescue doses are often not accurately documented by providers or RNs. Therefore, it does not seem reliable to trust the information gathered from EMR pertaining to rescue dosing without having witnessed the doses being administered in person.

Limitations

Only a few limitations were identified throughout the completion of the study: lack of a clear start date for the new treatment protocol, differences in documentation between staff, and the potential for sampling bias.

During the early stages of data collection, it became evident that the new treatment protocol was not immediately implemented by every provider when it was first announced by ETCH. This prevented the original design of the study which was to use the treatment date as a means of dividing patients into the new vs old protocol groups. However, this limitation was easily solved by using a more objective and measurable approach to dividing groups based on the dose of MS when clonidine was administered.

Because the study is a retrospective chart review, accurate documentation was extremely important to maintaining the integrity of the study. The second limitation had to do with discrepancies between how staff members documented care in the EMR as previously discussed. More specifically, medication administration was not always precise in patient charts. Rescue doses of MS were often not scanned at the bedside, meaning RN's would have had to manually document that a rescue dose was administered. Additionally, providers would need to retrospectively chart an order for the dose. Because of the extra steps involved, rescue doses are often mislabeled or inaccurately numbered in the EMR. This made it difficult to standardize across the sample, but all documented doses were accounted for by individually counting every dose in the Medication Administration Record rather than relying on the sums listed in the EMR. However, if a dose was never documented, the researcher had no way of knowing or including these doses in the study.

Lastly, because convenience sampling was used, the study was limited by the potential for sampling bias. The researchers only had access to a given number of patient cases: those treated within the last few years at ETCH who received both MS and clonidine in the treatment of NAS but had no other medical diagnosis. Therefore, the results of this study supported the hypothesis in relation to the sample at hand, but it was unclear as to whether they can be generalized to the population.

Recommendations/Conclusions

Overall, the findings of this study strongly support the use of the new treatment protocol for neonatal abstinence syndrome patients at East Tennessee Children's Hospital. Clonidine should continue to be introduced earlier in the treatment of NAS because it was correlated with shorter hospital stays in the NICU, smaller doses of MS administered, and reduced need for tertiary drugs like phenobarbital.

The goal of all healthcare should be to manage symptoms in the safest, least invasive way possible with the patient's best interest always as the priority. This study demonstrates that using clonidine alongside less MS was *more* effective at treating NAS than higher doses of MS. Less MS is safer for patients because they are less likely to experience adverse reactions associated with opioids.

In the future, this study should be conducted on a large sample size with infants from multiple hospitals so that the results can be applied to the population of neonates as a whole rather than just those treated at ETCH. Additionally, more research is needed on the use of clonidine as a monotherapy for NAS. Current literature suggests that the syndrome can be managed solely using non-opioid treatment options which would be a positive transition in practice for the betterment of patients.

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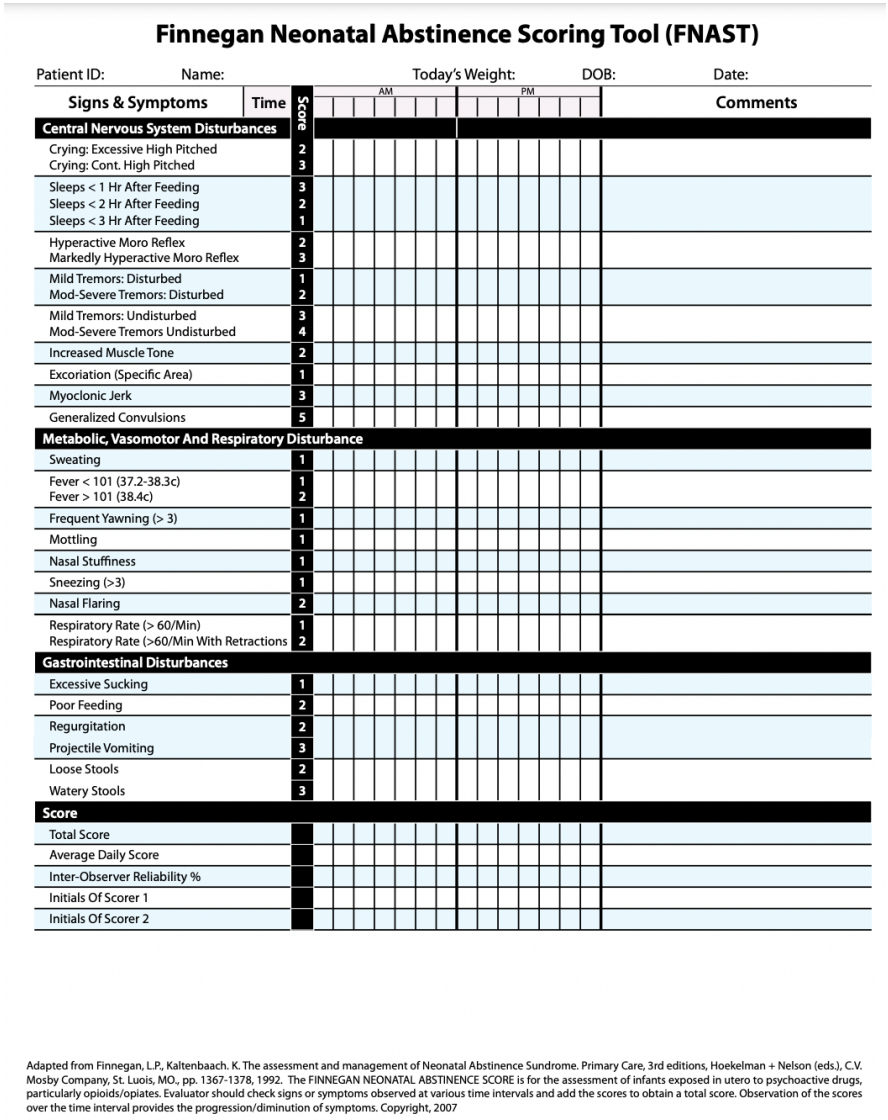
Appendix A

Finnegan Neonatal Abstinence Scoring Tool



Finnegan Neonatal Abstinence Scoring Tool (FNAST)

Patient ID: Name: Today's Weight: DOB: Date:

Signs & Symptoms	Time	Score	AM	PM	Comments
Central Nervous System Disturbances					
Crying: Excessive High Pitched		2			
Crying: Cont. High Pitched		3			
Sleeps < 1 Hr After Feeding		3			
Sleeps < 2 Hr After Feeding		2			
Sleeps < 3 Hr After Feeding		1			
Hyperactive Moro Reflex		2			
Markedly Hyperactive Moro Reflex		3			
Mild Tremors: Disturbed		1			
Mod-Severe Tremors: Disturbed		2			
Mild Tremors: Undisturbed		3			
Mod-Severe Tremors Undisturbed		4			
Increased Muscle Tone		2			
Excoriation (Specific Area)		1			
Myoclonic Jerk		3			
Generalized Convulsions		5			
Metabolic, Vasomotor And Respiratory Disturbance					
Sweating		1			
Fever < 101 (37.2-38.3c)		1			
Fever > 101 (38.4c)		2			
Frequent Yawning (> 3)		1			
Mottling		1			
Nasal Stuffiness		1			
Sneezing (>3)		1			
Nasal Flaring		2			
Respiratory Rate (> 60/Min)		1			
Respiratory Rate (>60/Min With Retractions		2			
Gastrointestinal Disturbances					
Excessive Sucking		1			
Poor Feeding		2			
Regurgitation		2			
Projectile Vomiting		3			
Loose Stools		2			
Watery Stools		3			
Score					
Total Score					
Average Daily Score					
Inter-Observer Reliability %					
Initials Of Scorer 1					
Initials Of Scorer 2					

Adapted from Finnegan, L.P., Kaltenbaach. K. The assessment and management of Neonatal Abstinence Syndrome. Primary Care, 3rd editions, Hoekelman + Nelson (eds.), C.V. Mosby Company, St. Luois, MO., pp. 1367-1378, 1992. The FINNEGAN NEONATAL ABSTINENCE SCORE is for the assessment of infants exposed in utero to psychoactive drugs, particularly opioids/opiates. Evaluator should check signs or symptoms observed at various time intervals and add the scores to obtain a total score. Observation of the scores over the time interval provides the progression/diminution of symptoms. Copyright, 2007

(Finnegan & Kaltenbaach, 2007)

Appendix B

Eat, Sleep, Console (ESC) Scale

Baby's Name: _____ Baby's Med Record #: _____ Date: _____

Time:										
ESC Assessment										
Poor Feeding due to NAS Y/N										
Sleeping <1 hour due to NAS Y/N										
Unable to Console within 10 minutes due to NAS Y/N										
Consoling Support Needed 1: Unable to console on own 2: Able to console with caregiver support within 10 minutes 3: Unable to console with caregiver support within 10 minutes										
Care Plan										
Recommend Care Team Huddle Y/N										
Management Decision: 1: Optimize non-pharmacologic Care 2: Initiate Medication Treatment 3: Continue Medication Treatment 4: Other (please describe)										
Parental/ Caregiver Presence 0: No parent present 1: < 1 hour 2: 1-2 hours 3: 2-3 hours 4: ≥ 3 hours										
Non-Pharmacologic Care (check all that were reviewed)										
Please answer: Increase/reinforce (I/R)										
Rooming In										
Parent/caregiver presence										
Skin-to-skin contact										
Holding by caregiver										
Safe swaddling										
Optimal feeding at early hungry cues										
Quiet, low light environment										
Non-nutritive sucking/pacifier										
Limiting visitors										
Clustering care										
Safe Sleep/fall prevention										
Was the infant bedside sheet complete for the shift?										
Parent/caregiver self-care and rest										

(AAH NICU Standardization Committee, 2019)

Appendix C

ETCH IRB Approval Form

EAST TENNESSEE Children's Hospital

INSTITUTIONAL REVIEW BOARD

April 13, 2022

Clair Flatt (Student, College of Nursing, UT), Jennifer Tourville, DNP UTK;

[Via Email]

The Institutional Review Board of East Tennessee Children's Hospital met in the Board Room. A list of Children's IRB members for 2022 is as follows, with an (*) identifying those not in attendance; (#) for those who attended the meeting via video conferencing: (PS) for Physician Scientist; (OS) for Other Scientist; and (NS) for Non-Scientist:

MEMBERS PRESENT

Dante Pappano, M.D. Chairman (PS)
Diana Burdick, MBA, RN (OS)
Rick Callaway, Director, Pastoral Care (NS)
Mary Pegler, Director, Child Life (NS)
Terry King, PharmD. (OS)
#Keith Jordan PharmD Community Representative, (OS)

MEMBERS ABSENT

*Michael Blake, MD (PS)
* Ria Dindial, MD (PS)
*John Ritter, Director Lab, (OS)
*Clinton Hermes, JD Community Representative, (NS)

6 members were present and made the quorum for the meeting.

New Protocol:

INVESTIGATOR: Clair Flatt (Student, College of Nursing, UT), Jennifer Tourville, DNP UTK;
ETCH# 286: The Effects of Clonidine on Outcomes in Patients with Neonatal Abstinence Syndrome

This new protocol was presented at a full board IRB meeting on April 13, 2022.

To maintain the privacy of patients, the Board is requesting a Certificate of Confidentiality to be filed.

East Tennessee Children's Hospital (ETCH) Institutional Review Board (IRB) reviewed the submission and granted full board approval for the study. Investigators may begin research once Certificate of Confidentiality is obtained.

This study has been granted a Waiver of HIPAA Authorization and Waiver of Informed Consent under category 45 CFR 46.116(f):
• The research involves no more than minimal risk to the participants, as procedures are limited to retrospective chart review only.
• The waiver or alteration does not adversely affect the rights and welfare of the subjects, as it is a medical record review with an appropriate protocol.
• The research could not practicably be carried out without using such information in an identifiable format.
• The research could not practicably be carried out without the waiver or alteration, as contact information in patient records may no longer be accurate, and all records during time are necessary in order for study to yield meaningful results
• Providing participants additional pertinent information after participation is not appropriate, as results are not intended to be individually relevant to patients.

IRB approval for this study will expire on April 12, 2023. Please submit a continuing review for this study by March 1, 2023 to ensure continuation of the study.

As a reminder, if there are any problems with the study or changes to the study design that relate to human subjects, please notify East Tennessee Children's Hospital's Institutional Review Board as soon as possible.

If you have any questions or concerns, please contact the IRB office at (865) 541-8290.

Sincerely,

Diana Burdick, MBA, BSN, RN, CPON
IRB Coordinator

Appendix D

Certificate of Confidentiality

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892
www.nih.gov

CERTIFICATE OF CONFIDENTIALITY

Number:
CC-OD-22-3033

Issued To
East Tennessee Children's Hospital

conducting research known as
The Effects of Clonidine on Outcomes in Patients with Neonatal Abstinence Syndrome

In accordance with the provisions of section 301(d) of the Public Health Service Act, 42 U.S.C. 241(d), this Certificate is issued to *East Tennessee Children's Hospital* to protect the privacy of subjects in the above named research study, which is collecting or using identifiable, sensitive information. *Claire Elizabeth Flatt* will serve as principal investigator. If there is a discrepancy between the terms used in this Certificate and section 301(d), the statutory language will control.

Research data and biospecimens containing identifiable, sensitive information collected or used during this study are covered by the Certificate beginning on the later of the approval date of this Certificate or the commencement of the project, until the collection or use of identifiable, sensitive information concludes. Identifiable, sensitive information protected by the Certificate and all copies thereof are protected for perpetuity.

The recipient of this Certificate shall comply with all requirements of subsection 301(d) of the Public Health Service Act. This Certificate does not represent an endorsement of the research project by the Department of Health and Human Services.

04/27/2022
Approval Date

ANGELA Chambers
NIH Certificates of Confidentiality Coordinator
Office of Extramural Research
National Institutes of Health