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Rescue Dosing as a Standardized Treatment Protocol for Neonatal Abstinence Syndrome to
Decrease Length of Hospital Stay

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Abstract

Introduction: Neonatal Abstinence Syndrome (NAS) is a collection of withdrawal symptoms following the abrupt discontinuation of a substance exposed to during pregnancy. East Tennessee Children's Hospital (ETCH) has altered their treatment protocol in attempt to decrease the length of stay (LOS) for their NAS patients. The purpose of this study was to compare the NICU LOS for NAS treated infants prior to and after implementation of a standardized treatment protocol that includes Rescue Dosing. Despite thorough research related to effective treatment, a consistent protocol has not been identified. It is unclear if a strict standardized treatment protocol can decrease the LOS for these infants.

Methods: ETCH introduced their current protocol in July 2014. A retrospective chart review was performed to collect data on the pharmacological treatment, LOS, and select demographic characteristics. Differences in LOS were analyzed using an independent t-test to determine if there was a significant difference in LOS pre- and post-protocol implementation.

Analysis: A total of 1,022 neonatal charts were reviewed. The average LOS for 345 neonates prior to initiation of the Rescue Dosing protocol was 23.9 days. After the introduction of the new standardized treatment protocol, the average LOS for 677 neonates decreased to 17.5 days. This was a statistically significant difference of 6.4 days. There was a significant decrease in NICU LOS after implementation of the new treatment protocol including Rescue Dosing and validates the use of Rescue Dosing.

Conclusion: Rescue Dosing as an intervention was found to be effective in reducing LOS, with a resultant reduction in hospital-related costs. It is recommended to utilize a standardized treatment protocol including Rescue Dosing in the treatment of NAS.

Rescue Dosing as a Standardized Treatment Protocol for Neonatal Abstinence Syndrome to Decrease Length of Hospital Stay

Introduction

Neonatal Abstinence Syndrome (NAS) is a compilation of withdrawal symptoms experienced by newborns following the abrupt discontinuation of a substance the fetus was exposed to during pregnancy. According to Wachman & Schiff (2016), NAS accounts for nearly 3% of all admissions into the Neonatal Intensive Care Unit (NICU) coupled with costs of around \$50,000 per admission.

In patients diagnosed with NAS, medications are used to control the signs and symptoms of withdrawal and to avoid complications such as seizures. It is vital to determine the need for pharmacological interventions promptly after diagnosis to decrease LOS and risk for fatality. Although the implementation of non-pharmacological interventions, and, later, pharmacological interventions have been shown to be effective for the treatment of NAS, there are many researchers who are finding that integrating these practices at varying points in the treatment process may not be the best option for every neonate with a NAS diagnosis. While many NICUs seem to be utilizing the same medications for minimizing the withdrawal symptoms, most lack a standardized approach to weaning which often leads to longer, more expensive stays in the NICU.

Each neonate exhibits the signs and symptoms of NAS and responds to treatments differently. However, recent studies have shown that a strict, standardized treatment protocol can minimize variance and improve communication among caregivers leading to an overall reduction in the LOS.

To decrease the NICU LOS for neonates diagnosed with NAS, East Tennessee Children's Hospital (ETCH) implemented a new treatment protocol with Rescue Dosing. Typically, a treatment protocol follows a specific pattern of taking a Finnegan score and medicating based on that score with no room for compensation. So, if the dose was not strong enough to decrease the Finnegan score effectively, the treatment regimen could be restarted leading to an increased LOS. Rescue Dosing is an additional dose of morphine on top of the scheduled dose which is ordered when the symptoms are not able to be managed at the current level. This protocol allows the patient to wean off morphine treatment at a steady rate without the possibility of needing to start the medication regimen process over. The purpose of this study is to evaluate the effectiveness of this treatment protocol in decreasing the NICU LOS in infants treated for NAS at ETCH. It is hypothesized that NAS infants treated with rescue dosing will have shorter LOS's than those that do not receive rescue dosing.

Review of Literature

PubMed was utilized to find sources pertaining to the treatment of NAS. Key words used were "Neonatal Abstinence Syndrome," "treatment," "protocol," and "weaning." After narrowing the results to include only sources within the last five years, 40 sources were reviewed. There were 13 sources found relevant to this study. The sources were excluded if they were outside of the United States or focused on non-pharmacological interventions. There were seven cohort studies, two randomized control trials, and four retrospective chart reviews. These sources were divided into pharmacological interventions and standardized treatment protocols.

Currently, there are a multitude of medications administered to wean NAS infants off narcotics including morphine, methadone, phenobarbital, buprenorphine, and clonidine. These medications differ in the symptoms treated, frequency and strength of dosing, long-term effects,

and their half-life. Morphine is often preferred due to how quickly and effectively it works although it requires many doses in a short amount of time and can prolong an infant's LOS. However, a standard plan of care was not found in the literature for the treatment of NAS infants.

Morphine versus Methadone

DeAtley, Burton, Fraley, & Haltom (2017) evaluated the effects of two different morphine treatment protocols. The only difference between the two protocols was the initial amount of morphine given. It was higher by 0.02 mg/kg/dose in the second protocol. There were 58 neonates with 33 receiving the first protocol and 26 receiving the second protocol. They found that the increased morphine dose reduced the LOS and duration of opioid exposure by seven days. However, they discovered a need for more studies using different amounts of morphine to determine the best initial dose because higher starting doses of morphine have been linked to an increased risk of over sedation which could jeopardize the treatment of an infant with NAS.

Burke and Beckwith (2017) followed 36 neonates suffering from NAS that were treated with either morphine or methadone to determine the impact these drugs had on their overall LOS and their level of development following treatment. The 19 neonates that were treated with morphine had a slightly shorter LOS than those treated with methadone as well as significantly higher scores in cognitive and gross motor areas of the Bayley Scales of Infant and Toddler Development. None of these results were statistically significant. This study was limited by the small sample size. However, they concluded that morphine would be the best choice for treatment based on the differences in LOS. Although infants receiving methadone treatment had a longer LOS, it was administered less frequently. The researchers determined that this was a benefit to the methadone treatment.

Brown, Hayes, & Thornton (2015) implemented a randomized control trial that included 31 neonates diagnosed with NAS to compare the duration of treatment for morphine therapy and methadone therapy. The duration of treatment was reported to be directly correlated to the LOS because this sample did not have any unresolved medical conditions that would require them to remain in the hospital after NAS treatment. The infants receiving methadone therapy had a shorter duration of treatment by seven days which would lead to a shorter LOS than the morphine therapy. They stated that the sample size in this study was a limitation and that it should be performed with a larger sample size to determine the accuracy of the results.

Hall, Meinen-Derr, & Wexelblatt (2015) conducted a study to evaluate two methadone protocols and their effects on duration of treatment, overall LOS, and total amount of methadone administered. The sample included 360 neonates with 267 neonates treated with the original methadone protocol while 93 were treated with the newly revised methadone protocol. The primary difference between the two protocols was the utilization of pharmacokinetic modeling in the revised protocol. It was shown that the revised protocol resulted in a shorter duration of treatment and LOS by three days. However, there was no difference in the amount of methadone administered. They recommend refining a standardized methadone protocol to reduce LOS and duration of treatment even further.

Each of these studies were conducted to compare methadone and morphine as well as variations in either type of therapy. The results were conflicting so there is no evidence that either medication or protocol is better suited for the treatment of NAS.

Adjunct Medications

While morphine and methadone are the medications of choice, other adjunct medications can be incorporated into the protocol to avoid the possibility of overdosing. Phenobarbital is safe

to use for treating seizures associated with NAS, but it presents the risk of interacting with the opioids exposed to in utero. Clonidine is preferred for less sedation but can cause hypotension and has negative effects when discontinued suddenly.

Devlin, Lau, & Radmacher (2017) performed a study between 2005 and 2015 at the University of Louisville Hospital comparing the effects of two protocols. The protocols differed in the adjunct medication being utilized, specifically phenobarbital and clonidine, alongside differing doses of morphine. The sample consisted of 190 neonates assigned to two different groups. The results showed that using morphine every three hours with clonidine as a supplemental therapy decreased the length of morphine therapy by 8.5 days, the need for adjunct therapy by 24%, and the overall LOS by nine days. They also evaluated the cost reduction associated with the decreased LOS to \$27,000 per patient in savings. They recommend the use of more intense morphine weaning to optimize the outcomes of treatment.

Buprenorphine administered sublingually is another medication used in NAS treatment. Kraft et al. (2017) performed a double-blind clinical trial to compare the treatment effects of morphine and buprenorphine with supplemental phenobarbital for uncontrolled symptoms. There were 33 neonates who received buprenorphine therapy and 30 neonates who received morphine therapy. Outcome variables included the duration of treatment, overall LOS, and the percentage of adjunct treatment. They found a shorter duration of treatment by 13 days and a shorter LOS by 12 days in the neonates treated with buprenorphine therapy. Adjunct phenobarbital was needed for five neonates in the buprenorphine therapy group and seven neonates in the morphine therapy group. The researchers stated that these findings suggest that buprenorphine could possibly be more effective than morphine. However, both medications continued to show the same adverse effects and the sample size was relatively small.

Hall et al. (2016) compared 38 neonates receiving sublingual buprenorphine therapy to 163 neonates receiving oral methadone therapy (n = 163) to determine if one protocol was more effective in decreasing the LOS. The neonates that received buprenorphine therapy had a shorter treatment duration by five days and a four day shorter LOS. The unequal group sizes were a limitation of the study as well as the different routes for the medications. However, the researchers suggest that, based on their findings, sublingual buprenorphine therapy may be better suited for select neonates.

These trials and studies suggest the need for further research into stringent protocol-based weaning rather than the logistics behind which medications individually reduce LOS and adverse effects. Each medication has specific strengths and weaknesses as well as a certain dependence on the circumstances of each neonate. Therefore, the type of medication only plays a part in the overall determination of effective treatment.

Standardized Treatment Protocols

Asti, Magers, Keels, Wispe, and McClead (2015) implemented a standardized morphine protocol for 92 neonates with 23 used as the baseline. They found that the average LOS was drastically reduced from 36 to 18 days. There were no readmissions after discharge for further treatments or complications. They reported adverse patient harm, impaired maternal-infant attachment, and significant health care costs were associated with prolonged LOS.

Similar results were found by Burnette, Chernicky, and Towers (2018). Their study included 395 neonates with 233 treated before the implementation of a standardized morphine weaning protocol and 162 treated with the new weaning protocol. The LOS was reduced from 23 days to 18 days in those neonates treated after the implementation of a strict standardized morphine protocol. The researchers used these findings to suggest the need for more

standardized protocol analysis at single sites. The limitation of this study was the sample consisted of primarily Caucasian neonates.

Hall et al. (2015) compared the outcomes of six hospitals pre- and post- implementation of a standardized protocol. The sample included 981 neonates. Each hospital compared its previous measured the LOS's for neonates, then a standardized treatment protocol was implemented in three of the six hospitals. They also collected data on the duration of opioid treatment using both protocols. The neonates in the three hospitals that utilized the standardized protocol had an average of 8 day shorter LOS and an average 11-day shorter duration of opioid treatment. A possible limitation of this study was the use of different medications at the hospitals. However, they found that protocol-driven weaning may be more effective in decreasing LOS and duration of opioid exposure than the actual type of medication.

Hall et al. (2014) examined the effectiveness of a new NAS weaning protocol. The sample consisted of 547 neonates with 130 being in a control group and 417 being treated with a new NAS weaning protocol. They evaluated the treatment duration and the overall LOS. The neonates treated with the NAS weaning protocol showed a shorter duration of treatment by 15 days and a shorter LOS by 10 days. The hospital variation and the different medications used in the control group were limitations of this study. The researchers recommended the use of a stringent treatment protocol to treat infants with NAS.

Patrick, Kaplan, Passarella, Davis, & Lorch (2014) compared the effectiveness of morphine, methadone and phenobarbital on duration of treatment, LOS and hospital charges. Six hospitals used morphine, six hospitals used methadone, and the other two hospitals used phenobarbital. The sample consisted of 1,424 neonates from 14 different hospitals They found that the hospitals using methadone therapy had a decreased duration of treatment by five days

and a decreased LOS by four days. However, there was no difference in hospital charges between the hospitals using methadone and those using morphine. The use of phenobarbital was associated with increased LOS, duration of treatment and hospital charges. After considering the possibility of case-mix, the researchers determined the hospitals varied in these aspects. Ultimately, they recommend the development of a standardized treatment protocol to improve care, outcomes, and cost.

Saunders et al. (2014) at East Tennessee Children's Hospital implemented an evidence-based NAS protocol to improve outcomes including LOS and post-wean stay. They conducted a retrospective analysis of 386 neonates before and after implementation to compare the LOS and post-wean stay. In those neonates treated after the implementation of the new protocol, the LOS was reduced by 10.35 days and the post-wean stay was reduced by 2.79 days. They reported rapid cycles of change during the implementation which created less control of confounding variables. The researchers recommend using a multidisciplinary approach to improve efficiency of weaning.

Each of these studies evaluated different medications and protocols to determine the importance of the actual medication in the treatment of NAS. These studies did not result in a clear recommendation for medication use. However, the use of a standardized protocol resulted in significant changes in LOS, duration of treatment and hospital costs.

The purpose of this study was to determine the effect of including Rescue Dosing in the standardized treatment protocol on neonatal outcomes treated for NAS. It was hypothesized that neonates who received the Rescue Dosing treatment protocol would demonstrate a shorter LOS and treatment duration than those treated with the prior treatment protocol at ETCH.

Methods

A quasi-experimental design was used to determine the effectiveness of the change in treatment protocol. Prior to July 2014, the treatment protocol used at ETCH did not include the option of an additional high dose of morphine for weaning, known as Rescue Dosing. The effectiveness of Rescue Dosing was determined by comparing the average LOS for patients treated prior to and after the implementation of Rescue Dosing.

Sampling

Neonates were included if they met the inclusion criteria of a neonate treated at ETCH for NAS from 2011 to 2018 with no additional medical condition. Any neonate with a post-wean stay greater than five days was excluded due to the probability of complications leading to the extended stay. This was a potential confounding factor that was accounted for prior to data collection.

A sample size of 200 neonates with 100 in each group was determined with a power analysis. The sample consisted of 1,022 neonates treated for NAS at ETCH from August 2011-April 2018. There were 345 neonates treated without Rescue Dosing and 677 neonates with the Rescue Dosing treatment protocol.

Data Collection and Measures

The data was collected from patient records by the IRB Specialist at ETCH and compiled into an excel sheet. All data was downloaded without patient identification. The data collected included diagnoses, age at admit, age at discharge, LOS post-wean, race, gestational age, body weight, zip, substance exposure in utero, medications and dosages. There were no measures used to confirm reliability of the data.

Analysis

Analysis was conducted using SPSS 19. A p-values of $< .05$ indicated significance.

Sample Characteristics

The sample consisted of 1,022 neonates who were diagnosed with NAS and treated at ETCH. There were 550 males (54%) and 470 females (46%) with 2 listed as unidentified. The neonates were 87% Caucasian, 5% African American, and 8% other. The birth weight ranged from 1220 grams to 4576 grams with a mean of 2989 grams. There were no significant differences in the demographic characteristics between the two groups.

Research Variables

The LOS post-wean and LOS frequencies were calculated for the entire sample before splitting the data into the two protocol groups. The number of days post-wean ranged from 0.4 days to 5 days with a mean of 3.8 days (sd = 0.39). The number of days for LOS ranged from 3 days to 56 days with a mean of 19.7 days (sd = 7).

Testing the Hypothesis

To determine if the LOS of neonates treated with rescue dosing was significantly less, a t-test calculated. There was statistically significant difference in the post-wean LOS between neonates who did and did not receive Rescue Dosing ($t = 6.15$, $df = 1020$, $p < .000$). The neonates in the group without Rescue Dosing had a longer post-wean ($x = 3.5$, $sd = 0.39$). then the neonates who received Rescue Dosing ($x = 3.3$, $sd = 0.37$) However, these results do not have clinical significance.

There was statistically significant difference in LOS between the neonates in the two groups ($t = 15.3$, $df = 1020$, $p < .000$). The neonates in the group prior to Rescue Dosing had a longer LOS ($x = 23.9$, $sd = 7.7$) compared to neonates who received Rescue Dosing ($x = 17.5$, $sd = 5.4$). There was a difference of 6.4 days between the two groups.

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