Official Title:	Clonidine as Adjunct to Morphine in the Management of Term and Near-term Infants with Neonatal Abstinence Syndrome
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Research protocol: Clonidine as Adjunct to Morphine in the Management of Term and Near-term Infants with Neonatal Abstinence Syndrome

Project summary:

Background: Neonatal abstinence syndrome (NAS) is an emerging epidemic. According to a study published in 2012, the incidence of NAS increased by a factor of 5 between the years 2000 to 2012. Opioids are the mainstay of treatment for NAS. Other drugs such as clonidine, phenobarbitone, buprenorphine are being used to limit the post-natal exposure to opioids in infants with NAS. Clonidine is an alpha 2 receptor agonist that can lessen withdrawal manifestations due to its sympatholytic action. Clonidine when used as monotherapy at daily dose of up to 12 µg/kilograms/day or as an adjunct to injure of opium at a dose of 6 µg/kilograms/day has been shown to reduce the duration of treatment by as much as 27%.

Methods: This is a pilot, prospective, randomized, double-blinded clinical trial to compare the duration of treatment in infants ≥ 36 weeks gestational age (GA) with NAS admitted to the NICU receiving morphine for ≤ 72 hours at the time of enrollment. Infants with seizures, congenital malformations, heart rate or blood pressure instability and other major medical problems will be excluded. Our secondary outcomes are duration of inpatient stay, maximum dose of morphine and cumulative dose of morphine used over the duration of treatment, measurement of heart rate and/or blood pressure fluctuations. After informed consent, infants will be randomized by the research pharmacist to either receive 12 µg/kilograms/day of clonidine or placebo as an adjunct with morphine for the duration of treatment of NAS. We plan to enroll a total of 32 study subjects over the duration of 24 months.

Outcome: We hypothesize that term and near-term infants with NAS receiving clonidine at 12 µg/kilograms/day will have a 30% reduction in the duration of treatment for NAS as compared to term and near-term infants with NAS receiving morphine monotherapy.

General Information:

Title: Clonidine as adjunct to morphine in the management of term and near term infants with neonatal abstinence syndrome

Sponsor/Funding: None

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Background:

Neonatal abstinence syndrome (NAS) is an emerging epidemic all over the world and has led to escalation of medical costs. Infants develop NAS due to withdrawal after birth from the continuous in utero exposure to opioids and other drugs of abuse (1). The incidence of NAS increased by a factor of 5 during the years 2000-2012 (2, 3). Opioids are the mainstay of treatment for NAS although there are concerns about possible short-term and long-term adverse effects of opioid therapy including adverse neurodevelopmental outcomes. Other drugs such as clonidine, phenobarbitone, buprenorphine are being used to limit the post-natal exposure to opioids in infants with NAS. The use of both morphine and clonidine is increasing in the management of infants with NAS (4). Clonidine is an alpha 2 receptor agonist that can lessen withdrawal manifestations with its sympatholytic action (5-7). Clonidine at a dose of 6 mcg/kg/day when used as an adjunct to opioid therapy for NAS has been shown to reduce the duration of pharmacotherapy by as much as 27% (8). Recently a pilot study reported reduction in treatment duration with clonidine monotherapy (doses up to 12mcg/kg/day) as compared to morphine monotherapy (median treatment duration of 28 days with clonidine vs. 39 days with morphine; p=0.02) (9) . There were no significant fluctuations in heart rate or blood pressure noted in the study subjects. We hypothesize that there will be a minimum of 30% reduction in the duration of opioid treatment in infants receiving 12mcg/kg/day of clonidine as an adjunct to standard morphine treatment as compared to infants receiving morphine monotherapy in the management of NAS.

Primary objective:

To compare the duration of opioid treatment in term and near-term infants with NAS receiving 12 mcg/kilograms/day of clonidine as an adjunct to morphine and term and near-term infants with NAS receiving morphine monotherapy for NAS treatment.

Secondary objectives:

- Duration of hospital stay
- maximum dose of morphine (mg/kg/day) reached and cumulative dose of morphine used over the duration of treatment (mg/kg)
- No. of episodes of bradycardia (HR< 60/min for a min of 20 seconds and not associated with apnea or signs of reflux such as emesis, regurgitation of milk into the mouth or nose, arching while feeding, no of episodes of tachycardia (> 200/min) and not related to pain (associated with hypertension and/or agitation) and no of episodes of hypotension (Blood pressure < 5th percentile).

Study Design:

This is a prospective randomized double blinded controlled trial comparing the duration of opioid treatment in term and near-term infants with NAS receiving 12 mcg/kg/day of clonidine as an adjunct to morphine and term and near-term infants with NAS receiving morphine monotherapy for NAS treatment.

Inclusion criteria:

Following infants will be approached for consent for participation in the study:

- Treatment duration $\leq$ 72 hrs. with morphine
- Gestational age (GA) $\geq$ 36 weeks
- Antenatal exposure to opioids

- Symptomatic with NAS as defined by 2 consecutive Finnegan scores ≥ 8 assessed 3 hours apart or 1 Finnegan score ≥ 12

Exclusion criteria:

Infants with the following conditions will be excluded from study participation

- Seizures
- Congenital malformations, genetic syndromes or the presence of TORCH infections
- Blood pressure instability
- Major medical problems
- Mothers of all term and near

Methodology:

a) **Screening**: All neonates ≥ 36 weeks GA, admitted to the NICU at HCMC and needing medical management of NAS will be screened for study criteria within 72 hours of starting morphine treatment for NAS. Infants will be identified by a designated investigator with regularly scheduled screening of admissions, GA, postnatal days and admission diagnosis. Screening will take place on an ongoing basis and not less than 3 times per week. The primary investigator shall maintain a screening log with names and MRNs of all infants approached for consent and whether or not the infant was enrolled in the study. If not enrolled, the reason will be recorded.

b) **Enrollment and Consent**: Families will be approached by one of the investigator as soon as possible after eligibility is ascertained to allow sufficient time for the family to ask questions about the study. Parental consent may be obtained any time during the first 72 hours of starting morphine treatment for management of NAS. Consent

will be documented on an IRB approved consent form. Each subject will be assigned a unique study identification number by the investigator after consent is obtained.

c) **Pre-randomization**: Once the infant is enrolled in the study, one of the investigators will notify the inpatient pharmacist by telephone for registration and randomization.

d) **Registration**: A log sheet of subjects registered with their names, study ID numbers, medical record number and dates of randomization will be kept by the inpatient pharmacy staff.

e) **Randomization** will be to two arms: Clonidine at 12 mcg/kg/day or placebo. A block randomization with 6 subjects in each block will be performed. Study group assignments will be made by the RP/inpatient pharmacy staff with the use of a randomization scheme provided by the primary investigator. The assignment will be 1:1 ratio.

f) **Treatment initiation:** The decision to start morphine for management of NAS shall be as per the standard of care in the NICU at HCMC. Consented and enrolled infants shall start receiving either clonidine or placebo within 72 hrs. of being on morphine for treatment of NAS.

g) **Route, Frequency, and Duration**: The clonidine or placebo will be given via oral route q 6hrs. The dose shall start at 6 mcg/kg/day for the first 24 hrs. and then subsequently increase to 12 mcg/kg/day and then remain the same for the duration of study period. Study subjects in both arms shall continue to receive morphine as per unit protocol. Study subjects will continue to receive non pharmacological measures such as holding, swaddling, low noise and reduced light environment as per the unit

policy. Parent rooming in and breast feeding will be encouraged when possible and as permitted as per the standard of care in the NICU.

h) **Placebo**: The infants on the placebo arm shall receive just the diluent with no clonidine drug in the solution. The placebo will be dispensed by the pharmacy. The placebo solution will be identical in color and volume to the actual clonidine drug and will be dispensed in the same syringe as clonidine. This will ensure true blinding of the investigators and NICU care team towards the randomization arm of the infant. Only the research/inpatient pharmacy staff shall be aware of the study arm of randomization of a study subject.

i) **Data Safety Monitoring:** A data safety monitoring board comprising of 2 independent physicians shall monitor the study subjects for adverse effects directly related to clonidine therapy. Primary investigators will be responsible for ensuring protocol compliance during the study period.

Data collection:

The baseline data on demographics and clinical factors (antenatal and postnatal) before randomization on each subject will be collected. Similarly, data on clinical factors will be collected during the study period. The information on medication such as morphine, Tylenol, phenobarbitone intake on each day will be prospectively collected using pharmacy and medical record chart. Information on cumulative morphine amount (mg/kg), max dose of morphine (mg/kg/dose) needed during the study period will be determined for all enrolled subjects. The additional information that will be collected includes but not limited to duration (days) of treatment, duration (days) of inpatient stay, type of enteral feeds (maternal breast milk vs. Formula), duration (days) of antibiotic use, sepsis defined as blood culture positivity or clinical

signs and symptoms of sepsis with the use of antibiotics for > 3 days, duration (days) of respiratory support if applicable, no. of episodes of bradycardia (HR< 60/min for a min of 20 seconds and not associated with apnea or signs of reflux such as emesis, regurgitation of milk into the mouth or nose, arching while feeding, no of episodes of tachycardia (> 200/min) and not related to pain (associated with hypertension and/or agitation) and no of episodes of hypotension (Blood pressure < 5th percentile).

Safety and Adverse Events management

This prospective study has been designed to minimize the risks to the patients enrolled. Clonidine is a drug that is commonly used in the medical management of infants with NAS. Previous studies have not shown any adverse effects with clonidine doses of up to 12 mcg/kg/day. The infants will receive continuous cardiac monitoring and monitoring of oxygen saturations by pulse oximetry throughout the study period as part of standard of care for management of NAS infants in the NICU. The investigators will be responsible for adherence to the study protocol. Protocol violations will be promptly reported to the IRB in the standard format. A data safety monitoring board comprising of 2 independent physicians shall look at episodes of adverse events in the study participants. To protect privacy of subjects, all links to subject identifiers will be decoded and subject data will be stored in locked cabinets.

Data management and statistical analysis

a) **Randomization:** Upon successful completion of necessary screening assessments and being confirmed to be eligible by the investigator, subjects will be randomized in 1:1 ratio to two groups: 1) 12 mcg/kg/day of clonidine as an adjunct to morphine, 2) placebo at 12 mcg/kg/day in addition to morphine. Each subject will be assigned a unique sequential subject number for identification throughout the entire course of the study. The

subject number will not be reused for any other participant in the study. Subjects who are discontinued or withdrawn from the study prior to randomization will be replaced.

b) **Blinding:** Parents/caregivers, investigational personnel, and all other study personnel except the research/inpatient pharmacist, will remain blinded to the identity of the treatment assignments until every subject has completed study treatment. Unblinding will only occur in the case of subject emergencies such as vital sign instability as described above. During the study, the treatment assignments will be available only to the basis pharmacist or the inpatient pharmacy staff.

c) **Samples for Analysis:** The "Intent-to-Treat" sample includes all subjects who are randomized into the study. Subjects will be grouped according to the treatment to which they are randomized.

d) **Statistical Analyses:**

Descriptive statistics will be used to summarize outcomes by treatment groups. For continuous variables, descriptive statistics will include the mean, median, standard deviation, minimum, maximum, number of available observations, and number of missing observations. For discrete variables, descriptive statistics will include frequencies and percentages, number of available observations and numbers of missing observations.

We will determine whether there are important baseline differences between the two groups despite randomization with respect to participant characteristics (e.g., gender, race/ethnicity, GA at birth, SGA[$<10^{th}$ percentile]). If any important differences are found, the primary analyses will be repeated after statistically adjusting for these differences. If distributional assumptions associated with a particular statistical procedure are violated, appropriate transformations will be made or non-parametric alternatives will

be used (e.g., Wilcoxon rank sum tests in place of two-sample t-tests). Infants enrolled but subsequently found to meet exclusion criteria will be analyzed separately.

Data storage and confidentiality:

We will use unique subject identification number to ensure confidentiality of data collected. The file linking the study identification number with identifiers will be stored in a locked cabinet accessible only to the investigators. Hard copies of data collection forms will be stored in a locked cabinet. All links to subject identifiers will be decoded to protect privacy of subjects. The records will be kept for 5 years after completing the study and publication of the findings.

Quality assurance:

The adherence to study protocol will be strictly enforced by the study investigators. A data safety monitoring board comprising of 2 independent physicians will monitor the study subjects for adverse effects directly related to the study medication. Consent will be documented on an IRB approved consent form. Each subject will be assigned a unique study identification number by the investigator after consent is obtained. A log sheet of subjects registered with their names, study ID numbers, medical record number, and dates of entry will be kept by the pharmacy staff and the investigators.

GRAPHIC STUDY OUTLINE:

Infant ≥ 36 weeks admitted to the NICU and started on morphine

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Screened for eligibility and meets inclusion criteria

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Written and informed consent obtained within 72 hrs. of starting morphine treatment

If consented, research pharmacist/inpatient pharmacy staff informed and the patient randomized by pharmacy staff

Infant receives either clonidine or placebo as per the randomization

↓

Study drug (clonidine/placebo) will be administered at 6 mcg/kg/day divided q 6 hrs for the first 24 hrs of the study period

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Study drug dose increased to 12 mcg/kg/day divided every 6 hrs after 24 hrs (if no adverse effects directly related to study drug administration reported in first 24 hrs

Infant continues on the same dose of study drug throughout the period of medical management of NAS

Morphine administration as per protocol

↓

Study drug weaned by 50 % after infant stable for 24 hrs on prn doses of morphine

Study drug stopped after infant stable for 24 hrs on the reduced study drug dose

Infant discharged after a min of 24 hrs of stable period off all drugs for management of NAS

Expected outcomes of the study:

The results of this study will be very important in understanding the effects of adjunctive use of 12 μg per kilogram per day of clonidine in addition to morphine in the management of current and near-term infants with NAS. This could have a bearing on reducing both the amount of morphine needed and the duration of inpatient stay for term and near term infants with NAS. This may result in significant reduction in health care costs.

Dissemination of results and publication policy:

The results of this study will be reported in a reputed medical journal and may be presented at national and international scientific meetings. The lead author will be the primary investigator, Kunal Gupta. Dr. Vinay Sharma will be a co-author on the publication. Parents of study patients, NICU staff, inpatient pharmacy staff and the research pharmacist will be dully acknowledged in the manuscript.

Duration of the project:

At the NICU at Hennepin County Medical Center, we care for 20-25 term and near-term infants with NAS per year. The study enrollment is expected to take place over 2 years from April 2018 to December 2020. The proofreading of data, statistical analysis and interpretation will be done over the next 4 months after completion of study procedures. Manuscript writing, editing and submitting for publication are anticipated to be completed by December 2021.

Problems anticipated:

The study enrollment period may last longer than anticipated in case of a reduction in the number of infants eligible for the study in the NICU. To ensure adherence to the study protocol, extensive nursing education will be done to familiarize them with the study protocol. The study investigators will ensure adherence to study protocol during the study period. All infants will be on cardiac monitors and on pulse oximetry monitoring during the study period as part of standard of care for these infants. These will help us in early identification of episodes of bradycardia (HR< 60/min for a min of 20 seconds and not associated with apnea or signs of reflux such as emesis, regurgitation of milk into the mouth or nose, arching while feeding, no of episodes of tachycardia (> 200/min) and not related to pain (associated with hypertension and/or agitation) and no of episodes of hypotension (Blood pressure < 5th percentile). A data safety monitoring board comprising of 2 independent physicians will meet after 15 patients have been enrolled into the study and oversee all episodes of adverse events during the study period. We expect a 60-80% rate of enrollment following a written and informed consent is obtained from the parents of the study subjects.

Vulnerable population:

The study aims to evaluate the effect of administering an adjunctive clonidine therapy in addition to morphine in current and near-term infants with NAS on duration of opioid treatment. Infants who are ≥ 36 weeks GA and needing morphine for the management of NAS in the NICU will be included in this study. The results from adult studies cannot be extrapolated to this vulnerable population as term and near term infants with NAS are physiologically very different from adults and have different pharmacokinetic properties and pharmacodynamic effects of clonidine. Hence it becomes necessary to include this vulnerable population as study subjects.

Ethics and consenting:

Clonidine is routinely used in pediatric as well as added population in the management of opioid dependence as a result of abuse or long-term inpatient opioid therapy. Clonidine is also used in neonates in various NICU's for mitigating signs and symptoms of withdrawal in infants with NAS. In this study, a written and informed consent will be taken from the parents of each study subject. Families will be approached by one of the investigators as soon as possible after eligibility is ascertained to allow sufficient time for the family to ask questions about the study. Consent will be documented on an IRB approved consent form. Each subject will be assigned a unique study identification number by the investigator after consent is obtained. A log sheet of subjects registered with their names, study ID numbers, medical record number, and dates of entry will be kept by the pharmacy staff and the investigator.

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