Cover Page

NCT04269161

NICU Oxygen Control Study

Protocol

May 6, 2023

Date: __5/6/23
Version Number: __ 8_____
Principal Investigator: __John Pardalos MD_____
Application Number: ___2003117_____
Application Title: NICU Oxygen Control Study
Funding source: NIH

Protocol

1. Abstract

Babies born less than or equal to 30 weeks gestational age or have a birth weight less than or equal to 1500 grams are at risk for developing long-term complications (chronic lung disease, retinopathy of prematurity, brain damage, necrotizing enterocolitis, or death) if they receive too much oxygen or not enough oxygen. Therefor all infants in the neonatal intensive care unit (NICU) that require oxygen are placed on a pulse oximeter that continuously measures the infant's saturation level. Our goal is to keep the oxygen saturation level in this group of infants in the 80's to low 90's range until the risk of retinopathy of prematurity diminishes and then it is increased to the term infant parameters. Preterm infants with respiratory distress may require respiratory support from a variety of devices ranging from a variety of ventilators to a variety of non-invasive devices. One of these non-invasive devices is called a high flow nasal cannula. This device provides flow of air to the infant through a cannula attached to the infant's nose. Another non-invasive device is called bubble CPAP. In this case a flexi-trunk interface is attached to the patient using nasal prongs alternated with a mask every 4 hours to prevent skin breakdown. With this device, the flow of air is passed through a column of water which provides a gentle vibration to the air entering the baby's lungs which may help the baby breathe easier. With either device the air is warmed and humidified to be gentler to the infant's lungs. Both devices also have a blender attached to them so that the percent oxygen in the air can be adjusted from 21% (or room air) to 100% oxygen depending on the needs of the infant to keep his/her oxygen saturation level in the desired range. Currently adjustments made to the percent oxygen require a healthcare provider to manually turn the knob on the blender in order to increase or decrease the percent oxygen being delivered to the infant to keep the infant's oxygen saturation level in the desired range.

We took these same devices and attached a computer that can receive information about the infant's oxygen saturation level from the pulse oximeter and can automatically turn the knob on the blender in order to adjust the oxygen level being delivered to the infant to keep the oxygen saturation level in the desired range. The computer also has an artificial intelligence algorithm in it, and it will learn to anticipate the patient's oxygen needs the longer it is attached to a patient. For safety concerns, the device also has a switch that the healthcare provider can use to turn the device to manual mode should the computer system not be able to keep up with the infant's condition.

With this study, we will compare how well the computer adjusts the oxygen concentration to keep the baby's oxygen saturation level in the desired range compared to the healthcare providers that must manually adjust the knob whenever the infant's saturation level falls out of range.

2. Objectives

The primary objective to this study is to determine if the computer can automatically keep the infant's oxygen saturation level in the desired range for a longer period of time compared to

the healthcare providers that must manually adjust the oxygen concentration whenever the infant's oxygen saturation level falls out of range.
Other objectives of this study are clinical validation of the oxygen control device and algorithm developed by the researchers at the University of Missouri by testing the transitions from automatic to manual control of the device; demonstrate the dynamic adaptability; and show that the response of the system in the automatic model is stable.
We will also monitor the frequency of acute events (apnea, bradycardia and/or desaturation events) to see if the frequency of these events will decrease when the oxygen saturation level is better controlled.

3. **Background** (N/A please see abstract section)

4. **Study Procedures**
    a. Whenever an infant who has been admitted to the Neonatal Intensive Care Unit (NICU) at one of the study sites is placed on a high flow nasal cannula or bubble CPAP by the primary healthcare team, the study personnel will determine if the infant meets inclusion criteria.
    b. The primary healthcare team caring for the infant will continue to adjust the flow on the high flow nasal cannula or the PEEP on the bubble CPAP per the patient's needs.
    c. The primary healthcare team will determine the oxygen saturation parameters for the patient. The study team will adjust the computer set point goal for the oxygen delivery system to be the median of that range.
    d. If the patient meets criteria, we will approach the parents to give consent to enroll the infant in the study.
    e. Once consent is obtained, the study personnel will switch the infant to the equivalent study device for up to 6 days but the infant's interface with the device will not be changed. The infant will be kept on the same pulse oximeter as well.
    f. The bedside nurse and respiratory therapist will be educated on how the device works and what to do if they have any questions. A two-page information sheet will be hanging from the device, so they have a reference to look at. This information sheet includes a frequently asked questions section. It also reminds them to call the study team for any questions.
    g. The bedside nurse will be asked to keep a log of events that may be contributing to potential changes in oxygen needs or desaturation events such as changing diapers, being held, feeding, repositioning the infant, IV starts, blood draws, blood transfusions, medications administered, etc. In addition, acute events (apnea, bradycardia, desaturation) and their resolution will be documented on the logs. They will also document when the interface on the device is switched from a mask to prongs or vice versa or the settings are adjusted by the primary healthcare team (flow rate on the HFNC, PEEP on the bubble CPAP). They will also document anytime they had to switch the device the manual mode to adjust the FiO2 faster than the computer was doing based on the infant's needs. They will then document when they switched the device back to the automatic mode to finish out the 6-hour period.
    h. Study personnel will collect the baby's medical history and mom's prenatal history. The baby's history including mom's prenatal history information produced by this study will be stored in the investigator's file and identified by a code number only. The code key connecting the baby's name to specific information about the patient will be kept in a separate, secure location in the investigator's office.
    i. We will continuously download the vital signs and pulse oximeter data from the monitor system for up to 24 hours prior to the study as well as throughout the study to see how well the healthcare providers kept the baby in the desired range during that time period.

- Continuously measure SpO2 using existing sensors in the NICU. A pulse oximetry unit will be used to continuously gather SpO2 data from the patients.
- Continuously measure heart rate using existing sensors in the NICU. A cardiorespiratory monitor will be used to continuously gather heart rate data from the patients.
- Continuously measure respiratory rate using existing sensors in the NICU. A cardiorespiratory monitor will be used to continuously gather respiratory rate data from the patients.
- Continuously measure FiO2 concentration. The computer system attached to the research device, will continuously keep track of the infant's SpO2, heart rate, respiratory rate and FiO2 being provided to the patient. This data will be downloaded and analyzed by the study personnel once the device is removed from the patient.

j. When the device is set on the manual mode, the healthcare providers will be responsible for adjusting the oxygen concentration to keep the infant in the desired saturation range set by the primary healthcare team.

k. When the device is set in the automatic mode, the computer will make the necessary adjustments to the oxygen concentration to keep the infant in the desired saturation range. The computer will strive to keep the oxygen saturation level at the median of the range set by the primary healthcare team.

l. The infant will be placed in one of these modes for 6 hours and then switched to the other mode for the next 6 hours. Ideally this will occur every 6 hours +/- 1 hour.

m. This cycle will be repeated for the next 132 hours (5.5 days) except at 48 and at 96 hours where it will be kept on the same mode for at 12- hour period in order to switch the time of day the infant is on automatic mode so it not always the same time of day for the full 6 days.

n. Infants will be randomized so some will start in the automatic mode (A) while others start in the manual mode (B). Due to concern that the time of day may play a role in the variation in the patient's oxygen need and/or the frequency of acute events, the patients will be randomly assigned to one of two tracks:
   - ABAB/ABAB/BABA/BABA/ABAB/ABAB
   - BABA/BABA/ABAB/ABAB/BABA/BABA

o. After completion of the 6 days (144 hours) on the study device, the infant will be switched back to the regular device used in the NICU.

p. While the infant is on the study device during the first 12 hours of the study, a member of the research team will remain at the infant's bedside to make sure the device remains operational, but they will not be allowed to adjust the oxygen concentration. The bedside nurse will be able to switch the device to manual mode anytime she/he feels the oxygen concentration needs to be adjusted faster than the computer is doing in the automatic mode.

q. The study will be stopped earlier if the primary healthcare team feels:
   - The infant requires more respiratory support than can be provided by the high flow nasal cannula or bubble CPAP device.
   - The infant no longer requires respiratory support and can be weaned off the high flow nasal cannula or bubble CPAP device.

5. **Inclusion/Exclusion Criteria**

   a. Inclusion criteria: infants admitted to the NICU who were less than or equal to 30 weeks gestational age or less than or equal to1500 grams at birth who are currently on

high flow nasal cannula or bubble CPAP and require at least 2 adjustments to the FiO2 per shift and/or have at least 2 desaturation events per shift.

b. Exclusion criteria: infants admitted to the NICU with congenital heart disease. Infants who are set on a minimum FiO2 set point by their healthcare provider, will also be excluded from this study.

6. Drugs/ Substances/ Devices

The high flow nasal cannula device that we use in the NICU consists of a oxygen blender that is mounted on an IV pole and a Fisher & Paykel Healthcare humidifier that is mounted to the same pole. Medical air and oxygen are introduced in the back of the blender that allows the oxygen concentration to range from 21% (or room air) to 100% oxygen by simply turning the knob on the blender. The flowmeter on the blender is used to adjust the flow of air out of the blender (usually 1-6 lpm). A tube connects the flowmeter with the humidifier where the air is heated and humidified. Another tube then connects the humidifier with the nasal cannula which is placed on the infant's face.

The bubble CPAP device that we use in the NICU consists of an oxygen blender that is mounted on an IV pole, a Fisher & Paykel Healthcare humidifier and a Fischer & Paykel Healthcare bubble CPAP generator that are mounted to the same pole. Medical air and oxygen are introduced in the back of the blender that allows the oxygen concentration to range from 21% (or room air) to 100% oxygen by simply turning the knob on the blender. A tube connects the flowmeter with the humidifier where the air is heated and humidified. Another tube then connects the humidifier to the inspiratory limb of the flexi-trunk which is placed on the infant's face. The expiratory limb from the flexi-trunk is connected to the bubble CPAP generator which is set to the desired PEEP (3-10 cm of H2O).

The study devices are exactly the same set ups as described above except for 3 differences. First, there is a computer attached to the IV pole that accepts input from a pulse oximeter. The computer registers the saturation level and determines if the level is within the prescribed range. Second, there is an attachment between the computer and the knob on the blender. If the oxygen saturation level isn't in the prescribed range, the computer can turn the knob on the blender using this attachment to either increase or decrease the amount of oxygen being delivered to the patient by 2% every 10 seconds as long as the oxygen saturation reading is considered reliable (the heart from the cardiac monitor and the pulse oximeter have to agree within 5 beats per min). Third, the device has an alarm that will sound if the FiO2 is increased or decreased by more than 10% from the baseline FiO2 requirement. For example, if the infant's baseline FiO2 needs were 35% and the FiO2 is increased to 45% while in the automatic mode, an alarm will sound so the nurse can evaluate why the infant is requiring 10% more oxygen than the baseline. The nurse can evaluate the infant to see if the oxygen device is no longer in the infant's nose and reposition it or notify the healthcare providers to have them determine if the infant's condition is deteriorating. If the infant truly needs the extra oxygen, the nurse can reset the baseline oxygen requirement to this new level and the machine will not alarm again until the oxygen level is again 10% out of range. The computer also has a switch that turns it from automatic to manual mode. If the healthcare provider needs to adjust the oxygen concentration faster than the computer is making a change, all they need to do is simply switch the button to manual and they can adjust the knob on the blender to whatever concentration they want.

Name of Medical Device: Automatic Oxygen Control System
Medical Device Description:

The device receives signals with SpO2 information along with the heart rate and respiratory rate. Using the measurements and a set-point, the device determines an FiO2 that is to be applied to a respiratory support system. The device uses a motor to control a blend valve which manipulates the FiO2.

If the device makes inappropriate settings to the FiO2, risk is eliminated since all of the alarms will be in place (as in current practice) and manual control will always be available.

There will be a total of three replications of the Automatic Oxygen Control System devices at each site. These three devices will be used under the supervision of a study engineer and/or healthcare provider.

There are no known difficulties in using the device.

The cost of the device is funded by the study.

Doctors, respiratory therapists, and nurses will be trained on how to use the device. They will receive training on how to turn the device off and on, switch between automatic and manual modes, and adjust the FiO2 settings on the device. This training will be conducted by the study personnel prior to placing the device on a patient. This training should take less than 5 minutes to complete. A member of the study personnel will be present at the infant's bedside during the first 12 hours of the study period the infant is attached to the device and then 1 hour daily to make sure the device is functioning properly. A member of the study team will also be on-call during the entire study period to answer questions about the device.

The study device will not be documented in the medical records. The study PI and study engineers will be trained in Medical Device Reporting principles.

The study will only last 144 hours. No follow up visits or tests are required.

This device is considered a non-significant risk device requiring no IDE.

7. Study Statistics

a. Primary outcome variable.
   - Mean elapsed time needed to re- establish SpO2 within the desired range after an alarm. Does the computer do a better job of keeping the patient in the desired saturation level range compared to the current manual mode? Does the patient return to the prescribed saturation level range quicker in the automatic mode compared to the manual mode?

b. Secondary outcome variables.
   - Proportion of time SpO2 is within the prescribed range computed using an area-under-the-curve approach. Is our device safe to use on neonates? Is the transition from automatic to manual mode smooth? Does the device respond appropriately to the patient's saturation level?
   - Does the frequency of acute events (apnea, bradycardia and/or desaturation events) decrease if the oxygen saturation level is kept under better control?

c. Our goal is to enroll 60 patients into the study. We expect to consent 70 subjects to account for drop-out.
d. Our pilot study of 6 patients demonstrated that when the device was in the automatic mode, the patient spent more time within the prescribed oxygen saturation goals and that it took less time for them to return to the prescribed oxygen saturation range whenever they were outside of the range. Even though this wasn't considered statistically significant, we felt that this was due to the fact the infants were only on the device for 12 hours (two 3-hour periods of automatic control and two 3-hour periods of manual control). This pilot study did show a significant decrease in the number of bradycardia events while the infants where in the automatic mode. With our current study, the patients will be on the device for 6 days so a total of 72 hours of automatic control and 72 hours of manual control, so we are hoping to find statistical significance in all our study metrics.
e. If the healthcare team determines that the patient's respiratory distress is worsening and he/she needs more support than can be provided by the high flow nasal cannula or bubble CPAP, the study will be terminated, and the patient will be placed on whatever device the healthcare team chooses. On the other hand, if the healthcare team determines that the infant is doing well enough that they no longer need the high flow nasal cannula or bubble CPAP, we will stop the study and allow the infant to be taken off the respiratory device.

8. Risks

a. The study high flow nasal cannula device and bubble CPAP device are the same exact set ups we currently use in the NICU except that there is a computer attached to the oxygen blender that can automatically adjust the FiO2 being delivered to the patient. A member of the research team will be at the baby's bedside to make sure it is operating properly for the first 12 hours and then daily for 1 hour to make sure everything is functioning appropriately. They will also be available by phone for the entire time the infant is on the device.

The bedside nurse and respiratory therapist will be educated on how the device works and what to do if they have any questions. A two-page information sheet will be hanging from the device, so they have a reference to look at. This information sheet includes a frequently asked questions section. It also reminds them to call the study team for any questions.

For the safety of every patient in the NICU, we have several redundant systems to monitor our patients. First every patient in the NICU is continuously monitored for their heart rate and respiratory rate. In addition, those infants requiring respiratory support of any type are kept on a pulse oximeter that continuously monitors the patient's oxygen saturation levels. If these vital signs fall out of the prescribed range, the monitor starts to alarm. At the beginning of each shift the nurses make sure the alarms of each of their patients ring on all their babies' monitors through a system known as alarm watch. Additionally, throughout the NICU, monitors are present so healthcare providers can monitor these vital signs in key locations throughout the unit. Furthermore, the heart rate and respiratory alarms ring directly to the nurse's special secure cellular phone used in the hospital that also functions as an alarm monitor so no matter where the nurse may be located in the NICU she can hear these alarms. To protect the confidentially of the patient's protected health information, the form used to gather the information from the medical record will be coded so the infant's name and medical record number will not be listed on the sheet. A separate sheet indicating

what code represents the patient's name and medical record number will be kept in a secure location away from the data forms. Once completed, the data forms will be kept in Dr. Pardalos' office at the MU site and in Dr. Amjad's office at the Florida site.

b. There is no financial risk to the participants.
c. The data safety and monitoring plan for this research study will consist of a local data monitoring board consisting of the primary investigator, co-investigators, and research study team members who will be responsible for monitoring data, recruitment, and subject confidentiality. The principal investigator and research team will meet to review the data at completion of the study procedure. Regular meetings will occur with the reporting of adverse events as outlined in the University of Missouri, IRB Reference Manual, and appendix. The IRB will be notified at the time of renewal of the frequency of monitoring, cumulative adverse event data, summary of assessment evaluating the safety of study subjects, summary of reviews to ensure subject participation and final conclusions regarding changes to the anticipated benefit to risk ratio of study participation and final recommendations related to continuing, changing, or terminating the study.

9. Benefits

Our pilot study of 6 patients demonstrated that when the device was in the automatic mode, the patient spent more time within the prescribed oxygen saturation goals and that it took less time for them to return to the prescribed oxygen saturation range whenever they were outside of the range. Even though this wasn't considered statistically significant, we felt that this was due to the fact the infants were only on the device for 12 hours (two 3-hour periods of automatic control and two 3-hour periods of manual control). This pilot study did show a significant decrease in the number of bradycardia events while the infants where in the automatic mode. With our current study, the patients will be on the device for 6 days so a total of 72 hours of automatic control and 72 hours of manual control, so we are hoping to find statistical significance in all our study metrics. In the future once this device receives FDA approval, preterm infants can be kept in the desired saturation range for longer periods of time and help minimize long-term complications (chronic lung disease, retinopathy of prematurity, brain damage, necrotizing enterocolitis or death).

Currently healthcare providers care for 2-3 patients in the NICU. To prevent alarm fatigue in our staff, we chose a wide range for our pulse oximeter alarms parameters to minimize the frequency of alarms. If they are in the middle of caring for another patient and another patient's saturations are only slightly out of range, they may take up to a few minutes to respond especially if the saturation level is high. This computerized system will be able to respond instantaneously whereby decreasing the risk for long-term complications. Currently no one knows for sure what the optimal saturation level range should be for preterm infants to prevent these long-term complications. Once we validate this device, we will be able to choose more narrow saturation levels to see if we can improve the outcomes of our patients.

10. Payment and Remuneration

a. N/A

11. Costs

a. There are no costs to the patients for this study. The grant will pay for the tubing needed to connect the high flow nasal cannula set-up or the bubble CPAP set-up to the study device.

12. Multiple Sites

a. The University of Missouri Women's and Children's Hospital (Columbia, Missouri) is the lead site.
b. All required approvals will be in place at each site prior to project implementation. The study will utilize a single IRB (sIRB). The Studer Family Children's Hospital at Ascension Health (Ascension Sacred Heart Pensacola) (Pensacola, Florida) will be an additional site for the study and will rely on the MU IRB for review. The MU IRB will be responsible for the oversite of the relying IRB.
c. Information that is relevant to protection of human subjects obtained from multiple sites will be managed as follows. Communications between sites will be handled using regularly scheduled (weekly) meetings to discuss the study. Also, any issues related to IRB will be discussed immediately by phone, text, and email. Each site has a clinical PI (Pardalos in Columbia, Missouri and Amjad in Pensacola, Florida) working at that location full time. All IRB documents (protocol, consent forms, etc.) will be stored on secure cloud storage using a provider under contract by MU (currently box.com) and using the MU IRB web-based IRB system. Further the clinical PIs (neonatologists) at both sites are affiliated with the University of Missouri and therefore have login access to the MU IRB web-based tools and document storage. This will allow instantaneous access of IRB documents for both study sites. Participating sites will be responsible for meeting other regulatory obligations, such as obtaining informed consent, overseeing the implementation of the approved protocol, and reporting unanticipated problems and study progress to the sIRB. Participating sites will communicate relevant information necessary for the sIRB to consider local context issues and state/local regulatory requirements during its deliberations. Participating sites will rely on the sIRB to satisfy the regulatory requirements relevant to the ethical review.

13. Conflict of Interest

a. Conflict of Interest Description: Dr. Amjad and Dr. Fales have a financial interest in a company called Intelligent Respiratory Devices, LLC (IRD). Intelligent Respiratory Devices, LLC has licensed intellectual property (IP) from MU. The IP relates to the device being studied in the IRB protocol.
b. Conflict of Interest Management:
    - John Pardalos, MD is the PI over the multicenter clinical trial in addition to the MU study site. He will oversee all activity relevant to the IRB protocol including data safety monitoring. Dr. Pardalos has no conflict of interest with respect to the clinical trial.
    - An independent statistician will be utilized for data analysis including for interim analysis and the final analysis for the clinical trial.
    - Affiliation with the company Intelligent Respiratory Devices, LLC will be disclosed in all publications and reports of study data.
    - Affiliation with the company Intelligent Respiratory Devices, LLC will be disclosed in the consent document to be signed by a parent or legal guardian.

14. References

Martin, R. Oxygen Monitoring and Therapy in the Newborn. UpToDate; April 18, 2016.

A. Faqeeh, R. Fales, J. Pardalos, R. Amjad, I. Zaniletti, and X. Hou, "Engineering Evaluation of the Performance of an Automatic Peripheral Oxygen Controller Using a Neonatal Respiratory Model," *ASME Journal of Medical Devices,* vol. 12, no. 3, pp. 031005, Sep, 2018.

Hou, Xuefeng, Akram Faqeeh, Tyler Shinn, and Roger Fales. “Anti-Windup and Disturbance Rejection Controller Design of an Automated Oxygen Control System for Premature Infants”, 40th International Conference of the IEEE Engineering in Medicine and Biology Society, July 17-21, 2018.

Faqeeh, Akram, Xuefeng Hou, Isabella Zaniletti, John Pardalos, Ramak Amjad, and Roger Fales. “Comparison of Automated and Manual Peripheral Oxygen Saturation Control Applied to One Human Subject at a High Target Range”, 40th International Conference of the IEEE Engineering in Medicine and Biology Society, July 17-21, 2018.

Hou, Xuefeng, akram Faqeeh, Ramak Amjad, John Pardalos and Roger Fales. “Clinical Evaluation of an Automatic Oxygen Control System for Premature Infants Receiving High Flow Nasal Cannula for Respiratory Support: A Pilot Study,” Journal of Medical Devices. 2022 Sep 1;16(3):031005. doi: 10.1115/1.4054250. Epub 2022 May 10. PMID: 35646226