An Evaluation of Early Use of the Tortle Midliner and Intraventricular Hemorrhage (IVH) Outcomes in Premature Babies: A Randomized Controlled Trial

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List of Abbreviations:

Apgar	Appearance, Pulse, Grimace, Activity, and Respiration
BW	birth weight
DR	delivery room
g	gram
IVH	intraventricular hemorrhage
kg	kilogram
LBW	low birth weight
NICU	neonatal intensive care unit
SAE	serious adverse event
VLBW	very low birth weight
WPH	Winnie Palmer Hospital for Women and Babies

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1. Research Synopsis

1.1 Study Title
An Evaluation of Early Use of the Tortle Midliner and Intraventricular Hemorrhage (IVH) Outcomes in Premature Babies: A Randomized Controlled Trial

1.2 Study Population
The study population will comprise inborn infants ≤30 6/7 weeks gestational age undergoing inpatient care in the Neonatal Intensive Care Unit at Winnie Palmer Hospital for Women and Babies.

1.3 Study Design
This study is a single-site prospective randomized controlled clinical trial.

1.4 Sample Size
The investigators for the study at Winnie Palmer Hospital for Women and Babies (WPH) anticipate a total enrollment of 150 neonates with 75 in each group (75 in control group and 75 in treatment group).

1.5 Study Duration
The study duration is estimated to continue until July 30, 2020.

1.6 Primary Objective
The primary objective of this study is to determine if infants positioned with the Tortle Midliner to optimize midline head positioning will have a better IVH outcome, determined by a decrease in rate of occurrence or severity of IVH, when compared to infants receiving the standard care (control group) with no Tortle Midliner intervention.

1.7 Secondary Objectives
None.

2. Background and Significance

Intraventricular hemorrhage (IVH) is defined as bleeding into the ventricles of the premature infant brain-the highest risk for the lowest gestational ages. IVH almost always occurs between birth and the first 72 hours of life. The four grades of IVH are based on the degree of bleeding; the greater the severity of the bleed, the more likely to have a poor outcome. Complications can include hydrocephalus, mental retardation, cerebral palsy and seizures. Neurologic sequelae can lead to death. Even for low grade bleeds the studies show the negative effects on cognitive scores and an increased incidence of learning disabilities. In addition, these same children often suffer from attention deficit disorder and other behavioral dysfunctions, which require intervention in order for the child to successfully integrate into school and society.

The incidence of IVH in very low birth weight infants (1500g) has declined from 40-50% in the early 1980s to 20% in the late 1980s. However, in the last two decades the occurrence of IVH has remained stationary. In extremely premature infants weighing 500-750g, IVH occurs in about 45% of neonates (Philip, Allan, Tito, & Wheeler, 1989).

Since increased risk of IVH can be associated with changes of intracranial pressure, many medical protocols supported by the research efforts of Bedwell have established IVH bundles which are designed to help reduce fluctuations in intracranial pressure while managing the micro-preemie infant during the first few days of life (Bedwell, Bright, & Sekar, 2015).

The correlation between IVH and head positioning of the extremely low birth weight infants has now made its way into research literature. Malusky suggests that venous obstruction can result from increased external pressure on the venous system when the micro-preemie infant has their head positioned to the side rather than maintaining a neutral position (Malusky & Donze, 2011). With this in mind many neonatal intensive care units (NICUs) around the world have instituted practices which include strict neutral positioning often combined with raising the head of the bed for all infants <1500 grams during their first three-plus days of life.

Therefore, we are aiming to conduct a prospective randomized controlled trial in order to answer the research question: Does early use of the Tortle Midliner reduce the incidence and/or level of severity of intraventricular hemorrhage if used in infants born at ≤ 30 6/7 weeks and neutral position is maintained for the first 72 hours of life? We hypothesize that the use of early consistent neutral positioning compared to the standard care (nested positioning) practiced in the NICU will reduce the risk of intraventricular hemorrhage in preterm infants born at ≤ 30 6/7 weeks and have a positive effect on the incidence and/or level of severity of intraventricular hemorrhage in this population.

3. Objectives

3.1 Primary Objective

The prime objective is to determine if early application of the Tortle Midliner for preterm infants, ≤ 3 hours following birth and with subsequent continuous use through 72 hrs. of life to ensure maintenance of optimal midline positioning (treatment group), will impact the IVH outcome as determined by a reduction in the rate and/or severity of IVH when compared to infants receiving the standard regimen of care (control group).

3.2 Secondary Objectives

None

4. Study design/methodology

This study will be registered in Clinical Trials (clinicaltrials.gov) with the primary endpoint being a difference in IVH incidence and severity. We propose to conduct a randomized controlled trial in preterm infants (gestational age ≤30 6/7 weeks) comparing the use of the Tortle Midliner and the standard of care practice (Control group). While blinding of study groups is always desirable in randomized studies, this will not be possible for this study.

Study Procedure

After eligibility of the infant is determined and the study informed consent is obtained from the parent or legal guardian, subjects will be randomized.

Randomization will follow a block randomization table that will determine if the infant will go into the group that will be positioned using the Tortle Midliner (Treatment Group) or not (Control Group).

All clinical care will be provided with consideration of the gestational age of the subject and follow NICU department guidelines and as ordered by physician and/or ARNP providers.

The key distinction for this study will be the use of the Tortle Midliner as a positioning aid in addition to standard of care for the Treatment Group, as opposed to solely standard practice of nesting and the use of rolls and other aids for the Control Group.

Treatment Group

The application and maintenance of the Tortle Midliner is within the scope of practice and skill-set of the NICU nursing and ancillary staff. The device has been in use in the WPH NICU since May 2016 when ordered by physician or nurse practitioner.

The use of the Tortle Midliner will be in addition to the NICU department process guidelines for positioning relevant to the gestational age of the subject. The Tortle Midliner will be applied no later than 3 hours following birth under the supervision of a

study investigator. The size/fit and application of the device will be according to the manufacturer's guidelines. The neutral midline head position, supine or slightly side-lying, with a bed elevation between 15° and 30° will be maintained during the first 72 hours of life. A member of the NICU physical therapy staff will perform and document a goniometry measurement (head/neck angle with head midline and perpendicular to shoulders, in line with the axial spine and not > than 5° deviation) a minimum of once daily during the first 72 hours of life and make any adjustments necessary, which is within their scope of practice.

Caregivers will document the NICU integrated flowsheet and the Sunrise electronic record with interventions regarding positioning, handling, skin assessment etc. per standard practice requirements.

The Tortle Midliner placement will be documented by clinical staff assigned to the subject's care every 2-4 hours on a tracking log. The active study period will end after the first 72 hours of life. The positioning device will be removed and the clinical care will continue according to NICU guidelines.

In the instance that phototherapy is ordered by the attending physician for babies in the treatment group, a compatible Tortle Midliner phototherapy eye shield will be used following manufacturer's size and guidelines.

Control Group

All clinical care for the control group will be within NICU department process guidelines relevant to the gestational age of the subject and as ordered by physician and/or ARNP providers. The neutral midline head position with the aid of nesting and/or rolls with a bed elevation between 15° and 30° will be maintained throughout position changes during the first 72 hours of life, which is standard practice. Caregivers will document the NICU integrated flowsheet and the Sunrise electronic record with interventions regarding positioning, handling, skin assessment etc. per standard practice requirements.

Data Collection

At Study Entry

Basic demographic information and delivery history will be collected.

Maternal Information- Only maternal information contained within the subject's record will be collected; the mother's record will not be accessed

Data collection will include: prenatal maternal conditions, maternal medications, mode of delivery, and delivery complications.

Clinical Data- collected from birth through the first 72 hours of life:

Procedures and conditions that may contribute to IVH will be collected, such as:
sepsis (positive blood culture, vasopressors, steroids, bolus administrations (fluids/meds), hypoglycemia (serum glucose <45) or hyperglycemia (serum glucose >200), hypercarbia (CO_2 >65mmHg), apnea/bradycardic episodes requiring stimulation, patent ductus

arteriosus, maximum respiratory support, suction events, line placements (PICC, IV, UAC/UVC) and/or needle punctures , UAC/UVC line collections, chest tube insertion, and any other noxious event

The subjects in both groups meet criteria for a standard of care head ultrasound at 6-8 days of life. Results from the head ultrasound report will be captured.

Clinical Outcomes Data – collected through date of discharge

The results of the last head ultrasound and/or magnetic resonance imaging (MRI) of the brain before discharge will be collected if these additional tests were ordered during the hospitalization (as solely determined by the attending neonatologist and not for study purposes).

Outcome data will include: days on mechanical ventilation throughout hospital stay, discharged home with G-Tube, discharged home on respiratory support (FiO2, mode/settings), discharged with shunt, and length of stay (# days).

Adverse Event/Serious Adverse Event

The device, Tortle Midliner, solely impacts the skin contact areas. Only adverse events related to skin breakdown requiring wound care consultation with treatment will be reported as an adverse event. The principal investigator will evaluate adverse events related to skin integrity.

Any death will be reported as a serious adverse event according to Orlando Health IRB policy.

Major Protocol Deviation

For the purpose of this study, the midline position will be maintained with consistent use of the Tortle Midliner for all randomized study subjects in the treatment group (Tortle group) from ≤ 3 hours to 72 hours from birth. If the device is not utilized for a period greater than 30 consecutive minutes, the situation will be evaluated by the principal investigator. A major protocol deviation will be reported if the device was not in place for any reason other than the safety or well-being of the subject.

Study Endpoint

The study period will be the first 72 hours of life with data collection for clinical outcomes to continue until discharge from the hospital, transfer to another institution, removal or withdrawal from the study, or death. There will be no additional contacts or follow-up for subjects beyond those time points.

The primary endpoint for the study is the difference in IVH incidence and severity between the two groups from birth through the first 72 hours of life.

5. Study Population

Each study subject must meet all of the indicated inclusion criteria and none of the exclusion criteria noted below:

5.1 Inclusion Criteria

1. Gestational age less than or equal to 30 6/7 weeks at birth
2. Less than 3 hours from birth
3. Informed consent obtained from parent or legal guardian prior to reaching time point for randomization

5.2 Exclusion Criteria

1. Presence of genetic/chromosomal abnormality, congenital hydrocephalus, congenital neuromuscular disorder, or other diagnosis determined to impact survival or generalizability of results
2. Unable to participate for any reason based on the decision of the principal investigator.
3. Infants born outside Winnie Palmer Hospital for Women and Babies

6. Study Duration/ Study Timeline

Projected start date approx. April 2018 following IRB approval)

• Stage 1	Enroll subjects following IRB approval through April 2020	24 months
• Stage 2	Data analysis through July 2020	3 months
• Stage 3	Poster, abstract and/or manuscript through January 2021	6 months

7. Statistical Analysis Plan

Sample Size Determination:

A sample size of 142 neonates with 71 in each group (71 in control group and 71 in intervention group) was determined in order to achieve 80% power to detect a 20% difference in IVH between the two groups, using a target rate of IVH of 15% in the intervention group. The test statistic used was the two-sided Z test with pooled variance. The significance level of the test would be 0.05.

We aim to allow for an additional 5% in sample size to adjust for either voluntary or involuntary withdrawal of some of the enrolled subjects. Upon reaching 142 enrollees the data will be reviewed. If any baby (ies) within the first 142 enrollees was withdrawn, the baby will be replaced according to the original randomized group, up to an additional 8 babies to ensure the power of the study and maintain a balance between the groups. A maximum of 150 babies will be enrolled.

Data Analysis:

Data analysis will include descriptive statistics with means and proportions. Comparative statistics will be used to compare IVH outcomes in the two groups. IVH outcome will be

determined by a reduction in the rate and/or severity of IVH. Any additional information on data points may be described in tables and/or graphs.

8. Informed Consent Process

The patient's parent or legal guardian will be approached by the principal investigator or sub-investigator and the study will be explained in clear, layperson language. All study procedures will be disclosed. Risks to the patient will be explained; no individual patient benefits will be promised. The patient's parent or legal guardian will be given the opportunity to ask questions and confer with family members and others. If the patient's parent or legal guardian elects to consent to the trial, he/she will sign and date the consent form.

The original signed form will remain with the investigator in the study file; a copy will be given to the parent or legal guardian and a copy will be filed in the official medical record as well.

9. Privacy and Confidentiality

Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, only the study investigators and regulatory coordinator will have access to the case reports and subject records. All records will be kept in a locked, password- protected computer as well. All paper case report forms and source documents will be maintained in a secured area within a locked office and maintained for a minimum of three years after the completion of the study.

10. Risk/Benefit

This study involves a product, the Tortle Midliner, already on the market and available for commercial use for prevention of cranial asymmetry and head preference in infants 0 to 6 months of age. The product being evaluated is a breathable, cotton, Lycra and foam beanie device, with two positioning rolls. The Tortle Midliner has been in use in the WPH NICU since May 2016.

10.1 Risk to participants

This study involves the use of a product in direct contact with the infant's skin. There remains a very small chance of skin breakdown. Frequent skin assessments (as is the standard care practice in the NICU) will help minimize this risk.

10.2 Benefits to Participants

The product under evaluation is already approved for use in the neonatal population. However, the impact on the rate and severity of IVH has not been studied. As such, it is not possible to predict whether or not any direct benefit will result from the use of this product to prevent or reduce IVH.

11. Safety Monitoring, Interim Analysis, and Stopping Rules

Safety will be monitored by the review of adverse events and serious adverse events for each patient. Any concerns regarding the safety of the device will be evaluated by the principal investigator, documented, and reported according to IRB policy.

12. Conflict of Interest

No relevant financial interest or affiliations with any commercial interests for any member of the study team

13. Publication and Presentation Plans

A manuscript will be prepared upon completion of this study and submitted for possible publication in a journal with a focus on neonatal or rehabilitation meditation. The data may also be presented at future neonatal and/or rehabilitation conferences.

14. References

Bedwell, S. M., Bright, B., & Sekar, K. C. (2015). Decrease in Incidence of Intraventricular Hemorrhage (IVH) After the Introduction of an IVH Prevention Bundle in the NICU. *The University of Oklahoma Medical Center.*

Malusky, S., & Donze, A. (2011, November). Neutral Head Positioning in Premature Infants for Intraventricular Hemorrhage Prevention: An Evidence-Based Review. *Neonatal Network, 30*(6), 381-396.

Philip, A., Allan, W., Tito, A., & Wheeler, L. (1989, November). Intraventricular Hemorrhage in Preterm Infants: Declining Incidence in the 1980s. *Pediatrics, 84*(5), 797-801.

15. Appendices

15.1 Data Collection Sheets (Baseline, NICU, Day 1, Day 2, Day 3, Head Ultrasound, Final Clinical Outcome)

15.2 Tortle Bedside Log

15.3 Tortle Rehab Assessment Log