GLYCERIN SUPPOSITORIES USED PROPHYLACTICALLY IN PREMATURE INFANTS (SUPP): A PILOT STUDY FOR A MULTICENTRE RANDOMIZED CONTROLLED TRIAL

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TITLE: Glycerin Suppositories Used Prophylactically in Premature infants (SUPP): A Pilot Study for a Multicenter Randomized Controlled Trial

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LAY ABSTRACT

Feeding is a significant challenge for premature babies in the neonatal intensive care unit. These infants have immature digestive tracts and may not have normal bowel movements until a week or more after birth. One way to help premature babies is by giving them a medication called glycerin suppositories. This treatment is already used in many hospitals around the world. Unfortunately, previous studies have not shown for sure that this medication is actually helpful. In fact, there are some signs that using glycerin suppositories in premature infants may be harmful. We conducted a small study involving 22 premature infants randomized to either glycerin suppositories or a placebo. We found that it is safe and practical to do a larger study on this treatment involving multiple hospitals and hundreds of premature babies. The larger study will have enough participants to full show the risks and benefits of using glycerin suppositories to treat these infants.

ABSTRACT

BACKGROUND: Adequate feeding is a significant challenge for premature infants in the neonatal intensive care unit. These patients are often treated with glycerin suppositories to stimulate the passage of meconium and prevent feeding intolerance. Unfortunately, the evidence for this practice is limited and inconclusive.

METHODS: We conducted a systematic review on the use of glycerin suppositories and enemas in premature infants. Following this, we conducted a pilot study for a multicenter randomized controlled trial of premature infants randomized to glycerin suppositories or a placebo procedure once daily. Outcomes included rate of recruitment, rate of reaching the primary endpoint of full enteral feeds, treatment-related adverse events, and cost.

RESULTS: Twenty-two infants were recruited and randomized active treatment or the placebo procedure. Gestational age was 24-32 weeks and birth weight was 500-1500 grams. During the study period, 61 infants were screened, 46 (75%) were eligible and approached for consent, 25 (54%) consented to participate, 22 (48%) were randomized, and 19 reached the primary endpoint of full enteral feeds. Three infants (14%) experienced rectal bleeding 5 to 43 days after completing study treatments. An anal fissure was also noted in two of these patients (9%). There were no cases of rectal perforation or necrotizing enterocolitis. Protocol violations occurred during 14 of 130 (11%) treatment days. The total cost for running this pilot study was estimated to be

$16,000. A revised sample size calculation for the multicenter study indicated that 72 infants would be required to detect a treatment effect of 2 days faster to full enteral feeds.

CONCLUSIONS: This external pilot study suggested that conducting a multicenter randomized controlled trial of glycerin suppositories in premature infants is feasible and safe. In the multicenter trial, we recommend tolerating a lower platelet count in the exclusion criteria, using a fixed rather than variable treatment duration, conducting follow-up assessments at predefined time points, and conducting an interim analysis to ensure that treatment is not associated with increased risk of necrotizing enterocolitis.

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I would also like to thank the members of the "SUPP Trial Team": Dr. Jorge Zequiera, for his early interest in this project; Dr. Anna Shawyer, for collaborating on the systematic review; Dr. Connie Williams, whose coordination within the Neonatal Intensive Care Unit was essential; Julia Pemberton, who hand-picked the research personnel for this trial; and Stephanie Becker, our nursing liaison and architect of the now famous "poop legend."

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LIST OF ALL ABBREVIATIONS AND SYMBOLS

95% CI – 95% confidence interval

NEC – necrotizing enterocolitis,

NICU – neonatal intensive care unit

MD – mean difference

RR – risk ratio

SD – standard deviation

DECLARATION OF ACADEMIC ACHEIVEMENT

The core elements of this Thesis are: (1) The Systematic Review and Meta-analysis and (2) Results from the Pilot Study. For the systematic review, I completed the initial literature search, developed data abstraction forms, reviewed titles and abstracts, completed data abstraction, analyzed data in Review Manager, and wrote the first and final draft of the manuscript. I am indebted to Alla Iansavichene BSc MLIS, who developed and executed the structured search of Medline, Embase, and the Cochrane Library. Dr. Anna Shawyer kindly acted as my co-reviewer, and independently reviewed titles and abstracts and completed data abstraction in duplicate. Drs. Shawyer, Rosenbaum, Jones, Williams, and Walton reviewed the manuscript and provided feedback.

In regards to the pilot study, I designed the study protocol, helped obtain funding, completed the ethics review, assisted with trial management, analyzed data, and wrote the first and final draft of the manuscript. Henrietta Blinder revised the study protocol, created case-report forms, trained the charge nurse nurses, obtained consent from parents or guardians, and collected data. Julia Pemberton assisted with the grant application, ethics review, and trial registration. Dr. Connie Williams assisted with the grant application, ethics application, and trial management. Dr. J. Mark Walton conceived this study, helped complete the grant application, and assisted with trial management. Drs.

Rosenbaum, Jones, and all of the individuals listed above reviewed the manuscript and provided feedback.

For the purposes of transparency, I included the following documents as appendices: (1) grant application for the pilot study (which was initially written and submitted as the course paper for Health Research Methodology 730); (2) pilot study protocol (which underwent several revisions following feedback from the Neonatal Research Committee, Hamilton Integrated Research Ethics Board, Health Canada, and the reviewers and Editorial Board for Pilot and Feasibility Studies); and (3) stooling legend (developed primarily by Stephanie Becker) to help standardize the duration of study treatments during the pilot study. Dr. Jorge Zequiera completed a preliminary literature review on this topic, and is included as an author on the grant application and study protocol. These three appendices are meant to provide context but do not represent credit towards the completion of this Thesis.