**Post-extubation Non-invasive Respiratory Support Pressure levels in Preterm Neonates: A Prospective Comparative Evaluation Research Study**

**[Protocol Summary; prepared by Amit Mukerji, McMaster University]**

**Brief Background:** The optimal post-extubation pressure level on non-invasive respiratory support modes – irrespective of the choice of the specific non-invasive mode – that optimizes extubation success and improves clinical outcomes remains unknown.

**Objective:** To determine the optimal initial non-invasive pressure support level following extubation in preterm neonates.

**Specific Research Question:**

Population: Preterm neonates with **GA <29 weeks** and **>72 hours chronological age** and **<32 weeks’ postmenstrual age** being extubated to any non-invasive respiratory support mode. Infants with chromosomal/genetic/congenital abnormalities will be excluded.

Intervention: Initial non-invasive pressure level = Pre-extubation pressure level **+ 2 cmH2O**

Control: Initial non-invasive pressure level = Pre-extubation pressure level

Outcomes: 1. Post-extubation failure within 72 hours; 2. Post-extubation failure within 7 days; 3. Duration of all respiratory support; 4. BPD; 5. Death prior to discharge; 6. BPD or Death prior to discharge; 7. Air leak syndromes in first 7 days post-extubation; 8. Intestinal perforation in first 7 days post-extubation

**Study Design:**

This will be a **prospective comparative effectiveness research study based on real-world practices** across participating tertiary NICUs in Canada. Centres will self-select whether to use intervention or control arm pressure levels as well as a single non-invasive support mode as the initial mode of choice for the duration of the study. Only the first eligible extubation will be included as part of this study for analysis.

Extubation criteria: While specific extubation criteria will not be mandated, extubation guidelines (**appendix A**) in relation to ventilator settings will be suggested. Data on pre-extubation settings will be captured as part of this study, as well as specific baseline clinical variables (**TBD**) believed to influence extubation success.

Use of spontaneous breathing trials (SBTs): There will be no specific recommendations on this from the study protocol. Centres that utilize such strategies may continue to do so. The use of an SBT, the type of SBT and its duration for each individual patient will be captured as a baseline variable.

Immediate post-extubation non-invasive support: Will be determined based on the individual centre’s choice and initial support mode, and practice within that centre will be standardized accordingly. **Table 1** outlines the initial support levels based on the pre-extubation support levels. *Choice of initially employed interface will be limited to short bi-nasal prongs and/or nasal masks*.

Escalation and weaning of non-invasive support: Will not be mandated as part of this study and will be left to the clinician’s discretion. This will include use of any non-invasive support mode as well as interfaces as chosen by the healthcare practitioner.

Re-intubation criteria: In contrast to extubation criteria, specific minimum re-intubation criteria will be mandated (**appendix B**) if escalation of non-invasive support (escalation levels and limits based on clinical team’s discretion) does not result in resolution of the signs/symptoms as outlined within the criteria. Data on reasons for re-intubation (within 7 days post-extubation only) will be captured, as well as non-invasive support mode and pressures/settings immediately prior to re-intubation.

**Table 1:** Initial post-extubation support levels based on mode and assigned group

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| **Post-extubation mode** | **Intervention group settings** | **Control group settings** |
| CPAP | PEEP = Pre-extubation MAP + 2 cmH2O | PEEP = Pre-extubation MAP |
| Bi-phasic CPAP\* | Lower PEEP = Pre-extubation MAP + 1 cmH2O  Higher PEEP = Lower PEEP + 3 cmH2O | Lower PEEP = Pre-extubation MAP – 1 cmH2O  Higher PEEP = Lower PEEP + 3 cmH2O |
| NIPPV† (from conventional ventilation) | PEEP = Pre-extubation PEEP + 2 cmH2O  PIP = Pre-extubation PIP + 2 cmH2O | PEEP = Pre-extubation PEEP  PIP = Pre-extubation PIP |
| NIPPV† (from high frequency ventilation) | PEEP = Pre-extubation MAP – 2 cmH2O  PIP = NIPPV PEEP + 12 cmH2O | PEEP = Pre-extubation MAP – 4 cmH2O  PIP = NIPPV PEEP + 12 cmH2O |
| NIV-NAVA‡ (from conventional ventilation) | PEEP = pre-extubation PEEP + 2 cmH2O | PEEP = pre-extubation PEEP |
| NIV-NAVA‡ (from high frequency ventilation) | PEEP = pre-extubation MAP – 2 cmH2O | PEEP = pre-extubation MAP – 4 cmH2O |

**\***Rate = 20; i-time = 1 second; †Rate = 40; i-time = 0.5 second; ‡NAVA level as determined by clinician

**Analysis, Statistics and Sample Size:** Baseline, demographic and outcome variables will be compared between the groups using appropriate univariate analyses. For the primary outcomes (extubation failure within 72 hours and 7 days), adjusted analyses will be conducted after adjusting for potential confounders as well as accounting for centre-based variation. No adjustments for multiple comparisons will be made and a P value <0.05 will be considered statistically significant.

Assuming a baseline extubation failure rate of 35%, to show a clinically meaningful decrease by 10% will require a sample size of 440 per group (assuming equal distribution of numbers between the groups; α=0.05 and β=0.10). Based on numbers of infants extubated annually in the eligibility window – it will require 2 years to achieve the required sample size.

**References:**

**Appendix A:** *Recommended* Extubation Criteria (with respect to ventilator settings only)

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| **Mode of IMV** | **Suggested Extubation Settings** |
| Conventional ventilation | PIP ≤20 cmH2O; PEEP ≤8 cmH2O  Set Rate ≤ 40 bpm  FiO2 ≤50% |
| High frequency oscillation | MAP ≤10 cmH2O  FiO2 ≤50% |
| High frequency jet ventilation | PIP ≤20 cmH2O; PEEP ≤8 cmH2O  FiO2 ≤50% |

**Appendix B:** *Mandated* re-intubation criteria (applicable for the 1st 7 days post-extubation only). At least one or more of the following must be present prior to re-intubation:

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| 1. FiO2 requirement >50% or rise in FiO2 >20% in ≤12 hours |
| 1. High CO2 with pH <7.20 (respiratory acidosis) on arterial or capillary blood gas |
| 1. Increased work of breathing (*with* RR >80 bpm) |
| 1. Apnea/Desaturation/Bradycardia spells (>1 requiring bagging or >4/hour requiring moderate stimulation x 4 hours) |
| 1. Need for intubation related to non-respiratory pathology (such as development of intestinal perforation, sepsis) |

Note: These are *minimum* criteria – i.e. a clinician may elect to leave a patient on non-invasive support even if the criteria above are met, but may not re-intubate in the absence of at least one of the above criteria.

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