

BMJ Open Normal saline instillation versus no normal saline instillation And lung Recruitment versus no lung recruitment with paediatric Endotracheal Suction: the NARES trial. A study protocol for a pilot, factorial randomised controlled trial

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ABSTRACT

Introduction Endotracheal suction (ETS) is a frequent and necessary airway intervention for the intubated child. The aim of ETS is to clear the endotracheal tube and airways of respiratory secretions; however, the methods of performing ETS are varied. Internationally a number of ETS treatments are in use. Many have not been rigorously evaluated in a randomised controlled trial setting, and it is uncertain whether any are associated with better outcomes for the critically ill child. With approximately 50% of paediatric intensive care admissions requiring intubation, ETS interventions that maximise the efficacy and minimise the complications of ETS could translate to improved health for substantial numbers of critically ill children, and significant cost savings. The primary aim of the study is to examine two ETS interventions, normal saline instillation and lung recruitment, to determine if it is feasible to conduct a full efficacy trial.

Methods and analysis NARES (Normal saline instillation versus no normal saline instillation And lung Recruitment versus no lung recruitment with paediatric Endotracheal Suction) is a single-centre, pilot, factorial randomised controlled trial conducted in a tertiary referral paediatric centre in Brisbane, Australia. Children (aged 0–16 years) are eligible if they are intubated with an endotracheal tube and mechanically ventilated. Two intervention pairs will be compared using a 2×2 factorial design: (1) normal saline instillation versus no normal saline instillation; and (2) lung recruitment versus no lung recruitment. The primary outcome is study feasibility measured by a composite analysis of eligibility, recruitment, retention, protocol adherence and missing data. Secondary outcomes are ventilator-associated pneumonia, SpO₂/FiO₂ ratio, lung compliance, end expiratory level and regional tidal volume.

Ethics and dissemination Ethical approval to conduct the research has been obtained. Dissemination of the research findings will be undertaken, guided by the Consolidated Standards of Reporting Trials statement recommendations. Protocol content was guided by

Strengths and limitations of this study

- The factorial randomised controlled design allows for the testing of two intervention pairs within the one trial.
- Normal saline and lung recruitment interventions are not amenable to blinding of patients, clinical or research staff.
- The risk of selection and allocation bias will be reduced through the use of computer-generated randomisation and allocation concealment.

the Standard Protocol Items: Recommendations for Interventional Trials 2013 statement.

Trial registration number ACTRN12617000609358; Pre-results.

INTRODUCTION

Approximately 50% of children admitted to intensive care require the insertion of an endotracheal tube (ETT) to facilitate mechanical ventilation.¹ For the intubated and mechanically ventilated child, endotracheal suction (ETS) is a vital airway intervention used to clear pulmonary secretions and maintain ETT patency. An intubated child can receive up to 40 ETS procedures per episode of mechanical ventilation.² ETS is a complex procedure and children are vulnerable to the risk of adverse events associated with ETS. ETS-related complications such as atelectasis, impaired gas exchange, decreased lung compliance^{3,4} and ventilator-associated pneumonia (VAP)^{3,5,6} can

prolong a child's length of mechanical ventilation and subsequent survival.

Hospital-acquired VAP has an estimated prevalence of 12% among paediatric intensive care unit (PICU) patients.⁷ In adults it is the leading cause of death from hospital-acquired infections, with an attributable mortality rate as high as 55% of critically ill patients, dependent on study population.^{8–10} VAP can occur when pathogenic micro-organisms are inhaled or aspirated from the oropharynx or gastrointestinal tract, and tracheal intubation is the leading risk factor for VAP.¹¹ An essential component in preventing ETS-related complications such as VAP is evidence-based ETS practices. Internationally a variety of ETS interventions are in use; however, a consensus regarding ETS best practice is yet to be reached.

Normal saline instillation (NSI) is believed to be 'common practice' with ETS in mechanically ventilated infants and children.^{12–14} The basic tenet of NSI use is that it will dilute tenacious respiratory mucous,¹⁵ enhance secretion clearance and reduce surface tension in the distal airways.^{16 17} However, our recent integrative review found limited evidence regarding NSI efficacy on clinically significant end points such as respiratory mechanics and VAP.¹⁸ In no study was the clinical relevance explored by reporting the incidence of lung injury, ventilator hours or length of PICU admission.

Recent evidence supports the inclusion of a lung recruitment (LR) manoeuvre, as a strategy to reduce pulmonary derecruitment post ETS. LR aims to increase the transpulmonary pressure to maximise alveolar opening and gas exchange surface area.^{19 20} A comprehensive review on LR in paediatrics was published in 2015 and found LR may be useful to restore lung volume following ETS and circuit disconnection.²⁰ With the restoration of lung volume, gas exchange is also improved.

The use of LR may also reduce the time of dependence on mechanical ventilation and subsequent PICU outcomes.²¹ A systematic review protocol of LR in mechanically ventilated paediatric patients has recently been registered with PROSPERO (International prospective register of systematic reviews).²²

There is limited high-level scientific evidence informing the safe and efficient accomplishment of ETS in the paediatric population. This is largely in part due to the lack of clinical trial data to inform bedside practice. ETS-related interventions such as NSI and LR have not been rigorously tested in randomised controlled trials (RCT), and it is not known whether they are associated with a reduced incidence of VAP or improved gas exchange and respiratory mechanics. It is consequently important that ETS in the PICU be performed safely and effectively and that methodologically rigorous trials are performed to establish the effectiveness of ETS treatments NSI and LR.

The first step in evaluating these complex interventions for ETS is to undertake pilot and feasibility work before commencing a full-scale evaluation. The UK's Medical Research Council framework for evaluating complex

intervention was used to guide this study protocol.²³ The NARES (Normal saline instillation versus no normal saline instillation And lung Recruitment versus no lung recruitment with paediatric Endotracheal Suction) RCT has three objectives and will compare two ETS-related interventions, (1) NSI versus no NSI and (2) LR versus no LR:

1. to determine it is feasible to conduct a factorial RCT to test the efficacy and safety of NSI and LR with paediatric ETS
2. to determine if, in mechanically ventilated children requiring ETS, (1) NSI is superior to (2) no NSI to prevent VAP and improve measures of respiratory mechanics
3. to determine if, in mechanically ventilated children requiring ETS, (1) LR is superior to (2) no LR to prevent VAP and improve measures of respiratory mechanics, gas exchange and lung volume.

METHODS AND ANALYSIS

Design and setting

An RCT using a 2x2 factorial design will be conducted in a single-centre Australian PICU. The PICU is a tertiary referral, specialist teaching facility that provides advanced life support interventions including extracorporeal life support to Queensland infants and children from birth to 18 years of age. In 2015 the PICU had 1965 admissions, of which 825 were mechanically ventilated.¹ The factorial design allows for the comparison of two intervention pairs simultaneously: (1) NSI and no NSI and (2) LR and no LR^{24–26} (table 1).

Sample size and study power

The target sample size for the trial is 100, providing 50 participants per intervention comparison. Power level was not a valid consideration for sample size for this pilot study. Sample size was based on recommendations for pilot trial sample sizes.²⁷

Participants

Consecutive patients admitted to the PICU including direct admissions, ward transfers, postoperative admissions and retrievals will be screened for eligibility. Inclusion and exclusion criteria are provided in table 2. If the child deteriorates and requires treatment escalation, including high-frequency oscillation ventilation or extracorporeal life support, the participant will be withdrawn from the study.

Table 1 Four groups within factorial randomised controlled trial

2x2 factorial	LR	No LR
NSI	NSI and LR	NSI, no LR
No NSI	LR, no NSI	No LR, no NSI

LR, lung recruitment; NSI, normal saline instillation.

Table 2 Inclusion and exclusion criteria for the NARES trial

Inclusion criteria	Exclusion criteria
<ul style="list-style-type: none"> ▶ 0 (>37 weeks' gestation)–16 years of age (15 years+364 days) ▶ Oral or nasal endotracheal tube ▶ Conventional mechanical ventilation ▶ Likely to be ventilated for >24 hours* 	<ul style="list-style-type: none"> ▶ Cardiac surgery in this admission† ▶ Air leak syndrome‡ ▶ Ventilated for >48 hours prior to screening ▶ Previous study enrolment in this hospital admission ▶ Pulmonary hypoplasia ▶ Current diagnosis of ventilator-associated pneumonia ▶ Tracheal reconstruction ▶ Cystic fibrosis

*Determined as per patient plan in morning or evening medical rounds.

†Postcardiac surgery patients are excluded from enrolment due to the safety considerations associated with the lung recruitment manoeuvre.

‡In the presence of an air leak syndrome, it is at the discretion of the treating physician to include or exclude the patient in the trial.

NARES, Normal saline instillation versus no normal saline instillation And lung Recruitment versus no lung recruitment with paediatric Endotracheal Suction.

Interventions

Normal saline instillation

Participants in the NSI group will have 0.1 mL/kg (maximum dose of 2.0 mL) of 0.9% sodium chloride solution instilled with each ETS event. NSI dose was determined by study team consensus, on review of published protocol doses^{13 14 28} and in consideration of the recommendations for promoting intervention fidelity (standardised treatment dose for all study participants).²⁹

Lung recruitment

The LR manoeuvre will consist of an increase in positive end expiratory pressure (PEEP) by a factor of 2 from baseline PEEP (maximum of 18 cmH₂O) for 2 min,^{30 31} without modification of other ventilator parameters. This will occur at the completion of the ETS event and on reconnection to the ventilator.

ETS procedures

ETS will be performed when clinically indicated and as per standard practice for the site PICU (box 1).³² Inline or closed ETS is not routinely used in the unit, so all ETS procedures will be performed using the open ETS technique.

Escalation of treatment in no NSI arms

This will occur as per the discretion of the bedside clinician. If there is a suspected tube occlusion or mucous plug negatively affecting oxygenation and ventilation, clinicians are advised to proceed with ETS as directed by the medical officer. All escalations of treatment will be recorded in MetaVision (iMDsoft) and on the case report form (CRF).

Concomitant therapies

Respiratory interventions such as bronchopulmonary lavage will be performed at the discretion of the treating clinician and will be recorded on the CRF.

Outcome measures and definitions

The primary outcome is feasibility of a factorial RCT as established by a composite analysis of feasibility criteria

as described by Thabane *et al*³³ and Hertzog.²⁷ Full definitions of both primary and secondary outcomes are provided in box 2.

Recruitment, randomisation, allocation concealment and blinding

The clinical research nurse (CRN) will screen patients Monday to Friday, obtain written consent and undertake randomisation. A central web-based randomisation service via Griffith University (<https://www151.griffith.edu.au/random>) will be used to randomise patients and ensure allocation concealment. Randomisation will occur twice (once for each intervention pair) and be generated on a 1:1 ratio between groups. Randomisation will be stratified by reason for intubation (respiratory vs non respiratory), with randomly varied block sizes (4 and 6) within each stratum. NSI

Box 1 Endotracheal suction procedure

1. Two appropriately skilled staff to perform the procedure.
 2. Hand hygiene.
 3. Wear personal protective equipment.
 4. Assemble suction equipment, suction catheter size (2× endotracheal tube (ETT) internal diameter size).
 5. Disconnect patient from the ventilator.
 6. Use clean hand/dirty hand technique, perform suction using dedicated clean hand.
 7. Insert suction catheter only to a depth of 0.5 cm past the end of the ETT (length is determined using centimetre markings on the ETT).
 8. Total suction procedure should be less than 15 s.
 9. Suction is only applied (70 mm Hg) during catheter withdrawal and for no longer than 5 s.
 10. Suction catheter can be used for repeated suction during the same suction episode.
 11. Discard suction catheter if contaminated during the endotracheal suction procedure or on completion of the suction.
 12. Manually ventilate the patient (return of baseline SpO₂) prior to reconnecting to the ventilator.
- SpO₂, oxygen saturation

Box 2 Primary and secondary outcomes of the NARES trial

Primary outcome

Feasibility of full efficacy trial will be established by a composite analysis of the following:

- ▶ *Eligibility*: $\geq 75\%$ of patients screened will be eligible.
- ▶ *Recruitment*: $\geq 70\%$ of eligible patients agree to enrol.
- ▶ *Retention*: $\leq 15\%$ of patients withdraw from the study or are lost to follow-up.
- ▶ *Protocol adherence*: $\geq 80\%$ of participants will receive their allocated treatment throughout their study participation.
- ▶ *Missing data*: $< 10\%$ of data are missed.

Secondary outcomes

- ▶ $\text{SpO}_2/\text{FiO}_2$.⁴²
- ▶ Lung compliance (C_{dyn} , mL/cmH₂O).
- ▶ End expiratory level.
- ▶ Regional tidal volume.
- ▶ Ventilator-associated pneumonia: patients ventilated for more than 48 hours with two or more serial chest imaging test results with at least one of the following: new or progressive and persistent infiltrate, consolidation, cavitation, pneumatoceles (infants ≤ 1 year old); patients without underlying pulmonary or cardiac disease (eg, respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary oedema or chronic obstructive pulmonary disease), one definitive imaging test result is acceptable. In addition the patient must have at least one of the following: fever ($> 38.0^\circ\text{C}$), leucopaenia ($\leq 4 \times 10^9/\text{L}$ WBC) or leucocytosis ($> 12 \times 10^9/\text{L}$ WBC), and at least two of the following criteria: new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, new onset or worsening cough, or dyspnoea, or tachypnoea, rales or bronchial breath sounds, or worsening gas exchange (eg, O_2 desaturations (eg, $\text{PaO}_2/\text{FiO}_2 < 240$), increased oxygen requirements, or increased ventilator demand). The following are alternate criteria for diagnosing infants (< 1 year): worsening gas exchange (eg, O_2 desaturations (eg, pulse oximetry $< 94\%$), increased oxygen requirements, or increased ventilator demand), and at least three of the following: temperature instability, leucopaenia ($\leq 4 \times 10^9/\text{L}$ WBC) or leucocytosis ($> 15 \times 10^9/\text{L}$ WBC) and left shift ($> 10\%$ band forms), new onset of purulent sputum or change in character of sputum, or increased respiratory secretions or increased suctioning requirements, apnoea, tachypnoea, nasal flaring with retraction of chest wall or nasal flaring with grunting, wheezing, rales, or rhonchi, cough or bradycardia (< 100 beats/min) or tachycardia (> 170 beats/min). Alternate criteria for children aged 1–12 years include the presence of at least three of the following: fever ($> 38.0^\circ\text{C}$) or hypothermia ($< 36.0^\circ\text{C}$), leucopaenia ($\leq 4 \times 10^9/\text{L}$ WBC) or leucocytosis ($\geq 15 \times 10^9/\text{L}$ WBC), new onset of purulent sputum or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements, new onset or worsening cough, or dyspnoea, apnoea, or tachypnoea, rales or bronchial breath sounds, or worsening gas exchange (eg, O_2 desaturations (eg, pulse oximetry $< 94\%$), increased oxygen requirements, or increased ventilator demand.^{43 44}

FiO_2 , fraction of inspired oxygen; PaO_2 , partial pressure of oxygen in arterial blood; SpO_2 , oxygen saturation; WBC, white blood cells.

and LR are not amenable to blinding of patients, clinical staff or CRNs. Participants are enrolled in the treatment phase of the study for 48 hours, or until tracheal extubation, whichever occurs first.

Measurements

Changes in oxygen saturation (SpO_2)/fraction of inspired oxygen (FiO_2), dynamic compliance (C_{dyn}) will be compared at baseline (2 min pre-ETS), post-ETS, 2 min post-ETS (post-LR if applicable) and 10 min post-ETS. Secondary outcome data will be collected on the bedside monitor (Phillips, IntelliVue) and mechanical ventilator (SERVO U/I (Maquet) or Bellavista 1000 (imtmedical)) and stored on the clinical information system MetaVision (iMDsoft). Changes in end expiratory level (EEL) and regional tidal volume (V_T) will be assessed continuously during the ETS episode using electrical impedance tomography (EIT). EIT allows you to visualise regional ventilation and change in functional residual capacity.³⁴

We have previously shown EIT can measure changes in lung volume following disconnection of the ETT.³⁵ EIT measurements will be performed once per day during an ETS event using 16 electrodes and a reference electrode (PulmoVista 500, Dräger Medical, Lübeck, Germany). Changes in EEL and V_T will be compared at baseline (pre-ETS), post-ETS and 60 min post-ETS. The following criteria will be used to select these periods³⁶:

1. length of 3–5 breaths
2. regular breathing rate (synchronised with the ventilator)
3. stable V_T and end expiratory lung volume
4. rejection of the first breath if a respiratory pause preceded the tidal breathing period.

Data collection

Data will be entered onto the CRF directly from the source data using the electronic data platform REDCap V.7 (Research Electronic Data Capture, Vanderbilt; <http://project-redcap.org/>). A screening log will record patient information including name, diagnosis, severity of illness assessment (oxygenation index),³⁷ eligibility, recruitment and group allocation. All patients admitted to PICU during the data collection period will be recorded on the screening log (24 hours, 7 days a week). Screening log data will be used to inform feasibility outcomes (eligibility, recruitment and retention, and protocol adherence). Demographic variables to be collected include age, sex, weight, admission source, admission time (PICU), diagnosis, date and time of intubation, and ETT size. In addition the CRN will collect data on the primary and secondary outcomes. A protocol violation will be defined as ‘the randomised intervention was never performed’. A protocol deviation will be defined as ‘the incorrect intervention was used for a portion of study enrolment’. The investigating team will have access to and ownership of the final trial data set.

Statistical methods

As the pilot trial is not powered to detect statistical significance, statistical analysis will be used for piloting purposes only. Comparability of groups at baseline will be assessed using clinical parameters and reported using descriptive statistics. Mean and SD will be used to report normally

distributed continuous data, and median and IQR will be used for interval data that cannot be approximated with a normal distribution. The primary outcome measure of feasibility will be reported descriptively, against predefined criteria using frequency (percentages) for categorical data. Incidence rates of VAP per 1000 ventilator days and 95% CIs will be calculated using Poisson regression. For secondary outcomes measured using interval data ($\text{SpO}_2/\text{FiO}_2$, C_{dyn} , EEL, V_T), linear regressions will be run in a pairwise sequential manner to compare NSI vs no NSI, and for LR vs no LR, with assessment of a possible interaction effect between NSI and LR. In all analyses the patient will be the unit of analysis. The primary analyses will be undertaken on an intention-to-treat basis, in order to investigate the effect of treatment allocation. Because it is not known how high the level of treatment non-compliance will be, secondary analyses will be undertaken on a per-protocol basis, in order to assess the effect of treatment receipt. All per-protocol analyses will be clearly labelled and cautiously interpreted as indicating the maximum potential of these interventions. Data will be analysed using IBM SPSS Statistics V.22. An alpha value of 0.05 will be considered statistically significant.

Ethics and dissemination of results

Ethics

The NARES trial is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR) (ACTRN12617000609358). Informed consent will be sought prior to enrolling patients. A participant information sheet will be provided to patient representatives. Participants will not be identified by name, and confidentiality of all medical record information will be preserved, with all participants' details entered in coded format. Protocol amendments will be submitted to the HRECs for approval and changes will be communicated to the ANZCTR.

Data safety monitoring committee and SAE reporting

An independent Data and Safety and Monitoring Committee comprising experts in clinical trials and intensive care medicine has been established. Serious adverse events (SAEs) will be recorded on the CRF. SAEs are defined in accordance with The Australian Clinical Trial Handbook and include any event that is fatal, life-threatening, permanently disabling, incapacitation or prolongs a hospital stay.³⁸ All SAEs will be reported to the site ethics committee within 48 hours.

Dissemination

The Standard Protocol Items: Recommendations for Interventional Trials 2013 explanation and elaboration: guidance for protocols of clinical trials, and the Consolidated Standards of Reporting Trials (CONSORT) extension to randomised pilot and feasibility trials, were used to guide protocol and study design.^{39 40} All dissemination will be undertaken using the CONSORT 2010 statement: extension to randomised pilot and feasibility trials⁴⁰ and

the Template for Intervention Description and Replication checklist.⁴¹

Trial status

Recruitment of patients to the NARES trial commenced on 16 October 2017; five patients have been enrolled in the study.

DISCUSSION

ETS-related complications are common and ETS interventions applied during a child's episode of mechanical ventilation vary. The lack of evidence concerning NSI and LR with ETS has led to nurses to make ETS intervention decisions in a vacuum of evidence. This has resulted in unstandardised practice. To progress knowledge regarding the benefits and risks of NSI with paediatric ETS, a large RCT needs to be undertaken to provide definitive information on the safety and efficacy of NSI. The first step in this process would be to conduct feasibility work to determine sample calculations, identify outcome measures and test research processes including intervention fidelity and research protocols.²³

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Contributors JAS conceived the study, developed the protocol, wrote funding applications, drafted and revised the final manuscript. MC, MLM and AS conceived the study, developed the protocol, and revised and approved the final manuscript. DAL assisted with protocol development and revised and approved the final manuscript. RSW contributed to statistical methods and revised and approved the final draft.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Ethics approval was sought and obtained for the NARES trial from Children's Health Queensland (CHQ) HREC/16/QRCH/374 and Griffith University reference 2017/065.

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