ABSTRACT

Introduction Endotracheal tube (ETT) insertion depth estimation is important for optimal placement of ETT tip and balanced ventilation of the lungs. Various methods are available to determine the ETT insertion depth. The Neonatal Resuscitation Programme recommends the gestational age and nasal-tragus length (NTL) methods for estimating ETT insertion depth during cardiopulmonary resuscitation. However, the prospective data comparing these two methods is lacking.

Methods and analysis This is an open-label multi-centre randomised controlled trial, where gestational age and NTL methods will be used to determine the initial ETT insertion depth in term and preterm infants that are less than 28 days old, requiring oral intubation in the delivery room or neonatal intensive care unit (NICU).

Sites and sample size The trial is aimed to recruit 454 infants over 3 years across tertiary level NICUs.

Outcomes The primary outcome includes an optimally positioned ETT, defined as an ETT tip between the upper border of the first thoracic vertebra and the lower border of the second thoracic vertebra. The outcome is assessed by a paediatric radiologist, who will be masked to the group assignment. Secondary outcomes are malpositioned ETT tips, pneumothorax, ETT repositioning, chronic lung disease, invasive ventilation days, and death.

Analysis Data will be analysed using the intention-to-treat principle. The primary and categorical secondary outcomes will be compared using the $\chi^2$ test. Adjusted risk ratios of outcomes will be calculated along with 95% CIs through multivariable logistic regression analysis, including covariates deemed biologically to influence the outcomes.

Ethics and dissemination The study has been approved by the PNU Research Ethics Board (20-0148) and the respective ethical review boards of the participating centres. The results will be disseminated through conference meetings, social media platforms, and publications in scientific journals.

Trial registration number NCT04393337.

Strengths and limitations of this study

► ELEGANT trial is an open-label, multicentre trial investigating the accuracy of two Neonatal Resuscitation Programme recommended endotracheal tube (ETT) insertion depth methods.

► Term and preterm infants requiring oral intubation in NICU or delivery room will be enrolled.

► Optimally positioned ETT is the primary outcome assessed by the blinded paediatric radiologist.

► Impractical to blind interventions and investigating only oral intubation are trial limitations.

INTRODUCTION

Most infants are vigorous at birth, but some infants require assisted respiratory support, including positive pressure ventilation and endotracheal intubation.1 Endotracheal intubation is a potentially life-saving measure in infants with severe hypoxia, cardiopulmonary arrest and extremely premature lungs. Endotracheal intubation is recommended when positive pressure ventilation with a face mask does not result in clinical improvement of an infant.2 Although an endotracheal tube (ETT) is the most reliable way of providing positive-pressure breath, the critical factor determining the maximal efficacy of positive-pressure ventilation is the optimal placement of the ETT tip. ETT tip should be placed in a position that allows proportional ventilation of the lungs. A misplaced ETT tip can result in heterogeneous lung expansion, lung collapse, pneumothorax and asymmetrical surfactant distribution, which may eventually lead to chronic lung disease.3 There are various methods available to determine the initial depth of ETT. Some of these methods are based on the infant’s
METHODS

Trial hypothesis
To determine whether estimating ETT insertion depth using gestational age is more accurate than that using NTL method in preterm neonates requiring endotracheal intubation and also to determine whether gestational age or NTL method is more accurate in preterm neonates requiring endotracheal intubation.

Primary outcome
The primary outcome is the proportion of correctly positioned ETT on the chest X-ray. ETT is considered optimally positioned if the tip of the ETT lies between the upper border of the first thoracic vertebra (T1) and the lower border of the second thoracic vertebra (T2).

Secondary outcomes
The secondary outcomes include

- ETT tip above the upper border of T1.
- ETT tip below the lower border of T2.
- Pneumothorax.
- ETT repositioning (advance or withdrawn) following chest X-ray.
- Oxygen therapy at 28 days.
- Oxygen therapy or positive pressure support (including nasal cannula <2L/min and >30% oxygen, nasal cannula >2L/min and any oxygen, continuous positive airway pressure, and any oxygen, or invasive respiratory support and any oxygen) at 36 weeks postmenstrual age.
- Duration of invasive ventilation.
- Death before discharge.

Trial procedures

Informed consent
Written consent will be obtained after the parents have been given a full verbal explanation and written description (online supplemental information 1). An explanation of the consent will be conducted with the parents in their native language. A hospital-based adult interpreter will be used where required. A deferred written consent (after initial verbal assent) where prior written consent is not feasible as the study does not involve additional risk or investigations to the participants and the interventions are otherwise considered as standard practice recommendations by the NRP and hospital sites.
Trial interventions
The studied interventions in this study will be two different estimation methods for ETT insertion depth in oral intubation in neonates. The two methods are the gestational age method and the NTL method. In the gestational age method, the ETT insertion depth is obtained from the gestational age chart adapted from Kempley et al.14 In the NTL method, the ETT insertion depth is calculated based on the formula—the distance from nasal septum tip to ear tragus+1 cm. The details of these two estimation methods are provided in online supplemental information 2, which also illustrates the positioning of the neonate before obtaining the chest X-ray.

Randomisation
Eligible infants will be randomly assigned using a 1:1 ratio to the ‘NTL method’ or ‘gestational age method’. The randomisation is stratified by gestational age at birth (<28 weeks and >28 weeks) and the participating centre. The randomisation sequence is generated by an independent researcher with a computer at the website www.sealedenvelope.com hosted by King Abdullah bin Abdulaziz University Hospital (KAUH), Saudi Arabia. The randomised sequence is integrated into the in-built randomization module within the Research Electronic Data Capture (REDCap) system by the independent researcher. Therefore, the sequence is inaccessible to the trial investigators.

Allocation concealment
Allocation will be concealed by incorporating the random permuted blocks of size 2 and 4 sequences within the REDCap system.

Blinding
This will be an open-label trial. Blinding of the clinicians, nurses, and patient caregivers is impractical. However, to minimise the bias, the method used to estimate the ETT insertion depth will not be mentioned to the patient caregivers explicitly nor recorded in the patient charts. The primary outcome assessment will be blinded by masking the consultant paediatric radiologist to the group assignment. Similarly, the consultant paediatric radiologist will determine the following secondary outcomes—ETT tip above the upper border of T1, ETT tip below the lower border of T2 and pneumothorax. The trained research assistant will determine the other secondary outcomes (ETT repositioning after the X-ray, oxygen therapy at 28 days, oxygen therapy or positive pressure support at 36 weeks postmenstrual age, duration of invasive ventilation, and death before discharge).

Structure and duration of trial
The trial aims to recruit 454 infants (see under sample size) from multiple tertiary-level NICUs over 3 years.

Data collection
Data required for the trial will be collected from the clinical notes and radiological records using the data collection forms (online supplemental information 3). No additional laboratory or blood tests will be required.

Early cessation
The trial steering committee will receive recommendations from the data monitoring committee if the trial requires early termination following the interim data analyses and evidence from relevant studies. The following measures were agreed to consider stopping the trial, wholly or partly (subgroups), after an interim analysis that will be conducted following enrolment of 200 participants.

1. An absolute difference of greater than or equal to 25% in the primary outcome between the study groups.
2. An absolute difference of less than 5% in the primary outcome between the study groups.
3. A rate of less than 20% in the primary outcome in either of the groups.

The purpose of the interim analysis is to evaluate the safety and futility rather than the efficacy. Therefore, no p value adjustment is proposed.

Safety reporting
Any unexpected serious events (death, any life-threatening event, any event that will prolong the hospitalisation or any event that will result in disability) will be reported to the data safety monitoring committee. The committee will evaluate the risks versus benefits associated with the study or the study interventions. The committee may recommend early cessation depending on the interim data analyses.

Statistics and analysis
Sample size
Our unpublished data showed using the NTL method for estimating ETT insertion depth in term and preterm infants result in 35% of correctly positioned ETT tips. The data is similar to the randomised20 and non-randomised21 studies that showed similar accuracy (32%–37%) with the NTL method for estimating ETT insertion depth. With 90% power and two-sided 5% significance, to detect an absolute increase of 15% in optimally positioned ETT tips using the gestational age method, we will require 454 participants.

We calculated sample size using nQuery Advisor Sample Size Calculator V.8.3.0.0.22

Statistical analysis
Data will be analysed based on the intention-to-treat principle. Univariate analyses will be performed to compare baseline demographic factors between the two groups (online supplemental information 4). A mean with standard deviation (normal data) or median with IQR (skewed data) will be obtained for continuous variables and numbers and percentages for categorical variables. Independent t-test (normal data) or Mann-Whitney U test (skewed data) for continuous variables and χ² or Fisher exact test for categorical variables when appropriate will be used to analyse the groups. SAS V.9.4 will be used for
the conduct of all analyses. A detailed Statistical Analysis Plan will be developed before the interim analysis.

Analysis of primary outcome
Adjusted risk ratios of a successful outcome will be calculated along with 95% CIs. Adjusted ratios will be determined using multivariable logistic regression analysis, including covariates deemed biologically to influence the primary outcome (online supplemental information 5). In addition, principles of best model practices will be followed (including assessment of collinearity among included variables) and determination of the predictive ability of the model using the area under the curve. Outcomes will be reported as shown in ghost tables in online supplemental information 6.

Analysis of secondary outcomes
Similar analyses as above will be performed for all secondary outcomes that are categorical variables. Online supplemental information 5 lists variables included in the regression models for each secondary outcome. Outcomes will be reported as shown in ghost tables in online supplemental information 6.

Handling missing data
Missing data will be evaluated in terms of their pattern (eg, missing completely at random, missing at random, etc). All analyses will be based on a listwise deletion approach where observation with complete values will be only considered for analysis missing completely at random. Multiple imputation approaches will be applied for variables with missing values at random to impute the missing values using the recommended method.23

Quality control and assurance
Site initiation and training
The local research team will be trained in the protocol and the trial procedures in conjunction with the local principal investigator. They will deliver the training to the site physicians, respiratory therapists and nurses. In addition, the local research team will act as a point of contact for the primary coordinating centre (KAAUH) and troubleshoot as the need arises.

Data collection, confidentiality and monitoring
We will use the data collection form (online supplemental information 3) to abstract data from patient medical records (either on paper or converted to a password-protected excel sheet) and will store it in locked office cabinets at participating sites or on a password-protected, encrypted USB drive. The primary study site, KAAUH, will initiate the data-sharing agreement (DSA). All the data will be entered from all participating centres into a single REDCap database, which will be managed from KAAUH once the DSA has been finalised among all centres.

Patient and public involvement
No patient involved.

DISCUSSION
This clinical trial comparing the gestational age and NTL methods will provide valuable data for clinicians determining the ETT insertion depth during oral endotracheal intubation. The findings from the clinical trial will also help address the knowledge gap in this research area and help update the NRP guidelines and recommendations. The study will also investigate the effect of gestational age on either of the methods. Though the trial is not powered for important respiratory outcomes, such as air leak, ventilation days, chronic lung disease, it will also provide comparative data assessing the impact of the estimation methods on these outcomes.

This trial is well powered for detecting the important differences between the gestational age and NTL methods for estimating ETT insertion depth. Given the large number of participants to study, we anticipate few challenges enrolling the study population. The two most significant challenges include the COVID-19 pandemic and less-invasive surfactant administration (LISA). COVID-19 pandemic-related restrictions have resulted in limited accessibility for physicians to discuss essential elements of the consent process and delayed ethical approval of additional centres. Nonetheless, we aim to keep up the enrolment with verbal assent and telephonic conversations with the parents. In addition, following LISA initiation, the rate of endotracheal intubation has come down in few study centres. Hence, additional centres from the USA are currently pending to be added as study centres for this study. In addition, these site recruitment efforts will focus on centres where LISA is not yet established.

ETHICS AND DISSEMINATION
We will conduct the trial according to The Declaration of Helsinki (amended 2008) and The International Conference of Harmonization guidelines for Good Clinical Practice (E6). Our study has been approved by the PNU Research Ethics Board (20-0148) and the respective ethical review boards of the participating centres in Saudi Arabia. Additional centres will be included following the approval by the respective institutional review boards as they are currently pending approval in the USA. We will disseminate the results to the local and international neonatal community by presenting the trial findings at various paediatric and neonatal society meetings, publishing the findings in peer-reviewed journals and disseminating them through social media platforms.

Author affiliations
1Pediatrics, King Abdullah bin Abdulaziz University Hospital, Princess Nora bint Abdulkarim University, Riyadh, Saudi Arabia
2Pediatrics, King Fahad Hospital, AlBaha, Saudi Arabia
3Pediatrics, AlBaha University, AlBaha, Saudi Arabia
4Pediatrics, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia
5Pediatrics, King Fahad Medical City, Riyadh, Saudi Arabia
6Radiology, King Abdullah Bin Abdulaziz University Hospital, Riyadh, Saudi Arabia
Correction notice This article has been corrected since it was published. The funding statement has been corrected.


Funding Princess Nora Bint Abdulrahman University is the source of funding.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Abdul Razak http://orcid.org/0000-0002-6185-3694
Abdullah Alismail http://orcid.org/0000-0002-7844-8943

REFERENCES