



Extubation strategies in neuro-intensive care unit patients and associations with outcomes: the ENIO multicentre international observational study

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Background: Prolonged invasive ventilation is common in patients with severe brain injury. Information on optimal management of extubation and on the use of tracheostomy in these patients is scarce. International guidelines regarding the ventilator liberation and tracheostomy are currently lacking.

Methods: The aim of 'Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes' (ENIO) study is to describe current management of weaning from invasive ventilation, focusing on decisions on timing of tracheal extubation and tracheostomy in intensive care unit (ICU) patients with brain injury. We conducted a prospective, international, multi-centre observational study enrolling patients with various types of brain injury, including trauma, stroke, and subarachnoid haemorrhage, with an initial Glasgow Coma Score equal or less than 12, and a duration of invasive ventilation longer than 24 hours from ICU admission. ENIO is expected to include at least 1,500 patients worldwide. The primary endpoint of the ENIO study is extubation success in the 48 hours following endotracheal tube removal. The primary objective is to validate a score predictive of extubation success. To accomplish this, the study population

will be randomly divided to a development cohort (2/3 of the included patients) and a validation cohort (the remaining 1/3). Secondary objectives are: to determine the incidence of extubation success rate according to various time-frames (within 96 hours, >96 hours after extubation); to validate (existing) prediction scores for successful extubation according to various time-frames and definitions (i.e., tracheostomy as extubation failure); and to describe the current practices of extubation and tracheostomy, and their associations.

Discussion: ENIO will be the largest prospective observational study of ventilator liberation and tracheostomy practices in patients with severe brain injury undergoing invasive mechanical ventilation, providing a validated predictive score of successful extubation.

Trial registration: The ENIO study is registered in the Clinical Trials database: NCT 03400904.

Keywords: Weaning; ventilator liberation; extubation; tracheostomy; brain injury; traumatic brain injury; subarachnoid haemorrhage; intra-cranial haemorrhage

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Introduction

In patients with severe brain injury, invasive mechanical ventilation (MV) is often required to prevent aspiration and correct hypoxemia, hyper and hypocapnia which can induce secondary brain insults (1). Patients with severe brain injury usually have longer durations of MV and poorer outcome compared to the general ICU population (2). Patients with severe brain injury have not been considered in international guidelines regarding the weaning from MV (3), and consequently specific recommendations are lacking.

The extubation process in brain injured patients is complex because both extubation failure and delayed extubation increase morbidity and mortality (4). The decision to extubate remains a major clinical problem in this population since extubation failure are reported as high as 38% (5). On the other hand, delaying extubation increases the risk of ventilator-associated pneumonia (VAP) without decreasing the risk of extubation failure (4). Prevention of delayed extubation is therefore one of the most promising intervention targets for improving outcome, but robust models to predict successful extubation are needed. There are few studies, mainly single-center in design, regarding extubation readiness in patients with brain injury undergoing MV (4,5), and no validated scores to guide the intensivist in this decision making process.

To answer these questions, we established Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes (ENIO) an international multi-center observational study. The primary objective is to validate a score predictive of extubation success in the 48

hours following extubation, and thus to improve the ventilator liberation process in patients with brain injury. Secondary objectives of ENIO are: to measure extubation success rates according to various time-frames and definitions; to validate a score predictive of extubation success when modifying both time-frame and definition of extubation success; to describe practices regarding tracheostomy; and last to delineate the association between extubation failure and outcome.

Methods

The ENIO study is a prospective multi-centre international observational cohort study.

The following national and international research networks are involved in the project's endorsement, recruitment of centres and promotion of the study: PROtective VEntilation Network, European Society of Intensive Care Medicine, Society of Critical Care Medicine, French Society of Anesthesiology and Critical care (SFAR), Colegio Mexicano de Medicina Critica. One national investigator coordinates the study in each country in order to recruit participating centres, ensure adequate IRB and administrative processes and answer potential queries from local investigators. Depending on local rules and regulations, either a national or a local IRB approval could be obtained. Considering the pure observational nature of the study, patient's consent is usually waived, but this point is variable considering each nation's laws and regulations, and institution-specific regulations. However, oral and written information, general consent for use of observational data

could be delivered to the patient or next-of-kin, whenever the patient's recovery was deemed inadequate, according to local rules and regulations. A specific translation of the original document was performed whenever appropriate (English, French, Spanish...). The first national IRB approval was obtained in France in November 2017 (Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7-11-2017).

Ethical statement

The study will be conducted according to the principles of the Declaration of Helsinki (version of 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO) (6). Data management, monitoring and reporting of the study will be performed in accordance with the ICH-GCP Guidelines (7). All participating centres must submit the study to their local or national IRB/IEC and obtain a document of proof that the study has been subject to IRB/IEC review and given approval opinion. Considering that all study data are part of routine practice, IRB approval may not be required in some centres. However, where ethical approval is required, this approval must be obtained before the start of inclusion. If authorization/approval/notification by the regulatory authority(ies) is applicable locally, this document should be obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s). This is a strictly observational study. Therefore, informed consent may not be mandatory for participation in some centers. Oral and written information regarding participation will be provided to the patients, when neurological recovery is sufficient, and to the next-of-kin in other cases. The information form will be modified according to local regulations, to make each IRB/IEC free in the decisions and organizations. In France, a nationwide IRB ethical statement was obtained (Groupe Nantais d'Éthique dans le Domaine de la Santé, positive approval No. 17-11-2017). The first patient was included in Amsterdam, Netherlands, in June 2018 (IRB approval W18_121#18.152). At this point, the inclusions are under way. All centres are currently either including patients after having obtained IRB approval, or are currently undergoing the IRB approval process.

Inclusion criteria

We will consider as eligible for the study consecutive patients ≥ 18 years old admitted to the ICU with "brain injury" defined here as a pathological process of the central nervous system (see below), an estimated or clinically evaluated

Glasgow Coma Score ≤ 12 before endo-tracheal intubation, and requiring effective invasive MV ≥ 24 hours. Pathological processes of the central nervous system considered here are traumatic brain injury, aneurysmal subarachnoid haemorrhage, intra-cranial haemorrhage, ischemic stroke, central nervous system infection (brain abscess, empyema, meningitis, encephalitis), and brain tumour.

Patients are included when the liberation from mechanical ventilation is performed (extubation and/or tracheostomy). The first episode of extubation is recorded. Participating centres are expected to screen and enroll patients during a minimal period of 6 months.

Exclusion criteria

Patients will be excluded if they have any of the following: less than 18 years old, pregnancy, spinal cord injury above T4, resuscitated post-cardiac arrest, Guillain-Barré syndrome, death before extubation, withdrawal of Life-Sustaining Treatment (WLST) in the first 24 hours after ICU admission, terminal extubation in the setting of WLST during ICU course, major respiratory co-morbidities (defined as chronic oxygen at home, chronic obstructive pulmonary disease grade III or IV of the Gold classification), and major chest trauma (Abbreviated Injury Score ≥ 3).

Primary study endpoint

The primary endpoint is the incidence of extubation success in the 48 hours following extubation, according to international guidelines (3).

Primary objective

The primary objective is to validate a score predictive of extubation success in patients with brain injury requiring invasive MV. The validation of the score is described in the statistical analysis.

Secondary study endpoints and secondary objectives

The secondary endpoints and objectives are the incidence of delayed extubation [defined as the number of days that elapsed between the first successful spontaneous breathing trial and extubation day (8)], the incidence of extubation success according to different timings of re-intubation [≤ 96 hours, >96 hours (9-11)] and definition [i.e., tracheostomy without extubation attempt as

failure (8)], the causes of extubation failure, the incidence and reason for tracheostomy, the impact of extubation failure, weaning, delayed extubation and tracheostomy on outcomes [ventilator acquired pneumonia (VAP) (12), use of non-invasive ventilation, duration of MV, ICU length of stay, in ICU-mortality, in-hospital mortality].

Data collection

Demographic and baseline data are collected: age, height, weight, type and severity of BI and neuro-surgical management. Respiratory data such as MV parameters and PaO₂, PCO₂ will be recorded at day1, day 3 and day 7 after ICU admission. The management of sedation will be collected at day1, day 3 and day 7 after ICU admission. Specific data are collected during the weaning process, as well as a standardized physical examination on the day of extubation/tracheostomy. In-ICU events such as health care related pneumonia, length of MV, ICU length of stay (LOS) and in-ICU mortality are recorded. Follow-up will be completed at hospital's discharge. The complete dataset is available in the Supplementary File.

Sample size calculation

According to previously published data, the incidence of extubation failure in the brain injury population ranges from 10% to 38% (5), but more recent data suggest an average incidence of 22% extubation failure (8). We wish to include at least 1,500 patients with an attempt of extubation and/or performance of tracheostomy in order to screen 300 patients with an extubation failure, which would allow us to evaluate at least 30 variables in the multivariable analysis (13).

Statistical analysis

Student's *t*-test or Mann-Whitney U-tests are used to compare continuous variables and chi-squared tests are used for categorical variables. Data are expressed as means (SD), medians (interquartile range) and proportions when appropriate.

Primary outcome analysis

The analysis and reporting of the study will comply with the TRIPOD statement (EQUATOR network: <https://www.equator-network.org/reporting-guidelines/tripod-statement/>). For the primary outcome, the definition of extubation success will be studied within the recommended

48-hour time-frame (13). The main objective is to create a score which predicts extubation success. The cohort will be divided into two: 2/3 of patients will be randomly allocated to the development cohort. Internal validation will be performed (I) on the sample used to train the model using 10-fold cross-validation, (II) on the data not used to train the model. The remaining 1/3 of the patients will provide the validation cohort. For the selection of variables, a penalised model such as the LASSO (Least Absolute Shrinkage Selection Operator) will be performed (14). A multivariable logistic regression model regarding extubation success will be performed with the selected variables.

The performance of the model will be evaluated with ROC curves. Sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios will be calculated for several probability threshold identified from the ROC curves. The calibration will be evaluated using a calibration plot as well as the Hosmer-Lemeshow test. The overall performance of the model will be evaluated with the R²/Brier test.

Sensitivity analyses

Owing to the various time-frames proposed regarding extubation success/failure (13), further models will be built, with the same methods. First the time frame of extubation success will be modified: ≤96 hours after extubation, >96 hours after extubation. Second, the definition of extubation success/failure is a matter of discussion in patients with brain injury. Some authors have proposed that tracheostomy should be considered as failure even when extubation was not attempted because deemed at high risk of failure in severely comatose patients (13). Hence in the second sensitivity analysis, a model will be elaborated when considering tracheostomy as an extubation failure. Finally, some causes of extubation failure like post-extubation stridor are not specific to patients with brain injury. A third model will be built by excluding patients with extubation failure because of post-extubation stridor.

Secondary outcomes analyses

The incidence and causes of extubation failure will be described, according to pre-defined time-frames and definitions. Time-to-event variables will be analysed using Cox regression and visualized by Kaplan-Meier. A univariate analysis comparing the outcomes of patients with or without extubation success will be performed:

health-care associated pneumonia, tracheobronchitis, duration of invasive and non-invasive MV, in-ICU and in-hospital mortality. A specific regression model, regarding the risk factors of in-hospital mortality will be elaborated with the same methodology described above. The model will be adjusted on neurologic severity and extubation success will be added in the model. Finally, we will study the consequences of delayed extubation on in-hospital mortality. Again, a specific multivariable logistic regression model will be elaborated. We will also compare the outcome of patients with and without tracheostomy with another specific model. Statistical significance is at a P value of <0.05 .

Missing data

A multiple imputation by chained equations (MICE) will be performed in the setting of missing data. We will study the rate of missing data for each variable, the link between missingness and outcomes and sensitivity analysis in complete cases.

Statistical analysis will be performed with R 3.6.1 (The “R” Foundation for Statistical Computing, Vienna, Austria).

Discussion

General overview

In 2007, an international expert panel elaborated guidelines about the weaning of MV in the ICU (3). In order to safely perform extubation in the ICU, an adequate mental status was recommended (3), which remains highly challenging in patients with ongoing neurological impairment. Since then it has been highlighted that neurologic patients experience a high rate of extubation failure compared to other ICU populations (15) in spite of adequate respiratory parameters (5). Extubation failure is nonetheless associated with worse outcome (4). These data emphasize an urgent need for a reappraisal of extubation in critically ill neurologic patients.

Strengths of the study

The ENIO study will be the largest study regarding the weaning of MV in patients with brain injury. We will be able to gather multisite data on diverse management practices, which will avoid potential single-center biases. Moreover, the study has been specifically designed to evaluate ventilatory, sedation and weaning and post-extubation management. The

continuum of respiratory management is thus described. Owing to the ongoing modifications of non-invasive MV strategies (high flow oxygen nasal cannula for instance), specific data will be collected. We will provide an extensive overview of the respiratory and weaning management of patients with brain injury.

Previous studies have identified various clinical features compatible with successful extubation, such as visual pursuit (8), the FOUR score (16) or fluid balance (17). However, these studies have methodological limitations which preclude definite conclusions. These studies are often mono-centric (16,17), some clinical features such as the gag reflex are not always tested (8) and the definition of the Glasgow Coma score in intubated patients, which remains controversial (18), is not always available (4). Thus, the ENIO study is designed to provide extensive data about clinical parameters compatible with successful extubation: delayed extubation (8), gag reflex, visual pursuit, swallowing, cough, leak test, maximum pressure trigger, fluid balance, etc. A standardized definition for these items is provided in the datasheet in order to decrease subjectivity. Regarding the evaluation of arousal, taking into account the complexity of the Glasgow Coma Scale evaluation in intubated patients, each subscore will be separately measured and a standardized evaluation of the verbal component is performed, according to previous studies (8).

The timing of extubation failure has been recently challenged (9,19), but there is no consensus about the exact time frame. A large North-American database study has recently identified that a 96-hour time frame could screen 90% of extubation failure (10). We will thus screen extubation failure in the first 48 hours following extubation according to guidelines (3), but we will also screen for extubation failure in longer time-frames.

The association between extubation failure and outcome is also controversial. It has been argued that extubation failure is secondary to the patient’s severity (3). To this day, studies have found an association between a longer duration of MV and extubation failure (8,16). However, these associations were reported in univariate analysis and no stratifications were made based on neurologic severity. The sample size of the ENIO should provide the power to more definitively explore this association.

Limitations of the study

The performance of the study is done on a purely voluntary basis, but we assume that participating centers

will be highly involved in the process, as the time-frame of inclusion is short. Since this is not an interventional study, we will not be determining the impact of our clinical score on intubation failure rates in daily practice. The design of a clinical trial evaluating the impact of the score presents some major challenges. To this day, a large observational study on this topic remains probably the best methodological tool. We also expect there will be missing data in our cohort; we will perform a multiple imputation analysis in order to address this methodological issue.

Measures against poor use of statistics

The pre-planned statistical analysis was designed to minimize the misuse of statistics. In particular, we will elaborate multiple models since the definition and time-frame of extubation success remains controversial. The sample size will enable us to provide a development and a validation cohort in independent patients, with extensive evaluation of models (prediction, calibration and performance) with penalized models (LASSO) according to broadly accepted standards in methodology.

Furthermore, to this day the following ancillary studies are being elaborated:

- (I) Ventilator settings (PEEP, plateau pressure, tidal volume) and association with outcomes (incidence of health-care related pneumonia, acute respiratory distress syndrome, ventilator free days);
- (II) Association between obesity and outcome (weaning failure and extubation, incidence of incidence of health-care related pneumonia, acute respiratory distress syndrome, ventilator free days and mortality);
- (III) Blood gas targets. Association between hyperoxia and hypoxia, CO₂ range (normo/hypo) and outcome (incidence of health-care related pneumonia, acute respiratory distress syndrome, ventilator free days and mortality);
- (IV) ICU respiratory complications (incidence and risk factors);
- (V) Association between external ventricular drainage and intra-cranial hypertension;
- (VI) Some patients might develop elevated CO₂ in spite of adequate tidal volume and respiratory rate management. The aim of this ancillary study is to delineate the incidence of elevated CO₂ blood levels, the risk factors and association with outcome, since elevated CO₂ is associated with outcome.

What this study will add in the field

The ENIO study is the largest study of the weaning of MV in patients with brain injury. We will be able to provide specific data and guidance in order to help physicians faced with this challenging extubation process. Owing to the sample size, a secondary objective is to delineate which patients could benefit from tracheostomy. We will also provide an accurate incidence of extubation success in this population which will create the basis and help calculate sample size for future interventional trials.

How results could be used

The results will be presented at national and international congresses as abstracts and communications. The main results will be submitted as a manuscript to a medical journal with peer review process and indexed in PubMed. The dataset will be available for investigators in the network to encourage ancillary studies. The steering committee will check for medical relevance of ancillary studies and the pre-planned statistical analysis.

Conclusions

In conclusion, the ENIO study is a large-scale international multisite observational study on the weaning and extubation of patients with brain injury undergoing invasive MV. We will provide extensive neurologic and respiratory evaluation in the weaning process. The sample size should allow us to validate a predictive score to evaluate successful extubation in this population. The inclusion should be finalized in winter 2019-spring 2020.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/atm.2020.03.160>). Pr Karim Asehnoune received fees from Baxter, Edwards, LFB, Fisher and Payckel, out of the scope of the present work. The other

authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The first national IRB approval was obtained in France in November 2017 (Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7-11-2017).

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