Title: Multi-center, observational, prospective study of endotracheal intubation among the critically ill: HEModynamic and AIRway (HEMAIR) management protocol

Running title: HEMAIR Protocol

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For HEMAIR Investigators team*

*Appendix A

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Abstract

**Background:** Endotracheal intubation can occur in up to 60% of critically ill patients. Despite the frequency with which endotracheal intubation may occur, the current practice is largely unknown. This is relevant as advances in airway equipment, i.e., video laryngoscopes, have become more prevalent leading to possible improvement of care delivered during this process. In addition to new devices, a greater emphasis on airway plans and choices in sedation have evolved, although the influence on patient morbidity and mortality is largely unknown. Thus, through a multi-center prospective study, our aim was to derive and validate prediction models for immediate airway and hemodynamic complications of intensive care unit intubations.

**Methods/Design:** A multi-center, observational, prospective study of adult critically ill patients admitted to both medical and surgical intensive care units at participating sites throughout 8 health and human services regions of the country for which endotracheal intubation was needed was conducted. A steering committee composed of both anesthesia and pulmonary critical care physicians proposed a core set of data variables as a data collection form to be used within the multiple intensive care units across the country during the time of intubation. The data collection form consisted of two basic components, focusing 1- on airway management and 2- on hemodynamic management. The form was generated using RedCap and distributed to the participating centers. Quality checks on the dataset was performed several times from each center to arrive at less than 10% missing values for each data variable and subsequently entered into a database. The primary outcomes will focus on both derivation and validation of airway and hemodynamic models to predict immediate airway and hemodynamic complications of intensive care unit intubations.
**Discussion:** The overall goal of this multi-center prospective study is to arrive at a prediction model for both immediate airway and hemodynamic complications thus allowing critical care physicians to be better prepared to address these occurrences and improve the quality of care delivered to the critically ill.

**Trials registration:** Clinicaltrials.gov identifier NCT02508948 (07/21/2015)

**Keywords:** airway; endotracheal intubation; hemodynamics; intensive care unit; multi-center; prospective study
**Background:**

Significance:

When compared to other settings such as the operating room, endotracheal intubation in the intensive care unit (ICU) carries with it a higher morbidity and mortality, likely due to many factors including a lack of physiologic reserve [1-3]. For example, the incidence of a difficult airway in the ICU may be as high as 23% [2]. Unwanted effects associated with endotracheal intubations performed in the ICU include, but are not limited to, arterial desaturation, cardiovascular decompensation, esophageal intubation, regurgitation of gastric contents, and cardiac arrest [3-5]. Additionally, as intubation attempts increase, the rate of complications also increases [6]. In recognition of the above, institutions across the country have developed intubation bundles to reduce these unwanted effects. Moreover, the use of a systematic approach to or protocol for endotracheal intubation may reduce intubation complications [7-9]. This was recently demonstrated in a trial utilizing an intubation protocol whereby immediate life-threatening complications surrounding ICU intubations were reduced [10].

**Challenges in endotracheal intubation:**

Recently, there have been a variety of new devices emerging that are designed to assist with a difficult airway, such as video laryngoscopes. These devices have been reported to reduce unwanted effects of endotracheal intubation, i.e., a failed airway. In addition to new devices, intubation checklists and sedative choices have undergone changes with uncertain effects on patient morbidity and mortality. Currently, many clinicians use the newer devices such as video laryngoscopes as evidence indicates that these devices result in better laryngeal view and improved intubation difficulty score with less risk of a failed airway as compared to conventional
techniques (direct laryngoscopy) [11-15]. Moreover, these newer devices are user friendly even in unfamiliar hands [16]. A recent meta-analysis comparing video laryngoscopy versus direct laryngoscopy reported similar findings with risk of difficult airway, Cormack 3/4 grades, and esophageal intubation decreased with the use of video laryngoscopy. Also, the first-attempt success rate was higher with video versus direct laryngoscopy. Additional outcomes such as severe hypoxemia, severe cardiovascular collapse, or airway injury were not different between the two devices [17]. Moreover, video laryngoscopy maintains its effectiveness when used emergently [18]. Despite the evidence for the newer devices, not all providers utilize these modalities, possibly due to inexperience with the newer techniques or evidence suggesting no benefit [19-20]. As an example, a recent study surveying Canadian resuscitation physicians demonstrated that most use direct laryngoscopy as their “go-to” device for emergent endotracheal intubations [21]. Similarly, ICU physicians in Israel seem to prefer fiberoptic intubation for routine airway management when surveyed [22].

Medications and Procedural Advances in field:

Along the same lines as airway equipment, sedatives used during endotracheal intubation have evolved over time. Over the years, evidence has suggested that the use of etomidate in the critically ill, especially in sepsis, may be associated with increased morbidity and mortality [23-25]. However, other studies find no associations with etomidate and patient outcomes [26-27]. Etomidate traditionally has been a favored induction drug because of its favorable hemodynamic profile. However, with mounting evidence for adrenal suppression and possible associations with mortality in septic patients, the clinician now struggles with the ideal sedative for endotracheal intubation [28-30]. Other agents and/or admixtures have shown promise [31-32]. Not only has the choice of induction medications changed in recent years, but recent evidence
suggests that the use of paralytics may help facilitate endotracheal intubation [33-34]. In addition, paralytics are now recommended in the setting of acute respiratory failure with evidence demonstrating improved outcomes [35]. However, certain situations may preclude their use [36].

**Approach:**

In order to examine the current endotracheal intubation practice among the critically ill, a multi-center, observational, prospective study of adult critically ill patients was conducted from July 2015 to January 2017 involving 20 ICUs. The primary aim was to characterize the current practice of endotracheal intubation in the critically ill with a focus on deriving and validating a prediction model for both immediate airway and hemodynamic complications.

**Specific Aims:**

Aim 1: To derive and validate a prediction model for airway difficulty among the critically ill as defined by ≥ 3 attempts at laryngoscopy and/or the need for another operator [37].

Aim 2: To derive and validate a prediction model for hemodynamic compromise, i.e., post-intubation hypotension [defined as a decrease at any point in mean arterial pressure < 65 mmHg; systolic blood pressure < 80 mm Hg and/or a decrease in systolic blood pressure of 40% from previous; or the introduction of, or increase in infusion rate of, any vasoactive agent during the 30 minute window following endotracheal intubation] [38-39].

Aim 3: To derive and validate a predication model for hypoxemia defined as a decrease in SpO₂ < 88% during the procedure.
Methods:

Mayo Clinic Rochester institutional review board approved the current study protocol. Institutional Review Board #15-002328.

Design/Setting:

Multi-center, observational, prospective study of adult critically ill patients admitted to both medical and surgical ICUs at the listed participating sites [Appendix A], who meet the criteria designated below for which endotracheal intubation was needed.

Inclusion Criteria:

1) Adult patients (≥ 18 years)

2) Admission to medical or surgical ICU

3) Endotracheal intubation performed from July 2015 to January 2017

Exclusion Criteria:

1) Pediatric patients (< 18 years)

2) Endotracheal intubations occurring in non-ICU locations

Study Enrollment Procedures:

All adult endotracheal intubations across all ICUs were eligible for this study. Given that this procedure is an unpredictable event, the patients were not able to consent or a health-care power of attorney was not readily available, and the sites were to initiate immediate data collection, obtaining informed consent was impractical. In addition, the observational study design did not
impact the procedures performed, devices used, or medications given to patients whose de-
identified data were captured in this study. Thus, this study was conducted under a waiver of
consent and authorization. In order to be compliant with the study protocol, all sites were
responsible for entering the vast majority of endotracheal intubations performed at their
institutions.

Study protocol:

A steering committee oversaw the administration of the protocol and was comprised of both
anesthesia and pulmonary critical care physicians. A data collection form was created which
focused on two periprocedural aspects of the intubation process including airway and
hemodynamic management and was used at all participating sites. Regarding airway
management, rapid sequence intubation was defined a priori according to Sellick [40]. Although
the participating sites obtained formal training in the use of the data collection form prior to
study initiation, on-line content in the form of a web link was established to answer frequently
asked questions as well as to establish a forum among the investigators with all questions related
to the study discussed [www.hemairregistry.org]. Moreover, monthly HEModynamic and
AIRway (HEMAIR) investigator meetings were conducted to further provide a platform for
questions and discuss future collaborations with a newsletter sent afterwards to participating sites
[See Appendix B]. The data collection form was uploaded into RedCap during data entry. Data
was obtained by the proceduralist or site study coordinator and verified by the primary
investigative team. Please see appendix C for the data collection form utilized in the present
study.
Data Management:

Each clinical site was responsible for patient enrollment and data collection and provided a research investigator responsible for capturing and entering the study data into the study database during the collection time period. The study database was housed and managed at Mayo Clinic, including running period basic data quality monitoring queries. Data collection on outcome measures were done weekly by trained study coordinators at each site.

Statistical Analysis:

For descriptive summaries, continuous measurements will be represented as mean ± standard deviation for parametric distributions and median – interquartile range for non-parametric distributions. Dichotomous variables will be represented as counts and percentages. For descriptive studies, all procedures will be included for patients who require endotracheal intubation more than once during the same ICU stay. For hypothesis testing we will consider two-tailed tests of less than 0.05 to be statistically significant and will report point estimates and 95% confidence intervals. The first endotracheal intubation in the ICU will be used in analyses to assess for associations between predictors and an adverse outcome. Model building will be performed using lasso regression with 10-fold cross-validation. In all cases, distributional assumptions will be assessed with appropriate transformations used as necessary. Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc) and R statistical software version 3.4.1 (R Foundation for Statistical Computing) will be used for all analyses.

Sample Size:

We based our sample size on the occurrence of intubation complications. Since we are most concerned with occurrence of airway related complications (difficult intubation), and
hemodynamic complications (hypotension), our sample size is powered for the occurrence of these two complications. Difficult intubation was defined in our study with an expected incidence of 12% with 11% incidence of hypotension during the peri-intubation period [37, 41]. Thus, we determined that an effective sample of 804 was sufficient to provide statistical power to detect an incidence of 12% with precision/margin of error of 1%. However, we included over 1000 patients from all sites to answer any subsequent secondary and tertiary hypotheses.
Discussion:

The HEMAIR study did not alter the care that patients received. The physical rights and welfare of patients were not hindered as a result of participation in this study. Additionally, sharing de-identified data protected the privacy of the patients. With these procedures and requirements in place, the rights and welfare of subjects were not adversely affected by study participation or the waiver of consent/authorization. This multi-center, prospective trial will be among the first to include a large diverse patient population from across the United States with a large sample size. The potential benefits would include deriving and validating prediction models for immediate severe complications regarding airway and hemodynamic management surrounding intubations among the critically ill. With this information, it is our hope that the clinician will have a tool to predict which patients will become unstable during this procedure so as to adjust treatment plans allowing improved quality of care delivered during this procedure. This prospective observational trial is even more important as post-intubation hypotension/hemodynamic derangement is noted by some to occur at a fairly high rate leading to possibly increased risk of mortality [42].
Abbreviations:

HEMAIR: HEModynamic and AIRway

ICU: intensive care unit
Declarations:

*Ethical approval and Consent to Participate:*

Mayo Clinic Rochester institutional review board approved the current study protocol. Institutional Review Board # 15-002328. This study was under waiver of informed consent given the observational nature of the study with the use of de-identified data.

*Consent to Publish:*

Not applicable.

*Availability of Data and materials:*

Not applicable.

*Competing interests:*

No financial or non-financial competing interests in relation to this manuscript are declared by any of the authors.

*Funding:*

The study protocol has not undergone peer-review by a funding body as.

*Authors’ contributions:*

NJS is the principal investigator (PI) of the HEMAIR study. RK is the lead study coordinator and co-PI. DS is the chief statistician. MOS and DAD are trial co-investigators. All authors have read and approved the final manuscript.
Acknowledgements:

None.

Study Status:

The study is currently undergoing data analysis.

Related Articles:

The results of the study have not been published as we are currently undergoing data analysis.
References


Legends:

Appendix A: HEMAIR site investigators.
Appendix B: HEMAIR newsletter.

Appendix C: HEMAIR data collection form.