Published in final edited form as:

J Adv Nurs. 2019 May ; 75(5): 1108–1118. doi:10.1111/jan.13920.

Nursing oral suction intervention to reduce aspiration and ventilator events (NO-ASPIRATE): A randomized clinical trial

Mary Lou Sole^{1,2}, Steven Talbert¹, Xin Yan³, Daleen Penoyer⁴, Devendra Mehta², Melody Bennett², Aurea Middleton², and Kimberly Paige Emery^{1,2}

¹University of Central Florida College of Nursing, Orlando, Florida

²Orlando Health, Orlando, Florida

³University of Central Florida College of Sciences, Orlando, Florida

⁴Center for Nursing Research and Advanced Nursing Practice, Orlando Health, Orlando, Florida

Abstract

Aim: The primary aim of this study is to compare an oropharyngeal suction intervention versus usual care on microaspiration in intubated patients. Secondary aims are to evaluate the intervention on ventilator-associated condition rates, time to occurrence and compare tracheal-oral α -amylase ratios between groups.

Design: Prospective randomized clinical trial.

Methods: The study received funding from the National Institutes of Health in February 2014 and Institutional Review Board approval in July 2013. Over 4 years, a convenience sample of 600 orally intubated, ventilated adult patients will be enrolled within 24 hr of intubation. The target sample is 400 participants randomized to the two groups. The intervention involves enhanced suctioning of the mouth and oropharynx every 4 hr, while the usual care group receives a sham suctioning. The research team will deliver usual oral care to all patients every 4 hr and collect oral and tracheal specimens every 12 hr, to quantify α -amylase levels to detect aspiration of oral secretions. Study completers must be enrolled at least 36 hr (baseline and three paired samples). Outcomes include α -amylase levels, percent of positive specimens, ventilator-associated conditions, length of stay, ventilator hours, and discharge disposition.

Discussion: Enrolment has closed, and data analysis has begun. Subgroup analyses emerged, contributing to future research knowledge.

Correspondence: Mary Lou Sole, University of Central Florida College of Nursing, Orlando, FL., mary.sole@ucf.edu.

AUTHOR CONTRIBUTIONS

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE [<http://www.icmje.org/recommendations/>]):

1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. drafting the article or revising it critically for important intellectual content.

CONFLICT OF INTEREST

No conflict of interest has been declared by the authors.

Trial Registration: This trial is registered in the National Institutes of Health U.S. National Library of Medicine [ClinicalTrials.gov](https://clinicaltrials.gov) registry. The trial identification number is NCT00654321.

Impact: Standardized interventions have reduced but do not address all risk factors associated with ventilator-associated conditions. This study provides the potential to reduce microaspiration and associated sequelae in critically ill, intubated patients.

Keywords

amylase; aspiration; mechanical ventilation; nursing; pepsin; pneumonia; ventilator-associated conditions

1 | INTRODUCTION

Mechanical ventilation (MV) is frequently needed to treat patients with respiratory failure in intensive care units (ICUs) worldwide. Many complications result from MV, including microaspiration, which can potentially lead to ventilator-associated pneumonia (VAP). The United States Centers for Disease Control and Prevention (CDC, 2013) recognizes VAP under the broader category of ventilator-associated events or conditions (VAC). VAC are often consequences of microaspiration of secretions, defined as leakage of secretions around the endotracheal tube (ETT) cuff, that may result in lung injury or VAP (Nseir, Zerimech, Jaillette, Artru, & Balduyck, 2011). Both VAC and VAP result in prolonged MV and length of stay (LOS) in both the ICU and hospital. In addition, VAC has been associated with a two-fold increase in mortality (Klompas et al., 2011). Standardized interventions have reduced incidences of VAP but do not fully address the risk factors (Rawat et al., 2017). Recognizing microaspiration in this population to reduce complications has been challenging; however, emerging evidence worldwide suggests α -amylase may be indicative of microaspiration and/or VAP in the MV population (Dewavrin et al., 2014; Filloux et al., 2013; Qu et al., 2018; Samanta et al., 2018; Weiss, Moazed, Dibardino, Swaroop, & Wunderink, 2013; Weiss, Moazed, & Wunderink, 2011). Using α -amylase as a biomarker, the targeted intervention proposed in this study to decrease microaspiration may significantly reduce harm.

1.1 | Background

This intervention study is based on a physiological model describing secretion microaspiration around the ETT cuff leading to VAC (Figure 1) (Boots, Udy, Holley, & Lipman, 2010; CDC, 2004, 2013; Craven, Chroneous, Zias, & Hjalmarson, 2009). ETT placement interferes with mucociliary clearance and cough and injures the tracheal epithelia (Craven & Steger, 1997). The ETT also maintains the glottis in an open position, providing a direct opening for microaspiration. Oropharyngeal secretions become colonized with pathogens from a variety of sources, including gastric contents (Nseir, Zerimech, Jaillette et al., 2011). Aspirated secretions also trigger pulmonary aspiration syndromes (Marik, 2011). Lung inflammation and infection can result in increased oxygenation requirements leading to VAC.

Interventions, such as head of bed (HOB) elevation, oral antisepsis, and ETT cuff pressure management address some, but not all, of the risks for microaspiration. This protocol tests an additional intervention—enhanced oropharyngeal suction, every 4 hr, using a suction catheter designed to reach secretions in the oropharynx. We hypothesize that reducing the

volume, or potential aspiration “load,” of oropharyngeal secretions will reduce the risk for microaspiration.

Assessment of α -amylase in tracheal secretions is a newer bio-marker to assess for microaspiration, our primary outcome. Although α -amylase is present in saliva, it should not be present in the lungs. Several studies have detected α -amylase in tracheal secretions, indicating aspiration of oral contents (Abu-Hasan, Brookes, Neal, & ElMallah, 2012; Clarke, Bain, Davies, Levin, & Lambert, 1981; Nandapalan, McIlwain, & Hamilton, 1995; Rennard et al., 1990; Tripathi, Mirant-Borde, & Lee, 2011; Weiss et al., 2011, 2013). Weiss et al. (2013) reported levels of α -amylase in secretions obtained by bronchoalveolar lavage within 72 hr of intubation; elevated levels were associated with peri-intubation aspiration risk factors and were predictive of bacterial pneumonia. Qu et al. (2018) found that increased tracheal aspirate α -amylase levels were associated with preintubation aspiration risk factors. Alpha-amylase levels were also significantly higher in VAP patients compared with non-VAP patients (Qu et al., 2018; Samanta et al., 2018). When α -amylase is detected in tracheal secretions, the amount detected in relation to the oral secretion value (tracheal/oral ratio) may also be a significant finding (Nandapalan et al., 1995); therefore, we are exploring changes in this ratio.

A secondary outcome is VAC incidence, which encompasses a broad range of complications associated with MV. The use of objective VAC criteria (CDC, 2018) provides a more expansive definition in terms of identifying incidence and mortality rates among critically ill patients versus VAP criteria (Klompas, 2017).

1.1.1 | Oropharyngeal secretion removal is an overlooked intervention—The intervention focuses on removing oropharyngeal secretions to prevent microaspiration. We define this intervention as the regular removal of secretions from the mouth and oropharynx with a long oropharyngeal suction catheter. Reductions of VAP and shorter durations of MV and ICU LOS have been reported when oral suctioning was done immediately before turning (Chao, Chen, Wang, Lee, & Tsai, 2009; Tsai, Lin, & Chang, 2008), and when oral suctioning was done continuously with a saliva ejector (Chow, Kwok, Luk, Law, & Leung, 2012). Quality improvement studies reported VAP reductions when oral suction was completed every 4 (suction swab) or 6 hr (oropharyngeal suction catheter) (Blamoun et al., 2009; Garcia et al., 2009).

Suctioning practices and devices to remove oropharyngeal secretions vary widely and are not evidence based. Traditionally, rigid or semirigid tonsil suction devices (Yankauer) or swabs are used to remove secretions (Sole & Bennett, 2011; Sole et al., 2003). During a previous study (Sole & Bennett, 2011; Sole, Bennett, Talbert, & Penoyer, 2011), we observed suctioning with a swab or a tonsil suction device an average of every 4 hr; however, in several patients it was done only once in 12 hr.

Suction swabs or a semirigid tonsil suction devices are used when additional secretion removal is needed. However, because of their shorter lengths, the swab and tonsil suction devices reach secretions primarily in the mouth, rather than the oropharynx.

1.1.2 | Preliminary studies—Our preliminary work identified that oropharyngeal suction frequency varies widely and that the tonsil suction device is preferred (Sole & Bennett, 2011; Sole, Byers, Ludy, & Ostrow, 2002; Sole et al., 2003). In a simulated setting, we determined that the oropharyngeal suction catheter was more effective than either a suction swab or tonsil suction device in removing oropharyngeal secretions (Sole, Penoyer, Bennett, & Bertrand, 2010). Oral care kits at the study site include two oropharyngeal suction catheters designed for concurrent use with tooth brushing; however, average use is less than once per day (Bertrand, Hollandsworth, Sole, & Grano, 2011). Many patients have large volumes of oropharyngeal secretions that can be potentially aspirated (Sole, Bennett, et al., 2011; Sole, Marano, Bennett, Mehta, & Ashworth, 2012; Sole, Middleton, et al., 2012; Sole, Poalillo, Byers, & Ludy, 2002; Sole, Talbert, et al., 2012). We suctioned an average of 7.5 ml of secretions within a 4-hr interval and volumes as high as 25 ml were removed (Sole, Bennett, et al., 2011). Oral secretion removal can be achieved without complications with three passes with the oropharyngeal suction catheter over an average total duration of 48.1 s (Sole, Bennett, et al., 2011; Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012). In a pilot study of 13 critically ill patients, all patients had α -amylase present in the oral secretions and six (46%) had α -amylase detected in the first tracheal sample (Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012). A second specimen obtained 1–4 hr later showed a reduced value and only four patients (31%) with α -amylase in the tracheal secretions. These findings support that microaspiration occurs in the study population and may be reduced with enhanced oral suctioning.

2 | THE STUDY

2.1 | Aims

2.1.1 | Primary objective

Aim 1: The primary objective of this project is to compare the effects of the NO-ASPIRATE intervention versus usual care on microaspiration of oral contents in critically ill intubated patients.

H1.1: Participants in the NO-ASPIRATE group will have a significantly lower percentage of tracheal secretions with α -amylase present as compared with those in the usual care group.

H1.2: Participants in the NO-ASPIRATE group will have a lower mean value of α -amylase in tracheal secretions as compared with those in the usual care group.

2.1.2 | Secondary objectives

Aim 2: To evaluate the NO-ASPIRATE intervention versus usual care on VAC rate and time to occurrence.

H2.1: Participants in the NO-ASPIRATE group will have a significantly lower rate of VAC as compared with those in the usual care group.

H2.2: The number of VAC-free days will be longer in those in the NO-ASPIRATE group as compared with the usual care group.

Aim 3: To explore changes in the ratio of α -amylase in the tracheal aspirate to that in oral secretions (tracheal/oral ratio) between groups over time.

H3.1: Participants in the NO-ASPIRATE group will have a significantly lower tracheal/oral α -amylase ratio over time as compared with those in the usual care group.

2.2 | Methodology

A prospective, two-group, single-blind, randomized clinical trial design has just been completed.

2.2.1 | Screening and enrolment—A convenience sample of approximately 600 patients will be enrolled within 24 hr of intubation and MV to maximize the effects of the intervention. Trained research staff will be available for approximately 18 hr each day, 7 days per week, to facilitate enrolment.

2.2.2 | Randomization and blinding—Our statistician developed a blocked randomization procedure, using different sized blocks, to ensure balanced assignment without being able to predict group assignment (Craven et al., 2009). Since about 65% of participants will be intubated with a specialized ETT with subglottic suction (SS-ETT), we will stratify randomization by type of ETT to ensure that approximately half of those with and without the SS-ETT are randomly assigned to each group. Stratification will help to address type of tube as a potential confounding variable.

A member of the study team not involved in data collection will place group assignments for each type of ETT in numbered, sealed, opaque envelopes. On consent and enrolment, study personnel will identify the type of ETT and open the appropriate envelope to determine group assignment. Only study team members who provide the intervention will know the participants' assigned groups. ICU personnel, and participants and family members, will be blinded to group assignment.

2.2.3 | Study population—The study population will be selected from patients in one of four ICUs: trauma, neuroscience, multisystem, and cardiac at the participating medical centre. Potential participants must be orally intubated and managed on a mechanical ventilator.

Patients ($N = 600$) will be enrolled if they meet the following *inclusion criteria*: (a) 18 years of age; (b) oral ETT intubation with MV; (c) intubated 24 hr; and (d) expected to remain intubated 36 hr after enrolment. *Exclusion criteria*: (a) documented aspiration at time of intubation; (b) intubation to treat known aspiration; (c) treatment with rescue MV therapies (high-frequency oscillator ventilation or extracorporeal membrane oxygenation); (d) reintubation for any reason; (e) contraindications to receiving the intervention (e.g., oral injuries); (f) history of lung or head/neck cancers that may produce α -amylase in the lungs;

(g) history of disease that affects saliva production (e.g., Sjögren's syndrome); and (h) prisoners.

2.2.4 | Power analysis—We used data from our pilot work and input from our consultants to estimate sample size and attrition. A final sample size of 400 will allow us to detect a 15% reduction in the proportion of specimens that are positive for α -amylase (primary aim) at an alpha level of 0.05 with a power of 0.87 (*H1.1*). The sample size will be able to detect differences in mean values of α -amylase with an effect size (*d*) of 0.25, alpha 0.05, and power of 0.80 (*H1.2*). Since VAC, our secondary aim, is a newer measure, we used data from recent studies to provide sample estimates. A final sample size of 400 will allow us to detect a 12.7% reduction in VAC with an alpha of 0.05 and power of 0.80 (*H2.1*). We will over enrol by 50% to account for attrition, for a targeted enrolment of 600 patients.

2.2.5 | Overview of procedures—Following enrolment, trained research assistants (RAs) will collect baseline data, implement the assigned intervention (NO-ASPIRATE or usual care/sham), and collect specimens. The RA will then implement care as designated by study arm every 4 hr. Figure 2 summarizes the procedures for each group. RAs will be trained Registered Nurses who have experience caring for patients on MV.

To control for possible differences in usual oral care practices, the RA will perform oral cleansing and suctioning with a suction swab after delivering the NO-ASPIRATE or sham intervention using the hygiene components from the oral care kit. The RA will also perform tooth brushing every 12 hr. Oral antisepsis will be done after obtaining specimens for α -amylase. Staff will use the available tonsil suction device or swabs if oral suctioning is indicated between the scheduled interventions. Additional oral suctioning will be recorded and controlled for, if applicable.

2.2.6 | NO-ASPIRATE intervention—The NO-ASPIRATE intervention involves enhanced suctioning of the mouth and oropharynx every 4 hr with an oropharyngeal suction catheter. The catheter (Sage Products, Cary, IL) is approximately 8.25 inches (21 centimetres [cm]) long and is one that we tested in the simulated setting as being most effective in removing secretions (Sole et al., 2010). This length and pliability of the oropharyngeal suction catheter facilitate manipulation of the catheter around the ETT to reach secretions in the oropharynx. During the intervention, the oropharyngeal suction catheter will be positioned to reach both sides of the mouth and the oropharynx. Suctioning will be done using standard suction pressures until secretions are no longer audible or visible, for a duration of about 45 s (Chulay & Seckel, 2012; Sole, Bennett, et al., 2011). We performed this procedure in previous studies without any adverse issues, such as gagging or oral trauma (Sole, Bennett, et al., 2011; Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012). However, participant response will be observed and the procedure will be stopped if intolerance is noted.

2.2.7 | Usual care/sham intervention—A sham intervention will be delivered to those in the usual care group. Trained RAs will insert the suction catheter into the participant's mouth and mimic the suction procedure for 45 s without occluding the suction port. The usual care/sham intervention will be done every 4 hr.

2.2.8 | Data collection—Data will be collected at enrolment and at regular intervals (Table 1), including demographic and physiological data to describe the sample and test equivalence between groups. We will also collect data related to factors that might result in microaspiration and VAC to assist in interpretation of findings.

Approximately 20 min will be allocated per participant to deliver the intervention and obtain specimens. A daily schedule will be developed to facilitate data collection from multiple participants. We will allow a 30-min window before and after the scheduled time to deliver the intervention to account for patient care activities. If the participant is off the unit during the scheduled time, the intervention will be delivered on return to the unit. Delays or omissions in providing the intervention will be recorded in the study record. These data will allow us to calculate the number of scheduled interventions that are completed each day (dose), which may be useful in interpreting findings.

2.2.9 | Paired specimens of oral and tracheal aspirates for α -amylase—The RA will obtain both an oral and tracheal specimen for α -amylase at enrolment and every 12 hr. Oral secretions will be collected into a trap (Medline, Mundelein, IL) during the NO-ASPIRATE or usual care/sham intervention. Following this procedure, the RA will suction the participant's ETT per standard procedure (closed ETT suction with hyperoxygenation) to retrieve tracheal secretions into a specimen trap. Obtaining specimens every 12 hr will provide longitudinal data regarding microaspiration. We tested these procedures in a preliminary study (Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012). Since ETT suctioning should be done based on the identified need (Chulay & Seckel, 2012), the RA will assess the participant for cues identifying suctioning need before obtaining the specimen: audible crackles over the trachea, sawtooth pattern on the ventilator flow waveform, cough, high peak inspiratory pressure, visible secretions, or changes in oxygen saturation (Nseir et al., 2007; Sole, Marano, et al., 2012). If suctioning is not indicated at the scheduled time, the RA will collaborate with the participant's nurse to notify the RA when suctioning is indicated. Time of specimen collection (or omissions) will be noted. All oral and tracheal specimens will be frozen to -20°C until the assays are run.

2.2.10 | Endpoints—The intervention will be delivered per protocol until one of the following endpoints is met: (a) ETT removed (extubation); (b) tracheostomy performed; (c) 14 days of enrolment; or (d) other exclusion criterion met (e.g., rescue ventilation). Extending the intervention to 14 days will allow us a better opportunity to address the secondary aim of VAC. At the study site, the median time to tracheostomy is 8 days; 85% of patients on prolonged MV undergo a tracheostomy by day 14 (Sole, Talbert, et al., 2012). This duration of enrolment is longer than that reported in other intervention studies (Metheny, Davis-Jackson, & Stewart, 2010; Munro, Grap, Jones, McClish, & Sessler, 2009; Nseir, Zerimech, Fournier, et al., 2011; Nseir, Zerimech, Jaillette et al., 2011). Patients must be enrolled at least 36 hr to be included in analysis.

2.2.11 | Measurement of primary and secondary outcome variables

Microaspiration: Assays of the biomarker, α -amylase, in paired oral and tracheal specimens will be performed in the specialty laboratory per standard procedures. Laboratory

personnel will be blinded to study group. Alpha-amylase activity in the paired samples will be analysed using the Stanbio α -amylase LiquiColor Reagent Kit. An α -amylase value of $0.6 \mu\text{mol min}^{-1} \text{ml}^{-1}$ will be considered positive. No α -amylase should be detected; the value $0.6 \mu\text{mol min}^{-1} \text{ml}^{-1}$ is the lowest possible concentration of amylase that can be detected with the method's analytic sensitivity. The total values of α -amylase in secretions will be recorded. Alpha-amylase that is detected would be either of oropharyngeal or gastrointestinal origin, as the presence from pancreatic source would be unlikely. The additional step of using a specific inhibitor for salivary α -amylase demonstrated to be unnecessary in airway samples during our preliminary study. The paired oral-tracheal samples evaluated in the preliminary study detected large amounts of α -amylase in the oral secretions of all participants and smaller amounts in those who also had positive results in tracheal secretions (Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012).

To address Aim 1 and *Hypothesis 1.1*, total values of α -amylase will be recorded and each tracheal aspirate will be coded as either positive or negative for α -amylase. A laboratory physician, also blinded to study group, will verify the results of each assay. The percentage of positive specimens for the biomarker will be calculated for each subject. For *Hypothesis 1.2*, the mean and median values of α -amylase will be calculated.

VAC: Ventilator-associated condition will be determined using the CDC/NHSN criteria (United States Department of Health and Human Services, Centers for Disease Control and Prevention, 2013). We will assess ventilator data (oxygen [FiO_2] and positive end-expiratory pressure [PEEP]) daily from the medical record to assess for worsening oxygenation status. We will assess for VAC 2 days beyond the last intervention. To address Aim 2 and *Hypotheses 2.1* and *2.2*, we will record VAC as positive or negative. We will also record the time to VAC in days (0.1 day increments). Our primary endpoint is VAC; however, we will also report probable VAP in our analyses as applicable.

Tracheal/oral ratio of α -amylase: To address Aim 3 and *Hypothesis 3.1*, the ratio of the tracheal value to the oral value of α -amylase for each paired sample will be calculated.

2.2.12 | Data management and integrity—We will record data in electronic format (REDCapTM) on computers that are password protected and used solely for the study. We will use the software data validation features to ensure accuracy of data entry. The PD will monitor study records for completeness. Electronic medical record data accuracy will be reviewed for 10% of participants during the first month of the study. Errors will be corrected, and retraining will be done as necessary. Following the initial audit, 5% of the files will be audited quarterly for completeness and accuracy; we will create an audit trail to identify and correct issues and/or errors (Hulley, Cummings, Browner, Grady, & Newman, 2007). If causes of error other than random variation are identified, we will change our procedures.

2.3 | Ethical considerations

The hospital and university Institutional Review Boards (IRBs) approved the study in July 2013. Approval was renewed on an annual basis. The principal investigator (PI), PD, or RAs will obtain informed consent from the patient (if competent to provide consent) or legally authorized representative (proxy) as soon as feasible after admission, within the designated enrolment period. Using data from previous studies, we expect that nearly all consents will come from the proxy. Study personnel will approach the patient or proxy, explain the study and obtain consent. A standardized script will be used. The consent process will be available in both English and Spanish and an interpreter will be available, if needed, through the hospital's translation services. Consent will be documented. The patient or proxy will be given a copy of the consent form.

If during the course of the study, a participant becomes alert enough to understand the study and research processes and the proxy has provided initial consent for participation, we will obtain verbal assent (nodding) or writing (yes/no) for continuation in the study from the participant. Should the participant gain sufficient cognitive ability to provide consent while enrolled, the study personnel will obtain his/her signature on the consent form.

2.4 | Validity and reliability

2.4.1 | Statistical analysis plan—The biostatistician will oversee randomization, data safety monitoring reports, and analysis. Participants will be randomly assigned to each of the two treatment groups at a 1:1 ratio and stratified by ETT type. Participant characteristics at baseline will be examined to evaluate demographics between groups. Continuous variables will be compared using independent sample *t* test. Categorical variables will be compared using Pearson's chi-squared. All planned analyses will be based on the intent-to-treat population. An alpha level of 0.05 will be used for all analyses.

Analysis of hypothesis 1.1: Percentages of tracheal secretions of α -amylase present for both groups will be computed. The percentage difference between the two groups will be calculated. Logistic regression will be used to assess the percentage difference while adjusting for the prognostic covariates.

Analysis of hypothesis 1.2: Values of α -amylase in tracheal secretions will be collected for each participant every 12 hr during the study. Treatment effect based on these values over time will be evaluated by the generalized linear models using the generalized estimating equation (GEE) method (Liang & Zeger, 1986; Zeger & Liang, 1986). In addition, the generalized linear models will be used to assess change in mean values of α -amylase over time, adjusting for prognostic covariates.

Analysis of hypothesis 2.1: Percentages of VAC for both groups will be computed. The percentage difference between the two groups will be calculated. The logistic regression will be used to assess the percentage difference adjusting for the prognostic covariates.

Analysis of hypothesis 2.2: Time to VAC event for both groups will be assessed using the Cox proportional hazard model (Kaplan & Meier, 1958). The hazard ratio of NO-

ASPIRATE group versus the usual care group will be computed. Kaplan–Meier estimators for both groups will be graphically presented (Cox, 1972). The Cox proportional hazard model will be used to assess the difference adjusting for the prognostic covariates.

Analysis of hypothesis 3.1: Treatment effect on reducing tracheal/oral salivary amylase ratio over time will be assessed by the generalized linear models using the GEE method (Liang & Zeger, 1986; Zeger & Liang, 1986). In addition, the generalized linear models will be used to assess ratios over time adjusting for prognostic covariates.

3 | DISCUSSION

3.1 | Training and data management

3.1.1 | Personnel training and fidelity—At the beginning of the study, the PI and PD will develop a comprehensive study operations manual. Content will include procedures and checklists for participant enrolment, delivery of the NO-ASPIRATE and usual care/sham interventions, data collection, and ongoing reporting related to the study (e.g., IRB and Data and Safety Monitoring Board [DSMB]).

The PI and PD will train the RAs in all study-related procedures. Initial training for the NO-ASPIRATE intervention, the usual care/sham intervention and specimen collection will be conducted in a simulation laboratory, followed by observation in the clinical setting. Interrater reliability will be established for delivery of the NO-ASPIRATE and usual care/sham interventions and for review of the medical record for study-related data. A kappa of at least .90 will be achieved between data collectors. To ensure treatment fidelity, additional re-assessment and related training will be done every 6 months.

Treatment fidelity and effect of usual care will be addressed by reinforcing existing protocols for HOB elevation, daily interruption of sedation, and ETT cuff pressure (20–30 cm H₂O). To control for usual oral care practices, we will deliver oral care suctioning and cleansing/antisepsis interventions to both groups. We will also record documentation of additional oral suctioning interventions and method/tolerance of enteral feedings.

3.2 | Data safety monitoring

Since we are using a clinical trial approach, we will establish an independent DSMB to oversee the study and review any adverse events. The DSMB will include an intensivist, a nursing manager, and a master's or doctoral-prepared critical care nurse. None of the members will be directly associated with the project. The DSMB will be convened at the start of the study and will meet every 6 months thereafter. More frequent monitoring will be done if recommended by the DSMB or if issues are identified.

3.3 | Limitations

3.3.1 | Risk/benefit—The study is associated with minimal risks in that all study-related procedures are considered inclusive in the care of the MV patient. Removal of secretions is an independent nursing action that is routinely done. We propose to enhance secretion removal through a protocol-driven procedure done every 4 hr. We do not anticipate that this

frequency of oral suction poses a risk to participants, as nurses have the option to suction as needed with various devices. A study conducted in Asia tested a device that was kept in the mouth for continuous suction and reported no adverse issues (Chow et al., 2012). We have observed that patients may awaken during oral care interventions, but they fall back to sleep immediately after it is done. We have performed this procedure (NO-ASPIRATE) to obtain specimens in previous studies without any adverse issues, such as gagging or oral trauma (Sole, Bennett, et al., 2011; Sole, Marano, et al., 2012; Sole, Middleton, et al., 2012; Sole, Talbert, et al., 2012). However, participant response will be observed as part of ongoing monitoring.

Oral care kits are standard for each patient, with supplies for oral suction, cleansing every 4 hr, and tooth brushing every 12 hr. We will use the same brand of oropharyngeal catheter that is packaged in the kits on a scheduled every 4 hr basis to those in the NO-ASPIRATE group.

All participants will get usual care to prevent microaspiration, including HOB elevation, management of enteral feedings, assessment of readiness to wean from MV, and management of ETT cuff pressure within recommended ranges. We will purchase all study-related supplies, including the oropharyngeal suction catheters, sputum traps, and materials needed to run the α -amylase assays. No additional costs will be associated with participation.

Those assigned to the NO-ASPIRATE intervention arm may have a reduced risk of microaspiration and VAC. It is also possible that participants will have no direct benefit from the study. Patients in the future who are intubated and receiving MV may benefit from knowledge gained in this study. The potential benefit of the intervention to future patients is very high if a resulting reduction in microaspiration and VAC occurs.

3.4 | Current status

Patient enrolment ended during the last quarter of 2017. Attrition was less than expected and we stopped enrolment at 513 participants with 410 completing the protocol for the minimum of 36 hr. Of these completers, there were 206 in the NO-ASPIRATE group and 204 controls. The randomization technique was successful, as comparison of group demographics revealed no significant differences between groups for age, gender, or ethnicity.

We requested a no-cost extension since data collection and analysis extended longer than the planned timeline. Analysis of oral and tracheal α -amylase specimens was completed during the first quarter of 2018. We modified the proposal and consent to include testing for pepsin using supplemental university funding for a subgroup of participants. Our statistical analysis will include amylase values for all participants and pepsin values for a large subgroup.

Now that all specimens are analysed, data evaluation and exploration have begun. Univariate analyses help us identify any outliers or missing values. If found, a member of the research team was tasked with confirming or completing the specific value. Once univariate analyses and variable confirmation are complete, the biostatistician will use the data to answer our

research questions. This process stimulates new ideas for subgroup analysis and future research.

We have already identified two interesting subgroup analyses. The first subgroup analysis is evaluating the association between our outcome variables (including pepsin) and type of ETT. Patients in both groups were intubated with either a traditional ETT or one with subglottic suctioning. We have an opportunity to do both within and between group analyses. The second subgroup analysis will evaluate the NO-ASPIRATE intervention in patients who remain intubated for more than 4 days. Existing VAP research reports on patients intubated 4 days. Approximately 66% of our study population remained intubated for four or more days. This allows us to evaluate a group of patients historically excluded from VAP research.

4 | CONCLUSION

The NO-ASPIRATE protocol offers insight for critical care nurse researchers in attaining improved outcomes in intubated patients. Study findings will likely be of interest to clinicians worldwide, as complications of ventilation are prevalent and costly. A standardized nursing intervention that may improve clinical and/or financial outcomes for MV patients is clinically significant. This study also assists in furthering the examination of prognostic capabilities of α -amylase as a biomarker of microaspiration.

ACKNOWLEDGEMENTS

This study received financial support from the NIH in February of 2014. The NIH grant number is 1R01NR014508-01A1. No other acknowledgements are noted in this study.

Funding information

This study received financial support from the NIH. The NIH grant number for the NO-ASPIRATE study is 1R01NR014508-01A1.

REFERENCES

- Abu-Hasan M, Brookes J, Neal D, & ElMallah MK (2012). Salivary amylase level in bronchoalveolar fluid as a marker of chronic aspiration of oral secretions in children. *American Journal of Respiratory and Critical Care Medicine*, 185, A6133.
- Bertrand J, Hollandsworth A, Sole ML, & Grano J (2011). Airway management practices documented in the electronic medical record: A quality improvement project. Orlando, FL: Orlando Regional Medical Center.
- Blamoun J, Alfakir M, Rella ME, Wojcik JM, Solis RA, Anees Khan M, & DeBari VA (2009). Efficacy of an expanded ventilator bundle for the reduction of ventilator-associated pneumonia in the medical intensive care unit. *American Journal of Infection Control*, 37, 172–175. 10.1016/j.ajic.2008.05.010 [PubMed: 18945515]
- Boots RJ, Udy A, Holley A, & Lipman J (2010). Preventive strategies for ventilator associated pneumonia. *Current Respiratory Medicine Reviews*, 6, 238–252. 10.2174/157339810793563758
- Chao YF, Chen YY, Wang KW, Lee RP, & Tsai H (2009). Removal of oral secretion prior to position change can reduce the incidence of ventilator-associated pneumonia for adult ICU patients: A clinical controlled trial study. *Journal of Clinical Nursing*, 18(1), 22–28. 10.1111/j.1365-2702.2007.02193.x [PubMed: 19120729]
- Chow MC, Kwok SM, Luk HW, Law JW, & Leung BP (2012). Effect of continuous oral suctioning on the development of ventilator-associated pneumonia: A pilot randomized controlled trial.

- International Journal of Nursing Studies, 49, 1333–1341.10.1016/j.ijnurstu.2012.06.003 [PubMed: 22749332]
- Chulay M, & Seckel MA (2012). Suctioning: Endotracheal or tracheostomy tube In Lynn-McHale Weigand D (Ed.), AACN procedure manual for critical care (6th ed.). (pp. 79–87). Philadelphia, PA: Elsevier-Saunders.
- Clarke PD, Bain BC, Davies A, Levin GE, & Lambert HP (1981). Aspiration in seriously ill patients: A study of amylase in bronchial secretions. *Journal of Clinical Pathology*, 34, 803–805. 10.1136/jcp.34.7.803 [PubMed: 6167594]
- Cox DR (1972). Regression models and lift-tables. *Journal of the Royal Statistical Society*, 34, 187–220.
- Craven DE, Chroneous A, Zias N, & Hjalmarson KI (2009). Ventilator-associated tracheobronchitis: The impact of targeted antibiotic therapy on patient outcomes. *Chest*, 135, 521–528. 10.1378/chest.08-1617 [PubMed: 18812452]
- Craven DE, & Steger KA (1997). Hospital-acquired pneumonia: Perspectives for the healthcare epidemiologist. *Infection Control and Hospital Epidemiology*, 18, 783–795. 10.2307/30141328 [PubMed: 9397379]
- Dewavrin F, Zerimech F, Boyer A, Maboudou P, Balduyck M, Duhamel A, & Nseir S (2014). Accuracy of alpha amylase in diagnosing microaspiration in intubated critically-ill patients. *PLoS ONE*, 9(3), 1–8. 10.1371/journal.pone.0090851
- Filloux B, Bedel A, Nseir S, Mathiaux J, Amadeo B, Clouzeau B, & Boyer A (2013). Tracheal amylase dosage as a marker for microaspiration: A pilot study. *Minerva Anestesiologica*, 79, 1003–1010. [PubMed: 23652170]
- Garcia R, Jendresky L, Colbert L, Bailey A, Zaman M, & Majumder M (2009). Reducing ventilator-associated pneumonia through advanced oral-dental care: A 48-month study. *American Journal of Critical Care*, 18, 523–532. 10.4037/ajcc2009311 [PubMed: 19635805]
- Hulley SB, Cummings SR, Browner WS, Grady DG, & Newman TB (2007). *Designing clinical research* (3rd ed.) Philadelphia, PA: Lippincott-Williams & Wilkins.
- Kaplan EL, & Meier P (1958). Nonparametric estimation from incomplete observations. *Journal of American Statistical Association*, 53, 457–481. 10.1080/01621459.1958.10501452
- Klompas M (2017). Ventilator-associated events 5 years later. *Respiratory Care*, 62, 1501–1503. 10.4187/respcare.05890 [PubMed: 29061911]
- Klompas M, Khan Y, Kleinman K, Evans RS, Lloyd JF, Stevenson K, & Platt R (2011). Multicenter evaluation of a novel surveillance paradigm for complications of mechanical ventilation. *PLoS ONE*, 6(3), 1–7. 10.1371/journal.pone.0018062
- Liang K-Y, & Zeger SL (1986). Longitudinal data analysis using generalized linear models. *Biometrika*, 73(1), 13–22. 10.1093/biomet/73.1.13
- Marik PE (2011). Pulmonary aspiration syndromes. *Current Opinion in Pulmonary Medicine*, 17, 148–154. 10.1097/MCP.0b013e32834397d6 [PubMed: 21311332]
- Metheny NA, Davis-Jackson J, & Stewart BJ (2010). Effectiveness of an aspiration risk-reduction protocol. *Nursing Research*, 59(1), 18–25. 10.1097/NNR.0b013e3281c3ba05 [PubMed: 20010041]
- Munro CL, Grap MJ, Jones DJ, McClish DK, & Sessler CN (2009). Chlorhexidine, toothbrushing and preventing ventilator-associated pneumonia in critically ill adults. *American Journal of Critical Care*, 18, 428–437. 10.4037/ajcc2009792 [PubMed: 19723863]
- Nandapalan V, McIlwain JC, & Hamilton J (1995). A study of alpha-amylase activity in tracheobronchial secretions of seriously ill patients with tracheostomies. *Journal of Laryngology and Otology*, 109, 640–643. [PubMed: 7561472]
- Nseir S, Duguet A, Copin MC, De Jonckheere J, Zhang M, Similowski T, & Marquette CH (2007). Continuous control of endotracheal cuff pressure and tracheal wall damage: A randomized controlled animal study. *Critical Care*, 11, R109 10.1186/cc6142 [PubMed: 17915017]
- Nseir S, Zerimech F, Fournier C, Lubret R, Ramon P, Durocher A, & Balduyck M (2011). Continuous control of tracheal cuff pressure and microaspiration of gastric contents in critically ill patients. *American Journal of Respiratory and Critical Care Medicine*, 184, 1041–1047. 10.1164/rccm.201104-0630OC [PubMed: 21836137]

- Nseir S, Zerimech F, Jaillette E, Artru F, & Balduyck M (2011). Microaspiration in intubated critically ill patients: Diagnosis and prevention. *Infectious Disorders Drug Targets*, 11, 413–423. 10.2174/187152611796504827 [PubMed: 21679139]
- Qu G, Fang X, Xu Y, Shi M, Wang Y, Gong M, & Fang H (2018). Predictive value of amylase in tracheal aspirates for ventilator-associated pneumonia in elderly patients. *Clinical Respiratory Journal*, 12, 1685–1692. 10.1111/crj.12729 [PubMed: 29087039]
- Rawat N, Yang T, Ali KJ, Cohen MD, Farley DO, Lubomski LH, & Klompas M (2017). Two-state collaborative study of a multi-faceted intervention to decrease ventilator-associated events. *Critical Care Medicine*, 45, 1208–1215. 10.1097/CCM.0000000000002463 [PubMed: 28448318]
- Rennard SI, Ghafouri M, Thompson AB, Under J, Vaughan W, Jones K, & Robbins RA (1990). Fractional processing of sequential bronchoalveolar lavage to separate bronchial and alveolar samples. *American Review of Respiratory Disease*, 141(1), 208–217. 10.1164/ajrccm/141.1.208 [PubMed: 2297178]
- Samanta S, Poddar B, Azim A, Singh RK, Gurjar M, & Baronia AK (2018). Significance of mini bronchoalveolar lavage fluid amylase level in ventilator-associated pneumonia: A prospective observational study. *Critical Care Medicine*, 46(1), 71–78. 10.1097/CCM.0000000000002774 [PubMed: 29053492]
- Sole ML, & Bennett M (2011). Suctioning and airway management practices (STAMP 2011) of registered nurses (RNs) and respiratory care practitioners (RCPs). *Critical Care Medicine*, 39(12), A341 10.1097/01.ccm.0000408627.24229.88
- Sole ML, Bennett M, Talbert S, & Penoyer DA (2011). Oropharyngeal secretion volume in intubated patients: The importance of oral suctioning. *American Journal of Critical Care*, 20(6), e141–e145. 10.4037/ajcc2011178 [PubMed: 22045150]
- Sole ML, Byers JF, Ludy JE, & Ostrow CL (2002). Suctioning techniques and airway management practices: Pilot study and instrument evaluation. *American Journal of Critical Care*, 11(4), 363–368. [PubMed: 12102437]
- Sole ML, Byers JF, Ludy JE, Zhang Y, Banta CM, & Brummel K (2003). A multisite survey of suctioning techniques and airway management practices. *American Journal of Critical Care*, 12(3), 220–230. [PubMed: 12751396]
- Sole ML, Marano A, Bennett M, Mehta D, & Ashworth S (2012). Clinical indicators for endotracheal suctioning in adult patients receiving mechanical ventilation (abstract). *Critical Care Medicine*, 40(12), U127.
- Sole ML, Middleton A, Allen K, Mehta D, Bennett M, Conrad J, & Ashworth S (2012). Pepsin and salivary amylase in oral and tracheal secretions: A pilot study (abstract). *Critical Care Medicine*, 40(12), 127.
- Sole ML, Penoyer DA, Bennett M, & Bertrand J (2010). Oropharyngeal secretion removal in intubated patients Paper presented at Southern Nursing Research Society Annual Research Conference Austin, TX.
- Sole ML, Poalillo FE, Byers JF, & Ludy JE (2002). Bacterial growth in secretions and on suctioning equipment of orally intubated patients: A pilot study. *American Journal of Critical Care*, 11(2), 141–149. [PubMed: 11888126]
- Sole ML, Talbert S, Penoyer DA, Sokol S, Bennett M, & Wilson J (2012). Characteristics and outcomes of critically ill patients who require a percutaneous tracheostomy (abstract). *Critical Care Medicine*, 40(12), U124.
- Sole ML, Xiaogang S, Talbert S, Penoyer DA, Kalita S, Jimenez E, & Bennett M (2011). Evaluation of an intervention to maintain endotracheal tube cuff pressure within therapeutic range. *American Journal of Critical Care*, 20(2), 109–117. 10.4037/ajcc2011661 [PubMed: 21362715]
- Tripathi A, Mirant-Borde MC, & Lee A (2011). Amylase in bronchoalveolar lavage as a potential marker of oropharyngeal-to-pulmonary aspiration. *American Journal of Respiratory and Critical Care Medicine*, 183, A4616.
- Tsai HH, Lin FC, & Chang SC (2008). Intermittent suction of oral secretions before each positional change may reduce ventilator-associated pneumonia: A pilot study. *The American Journal of the Medical Sciences*, 336, 397–401. 10.1097/MAJ.0b013e31816b8761 [PubMed: 19011396]

- United States Department of Health and Human Services, Centers for Disease Control and Prevention. (2004). Guidelines for preventing health-care-associated pneumonia, 2003: Recommendations of the CDC and the Healthcare Infection Control Practices Advisory Committee. *Respiratory Care*, 49, 926–939. [PubMed: 15320333]
- United States Department of Health and Human Services, Centers for Disease Control and Prevention. (2013). Surveillance for ventilator-associated events. Retrieved from <http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html>.
- United States Department of Health and Human Services, Centers for Disease Control and Prevention. (2018). Ventilator-associated event (VAE) Retrieved from https://www.cdc.gov/nhsn/PDFs/pscManual/10-VAE_FINAL.pdf
- Weiss CH, Moazed F, Dibardino D, Swaroop M, & Wunderink RG (2013). Bronchoalveolar lavage amylase is associated with risk factors for aspiration and predicts bacterial pneumonia. *Critical Care Medicine*, 41, 765–773. 10.1097/CCM.0b013e31827417bc [PubMed: 23314582]
- Weiss CH, Moazed F, & Wunderink RG (2011). Bronchoalveolar lavage fluid amylase is elevated in patients with a high risk of aspiration. *American Journal of Respiratory and Critical Care Medicine*, 183, A3915.
- Zeger SL, & Liang K-Y (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, 42(1), 121–130. 10.2307/2531248 [PubMed: 3719049]

Why is this study needed?

- Complications associated with mechanical ventilation, including microaspiration, are associated with high mortality rates and financial costs in the hospital intensive care unit setting worldwide.
- Despite the associated clinical benefits of oropharyngeal suctioning for patients requiring mechanical ventilation, no standardization of this nursing intervention exists in clinical practice.
- Evaluating the impact of a standardized oropharyngeal suctioning intervention on microaspiration and complications of mechanical ventilation assists in developing standardized nursing interventions.

FIGURE 1.
Study framework

FIGURE 2.
Procedures for NO-ASPIRATE and usual care groups

TABLE 1

Study variables

Variable	Source	When	Purpose
Outcome variables			
<i>Outcome:</i> Microaspiration; % tracheal specimens positive for α -amylase; mean value of α -amylase in tracheal secretions	Assays of α -amylase in tracheal aspirate	Enrolment Every 12 hr Duration: up to 14 days while intubated	<i>Aim 1—</i> Microaspiration
<i>Outcome:</i> VAC—yes/no	Medical record data: <ul style="list-style-type: none"> Ventilator setup: PEEP, oxygen level Temperature White blood count/culture results New antibiotics/duration 	Daily Assess for 2 days beyond the last intervention	<i>Aim 2—</i> VAC
<i>Outcome:</i> Ratio of α -amylase in tracheal and oral secretions	Assays of α -amylase from paired tracheal and oral specimens	Enrolment Every 12 hr Duration up to 14 days	<i>Aim 3—tracheal/oral ratio of α-amylase</i>
Demographic data			
ETT information (time of intubation, type ETT, size ETT)	Observation Medical record	Enrolment	Describe sample Stratify by ETT type
Age, gender, ethnicity, diagnoses	Medical record	Enrolment	Describe sample Compare groups
Comorbidities: COPD; immune-compromise; chronic heart, liver, or renal failure	Medical record	Enrolment	Describe sample Compare groups
Acuity and outcomes: APACHE II, SAPS, ventilator days, LOS	Hospital database	Completion of participation in study	Describe sample Test group equivalence
Physiological status: vital signs, oxygen saturation, sedation level	Medical record	Enrolment Daily (a.m.)	Describe sample Test equivalence
Potential risk factors for microaspiration and VAC			
Backrest elevation (daily average)	Observation	Every 4 hr	Test equivalence
GI data: tubes, nutritional support; gastric residual, distention; vomiting	Medical record Observation	Enrolment Daily (a.m.)	Test equivalence
ETT: min, max, mean daily cuff pressure; repositioning; cuff issues	Medical record	Daily	Test equivalence
Oral care: additional interventions, type of antiseptic	Medical record Intervention documentation	Daily	Test equivalence
GI medications: Histamine blockers, proton pump inhibitors, antacids, sucralfate	Medical record	Enrolment Daily (a.m.)	Test equivalence
Mobility and transport off unit	Medical record/observation	Every 4 hr	Test equivalence

Notes. APACHE: acute physiologic assessment and chronic health evaluation; COPD: chronic obstructive pulmonary disease; ETT: endotracheal tube; GI: gastrointestinal; LOS: length of stay; PEEP: positive end-expiratory pressure; SAPS: simplified acute physiology score; VAC: ventilator-associated condition.