Randomized Pilot Trial of Two Modified Endotracheal Tubes To Prevent Ventilator-associated Pneumonia

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Abstract

Rationale: Ventilator-associated pneumonia (VAP) is a prevalent and costly nosocomial infection related to instrumentation of the airway with an endotracheal tube (ETT), enabling microaspiration of contaminated secretions. Modification of the ETT design to reduce microaspiration and/or biofilm formation may play an important role in VAP prevention. However, there is insufficient evidence to provide strong recommendations regarding the use of modified ETT and unaddressed safety concerns.

Objectives: We performed a pilot randomized controlled trial comparing two modified ETTs designed specifically to prevent VAP, with the standard ETT, to test the feasibility of and inform planning for a large, pivotal, randomized trial.

Methods: This study was conducted with institutional review board approval under exception from informed consent. We randomized in a blinded fashion patients undergoing emergency endotracheal intubation both out of and in hospital to receive one of three different ETT types: (*1*) a polyurethane-cuffed tube (PUC-ETT), (*2*) a polyurethane-cuffed tube equipped with a port for continuous aspiration of subglottic secretions (PUC-CASS-ETT), or a (*3*) standard polyvinylchloride-cuffed tube (PVC-ETT). In addition to investigating feasibility and safety, the study coprimary end points were tracheal bacterial colonization reaching a cfu count $>10^6$ cfu per milliliter and the incidence of invasively diagnosed VAP.

Measurements and Main Results: A total of 102 subjects were randomized and met the eligibility criteria. Randomization procedures performed well and integrity of blinding at randomization was maintained. The majority of intubations occurred in the hospital setting (n = 77), and the remainder occurred out of hospital (n = 25). Compared with the PVC-ETT, there were no significant differences in tracheal colonization for PUC-ETT (odds ratio [OR], 0.98; 95% confidence interval [CI], 0.31–3.09) or for PUC-CASS-ETT (OR, 1.26; 95% CI, 0.42–3.76). There were no differences in the risk of invasively diagnosed VAP (OR, 1.14; 95% CI, 0.21–6.08 for PUC-ETT; OR, 1.47; 95% CI, 0.30–7.10 for PUC-CASS-ETT), or of clinically diagnosed VAP by either clinical signs or chest radiograph criteria. We did not observe unexpected or serious adverse events related to the devices.

Conclusions: A randomized trial of ETTs inserted during emergency intubation for the prevention of VAP is feasible and did not appear to carry heightened safety concerns. These preliminary data did not suggest different patterns of tracheal colonization or occurrence of VAP among the study groups.

Clinical trial registered with www.clinicaltrials.gov (NCT01744483).

Keywords: subglottic suction; microaspiration; clinical trial; nosocomial pneumonia

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Hospital-acquired pneumonia that develops after 48 hours or more of tracheal intubation and mechanical ventilation is termed ventilator-associated pneumonia (VAP). VAP is a common clinical problem with substantial morbidity and financial burden (1). VAP has been shown to increase intensive care unit (ICU) length of stay and ICU cost and in some studies has been associated with excess mortality (1). Importantly, health care–associated pneumonia is one of the metrics of hospital quality performance by the Joint Commission.

One approach to VAP risk reduction is the redesign of the endotracheal tube (ETT) to reduce microaspiration of bacteria-contaminated secretions. The best-studied technique to prevent leakage of secretions around the cuff of the ETT is the application of suction for aspiration of subglottic secretions via an ETT equipped with an orifice just above the tube cuff. A recent metaanalysis examined the data from 13 randomized controlled trials (RCTs) of subglottic suctioning and estimated a 45% reduction in the risk of VAP on the basis of the pooled results (relative risk, 0.55; 95% confidence interval, 0.46–0.66) (2). Findings were similar when the analysis was restricted to studies with high methodological quality. The pooled data also indicated that subglottic suction reduced the duration of mechanical ventilation and ICU length of stay, without effect on mortality. However, there are methodological concerns with many of the studies evaluating subglottic suctioning (3). In addition, significant, unaddressed safety concerns are associated with the use of subglottic suctioning, including experimental data suggesting a risk of serious laryngeal and/or tracheal injury related to the device and associated technique (4–6).

Another approach to reducing microaspiration is the modification of the shape and/or material and physical structure of the ETT cuff (7). In particular, the composition of the ETT cuff can favor microaspiration of secretions through folds that develop in the cuff over time (8–11). Three small RCTs and a longitudinal analysis suggested that use of a polyurethane-cuffed ETT (PUC-ETT) was associated with a reduced incidence of VAP compared with intubation with a standard polyvinylchloride-cuffed ETT (PVC-ETT) (12–15). However, a recent, large, randomized trial found no differences in tracheal bacterial colonization or in the incidence of VAP in terms of either cuff composition or cuff shape (16). None of these studies detected a difference in duration of mechanical ventilation or ICU length of stay or in mortality between groups. It is also unclear if combining modifications in cuff composition and/or shape with subglottic suctioning would offer incremental benefits in VAP prevention (12).

Because of the uncertainties about the efficacy and safety of ETTs designed to prevent VAP, a large, well-conducted phase III randomized trial is necessary. To inform planning for and determine the feasibility of such a comparative effectiveness trial, we designed a pilot study comparing three types of ETTs in mechanically ventilated, critically ill patients. Our trial was also designed to be pragmatic in capturing all patients at risk of the development of VAP, rather than attempting to select only patients at the highest risk. Our hypothesis was that specially designed ETTs reduce the occurrence of invasively diagnosed VAP via the reduction of tracheal microaspiration, compared with the standard PVC-ETT. Our primary end point was the semiquantitative count of bacterial tracheal colonization during tracheal intubation. Our coprimary end point was the occurrence of invasively diagnosed VAP. An important feature of this study was its special focus on the evaluation of the safety profile of these newly designed ETTs.

Methods

Trial Design

The study was a pilot, randomized controlled, parallel-group design assigning patients undergoing emergency tracheal intubation to receive one of three different tracheal tubes, two of which include design features that may help reduce the risk of VAP: (*1*) a PUC-ETT (Mallinckrodt Oral/Nasal Tracheal Tube Seal Guard; Medtronic, Dublin, Ireland), (*2*) an ETT with a polyurethane cuff that is also fitted with a lumen to allow continuous aspiration of subglottic secretions (PUC-CASS-ETT) (Mallinckrodt Evac Oral Tracheal Tube Seal Guard; Medtronic), or (*3*) a standard PVC-ETT (Mallinckrodt Hi-Lo Oral/Nasal Tracheal Tube; Medtronic). Both PUC tubes had conical-shaped cuffs, whereas the standard tube had a cylindrical cuff. Adult patients requiring tracheal intubation in the prehospital or hospital setting for acute respiratory failure were randomly assigned 1:1:1 to be intubated with one of the three ETTs. The study was approved by the institutional review board and was conducted under exception of informed consent. There were no changes to the trial design after the study commencement.

Trial Regulatory Oversight

An exception from informed consent was obtained from the University of Washington Investigational Review Board at the time of randomization (tracheal intubation) because of the narrow therapeutic window. Informed consent for participation in the study was obtained at the earliest opportunity, but after eligibility criteria were met. Efforts to identify and approach the patient's legal next of kin for informed consent began as soon as the research team learned via notification or electronic data tracking that a subject had been randomized, with a goal of gaining informed consent within 72 hours of randomization. Approval from the Food and Drug Administration was also obtained because the study was device related and involved exception from informed consent.

Participants

Eligibility criteria. Subjects eligible to participate in the trial were adults (≥18 yr of age) requiring emergency orotracheal intubation outside of hospital by Seattle Medic One and routed toward Harborview Medical Center, or requiring emergency in-hospital orotracheal intubation within Harborview Medical Center, Seattle, WA. After orotracheal intubation with one of the study devices, to meet all eligibility criteria for trial participation, subjects had to be admitted to one of the ICUs at Harborview Medical Center.

Exclusion criteria. Patients with out-of-hospital cardiac arrest (active cardiopulmonary resuscitation) were not eligible to participate, to avoid concurrent enrollment in multiple exception-from-informed-consent studies. Additional exclusion criteria included the following: (*1*) the use of a non–study-designated intubation device (this included intubations in the operating room or outside the study network, such as those occurring in an outside hospital or by other emergency response teams not participating in the

trial); (*2*) airway management other than orotracheal intubation, such as nasal intubation or tracheostomy); (*3*) patients with permanent tracheostomy; and (*4*) federally protected populations including children (age <18 yr), pregnant women, and prisoners.

Randomization Procedures

Sequence generation. A computer-generated random sequence was obtained from a sequence of uniformly distributed random numbers between 0 and 1. We then used the inverse transform sampling method to assign the random sequence. Two different randomization lists were generated for out-of-hospital and in-hospital settings.

Allocation concealment mechanism. The intervention assignment in the out-of-hospital setting occurred by randomly assigning each medic unit to carry one of the three ETTs. Each medic unit was assigned a unit study number. Three blocks of 12 random numbers were generated, so that every 4 weeks the ETT supplies were randomly reassigned to each medic unit for the duration of the study, corresponding to approximately three 4-week periods.

For patients enrolling in the study while already hospitalized, intubation packets were randomly assigned 1:1:1 to contain one type of ETT: PUC-ETT, PUC-CASS-ETT, or PVC-ETT. The packets were labeled with a study number for identification and tracking of the study devices. The intubation packets were sealed with an opaque wrapping so that the assignment occurred in a blinded fashion. Two sizes of study ETTs, internal diameters (I.D.s) 7.0 and 7.5, were provided in each packet, with the instruction that women should receive a 7.0 I.D. and men a 7.5 I.D. size. After randomization, a sealed and appropriately sized ETT of the same randomization assignment was kept at the patient's bedside for the purpose of minimizing crossovers in the event of a reintubation.

Implementation. Participants were enrolled by paramedics riding on rigs serving the Seattle metropolitan area. In the hospital setting, the supplies to perform intubation were prepared by respiratory therapists. Providers were not aware of the type of ETT until they opened the study kit, before which the decision to secure the airway had been made. The study kits contained instructions for completing the initial randomization procedures and included the supplies to collect the first tracheal aspirate immediately after intubation, study labels, bracelets to allow patient identification by the study personnel, and self-addressed envelopes for returning the unused study device. A phone system and a real-time data capture system allowed immediate notification of the study personnel of a subject randomization. All patients admitted to the ICU and receiving mechanical ventilation were further screened twice daily to ensure complete tracking of all study devices.

Blinding

The kits containing the study devices were sealed in opaque envelopes. In the out-of-hospital setting, we randomized the vehicles to carry a certain type of ETT for 4 weeks, and then we restocked the supplies every 4 weeks. Because the frequency of intubation by a team riding a given vehicle is relatively low, this offered protection against the ability to predict the type of ETT for the next package. In the hospital setting, all airway cart locations were supplied with the study ETTs and were restocked on a regular basis. A limited supply of conventional non–study ETTs was available for use only in protected populations or in patients already enrolled in another exception-from-informed-consent study.

Concomitant Treatments That Affect VAP Rate

At Harborview Medical Center, VAP-preventive measures are standardized across all ICUs and monitored for compliance. These measures include guidelines for discontinuation of stress ulcer prophylaxis in the absence of risk factors when caloric intake via enteral nutrition is at goal, guidelines for semirecumbent positioning at 30 to 45 degrees head tilt unless contraindicated by hemodynamic instability or orthopedic injuries, and guidelines for oral hygiene/decontamination. As such, all mechanically ventilated patients receive oral care every 8 hours that includes cleaning with 0.12% chlorhexidine solution. In addition, hand hygiene before and after patient contact is mandated, with compliance monitored by the hospital infection control program. Lastly, ETT cuff pressures are measured by respiratory therapists every 8 hours and cuff pressures are adjusted to maintain a pressure between 25 and 30 cm H_20.

Study Procedures

Subjects were monitored in the ICU until extubation, discharge, or death. All study participants had daily tracheal aspirates examined for quantitative bacterial cultures until extubation, death, or 7 days of tracheal intubation and mechanical ventilation had been reached. Laryngeal function was evaluated after extubation.

Determination of tracheal bacterial colonization. Tracheal aspirates were obtained by respiratory therapists using an aseptic technique and were sent to the research microbiology laboratory for processing and culture. The coprimary end point for the pilot study was the proportion of patients with bacterial colonization of the trachea at the threshold quantity of $\geqslant 10^6$ cfu per milliliter on the day of extubation or Day 4 of ventilation, whichever came first. We also evaluated intermediate threshold values ($\geqslant 10^5$ cfu/ml) and the absolute burden of bacterial growth (average cfu/mL per group). We defined tracheobronchitis as bacterial colonization $\geqslant 10^6$ cfu per milliliter combined with clinical signs of infection (17).

Diagnosis of pneumonia in mechanically ventilated patients. The second coprimary end point was the occurrence of invasively diagnosed VAP during ICU stay. For study purposes, VAP was diagnosed on the basis of the CDC definition as well as modified CDC criteria that are used to guide diagnosis and treatment of VAP at Harborview Medical Center (Table 1). At Harborview, the prevention, diagnosis, and treatment of VAP are guided by hospital-wide guidelines directed at nursing, respiratory therapy, and physician practice that emphasize an invasive approach to diagnosis and that are based on CDC definitions. The only Harborview modification of the CDC definition is that patients with a diffuse lung injury pattern on chest radiography are considered to meet the radiographic criteria for VAP.

We developed a comprehensive mechanism to identify VAP and respiratory events using a systematic, algorithmic approach that was based on the CDC definition of invasively diagnosed VAP. In the first step, we identified daily clinical signs of respiratory infection, including fever, leukocytosis or leukopenia, and

Table 1. Study definition of ventilator-associated pneumonia (CDC criteria)

1.	Radiographic abnormality consistent with pneumonia (i.e., new or persistent focal infiltrate[s]) Modified CDC (Harborview Medical Center) criteria: Above findings or diffuse lung injury pattern
	AND
2.	One or more of the following: a. Fever (temperature >38.0°C) b. Leukocytosis or leukopenia
	AND
3.	One or more of the following: a. New-onset purulent sputum, change in sputum character, or increased respiratory secretions or suctioning requirement b. Worsening gas exchange (Pa_{O_2}/FI_{O_2} ratio ⩽240, increased oxygen requirements, or increased ventilatory demand)
	AND
4.	Cultures from bronchoalveolar lavage or mini–bronchoalveolar lavage containing ⩾10^4 cfu/ml Or Protected specimen brush containing ⩾10^3 cfu/ml

Definition of abbreviation: CDC = Centers for Disease Control.

changes in sputum character or worsening gas exchange (clinical signs). In the second step, among patients identified on the basis of clinical signs, investigators blinded to group assignment screened chest X-rays on a daily basis to identify radiographic abnormalities consistent with pneumonia (chest radiograph criteria). A subject with clinical signs and chest radiograph criteria was considered to meet the criteria for a clinical diagnosis of VAP on the basis of screening of the above variables. A prompt recommending the performance of a bronchoalveolar lavage was paged to the physician of record if their patient(s) met the set of clinical signs and chest radiograph criteria. These steps were taken to ensure that all subjects who met the clinical criteria for suspicion of VAP were considered for an invasive workup, although the latter was done at the discretion of the medical team. This evaluation with the appropriate prompt was conducted daily for each patient during the intubation period. In the third step, we defined confirmed cases of VAP as the simultaneous presence of clinical signs, chest radiograph criteria, and cultures from bronchoalveolar lavage or mini–bronchoalveolar lavage (Combicath, Plastimed, Le Plessis-Bouchard, France) containing at least 10^4 cfu per milliliter or a protected specimen brush containing at least 10^3 cfu per milliliter.

Safety evaluation. Evaluation of the short-term effects of the ETT on the airway included subjective and objective measures of laryngeal anatomy and function, in addition to any device-related adverse events. Data collected included presence of cuff leak with the balloon down in the presence of 25 cm H_2O of positive pressure just before extubation, occurrence of stridor immediately after extubation, administration of racemic epinephrine and/or helium–oxygen gas mixture after extubation, reintubation within 24 hours because of upper airway complications such as stridor or obstruction, gross dysphagia (coughing or inability to swallow water), dysphonia (hoarseness or aphonia), dyspnea, or stridor within 48 hours after extubation; these variables were quantified using a laryngeal dysfunction score (*see* online supplement).

Long-term safety was assessed by ascertaining by phone interview the persistence of airway sequelae 2 months after extubation.

Statistical Methods

The study followed an intention-to-treat approach. We computed the power of this study to determine changes in the proportions of bacterial colonization between each of the two treatment arms, PUC-ETT and PUC-CASS-ETT vs. PVC-ETT. Assuming a 45% proportion of tracheal colonization of 10^6 cfu per milliliter within 4 days of tracheal intubation in the standard care group (PVC), a sample size of 90 patients (30 per treatment arm) would provide 80% power to detect a 30% absolute reduction in the proportion of patients with emergence of significant new tracheal colonization, with a type I error rate of 10%. A tendency to detect a difference in this end point would support the hypothesis that prevention of microaspiration and tracheal colonization may be one of the mechanisms in the reduction of VAP.

For the coprimary end points, tracheal colonization and invasively diagnosed VAP, the variables are binary. The data were analyzed using logistic regression. The primary comparisons were the odds ratio of a positive culture or the odds ratio of invasively diagnosed VAP between the study groups (1) PUC-ETT and PVC-ETT and the odds ratio of a positive culture between (2) PUC-CASS-ETT and PVC-ETT.

Secondary end points included ventilator-free days, cumulative Sequential Organ Failure Assessment score, length of ICU, and length of hospital stay. We compared mean hospital length of stay, mean ventilator-free days, and mean cumulative Sequential Organ Failure Assessment score between treatment groups using linear regression.

For safety end points, the proportion of patients with short-term airway sequelae after extubation and long-term airway sequelae at 2-month follow-up were summarized by treatment group assignment and were compared.

Results

Enrollment and Exclusions

After obtaining approval from the regulatory authorities, the study started enrolling patients on December 12, 2012, and enrollment was completed on February 14, 2013. Enrollment proceeded at the expected rate, with a total of 117 subjects randomized (Figure 1). In the planning of the study, we anticipated randomizing 120 patients over 3 months. Subsequent to initial randomization (defined as insertion of a study ETT), we anticipated a total of 90 subjects would meet the eligibility criteria and be enrolled in the study. Our enrollment was ahead of expected, with 102 patients enrolled.

Randomization Procedures

The randomization procedures performed well. The groups and baseline characteristics measured were numerically well balanced (Table 2). We were able to track all study devices with the use of appropriate labeling and via a phone notification system. As expected, the majority of intubations occurred in the hospital setting (n = 77), and the remainder occurred outside the hospital, before hospital admission (n = 25). Four patients were rerandomized at the time of a second endotracheal intubation. Of those, three crossed over to a different study group. Overall, 20 patients required reintubation: 10 with the same ETT as the group they were originally assigned to, 3 with an ETT of a different study group, and 7 with a non–study ETT.

Table 2. Baseline characteristics

Variable	PVC-ETT (*n* = 36)	PUC-ETT (*n* = 32)	PUC-CASS-ETT (*n* = 34)
Age at intubation, mean (SD), yr	55 (19)	53 (16)	55 (17)
Sex, No. (%)			
Female	9 (25)	11 (34)	10 (29)
Male	27 (75)	21 (66)	24 (71)
Ethnicity, No. (%)			
Hispanic/Latino	1 (3)	3 (10)	3 (9)
Not Hispanic/Latino	32 (97)	26 (90)	30 (91)
Race, No. (%)			
White	23 (64)	25(78)	24 (70)
Black	5 (14)	3 (9)	5 (15)
Other	8 (22)	4 (13)	5 (15)
Height, cm (SD)	172 (11)	172 (11)	173 (11)
Weight, kg (SD)	85 (32)	78 (13)	78 (14)
Type of admission, No. (%)			
Medical	31 (86)	29 (91)	27 (79)
Surgical emergency	5 (14)	3 (9)	7 (21)
SAPS II, mean (SD)	60 (14)	57 (12)	60 (12)
CAP, No. (%)	2 (6)	6 (19)	6 (18)
Location of intubation, No.(%)			
Out of hospital	9 (25)	11 (34)	4 (12)
In hospital	27 (75)	21 (66)	30 (88)
Reintubation, No. (%)	4 (11)	8 (25)	1 (3)
Crossover, No.	1→(PUC)	2→(PVC, PUC-CASS)	0

Definition of abbreviations: CAP = community-acquired pneumonia; ETT = endotrachel tube; PUC = polyurethane cuff; PUC-CASS = polyurethane cuff with continuous aspiration of subglottic secretions; PVC = polyvinylchloride cuff; SAPS = Simplified Acute Physiology Score.

Efficacy

Ventilator-associated events are presented in Table 3. There were no significant differences in the rate of tracheal colonization, the percentage of patients with tracheobronchitis, the percentage of patients meeting the criteria for VAP by either clinical signs or chest radiograph criteria, or the percentage of patients with either clinically diagnosed or invasively diagnosed VAP. Likewise, there were no significant differences in secondary endpoints, including length of stay and mortality (Table 4).

Safety

Sixteen serious adverse events occurred; all were deaths, and none were found to be causally related to the study device. There were two airway-related complications. One patient in the PUC-ETT group presented with postextubation stridor and required immediate reintubation. The other airway-related adverse effect was observed after hospital discharge in a patient randomized to the PVC-ETT group who complained of persistent dyspnea and hoarseness. The medical monitor determined that the respiratory symptoms were moderate in severity and were "probably" related to the study device. The patient was followed until resolution of symptoms. No other short- or long-term airway complications occurred.

The mean laryngeal score immediately after extubation and the frequency of minor airway-related events are shown in Table 5.

Discussion

In this pilot, randomized controlled trial comparing two ETTs specifically designed to reduce microaspiration and prevent VAP with a conventional ETT, we have established the feasibility of performing a larger, phase III trial of similar design. Our trial was designed specifically to capture all patients at risk of VAP, and we did not use selection criteria to try to specifically identify higher-risk patients. Furthermore, we enrolled patients who were intubated outside of the hospital, which is a cohort that had not been included in prior trials comparing ETTs for the prevention of VAP. We believe that this is an important facet of our study design, in that practical application of VAP-preventive measures should be applied ideally to all patients at risk and should furthermore not require risk-stratification at the time of an emergency procedure (tracheal intubation). This is also the first trial that we are aware of that compares three types of tracheal tube: a conventional polyvinylchloride-cuffed tube; a tapered polyurethane-cuffed tube; and a tube with both a polyurethane cuff and an additional port to allow subglottic suctioning.

Although this was a pilot study and was not designed to establish efficacy, we were unable to detect an effect on bacterial colonization of the trachea (an indicator of microaspiration burden), tracheobronchitis, or VAP. This is a potential source of concern for designing a phase III efficacy trial, but the less-than-expected effect size and lack of consistency with previous studies compellingly justify the need for a definitive trial. Furthermore, the incidence of invasively diagnosed VAP was relatively low, which further challenges the design of a phase III trial in that a large number of enrolled subjects would likely be necessary to show efficacy of the intervention(s). Why the incidence of VAP was low compared with previous reports is that our study population, consisting of patients requiring emergency intubation and ICU admission, was relatively unselected. We consider this feature a strength of the study, because this pragmatic approach reflects the reality of clinical practice in the setting of emergency intubation.

Although numerous previous small-to-medium sized trials have suggested that subglottic suctioning is efficacious in reducing the incidence of VAP, effects on mortality and the cost-effectiveness of the device have not been established (2). It may be that an effect on mortality is an unrealistic expectation. Although earlier studies using a case-control design suggest that the mortality attributable to VAP is between 15 and 48% (18–22), a more recent, sophisticated analysis suggests that VAP-attributable mortality is closer to 1% (23). Thus, it is possible that no VAP-preventive intervention will demonstrate a significant effect on mortality.

Alternatively, the cost-effectiveness of devices designed to prevent VAP is relevant given the cost (and possible risk) associated with their use. In 2001, Shorr and O'Malley estimated that subglottic suctioning would save an average of approximately $5,000 per case of VAP prevented (24). However, in their study, the greatest cost incurred by VAP was caused by additional time spent in the ICU, which, on the basis of previous published data, they estimated at 5 days. A recent metaanalysis suggests that this assumption may have been an overestimate, because the effect of subglottic suctioning

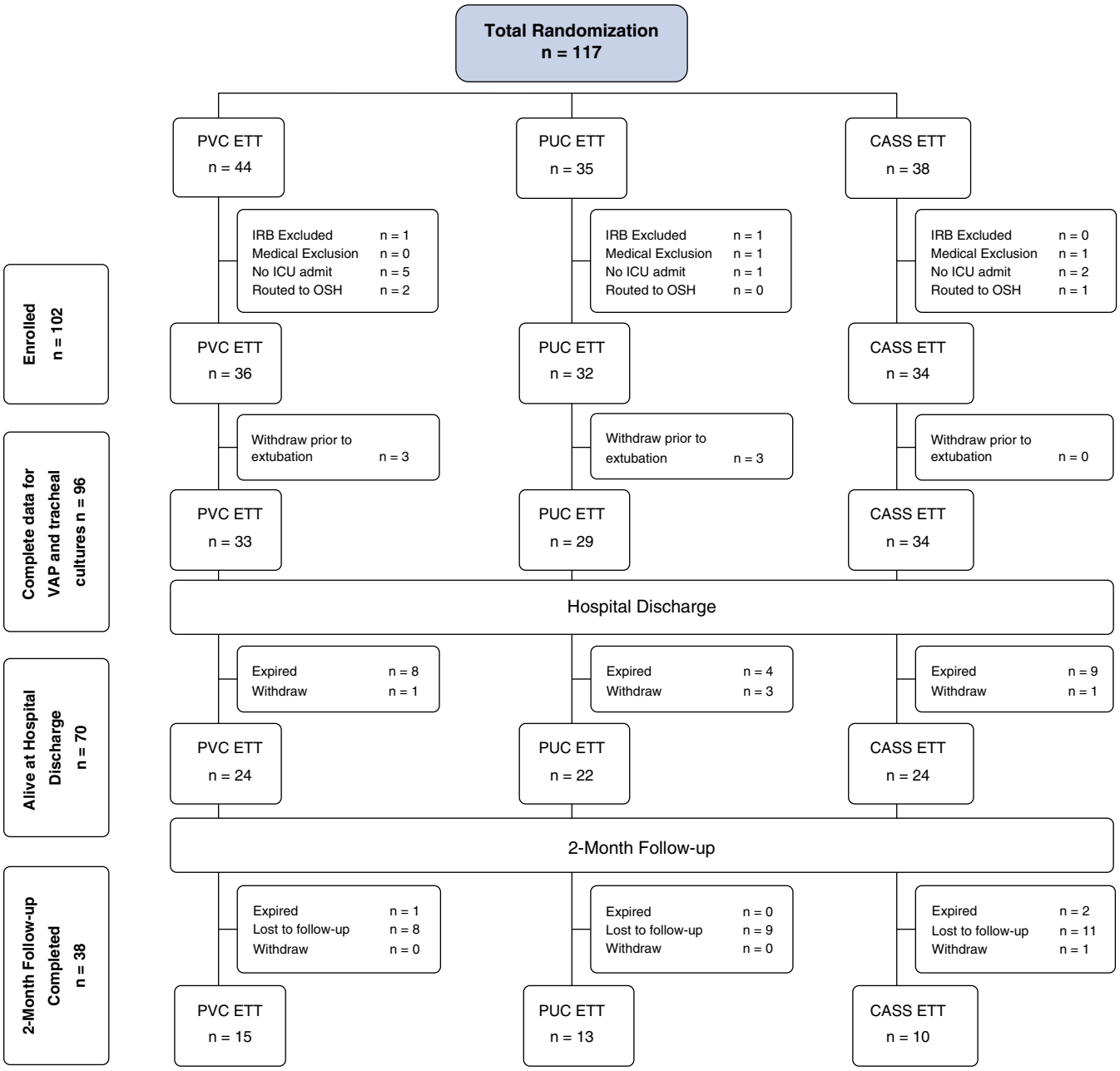

Figure 1. Study CONSORT flowchart. CASS-ETT = endotracheal tube equipped with a port for continuous aspiration of subglottic secretions; ICU = intensive care unit; IRB = institutional review board; OSH = outside hospital; PUC-ETT = polyurethane-cuffed endotracheal tube; PVC-ETT = polyvinylchloride-cuffed endotracheal tube; VAP = ventilator-associated pneumonia.

on ICU length of stay was found to be weak because of high heterogeneity, with an average reduction in length of stay of only 1.5 days (2). Likewise, the effect on reduction in duration of mechanical ventilation was small and was associated with significant heterogeneity; no effect on hospital length of stay was discernable Thus, it is imperative that a phase III randomized controlled trial of VAP-prevention devices include a rigorous cost-effectiveness component.

An important concern regarding devices designed to reduce VAP is safety. None of the numerous studies comparing subglottic suctioning ETTs with conventional ETTs attempted to identify prospectively and systematically airway complications associated with tracheal intubation. Yet a laboratory study reported widespread tracheal mucosal injury in sheep that underwent continuous subglottic suctioning for 72 hours (4). Safety concerns regarding PUC-ETTs have not been raised. However, a future phase III trial of tubes for VAP-prevention must include a rigorous safety evaluation. Our pilot study established the feasibility of this type of assessment with monitoring of both short-term and long-term airway complications.

Table 3. Ventilator-associated events

Variable	PVC-ETT (*n* = 36)	PUC-ETT (*n* = 32)	PUC-CASS-ETT (*n* = 34)
Primary end point			
Tracheal colonization* ($\geq 10^6$), No. (%)	8 (22)	7 (22)	9 (26)
Effect size, OR (95% CI)	Referent	0.98 (0.31–3.09)	1.26 (0.42–3.76)
Time to colonization* ($\geq 10^6$) (HR)	Referent	1.02 (0.37–2.81)	1.20 (0.46–3.11)
Tracheal colonization* and clinical signs of infection, No. (%)	3 (8)	2 (6)	1 (3)
Secondary end points			
VAP (CDC criteria), No. (%)	10 (28)	10 (31)	9 (26)
Effect size (95% CI)	Referent	1.18 (0.42–3.36)	0.94 (0.33–2.69)
Time to VAP (CDC criteria) (HR)	Referent	1.23 (0.51–2.95)	0.91 (0.37–2.24)
VAP (Harborview Medical Center criteria), No. (%)	14 (39)	13 (41)	10 (29)
Effect size, 95% CI	Referent	1.08 (0.41–2.84)	0.65 (0.24–1.77)
Time to VAP (Harborview Medical Center criteria) (HR)	Referent	1.13 (0.53–2.42)	0.69 (0.30–1.56)
Tracheal colonization ($\geq 10^4$), No. (%)	13 (36)	11 (34)	16 (47)
Effect size (95% CI)	Referent	0.93 (0.34–2.51)	1.57 (0.60–4.10)
Time to colonization ($\geq 10^4$) (HR)	Referent	0.94 (0.42–2.10)	1.31 (0.63–2.73)
Clinical signs VAP, No. (%)	5 (14)	5 (16)	6 (18)
Clinical signs and chest radiograph, No. (%)	3 (9)	5 (17)	4 (12)
Clinical VAP (AB treatment), No. (%)	1 (3)	4 (14)	2 (6)
Sputum, No. (%)	11 (33)	9 (31)	11 (32)
Radiographic abnormality, No. (%)			
CDC	10 (28)	10 (31)	9 (26)
Harborview Medical Center	14 (39)	13 (41)	10 (29)
Bronchoscopy or mini–bronchoalveolar lavage procedures†			
No. of patients, No. (%)	5 (14)	8 (25)	5 (15)
No. of events	10	10	7
Positive lower respiratory cultures‡			
No. of patients, No. (%)	2 (6)	4 (13)	4 (12)
No. of events	4	4	4
Hospital-acquired pneumonia	3	2	1
Baseline colonization $>10^4$, No. (%)	26 (72)	20 (76)	26 (63)
Effect size, OR (95% CI)	Referent	0.64 (0.23–1.78)	1.25 (0.43–3.67)
Baseline colonization $>10^6$, No. (%)	8 (22)	4 (13)	13 (38)
Effect size, OR (95% CI)	Referent	0.50 (0.13–1.85)	2.17 (0.76–6.17)

Definition of abbreviations: AB = antibiotic; CDC = Centers for Disease Control; CI = confidence interval; ETT = endotrachel tube; HR = hazard ratio; PUC = polyurethane cuff; PUC-CASS = polyurethane cuff with continuous aspiration of subglottic secretions; OR = odds ratio; PVC = polyvinylchloride cuff; VAP = ventilator-associated pneumonia.

*Tracheal colonization is defined as aspirate growing a colony count $\geq 10^6$ cfu/ml; tracheal cultures were obtained until extubation or Day 7 of intubation.

†Some patients had more than one procedure performed.

‡Positive lower respiratory cultures from bronchoalveolar lavage, mini–bronchoalveolar lavage, or protected specimen brush.

Limitations

Tracheal colonization is an often-used surrogate end point because it precedes VAP development and appears to be in the causal pathway for VAP (25–27). We chose $\geq 10^6$ cfu per milliliter as the threshold value for comparison to maximize specificity regarding an invasive diagnosis of VAP (28).

Although unlikely, if paramedics were able to guess the ETT type by the end of the 4-week period, the integrity of the randomization was

Table 4. Other study end points

Variable	PVC-ETT (*n* = 36)	PUC-ETT (*n* = 32)	PUC-CASS-ETT (*n* = 34)
Duration of first intubation, mean (SD)	2.8 (3.7)	3.4 (4.1)	4.7 (11.7)
Days of mechanical ventilation, mean (SD)	4.5 (4.3)	5.6 (7.2)	6.5 (12.7)
Duration of ICU stay, median survival time	10.2	7.7	10.1
Duration of hospitalization, median survival time	22.1	19.5	23.8
Death, No. (%)	9 (25)	5 (16)	9 (26)

Definition of abbreviations: ETT = endotrachel tube; ICU = intensive care unit; PUC = polyurethane cuff; PUC-CASS = polyurethane cuff with continuous aspiration of subglottic secretions; PVC = polyvinylchloride cuff.

Table 5. Safety, adverse events, and serious adverse events

Variable	PVC-ETT (*n* = 36)	PUC-ETT (*n* = 32)	PUC-CASS-ETT (*n* = 34)
Tracheostomy, No.	3	4	3
Laryngeal score at extubation, mean (SD)	0.89 (1.48)	0.88 (1.23)	0.50 (0.86)
Dysphagia, No. (%)	6 (17)	4 (13)	2 (6)
Dysphonia, No. (%)	9 (25)	9 (28)	8 (24)
Stridor, No. (%)	1 (3.8)	1 (4.2)	0 (0)
Laryngeal injury at follow-up, No. (%)	7 (44)*	4 (25)†	5 (31)‡
SOFA score, mean (SE)	4.1 (0.55)	3.7 (0.57)	5.3 (0.56)
SAEs, No. (%)			
Deaths unrelated to device	9 (25)	5 (16)	9 (26)
Adverse events, No.			
Airways complications	1	1	—
Other complications	—	—	1

Definition of abbreviations: ETT = endotrachel tube; PUC = polyurethane cuff; PUC-CASS = polyurethane cuff with continuous aspiration of subglottic secretions; PVC = polyvinylchloride cuff; SAE = serious adverse event; SOFA = Sequential Organ Failure Assessment score.
*n = 18.
†n = 14.
‡n = 13.
—, no events.

still maintained because of the medical necessity of securing the airways.

Conclusions

A randomized trial of ETTs inserted during emergency intubation for the prevention of VAP is feasible and did not appear to carry heightened safety concerns. These preliminary data did not suggest different patterns of tracheal colonization or occurrence of VAP among the study groups. A larger trial to determine the efficacy of modified ETT to prevent VAP would be necessary. ■

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