Intensive Care Med (2006) 32:888–893
DOI 10.1007/s00134-006-0125-6

EXPERIMENTAL

Lorenzo Berra
Francesco Curto
Gianluigi Li Bassi
Patrice Laquerriere
Andrea Baccarelli
Theodor Kolobow

Antibacterial-coated tracheal tubes cleaned with the Mucus Shaver

A novel method to retain long-term bactericidal activity of coated tracheal tubes

Received: 4 June 2005
Accepted: 21 February 2006
Published online: 19 April 2006

Electronic supplementary material
The electronic reference of this article is http://dx.doi.org/10.1007/s00134-006-0125-6. The online full-text version of this article includes electronic supplementary material. This material is available to authorised users and can be accessed by means of the ESM button beneath the abstract or in the structured full-text article. To cite or link to this article you can use the above reference.

L. Berra (✉)
Massachusetts General Hospital,
Department of Anesthesia and Critical Care,
Boston MA, USA
e-mail: lberra@partners.org
Tel.: +1-617-7269367

F. Curto · G. Li Bassi · T. Kolobow
National Institutes of Health, Section on Pulmonary and Cardiac Assist Devices, Pulmonary Critical Care Medicine Branch, Department of Health and Human Services, Bethesda MD, USA

P. Laquerriere
National Institutes of Health, Division of Bioengineering and Physical Science, Office of Research Services, Department of Health and Human Services,
Bethesda MD, USA

A. Baccarelli
National Institutes of Health, Genetic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute,
Bethesda MD, USA

Abstract *Objective:* To assess the long-term benefit from antibacterial coatings of the tracheal tube (ETT), and to keep clean the lumen of the ETT. *Design:* Experimental animal study. *Setting:* USA National Institutes of Health. *Subjects:* Twelve sheep. *Interventions:* Twelve ETTs were internally dip-coated with a silver-sulfadiazine in polyurethane. We developed a concentric inflatable silicone rubber "razor", the Mucus Shaver (MS), to shave the ETT lumen free of mucus. In a single pass, we cleaned all mucus from the internal surface of the ETT. Control group: Five intubated sheep were mechanically ventilated for 72 h. The ETT was suctioned every 6 h. Study group: Six sheep were intubated and mechanically ventilated for 72 h. The ETT was suctioned and cleaned with the MS every 6 h. An additional sheep was intubated and mechanically ventilated for 168 h. Bacteriologic studies and scanning electron microscopy were performed to assess bacterial colonization and thickness of secretions on the internal surface of the ETT. *Measurements and main results:* In the control group, the ETT was always heavily colonized: median debris thickness was 380 μm, range 270–550 μm. In the study group, there was no colonization and no secretions in the ETT, except for three ETT that were colonized solely at the very tip. *Conclusions:* Silver-based coating of ETT cleaned with the MS every 6 h significantly reduces accumulation of mucus/secretion and bacterial growth within the ETT following 72 h of mechanical ventilation.

Keywords Endotracheal tube · Tracheal tube suctioning · Bactericidal agents · Mucus Shaver · Mechanical ventilation · Bacterial biofilm

Introduction

After a few days of mechanical ventilation (MV), the lumen of the endotracheal tube (ETT) is coated with a thick bacterial biofilm, which is a potential source for bacterial colonization of the lower respiratory tract and ventilator-associated pneumonia (VAP) [1, 2]. Accumulation of mucus/secretions on the interior of the ETT effectively lowers the cross section of the ETT and increases significantly the work of breathing in intubated patients, who then require increased MV support, with prolonged intubation and ICU stay [3, 4, 5, 6, 7].

Bactericidal-coated ETTs offer promise to prevent VAP [8]. Recent studies showed that such ETTs may retard bacterial colonization of the ETT, but ultimately become heavily colonized [9]. We have previously designed a novel device, the Mucus Shaver[1] (MS), to keep the internal surface of the ETT free from mucus secretions [10]. We now proceed, in studies in sheep, to investigate whether or not keeping the internal surface of a silver-based coated ETT clean by regular use of the MS, may retain the tube's full bactericidal effects.

Materials and methods

This study was approved and conducted at the National Institutes of Health animal research laboratory, Bethesda, MD, USA [11].

Animals

This study involved 12 sheep.

Study group: Six sheep were intubated with silver-sulfadiazine-coated ETTs and MV for 72 h; an additional sheep was MV for 168 h. Following suctioning the ETT every 6 h, we introduced the MS into the ETT, advanced it as far as the tip of the ETT, inflated the balloon, and rapidly retrieved the balloon with all mucus entrained [10]. Weights of secretions recovered from the ETT with the MS were recorded.

Control group: Five sheep were intubated with silver-sulfadiazine coated ETTs and mechanically ventilated for 72 h. Every 6 h, the ETT was suctioned through a standard 14-Fr suction catheter.

The final tracheal suction and/or mucus shaving were performed 6 h before election euthanasia of the sheep. All sheep in both groups were prone, in a gantry, and rotated every 6 h from one to the other semi-lateral body position, to maintain orientation of the ETT horizontal [12].

ETT coating

We prepared a dispersion containing silver-sulfadiazine and polyurethane in *N*,*N*-dimethylacetamide. A standard ETT with internal diameter (ID) of 8 mm was inserted into a hollow transparent acrylic tube to keep it straight, and the tip of the ETT was immersed in the dispersion, which was rapidly aspirated up to the level of the connector piece. Immediately thereafter, the ETT was drained for 2–4 s and placed horizontally in a rotational device, through which a gentle stream of air was passed to facilitate solvent evaporation. The coated ETT was then removed from the plastic tube and sterilized with ethylene oxide gas (see electronic supplementary material, S.F1).

Mucus Shaver

As previously described [10], to clean adult-size standard ETTs, we attached to a 3.0-mm outside diameter (OD; 2.0 mm ID), 28-cm-long plastic tube (Hytrel, E.I. Dupont) a 2-cm-long injection-molded silicone rubber (GE CE-4524) tube (ID 3.5 mm; OD 4.5 mm) with two or more 1.0-mm-wide and 0.5-mm-high "shaving rings" fitted. For added safety, we incorporated into the distal end a radio-opaque stainless steel bead, attached to a fine braided stainless steel wire, to facilitate retrieval in the unlikely event that an event such as tear, adhesive failure, or abuse caused loss of the inflatable MS (see electronic supplementary material, S.F2 and S.F3).

Bacteriologic studies

Endotracheal tube sampling and microbiological studies were performed as described previously [8].

In brief, three samples of ETT secretions were collected at 6 cm (ETT1), 16 cm (ETT2) and 26 cm (ETT3) from the ETT connector piece for quantitative bacteriologic studies. When no mucus/secretions were grossly visible, a cotton swab was dragged along the lumen of the ETT for qualitative bacteriologic studies (ETT swab).

A 1-cm-long section of the distal ETT (28–29 cm from the connector piece) was cut and the lumen of the ETT was studied with a scanning electron microscope (SEM).

Animal preparation and care

Sheep were anesthetized (induction: ketamine, 7 mg kg^{-1}; maintenance: sodium pentobarbital, 2 mg kg^{-1} h^{-1}), paralyzed (pancuronium bromide, 0.1 mg kg^{-1} h^{-1}), and mechanically ventilated (volume-controlled ventilation: tidal volume 8–10 ml kg^{-1}, respiratory rate 14–25 breaths min^{-1}, PEEP 5 cmH_2O, FiO_2 0.4), using a Servo 900C ventilator (Siemens Elema, Solna, Sweden). $PaCO_2$ was kept between 35–45 mmHg; FiO2 was adjusted to maintain PaO_2 above 80 mmHg, with peak airway pressure under 20 cm H_2O. A heated (37.5°C) respiratory humidifier

[1] Patent applied for by National Institutes of Health

(MR850 JHU; Fisher&Paykel, Auckland, New Zealand) was connected to a sterile heated infant ventilator circuit (Isothermal respiratory circuit, circuit MR850, Allegiance Healthcare Corporation, IL, USA). Hemodynamic and respiratory parameters, body temperature, blood gas analysis, blood cell counts, urinary output, chest X-ray films, fluid replacement, and parenteral nutrition were monitored/administered as previously described [12]. At the end of the study, sheep were killed with an overdose of sodium pentobarbital. The autopsy was necessary to: (1) visually inspect and record with photographs the trachea, bronchi, lungs, and abdominal organs for adverse reaction due to the coating; (2) perform histological studies on tissue samples of the trachea, bronchi and lungs; (3) store samples from trachea, bronchi, lungs, and blood for possible leaching studies.

Statistical analysis

All analyses were conducted using nonparametric methods. We tested for differences between the two study groups using the Wilcoxon two-sample test and Fisher's exact test, respectively, for continuous and categorical variables. A two-sided p value of 0.05 was considered statistically significant (software used: Stata 8.0).

Results

Clinical parameters

All 12 young female Dorset sheep (median body weight 35 kg, range 28–37 kg) were considered healthy based on

Table 1 Bacteriologic studies and scanning electon microscopy of the coated ETTs

	Sheep #	MV[a]	Bacterial species[b]	ETT 1[c] cfu/g	ETT2[d] cfu/g	ETT 3[e] cfu/g	ETT 1[f] swab	ETT 2[g] swab	ETT 3[h] swab	SEM thickness[i] μm
	1	72	*Ps*	0	0	1.9×10^7				380
	2	72	*Kp*	5.9×10^9		0				450
			Ap	5.6×10^7	1.1×10^9					
			Ps		4.4×10^5					
	3	72	*Sa*	9.3×10^6	2.0×10^7	1.0×10^7				320
Control			*βHS*	9.3×10^6	2.0×10^7	1.0×10^7				
group	4	72	*EC*	4.0×10^2	6.5×10^2	2.3×10^2				550
			Pa	1.3×10^5	5.0×10^4					
			αS	6.0×10^4	5.0×10^4	8.5×10^3				
			Mo	6.0×10^3						
	5	72	*Pa*	3.8×10^7	4.8×10^7	3.7×10^7				270
	median			1.0×10^7	4.0×10^7	1.0×10^7				380
	range			0–6.0×10^9	0–1.1×10^9	0–3.7×10^7				270–550
	6	72	*Sa*	0	0	4.0×10^5				10
	7	72		ns	0	0	0			15
	8	72		0	ns	0		0		8
	9	72	*Co*	ns	ns	9.8×10^7	0	0		0
Study	10	72		ns	ns	ns	0	0	0	0
group	11	72	*Co*	ns	ns	4.3×10^7	0	0		0
			Ap			3.9×10^7				
	12	168	*Sa*	ns	ns	ns	0	0	0	0
	median			0	0	0				0
	range			0–0	0–0	0–9.8×10^7				0–15
	p-value[j]			0.007	0.007	0.56				0.004

[a] Hours of mechanical ventilation
[b] Abbreviation: *Ap* = *Arcanobacterium pyogenes*, *Co* = *Corynebacterium*, *EC* = *E. Coli*, *Pa* = *Pasteurella*, *Pa* = *Pseudomonas aeruginosa*, *Sa* = *Staphylococcus aureus*
[c] Bacterial count (cfu/g) of secretions retrieved at 6 cm from the ETT connector piece. Abbreviation: ns = no secretion to sample
[d] Bacterial count (cfu/g) of secretions retrieved from 16 cm from the ETT connector piece. Abbreviation: ns = no secretion to sample
[e] Bacterial count (cfu/g) of secretions retrieved at 26 cm from the ETT connector piece. Abbreviation: ns = no secretion to sample
[f] Qualitative bacteriologic studies (cotton swab) of lumen of the ETT at 6 cm from the ETT connector piece. Note: 0 = no growth
[g] Qualitative bacteriologic studies (cotton swab) of lumen of the ETT at 16 cm from the ETT connector piece. Note: 0 = no growth
[h] Qualitative bacteriologic studies (cotton swab) of lumen of the ETT at 26 cm from the ETT connector piece. Note: 0 = no growth
[i] Microns (μm) of thickness of the bacterial biofilm, or proteinaceuos accumulation on the internal surface of the ETT at 29–29 cm from the connector piece
[j] p-value for difference between the Control group and the Study group (Wilcoxon (Mann-Whithey) ranksum test)

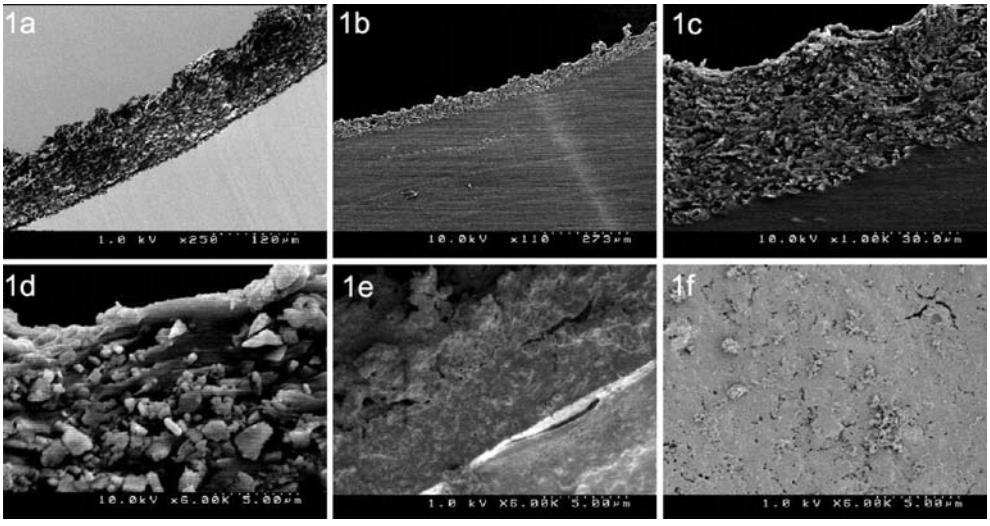

Fig. 1 **a** Cross section of a new (never used) coated ETT with a silver-based dispersion in polyurethane. Thickness of the coating is approximately 100 μm (magnification × 250). **b** Cross section of a coated ETT after 168 h of MV, cleaned with the MS (sheep 12). Note total absence of secretions (magnification × 110). **c** Higher magnification of the same ETT (magnification × 1000). **d** There is no accumulated material on the surface. The granular nature of the silver dispersion in polyurethane is readily apparent (magnification × 6000). **e** Cross section of coated ETT cleaned with standard suctioning (no MS) after 72 h of MV (sheep 3), with thick mucus layer on the coating (magnification × 6000). **f** View from above of same ETT, with bacterial colonies on top of the mucus layer that uniformly covered the whole surface of the coated ETT (magnification × 6000)

clinical findings, laboratory data, and chest X-ray films. PaO_2/FiO_2, body temperature, and white blood cell counts were unremarkable throughout the study. At autopsy, no gross abnormalities were found in any sheep of either group, and the tracheal mucosa appeared unremarkable in all.

Appearance, microbiological findings and SEM studies of the ETT

Control group: On visual inspection, dense, sticky mucus/secretions covered the entire length of the ETT. The thickest mucus was always observed in the dependent (bottom) parts of the ETT, most likely due to gravitational forces. Secretions were colonized with pathogenic and non-pathogenic bacteria in 12 of 15 samples (5 of 15 were multi-bacterial colonization) (Table 1). On SEM, the tip of the ETT had a thick layer (median 380 μm, range 270–550 μm) of adherent bacterial biofilm on the ETT surface (Fig. 1e, f).

Study group: on visual inspection the ETT appeared clean; only few secretions could be retrieved from the tip (ETT3) of 5 of 7 ETT; and both from 2 of 7 ETT in the center (ETT2), and in the proximal part of the ETT (ETT1) (Table 1). Secretions, when present, accumulated only on the dependent part of the ETT, and appeared to be thin, fluid, clear, not adherent to the ETT. Three of 21 ETT samples showed bacterial growth; all 3 were retrieved from the very tip of the ETT (ETT3) (Table 1).

Overall, 4 of 5 ETTs in the control group and 0 of 7 ETTs in the study group were colonized at 6 cm and 16 cm from the ETT connector ($p = 0.01$); 4 of 5 ETTs in the control group and 3 of 7 ETTs in the study group were colonized at 26 cm ($p = 0.29$), the tip of the ETT. SEM showed complete absence (or presence of a layer only a few micrometers thick) of proteinaceous material ($p = 0.004$, versus control group for thickness of the mucus layer); bacteria were never seen (Fig. 1b–d, ETT SEM of sheep 12, ventilated 7 days. Note absence of all deposit, and bacterial growth; the ETT appeared new on visual inspection).

The median (range) of the wet and dry secretions retrieved with suctioning and MS were, respectively, 229.5 mg (44–1064 mg) and 28.6 mg (6–571 mg). The total time (from disconnection from the ventilator, to reconnection) required to clean the ETT with the MS averaged 5–10 s. No complications were associated with this procedure.

Discussion

Several studies have suggested that substantial narrowing of the intraluminal diameter of ETTs by accumulation of debris was related to the duration of intubation and to the presence or otherwise of VAP [1, 2, 6, 8]. Such narrowing may significantly increase the likelihood of ETT occlusion and increase airway resistance, which can contribute to failure to be weaned off mechanical ventilation [3–7].

Methods now universally used to clean the ETT are inadequate to remove the bulk of mucus. In our studies we used healthy sheep. Based on previous studies [12], we decided to perform tracheal suctioning every 6 h, different from patients where tracheal suction is performed every

1–3 h. Clinical studies have shown that narrowing of ETT lumen due to accumulation of secretions remains common in patients mechanically ventilated [6, 7].

Mucus and secretions within the ETT after as little as 1 day of MV are almost always heavily colonized with bacteria, in spite of the best efforts of attending staff [5, 6, 7, 10, 12, 13]. It follows that preventing heavy bacterial colonization of the ETT through bactericidal coating of the lumen, alone, is of only marginal, temporary benefit to the patient.

We have previously shown benefits of periodical use of the MS to keep standard ETTs clean of mucus/secretions [10]. In studies reported here, we showed that coated ETTs, when cleaned with the MS, retained excellent bactericidal properties throughout the study, as there was no accumulation of secretions or formation of bacterial biofilm. Hence, the use of the coated ETT, combined with its meticulous cleaning with the MS, prevented all bacterial growth within the proximal and middle parts of the ETT in studies lasting up to 72 h of MV.

Neither deep suctioning nor the MS kept the area below the cuff perfectly clean, as secretions invariably accumulated in the area below the cuff and reached the most distal part of the ETT (tip), from which we retrieved at autopsy small amounts of mucus in the study group sheep with bacterial growth in three of seven sheep.

Our studies showed that, by cleaning the bactericide-coated ETTs with the MS, most bacterial colonization of the ETT during the course of 72 h of MV was prevented. The internal surface of the ETT remained always free of colonization, and in only three sheep was the very tip of the ETT colonized.

Clinical studies [1, 2, 6] have provided evidence that the ETT might be a risk factor in the development of VAP, because heavily colonized biofilm fragments might be translocated from within the ETT to the trachea, the tracheo-bronchial tree, and the lungs. ETTs coated with bactericidal agents may prevent bacterial colonization and biofilm formation on its internal surface. Laboratory studies [9, 14] have shown that silver-based compounds can prevent/delay bacterial colonization of ETTs, but clinical studies are required to demonstrate whether or not such ETTs coated with bactericidal agents can reduce the incidence of VAP.

This study has some limitations. First, it was performed in sheep, and only one animal was mechanically ventilated for as long as 7 days. To confirm these laboratory observations, clinical studies are planned in patients undergoing prolonged intubation to determine benefit of cleaning bactericide-coated ETTs with the MS. Such studies will help determine whether clinical benefits can occur, such as shorter duration of MV, prevention of ETT narrowing and occlusion, and prevention of VAP. Second, we used silver-sulfadiazine in polyurethane-coated ETTs in this study; hence, our result may not be applicable to different silver-based coatings. Third, this study lacks a control group using the MS, and standard ETTs. However, we have since reported use of the MS [10] in animal studies, and we have shown absence of biofilm formation, on the internal surface of standard ETTs after 72 h of MV. However the small added cost of a silver-sulfadiazine-coated ETT, combined with the evidences that standard ETTs are rapidly colonized, suggests that it would be beneficial to combine the MS and silver-coated ETTs.

The reduction in mucus secretions and bacterial growth in the coated ETT regularly cleaned by the MS makes us believe it may be possible to improve the care of patients who require intubation and MV.

Acknowledgements. The authors thank Martha Vaughan, MD (Deputy chief, Pulmonary and Critical Care Medicine Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA) and Joel Moss, MD, PhD (Chief, Pulmonary and Critical Care Medicine Branch, National Heart, Lung and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA) for critical review of the manuscript, and the staff of the Laboratory for Animal Medicine and Surgery, National Heart, Lung and Blood Institute, National Institutes of Health, and of the Veterinary Resources Program, National Institutes of Health, for assistance throughout the animal studies and bacteriologic analysis.

References

1. Adair CG, Gorman SP, Feron BM, Byers LM, Jones DS, Goldsmith CE, Moore JE, Kerr JR, Curran MD, Hogg G, Webb CH, McCarthy GJ, Milligan KR (1999) Implications of endotracheal tube biofilm for ventilator-associated pneumonia. Intensive Care Med 25:1072–1076
2. Inglis TJ, Millar MR, Jones JG, Robinson DA (1989) Tracheal tube biofilm as a source of bacterial colonization of the lung. Clin Microbiol 27:2014–2018
3. Shapiro M, Wilson RK, Casar G, Bloom K, Teague RB (1986) Work of breathing through different sized endotracheal tubes. Crit Care Med 14:1028–1031
4. Heyer L, Louis B, Isabey D, Lofaso F, Brochard L, Fredberg JJ, Harf A (1996) Noninvasive estimate of work of breathing due to the endotracheal tube. Anesthesiology 85:1324–1333
5. Glass C, Grap MJ, Sessler CN (1999) Endotracheal tube narrowing after closed-system suctioning: prevalence and risk factors. Am J Crit Care 8:93–100
6. Shah C, Kollef MH (2004) Endotracheal tube intraluminal volume loss among mechanically ventilated patients. Crit Care Med 32:120–125

7. Boque MC, Gualis B, Sandiumenge A, Rello J (2004) Endotracheal tube intraluminal diameter narrowing after mechanical ventilation: use of acoustic reflectometry. Intensive Care Med 30:2204–2209
8. Berra L, De Marchi L, Yu ZX, Laquerriere P, Baccarelli A, Kolobow T (2004) Endotracheal tubes coated with antiseptics decrease bacterial colonization of the ventilator circuits, lungs, and endotracheal tube. Anesthesiology 100:1446–1456
9. Olson ME, Harmon BG, Kollef MH (2002) Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. Chest 1:863–870
10. Kolobow T, Berra L, Li Bassi G, Curto F (2005) A novel system for the complete removal of all secretions from within the tracheal tube: "The Mucus Shaver". Anesthesiology 102:1063–1065
11. Guide for the care and use of laboratory animals (1996) Washington D.C., National Academy Press, pp 1–80
12. Panigada M, Berra L, Greco G, Stylianou M, Kolobow T (2003) Bacterial colonization of the respiratory tract following tracheal intubation-effect of gravity: an experimental study. Crit Care Med 31: 729–737
13. Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report, CDC/MMWR: Guidelines for Prevention of Nosocomial Pneumonia. January 03, 1997 / 46(RR-1);1–79. Available on line at: http://www.cdc.gov/mmwr/preview/mmwrhtml/00045365.htm Accessed January 8, 2004
14. Pacheco-Fowler V, Gaonkar T, Wyer PC, Modak S. (2004) Antiseptic impregnated endotracheal tubes for the prevention of bacterial colonization. J Hosp Infect 57:170–174
15. Girou E, Buu-Hoi A, Stephan F, Novara A, Gutmann L, Safar M, Fagon JY (2004) Airway colonization in long-term mechanically ventilated patients Effect of semi-recumbent position and continuous subglottic suctioning. Intensive Care Med 30:225–233