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Selective decontamination of subglottic area in mechanically ventilated patients with multiple trauma

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Abstract *Objective:* To determine whether selective decontamination locally in the subglottic area (SDSA) reduces tracheal colonization and prevents ventilator-associated pneumonia (VAP) in patients with multiple trauma. *Design and setting:* A prospective randomized, controlled, clinical study in a 14-bed general intensive care unit of a university hospital. *Patients:* 79 consecutive multiple trauma patients admitted to the ICU who were expected to be mechanically ventilated for more than 5 days; 61 patients completed the protocol. *Intervention:* Patients were randomly assigned to receive SDSA using a continuous infusion of a suspension containing three nonabsorbable antibiotics (polymyxin, tombramycin, and amphotericin B; *n*=30) or placebo (*n*=31). *Measurements:* The incidence of bronchial and gastric colonization and the number of cases of VAP were recorded. Gastric fluid and tracheal secretion cultures were obtained soon after intubation and thereafter every 4 days. Etiological diagnosis of VAP was based on samples taken by a specific protected double catheter set. *Results:* VAP developed in 5 of 30 (16.6%) patients receiving SDSA and 16 of 31 (51.6%) patients receiving placebo. Negative bronchial secretion cultures were found in 14 of 30 (46.6%) patients in the SDSA group and in only 3 of 31 (9.6%) patients in the control group. No patient with negative bronchial secretion culture developed VAP. No significant differences in outcome were found. *Conclusions:* The SDSA is an effective and safe type of chemoprophylaxis against tracheal colonization and can significantly reduce the incidence of VAP in mechanically ventilated patients with multiple trauma.

Keywords Ventilator-associated pneumonia · Mechanical ventilation · Selective decontamination · Chemo-prophylaxis · Multiple trauma

Introduction

Ventilator associated pneumonia refers specifically to bacterial nosocomial pneumonia that may develop in mechanically ventilated patients. VAP is the most common infection documented in intensive care medicine with reported incidence rates of 3–52% depending on the patient population studied and the diagnostic criteria used [1, 2]. Although debate is ongoing about the mortality attributable to VAP, there is no doubt that it causes significant morbidity by increasing the duration of mechanical ventilation and the hospital stay [3]. VAP that develops within 48–96 h after tracheal intubation is usually termed early onset pneumonia while VAP that occurs after this period is considered as late onset pneumonia. Pneumonia that develops during the first 48 h after initiation of mechanical ventilation is not considered as VAP.

The pathogenesis of VAP is usually associated with two important processes: bacterial colonization of the

aerodigestive tract and aspiration of contaminated fluid into the lower airways [4]. Therefore the main strategies aimed at preventing VAP usually focus on reducing the burden of bacterial colonization in the aerodigestive tract and/or decreasing the incidence of aspiration [5]. In particular, subglottic secretion drainage, semirecumbent position and selective decontamination of the digestive tract (SDD) have been used to prevent VAP.

The aim of this study was to determine whether local selective decontamination in the subglottic area (SDSA) reduces tracheal colonization and prevents ventilator associated pneumonia in mechanically ventilated patients with multiple trauma.

Patients and methods

Patients

Eligible for the study were 79 consecutive patients with multiple trauma admitted to the intensive care unit (ICU) who required intubation and had an expected time for mechanical ventilation exceeding 5 days. The study was performed in the 14-bed polyvalent ICU of a 750-bed university hospital and was approved by the Scientific Committee of the University Hospital of Ioannina. Informed consent was obtained from the patients or the nearest next of kin. Inclusion criteria were the absence of cardiopulmonary disease, negative chest radiography, and a PaO_2/FIO_2 ratio higher than 300 mmHg. Eighteen patients were excluded: seven were extubated, four developed pneumonia during the first 48 h of mechanical ventilation, one underwent tracheotomy, and six died. The study population thus consisted of 61 patients.

Study design

Consecutive admissions to the intensive care unit were randomized to receive either SDSA (n=40) or placebo (n=39). Of the 61 patients completing the study 31 received SDSA and 30 received placebo. Their baseline characteristics are presented in Table 1. The patients were intubated either in the ICU or in the Emergency Department using the same type of endotracheal tube (HI-LO Evac, Mallinckrodt Laboratories, Athlone, Ireland) which is equipped with an additional lumen for improved access to the subglottic area. The lumen is integrated into the wall of the tracheal tube ending in a dorsal opening just above the cuff. The attending physician selected the size of each endotracheal tube. Patients remained intubated and mechanically ventilated for 2 weeks (13±5 days in the SDSA group, 14±3 days in the control group). One patient in the SDSA group and five in the control group required long-term (more than 24 h) noninvasive mechanical ventilatory support after extubation.

SDSA was administered by continuous infusion of a suspension containing 73 mg polymyxin E, 73 mg tobramycin, and 500 mg amphotericin B in 500 ml 0.9 saline solution at an infusion rate of 2 ml/h in the subglottic area for the entire period of the study (Fig. 1). The minimal cuff volume and pressure necessary to prevent air leaking around the cuff were used. The infused fluid was removed by suction of the oropharygeal area. Suction was performed frequently, at least once per hour, and in some cases continuously. All patients had an nasogastric tube in place and the body position was, if possible, semirecumbent at a 30–45° angle.

Gastric and tracheal secretion cultures were obtained soon after intubation and thereafter every 4 days. Tracheal secretions were taken by bronchial suction in a sterile container (Mucus Specimen Trap, Pennine, Healthcare, Derby, UK). The suction catheter was placed at the level of the carina. The distance of the carina from the tip of the endotracheal tube was measured by chest radiography. Gastric secretions were also collected in a sterile container by suction via nasogastric tube in the morning just before the beginning of enteral nutrition. Regarding patients in whom VAP was suspected, the diagnosis and cause were confirmed by a quantitative culture of secretions in a protected specimen collected by a double catheter set (telescoping plugged catheter) either blind or bronchoscopically. The decision as to which patients had VAP was made at daily meetings of the infection team, including a chest physician, a radiologist, and a physician with experience in infectious diseases (blind to the patient's group assignment). At this meeting the attending physician presented the patient's clinical and laboratory data, and the team decided on the presence or absence of VAP.

Data collection and definition

The following characteristics were prospectively recorded: age, sex, Glasgow Coma Score, and severity of illness based on the Acute Physiology and Chronic Health Evaluation II [6]. The fol-

Table 1 Baseline characteristics of patients receiving selective decontamination locally in the subglottic area (*SDSA*) and controls at the time of ICU admission and risk factors for ventilator-associated pneumonia (*VAP*) during study period (*APACHE II* Acute Physiology and Chronic Health Evaluation II)

	SDSA (n=31)	Controls (n=30)	p
Age (year)	39.1±19.42	36.86±19.00	NS
Sex: M/F	24/77	23/76	NS
APACHE II	18.06±3.8	19.12±4.5	NS
Glasgow Coma Scale	7.6±2.8	8.1±2.4	NS
Days on tracheal intubation	13±5	14±3	NS
Days on mechanical ventilation before VAP	9.1±4.3	6.7±3.9	<0.02
Lung contusion	3 (10%)	2 (6.5%)	NS
Mortality	5 (16%)	7 (23%)	NS
Mortality of VAP patients	2/5 (40%)	3/7 (43%)	NS
Risk factors for VAP			
Supine position	0 (0%)	1 (3.2%)	NS
Receiving antacids, H_2 blockers or sucralfate	8 (26%)	6 (19%)	NS
Receiving antibiotics at randomization or prior to developing VAP	6 (20%)	7 (22%)	NS

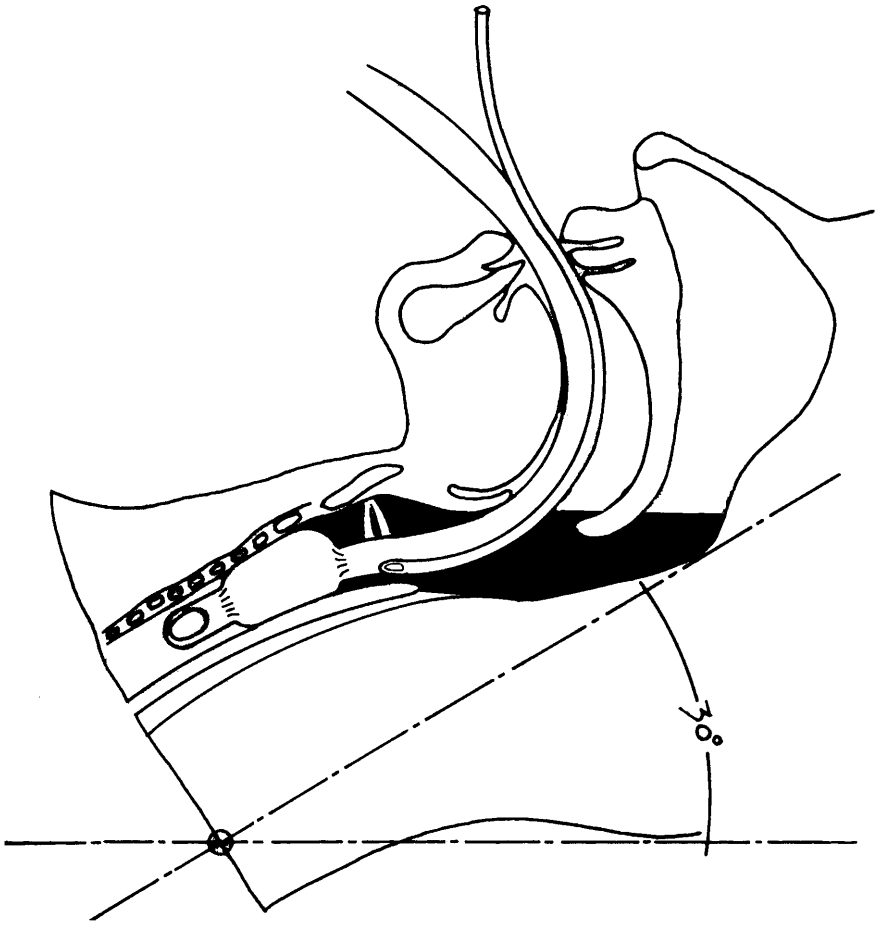

Fig. 1 Schematic diagram depicting the endotracheal tube, which is equipped with an additional lumen ending in the subglottic area

lowing risk factors for VAP were also recorded: the occurrence of a witnessed aspiration event or reintubation, the supine positioning, and the administration of drugs such as H_2 blockers or sucralfate, paralytic agents and antibiotics during study period. Six patients in the SDSA group and seven in the control group received antibiotics for infections other than VAP, predominantly urinary tract infection (amoxicillin/clavulanate, fluoroquinolones, gentamicin, ticarcillin/clavulanate).

VAP was suspected in the presence of new and persistent pulmonary infiltrates in addition to two of the following criteria: body temperature>38.3°C, leukocytosis (>12,000 leukocytes/mm^3) or leukopenia (<4,000 leukocytes/mm^3) and purulent tracheal secretions. The diagnosis of VAP was confirmed by quantitative cultures.

Follow-up was the period of the patient's stay in the ICU.

Microbiological processing

A bronchoscopic or blind protected sample was taken on the day of suspicion of pneumonia by a specific double catheter set (Compicath Laboratoire Plastimed, Saint-Leu-La Foret, Cedex, France). The catheter was inserted through the endotracheal tube into the pulmonary tract in a wedged position. The catheter was pulled back 1–2 cm, and the inner catheter was advanced through the slit of the proximal hilt thus expelling the distal polyethylene glycol plug. Then the hilt was removed. Three brief aspirations were performed using a 10-ml sterile syringe connected to the inner catheter. The collected volume of secretions retrieved by this protected method was 2×10^{-3}–10^{-2} ml. The inner catheter was withdrawn into the outer sheath, and the whole set was removed. The tip of the outer sheath was wiped with a sterile gauze and cut with sterile scissors. The inner catheter was pushed out and flushed with saline solution to obtain 1 ml in a tube. This results in a 100- to 1000-fold dilution. The sample was transferred to the microbiology and cultured laboratory for aerobic and anaerobic micro-organisms. A growth of at least 10^3 cfu/ml was considered significant, corresponding to an initial concentration of 10^5–10^6 bacteria/ml in the retrieved secretions. This technique allows acquisition of lower respiratory tract specimens similar in amount comparable to brushing and is at least as accurate as the technique with protected catheter brushing [7].

Statistical analysis

All data are expressed as mean±SD. The qualitative variables were compared by the χ^2 test. Continuous variables were compared using Student's *t* test. Results were considered significant at $p<0.05$. We calculated that about 30 patients per group would be needed to determine statistical significance between two groups at a power of about 0.8 with $\alpha=0.05$.

Results

VAP developed in 21 of the 61 patients (cumulative incidence 34.4%), 5 of the 31 (16%) patients receiving

Table 2 Characteristics of pneumonia in study patients

	SDSA (*n*=31)	Controls (*n*=30)	p
Cumulative incidence[a]	5/31 (16%)	16/30 (53%)	<0.01
Incidence density[b]	12.40	36.44	<0.01
Early onset pneumonia[c]	3/5 (10%)	7/16 (23%)	NS
Late onset pneumonia[d]	2/5 (6%)	9/16 (30%)	NS
Micro-organisms isolated from 21 patients with VAP			
Gram-positive cocci	3/5 (10%)	6/16 (20%)	NS
Gram-negative cocci	2/5 (6%)	8/16 (26%)	NS
Pseudomonas aeruginosa	0/5	1/16	NS
Enterobacteriacae	1/5	6/16	NS
Acinetobacter	1/5	1/16	NS
Uncertain	0/5	2/16	NS
Negative tracheal cultures	14/31 (45%)	3/3 (10%)	<0.001
Positive gastric cultures	8/31 (26%)	10/30 (33%)	NS
Identical micro-organisms in VAP and tracheal cultures	3/5 (10%)	12/16 (40%)	<0.05

[a] Percentage of patients with pneumonia
[b] Episodes of pneumonia/1000 ventilator days
[c] Pneumonia that occurs within 48–96 h after tracheal intubation
[d] Pneumonia that occurs after 96 h from tracheal intubation

SDSA and 16 of the 30 (53%) patients receiving placebo (p<0.01) (Table 2). Negative bronchial secretion cultures were found in 14 of the 31 (45%) SDSA patients and only 3 of 30 (10%) control patients (p<0.001). None of the patients with negative bronchial secretion cultures developed VAP. The micro-organisms isolated in patients with VAP were the same as those previously isolated from tracheal secretions in 85% of the cases. No significant difference in outcome was found between the two groups. The duration of mechanical ventilation prior to development of VAP was 9.1±4.3 days in the SDSA group and 6.7±3.9 days in the control group (p=0.02). The length of stay in the ICU was shorter in SDSA patients than in controls (16±7 vs. 23±8 days, p<0.05). No resistance to micro-organisms due to polymyxin, tobramycin, or amphotericin B was observed.

Discussion

In this randomized controlled study we found that SDSA in mechanically ventilated multiple trauma patients reduced tracheal colonization by 46% and the incidence of VAP by 70%. The length of stay in the ICU was also reduced, but the duration of mechanical ventilation was not affected. There is no clear explanation for this discrepancy, although one possible explanation is that more control patients required noninvasive mechanical ventilation, and that this was the reason for a longer stay in the ICU.

Because leakage of infused antibiotic suspension around the cuff is quite possible, the reduction in tracheal colonization may simply reflect the difficulty of microbes to grow in an environment with antibiotics. However, the concentration of tobramycin in tracheal secretions was at a nondetectable level.

It was not possible for the diagnosis of VAP to be incorrect because it was based on established clinical criteria and was always confirmed by quantitative cultures. Only in two cases in the placebo group was the causative agent of VAP uncertain, meaning that two micro-organism were found in more than 10^3 cfu/ml. Patients in whom the diagnosis of pneumonia was problematic, for example, patients with acute lung injury (PaO_2/FIO_2<300 mmHg), were excluded from the study.

Despite an increased understanding of the pathogenesis of VAP, prevention remains a challenge. Independently of the actual source of the pathogenic bacteria producing VAP (exogenous or endogenous), the crucial point in the pathogenesis is the aspiration of contaminated secretions accumulated in the subglottic area just above the cuff of the tracheal tube. In recent years subglottic secretion drainage has been used as a preventive method [8, 9, 10]. The subglottic fluid is drained along the channel with suction. This can reduce but not eliminate the volume of fluid aspirated into the lungs. Such a method reduced the incidence of VAP from 29.1% to 13% with intermittent drainage [8] and from 32.5% to 18.4% with continuous drainage of the subglottic space [9]. This preventive method has roughly the same cost as SDSA. SDSA reduced VAP by 70% and subglottic suction by 45–55% compared to controls, but it cannot be concluded whether SDSA is more effective than subglottic suction since these two techniques were not compared in the present study.

Gastric colonization was found in one of three to four of the study population. No relationship was observed between the colonized micro-organisms in the gastric content and the micro-organisms which caused VAP. These findings do not support a significant role for gastric colonization in the development of VAP, and they

are in agreement with those of Bonten and coworkers [11].

Keeping patients in a semirecumbent position may be helpful in reducing nosocomial pneumonia, as it has previously been demonstrated that this position prevents aspiration and thus the passage of bacteria into the airways [12]. In our study the majority of patients were placed in a semirecumbent position, maintaining the advantage of that position.

Among the more common but still controversial pharmacological strategies for preventing VAP is selective digestive decontamination. It consists of non absorbable antibiotics applied locally to the oropharynx and through the nasogastric tube to the stomach [13]. In many trials treatment with systemic antibiotics has been added in the first days to prevent early infections The concept of SDD was developed by Stoutenbeck et al. [13] in the early 1980s following the observation that one particular group of pathogens was responsible for most episodes of pneumonia. Two main concepts have evolved for the prophylaxis of infections by SDD. First of all, it reduces aerobic gram-negative rods and secondly, it has no effect on anaerobic gut flora. Since its more widespread introduction in the early 1980s, SDD has been assessed by nearly 50 controlled trials and has been the subject of numerous meta-analyses and systematic reviews [14, 15, 16, 17, 18]. A recent meta-analysis did conclude that SDD combining topical and systemic antibiotics can reduce respiratory tract infections and overall mortality in critically ill patients [14]. However SDD using only non enterally absorbable antibiotics does not appear to affect mortality [17]. The effect may be more prominent for certain patient populations such as surgical patients [16]. Nevertheless, despite its extensive evaluation, the use of SDD remains controversial because of concern regarding increases in colonization rates with multi-resistant pathogens and the cost associated with more wide-spread antimicrobial use [14, 19, 20]. Furthermore, beneficial effects on the duration of mechanical ventilation, ICU stay, antibiotics used and improved cost-effectiveness have not been shown unequivocally [21, 22]

Our method is a specific type of selective decontamination of a small but crucial area in the pathogenesis of VAP, the subglottic area just above the tracheal tube cuff using the classic SDD suspension consisting of three nonabsorbable antibiotics. This type of regional decontamination has the advantage of leaving essentially undisturbed the indigenous flora, which is thought to play a role in the resistance to colonization by potentially pathogenic micro-organisms. SDSA has a significantly lower cost and requires less nursing time than classical SDD. The limitation of this method is that it protects only from VAP.

Our findings show that the majority of VAPs in the SDSA group, were characterized early and were caused by Gram-positive cocci. This raises the question of whether another anti-Gram-positive-coccus-antibiotic should be added to the SDSA fluid. Furthermore, systemic chemotherapy for a few days could further reduce the early VAP.

We conclude that SDSA is an effective and safe type of chemoprophylaxis against tracheal colonization and respiratory tract infection in critically ill with multiple trauma patients. Further studies are needed to clarify whether the combination of this method with parenteral antibiotic administration is more effective in reducing the incidence of VAP.

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