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Major article

Prospective observational study to compare oral topical metronidazole versus 0.2% chlorhexidine gluconate to prevent nosocomial pneumonia

Ying Chen MD, PhD [a,1], En-Qiang Mao MD, PhD [a,1], Yi-Jun Yang RN [a], Shu-Yuan Zhao RN [a], Cheng Zhu MD [a], Xiao-Fei Wang MD, PhD [b], Feng Jing RN [a], Hui-Qiu Sheng MD [a], Zhi-Tao Yang MD, PhD [a,c,*], Er-Zhen Chen MD, PhD [a]

[a] *Emergency Department & Emergency Intensive Care Unit, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China*
[b] *Department of Respiratory Diseases, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China*
[c] *Pôle Sino-Français de Recherches en Science du Vivant et Génomique, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China*

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Background: Nosocomial pneumonia is one of the most common health care–associated infections in intensive care units (ICUs) worldwide, attributing to high morbidity and mortality. Our study aim is to investigate the effectiveness of oral hygiene with 0.2% chlorhexidine gluconate (CHX) and 0.08% metronidazole (MDE) influencing the microbiologic epidemiology and incidence of nonintubation pneumonia (NIP) and ventilator-associated pneumonia (VAP).

Methods: Patients who stayed >48 hours in the emergency ICU between 2008 and 2012 were enrolled and provided oral hygiene by swabbing with 0.08% MDE twice daily until discharge or death during the first year (period M), whereas CHX was applied during the following 3 years (period C). The incidence and microbiologic epidemiology of NIP and VAP were studied.

Results: There were 873 patients enrolled. There were 44 episodes of NIP and 25 episodes of VAP that occurred among 212 patients in period M, and 84 episodes of NIP and 49 episodes of VAP occurred among 661 patients in period C. Overall, the rate of NIP and VAP decreased year by year. *Acinetobacter baumannii* was the most frequently identified bacteria for NIP (22.9%) and VAP (25.3%), with an annual ascent. Few changes were observed on bacteria distribution for NIP and VAP.

Conclusions: Oral hygiene with CHX, having reduced the incidence of nosocomial pneumonia among critical ill patients, suggests a benefit of oral hygiene in decreasing the incidence of nosocomial pneumonia, including VAP in ICUs, but not bacterial epidemiology.

Nosocomial pneumonia (NP), of which a subset is named ventilator-associated pneumonia (VAP), is one of the most common health care–associated infections in intensive care units (ICUs) worldwide, attributing to high morbidity and mortality.[1-3] NP, especially VAP, results in increased length of hospital and ICU stay, prolonged mechanical ventilation, increased cost of illness, and excessive utilization of antimicrobials.[4,5]

Nosocomial infections usually occur in immunocompromised patients, especially ICU patients with difficulties in oral hygiene and swallowing, leading to degradations of salivary properties and the microbial environment that allow increasing bacterial colonization at the oropharyngeal level, where the pathogens are aspirated into the lung and failed to clear by host defenses resulting in development of lung infections. It is a pivotal step in the pathogenesis of NP that periodontitis and proliferation of dental plaque due to colonization of pathogens including aerobic, anaerobic,

* Address correspondence to Zhi-Tao Yang, MD, PhD, Emergency Department & Emergency Intensive Care Unit, Pôle Sino-Français de Recherches en Science du Vivant et Génomique, Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, No 197 Ruijin Er Rd, Shanghai 200025, China.
E-mail address: yangzhitao@hotmail.fr (Z.-T. Yang).

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[1] Y.C. and E.-Q.M. have made equal contributions to this article.

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and filamentousmicroorganisms, which potentially invade the lower respiratory tract.[6-8] Similarly, Heo et al[9] has shown that respiratory pathogens isolated from the lung are often genetically indistinguishable from strains of the same species isolated from the oral cavity in patients who receive mechanical ventilation, and the dental plaque serves as an important reservoir for respiratory pathogens.[6]

Nonabsorbable antibiotics or antiseptics to decontaminate the oral cavity or oropharyngeal cavity were applied as a strategy for prevention of nosocomial infections, which demonstrated a significant effect in reduction of NP or VAP in several studies.[10-13] Because of high risk of natural selection, choosing an optimal antibiotic or antiseptic is the key point for oral hygiene. In the last 2 decades, a lot of antiseptics or antimicrobials, such as gentamicin, colistin, vancomycin, and povidone iodine, have been studied for the prevention of NP and VAP. The antiseptic, chlorhexidine gluconate (CHX), applied frequently to prevent nosocomial infections in the ICU has been evaluated with inconsistent results on its effectiveness to reduce the occurrence of respiratory infections.[14-18] Metronidazole (MDE) is a nitroimidazole antibiotic medication used particularly for anaerobic bacteria and protozoa, while being used for the initial episodes of mild-to-moderate *Clostridium difficile* infection. It is also prescribed for dental infections, periodontitis, and stomatitis of bacterial origin. Then MDE used to be a conventional oral hygiene strategy in our ICU. This study was aimed to investigate whether sustained implementation of oral hygiene with CHX or MDE could effectively reduce the incidence of NP in ICU patients and the concomitant microbiological changes.

MATERIALS AND METHODS

Study population

This was a prospective clinical study conducted in the emergency intensive care unit (EICU), an 18-bed medical-surgical mixed ICU, of a tertiary care teaching hospital in Shanghai, China. All patients admitted to the EICU between May 1, 2008, and April 30, 2012, were consecutively enrolled in the study.

The exclusion criteria were as follows: (1) absence of consent; (2) age <18 years; (3) pregnancy; (4) readmission to the ICU; (5) expecting to stay in the ICU <48 hours; (6) confirmed diagnosis of pneumonitis before admission in the ICU or establishment of artificial airway; (7) known hypersensitivity to CHX; (8) do not rescue or intubate order; (9) transfer from another ICU; and (10) preadmission immunosuppression (eg, HIV, used or using immunosuppressant in last 30 days, long-term steroid therapy, neutropenia: white blood cell count $<0.5 \times 10^9$/L).

A standard care protocol was performed in all patients of the EICU, including a semirecumbent body position while maintaining a head elevation of ≥30° if possible; nasogastric, nasointestinal, or jejunostomy feeding tube placed in patients with eating or swallowing difficulties; and periodic verification of the residual gastric volume every 6 hours (residual gastric volume <250 cm^3 was considered acceptable) and stopping of proton pump inhibitors once enteral nutrition or normal eating started. Endotracheal suction was implemented every hour with a closed system in all intubated patients who would accept a tracheotomy if mechanical ventilation prolonged for >2 weeks. In addition, a physical therapy with vibration expectoration machine was applied twice a day in all patients without contraindication, but selective digestive decontamination and continuous suction of subglottic secretions was not performed in any patient.

This study was approved by the Medical Ethics Committee of Ruijin Hospital, affiliated with Shanghai Jiaotong University. Written informed consent was obtained from each patient or representative of each patient before enrollment.

Study design

Eligible patients were enrolled in our study after giving informed consent and following baseline assessment and were assigned into 4 periods: period M, which included patients admitted from May 1, 2008-April 30, 2009, who had received oral hygiene as follows: swabbing of the oral mucosa, teeth, and tongue with sponge pellets impregnated with 20 mL of 0.08% MDE twice daily until discharge from ICU or death, which was a conventional oral hygiene procedure in our ICU; and period C, which was further subdivided into periods C1, C2, and C3. In these periods, the patients received the same strategy of oral hygiene with 20 mL of 0.2% CHX when the patients were admitted into the ICU in May 1, 2009-April 30, 2010, May 1, 2010-April 30, 2011, and May 1, 2011-April 30, 2012, respectively.

Sampling and microbiology

In nonintubation patients, 2 induced sputum specimens were obtained by applying inhalation of 5% hypertonic saline solution for 15 minutes on clinical indication after morning oral hygiene. Endotracheal aspirates were obtained from all intubated patients using a sterile suction catheter placed into the endotracheal tube with a closed system on suspicion of NP once weekly at absence of clinical indication. The specimens were judged eligible on the condition that sputum and endotracheal aspirates showed >25 pus cells and <10 squamous epithelial cells per field. All samples were sent to the clinical microbiology department of Ruijin Hospital. Semiquantitative cultures were performed to identify the causative organism, and antibiotic susceptibility testing was performed as appropriate. A culture was considered positive if isolation of $\geq 10^4$ colony forming units/mL of bacteria was found.

Definitions

Nosocomial nonintubation pneumonia (NIP) is defined as pneumonia that occurs ≥48 hours after admission when a nonintubation patient had the following signs or symptoms: new onset of purulent sputum or change in character of sputum, with a new or progressive infiltrate and consolidation, cavitation, or pleural effusion on chest radiograph, which was not present at the time of admission.[19] VAP refers to pneumonia that arises >48 hours after endotracheal intubation and mechanical ventilation which was not present at the time of intubation.[19]

Two independent experienced physicians assessed daily all patients using the modified clinical pulmonary infection score (CPIS)[20] until discharge from the ICU or death. The objective diagnostic criteria for NP consisted of a modified CPIS ≥6 after 48 hours of admission or mechanical ventilation. Bacteria isolated from patients without clinical manifestations of infection and a modified CPIS <6 were considered as colonization.

Data collection

Patients were followed-up until discharge or death. Demographic and clinical data, including medical history, diagnosis, date of intubation, onset of NP, and microbiologic results, were collected. Severity of the condition was assessed with the Acute Physiology and Chronic Health Evaluation II score at admission to the ICU.[21]