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Prehospital oral chlorhexidine does not reduce the rate of ventilator-associated pneumonia among critically ill trauma patients: A prospective concurrent-control study☆,☆☆

Nicholas M. Mohr, MD, MS [a,b,*], Carlos A. Pelaez Gil, MD [c], Karisa K. Harland, PhD, MPH [a], Brett Faine, PharmD [d], Andrew Stoltze, MD, JD [a], Kent Pearson, MD [b,e], Azeemuddin Ahmed, MD, MBA [a]

[a] Department of Emergency Medicine, University of Iowa Carver College of Medicine, Iowa City, IA
[b] Division of Critical Care, Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, IA
[c] Department of Surgery, University of Iowa Carver College of Medicine, Iowa City, IA
[d] Department of Pharmaceutical Services, University of Iowa Hospitals and Clinics, Iowa City, IA
[e] Department of Anesthesia, University of Iowa Carver College of Medicine, Iowa City, IA

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ABSTRACT

Purpose: The purpose of the study was to test the hypothesis that prehospital oral chlorhexidine administered to intubated trauma patients will decrease the Clinical Pulmonary Infection Score (CPIS) during the first 2 days of hospitalization.
Materials and methods: Prospective interventional concurrent-control study of all intubated adult trauma patients transported by air ambulance to a 711-bed Midwestern academic trauma center over a 1-year period. Patients transported by 2 university-based helicopters were treated with oral chlorhexidine after intubation, and the control group was patients transported by other air transport services.
Results: Sixty-seven patients were enrolled, of which 23 received chlorhexidine (9 patients allocated to the intervention were not treated). The change in CPIS score was no different between the intervention and control groups by intention to treat (1.06- vs 1.40-point reduction, $P = .520$), and no difference was observed in tracheal colonization (29.0% vs 36.7%, $P = .586$). No differences were observed in the rate of clinical pneumonia (8.7% vs 8.6%, $P = .987$) or mortality ($P = .196$) in the per-protocol chlorhexidine group.
Conclusions: The prehospital administration of oral chlorhexidine does not reduce the CPIS score over the first 48 hours of admission for intubated trauma patients. Further study should explore other prehospital strategies of reducing complications of critical illness.

1. Introduction

Ventilator-associated pneumonia (VAP) has been recognized as a significant complication of critical illness [1]. Ventilator-associated pneumonia increases mortality by 10% to 15% with a cost that is estimated at greater than $40 000 per case [2–4]. Multiple studies have identified risk factors for developing VAP, and guideline adherence has been shown to decrease the incidence of VAP [5].

Currently, VAP-prevention strategies have been focused on intensive care units (ICUs). Additional non-ICU risk factors have been identified that increase patients' risk for developing VAP: emergency department (ED) length of stay [6], number of intrahospital transfers out of the ICU [7], and prehospital intubation [8–10]. In one study, 20% of patients intubated in the ED subsequently developed VAP [11]; and some authors have recommended implementing VAP-prevention strategies before admission to the ICU [12,13].

Trauma patients are at increased risk of VAP, with a reported incidence of 11% to 33% [14,15]. Among trauma patients who survive their initial injuries, hospital-acquired infections are one of the leading causes of posttraumatic death [16]. Several reasons have been proposed for this association, including severity of traumatic injuries, surgical interventions, prolonged ICU treatment, and the microbial ecology of traumatic wounds.

One of the effective VAP-prevention strategies that has permeated US ICUs is the use of oropharyngeal decontamination with chlorhexidine gluconate 0.12% [17,18]. Chlorhexidine is an antiseptic solution that is applied to the mouth of an intubated patient to decontaminate oral secretions that may colonize the lower airways. No VAP prevention guidelines exist outside the ICU, so strategies to prevent nosocomial

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* Corresponding author at: University of Iowa Carver College of Medicine, 200 Hawkins Dr, 1008 RCP, Iowa City, IA 52242. Tel.: +319 353 6360; fax: +319 353 7006.
E-mail addresses: nicholas-mohr@uiowa.edu (N.M. Mohr), carlos-pelaezgil@uiowa.edu (C.A. Pelaez Gil), kari-harland@uiowa.edu (K.K. Harland), brett-faine@uiowa.edu (B. Faine), andrew-stoltze@uiowa.edu (A. Stoltze), kent-pearson@uiowa.edu (K. Pearson), azeemuddin-ahmed@uiowa.edu (A. Ahmed).

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infections secondary to traumatic injury are not routinely applied in the prehospital environment or in the ED [19].

The primary objective of this study was to test the hypothesis that oral chlorhexidine administered in the prehospital environment would decrease Clinical Pulmonary Infection Score (CPIS) over the first 48 hours of hospitalization. Secondary outcomes included the degree of tracheal colonization, early VAP (onset $\leq$ 5 days), adverse events, ventilator days, length of stay, and 28-day mortality.

2. Materials and methods

2.1. Study design, setting, and participants

We conducted a prospective, interventional open-label study of intubated trauma patients being transported by helicopter air ambulance in interhospital transfer to a 36-bed surgical ICU at a 711-bed Midwestern academic level I trauma center between October 21, 2013, and October 20, 2014. Patients transferred by a university-based 2-helicopter air ambulance service were treated with oral chlorhexidine as part of a quality improvement initiative (intervention group). Patients transferred by other air ambulance services were not treated with chlorhexidine and served as the control group. Patients were allocated to air transport service by the emergency physician in the transferring hospital (not part of the study), as each transferring hospital independently selects the air service that will transport their patients. Historical data collected from 2005 to 2011 demonstrate no difference in baseline VAP rate stratified by transport service (9.9% vs 9.3%, $P = .823$) [20].

All adult (age $\geq$ 18 years) patients who had sustained a traumatic injury, had been seen in a transferring ED before transport, and were intubated were included. Exclusion criteria included the following: known pregnancy, prisoners, pneumonia diagnosed and treated before transfer, known allergy to chlorhexidine gluconate, tracheostomy or cricothyroidotomy, massive aspiration at the time of intubation, and nonsurvivable injuries expected to die within 24 hours and being managed expectantly. The study was reported in accordance with the Standards for Quality Improvement Reporting Excellence statement and the Strengthening Reporting of Observational Studies in Epidemiology guidelines [21,22]. The study was determined not to qualify as human subjects research by our local institutional review board (quality improvement activity), and the study protocol was registered on ClinicalTrials.gov protocol NCT01902446.

2.2. Intervention

Patients in the intervention group were treated with intraoral administration of chlorhexidine gluconate 0.12% solution. Chlorhexidine was packaged in a syringe with 5-mL aliquots and was administered by applying to oral surfaces, then swabbing with a disposable swab stick for 15 seconds. No oral suctioning was performed for at least 30 seconds after administration. Chlorhexidine was administered in the helicopter after loading the patient from the transferring hospital, usually within the first few minutes of flight. Flight crew members completed a case report form after the flight that screened for adverse events potentially related to chlorhexidine administration.

2.3. Definitions

The primary outcome was the change in CPIS score between admission and hospital day 2. The CPIS score is a composite score that awards points for temperature, white blood cell count, character of tracheal secretions, Pao_2/Fio_2 ratio, and chest radiograph [23]. For the purpose of CPIS scoring, 2 investigators blinded to treatment allocation scored daily chest radiographs. *Clinical pneumonia* was defined as a patient judged by an independent panel of clinicians to have sufficient clinical criteria and culture data to warrant a course of empiric antimicrobial therapy. This outcome was adjudicated by consensus of 3 independent board-certified critical care physicians blinded to group allocation and study aims. *CDC-defined VAP* was defined objectively using the Centers for Disease Control and Prevention definitions [5]. *Ventilator-free days* were defined as the number of days within 28 days after admission that a patient was alive and not requiring mechanical ventilation. Adverse events were defined during helicopter transfer as inadvertent extubation, new oral skin ulceration or lesion, bleeding in tracheal secretions, suspected chlorhexidine in tracheal secretions, or unexplained episodes of hypoxemia during transport. *Early ventilator-associated pneumonia* was defined as diagnosis within 5 days of hospital admission based on microbiological data collected previously at our institution [20]. *Nonsurvivable injury* was defined as a patient identified by the primary critical care team or a consulting service as having a nonsurvivable injury and, as a consequence, limiting care that was offered (eg, neurosurgical intervention) with immediate or planned compassionate extubation within 24 hours.

2.4. Procedures

All patients were enrolled by a study investigator at the time of ICU arrival, and a baseline tracheal aspirate was collected for semiquantitative culture. A research assistant collected clinical data each day for the first 5 days of hospitalization using a standard case report form. The bedside nurse assessed the daily character of respiratory secretions. Each patient who remained intubated at day 2 had another tracheal aspirate collected for semiquantitative culture. All patients were reevaluated at either hospital discharge or 28 days after hospital admission (whichever came first) to collect data on clinical outcomes, including duration of intubation, tracheostomy, and survival. No patients were followed after hospital discharge.

2.5. Safety analysis

A preplanned interim safety analysis was performed by the physician safety monitor after 10 patients had been enrolled in the intervention group. Only adverse event data were reviewed at the safety analysis, and no interim analysis was done on the primary or secondary clinical outcomes.

2.6. Sample size

As a pilot study, we powered the study to detect a 2-point difference in CPIS. Originally, we calculated that assuming 1:1 allocation ratio (power = 80%, $\alpha = 5\%$, 2-tailed test), we would require 24 patients in each group [24]. The steering committee recommended stopping the trial (blinded to results) after 1 year because we had achieved the prespecified power through robust enrollment in the control group.

2.7. Analysis

2.7.1. Primary outcome

The primary outcome was the change in CPIS score over the first 2 days of hospitalization and was evaluated using a 2-tailed independent-samples *t* test. Baseline characteristics were compared; and if significant differences in severity of illness were observed, multivariable linear regression was planned to adjust for baseline differences in illness severity. The primary outcome was evaluated using intention-to-treat methodology, but per-protocol analysis was also planned.

2.7.2. Secondary outcome

Secondary outcomes were evaluated using basic inferential statistics. Tracheal colonization was reported as a semiquantitative value (eg, no growth, rare growth) at both ICU admission and on hospital day 2, and was analyzed using a Fisher exact test. The change in tracheal colonization between admission and day 2 was compared using a paired *t* test. The rate of early VAP, tracheostomy rate, and mortality were