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Original Article

Anaesthesia Section

Efficacy of Gentamicin versus Chlorhexidine as a Sole Prophylactic Oral Decontaminant in Reducing the Incidence of Ventilator Associated Pneumonia: A Randomised Clinical Study

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ABSTRACT

Introduction: Ventilator Associated Pneumonia (VAP) is the second most common nosocomial infection. Aspiration of bacteria from the upper digestive tract is important in the pathogenesis of this infection. Oral decontamination using antiseptic like chlorhexidine reduces the incidence of VAP but not mortality. There is conflicting results about oral decontamination with antibiotics in preventing VAP, some suggesting benefit and others showing no benefit.

Aim: To use two different prophylactic oral decontaminant, gentamicin and chlorhexidine, to compare the incidence of VAP, prevalence of bacterial flora, duration of Intensive Care Unit (ICU) stay, and mortality.

Materials and Methods: This double-blind, randomised, clinical study was conducted at Sir Sunder Lal Hospital, Banaras Hindu University, Varanasi, Uttar Pradesh, India, from January 2017 to December 2018. Patients intubated within 24 hours of admission and who needed mechanical ventilation with an expected duration of more than 48 hours were included. All the adult patients between age group 18-50 years were studied. Patients were randomised to receive either Topical Antimicrobial Prophylaxis (TAP) with 2% gentamicin (Group G) or 2% chlorhexidine (Group C). Patients were followed until extubation or death. Sequential cultures from endotracheal tube were sent on days 3,7,14, and 21, and for oropharyngeal swab culture were sent on days 0, 3,7,14 and 21. VAP was diagnosed with the help of Clinical Pulmonary Infection Score (CPIS).

Results: Out of 151 patients, 82 patients were in group G (2% gentamicin) and 69 in group C (2% chlorhexidine). On follow-up of various interval among both the groups, CPIS increased with ICU stay but incidence of VAP was comparable between the groups (50% vs 71%, p-value=0.009). *Pseudomonas* was found to be most prevalent bacteria among both the groups. Discharge rate from ICU was higher in group G (54.9%) than group C (52.2%) (p-value=0.744). The mortality rate was higher in the group C (43.9%) than group G (44.9%) (p-value=0.744).

Conclusion: Prophylactic oral-decontamination with gentamicin or chlorhexidine does not reduce incidence of VAP and outcome among ICU patients. Gentamicin could be a better option for patients on ventilator because it may lead to less colonisation of *Pseudomonas* in oral cavity along with lower CPIS in the later stages of VAP.

Keywords: Clinical pulmonary infection score, Oral decontamination, Outcome

INTRODUCTION

Ventilator Associated Pneumonia (VAP) is the leading cause of morbidity and mortality among patients on ventilator. Its incidence ranges from 9-27%, with a crude mortality exceeding 50% [1-4]. Aspiration of secretion containing different bacteria from the upper digestive tract to respiratory tract is important route of pathogenesis [4,5]. VAP is usually diagnosed on the basis of a combination of criteria such as the presence of fever and leukocytosis, the results of tracheal-aspirate cultures, and the presence of infiltrates on a chest radiograph [6]. Because VAP has been associated with increased morbidity, longer hospital stay, increased mortality and increased healthcare costs, its prevention is a major challenge for intensive care medicine.

Two different interventions intended to decrease the oral bacterial load are Selective Decontamination of the Digestive tract (SDD) through administration of non absorbable antibiotics by mouth or nasogastric tube, and oral decontamination with topical oral application of antibiotics or antiseptics. Previous meta-analysis of SDD found significant reduction in VAP incidence among treated patients [7-15]. However, this approach of oral decontamination with antibiotics has limitations because of the concern of the emergence of antibiotic-resistant bacteria. Therefore oral decontamination alone may be a more attractive option because it requires only a fraction of the antibiotics used in SDD.

Recommendations for preventing nosocomial pneumonia in acutely ill patients from the Centers for Disease Control (CDC) and the Healthcare Infection Control Practices Advisory Committee (HICPAC) state only to implement a comprehensive oral hygiene program which may include an antiseptic agent like chlorhexidine gluconate, while, there is no recommendation for routine use of topical antimicrobial agents for oral decontamination [16-19]. Trials on oral decontamination using antibiotics have generated conflicting results [20,21]. In contrast to antibiotics, antiseptics act rapidly at multiple target sites and have less chance of drug resistance. Recently a meta-analysis of four trials on chlorhexidine failed to show a significant reduction in VAP incidence [22]. However, two further meta-analysis on chlorhexidine for prevention of VAP suggested benefit from this approach [23].

So, the conflict about the routine use of antibiotics or antiseptic for oral decontamination for VAP-prevention remains unsolved. To the best of our knowledge no trial directly compared antiseptic with antibiotic oral decontamination. So, a further study comparing antibiotics with antiseptic oral decontamination while incorporating stringent infection surveillance is the need of the hour. This clinical trial aimed to compare oral decontamination with gentamicin and chlorhexidine to prevent VAP incidence. The primary outcome measure was to compare incidence of VAP. Secondary outcomes included the prevalence of various bacteria in the endotracheal tube aspirate cultures, and the mortality rate.

MATERIALS AND METHODS

This double-blind, randomised interventional study was conducted from 1st January 2017 to 31st December 2018 in the ICU of Sir Sunder Lal Hospital, Banaras Hindu University, Varanasi, Uttar Pradesh, India. Ethical clearance for the study was obtained from ethical committee of institute prior to the study (ECR/526/Inst/UP/2014).

Inclusion criteria: Patients in the age group of 18-50 years admitted in ICU and who intubated within 24 hours of admission and needed mechanical ventilation with an expected duration of atleast two days were included in the study.

Exclusion criteria: Patients with oral malignancy, plaque, submucosal fibrosis, immunocompromised patients, patients with limited mouth opening where oral intubation is not possible, no prophylactic antibiotics were administrated through the nasogastric tube and history of allergy were excluded from the study.

Sample size estimation: Sample size was estimated using the following formula:

$n=DEFF*Np(1-p)]/[(d^2/Z^2_{1-}\alpha_{/2}*(N-1)+p*(1-p)]$

where,

DEFF=Design effect [24]

N=Population size

p=Estimated proportion [24]

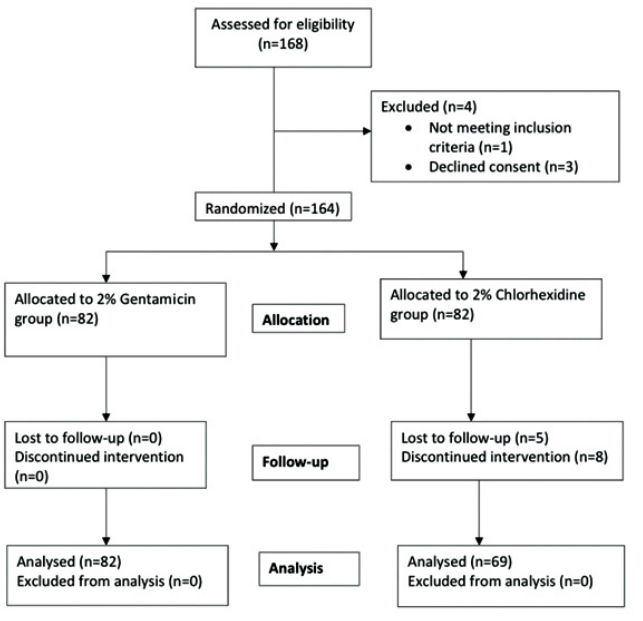
q=1-p

d=desired absolute precision or absolute level of precision

z=level of confidence according to the standard normal distribution (for a level of confidence of 95%), z=1.96

Population size (for finite population correction factor) (*N*):	1000000
[25] Incidence of early-onset VAP (within 96 hours) in the population (*p*):	27%±8
Confidence limits as % of 100 (absolute +/-%)(*d*):	8%
Design effect (for cluster surveys-*DEFF*):	1

Considering 95% confidence interval and 8% margin of error, total calculated sample size was 120 (60 in each group). Patients were randomised through simple randomised sampling to receive either TAP with 2% gentamicin (Group G) or to 2% chlorhexidine (Group C) [Table/Fig-1]. Studied drugs were applied in the buccal cavities with gloved finger every 6 hours after intubation for study duration. The application of the drugs were started within 24 hours of intubation and administered six hourly (four times daily), after removing remnants of the previous dose with a gauze moistened with saline (NaCl 0.9%). Patients were followed until extubation or death. Because 95% of the first episodes of VAP occur within the first three weeks of ventilation, application of studied drugs were limited to 21 days [26].



[Table/Fig-1]: CONSORT diagram.

Demographic data (like age, sex, medical specialty, pre-existent diseases, and length of hospital stay before admission to ICU) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores [19] were recorded on admission. Routine investigations along with sample such as blood, urine, sputum or endotracheal aspirate, oropharyngeal swab were obtained at the time of admission or within half an hour of administration of empirical antibiotics therapy in all the patients. Sequential cultures for oropharyngeal swab culture and endotracheal aspirate culture were sent on days 0,3,7,14, and 21 so on as per the ICU protocols. All participating ICUs had standard care protocols in which a semirecumbent body position with head elevation of 30° or greater was maintained, if possible. The CPIS was recorded to diagnose VAP. It includes six variables-fever, leukocytosis, tracheal aspirates, oxygenation, radiographic infiltrates, and semi-quantitative cultures of tracheal aspirates with Gram stain. It was calculated at days 0,3,6,9,12,15,18, and 21. VAP was positive if the subject had a CPIS greater than or equal to six [27].

STATISTICAL ANALYSIS

Statistical analyses was performed using the statistical software Statistical Package for the Social Science (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA) software for MS-windows. Descriptive frequencies were expressed using mean (standard deviation) and median (range). Difference between means of continuous variables were compared using the unpaired Student's t-test and Analysis of Variance (ANOVA), as applicable, and that of categorical variables with the Chi-square test. The critical value of 'p' indicating the probability of significant difference was taken as <0.05 for comparison.

RESULTS

The basic demographic data as well as disease severity was similar in both the groups [Table/Fig-2].

Variables	Group G	Group C	p-value
Total number of patients	82	69	
Age (years) (Mean±SD)	33.21±9.182	33.75±10.519	0.734
Sex (M/F)	41/41	33/36	0.790
Apache II Score (Mean±SD)	21.90±9.456	22.58±9.238	0.658
Duration of stay in ICU (days)	8.28	12.90	0.058

[Table/Fig-2]: Demographic data.

CPIS was comparable (50% vs 71%, p-value=0.009) in both the groups except on day 9 and 12, where it was significant in the chlorhexidine group (p-value <0.05) [Table/Fig-3].

Days	Group G	Group C	t-value	p-value
Day 3	4.43±1.396	4.7±1.701	1.144	0.254
Day 6	5.23±1.411	5.67±1.344	1.590	0.115
Day 9	5.63±1.713	6.61±1.135	3.042	0.004
Day 12	5.92±1.487	7.20±1.243	2.483	0.019
Day 15	7.27±1.032	7.62±1.009	0.751	0.460
Day 18	7.43±.976	7.78±.1.563	0.516	0.614
Day 21	6.25±957	7.88±2.416	1.270	0.233

[Table/Fig-3]: Comparison of CPIS in both groups.
p-value <0.05 considered significant

On comparing the total oropharyngeal swab culture between the two groups, prevalence of *Pseudomonas* was found to be significantly lower in the gentamicin group (p-value <0.05) [Table/Fig-4].

Prevalence of different species of bacteria in endotracheal aspirate culture was similar in both the groups (p-value>0.05) [Table/Fig-5].

Organism	Group G (n,%) (N=82)	Group C (n,%) (N=69)	Chi-square value	p-value
Streptococcus	51 (62.1)	50 (72.4)	0.62	0.43
Staphylococcus	43 (52.4)	35 (50.7)	0.009	0.92
Acinetobacter	38 (46.3)	38 (55.0)	0.418	0.518
Klebsiella	26 (31.7)	31 (44.9)	1.499	0.220
Pseudomonas	14 (17.0)	24 (34.7)	4.22	0.039
Candida	22 (26.8)	21 (30.4)	0.054	0.816
Other	21 (25.6)	23 (33.3)	0.522	0.470

[Table/Fig-4]: Comparison of orophraygeal culture.
A p-value <0.05 is considered to be statistically significant

Organism	Group G (n,%) (N=82)	Group C (n,%) (N=69)	Chi-square value	p-value
Acinetobacter	16 (19.5)	12 (17.3)	0.015	0.9014
Klebsiella	8 (9.7)	12 (17.3)	1.295	0.2552
Staphylococcus aureus	7 (8.5)	5 (7.24)	0.051	0.8221
Pseudomonas	7 (8.5)	12 (17.3)	1.180	0.2773
Enterococci	1 (1.2)	4 (5.7)	1.231	0.2672
Micrococci	0	1 (1.44)	0.008	0.9309
Streptococci	1 (1.2)	1 (1.44)	0.015	0.9021
Citrobacter	1 (1.2)	1 (1.44)	0.015	0.9021
Other	0	1 (1.44)	0.008	0.9309
Total	41 (50)	49 (71)		

[Table/Fig-5]: Comparison of endotracheal aspirate culture.
A p-value <0.05 is considered to be statistically significant

Final outcome variables for all the patients were classified as either discharge from ICU, death or Discharge on Patient's Request (DOPR) for both the groups. Deaths in groups G and C was 43.9% and 44.9%, respectively. Both groups were comparable for outcome variable [Table/Fig-6].

Outcome	Group G (n,%) (N=82)	Group C (n,%) (N=69)	Total (n,%) (N=151)
Discharge	45 (54.9)	36 (52.2)	81 (53.6)
Death	36 (43.9)	31 (44.9)	67 (44.4)
Discharge on patient's request	1 (1.2)	2 (2.9)	3 (2.0)
Total	82 (100.0)	69 (100.0)	151 (100.0)

[Table/Fig-6]: Final outcome (p-value=0.744).

DISCUSSION

Ventilator Associated Pneumonia (VAP) is the most frequent infection in mechanically ventilated patients. The risk of developing VAP increases by 1-3% for each day spent on the ventilator [28,29]. The pathogenesis is thought to involve microaspiration of oropharyngeal microorganisms, which enter into the lower respiratory tract via leakage around the endotracheal tube cuff or directly through the tube.

The current study included the patients, who were on mechanical ventilation for more than 48 hours, hereby a total 82 patients were selected for oral decontamination with gentamicin and 69 patients with chlorhexidine. It was found that mean CPIS scores at day 9 and 12 in group G were significantly less than group C. This means that gentamicin significantly reduced the mean CPIS score. However, the mean CPIS scores later were not significantly different. The possible explanation for these results might be that with increase a duration of ICU stay, multiple resistant bacteria colonised the patients airway. Therefore, gentamicin could not provide protection against these resistant organisms. Also, tracheal growth of bacteria was not inhibited because antibiotic was used locally in oropharynx. In contrast, a randomised controlled trial was conducted by Bergmans DCJJ et al., to prevent VAP by modulation of oropharyngeal colonisation with TAP (gentamicin/colistin/vancomycin), without influencing gastric and intestinal colonisation and without systematic prophylaxis showed that modulation of oropharyngeal colonisation with antibiotics effectively reduce the incidence of late onset VAP [30].

Oropharyngeal swab culture results showed significant reduction in prevalence of *Pseudomonas* in gentamicin group. While the difference in prevalence of other bacteria were not statistically significant. Similar findings were reported by Rodriguez-Roldan JM et al., they found that selective oral decontamination with a paste having amphotericin B, colistin sulphate and tobramycin combination reduced the colonisation and pneumonia as compared to placebo [21]. The current study shows that prevalence of various bacteria in tracheal aspirate was similar among both the groups. This shows that oral decontamination with either of the selected drugs does not significantly modulate the incidence of one particular bacteria. Length of ICU stay and final outcome among both the groups were comparable. These findings are supported by Abele-Horn M et al., [20], they conducted a randomised controlled trial using amphotericin B, colistin, and tobramycin combination and applied it to the oropharynx. They concluded that Selective Oral Decontamination (SOD) significantly reduced the colonisation and pneumonia, while, the length of stay in the ICU, duration of ventilation, and mortality were similar. A meta-analysis by Chan EY et al., concluded that oral decontamination of mechanically-ventilated adults using antiseptics is associated with a lower risk of VAP. Neither antiseptic nor antibiotic oral decontamination reduced mortality or duration of mechanical ventilation or stay in the ICU [31].

Previous studies used lower concentration of chlorhexidine (0.12%, 0.2%). That is why chlorhexidine was not effective in most of the trials. The index study used a higher concentration of chlorhexidine (2%). Oral gentamicin was used for digestive decontamination to reduce resistant bacterial loads in surgical patients. Current study is novel as oral gentamicin was used for selective oral decontamination.

Limitation(s)

This study did not include a control group to know the significant effect of gentamicin or chlorhexidine for VAP prevention in comparison with a placebo. Secondly, development of resistance among bacteria against antibiotics were not taken into consideration. Current study used gentamicin only, as it covers preferentially gram negative bacteria. A combination of antibiotics along with antifungal agent may cover broader spectrum of bacteria and fungi.

CONCLUSION(S)

This study showed that prophylactic oral-decontamination with gentamicin is non superior to chlorhexidine in reducing the incidence of VAP as well as outcome among patients on ventilator but gentamicin could be a better option as it leads to less colonisation of *Pseudomonas* in oral cavity along with lower CPIS in the later stages of VAP.

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