

DEVELOPMENT OF A CHLORHEXIDINE MOUTHWASH FOR ORO-PHARYNGEAL DECONTAMINATION (OPD) TO BE USED IN A FUTURE CLINICAL STUDY IN CRITICALLY ILL PATIENTS - 1ST COMMUNICATION

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OBJECTIVE

Up to 50% of critically ill patients requiring mechanical ventilation will eventually develop pneumonia. The mortality rate attributed to these nosocomial infections can exceed 60% with a significant prolongation of hospitalization and increased costs. The application of selective digestive decontamination (SDD) using antibiotics has been shown to be effective but may play a role in the emergence of multi-resistant strains. OPD with antiseptic appears to be a new and very promising concept. In this study chlorhexidine was chosen as the antiseptic.

INTRODUCTION

Ventilator-associated pneumonia (VAP)

The prevalence of nosocomial infection was 20.6% in 10,038 patients from 1,417 European ICUs in 1992 included in the European Prevalence of Infection in Intensive Care (EPIC) study which reported by Vincent et al. Pneumonia was the most common NI (46.9%), followed by lower respiratory tract other than pneumonia (17.8%), urinary tract infection (17.6%) and laboratory-confirmed bloodstream infection (12%)¹.

Data collected from 112 medical ICUs between 1992 and 1997 included in the National Nosocomial Infection Surveillance System (NNIS) indicated that the incidence-density of VAP was 9.2%, corresponding to an incidence-density of 23.7 episodes per 1000 patient-days². VAP occurs in around 25% of mechanically-ventilated patients and its crude mortality ranges from 20% to 50%. An mortality between 10% and 27% was found in most published controlled studies^{3,4}.

Prevention of ventilator-associated pneumonia

Research for effective measures to prevent VAP were recently reviewed⁵. Most of them are related to the interruption or limitation of the continuous aspiration of contaminated oro-pharyngeal secretions. Selective digestive decontamination (SDD), semi-recumbent position (45-degree angle), and continuous subglottic aspiration of oro-pharyngeal secretions have been reported to be effective measures⁵. However, SDD has been implicated in the emergence and spread of antibiotic resistant bacteria and is no more recommended⁶. The development of disinfecting solutions, without antibiotics would help to reduce the continuous pressure on the emergence of resistant microorganisms.

Oral rinse with chlorhexidine gluconate 0.12% for use in patients undergoing heart surgery⁷ reduced both, the incidence of total nosocomial respiratory infection, and the use of non-prophylactic antibiotics. However the different alcohol content of the placebo in comparison with that of the chlorhexidine solution could lead to placebo detection during the trial. We also used a higher chlorhexidine concentration 0.2%.

MATERIAL AND METHODS

Development of a chlorhexidine mouthwash for OPD

The difficulty was in finding how to prepare the placebo solution. The four criteria used to develop the solution were:

- low alcohol content
- unit dose packaging
- patient compliance (especially taste)
- natural flavors.

This solution contained sweetening agents, solubilizing agents for the flavors and 10% alcohol. As it had no preservative, the solution was sterilized at 121°C for 15 minutes in infusion bottles to allow for a long expiry date (the study was over a period of 18 months). A tasting panel compared the chlorhexidine containing solution and the placebo. There was hardly any difference between the two preparations. Natural flavors were used instead of artificial ones that had a tendency to degrade on sterilization. Unit doses of 60 ml were prepared to be used from 4 to 6 times a day.

A small number of patients were chosen to test the acceptability of the preparation. Stability tests were carried out and there was no loss of chlorhexidine after 18 months at 25°C.

In vitro determination of the antimicrobial effect of the mouthwash

The microorganisms were introduced directly into the OPD or the PLACEBO solution (approximately 10⁷ CFU/ml). The contact time was fixed at 5 minutes. A sample was then taken and introduced into the solution containing the neutralizing agents (3% Tween 80 and 0.3% Lecithin in a PO₄-NaCl buffer). The neutralization was validated using *S. aureus*. The viable counts were determined after spreading on TSA + neutralizing agents (in duplicate). In certain cases, it was not possible to incorporate the neutralizing agents in the culture medium: *S. pneumoniae* (incubated in Blood Agar), *H. influenzae* (on Chocolate Agar) and *L. pneumophila* (on BCYE+ antibiotics).

RESULTS: IN VITRO ANTIMICROBIAL EFFICACY OF OPD

Table 1: Effect after 5 min contact time with OPD solution

Type of microorganism (source)	Reference CFU/ml	OPD CFU/ml	Placebo CFU/ml
<i>Pseudomonas aeruginosa</i> (ATCC 9027)	2.4x10 ⁷	< 10 ²	6.9x10 ⁶
<i>Burkholderia cepacia</i> *	2.8x10 ⁷	2.0x10 ³	1.2x10 ⁶
<i>Acinetobacter baumannii</i> *	7.5x10 ⁶	< 10 ²	6.3x10 ⁶
<i>Legionella pneumophila</i> (sg1) (water)	1.2x10 ⁶	1.1x10 ³	2.5x10 ⁶
<i>Stenotrophomonas maltophilia</i> *	2.3x10 ⁷	< 10 ²	3.0x10 ⁶
<i>Citrobacter freundii</i> *	2.7x10 ⁷	< 10 ²	1.4x10 ⁶
<i>Citrobacter koserii</i> *	3.1x10 ⁷	< 10 ²	1.3x10 ⁷
<i>Enterobacter cloacae</i> *	1.5x10 ⁷	< 10 ²	1.4x10 ⁷
<i>Escherichia coli</i> (ATCC 8739)	4.7x10 ⁷	< 10 ²	2.3x10 ⁷
<i>Hafnia alvei</i> *	1.6x10 ⁷	< 10 ²	1.1x10 ⁷
<i>Klebsiella pneumoniae</i> *	2.4x10 ⁷	< 10 ²	1.7x10 ⁷
<i>Proteus mirabilis</i> *	4.9x10 ⁷	2.5x10 ⁵	4.0x10 ⁷
<i>Proteus vulgaris</i> *	3.3x10 ⁷	< 10 ²	3.6x10 ⁷
<i>Serratia marcescens</i> *	3.1x10 ⁷	< 10 ²	1.6x10 ⁷
<i>Haemophilus influenzae</i> *	5.0x10 ⁷	< 10 ²	7.9x10 ⁶
<i>Staphylococcus aureus</i> (ATCC 25923)	5.3x10 ⁷	4.0x10 ²	4.8x10 ⁷
<i>Staphylococcus aureus</i> (ATCC 6538P)	6.3x10 ⁷	< 10 ²	-
CoNS (ATCC 12288)	6.8x10 ⁷	3.6x10 ³	4.7x10 ⁷
<i>Streptococcus pneumoniae</i> (ATCC 6305)	1.4x10 ⁷	< 10 ²	1.0x10 ⁶
<i>Streptococcus viridiae</i> (ATCC 10556)	1.2x10 ⁸	< 10 ²	1.0x10 ⁸
<i>Enterococcus faecalis</i> (ATCC 29212)	9.7x10 ⁷	1.7x10 ⁵	6.4x10 ⁷
<i>Candida albicans</i> (ATCC 10231)	1.4x10 ⁷	< 10 ²	5.5x10 ⁶
<i>Candida albicans</i> (ATCC 14053)	1.1x10 ⁷	< 10 ²	3.6x10 ⁶
<i>Aspergillus niger</i> (ATCC 16404)	1.4x10 ⁷	4.0x10 ⁵	1.0x10 ⁶

* Clinical strains supplied by the Central Laboratory of Bacteriology, HUG, Geneva.
CoNS: Coagulase-negative staphylococci

Table 2: Effect after 15 min contact time with OPD solution

Type of microorganism (source)	Reference CFU/ml	OPD CFU/ml	Placebo CFU/ml
<i>Proteus mirabilis</i> *	1.7x10 ⁷	2.0x10 ³	4.0x10 ⁷
<i>Staphylococcus aureus</i> (ATCC 25923)	3.0x10 ⁷	< 10 ²	4.8x10 ⁷
CoNS (ATCC 12288)	5.5x10 ⁷	< 10 ²	4.7x10 ⁷
<i>Enterococcus faecalis</i> (ATCC 29212)	9.7x10 ⁷	4.7x10 ³	6.4x10 ⁷

DISCUSSION

The majority of microorganisms were killed in 5 minutes (except *B. cepacia*, *L. pneumophila*, *P. mirabilis*, *S. aureus*, SCN and *E. faecalis*).

A test using 15 minutes contact time showed that in each case there was a diminution with time except for *E. faecalis*. We have tried to adapt this strain to chlorhexidine by subculturing the bacteria that survived the first contact. Under no circumstances did the regression rate of the population change significantly (D value). It is probable that a few viable bacteria remain after each treatment without there being a question of resistance and the eventual risk of proliferation of the strain.

CONCLUSION

In our study the *in vitro* tests demonstrated the activity of chlorhexidine against the majority of the clinical and ATCC bacterial strains tested using a contact time equivalent to that utilized clinically. Handwashing and mouthwashing with chlorhexidine could reduce the use of antibiotics in ICUs. **We can therefore recommend the use of 0.2% chlorhexidine mouthwash solution in a future clinical study in the prevention of VAP.**

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Bibliography

- Vincent JL. *JAMA* 1995;274:639-44.
- Richards MJ. *Crit Care Med* 1999;27:887-92.
- Fagon JY. *JAMA* 1996;275:866-9.
- Girou E. *Am J Respir Crit Care Med* 1998;157:1151-8.
- Kollef MH. *NEJM* 1999;340:627-34.
- Fridkin S. *Clin. Infect. Dis.* 1999;29:245-52.
- De Riso. 1996;109:1556-61.