Effect of daily application of a 0.05% chlorhexidine solution on the incidence of (aspiration) pneumonia in care home residents: design of a multicentre cluster randomised controlled clinical trial

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ABSTRACT

Introduction: Pneumonia is an important cause of death in care home residents. Dysphagia and poor oral health are significant risk factors for developing aspiration pneumonia. Oral hygiene care reduces the number of oral bacteria and the risk of aspiration pneumonia. However, it is not clear yet which oral hygiene care intervention is most efficacious in reducing the risk of aspiration pneumonia. The aim of the study is to assess whether the application of a 0.05% chlorhexidine-containing solution in addition to the usual daily oral hygiene care reduces the incidence of pneumonia in physically disabled care home residents with dysphagia.

Methods and analysis: The study was designed as a multicentre cluster randomised controlled clinical trial, with care homes as units of randomisation. During 1 year, 500 physically disabled care home residents with dysphagia will be followed. The intervention consists of applying a 0.05% chlorhexidine-containing solution twice daily, immediately after the usual oral hygiene care, whereas the control group receives no application after the usual oral hygiene care. The primary outcome is the incidence of pneumonia diagnosed by a physician, using a set of strictly described criteria. The effect of the intervention on the incidence of pneumonia will be determined using a Cox regression analysis. The secondary outcomes are correlations between incidence of pneumonia, age, gender, diagnosed diseases, dysphagia severity, care dependency, actually used medication, number of teeth and implants present and the presence of removable dentures.

Ethics and dissemination: Ethical approval was obtained from the Medical Ethical Committee of Radboud university medical centre: NL.nr: 41990.091.12. Written and informed consent will be obtained from all participating care homes and residents. The study’s findings will be published in peer-reviewed journals.

Strengths and limitations of this study

- This is the first multicentre cluster randomised controlled clinical trial which studies the effect of a daily application of a 0.05% chlorhexidine solution on the incidence of aspiration pneumonia in care home residents.
- The results of this study will contribute to the improvement of oral hygiene care for care home residents.
- A limitation of this study is a potential sample selection bias, because the cluster randomisation may result in random effect and cluster selection bias.

Trial registration number: The trial has been registered in the Netherlands in the National Trial Register: TC=3515.

INTRODUCTION

In care homes, pneumonia is the second most common infection after urinary tract infection, and the leading cause of death from infection.1 The incidence of pneumonia in care homes is 10-fold the incidence of pneumonia in the community.2 The risk of developing aspiration pneumonia in care home residents is also higher than in community-dwelling older people.3 Aspiration, with the risk of developing aspiration pneumonia, is defined as the inhalation of oropharyngeal or gastric contents into the larynx and lower respiratory tract.4 Dysphagia is involved in developing
aspiration pneumonia. A meta-analysis on dysphagia and aspiration pneumonia in frail older people confirmed that dysphagia is a significant risk factor for aspiration pneumonia with frail elderly people (OR=9.84; 95% CI 4.15 to 23.33), particularly with elderly people suffering from cerebrovascular disease: OR=12.93; 95% CI 8.61 to 19.44. Poor oral hygiene care in care homes causes the accumulation of dental plaque and colonisation of oral surfaces and dentures with respiratory pathogens. Aspiration of these pathogens might cause lower respiratory tract infections such as pneumonia. It is not the type of oral bacteria, but the amount of inhaled bacteria which is an important factor in developing aspiration pneumonia.

Care home residents often depend on nurses for their daily oral hygiene care. It has been found that care home residents in several countries have poorly cleaned teeth and removable dentures. Although it has been suggested that oral hygiene care, such as brushing the teeth after each meal, cleansing dentures once daily, and professional oral healthcare once weekly, reduces the number of oral bacteria in care home residents sufficiently, it is not quite clear which oral healthcare intervention is most efficacious in reducing the risk of aspiration pneumonia. A systematic review and meta-analysis has found a significant reduction of pneumonia in an intensive care unit among cardiac surgery patients receiving mechanical ventilation and oral hygiene care with different concentrations of chlorhexidine gluconate solutions. No significant reduction was found among non-cardiac surgery patients. To the best of our knowledge, no data are available on the reduction of pneumonia in care home residents using a chlorhexidine-containing solution additional to their daily oral hygiene care.

Recently, the literature published between January 2000 and April 2009 was systematically reviewed in order to find risk factors of aspiration pneumonia in frail elderly people. The following risk factors could be identified: age, male gender, lung diseases, dysphagia, diabetes mellitus, severe dementia, ACE I/D genotype deletion/deletion genotype, poor oral health, malnutrition, Parkinson’s disease, the use of antipsychotic drugs, and the use of proton-pump inhibitors. It was suggested that the presence of two or more of these risk factors could be an indicator that specific preventive oral healthcare is necessary for attempting to reduce the risk of developing aspiration pneumonia.

The results of the aforementioned studies showed that frail older people have a high risk of dysphagia with, as a consequence, a higher risk of developing aspiration pneumonia than individuals without dysphagia, and that the application of a chlorhexidine-containing solution in addition to usual daily oral hygiene care may reduce the risk of developing aspiration pneumonia. Therefore, the aim of the study is to assess whether the application of a 0.05% chlorhexidine-containing solution in addition to daily oral hygiene care reduces the incidence of pneumonia in physically disabled care home residents with dysphagia.

STUDY OBJECTIVES
The objectives of the study are rendered in the following research questions:

1. Is there any statistically significant difference with regard to the incidence of (aspiration) pneumonia between physically disabled care home residents with dysphagia, who in addition to their usual daily oral hygiene care use a 0.05% chlorhexidine-containing solution (intervention group), and physically disabled care home residents with dysphagia, who only receive the usual daily oral hygiene care (control group)?

2. Is there any statistically significant correlation between age, gender, diagnosed diseases, dysphagia severity, care dependency, actually used medication, the number of teeth and implants present, and the presence of removable dentures and the incidence of pneumonia in physically disabled care home residents with dysphagia who did or did not apply a 0.05% chlorhexidine-containing solution to their usual oral hygiene care?

METHODS AND ANALYSIS
Study design and setting
This study protocol was developed in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study design is a multicentre cluster randomised controlled clinical trial, with care homes as units of randomisation (figure 1). The study will be performed in different care home units in the Netherlands. After approaching the care homes, the care homes will be allocated randomly to either the intervention group or the control group, assigned by lot. The sample size of the participants in both groups will be monitored. The enrolment of all care home units will take place at different moments within 1 year. However, in one care home unit, all participants will start at the same time.

Power calculation
On the basis of a power calculation, 500 physically disabled care home residents with dysphagia will be followed during 1 year. The care homes are the units of randomisation and will be allocated randomly to the intervention or control group (figure 1). Factors taken into account in the sample size calculations are the distribution of the outcome variable in the population (σ) and the presumed effect of the intervention (μ1−μ2), the requested power (1−β), the α and the value of the intraclass correlation (design effect). The primary formula used to calculate the sample size is:

\[ n = \frac{2\sigma^2}{(\mu_1 - \mu_2)^2} \times f(\alpha, \beta) \]

Calculating the power, the incidence of pneumonia in care home residents is, in agreement with not internationally published incidence data for the year 2011.

\[ p = 0.05, \quad \text{twosided}, \quad \beta = 0.1, \quad \text{one} \text{care} \text{centre} \text{cluster} \text{randomised} \text{controlled} \text{clinical} \text{trial}, \quad \text{with} \text{care} \text{homes} \text{as} \text{units} \text{of} \text{randomisation} \]

\[ \frac{1}{n} = \frac{1}{2} \left( \frac{1}{\text{incidence} \text{in} \text{intervention} \text{group}} + \frac{1}{\text{incidence} \text{in} \text{control} \text{group}} \right) \]

\[ n = \frac{2\sigma^2}{(\mu_1 - \mu_2)^2} \times f(\alpha, \beta) \]

\[ n = 500 \]

\[ \text{control} \text{group} \]

\[ \text{intervention} \text{group} \]

\[ \text{incidence} \text{in} \text{control} \text{group} \]

\[ \text{incidence} \text{in} \text{intervention} \text{group} \]

\[ \text{power} \]

\[ \text{type} \text{error} \]

\[ \text{within} \text{care} \text{home} \text{unit} \]

\[ \text{within} \text{care} \text{home} \text{residents} \]

\[ \text{within} \text{physically} \text{disabled} \text{care} \text{home} \text{residents} \text{with} \text{dysphagia} \]

\[ \text{within} \text{incidence} \text{data} \text{for} \text{the} \text{year} \text{2011} \]

\[ \text{within} \text{nationally} \text{published} \text{incidence} \text{data} \]
largely assessed as 25%, the presumed reduction of the incidence is 40%, the requested power is 0.8, and the $\alpha$ is 0.05. If the true relative risk of failure of residents of the intervention group relative to residents of the control group is 0.6, 250 residents are needed in the intervention group and 250 residents in the control group in order to be able to reject the hypothesis that the risk difference equals 0% with probability (power) 0.8.

Recruitment of care homes and participants
The care homes will be selected from a database. Care home units with residents for short-term care or with cognitively impaired residents (mainly suffering from dementia) will be excluded from this study. After recruiting the care homes, the care homes will randomly be allocated to either the intervention group or the control group, assigned by lot. The care homes will receive information on the study in detail by post and email. After this mailing, all care homes will be called. If the care home agrees to participate, the principal investigator (VH) will organise an information meeting. Written informed consent by the board of the care home will be received before the start of the study. Only physically disabled residents with dysphagia are eligible to participate.

In the Netherlands, care homes contain somatic and psychogeriatric wards of primarily physically disabled residents and/or primarily cognitively impaired residents, respectively. The most common medical diagnoses in primarily physically disabled residents are cerebrovascular accidents (26%), other neurological diseases (7%), post-hip surgery status and other locomotor disorders (30%), malignancies (8%) and other miscellaneous diagnoses (29%). More than 85% of residents of psychogeriatric wards suffer from dementia. Most residents show a wide range of disabilities and handicaps, affecting autonomous activities of daily living, personal care, mobility and mental functions. The nursing staff, speech therapist and the responsible elderly care physician indicate if the resident on a somatic ward is cognitively and physically able to participate and is able to conduct the given instructions by the nursing staff.

Participants are recruited by a physician and a speech therapist of the care home. The recruited residents or their legal representatives will receive information, both by word of mouth and written, about the study. An information letter and the informed consent letter will be...
presented by the principal investigator or the nursing staff. Before giving their written informed consent, participants and/or their legal representatives will be given the opportunity to ask additional questions about the study.

Inclusion
Residents will be included when they meet the following criteria: aged 65 years or older, physically disabled and diagnosed with dysphagia. Dysphagia is defined as: “Difficulty with any stage of swallowing (oral, pharyngeal, oesophageal) and dysfunction in any stage or process of oral intake; includes any difficulty in the passage of food, liquid, or medicine during any stage of swallowing that impairs the client's ability to swallow independently or safely.” In this study, dysphagia will be determined as a dysfunction in the process of oral intake using the Functional Oral Intake Scale (FOIS). The FOIS reflects the functional oral intake of patients with dysphagia and has adequate reliability, validity and sensitivity to change in functional oral intake in patients with stroke. It is a seven-point scale (level 1–7), developed to systematically rate the functional level of oral intake of food and liquid. Residents with level 1 (nothing by mouth) till level 6 (total oral diet with multiple consistencies without special preparation but with specific food limitations) will be included. Level 7 shows a total oral diet with no restrictions and therefore no dysphagia. Dysphagia will be diagnosed by a speech therapist.

Residents who are cognitively impaired (mainly suffering from dementia), in a coma or vegetative state, terminally ill, dependent on mechanical ventilation, in day care, in short-term care, or already using an oral hygiene care solution, will be excluded. A physician has to withdraw a resident from the study when the resident's conditions have altered according to one of the exclusion criteria. However, in case pneumonia is the reason for the condition alteration, the pneumonia will be registered as a case with respect to the outcome variable. Withdrawn residents will not be replaced because otherwise, in order to determine the incidence of pneumonia, significant bias would be introduced by replacement.

Intervention and control groups
The intervention consists of applying a 0.05% chlorhexidine-containing solution (Perio-aid Maintenance 0.05%, Dentaid BeNeLux BV) twice daily immediately after the usual oral hygiene care. The application method depends on the severity of the dysphagia. The speech therapist indicates the application method by considering the FOIS level with respect to the toleration of thin liquids by the resident. Residents who tolerate thin liquids have to rinse with the 0.05% chlorhexidine-containing solution for 30 s twice daily immediately after the usual oral hygiene care. Residents with severe dysphagia, who cannot tolerate thin liquids, have to clean their teeth, gums, tongue, palate, and buccal mucosa with a gauze containing a 0.05% chlorhexidine-containing solution twice daily, immediately after the usual oral hygiene care. The control group receives the usual oral hygiene care without addition of an oral rinse. In both groups, the usual oral hygiene care is not standardised. When the usual oral hygiene care would be standardised, this would be an intervention as well and no effect of the additional chlorhexidine-containing solution could be established.

Monitoring
In the intervention group, the application of the chlorhexidine-containing solution will be guided and monitored after each period of 2 weeks by a group of visiting study assistants who have been instructed by the principal investigator about the use of a strict guiding and monitoring protocol. Every study assistant will visit the same care home ward(s) each time. In each care home, two trained internal study supervisors will monitor the usual daily oral hygiene care, including the application of the chlorhexidine-containing solution. The internal study supervisors will be nurses, dental hygienists or dentists. After every 2 weeks, the study assistants will monitor whether the chlorhexidine-containing solution has been used. The study assistants will monitor the potential side effects of the chlorhexidine-containing solution by oral assessments and by evaluations with the internal study supervisors. After each visit, the study assistants will report their findings using a standardised Clinical Report Form (CRF). The principal investigator will visit the intervention groups to evaluate the study with the internal study supervisors after 6 and 12 months after the start of the study. During those visits, the principal investigator will also do oral assessments with the participants in the intervention group for potential side effects of the chlorhexidine-containing solution. On top of that, the control groups will be monitored with the same monitoring protocol after each period of 4 weeks. In the control groups, the principal investigator will evaluate the study with the internal study supervisors at 6 months and at the end of the study. No follow-up monitoring of the participated care home residents will take place after the end of the study.

Data collection
Research data will be gathered at baseline by the principal investigator (the first author of this article) and the assistant examiners (dental hygienists and bachelor dental hygiene students). The assistant examiners are educated by the principal investigator to perform a short standardised oral examination and to gather data from the residents' medical records. This short standardised oral examination will determine the number of teeth and implants present and the presence of removable dentures. The following additional data are gathered from the patient's medical record: age, gender, diagnosed diseases and actually used medication. An
An overview of the data which will be collected is presented in Table 1. Subsequently, the level of care dependency will be determined by a care provider using the Care Dependency Scale.25

In case symptoms of pneumonia occur in the participating residents during this study, they will be physically examined by a physician. If pneumonia is diagnosed, the physician will inform the principal investigator in order to register the pneumonia as a case with respect to the outcome variable. The diagnosis and related clinical symptoms of pneumonia will be registered using a CRF. When a participant has more than one episode of pneumonia during the trial, all episodes will be monitored and reported. Any other alterations in medical conditions of the participant, such as hospitalisation, death or discontinuation of the study, will be reported by the physician using different CRFs. All CRFs will be collected by the assistant examiners every 2 weeks.

**Outcome measures**

The primary outcome variable is the incidence of pneumonia diagnosed by a physician, using a set of strictly described criteria. Since uniform criteria for diagnosing pneumonia in care home residents are lacking, a set of criteria will be assessed by a Delphi panel of experts before the start of the study. To determine the incidence of pneumonia, every episode of pneumonia with the included residents within the study period of 1 year will be registered.

Secondary outcomes are correlations between age, gender, diagnosed diseases, dysphagia severity, care dependency, actually used medication, number of teeth and implants present, and presence of removable dentures and the incidence of pneumonia in physically disabled care home residents with dysphagia who did or did not apply a 0.05% chlorhexidine-containing solution to their usual oral hygiene care.

**Statistical analysis**

The categorical and continuous variables will initially be subjected to an exploratory data analysis, applying a variety of mostly graphical methods and methods for testing the necessary assumptions. The effect of the intervention on the incidence of pneumonia will be determined using a Cox regression analysis. The intervention will be the independent variable, whereas the dependent variable is the occurrence of pneumonia. In addition to this main analysis, the influence of the other research variables on the incidence of pneumonia will be determined using an elaborate Cox regression analysis (age, gender, diseases diagnosed, dysphagia severity, care dependency, actually used medication, number of teeth and implants present and presence of removable dentures). These variables can be used in case any imbalance emerges in the clustering of the care homes. In this survival model, a frailty model which aims to account for heterogeneity caused by unmeasured covariates will be included to take into account the clustering of data within care homes. A 95% CI will be used with all estimated values. Recording the moment and the reason of withdrawal of participating residents facilitates the use of the data gathered from all participating residents for statistical analysis, even if they were withdrawn prematurely.

**ETHICS AND DISSEMINATION**

The study is conducted according to the principles of the Declaration of Helsinki (V.7c, 2004) and in accordance with the Medical Research Involving Human

<table>
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<th>Table 1 Data collected, outcomes, scales and collection moment</th>
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| Functional Oral Intake Scale | Level 1: Nothing by mouth  
Level 2: Tube dependent with minimal attempts of food or liquid  
Level 3: Tube dependent with consistent oral intake of food or liquid  
Level 4: Total oral diet of a single consistency  
Level 5: Total oral diet with multiple consistencies, but requiring special preparation or compensations  
Level 6: Total oral diet with multiple consistencies without special preparation, but with specific food limitations  
Level 7: Total oral diet with no restrictions | Baseline |
| Care Dependency Scale | Completely care dependent, score <25  
To a great extent care dependent, score 25–44  
Partially care dependent, score 45–59  
To a limited extent care dependent, score 60–69  
Almost independent, score >69 | Baseline |
| Patient’s medical record | Gender, age  
Medical diagnoses and medications used actually  
Number of teeth and implants, presence of removable dentures  
A set of strictly described criteria | Baseline  
When symptoms occur during study |


Open Access
Subjects ACT (WMO). The trial has been registered in the Netherlands in the National Trial Register: TC=3515.

Written and informed consent will be contained from all participating care homes and care home residents. In case a resident is incapacitated, their legal representative will be asked to consent instead. Regardless of informed consent, signs of objection expressed by the resident or deterioration of their health will be closely monitored. If any objection or deterioration of their health occurs, the study will be stopped immediately. Possible adverse events related to study participation will also be monitored closely. Implementation and conduct of the study will be monitored by the investigators (authors).

CRF will be handled and stored confidentially. These CRFs and residents’ personal data will be stored in two different files in order to ensure confidentiality. The data from both files cannot be traced to the participating residents. To safeguard these files, only the investigators have access to them by using a password.

The results of this study will be published in peer-reviewed journals and in relevant news channels for clinicians. Duplicate publication will be avoided.

DISCUSSION

Using cluster randomisation may result in random effect and cluster selection bias. Therefore, a frailty model which aims to account for heterogeneity, caused by unmeasured covariates, will be included in the Cox regression analysis to take into account the clustering of data within care homes.

Chlorhexidine is a widely used oral rinse that is often applied in critically ill populations. Adverse effects due to chlorhexidine are rare, but have been reported. Very rarely, applying a chlorhexidine-containing solution causes an allergic and/or hypersensitivity reaction. Other side effects are discoloration of teeth, removable dentures, mucosa or tongue, temporary taste disorder, swelling of salivary glands, and pain. However, these side effects are discoloration of teeth, removable dentures, mucosa or tongue, temporary taste disorder, swelling of salivary glands, and pain. However, these side effects are discoloration of teeth, removable dentures, mucosa or tongue, temporary taste disorder, swelling of salivary glands, and pain. However, these side effects are discoloration of teeth, removable dentures, mucosa or tongue, temporary taste disorder, swelling of salivary glands, and pain. 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