Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis

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CRD summary
The review findings were not conclusive but indicated that routine oral care with chlorhexidine gluconate may prevent lower respiratory tract infections in cardiac surgery patients receiving mechanical ventilation. Benefit was limited for non-cardiac surgery patients. This was a generally well conducted review. The authors' conclusions seem sufficiently cautious and likely to be reliable.

Authors' objectives
To assess the effects of routine oral care with chlorhexidine gluconate on patient outcomes in patients receiving mechanical ventilation.

Searching
PubMed, EMBASE, CINAHL and Web of Science were searched up to July 2013 without date or language restrictions. Search strategies were presented. Lists of included studies in previous meta-analyses and reference lists of relevant articles were searched manually.

Study selection
Eligible studies were randomised controlled trials (RCTs) that compared the effects of daily oral care with additional chlorhexidine versus a non-active control in adults who were receiving mechanical ventilation. Eligible trials were required to report at least one of the outcomes of pneumonia, mortality, duration of mechanical ventilation, intensive care length of stay, hospital length of stay and antibiotic use. Trials were excluded if they reported outcome data in less than 80% of the randomised patients.

Included trials were conducted in various countries including one in UK. Trials were published between 1996 and 2012. Most of the included trials were performed in non-cardiac surgical units but just over half of the patients included in this review were cardiac surgery patients. Most trials enrolled patients who required 48 hours, 72 hours or at least five days of mechanical ventilation.

Chlorhexidine was administered as a solution, oral rinse or gel at doses of 0.12%, 0.2% or 2% two to four times daily. Control groups received various types of inactive solutions or gels. Pulmonary outcomes were defined as "ventilator associated pneumonia" in non-cardiac trials; definitions differed for cardiac trials.

Two reviewers independently screened studies for inclusion; discrepancies were resolved through consensus.

Assessment of study quality
Two reviewers independently assessed study quality according to criteria of randomisation methods, allocation concealment, blinding and completeness of follow-up. Any discrepancies between reviewers were resolved by consensus.

Data extraction
Patient outcome data were extracted to calculate relative risks for dichotomous outcomes and mean differences for continuous outcomes, along with 95% confidence intervals, for each included study. Data were extracted on an intention-to-treat basis, where possible. Primary authors were contacted where necessary.

Two reviewers independently extracted outcome data; discrepancies were resolved by consensus.

Methods of synthesis
Where at least two studies reported data on outcomes, a Mantel-Haenszel random-effects model was used to estimate overall relative risks and weighted mean differences, along with 95% confidence intervals. Data were re-analysed using
Subgroup analyses were performed based on type of surgery (cardiac versus non-cardiac) and stratified by study design (open label versus double blind). Sensitivity analyses were conducted by excluding data from abstracts and for chlorhexidine dose and preparation. Statistical heterogeneity was assessed using the I² statistic.

Publication bias was assessed using funnel plots.

**Results of the review**

Sixteen studies (3,630 patients, range five to 954) were included in the review. Nine trials were double blind and seven had complete or no blinding. Most of the double blind and single blind trials also met other quality criteria. Trials with no blinding tended to be generally poorly reported in terms of quality criteria.

**Pulmonary outcomes** (16 RCTs): Incidence of pulmonary outcomes was statistically significantly reduced in patients receiving chlorhexidine (RR 0.73, 95% CI 0.58 to 0.92; 16 RCTs; I²=43%). Subgroup analyses indicated that reductions remained statistically significantly significant in cardiac patients (RR 0.56, 95% CI 0.41 to 0.77; three RCTs; I²=0%) but when stratified by study design the results were significant only in double blind studies. There were no statistically significant differences in incidence of ventilator-associated pneumonia in non-cardiac trials regardless of study design. Results for other analyses were not statistically significant (fully reported in the review).

**Mortality** (12 RCTs): There were no statistically significant differences in rates of mortality between treatment groups for the overall estimate or any additional analyses.

**Other outcomes:** There were no statistically significant differences between treatment groups for duration of mechanical ventilation (six RCTs), intensive care unit hospital stay (six RCTs) or hospital length of stay (three RCTs). Results on antibiotic use for individual trials were reported in the review.

There was no evidence of significant publication bias for pulmonary and mortality outcomes.

**Authors’ conclusions**

The findings were not conclusive but indicated that routine oral care with chlorhexidine may prevent lower respiratory tract infections in cardiac surgery patients. Benefit was limited for non-cardiac surgery patients.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. The literature search was satisfactory. Each stage of the review was performed in duplicate, which reduced the potential for bias.

Trial quality was assessed and formed part of the statistical analyses. Appropriate methods were used to combine data. The authors highlighted substantial heterogeneity and wide confidence intervals for mortality outcomes. They also highlighted the clinical heterogeneity across all included trials and acknowledged some of the limitations relating to definitions and reliability of ventilation associated pneumonia as an outcome.

This was a generally well-conducted review. The authors’ conclusions seem appropriately cautious and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that the lack of evidence that adding chlorhexidine to routine oral care benefited non-cardiac surgery patients should prompt re-examination of hospital policies recommending its use.

**Research:** The authors stated that large sufficiently powered RCTs were required to assess the safety and benefits of routine oral care with chlorhexidine. Future trials should include acute respiratory distress syndrome as an outcome. Further evaluation of potential increased mortality in non-cardiac patients was required.

**Funding**

Not stated.
Bibliographic details

PubMedID
24663255

DOI
10.1001/jamainternmed.2014.359

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Adult; Anti-Infective Agents, Local /therapeutic use; Antibiotic Prophylaxis; Chlorhexidine /analogs & derivatives /therapeutic use; Humans; Pneumonia, Ventilator-Associated /prevention & control; Respiration, Artificial /adverse effects; Risk

AccessionNumber
12014023439

Date bibliographic record published
08/04/2014

Date abstract record published
10/04/2014

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.