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Research Article

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Preoperative Nasopharyngeal Decolonization using Mupirocin and Chlorhexidine in Preventing Surgical Site Infection: A Meta-Analysis

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Abstract

Background: *Preoperative decolonization is a preventive strategy for surgical site infection. Clinical trials have been done to prove or disprove the efficacy of decolonization in the prevention of surgical site infection however; great heterogeneity in results was noted in many published studies.*

Objective: *The aim of this study is to determine whether preoperative decolonization reduces the risk of surgical site infection.*

Method: *PUBMED and Google free texts search terms: "decolonization" and "Surgical Site Infection" Inclusion criteria: >18 years old of either gender undergoing any surgery, studies included are all randomized controlled trials (RCT).*

Results: *Using the random effects model, the computed summary statistic was 0.59 (CI 0.37-0.94) in favor of the experimental treatment however due to substantial heterogeneity (Tau2 of 0.25 Chi 2 30.34 and I2 of 84%), we cannot draw definite conclusion from the meta-analysis. Subgroup analysis however using both mupirocin nasal swab and chlorhexidine gargle as preoperative decolonization generated the summary statistic 0.40 (CI of 0.23-0.69), no heterogeneity (Tau2 of 0, Chi2 of 0.09 and I2 of 0.), and was noted to be in favor of the experimental treatment.*

Conclusion: *Pre-operative decolonization using both mupirocin and chlorhexidine for preoperative decolonization showed that it could significantly prevent surgical site infection.*

Keywords: Preoperative Decolonization, Surgical Site Infection, Mupirocin, Chlorhexedine

Background of the Study

Surgical site infection (SSI) is a type of healthcare-associated infection in which a wound infection occurs after an invasive (surgical) procedure. A surgical site infection may range from a spontaneously limited wound discharge within 7–10 days of an operation to a life-threatening postoperative complication [1]. Another definition classified SSI as being either incisional or organ/space [1].

Superficial Incisional SSI	Organ/Space SSI
Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision and at least one of the following:	Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation and at least one of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.	1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.	2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.

3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culturenegative.	3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.	4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Most surgical site infections are caused by contamination of an incision with microorganisms from the patient's own body during surgery. Infection caused by microorganisms from an outside source following surgery is less common [2]. According to National Nosocomial Infections Surveillance System (NNIS), Staphylococcus aureus, coagulasenegative staphylococci, Enterococcus spp., and Escherichia coli remains to be the mostfrequently isolated pathogens. An increasing proportion of SSIs are caused by antimicrobial resistant pathogens, such as methicillin-resistant S. aureus (MRSA) [1]. The prevalence of S. aureus nasal carriage is approximately 20-25%, but varies among different populations. Age, underlying illness, race, certain behaviors, and the environment in which the person lives or works influence it. The link between S. aureus nasal carriage and development of subsequent S. aureus infections has been established in patients on hemodialysis, on continuous ambulatory peritoneal dialysis, and those undergoing surgery. S. aureus nasal carriers have a two-to tenfold increased risk of developing S. aureus surgical site or intravenous catheter infections. Thirty to 100% of S. aureus infections are due to endogenous flora and infecting strains were genetically identical to nasal strains [3].

The majority of surgical site infections are preventable. Measures can be taken in the pre-, intra- and postoperative phases of care to reduce risk of infection. Pre-operative phase prevention includes preoperative showering, nasal decontamination, and antibiotic prophylaxis [3]. In relation to our study, 3 treatment strategies may eliminate nasal carriage: locally applied antibiotics or disinfectants, systemic antibiotics, and bacterial interference. Among these strategies, locally applied or systemic antibiotics are most commonly used [3]. Some studies showed reduction of SSI with the application of mupirocin nasally and oropharyngeal rinse [1, 5]. Newer studies, however, such as the one conducted by Shuman et al failed to show any significant difference in the incidence of SSIs in patients who received preoperative decolonization from those who did not. Thus, results were varied and studies done yielded equivocal results, The aim of this study is to determine whether preoperative decolonization reduces the risk of surgical site infection [6].

Methods

Study Selection

Subjects included in the studies were analyzed according to the following inclusion criteria: subjects >18 years old of either gender scheduled to undergo any type of surgery (cardiothoracic, abdominal, orthopedic, head and neck). The subjects included may or may not have been screened for nasal carriage of S. aureus.

Exclusion criteria includes case reports, commentaries, guidelines, editorials, animal studies, risk factor studies, studies that did not include an intervention, or pediatric studies. The following were also excluded: presence of active infection from S. aureus at the time of randomization, known allergy to mupirocin or chlorhexidine, pregnancy, breast-feeding, use of mupirocin in the preceding 4 weeks, and presence of a nasal foreign body.

Types of Interventions

Types of preoperative decolonization consisted of intranasal mupirocin, oropharyngeal rinse or nasal ointment containing either chlorhexidine gluconate versus placebo.

Primary Outcome

The primary outcome is the decrease in the incidence of Surgical Site infection (SSI) treated with preoperative decolonization.

Data Source and Searches

A literature search using the PUBMED database and Google free texts were done using "decolonization" (MeSH OR free text) and "Surgical Site Infection" (MeSH OR free text), limited to human subjects, randomized controlled trials, and published articles only (Figure 1).

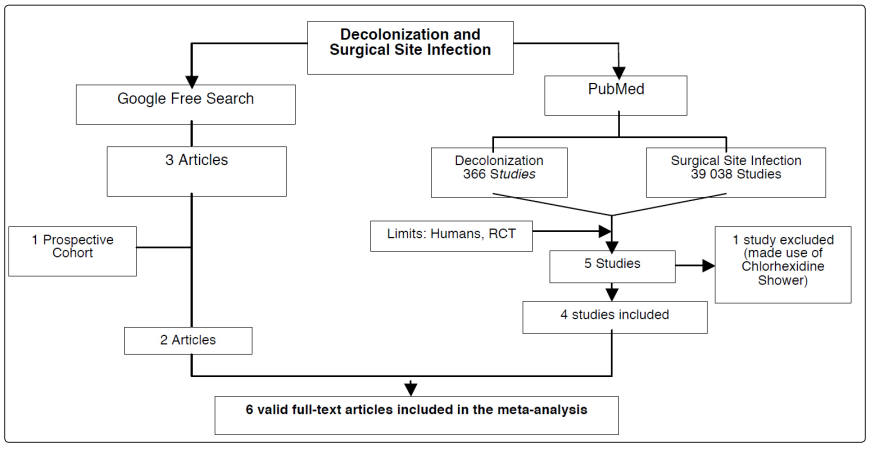

Figure 1: Diagram for systematic search of studies

Data Extraction and Validity Assessment

All randomized clinical trials were considered for inclusion in the meta-analysis, which were analyzed, discussed and appraised by the authors (M.B. and R.S.) according to the set criteria. A third investigator (G.O.) was available for arbitration in the event of discordance of the extracted data, but no significant disagreement was encountered.

Study Quality

The same reviewers assessed the quality of the included studies independently. The quality items assessed were allocation concealment, intention-to-treat analysis, completeness of follow-up, and blinding of investigators, participants and outcome assessors.

Assessment of Risk of Bias in Included Studies

All included studies are randomized, controlled trials. Each study was critically appraised with regards to methods of minimizing selection bias, performance bias, exclusion bias and detection bias. Three reviewers independently appraised each journal. All three studies included received a quality scale for meta-analysis overall score of not less than B.

Data Analysis and Synthesis

The data were entered in the Cochrane Review Manager Software version 5.0. All outcomes were examined using the random effects model whether significant or not. Dichotomous data were analyzed by calculating the odds ratio with 95% confidence interval and a significant p value of 1. All analyses were according to intention to treat principle wherein all randomized patients were included in the analysis of data. Forest plots were then interpreted whether results favored Decolonization or Placebo.

Table 1: Characteristics of the Studies Included

	Perl 2002	Kalmeijer 2002	Horiuchi 2006	Segers 2006	Bode 2010	Shuman 2012
Methods	**RCT**	**RCT**	**RCT**	**RCT**	**RCT**	**RCT**
Participants	Adults who underwent elective and non emergenc y cardiothor acic general non on cologic, gynecolog ic or neurologic surgical procedure s	Patients undergoing elective orthopedic surgery in which prosthetic implant was utilized	Patients positive for MRSA	Patients age > 18 years old who will undergo sternotom y	Patients positive for nasal Staphylo coccus aureus	Patients who will undergo head and neck surgery
Interventions	2 % mupirocin calcium ointement vs lacebo ointment	Mupirocin nasal ointment vs placebo (paraffin)	Mupirocin calcium hydrate TID x 5 days, intranasal mupirocin + inhalation of arbekacin sulfate BID, or intranasal mupirocin +inhalation of arbekacin sulfate + oral TMPSMX BID	0.12% Chlorhexi dine gluconate oral rinse and gel vs placebo	2% mupirocin ointment in combinati on with 40mg chlorhexi dine gluconate soap vs placebo ointment and placebo soap	2% mupirocin ointment and 2% chlorhexidi ne gluconate solution vsNone
Outcomes	Rate of S. aureus infections at surgical sites	Rate of surgical site infection	Post op PEG peristomal wound infection	Incidence of surgical site infection	Preventin g SSI	Incidence of surgical site infection
1. Randomization	Met	Met	Met	Met	Met	Met
2.Allocat ion Conce alment	Met	Met	Not Stated	Met	Met	Not Met
3.Baseline Charac teristics	Met	Met	Met	Met	Met	Met
4.Blinding of Partici pants	Met	Met	Not Stated	Met	Met	Not Met
5. Blinding of Caregivers	Met	Met	Not Stated	Not met	Met	Not Met
6. Blinding of outcome assess	Met	Met	Not stated	Not Stated	Not Stated	Not Met
Intention to treat	Met	Met	Partially Met	Met	Not Met	Met
Follow up rate	Met	Met	Met	Met	Met	Met
BIAS						
Selection Bias	Low Risk	Low risk	Intermediate Risk	Low Risk	Low Risk	Intermediate Risk
Performance Bias	Low risk	Intermediate risk	Intermediate risk	Intermediate Risk	Intermediate Risk	Intermediate Risk
Detection Bias	Intermediate Risk	Intermediate risk	Intermediate Risk	Low Risk	Low Risk	Intermediate Risk
Overall Rating	B	B	B	B	B	B

Assessment of Sources of Heterogeneity

Owing to the differences in study population, intervention and endpoints, the data extracted from each study were assessed for heterogeneity. This was done using a chi-square test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I2 test. An I2 value greater than 25% was considered to have low level of statistical heterogeneity while those greater than 50% and 75% were deemed to have moderate and high levels of heterogeneity, respectively. If the I2 measured was noted to be substantial (>50%), statistical analyses on the possible source of such was conducted. The influence of each study through its sample size and effect size were determined and were excluded one at a time to assess for robustness of results. Subgroup analysis was likewise done to address substantial heterogeneity.

Data and Analysis

Six studies were included in the analysis of pre-operative decolonization using mupirocin or chlorhexidine versus placebo in the prevention of surgical site infection. Using the random effects model studies showed substantial heterogeneity with Tau2 of 0.25, Chi 2 30.34 and I2 of 84%. Of the 5 studies Perl showed the greatest weight compared to other studies. The computed summary statistic was 0.59 with CI 0.37-0.94 in favor of the experimental treatment however due to substantial heterogeneity we cannot draw definite conclusion from this meta-analysis (Figure 2).

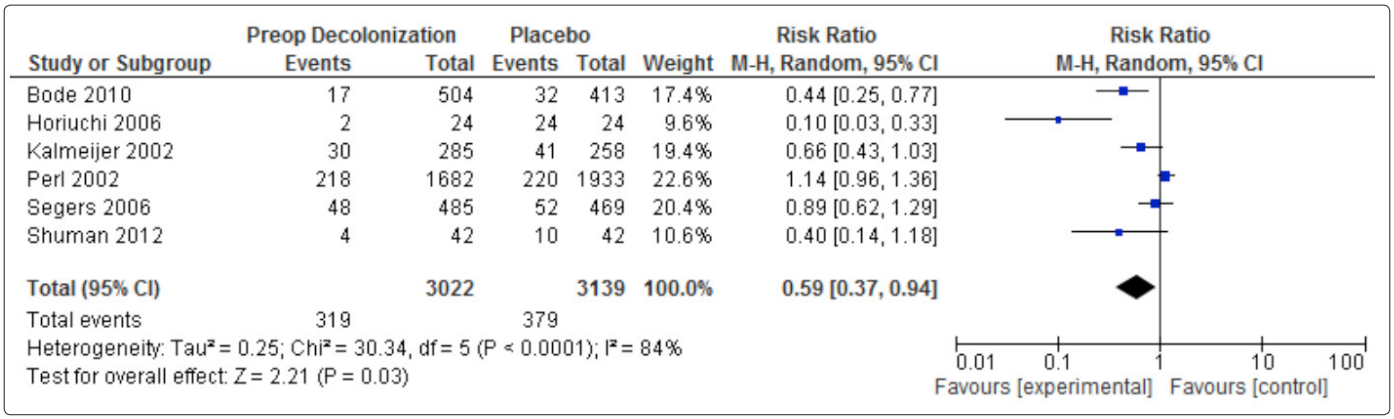

Figure 2: Preoperative Decolonization versus Placebo in preventing Surgical Site infection

Subgroup Analysis

The following is the subgroup analysis for studies which only used mupirocin in the prevention of SSI namely the ones done by Horiuchi et al in 2006, Kaljeimer et al in 2002 and Perl et al in 2002. The summary statistic generated was in favor of the experimental treatment at 0.46 with a 95% confidence interval of 0.15-1.43. However, there was substantial heterogeneity between the three studies with a Tau of 0.7, Chi2 of 20.86, and I2 of 90. Hence, we cannot draw conclusion from this meta-analysis (Figure 3).

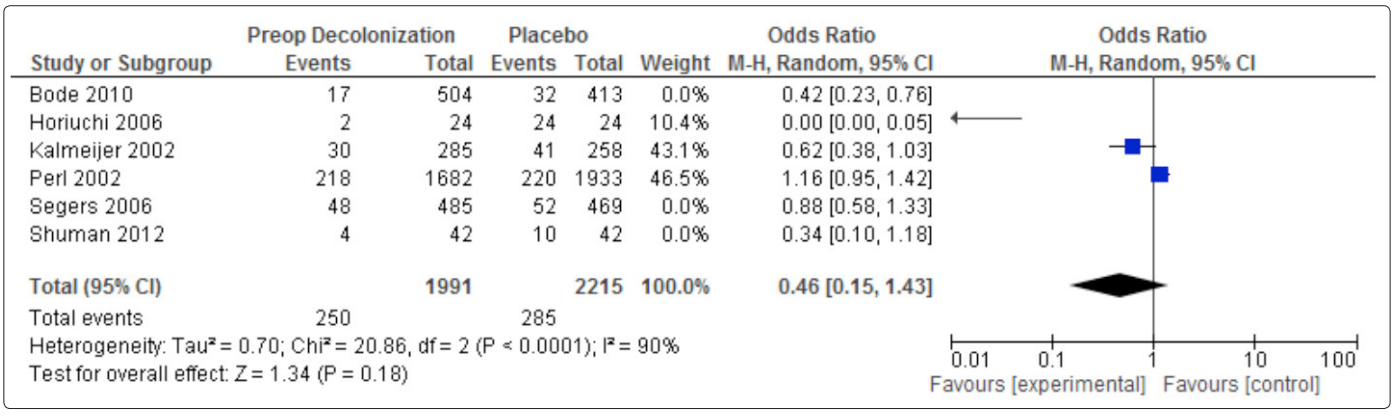

Figure 3: Subgroup analysis on studies which used mupirocin alone in preoperative decolonization versus placebo in preventing surgical site infection

Limiting the analysis to the two studies by Bode et al 2010 and Shuman et al 2012, which used both mupirocin nasal swab and chlorhexidine gargle for preoperative decolonization, no heterogeneity was appreciated with Tau2 of 0, Chi2 of 0.09, and I2 of 0. The summary statistic generated was 0.40 with a narrow 95% CI of 0.23-0.69 favoring treatment. Thus, we can conclude that the use of both mupirocin nasal swab and chlorhexidine gargle for preoperative decolonization may be effective in preventing SSIs.

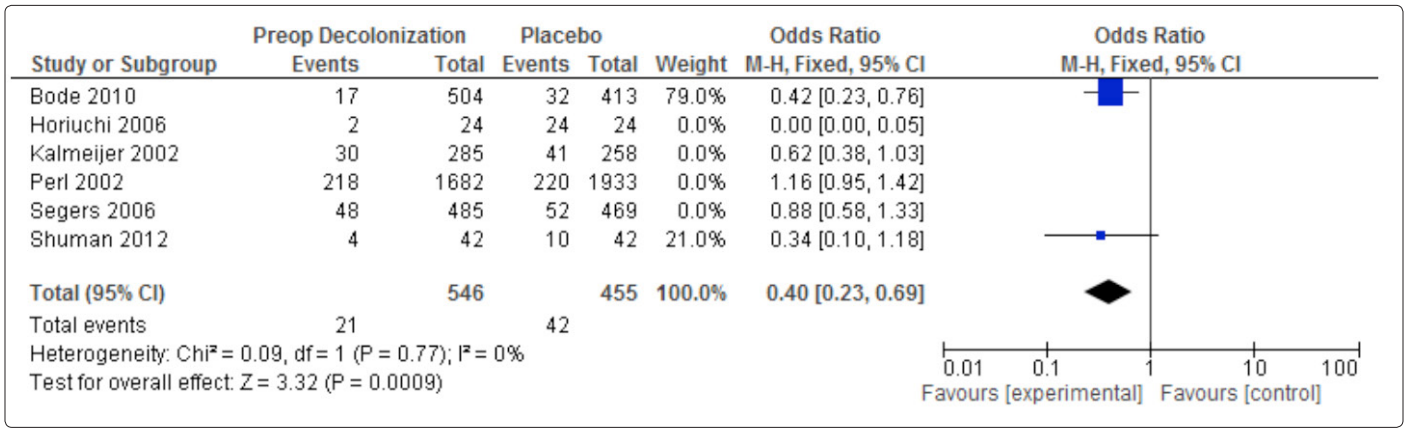

Figure 4: Subgroup analysis on studies which used both mupirocin and chlorhexidine in preoperative decolonization

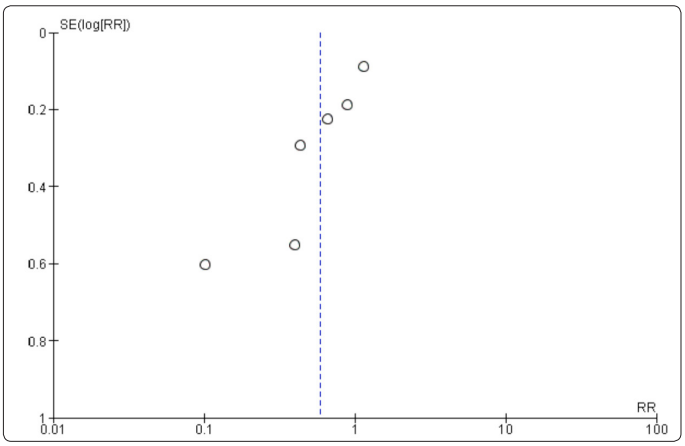

Figure 5: Funnel plot Pre-operative decolonization versus placebo in preventing surgical site infection

Above is the funnel plot generated from the six studies included in the meta-analysis. Asymmetry in funnel plots may indicate a possibility of publication bias in this meta-analysis.

Discussion

Surgical site infection can be defined as being present when pathogenic organisms multiply in a wound giving rise to local signs and symptoms. Infection in the surgical wound may prevent healing taking place so that the wound edges separate or it may cause an abscess to form in the deeper tissues. Thus prevention of the occurrence of SSIs is of utmost importance.

Subgroup analyses were conducted on the type of intervention used. Figure 3 was limited to studies, which used mupirocin alone versus placebo in the prevention of SSI (Perl 2002, Kaljeimer 2002 and Horiuchi 2006). In this subgroup analysis, there was marked heterogeneity between the three studies, which may be due to the different surgical interventions used (cardiothoracic surgery, orthopedic surgery and PEG insertion). One factor that we should consider is the possibility of mupirocin resistance. There are several studies in which high-level mupirocin resistance in S. aureus is associated with mupirocin decolonization failure. A randomized controlled trial done by Simor et al showed that the colonization with a strain of S. aureus with high-level mupirocin resistance was independently associated with decolonization failure [7]. Another study on prospective evaluation of mupirocin decolonization showed the posttreatment nares cultures on day 3 were low for high-level mupirocin resistant strains at 27.7% compared to those of mupirocin-susceptible strains (78.5%) [8]. The second subgroup analysis (Figure 4) was limited to the use of mupirocin and chlorhexidine as intervention (Bode 2010 and Shuman 2012). The fixed effects model was utilized in order to assure that the large sample size of the study of Bode et al 2010 would have minimal effect on the overall statistic. The summary statistic was in favor of the use of preoperative decolonization versus placebo. Set against the background of no heterogeneity, a more definite conclusion can be drawn such that the use of both mupirocin and chlorhexidine is effective in preventing surgical site infections. Mupirocin and chlorhexidine are considered to be relatively safe. However, since S. aureus strains can become resistant to mupirocin, one can recommend restricting the use of this agent to known carriers who are at risk for infection.

Potential Bias and Confounders

Studies included in this meta-analysis were all grade B. Aside from the differences on the study interventions, the majority of the studies included investigated the rate of surgical site infections after undergoing clean surgeries (i.e. those of the head and neck and orthopedic surgeries). Moreover, differences in the operative time according to the different surgeries investigated may also have effect on the incidence of SSIs.

Study Limitations

The study failed to include unpublished and local data. The study search also did not include other databases such as Embase, Medline and Clinical Trials.

Funding: None

Conflict of interest: None

Authors' Conclusion

Implications for Practice

Pre operative decolonization compared to placebo apparently showed significant effect in the prevention of Surgical Site infection. However there was great heterogeneity noted in the studies included in this meta-analysis hence the above conclusion cannot be drawn with certainty. Conducting a subgroup analysis on the use of both mupirocin and chlorhexidine for preoperative decolonization showed that it can significantly prevent surgical site infection.

Implications for Research

There are several trials regarding the effectiveness of pre-operative decolonization in preventing SSI though these studies are outdated. The combined analyses of statistics drawn from the different studies in this meta-analysis showed marked heterogeneity hence warranting the inclusion of more studies specifically local data. More studies on the use of mupirocin and chlorhexidine for preoperative decolonization should be done as the subgroup analysis conducted in this study showed significant effect on the said intervention in preventing surgical site infection.

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