Original article

Topical intrawound application of vancomycin powder in addition to intravenous administration of antibiotics: A meta-analysis on the deep infection after spinal surgeries

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\textbf{A B S T R A C T}

Background: The intrawound application of vancomycin powder in addition to intravenous administration of antibiotics has been reported to be an easy and cost-efficient technique for reducing the deep infection, which is a serious complication of spinal surgeries. The aim of the present meta-analysis was to derive a preliminary estimation on the clinical performance of this technique.

Hypothesis: The intrawound application of vancomycin powder in addition to intravenous administration of antibiotics may significantly reduce the risk of deep infection after spinal surgeries.

Materials and methods: Studies were identified from PubMed and EMBASE searches. After comprehensive review, data were extracted from eligible studies. A meta-analysis was performed to generate pooled odds ratio (OR) of this technique.

Results: Eight studies (4592 patients) were included. The pooled OR (95\% CI) was 0.22 (0.07–0.63), \(I^2\) value was 65.2\% \((P=0.005)\). The pooled ORs were stable in sensitivity analyses. No analysis of subgroup, meta-regression or publication bias was performed because of inadequate included studies.

Discussion: The intrawound application of vancomycin powder in addition to intravenous administration of antibiotics may significantly reduce the risk of deep infection after spinal surgeries. Further studies with large sample size and high quality are needed to provide more evidences.

\textit{Level of evidence:} II

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1. Introduction

The deep infection, which is very difficult to treat, represents a severe complication of spinal surgeries\cite{1} with a reported incidence rate ranging from 1.9–13\% \cite{2–6}. Additional surgical treatments are needed for the exploration, sampling and debridement. Meanwhile, the antibiotics therapy has to be intensively applied to eradicate the underlying infection. This complication significantly lengthens hospital stay, causes excessive health care costs and increases morbidities \cite{7,8}.

Prophylactic antibiotics are usually administrated systemically to prevent deep infections after spinal surgeries. However, the local ischemia, hematoma and seroma of surgical site impair the intravenous delivery of antibiotics, leading to inadequate local concentrations \cite{9}. Additionally, it has been reported that major spine infections are bacterial monomicrobial caused by \textit{Staphylococcus aureus} \cite{10}. Methicillin-resistant \textit{S. aureus} (MRSA) \cite{11}, which has widely spread, results in unsatisfactory responses to cephalosporin administrations.

To decrease the deep infection rate, adjunctive prophylaxes to cephalosporin administrations are primarily studied in past several decades. Recently, several groups reported the intrawound application of vancomycin powder in addition to intravenous administration of antibiotics in spinal surgeries; they demonstrated that it is easy, cost-efficient and promising for prophylaxis of deep infections \cite{5,12–18}. We conducted the present meta-analysis to quantitatively summarize the effect of intrawound vancomycin powder application in addition to intravenous administration of

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antibiotics in spinal surgeries, and providing evidences of further clinical applications.

2. Materials and methods

2.1. Study source

A systematic literature search was performed using PubMed and EMBASE databases, aiming on studies published until March, 2014. The object was limited to “human”. Medical Subject Heading (MeSH) terms “vancomycin”, “local”, and the other individual corresponding free terms were used. A comprehensive search of all reference lists of review articles was conducted to find potential relevant studies.

Inclusion criteria were as follows: (a) case-control design, (b) sample sizes of both control and experiment groups were equal to or larger than 10, (c) antibiotics were administrated intravenously before and after surgeries, (d) patients received spinal surgeries with or without intrawound vancomycin powder application, (e) follow-up equal to or longer than 1 month, (f) postoperative deep infections were diagnosed by bacterial cultures, (g) the effect of intrawound vancomycin powder application on postoperative infection was described by odds ratios (OR) and 95% confidential intervals (95% CI), or ORs (95% CI) can be calculated from the published data.

Studies were excluded on the basis of following criteria: (a) reviews, meta-analyses, abstracts or letters, (b) sample sizes of control or experiment group smaller than 10 pro group, (c) overlapping articles, (d) superficial infections, (e) the postoperative deep infection was not diagnosed by bacterial culture, (f) follow-up shorter than 1 month, (g) ORs or 95% CIs cannot be got from the published data.

Two individual investigators (QP and GJ) evaluated independently search results using predefined inclusion and exclusion criteria. Disagreements between two investigators were resolved by a third investigator (LX) after re-checking the original article and a discussion on evidences.

2.2. Data extraction and quality evaluation

Following data were extracted: first authors, years of publication, countries, sample sizes, participants' characteristics, vancomycin powder doses, vancomycin-related adverse reactions, responsible pathogens for infections, ORs (95% CIs) or data for OR (95% CI) calculation if there was no direct OR in article.

Qualities of included studies were evaluated using the Newcastle–Ottawa Scale (NOS). Each study was assessed based on three broad perspectives, including selection, comparability and exposure, with a score ranging from 0 to 9. We considered a study with an NOS score of 0–3, 4–6, 7–9 as low, medium, or high quality.

2.3. Statistical analysis

Effect measures of interest were OR and corresponding 95% CI. The OR (95% CI) was calculated by using $2 \times 2$ contingency table of intrawound vancomycin powder application and postoperative deep infection (SPSS 17.0, SPSS Inc., USA), if the original article had not provided it.

Statistical heterogeneity among studies was evaluated using the Cochran’s Q statistic, $P$ values, and $I^2$ statistics (Stata 12.0, Stata Corporation, USA). Heterogeneity was considered significant if $I^2$ value $>50$ or $P < 0.05$. Considering demographics of different cohorts, differences in performed surgeries and operators' experiences, the random-effects model was used to calculate the pooled OR (95% CI).

One-study - removed sensitivity analyses were performed to reflect the influence of the individual data and specific studies on the summary OR. Subgroup analyses, univariate and multivariable regression analyses were performed to find impact factors of the summary OR if sufficient studies were available. $P < 0.05$ was considered statistically significant. Publication bias was explored by Harbord-Egger analysis [19] if sufficient studies were available. $P < 0.05$ was considered statistical significant.

3. Results

A total of 2164 studies have been searched in PubMed and EMBASE (Fig. 1). Two thousand one hundred and fifty-four studies were excluded basing on their titles and abstracts. Rest, 11 studies were checked in full-text. Three studies [15,18,20] were excluded because of inadequate data on deep infection, deep infection was not determined by bacterial culture and the lack of follow-up information, respectively. Finally, eight studies [5,12–14,16,17,21,22] were included in this meta-analysis.

3.1. Characteristics and NOS scores of included studies

Eight included studies were published between 2011 and 2014. A total of 4592 patients were included. Characteristics of these studies and NOS scores were shown in Table 1. Clinical details were shown in Table 2.

3.2. The effect of intrawound vancomycin powder application on postoperative infections

The pooled OR (95% CI) was $0.22 (0.07–0.63)$, $I^2$ value was 65.2% ($P = 0.005$). Fig. 2 shows detail results.

3.3. Sensitivity analysis, subgroup analysis, meta-regression, and publication bias

In sensitivity analyses, by omitting one study at each time, the pooled ORs were not qualitatively changed, ranging from 0.23 to 0.47. Publications of two teams [21,22], which demonstrated insignificant effects of vancomycin on reducing deep infection, could be the cause of significant heterogeneity. The
Table 1
Patient characteristics and quality of included studies.

<table>
<thead>
<tr>
<th>First author</th>
<th>Country</th>
<th>Group with local vancomycin</th>
<th>Group without local vancomycin</th>
<th>Follow-up</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(year)</td>
<td></td>
<td>Sample size</td>
<td>Female</td>
<td>Age</td>
<td>Sample size</td>
</tr>
<tr>
<td>F. Sweet (2011)</td>
<td>USA</td>
<td>911</td>
<td>51%</td>
<td>56.0</td>
<td>821</td>
</tr>
<tr>
<td>K. O’Neill (2011)</td>
<td>USA</td>
<td>56</td>
<td>37%</td>
<td>54</td>
<td>79</td>
</tr>
<tr>
<td>J. Pahys (2013)</td>
<td>USA</td>
<td>195</td>
<td>–</td>
<td>–</td>
<td>806</td>
</tr>
<tr>
<td>R. Strom (2013)</td>
<td>USA</td>
<td>79</td>
<td>43%</td>
<td>60.0</td>
<td>92</td>
</tr>
<tr>
<td>C. Caroom (2013)</td>
<td>USA</td>
<td>40</td>
<td>–</td>
<td>59.8</td>
<td>72</td>
</tr>
<tr>
<td>R. Strom (2013)</td>
<td>USA</td>
<td>156</td>
<td>67%</td>
<td>64.0</td>
<td>97</td>
</tr>
<tr>
<td>V. Tubaki (2013)</td>
<td>India</td>
<td>433</td>
<td>46%</td>
<td>44.3</td>
<td>474</td>
</tr>
<tr>
<td>J. Martin (2014)</td>
<td>USA</td>
<td>156</td>
<td>65%</td>
<td>63.4</td>
<td>150</td>
</tr>
</tbody>
</table>

NOS: Newcastle–Ottawa Scale; –: no information.

Table 2
Clinical details of included studies.

<table>
<thead>
<tr>
<th>First author</th>
<th>Surgeries</th>
<th>Perioperative intravenous antibiotics</th>
<th>Wound irrigation</th>
<th>Intrawound vancomycin dose (g)</th>
<th>Vancomycin Related complications</th>
<th>Pathogens of infected cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>F. Sweet</td>
<td>Thoracic and lumbar instrumented spinal fusion</td>
<td>Cefazolin</td>
<td>–</td>
<td>2</td>
<td>No</td>
<td>S. aureus, coagulase negative staphylococcus organism</td>
</tr>
<tr>
<td>K. O’Neill</td>
<td>Posterior spinal fusion using pedicle screw and rod instrumentation</td>
<td>Cefazolin or clindamycin</td>
<td>Saline (2 Litter)</td>
<td>1</td>
<td>No</td>
<td>MRSA, Polymicrobial</td>
</tr>
<tr>
<td>J. Pahys</td>
<td>Posterior cervical surgery</td>
<td>Cephalosporin</td>
<td>–</td>
<td>0.5</td>
<td>–</td>
<td>MSSA</td>
</tr>
<tr>
<td>R. Strom</td>
<td>Occipitocervical and cervicothoracic fusion</td>
<td>Cefazolin or vancomycin</td>
<td>Saline with bacitracin (3 Litter)</td>
<td>1</td>
<td>No</td>
<td>MRSA, MRSA, coagulase - negative staphylococci, Gram-negative rods</td>
</tr>
<tr>
<td>C. Caroom</td>
<td>Posterior cervical decompression and instrumentation</td>
<td>–</td>
<td>Saline (volume not described)</td>
<td>1</td>
<td>No</td>
<td>MRSA, Methicillin – resistant Coagulase - negative staphylococci species</td>
</tr>
<tr>
<td>R. Strom</td>
<td>Lumbar laminectomy and posterior fusion</td>
<td>Cefazolin or vancomycin</td>
<td>Saline with bacitracin (3 Litter)</td>
<td>1</td>
<td>No</td>
<td>MRSA, MRSA, coagulase - negative Staphylococci, gram - negative rods</td>
</tr>
<tr>
<td>V. Tubaki</td>
<td>Open spine surgery Thoracolumbar and lumbar spinal deformity surgery</td>
<td>Cefuroxime, Cefazolin, clindamycin, ciprofloxacin, piperacillin/tazobactam, or vancomycin</td>
<td>Saline (1 Litter)</td>
<td>1</td>
<td>–</td>
<td>S. aureus, Klebsiella</td>
</tr>
<tr>
<td>J. Martin</td>
<td>Lumbar laminectomy and posterior fusion</td>
<td>Cefuroxime, Cefazolin, clindamycin, ciprofloxacin, piperacillin/tazobactam, or vancomycin</td>
<td>Saline (2 Litter)</td>
<td>2</td>
<td>–</td>
<td>MSSA, MRSA, coagulase - negative staphylococci, Enterobacter cloacae, Serratia marcescens, Klebsiella pneumoniae, Citrobacter freundii</td>
</tr>
</tbody>
</table>

MRSA: Methicillin – resistant S. aureus; MSSA: Methicillin – sensitive S. aureus; –: no information.

Fig. 2. The pooled odds ratio of the intrawound application of vancomycin powder in addition to intravenous administration of antibiotics on the deep infection after spinal surgeries.
heterogeneity of pooled OR largely decreased to an insignificant level ($I^2$ value = 0.0%, $P=0.784$) after the omitting of their publications.

The amount of included studies was too small to conduct any sufficient additional analysis of subgroup, meta-regression or publication bias.

4. Discussion

This is the first meta-analysis which focuses specially on the combination of intrawound application of vancomycin powder and intravenous administration of antibiotics for the prophylaxis of deep infection after spine surgery. Findings of the present meta-analysis suggest that this technique could significantly reduce patients’ risk of deep infection after spinal surgeries.

Systemic administration of the first- or second-generation cephalosporins is commonly used as perioperative prophylaxis. Although MRSA has widely spread in past decades, the routine surgical prophylaxis using vancomycin as a primary agent is not popular because of their similar clinical effectiveness to cephalosporins and higher costs.

However, because of increasing concerns about MRSA and coagulase-negative staphylococcus, prophylactic vancomycin is recommended in several surgeries, such as the replacement of artifical joints and cardiac surgeries, of which the consequences of postoperative infections are severe. It is widely agreed that the deep infection after spinal surgeries is serious. It may lead to neurological deficit of legs, spinal instability, bony non-union or spinal deformity. Moreover, it significantly lengthens hospital stays and increases the burden of health care costs.

Compared to intravenous administration, the intrawound use of vancomycin for adjunctive prophylaxis in spinal surgeries is attractive because of the higher local concentration, less systemic antibiotic exposure and lower cost. As expected, the present study found that this technique, of which the pooled OR (95% CI) was 0.22 (0.07–0.63), may significantly decrease postoperative deep infection. H. Chiang, et al. [23] have recently reported that the intrawound use of vancomycin appears to protect against the infection of surgical site, the result of the present study agree with their conclusion. In addition to that, our analysis focussed more specially on the effect of this technique in deep infection after spine surgeries, included more original publications and could provide estimation with more strength and more preciseness.

Previously, F. Sweet, et al. [12] reported that the mean vancomycin level in wound remained 128 μg/mL on the third day after intrawound application of 2 g vancomycin powder. I. Gans, et al. [15] reported that the systemic vancomycin level was lower than 2.0 μg/mL on the first postoperative day in 49 out of 50 patients who received 0.5 g intrawound vancomycin. There was one patient with a systemic level of 3.2 μg/mL but it was lower than 2.0 μg/mL on the fourth day after surgery. Results of these two studies suggest that the intrawound application could sufficiently deliver vancomycin to surgical sites with very low systemic toxicities. Studies which parallel test intrawound and systemic vancomycin level are needed to further prove it.

Moreover, it has been demonstrated that about 300,000 US dollars per 1000 cases would be saved if the infection rate is decreased from 2.5% to 1.0 [12,18]. The reduction in health care cost is significanct considering the vancomycin powder only costs 12–44 US dollars per case [12,18,20]. The reduction of care cost could repre- sent another advantage of this technique.

Significant heterogeneity was detected among included studies. Two publications, which demonstrated that the intrawound use of vancomycin for adjunctive prophylaxis in spinal surgeries does not significantly decrease the deep infection rate, may be the source of heterogeneity, as indicated by the study-omitting analysis. It could be inferred that potential risk factors which impair the effect of intrawound use of vancomycin may exist. Further cohort studies should pay more attention on the analysis of risk factors in order to optimize the patient selection and improve the clinical performance.

Several limitations raised in this study should be considered. First, sample sizes of several included studies are relatively small, their results may be biased because of patient selection; the present meta-analysis cannot rule out such bias. Second, the quantity of included studies is small, which may reduce the strength of our results. Third, qualities of included studies were relatively low. Fourth, significant heterogeneities may limit generalization. Furthermore, no subgroup analysis, meta-regression or publication bias test was performed because of inadequate number of eligible studies.

In conclusion, the present meta-analysis found that the intrawound application of vancomycin powder in addition to intravenous administration of antibiotics may significantly reduce the risk of deep infection after spinal surgeries. However, the number of available studies is limited, it is important that larger and well-designed studies are performed in the future.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


