Original Article

Efficacy and safety of local gentamicin collagen implanting for preventing SSI following colorectal surgery: a systematic review and meta-analysis

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Abstract: Surgical site infection (SSI) after colorectal surgery is a common type of healthcare-related infections. Gentamicin Collagen Sponge (GCS) is one of the clinical measures to prevent SSI after colorectal surgery, but the effectiveness is still contentious. This study searched the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, Ovid EMBASE, Web of SCI, Pubmed, SCOPUS EBSCO and CINAHL. After screening, all included data was analyzed by RevMan software. Totally 1870 patients from 10 random clinical trials (RCTs) were included in this study. The infection rates of surgical site, superficial wound, deep wound, organ space infection and incision complication in the GCS group were all not significantly different compared to those in the control group. As stratified by follow-up duration and control types, the infection rates were also not significantly different between GCS group and control group. In the gentamicin dosage subgroup analysis, this meta-analysis found the incidence of SSI in GCS group was lower than that of control group when the gentamicin dosage was smaller than 200 mg (risk ratio (RR): 0.62; 95% credibility interval (CI): 0.42 to 0.93). GCS applied could decrease the SSI incidence in Western Europe. Low dose of gentamicin applied (less than or equal to 200 mg) in GCS could decrease the SSI incidence compared to control group, while high dose might prejudice wound healing.

Keywords: Gentamicin collagen sponge, colorectal surgery, surgical site infections

Introduction

Globally more than 1 million people get colorectal cancer every year, resulting in about 715,000 deaths as of 2010 up from 490,000 in 1990 [1]. According to World Health Organization report (World Cancer Report 2014, ISBN 978-92-832-0432-9), as of 2012, it is the second most common cause of cancer in women (9.2% of diagnoses) and the third most common in men (10.0%) [2]. At present, surgical operation is still one of the main means to treat colorectal cancer. Due to the high level of bacteria and complexity of the flora in colorectal cavity, SSI is more likely to happen in colorectal surgery than in other clean surgeries, such as cardiac surgery. As a main postoperative complication, SSI decreases quality of patients’ lives after surgery and increases their economic burden, even causes systemic sepsis resulting in death. Therefore, it is necessary to explore a method to effectively reduce the site infections of colorectal surgery.

In recent years, some measures, such as clean room technology and antibacterial agents, have been used in perioperative period to decrease the risk of postoperative infection. However, insufficient blood supply in post-traumatic site, postoperative tissue damage, and the rise of bacterial drug resistance might affect the preventive efficacy of antibiotics. GCS, an absorbable antibiotic carrier system, uses collagen sponge as the carrier of gentamicin, which can avoid ototoxicity and renal toxicity caused by systemic use of gentamicin. And it maintains a relatively high level of local drug concentration, which can effective against the biocompatibility and degradability of collagen in some drug resistance strains, and avert a second surgery to remove the carrier [3]. Since GCS was allowed in 54 countries in 1985, there have been one
million people using GCS as a topical antibiotic. It has been used for spur healing in wound, bone and soft tissue infection, cardiac surgery, abdominal operation, inguinal hernia repair, radical mastectomy and so on [4-10]. The effectiveness of GCS on preventing site infections after colorectal surgery yet remains controversial. Qualitative system evaluation proposed by AF. de Bruin [11] considered it was effective, but some randomized controlled trials drew different conclusions. Rutkowski [12] found GCS could reduce the infection rate without incision leakage, but it was ineffective when incision leakage existed. What is more interesting, a multicenter randomized controlled phase III clinical trials conducted by Elliott Bennett-Guerrero [13] drew an opposite conclusion: GCS could increase the risk of SSI after colorectal surgery.

So a systematic review was conducted to assess the effectiveness and security of GCS applied for preventing SSI after colorectal surgery by integrating international research materials.

Methods

Documentation retrieval and filtering

This study searched 7 databases including WEB of SCI, PUBMED, Cochrane centrial, MEDLINE (OVID), EMBASE, CINAHL (EBSCO) SCOPUS, China knowledge network database. The time range is from the day of the database founded to June 10th 2015. The search strategy was shown in Appendix 1. All references were screened by two independent staffs, and the data was extracted based on inclusive and exclusive criteria.

Inclusion criteria

Types of participants: Inpatient who had colorectal surgery (any operation);
Types of interventions: local application of GCS on surgical incision; blank control or using collagen sponge without gentamicin as placebo control;
Types of outcome measures: 1, primary outcomes were overall incision infection rate, incidence of incision complications, incidence of adverse reaction and allergic reaction; 2, Secondary outcomes were infection rates in superficial wound, deep wound, organ lacuna, and length of hospital stay; Types of studies: only RCTs were included.

Exclusive criteria

1. Patients who had second colorectal surgery;
2. Other interventions were applied topically on incisions; 3. Overall incision infection rate was not reported.

Data extraction

Two assessors independently extracted primary information, such as first author, publication date, nationality, research design, basic features, interventions and outcome data. Two assessors discussed when disagreement appeared and a third assessor may be brought in to decide if necessary.

Quality evaluation

Risk assessment table [14] was used to evaluate the bias risk of RCTs by the two assessors independently. The aspects been assessed were: whether random method was adopted; whether allocation concealment was performed; whether blinding method was adopted; whether the outcomes were incomplete; other biases. Two assessors discussed when disagreement appeared and a third assessor may be brought in to decide if necessary.

Statistics analysis

All included data was pooled by Rev. Man5.3. RRs and 95% CIs is calculated for dichotomous outcomes (risk ratio is the risk of infection in the intervention group divided by the risk of infection in the control group; a risk ratio of less than one indicates fewer infections in the intervention or adhesive drape group). Mean differences (MDs) and 95% CIs is calculated for continuous outcomes. Heterogeneity is assessed using the Chi-square test with significance being set at P < 0.10. In addition, we investigated the degree of heterogeneity by calculating the I² statistic, (heterogeneity is considered large if I² > 75%). When heterogeneity is large and source of the heterogeneity is inexplicable, randomized effect model is adopted to merge data and the result should be interpreted with caution. Otherwise, a fixed-effect model is adopted. When source of the heterogeneity is explicable, subgroup analysis is conducted. In this meta-analysis, we conducted 4 subgroup analysis stratified by follow-up duration (shorter than 30 days, between 30 days and 60 days,
GCS and SSI following colorectal surgery

and longer than 60 days), dose of gentamicin in GCS (smaller than 200 mg, larger than 200 mg) and control types (blank control, placebo control), ethnic groups (Western Europe, North America, Asia).

Results

Data filtering

Totally 5340 articles were obtained in initial retrieval, and 2635 duplicated articles were removed. 2562 articles were removed due to irrelevant title and abstract. Remaining 144 articles were screened in detail, 133 more were eliminated due to irrelevant summarize, animal research, letters, guide or irrelevant outcomes. One article was also excluded because the full text could not be obtained even after contacting the author [15]. Finally 10 articles were included in the meta-analysis. The screening process was shown in Figure 1.

Basic features of included studies

Basic features of included papers were shown in Tables 1 and 2. The 10 RCTs [12, 13, 16-23] were published between 1997 and 2014. A total of 1870 patients were included in this research, among them, 924 patients were in GCS group, and 946 patients were in control group. 2 of the 10 researches were performed in North America [13, 17], 7 in Europe [12, 16, 18-22], and 1 in Asia [23]. 9 researches were published in English [12, 13, 16-22], and 1 in Chinese [23]. 7 researches were single-center RCTs [12, 17, 19-23], and other 3 were multi-center RCTs [13, 16, 18]. 2 researches used placebo control [19, 21] and 8 used blank control [12, 13, 16-18, 20, 22, 23].

Bias risk assessment

Bias risk assessment of the selected articles was shown in Table 3. In order to increase baseline comparability, this meta-analysis had defined explicit inclusive and exclusive criteria before the data extraction. Some of the included researches claimed their design was randomized, but they did not actually mention any randomized protocol or they were just pseudo-random (allocated by the visit order). Among the 10 RCTs, 3 researches adopted participant blinding method, and 5 adopted outcome assessor blinding method.

Primary outcomes

All of the 10 RCTs [12, 13, 16-23] reported the primary outcomes. Result of this meta-analysis suggested that incision infection rate was not significant difference between GCS group and control group (RR=0.73, 95% CI=0.49-1.07, P=0.10), and medium heterogeneity (I²=69%) existed. There is no significant difference between incidence of incision complications in GCS group and control group (RR, 1.28; 95% CI= 0.85-1.95; P=0.24) according to 4 included articles [12, 16, 20, 21], with little heterogeneity (I²=4%). No side reaction such as allergy was reported. The results were shown in Table 4.

Secondary outcomes

As Table 4 shown, superficial wound infection rate was not significant difference between GCS group and control group (RR=1.31; 95% CI=0.96-1.79; P=0.09), with little heterogeneity (I²=18%).

Figure 1. A flow diagram of the studies selection process.

Figure 1. A flow diagram of the studies selection process.
**Table 1. Characteristics of included studies**

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Setting</th>
<th>Sample Size</th>
<th>Gentamicin sponge</th>
<th>Operation</th>
<th>Local Gentamicin</th>
<th>Follow-up (days), Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett-Guerrero et al.</td>
<td>2010</td>
<td>Multicenter (USA)</td>
<td>602</td>
<td>Innocoll Technologies (Gallowston, Ireland)</td>
<td>open or laparoscopically assisted colorectal surgery</td>
<td>260 mg</td>
<td>60, ↑surgical site infection</td>
</tr>
<tr>
<td>Collin, A</td>
<td>2013</td>
<td>Multicenter (Sweden)</td>
<td>102</td>
<td>(Collatamp® G, Scher-ing-Plough AB, Stockholm, Sweden</td>
<td>APR</td>
<td>200 mg</td>
<td>30, 60, No difference</td>
</tr>
<tr>
<td>Gomez, G. G. V</td>
<td>1999</td>
<td>Single-center (Mexico)</td>
<td>73</td>
<td>N/R</td>
<td>N/R</td>
<td>130 mg</td>
<td>N/R, ↓Surgical site infection</td>
</tr>
<tr>
<td>Guuessner, U</td>
<td>2001</td>
<td>Multicenter (Germany)</td>
<td>97</td>
<td>Septocoll (Merck Biomaterial GmbH, Darmstadt, Germany)</td>
<td>APR</td>
<td>210 mg</td>
<td>30-60, ↓surgical site infection</td>
</tr>
<tr>
<td>Haase, O</td>
<td>2005</td>
<td>Single-center (Germany)</td>
<td>82</td>
<td>Sulmecin® Implant, Essex Pharma, Munchen, Bayern, Germany</td>
<td>loop-ileostomy closure</td>
<td>N/R</td>
<td>30, No difference</td>
</tr>
<tr>
<td>Marek P. Nowacki</td>
<td>2005</td>
<td>Single-center (Poland)</td>
<td>229</td>
<td>GaramycinSchwamm; Shering Plough, Kenilworth, NJ, USA</td>
<td>open or laparoscopically assisted colorectal surgery</td>
<td>N/R</td>
<td>130 mg &gt;60, ↓surgical site infection</td>
</tr>
<tr>
<td>Pochhammer, J</td>
<td>2014</td>
<td>Single-center (Poland)</td>
<td>291</td>
<td>Gentacoll resorb®, Resorba Medical GmbH, NGrnberg, Germany</td>
<td>laparoscopically assisted colorectal surgery</td>
<td>N/R</td>
<td>30, No difference</td>
</tr>
<tr>
<td>Rutkowski, A</td>
<td>2014</td>
<td>Single-center (Poland)</td>
<td>176</td>
<td>Garamycin® Innocoll, Athlone, Co., Westmeath, Ireland</td>
<td>open or laparoscopically assisted colorectal surgery</td>
<td>260 mg</td>
<td>&gt;60, No difference</td>
</tr>
<tr>
<td>Rutten Hj</td>
<td>1997</td>
<td>Single-center (Holland)</td>
<td>221</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R, ↓Surgical site infection</td>
</tr>
<tr>
<td>Tiexin Zhang</td>
<td>2014</td>
<td>Single-center (China)</td>
<td>156</td>
<td>N/R</td>
<td>N/R</td>
<td>260 mg</td>
<td>60, ↑surgical site infection</td>
</tr>
</tbody>
</table>

N/R, not reported; ↓, decreased; ↑, increased; APR: abdominoperineal resection of the rectum.

**Table 2. Outcomes of included studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>SSI</th>
<th>SWI</th>
<th>DWI</th>
<th>Organ space infection</th>
<th>Postoperative hospital length of stay</th>
<th>Other Wound complication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GCS</td>
<td>Control</td>
<td>GCS</td>
<td>Control</td>
<td>GCS</td>
<td>Control</td>
</tr>
<tr>
<td>Bennett-Guerrero, E</td>
<td>83/274</td>
<td>62/292</td>
<td>56/274</td>
<td>41/292</td>
<td>23/274</td>
<td>18/292</td>
</tr>
<tr>
<td>Gomez, G. G. V</td>
<td>3/34</td>
<td>14/32</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Guuessner, U</td>
<td>3/49</td>
<td>10/48</td>
<td>5/49</td>
<td>1/48</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Haase, O</td>
<td>4/40</td>
<td>4/40</td>
<td>4/40</td>
<td>4/40</td>
<td>2/40</td>
<td>2/40</td>
</tr>
<tr>
<td>Marek P. Nowacki</td>
<td>11/106</td>
<td>13/112</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Pochhammer, J</td>
<td>8/97</td>
<td>13/96</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Rutkowski, A</td>
<td>16/86</td>
<td>22/85</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Rutten Hj</td>
<td>6/107</td>
<td>21/114</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
<td>N/R</td>
</tr>
<tr>
<td>Tiexin Zhang</td>
<td>24/79</td>
<td>18/77</td>
<td>13/79</td>
<td>11/77</td>
<td>7/79</td>
<td>5/77</td>
</tr>
</tbody>
</table>

*placebo group; b blank group; SSI: Surgical Site Infection; SWI: superficial wound infection; DWI: deep wound infection; N/R: not reported.
Table 3. Bias risk assessment of the randomized controlled trials

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennett-Guerrero, E</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Collin, A</td>
<td>Low risk</td>
<td>Low risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Gomez, G. G. V</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Gruessner, U</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>High risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Haase, O</td>
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<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Marek P. Nowacki</td>
<td>High risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Pochhammer, J</td>
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<td>Low risk</td>
<td>Low risk</td>
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<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Rutkowski, A</td>
<td>Low risk</td>
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<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Rutten Hj</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Tiexin Zhang</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
<td>Low risk</td>
<td>Unclear risk</td>
<td>Unclear risk</td>
</tr>
</tbody>
</table>

Table 4. The results of comparison between GCS group and control group in primary outcomes and secondary outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Subgroups</th>
<th>N</th>
<th>OR (95% CI)</th>
<th>Homogeneity</th>
<th>Publication Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incision infection rate</td>
<td>-</td>
<td>10</td>
<td>0.73 (0.49-1.07)</td>
<td>0.10</td>
<td>28.74</td>
</tr>
<tr>
<td>follow-up time</td>
<td>overall</td>
<td>10</td>
<td>0.73 (0.49-1.07)</td>
<td>0.10</td>
<td>28.74</td>
</tr>
<tr>
<td></td>
<td>&lt;30 days</td>
<td>3</td>
<td>0.77 (0.50-1.19)</td>
<td>0.24</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>30-60 days</td>
<td>3</td>
<td>1.27 (1.00-1.62)</td>
<td>0.05</td>
<td>6.11</td>
</tr>
<tr>
<td></td>
<td>&gt;60 days</td>
<td>3</td>
<td>0.88 (0.64-1.21)</td>
<td>0.43</td>
<td>0.98</td>
</tr>
<tr>
<td>Dose of gentamicin</td>
<td>≤200 mg</td>
<td>3</td>
<td>0.62 (0.42-0.93)</td>
<td>0.02</td>
<td>5.06</td>
</tr>
<tr>
<td></td>
<td>&gt;200 mg</td>
<td>4</td>
<td>1.16 (0.93-1.45)</td>
<td>0.19</td>
<td>9.72</td>
</tr>
<tr>
<td>Control type</td>
<td>blank control</td>
<td>8</td>
<td>0.92 (0.76-1.11)</td>
<td>0.38</td>
<td>28.31</td>
</tr>
<tr>
<td></td>
<td>placebo control</td>
<td>2</td>
<td>0.70 (0.35-1.41)</td>
<td>0.32</td>
<td>0.39</td>
</tr>
<tr>
<td>Incision complications</td>
<td>-</td>
<td>4</td>
<td>1.28 (0.85-1.95)</td>
<td>0.24</td>
<td>3.11</td>
</tr>
<tr>
<td>Superficial wound infection rate</td>
<td>overall</td>
<td>4</td>
<td>1.31 (0.96-1.79)</td>
<td>0.09</td>
<td>3.67</td>
</tr>
<tr>
<td>Deep wound infection rate</td>
<td>-</td>
<td>2</td>
<td>1.43 (0.82-2.49)</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>Organ lacuna infection rate</td>
<td>-</td>
<td>4</td>
<td>1.06 (0.59-1.9)</td>
<td>0.86</td>
<td>3.22</td>
</tr>
</tbody>
</table>
The deep wound infection rate in GCS group was not significant different to that of control group (RR=1.43; 95% CI=0.82-2.49; P=0.21), with little heterogeneity ($I^2=0\%$). There was no significant difference between GCS group and control group on outcome of organ space infection rate (RR=1.06; 95% CI=0.59-1.91; P=0.86), and a little heterogeneity ($I^2=7\%$) was found.

Five papers reported the hospital stays duration. Average length of hospital stays in GCS group was 5-13.8 days, while 5.45-16.3 days in control group. The shortening tendency of hospital stays duration in GCS group after surgery was not observed.

**Subgroup analysis**

**Follow-up time:** According to the follow-up time, this paper divided the included researches into 3 subgroups as follows: shorter than 30 days, between 30 days and 60 days, and longer than 60 days. SSI rates of all the 3 subgroups showed no significant difference between GCS group and control group. Results were shown in Table 4.

**Dose of gentamicin in GCS:** When Dose of gentamicin in GCS was less than or equal to 200 mg, GCS applying could decrease the SSI rate compared to control group (RR=0.62; 95% CI=0.42-0.93; P=0.02; $I^2=61\%$). But this finding was not observed in larger than 200 mg subgroup (RR=1.16; 95% CI=0.93-1.45; P=0.19; $I^2=69\%$). Results were shown in Table 4 and Figure 2.

**Control type:** According to the control type, this paper divided into blank control subgroup and placebo control subgroup. There were no significant different between GCS group and control group on incision infection rate in both 2 subgroups. They are respectively (RR, 0.92;
GCS and SSI following colorectal surgery

Figure 4. Funnel plot of this meta-analysis.

95% CI=0.76-1.11; P=0.38; I²=75%) and (RR, 0.70; 95% CI=0.35-1.41; P=0.32; I²=0%).

Ethnic group: In Western Europe, GCS applying could decrease the SSI incidence compared to control group (RR=0.66; 95% CI=0.49-0.89; P=0.006; I²=3%). But this founding was not observed in North America subgroup (RR=0.58; 95% CI=0.08-4.02; P=0.58; I²=91%) and Asia subgroup (RR=1.03; 95% CI=0.77-2.20; P=0.33). Results were shown in Table 4 and Figure 3.

Sensitivity analysis

Due to the heterogeneity existed, the sensitivity analysis was conducted. The result of the sensitivity analysis indicated that one research could influence the pooled results [11]. The pooled effect value changed significantly when this paper removed.

Assessment of publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature, and no asymmetry of the funnel plot was found, indicating the absence of a publication bias in this meta-analysis. Funnel plot was shown in Figure 4.

Discussion

The main results of this meta-analysis as following: 1. The preventive effect of SSIs after colorectal surgery in GCS group was not significant better than in control group; 2. GCS applying could decrease the SSI rate in Western Europe. 3. If gentamicin used was less than or equal to 200 mg, GCS was more effective on reducing SSIs after colorectal surgery than control. But these results were not found in more than 200 mg subgroups. One reason for this find may be that high concentration of GCS can stimulate local tissues and affect formation of epithelial tissue and new vessels. Previous research found that, in a short period after locally using GCS, a high concentration of gentamicin was detected at the wound site while the concentration in serum detected was low. With the deceasing of general toxicity, local concentration like this might lead to the appearance of multiple resistant bacteria [24]. It is worth noting that we found a trend that GCS may be helpful to prevent SSIs in a short time after the colorectal surgery, but harmful as the follow-up time got longer. There are two possible reasons for this trend: one is that the collagen used as sponge might cause adverse reactions. Bang K et al. [25] found GCS might hinder the formation of epithelial tissue and new vessels on rats. In his research, the wound seemed to heal at first when using GCS, but inflammatory reaction like redness and swelling developed after 15 days. Another reason is that the gentamicin is eluted too fast to maintain locally stable and effective concentration after locally implanting GCS. The study conducted by Friberg et al. [9] found that local concentration of gentamicin was very low 12 hours after implanting. A collagen sponge without effective antibiotics cannot prevent the growth of bacteria and then increases the infection risk. In addition, collagen, as a mechanical barrier, may affect the suture of the incision, and add the locally adhesive time of bacteria. Our results were different from a qualitative system assessment conducted by Bruin et al. [11], in which GCS was considered as helpful to reduce SSI. We included more new high quality RCTs than Bruin's research, so we considered this study was more persuadable.
Sensitivity analysis suggested the result of this study stable. BGE [13] was a multi-center RCT with a large sample and its quality was rigorously controlled. And we thought this study was of high quality and high credibility. Results as following, data was collected from field monitoring and source file, verified via central control system, and managed by an independent blind committee, groups were blinded, and data from multi-center (39 centers). Excluded this study, our meta-analysis reached the opposite conclusion, which means GCS is effective on preventing colorectal SSI. There are two reasons to explain this result: one is the ethnic difference. According to the subgroup analysis, this paper found the heterogeneity disappeared when analyzed by ethnic stratification, indicating that the pooled result was creditable. The other is that some studies having opposite conclusion with BGE had not reported follow-up time, which might be very important factor as it was observed in this multi-center trial that using GCS may be helpful in the early period of postoperation yet harmful after 3 weeks. In addition, study of Vaneerdeweg W [26] on rat model found that almost all rats used GCS showed anastomotic poor healing. However, conclusion about incision complications in this article could be false negative because most of data related to incision complications are passively collected by patient’s feedback yet no investigation like B ultrasonic was actively implemented on accepters, hence our conclusion that GCS is ineffective on preventing SSI should be interpreted and applied with caution for that it may not only be ineffective but also have opposite affection [26].

Limitations of the articles included lie in: 1. Regional limit, due to the poor representativeness of regions and races in the study, the conclusion of this study is inappropriate to be used universally. 2. Baseline comparability. Some researches didn’t describe diagnostic criteria, and most researches lacked the focus of operation process. Many factors might influence SSI were not reported, such as the duration of surgery and antibacterial agents used; 3. the follow-up time and the dose of gentamicin in GCS was varied in the researches included, and some even did not report these indexes which might affect the outcomes; 4. this research was based on GCS’s effect of preventing SSIs after colorectal surgery and the conclusion can’t be applied to the generalized effect of GCS on treating infections.

We suggest that future researches in related fields should unify the standard of SSI diagnose, apply the measures for preventing SSI (such as preventive using of antibacterial agents, antibiotics application during operation) according to the latest international guide, and complete the baseline description in both experiment group and control group. Especially the follow-up time should be unified (15 days, 30 days, longer than 30 days) and the outcome should be described in different stages. Future studies should explore whether locally high concentration of gentamicin affect the healing of surgical wound, which could furthermore facilitate the subgroup analysis of GCS’s effectiveness on SSI in short period after operation and verify whether GCS would increase the SSI in long term after operation. What is more, since no definite effects were observed in this article, GCS applied in clinical to prevent SSIs after colorectal surgery should be cautious. From the result of this research, more high quality RCTs need to be conducted to verify the effectiveness and security of GCS in preventing SSIs after colorectal surgery. Furthermore, animal experiments should be performed to observe whether the local adverse reactions are existed after GCS implanting, such as local stimulation and allergy which may affect the healing of wound.

GCS applied could decrease the SSI incidence in Western Europe. Low dose of gentamicin in GCS applied (less than or equal to 200 mg) could decrease the SSI incidence compared to control group, while high dose might prejudice wound healing.

Disclosure of conflict of interest
None.

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References


GCS and SSI following colorectal surgery


Appendix 1. The search strategy

MEDLINE(OVID)In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present; Ovid MEDLINE(R) Daily Update June 10, 2015 ([mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]).

5. “Septocoll”.mp.
8. “fleece”.mp.
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
11. “colon*”.mp.
17. “rectal neoplasm*”.mp.
20. “colorectal neoplasm*”.mp.
21. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22. 10 and 21