Efficacy of Probiotics and Prebiotics in Prevention of Infectious Complications Following Hepatic Resections: Systematic Review and Meta-Analysis

Yu Gan, Song Su, Bo Li, Chen Fang

ABSTRACT

Background & Aims: Infections occurring after hepatic resection cause significant morbidity, mortality, and prolonged hospitalization. Probiotics and prebiotics are considered to offer protection against post-operative infections. We aimed to determine the effect of probiotics and prebiotics on the post-operative infection rate after hepatic resection by conducting a systematic review and a meta-analysis.

Method: We searched various databases, namely, the PubMed, Medline, Embase, and Cochrane Controlled Trials Registry (CENTRAL), for randomized controlled trials evaluating the effect of probiotics and/or prebiotics on the infection rate following hepatic resection. Extracted data were pooled and subsequently used in a meta-analysis with a random-effects model. Review was reported following the PRISMA guidelines.

Results: A total of 4 studies comprising 205 patients were included for our meta-analysis. The infection rates in the probiotic group and placebo group were 11.7% and 30.3%, respectively (p<0.001). The pooled risk ratio (RR) was 0.41 (95% confidence interval [CI]: 0.128–0.730). Subgroup analysis indicated that the wound infection rate in the probiotic group (5.3%) was significantly lower than that in the placebo group (RR: 0.387, 95% CI: 0.155–0.970, p=0.043). Furthermore, probiotics/prebiotics decreased the duration of hospital stay (-0.57 days; 95% CI: -0.861 to -0.274; p<0.001) and antibiotic use (mean difference: -3.89 days, 95% CI: -4.17 to -3.60; p<0.001). There was no significant statistical heterogeneity.

Conclusion: Our findings show that administration of probiotics and/or prebiotics prior to operation day decreases the infection rate post-liver resection and could shorten the duration of hospitalization and antibiotic use.

Key words: probiotics – post-resection – hepatic resection – meta-analysis.

INTRODUCTION

Hepatic resection is an important step in the treatment of several types of malignant hepatic neoplasms [1, 2]. In patients who can tolerate the procedure, hepatectomy improves the chances of achieving complete remission of both primary and secondary cancers [3–5]. Hepatectomy for hepatic malignancies has become increasingly common in recent years, and in experienced hands, the procedure has been reported to significantly improve the outcomes [6–17]. Despite the significant benefits of the procedure, the overall mortality rate associated with the procedure remains high, at about 3.5% [18]. Post-operative morbidity necessitating prolonged hospital stay after hepatic resection is also high at 10%–15% [18]. Moreover, infectious complications represent an independent risk factor of postoperative morbidity and mortality and are observed in 12% to 23% of patients experiencing hepatic resection, including respiratory infections, intra-abdominal infection, and wound infections [19, 20]. Postoperative infectious complications are particularly important as they decrease long-term survival [20].

Probiotics and prebiotics have been identified as protective agents against post-operative infections. The pre-surgical administration of antibiotics and the surgical trauma together cause imbalance of gut microbiome and intestinal epithelial barrier dysfunction, thereby triggering the translocation of enteric bacteria to the mesenteric lymph nodes [21]. Probiotics and prebiotics are believed to stabilize the intestinal...
bacteremia was diagnosed when blood culture was positive for bacterial growth. The following definitions of infections were used in this study: (a) wound infection was defined by the presence of purulent discharge appearing spontaneously or on surgical expression, with a positive culture study; (b) intra-abdominal infection was defined as purulent discharge collected from the abdomen that tested positive for bacterial growth on culture or as fluid collection requiring a drainage procedure.

Data extraction
Two investigators (Y.G. and S.S.) independently examined the abstracts of the extracted papers and selected those suitable for review. Discrepancies in their opinions were resolved by consulting another reviewer (B.L.). The key characteristics of each selected study were summarized, including the year of publication, country of study, study design, patient characteristics (age and gender), usage of probiotics and/or prebiotics, rate and type of postoperative infection, duration of hospital stay, ICU stay, and antibiotic duration and 30-day mortality rate. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [24], guidelines were applied in this meta-analysis.

Assessment of study quality
Each study was independently evaluated for quality by each of the investigators.

The risk of bias in RCTs was assessed using a modified version of the Cochrane Collaboration’s tool for assessing risk of bias [25]. Each trial was scored as high, low, or unclear risk of bias on the basis of the following aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias.

Statistical methods
To evaluate the differences in rate of infection between the intervention and the control groups, dichotomous data were analyzed using a risk ratio (RR) with 95% confidence intervals (CI). Chi-square and P tests were all performed to judge the heterogeneity of clinical trial results and decided the analysis model (fixed-effect model or random-effect model). The selection of fixed-effects model or random-effects model depended on the size of the heterogeneity among the included studies. The continuous variables were expressed as the mean±standard deviation (SD) and analyzed by mean difference (MD). Subgroup analyses were performed to assess any significant heterogeneity between subgroups (P>50% or p <0.10). Sensitivity analyses were performed to examine the effect of excluding lower quality studies Publication bias was assessed by using the funnel plot with the bias indicator test from the Egger test. Statistical analyses were performed with stata version 12 (Stata Corporation, College Station, TX, USA) and Review Manager, version 5.3 (Nordic Cochrane Centre, Oxford, England), with a 2-tailed p values of <0.05 being considered significant.

RESULTS
Search results
Our database search retrieved 127 unique references of which 123 were excluded on the basis of the above mentioned inclusion criteria. The four remaining RCTs [26-29] that satisfied the inclusion criteria were included in the meta-analysis; these studies together included a total of 205 participants (103 treated with probiotics/prebiotics and 102 controls) (Fig. 1). Three of these studies were from Japan, while the remaining one was from Germany (Table I). In the patient cohort, male patients were more than females (144 males), with the mean age of 62 years.

The type and quantity of the probiotics administered were different. In their respective intervention groups, all studies used fiber-rich and enteral nutrition in addition to the administration of probiotics and prebiotics, either alone or in combination (called symbiotics). In all the studies, the patients received antibiotic prophylaxis as a single intravenous drip infusion 30 minutes before surgery. Probiotic group received probiotics on the day of surgery in three trials [26, 28, 29]
and on the day before operation in one [27]. The endpoints examined were the overall rate of postoperative infection, type of postoperative infection, duration of ICU stay and hospital stay, adverse effects and 30-day mortality.

**Risk of bias**

We performed the risk of bias table based on the Cochrane Handbook for Systematic Review of Interventions (Fig. 2). All RCTs reported a clear inclusion and exclusion criteria and suggest a methodology of randomization, using a randomization sequence generated by computer. Among them, one RCT [29] showed that allocation concealment was achieved by a sealed envelope and demonstrated double blinding. We found a low risk of bias regarding incomplete outcome data or selective outcome reporting. Judgments regarding each risk of bias item were presented as percentages across all the included studies in Fig. 3.

**Meta-analysis**

**Rate and type of postoperative infections**

The present study included four RCTs and was designed to investigate the effect of probiotics on the incidence of infections. The infection rate in the probiotics group was 11.7%, whereas

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>No of patient</th>
<th>Male</th>
<th>Study design</th>
<th>Probiotics used</th>
<th>Control used</th>
<th>Time probiotic started</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugawara et al. [26]</td>
<td>Japan</td>
<td>41</td>
<td>23</td>
<td>Prospective RCT</td>
<td>Enteric nutrition + fibers + probiotic: 80 mL bottle of Yakult 400, 100- mL bottle of Bifiel</td>
<td>Enteric nutrition + fibers</td>
<td>On the day of operation and continued 14 days after</td>
</tr>
<tr>
<td>Kanazawa et al. [27]</td>
<td>Japan</td>
<td>21</td>
<td>15</td>
<td>Prospective RCT</td>
<td>Enteric nutrition + fibers + probiotic: Yakult BL Seichōyaku</td>
<td>Enteric nutrition + fibers</td>
<td>On the day of operation and continued 14 days after</td>
</tr>
<tr>
<td>Usami et al. [28]</td>
<td>Japan</td>
<td>32</td>
<td>29</td>
<td>Prospective RCT</td>
<td>Enteric nutrition + fibers + probiotic: Yakult BL Seichōyaku</td>
<td>Enteric nutrition + fibers</td>
<td>On the day of operation and continued 14 days after</td>
</tr>
<tr>
<td>Rayes et al. [29]</td>
<td>Germany</td>
<td>9</td>
<td>8</td>
<td>Prospective RCT</td>
<td>Enteric nutrition + fibers + probiotic: Synbiotic 2000</td>
<td>Enteric nutrition + fibers</td>
<td>On the day of operation and continued 10 days after</td>
</tr>
</tbody>
</table>

Fig. 1. PRISMA flow diagram of the systematic article selection process.

Fig. 2. Risk of bias graph: review of authors’ judgements regarding each risk of bias item presented as percentages across all included studies.
that in the control group was 30.3% (RR: 0.41, 95% CI: 0.23–0.73; p < 0.001), with low heterogeneity ($I^2$: 32.4%) (Fig. 4). In the control arm, wound infection was the most common cause of infection (15.2%), followed by intra-abdominal infection (14.1%). However, in the intervention group, the majority of infections were intra-abdominal (6.3%). A subgroup analysis of the infection types showed a significant decrease in the rate of wound infection in the intervention group (5.3%), as compared to the rate in the control group (15.2%) (RR: 0.387, 95% CI: 0.155–0.970, p=0.043), without statistical heterogeneity ($I^2$: 0%) (Fig. 5). No significant benefit of the administration of probiotics was noted on the rate of intra-abdominal infection (RR: 0.482, 95% CI: 0.2–1.163; p=0.104), without statistical heterogeneity ($I^2$: 0%) (Fig. 6).

**Duration of hospital stay and intensive care unit stay**

The use of probiotics/prebiotics significantly decreased the duration of hospital stay, with a mean difference (MD) of -0.57 days (95% CI: -0.861, -0.274; p<0.001) (Fig. 7), without statistical heterogeneity ($I^2$: 0%). However, no significant difference was noted in the duration of the ICU stay between the intervention group and control group (MD: -0.061 days, 95% CI: -0.322 to -0.444; $P=0.754$; $I^2$: 0%) (Fig. 8).
**Duration of antibiotic use**

The use of probiotics or prebiotics also shortened the duration of antibiotic use (MD= -0.460, 95% CI: -0.816, -0.105; p=0.11), (F: 0%) (Fig. 9).

![Fig. 9](image)

**Thirty-day mortality**

None of the studies had recorded any mortality occurring during the study period.

**Sensitivity analysis**

We also performed a sensitivity analysis whereby each study was eliminated from the analysis, one at a time. The results of the sensitivity analyses showed that there was no change in the direction or the statistical significance of the RRs or MDs obtained for any of the parameters considered or the level of heterogeneity in the analyses or subgroup analyses.

**Publication bias**

Publication bias was assessed by a funnel plot diagram. The funnel plot diagram of postoperative infections was symmetrical and did not indicate the existence of publication bias with the Egger test (p=0.716) (Fig. 10). However, this assessment cannot prove the absence of bias due to the small number of studies.

**DISCUSSION**

Hepatic resection involves the removal of a part of the liver, mainly for cancer or pre-cancerous growths. This procedure is a major surgery, and the risk of mortality and postoperative complications associated with this procedure is 3.5% and 10–15%, respectively (defined as complications resulting from prolonged hospital stay). Various proposals have been put forth for achieving a decrease in the rate of postoperative infectious complications after hepatic resection.

Our meta-analysis contained four RCTs with 205 participants. In all the four studies, both groups received enteral treatment within the first 24 hours of the operation, while the probiotic group received extra probiotics. This beneficial effect of probiotics may reduce infectious complications after surgery, especially high-risk hepatectomy [15, 27]. Our results strongly suggest that probiotics reduce postoperative infections.

Our results also showed that patients who received enteral nutrition and probiotics required a shorter duration of hospital stay and antibiotics administration than those who received enteral nutrition only, decreasing the overall cost, without causing any additional adverse effects. All studies provided data on mortality; the pooled analysis showed no significant differences between the two strategies. This may be attributed to the small number of studies included in this study.

A previous Cochrane review [30] evaluating different therapeutic agents showed that antibiotics, prebiotics and probiotics were able to prevent and manage infection complications after liver operation. This Cochrane review included two RCTs that compared the combination of prebiotics and probiotics to the use of enteral nutrition only [26, 27]. Similar to our meta-analysis, this review revealed that there was no difference between the two regimens in terms of mortality. However, contrary to our findings, their study did not show significant effect on the rate of bacterial infection or length of ICU stay or hospital stay. Their study did not provide any subgroup analysis on the infection types. The Cochrane review could not include the studies by Usami et al. [28] and Rayes et al. [29], which were published later. We believe that the differences between our findings and theirs may be attributed to the differences in the nature of the included studies.

Our meta-analysis has some limitations. Firstly the methodological quality of the trials included in the meta-analysis has important problems. Only one study had clear allocation concealment, and was double blinded. This high quality study could not show a difference between infections. The other three studies, although randomized, had no clear randomization technique, the allocation concealment was not clear, and they were not double blinded. Thus three sources of bias question their internal validity, especially the allocation concealment for selection bias, and the blinding for performance and detection biases. These lower quality studies showed a tendency for lower infections, the main outcome of interest in this meta-analysis.

Secondly, different brand, concentrations and usage of probiotics were recommended in this study, which may produce bias in this research. Three of the four included trials had chosen Yakult BL Seichōyaku (Yakult Honsha, Tokyo, Japan) as probiotics [26-28]. Another study [29], however, chose Synbiotic 2000R (Medipharm, Kägeröd, Sweden and Des Moines, Iowa, USA) as probiotics. Thirdly, our meta-analysis included four studies, but three of them were performed in the same country, which limits the generalizability of the
findings to some extent; nevertheless, the patient populations in the three studies differed widely. Additional studies across various ethnicities would help clarify whether race influences the extent of benefit obtained from the use of probiotics and/or prebiotics. Fourthly, only four RCTs were included, with the sample size in each trial being small in number.

CONCLUSION

Our findings show that administration of probiotics and/or prebiotics prior to operation day decreases the post-liver resection infection rate and could shorten the duration of hospitalization and antibiotics use. The meta-analysis included 4 RCTs, but only one with high quality. As the evidence quality is low, further research is required.

Conflict of interest: None to declare.


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REFERENCES


