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Efficacy and safety evaluation of paclitaxel-loaded metal stents in patients with malignant biliary obstructions

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ABSTRACT

Paclitaxel-eluting covered metal stents (PECMSs) and metallic stents covered with a paclitaxel-incorporated membrane (MSCPMs) have been developed to increase stent patency by preventing tumor ingrowth. However, few studies have compared their efficacy and safety compared with conventional covered metal stents (CMSs). This study aimed to compare differences in efficacy and safety between PECMS/MSCPM and CMS by meta-analysis. A search of PubMed and Embase was conducted for randomized controlled trials of PECMS/MSCPM and CMS in patients with malignant biliary obstructions published between January 1966 and August 2017. A meta-analysis was performed to compare clinical outcomes and complications between stent types. A total of 221 patients from three studies were included. There were no significant differences between PECMS/MSCPM and CMS in stent patency duration ($P = 0.128$) or survival time ($P = 0.363$). Risk did not differ between PECMS/MSCPM and CMS for stent malfunction (hazard ratio [HR]: 1.13, 95% confidence interval [CI]: 0.63–2.02, $P = 0.677$ for all stent malfunction; HR: 1.39, 95% CI: 0.68–2.85, $P = 0.362$ for stent occlusion caused by tumor ingrowth; HR: 0.80, 95% CI: 0.34–1.91, $P = 0.617$ for stent occlusion caused by distal stent migration or sludge impaction), or complications (HR: 1.54, 95% CI: 0.70–3.39, $P = 0.280$ for all complications; HR: 0.42, 95% CI: 0.14–1.30, $P = 0.131$ for pancreatitis). The exception was cholangitis-like symptoms, the risk for which was higher in PECMS/MSCPM compared with CMS (HR: 3.93, 95% CI: 1.08–14.29, $P = 0.038$). Although PECMS/MSCPM may be associated with higher risk of cholangitis-like symptoms, the overall results were similar between PECMS/MSCPM and CMS. Further studies are warranted in larger populations of patients.

Introduction

Endoscopic retrograde biliary drainage is an important method of nonoperative management for malignant biliary obstruction [1–3]. Self-expandable metal stents (SEMS) have been reported to be superior to plastic stents with respect to stent patency [4,5]. Early SEMS were uncovered and therefore had a risk of tumor ingrowth [6]. In response to this, partially and fully covered SEMSs were developed [7–9]. However, partially and fully covered SEMSs continued to become occluded because of tumor ingrowth, overgrowth, or chronic inflammation [10,11].

In recent years, drug-eluting stents (DES), especially paclitaxel-eluting stents, which promote the dose-dependent inhibition of proliferation of human epithelial gallbladder cells, fibroblasts, and pancreatic carcinoma cells in vitro, have been used as alternatives to bare metal stents, to address occlusion in patients with malignant biliary obstruction [12,13]. However, late stent occlusion still presents [14].

We conducted a meta-analysis of randomized controlled trials (RCTs) to compare differences in efficacy and safety between paclitaxel-eluting covered metal stents (PECMSs)/metallic stents covered with a paclitaxel-incorporated membrane (MSCPMs) and

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conventional covered metal stents (CMSs).

Methods

Search strategy

We conducted a literature search of PubMed (Medline) and Embase for articles published between the years 1966 and 2017, with no language restrictions. The key search terms utilized in the process were: “paclitaxel”, “incorporated”, “eluting”,” metallic”, “stents”, and “biliary.” In addition, we scrutinized the references of retrieved literature to identify further relevant studies.

Study selection

Retrieved research study articles were included for meta-analysis if they satisfied the following criteria: (1) the study design was an RCT; and (2) the outcomes included stent malfunction, or complications, or stent patency duration, or survival time. Nonhuman studies, conference abstracts, editorials, comments, and unpublished articles were excluded. If a trial had been reported more than once, we used the most recent published study results.

Data extraction

Data were extracted and checked independently by two authors. For each study, the following information was extracted: name of first author, year of publication, study location, participants' age and gender, duration of follow-up, number of participant incident cases, stent malfunction, complications, stent patency duration, and survival time.

Data analysis

Heterogeneity among studies was assessed using I^2 statistic, which describes the proportion of total variation in point estimate that is due to heterogeneity. For the I^2 metric, I^2 values of 25%, 50%, and 75% were set as cut-off points for low, moderate, and high degrees of heterogeneity, respectively. When heterogeneity was significant, we used a random effects model; otherwise, we used a fixed effect model. Forest plots were used to assess the overall risk estimate; and funnel plots were used to assess the overall publication bias. The meta-analyses were performed using STATA 11.0 software (STATA Corp).

Results

Study search

We initially identified 4662 articles from PubMed and Embase. Of these, three articles met the inclusion criteria. After evaluating the three articles in detail, all three were included. The literature search and selection procedure are shown in Supplementary Fig. 1.

Study characteristics

Supplementary Table 1 summarizes the general characteristics of the included studies. Combined, the three studies included 221 patients, 122 of whom had a PECMS/MSCPM and 99 a CMS. The mean follow-up time of the studies varied from 143 to 277 days. One trial was finally analyzed using the intent-to-treat method [15].

Clinical outcomes

The mean stent patency, a categorical variable indicating whether the stent is open (Fig. 1), and mean survival time duration,a quantitative variable indicating the patency time of stent (Fig. 2), were not significantly different between PECMS/MSCPM and CMS ($P = 0.128$ and 0.363, respectively). Stent malfunction, stent failure due to tumor invasion, stent blockage and other reasons (Fig. 3a), occurred in 38 (31.1%) of the 122 PECMS/MSCPM patients and 28 (28.3%) of the 99 CMS patients (hazard ratio [HR]: 1.13, 95% confidence interval [CI]: 0.63–2.02, $P = 0.677$). The main cause of stent malfunction was tumor ingrowth (Fig. 3b) (PECMS/MSCPM vs. CMS: HR: 1.39, 95% CI: 0.68–2.85, $P = 0.362$); other causes of stent malfunction were distal stent migration and sludge impaction (Fig. 3c) (PECMS/MSCPM vs. CMS: HR: 0.80, 95% CI: 0.34–1.91, $P = 0.617$). Except for cholangitis-like symptoms, complication rates did not differ significantly between the two groups (PECMS/MSCPM vs. CMS: 16.4% vs. 11.1%, HR: 1.54, 95% CI: 0.70–3.39, $P = 0.280$ for all complications (Fig. 4a); PECMS/MSCPM vs. CMS: 4.1% vs. 9.1%, HR: 0.42, 95% CI: 0.14–1.30, $P = 0.131$ for pancreatitis (Fig. 4b). In contrast, the rate of cholangitis-like symptoms (Fig. 4c) was significantly higher in PECMS/MSCPM (10.7%), compared with CMS (3.0%) (HR: 3.93, 95% CI: 1.08–14.29, $P = 0.038$). Begg's rank correlation test did not suggest the presence of publication bias for any clinical outcome in the follow-up period.

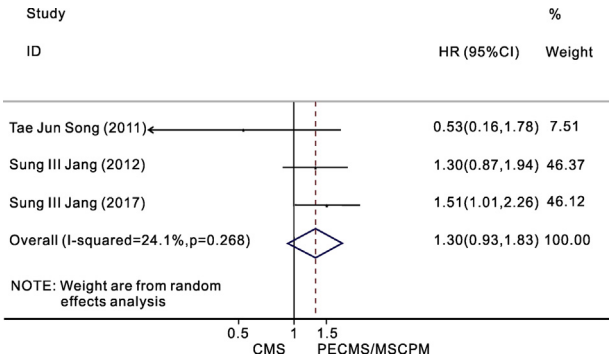

Fig. 1. Stent patency duration.

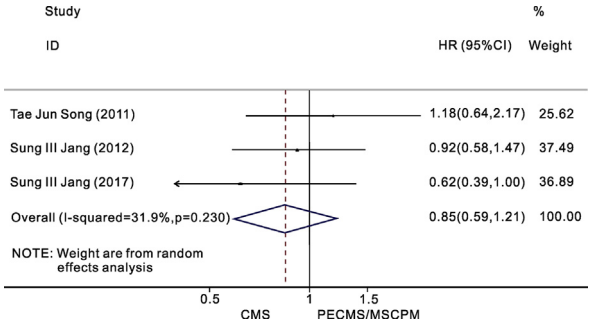

Fig. 2. Survival time.

Discussion

To our knowledge, this is the first meta-analysis comparing the clinical outcomes of PECMS/MSCPM with those of CMS in patients with malignant biliary obstruction. In this meta-analysis, CMSs had lower rates of cholangitis-like symptoms but showed a similar mean stent patency and mean survival time duration to PECMS/MSCPM.

Because the polyurethane used is biodegraded, in most cases the occlusion of CMSs over time is inevitable [16,17]. Paclitaxel has multiple pharmacologic effects including anti-proliferative, anti-

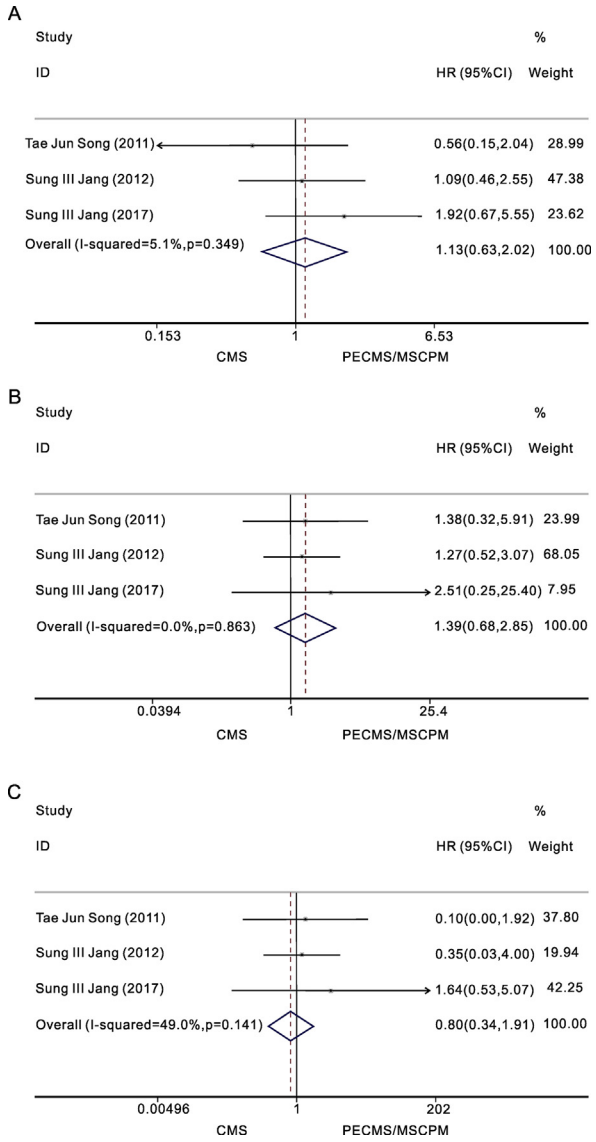

Fig. 3. (A) Stent malfunction (B) Stent occlusion caused by tumor in growth (C) Stent occlusion caused by distal stent.

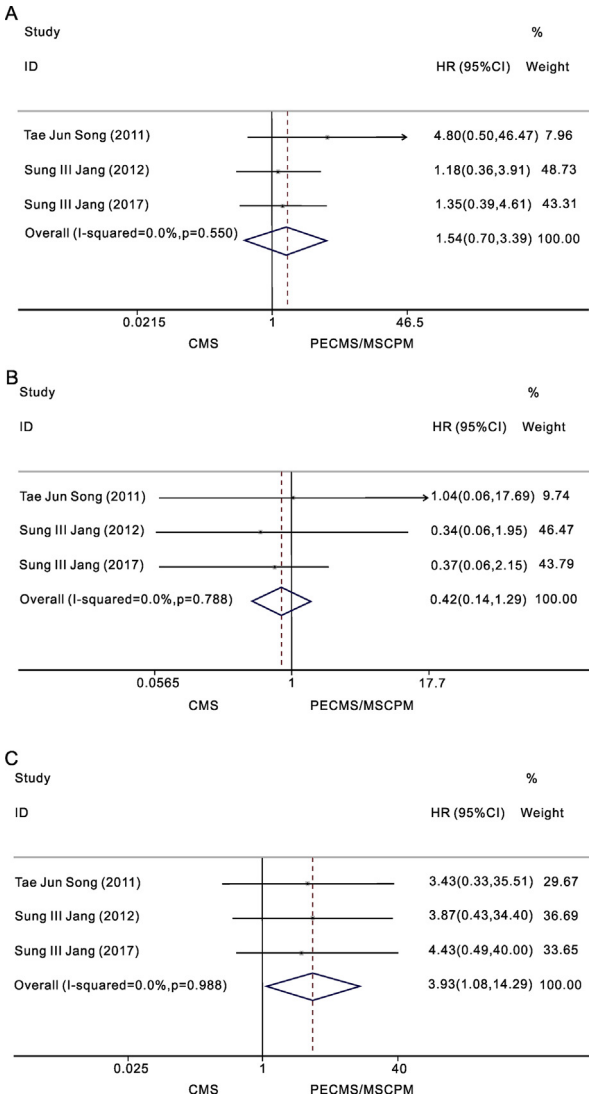

Fig. 4. (A) Complications (B) Pancreatitis (C) Cholangitis-like symptoms.

angiogenic, and apoptotic results [18], and has been shown to be effective in inhibiting the proliferation of biliary, esophagus, and pancreatic cancer cells in animal models [19–21]. A study on the application of PECMS in pigs by Lee et al. [13]. found that PECMS could provide a basis for the development of a new and safe treatment modality for malignant biliary obstruction. Of these positive results in animals, a few demonstrated better results than previous studies on CMS. However, in this meta-analysis, stent patency, survival time, and overall complications were not significantly different between the PECMS/MSCPM and CMS groups.

In contrast, we found that PECMS/MSCPM may be associated with a higher risk of cholangitis-like symptoms. However, the cumulative number of patients that developed cholangitis-like symptoms was only three. DES performance also depends on cancer type [22]. Patients with intrahepatic tumors by definition were less likely to be jaundiced, more likely to present with abdominal pain, and have higher 5-year survival rates compared with patients with perihilar or distal tumors. However, with the exception of Song et al. [23], the studies [14,15] in our meta-analysis did not analyze clinical outcome according to cancer type.

Our study had some advantages. First, we did not include case–control studies, thus excluding the inherent limitations of studies with a case–control design. Second, the cases were all from the East-Asian race group, and there may be a different response to stent type according to ethnic group. We also acknowledge some limitations; in particular, the sample size was relatively small and the analysis only included three RCTs, which may be of insufficient power to establish positive results.

In conclusion, the overall results were similar between PECMS/MSCPM and CMS. Further biological studies, larger randomized trials and large cohort studies were needed to validate these associations.

Disclosures section

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2018.10.533.

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