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Transarterial chemoembolization plus stent placement for the treatment of hepatocellular carcinoma with main portal vein tumor thrombosis: A meta-analysis

Sui WF *et al*. Therapy for HCC with main PVTT

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Abstract

BACKGROUND

To assess the clinical significance of transarterial chemoembolization+stent for the treatment of hepatocellular carcinoma with main portal vein tumor thrombosis.

AIM

To assess the clinical significance of transarterial chemoembolization + stent for the treatment of hepatocellular carcinoma with main portal vein tumor thrombosis.

METHODS

We searched English and Chinese databases. We assessed the quality of the included studies. We analyzed the characteristic data, tested heterogeneity, explored heterogeneity and tested publication bias.

RESULTS

In total, 8 clinical controlled trials were included. The results showed that the pressure in the main portal vein after stent placement was significantly lower than that after no stent placement. The cumulative stent patency and survival rates at 6 and 12 months

were lower in the transarterial chemoembolization + stent group than in the transarterial chemoembolization + stent + brachytherapy/radiotherapy group. The survival rates of patients treated with transarterial chemoembolization + stent for 6 and 12 months were greater than those of patients treated with transarterial chemoembolization alone.

CONCLUSION

For Chinese patients with hepatocellular carcinoma with main portal vein tumor thrombosis, transarterial chemoembolization + stenting was effective. The transarterial chemoembolization + stent procedure was more effective than transarterial chemoembolization alone. Transarterial chemoembolization + stent + brachytherapy/radiotherapy was more effective than transarterial chemoembolization + stenting was.

Key Words: Hepatocellular carcinoma; Transarterial chemoembolization; Portal vein tumor thrombus; Stent; Meta-analysis

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Core Tip: Portal vein tumor thrombus (PVTT) as an important indicator of poor prognosis existed in 44% of patients with hepatocellular carcinoma (HCC). Transarterial chemoembolization (TACE) is recommended as the standard first-line therapy in unresectable hepatocellular carcinoma. Some Chinese scholars showed that TACE combined with portal vein stent placement was safe and could prolong the survival time in HCC patients with PVTT.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common malignancies worldwide[1]. It is the fourth most common malignant tumor and the third most common cause of cancer-related death in China[2]. Portal vein tumor thrombus (PVTT), an important indicator of poor prognosis, occurs in 44% of patients with HCC[3]. PVTTs decrease the blood supply to the normal liver and cause deterioration of liver function, gastrointestinal bleeding and tumor recurrence[4]. HCC with PVTT was recognized as technically unresectable.

Transarterial chemoembolization (TACE) is recommended as the standard first-line therapy for unresectable hepatocellular carcinoma[5]. However, PVTT limits the effect of TACE and leads to liver failure because of portal vein obstruction. Three-dimensional conformal radiotherapy (3-DCRT) and I^{125} seeds have been shown to improve survival in HCC patients with main PVTT but not in those with worsened liver function[6,7]. However, the obstruction of the portal vein cannot be relieved immediately by 3-DCRT or I^{125} seeds alone.

Portal vein stent placement is a safe and effective therapy for promptly restoring flow and relieving portal hypertension caused by tumor thrombus. It prolonged survival in patients with HCC and main PVTT[8]. Several Chinese scholars have shown that TACE combined with portal vein stent placement is safe and can prolong the survival time of HCC patients with main PVTT[9,10]. However, large samples of current clinical trials for demonstrating the clinical significance of TACE plus stent placement for HCC patients with main PVTT are lacking, and no systematic analysis on the clinical significance of TACE plus stent placement for HCC patients with main PVTT in the Chinese population has been performed. Hence, this study aimed to carry out a meta-analysis to assess the clinical significance of TACE plus stent placement for Chinese patients with HCC and main PVTT.

MATERIALS AND METHODS

Search strategy

We performed a comprehensive literature search by using English-language databases, including PubMed, the Cochrane Library and Excerpt Medica Database and Chinese databases, including the Chinese National Knowledge Infrastructure (CNKI), Wanfang Data and CQVIP, up to 2019.

We used the following search terms in the field for title/abstract and/or keywords: "hepatocellular carcinoma", "transarterial chemoembolization" or "TACE" or "chemoembolization" and "portal vein tumor thrombus" and "stent". All the data were available from published papers.

Study selection

The studies selected met the following inclusion criteria: (1) The original research; (2) The study participants were human; (3) The study had clinical results, such as stent patency rates and survival rates; (4) The study showed the clinical value of TACE plus stent placement for HCC patients with main PVTT.

Data extraction and data quality assessment

Two doctors screened the titles and abstracts of potentially eligible studies independently and examined the full-text articles to determine whether they could be included. One doctor independently extracted the data, including author, country, publication year, design, treatment, and patient number. All the included studies were assessed for quality through the Cochrane Collaboration tool[11].

Data analysis

Softwear was used to analyze the data. For all analyses, $P < 0.05$ was considered to indicate statistical significance. Heterogeneity was assessed by using the chi-square test and I^2 statistics[12,13]. The I^2 statistic was applied to further assess heterogeneity. A $25\% \leq I^2 \leq 50\%$ indicated low heterogeneity. A value of $50\% < I^2 \leq 75\%$ indicated moderate heterogeneity. An $I^2 \geq 75\%$ indicated significant heterogeneity.

Subgroup analysis was performed to explore the source of heterogeneity.

Publication bias was evaluated using funnel plots[13]. When a funnel plot was asymmetrical, interpretation of the results was assessed critically. Otherwise, no publication bias existed.

RESULTS

Search strategy

We included 8 studies in this meta-analysis. Two studies were published in English[14,15]. Six studies were of Chinese descent[9,10,16-19] (Figure 1).

Data extraction and data quality assessment

The extracted data included the author, publication year, nation, study design, number of patients and therapies used in the experimental and control groups (Table 1).

The quality of the included studies was assessed. The tool included seven bias metrics, namely, random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. A summary and graphs of the risk of bias were constructed based on the investigators' judgments about each risk of bias item for each included study and are presented as percentages (Figure 2A and B).

Data analysis

We compared the changes in main portal vein pressure before and after the operation (Figure 3). The pressure in the main portal vein after stent placement was significantly lower than that before stent placement ($P < 0.00001$). The results showed that the stent decreased the main portal vein pressure. Heterogeneity existed in these results ($I^2 = 63\%$).

We compared the cumulative stent patency rates at 6 and 12 months (Figure 4A and B). The cumulative stent patency rates at 6 and 12 months were lower for the TACE + stent group than for the TACE + stent + brachytherapy/radiotherapy group ($P <$

0.00001). The results showed that stents without brachytherapy/radiotherapy were more obstructed by main PVTT. Heterogeneity did not exist in this study (I^2 = 0%).

We compared the survival rates at 6 and 12 months (Figure 5A and B). The overall survival (OS) rates at 6 and 12 months were lower for the TACE + stent group than for the TACE + stent + brachytherapy/radiotherapy group (P < 0.00001). The results showed that TACE + stent + brachytherapy/radiotherapy could prolong overall survival better than TACE + stent. Heterogeneity existed in these results (I^2 = 85%, 27%).

To explore the source of heterogeneity, we performed a subgroup analysis of the overall survival rates at 6 and 12 months (Figure 6). The results showed that the source of heterogeneity was the different therapies. The results showed that TACE + stent + brachytherapy/radiotherapy could prolong overall survival better than TACE + stent therapy, and TACE + stent therapy could prolong overall survival better than TACE alone (P < 0.00001).

To assess publication bias, funnel plot regressions were conducted, and no publication bias was found (Figure 7).

DISCUSSION

PVTTs are recognized as one of the most significant causes of recurrence and metastasis in HCC patients. The prognosis of HCC patients with PVTT is poor. The portal vein is the main nutrient vessel for the liver. It can be invaded by a tumor thrombus, which causes extensive intrahepatic metastases. When portal vein occlusion is accompanied by tumor thrombus, liver function fails, and the pressure of esophageal gastrointestinal bleeding increases, which is lethal for HCC patients.

Surgical resection can cure PVTT, but the high rate of recurrence after surgery and the high surgical requirements limit surgical resection[20]. 3-DCRT was also used for PVTT. The liver was sensitive to radiation and tolerated 30 Gy/3-4 wk. However, to cure PVTT, the radiation dose must be above 40 Gy, which can cause external radiation to the liver and body[21]. Because of the tumor thrombus in the hepatic artery, TACE can

lead to necrosis of the tumor and tumor thrombus. However, the effect of TACE on tumor thrombi is less than that on tumors because TACE indirectly affects tumor thrombi.

According to our meta-analysis, TACE plus a main portal vein stent decreased the pressure in the main portal vein. Furthermore, for HCC patients with main PVTT, TACE plus portal vein stenting improved the survival rate compared with TACE alone. TACE + stent + brachytherapy/radiotherapy could improve the stent patency and survival rates better than TACE + stent. Several studies have shown that portal vein stents serve as palliative remedies for malignant portal vein obstructions and could interrupt the infiltration and ingrowth of tumor thrombi in the portal vein to some degree[22,23], which was consistent with our meta-analysis. However, within a short period, owing to the mesh of the stent, the tumor thrombus might regrow into the stent, leading to reoccurrence and restenosis of the portal vein. Fortunately, TACE + stent + brachytherapy/radiotherapy is a practical superior treatment for HCC with main PVTT[14,24]. Because the stent pressed the tumor thrombus, 3-DCRT minimized the likelihood of treating PVTT exactly, which reduced the damage to the normal liver and benefited liver function. The 125 seeds were close to the tumor tissue to deliver continuous irradiation, which restrained the ability of the tumor thrombus to proliferate by damaging the DNA tumor cells. Consequently, the efficiency of TACE + stent + brachytherapy/radiotherapy may be better than TACE + stent and TACE alone for HCC patients with main PVTT. In the future, we can pay more attention to comparing the efficiency of TACE + stent + brachytherapy/radiotherapy and TACE + stent + radiotherapy for HCC patients with main PVTT.

There were several limitations in our meta-analysis: (1) Fifty RCTs were not included in the selected studies, which may have induced bias and affected our assessment of the management of HCC patients with main PVTT; (2) There was a lack of sufficient statistical data from multiple medical centers available to evaluate the efficacy of different therapies for patients with HCC and main PVTT; (3) Potential publication bias cannot be ignored, although our results showed no significant publication bias.

In summary, for HCC patients with main PVTT in the Chinese population, TACE + stent surgery was effective. The therapeutic benefits of TACE + stent were better than those of TACE alone. TACE + stent + brachytherapy/radiotherapy was more effective than TACE + stent was.

CONCLUSION

In summary, for HCC patients with main PVTT in the Chinese population, TACE + stent surgery was effective. The therapeutic benefits of TACE + stent were better than those of TACE alone. TACE + stent + brachytherapy/radiotherapy was more effective than TACE + stent was.

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