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WORD COUNT	2921	TIME SUBMITTED	27-JUL-2023 10:06AM
		PAPER ID	101547802

Name of Journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 85983

Manuscript Type: ORIGINAL ARTICLE

Case Control Study

Comparison of Ethanol-soaked Gelatin Sponge and Microspheres for Hepatic Arterioportal Fistula Embolization in Hepatic Cellular Carcinoma

ESG *vs.* Microsphere for Hepatic APFs

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Abstract

BACKGROUND

Hepatic arterioportal fistulas (APFs) was common in hepatocellular carcinoma (HCC), which are correlated with a poor prognosis, and often complicates anti-tumor treatments, including trans-arterial chemoembolization (TACE).

AIM

The objective was to compare the efficacy of ethanol-soaked gelatin sponges (ESG) and microspheres for the management of APFs and their impact on the prognosis of HCC.

METHODS

Patients diagnosed with HCC and hepatic APFs between June 2016 and December 2019 were retrospectively analyzed. The APFs were embolized with ESG (group E) or microspheres (group M) during TACE. The disease control rate (DCR) and objective response rate (ORR) were considered primary outcomes. The secondary outcomes included immediate and first-time follow-up APF improvement, overall survival (OS), and progression-free survival (PFS).

RESULTS

Ninety-one participants were enrolled in the study, with 46 in the E group and 45 in the M group. The DCR was 93.5% in group E and 91.1% in group M ($P = 0.714$). The ORRs were 91.3% and 66.7% in groups E and M, respectively ($P = 0.004$). The APFs improved immediately after the procedure in 43 (93.5%) E group and 40 (88.9%) M group participants, ($P = 0.485$). After two months, APF improvement was achieved in 37 (80.4%) and 33 (73.3%) participants in the E and M groups, respectively ($P = 0.421$). The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively ($P = 0.004$). The PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively ($P = 0.012$).

CONCLUSION

Compared to microspheres, ESG embolization showed a higher ORR and longer OS and PFS in HCC patients with hepatic APFs.

Key Words: hepatocellular carcinoma; arterioportal fistula; ethanol; gelatin sponge; microsphere; embolization.

Yuan G, Zhang L, Chen Z, Zhang C, Tian S, Gong M, Wang P, Guo L, Shao N, Liu B. Comparison of Ethanol-soaked Gelatin Sponge and Microspheres for Hepatic Arterioportal Fistula Embolization in Hepatic Cellular Carcinoma. *World J Gastrointest Oncol* 2023; In press

Core Tip: Hepatocellular carcinoma (HCC) is estimated to be the seventh most common cancer and the second leading cause of cancer related deaths worldwide in 2020. Hepatic arterioportal fistulas (APFs) was common in HCC, which often complicates anti-tumor treatments, including trans-arterial chemoembolization (TACE). Ethanol-soaked gelatin sponge combines the advantages of alcohol and gelatin sponge, contributes to better local control for hepatic APFs, and improves the survival of patients with HCC.

INTRODUCTION

Hepatocellular carcinoma (HCC) was estimated to be the seventh most common cancer and the second leading cause of cancer-related deaths worldwide in 2020, with 905,677 new cases and 830,180 deaths recorded annually.[1] Hepatic arterioportal fistulas (APFs), defined as fistulas between the hepatic artery and the neighboring portal vein,[2, 3] are common in HCC due to tumor infiltration, vascular damage,[4] or remodeling of the cirrhotic parenchyma.

Hepatic APFs may cause portal hypertension, ascites, and varices,[5] which are strongly correlated with a poor prognosis.[6] The presence of hepatic APFs often complicates antitumor treatments, including transarterial chemoembolization (TACE).

Chemotherapy agents and embolic materials run off through fistulas, and tumor cells may detach from the hepatic artery, resulting in portal vein thrombosis. [7]

Many materials have been used to treat hepatic APFs, including gelatin sponges,[8] microspheres,[9] coils,[10] histoacryl,[10] absolute ethanol,[10] polyvinyl alcohol particles,[10] and ethanol-soaked gelatin sponges (ESG).[11, 12] ESG combines the advantages of alcohol and gelatin sponges, providing convincing effects at different APF stages. [12] However, to the best of our knowledge, no study has compared the efficacies of ESG and microspheres. We conducted a retrospective study to evaluate the efficacy of ESGs and microspheres in the treatment of HCC with hepatic APF.

MATERIALS AND METHODS

Patients with HCC and hepatic APF treated with TACE and ESG (group E) or microspheres (group M) were enrolled between June 2016 and December 2019. The study protocol was approved by the ethics committee of the leading center. The requirement for written informed consent was waived due to the retrospective nature of this study. All work was performed in compliance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the 1975 Declaration of Helsinki (revised in 2000).

The inclusion criteria were as follows: (1) confirmed diagnosis of HCC based on the American Association for the Study of Liver Diseases practice guidelines;[13] (2) hypervascular tumor with Barcelona Clinic Liver Cancer (BCLC) Staging A–C; (3) hepatic APF confirmed by angiography; (4) predicted life span ≥ 1 year; and (5) Karnofsky score > 70.

The exclusion criteria were as follows: (1) other malignancies within 5 years, (2) Child-Pugh score ≤ 10, and (3) severe coagulopathy (prothrombin time > 17s and/or platelet count ≤ 60×10^9/L).

Treatment of APF

For group E, a gelatin sponge (Alicon Inc., Hangzhou, China) of appropriate size was mixed with 10 mL iodixanol injection (Hengrui Co. Ltd, Lianyungang, China) and 10

mL of ethanol (Lingfeng Inc, Shanghai, China). For the M group, microspheres (Embosphere, Merit Medical, UT, USA) of appropriate size were mixed with 10 mL iodixanol. DSA was performed after catheterization of the celiac or superior mesenteric artery and digital subtraction angiography (DSA) was performed to validate the location and size of hepatic APFs (Figure 1). APFs were classified according to a previous study by Zhou *et al.* [12] (Table 1). Each APF feeding artery was super-selected using a 2.7 F microcatheter. Either ESG or the microspheres were injected under fluoroscopic guidance until the fistula was blocked. If the fistula was not completely blocked, coils were used. DSA was repeated to confirm the complete embolization of the APFs (Figure 2).

The TACE procedure

After APF embolization, the microcatheter was advanced into each feeding artery of the HCC. An emulsion of poppy Lipiodol (Hengrui Co. Ltd., Lianyungang, China) and epirubicin (Qilu Co. Ltd., Jinan, China) was injected *via* the microcatheter until complete embolization of the tumor was achieved (Figure 3).[14]

Follow-up

Follow-up was conducted every 2 mo and included standard blood count, liver functional tests, alpha fetoprotein (AFP), and abdominal contrast-enhanced CT (CECT) or magnetic resonance (MR) imaging. The images were interpreted based on the consensus of three skilled interventional radiologists.

TACE was repeated if tumor recurrence was detected on CECT or MR. If APF recurrence with a grade ≥ 2 was observed, ESG or microsphere APF embolization of was repeated; however, if APFs did not recur, TACE was the only procedure performed. The follow-up intervention was determined based on the tumor condition and general status.

Overcome measures

The modified Response Evaluation Criteria in Solid Tumors (mRECIST) for HCC[15] were applied to assess tumor response after 4 mo. The disease control rate (DCR) and objective response rate (ORR) were considered primary outcomes. The

secondary outcomes included immediate and first-time follow-up of APF improvement, overall survival (OS), and progression-free survival (PFS).

Immediate APF improvement was defined as a decrease in grade to 1 or 0. First-time follow-up APF improvement was defined as a decrease of at least two grades confirmed by angiography in the second session, whereas APF progression was defined as an increased grade at the first-time follow-up angiography. If the grade remained the same or decreased by one, the APFs were not considered to improve. OS was defined as the time interval between the initial TACE and death or the last follow-up. PFS was defined as the time interval between the initial TACE and disease progression or death.

Statistical analysis

Continuous variables were analyzed using Student's t-test if the variables were normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were analyzed using the c^2 or Fisher's exact tests.

Survival curves were calculated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was defined as a two-tailed P value < 0.05. All statistical analyses were conducted using SPSS software (version 24.0; IBM Inc., Armonk, NY, USA).

RESULTS

Participant characteristics

A consecutive series of 91 patients was enrolled. During TACE, the APFs were embolized with ESG in 46 participants, and with microspheres in 45 participants. The ratios of men to women were 33/13 in the E group and 33/12 in the M group (c^2 = 0.029, P = 0.865), with a mean age of 63.4 ± 8.5 and 58.4 ± 10.1 years (P = 0.092), respectively. The etiologies included HBV (38/46, 82.6% in the E group and 39/45, 86.7% in the M group), hepatitis C (4/46, 8.7% in the E group and 2/45, 4.4% in the M group), HBV + HCV (2/46, 4.3% in the E group and 2/45, 4.4% in the M group), and alcohol consumption (2/46, 4.3% in the E group and 2/45, 4.4% in the M group) (P = 0.952). No significant differences in Child-Pugh stage, BCLC stage, or tumor location

were observed between the two groups. Mean tumor diameters were 6.8 ± 2.9 mm and 7.1 ± 1.6 mm in groups E and M (P = 0.765), respectively. Portal vein thrombi were found in 24 participants (24/46, 52.2%) in the E group and 22 participants (22/45, 48.9%) in the M group (c^2 = 0.098, P = 0.754), respectively. Treatments before TACE included surgery, microwave ablation (MWA), radiofrequency ablation (RFA), TACE, radiation, and TACE + MWA/RFA. We found no significant differences in previous treatments between the two groups (P = 0.925). The median levels of alpha-fetoprotein (AFP) were 137 (interquartile range (IQR):9.8, 970.1] and 114.9 (IQR:3.7, 725.7) ng/mL in groups E and M, respectively (P = 0.734). APF grades 1, 2, 3, 4, and 5 were recorded in 5 (5/46, 10.9%) and 6 (6/45, 13.3%); 15 (15/46, 32.6%) and 16 (16/45, 35.6%); 11 (11/46, 23.9%) and 14 (14/45, 31.1%); 9 (9/46, 19.6%), and 7 (7/45, 15.6%); and 6 (6/46, 13%) and 2 (2/45, 4.4%) participants in the E and M groups, respectively (P = 0.636) (Table 2).

The mean follow-up period was 35.3 ± 2.7 mo in the E group and 30.9 ± 3.8 mo in the M group (P = 0.195). After 4 mo, complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD) were achieved in 18 (18/46, 39.1%) and 8 (8/45, 17.8%) patients; 21 (21/46, 45.7%) and 18 (18/45, 40%) patients; 4 (4/46, 8.7%) and 15 (15/45, 33.3%) patients; and 3 (3/46, 6.5%) and 4 (4/45, 8.9%) participants in the E and M groups, respectively (P = 0.014). The DCR was 93.5% (43/46) in group E and 91.1% (41/45) in group M (P = 0.714). The ORRs were 91.3% (42/46) and 66.7% (30/45) in groups E and M, respectively (P = 0.004).

The APFs immediately improved after the procedure in 43 (43/46, 93.5%) and 40 (40/45, 88.9%) participants in groups E and M, respectively, (P = 0.485). After two months, APF improvement was achieved in 37 (37/46, 80.4%) and 33 (33/45, 73.3%) participants in the E and M groups, respectively (P = 0.421). The median AFP levels at 4 mo after the procedure were 28.48 (IQR:4, 257.9) and 45.25 (IQR:4.43, 359.5) ng/mL in groups E and M, respectively (P = 0.045). After 4 mo, the difference in the Child-Pugh class distribution between the E and M groups was not significant (P = 0.083) (Table 3).

The OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively (c^2 = 10.3, P = 0.004; Figure 4) (Table 3). The PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively (P = 0.012; Figure 5) (Table 3).

DISCUSSION

According to the updated Barcelona Clinic Liver Cancer (BCLC) prognosis and treatment strategy,[16] TACE is recommended for treating intermediate-stage B HCC. With its tendency to infiltrate portal and hepatic venous structures, HCC is often accompanied by APFs, which may reduce the therapeutic benefits of TACE.[7] Our study focused on comparing ESG and microspheres in the treatment of hepatic APFs. The DCR was 93.5% (43/46) in group E and 91.1% (41/45) in group M (P = 0.714). The ORRs were 91.3% and 66.7% in groups E and M, respectively (P = 0.004). OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively (P = 0.004). PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively (P = 0.012; Figure 5) (Table 3).

Gelatin sponges and microspheres have several disadvantages for the treatment of hepatic APF. Gelatin sponges are absorbed 2–3 wk after the procedure, and the APFs can be recanalized. Microspheres have a physical embolic effect without protein degradation of the vascular wall. Ethanol has been widely used in the embolization of arteriovenous malformations,[17] which can denature blood proteins, dehydrate vascular endothelial cells, and cause segment fractures in the vascular wall.[18-20] Compared with gelatin sponges alone, ethanol has demonstrated an improved long-term effect on hepatic APFs.[21] However, because of its liquid properties, ethanol alone is not suitable for shunts with high blood flow. ESG combines the advantages of ethanol and gelatin sponges, promoting local control of hepatic APFs and liver tumors.[12]

In our study, the immediate improvement and first-time follow-up rates of APFs in group E were not significantly higher than those in group M (93.5% and 88.9%, P = 0.485; 80.4% and 73.3%, P = 0.421, respectively). These results indicate that both ESG and microspheres had similar short-term effects in the treatment of hepatic APFs. The immediate improvement rate in group E was comparable to the 97% reported by Zhou

et al,[12] whereas the first-time follow-up APF improvement rate was higher in both groups than that reported by Zhou *et al* (54%).[12] This discrepancy may be due to the higher proportion of grade 1–3 APFs in our study.

Our study investigated tumor response 4 mo after the procedure and revealed that the CR, PR, SD, and PD rates were 39.1% and 17.8%; 45.7% and 40%; 8.7% and 33.3%; and 6.5% and 8.9% in the E and M groups, respectively (P = 0.014). Moreover, the ORR was 84.8% and 57.8% in groups E and M, respectively (P = 0.004). These results indicate that compared with microspheres, ESG led to complete long-term control of hepatic APF, including physical blockade and chemical destruction, and yielded a significantly better local tumor response. Both the DCRs (93.5%) and ORRs (84.8%) of group E patients were higher than those reported in Zhou's study (81.9% and 42.6 %, respectively).[12]Three possible reasons may account for this result. First, tumor response in our study was evaluated 4 mo after the procedure, which provided an additional chance for tumor control. Second, the percentage of participants with portal vein thrombus (52.5%) was lower than that reported in Zhou's study. And third, the proportion of grade 1–3 APFs in our study was higher, resulting in a better embolic response.

The OS, PFS, and median AFP levels 4 mo after the procedure in the E group were significantly better than those in the M group. This outcome may be attributed to the complete blockage of hepatic APFs and well-controlled tumors.Compared with microspheres, ESG embolization showed complete long-term blockade of hepatic APFs, and therefore improved the local control of HCC and survival of patients with HCC.

Nevertheless, this study had one limitation. As a retrospective study, selection bias may have reduced the value of the results. Further prospective studies are required to validate these findings.

CONCLUSION

Compared with microspheres, ESG embolization showed a higher ORR and longer OS and PFS. These findings may contribute to the selection of embolic agents for treating hepatic APFs in patients with HCC.

ARTICLE HIGHLIGHTS

Research background

Hepatic arterioportal fistulas (APFs) are common in HCC due to tumor infiltration, vascular damage, and remodeling of the cirrhotic parenchyma. The presence of hepatic APFs often complicates antitumor treatments, including transarterial chemoembolization (TACE).

Research motivation

Ethanol-soaked gelatin sponges (ESG) combine the advantages of alcohol and gelatin sponges, showing a convincing effect at different stages of hepatic APFs; however, no study to date has compared the efficacy of ESG and microspheres.

Research objectives

This retrospective study was conducted to compare the efficacy of ESG and microspheres in the management of APFs and their impact on HCC prognosis.

Research methods

APFs were embolized using ESG (group E) or microspheres (group M) during TACE. The disease control rate (DCR) and objective response rate (ORR) were considered primary outcomes. The secondary outcomes included immediate and first-time follow-up APF improvement, overall survival (OS), and progression-free survival (PFS).

Research results

The DCR was 93.5% in group E and 91.1% in group M (P = 0.714). The ORRs were 91.3% and 66.7% in groups E and M, respectively (P = 0.004). In 43 (93.5%) E

group and 40 (88.9%) M group participants, the APFs improved immediately after the procedure (P = 0.485). After two months, APF improvement was achieved in 37 (80.4%) and 33 (73.3%) participants in the E and M groups, respectively (P = 0.421). OS was 26.2 ± 1.4 and 20.6 ± 1.1 mo in groups E and M, respectively (P = 0.004). PFS was 16.6 ± 1.0 and 13.8 ± 0.7 mo in groups E and M, respectively (P = 0.012).

Research conclusions

Compared to microspheres, ESG embolization demonstrated a higher ORR and longer OS and PFS in HCC patients with hepatic APFs.

Research perspectives

These findings may aid in the selection of embolic agents for treating hepatic APFs in patients with HCC.

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