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Safety and Efficacy of Glass Membrane Pumping Emulsification Device in Transarterial Chemoembolization for Hepatocellular Carcinoma: First Clinical Outcomes

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Abstract. *Aim: Novel glass membrane pumping emulsification devices (GMDs) enable the formation of a high-percentage water-in-oil emulsion with homogeneous and stable droplets. Although GMDs are expected to improve therapeutic effects in transarterial chemoembolization (TACE) for hepatocellular carcinoma (HCC), clinical outcomes are not yet available. Patients and Methods: A total of 26 patients with unresectable HCC who underwent TACE using a GMD were analyzed retrospectively. Ethiodized oil was mixed with epirubicin solution using a GMD. The emulsion was injected into the tumor-feeding artery, followed by embolization. Results: The median size of HCCs was 28 (range=15-60) mm, and 15 nodules were solitary. Overall treatment effects were complete response in 18 cases (90%) and partial response in two (10%). The local recurrence rate at 6 months was 24.2%. No major complication was observed except for grade 4 elevations of liver enzymes in one case. Conclusion: TACE using a GMD is effective and safe in clinical practice.*

Since the first report of 120 cases of hepatic artery embolization by Yamada et al. in 1983 (1), transarterial chemoembolization (TACE) has undergone many improvements and has an established position as a standard treatment for hepatocellular carcinoma (HCC) (2). Ethiodized oil (Lipiodol; Guerbet, Villepinte, France) is widely used not only as a carrier for a chemotherapeutic agent but also as an embolizing agent in TACE (3). When mixed with anticancer agents as a water-in-oil emulsion, ethiodized oil provides sustained release of anticancer agents and enhanced embolization in the targeted area (4).

MicroMagic (Piolax Medical Devices, Yokohama, Japan), a glass membrane pumping emulsification device (GMD) which was created with volcanic ash, contains a disk-shaped glass membrane having numerous 50 μm-sized pores (5). This GMD enables the formation of a higher percentage water-in-oil emulsion with homogeneous and stable droplets compared to the conventional 3-way stopcock pumping technique, therefore it is expected to improve the therapeutic outcome of TACE (6). However, the clinical outcomes of using this GMD in TACE are still unclear. In this study, we aimed to evaluate the therapeutic efficacy and safety of TACE using this GMD in clinical practice.

Patients and Methods

Study population. Among 276 patients who underwent TACE for HCC at Nagoya University Hospital (Nagoya, Aichi, Japan) from 2019 to September 2021, 26 who were treated by TACE using a GMD were included in this study. The therapeutic efficacy and safety of TACE using a GMD were retrospectively investigated. This study was approved by the Ethics Committee of Nagoya University Hospital (2021-0247).

TACE. All TACE procedures were performed according to the standard treatment protocol (2). Epirubicin hydrochloride (50 mg Epirubicin; Nippon Kayaku, Tokyo, Japan) was dissolved in 2.5 ml of contrast agent iopamidol (Iopamiron; Bayer, Osaka, Japan). Ethiodized oil was then mixed with epirubicin solution using a GMD. The ratio of epirubicin solution to lipiodol was 1:2. The emulsion was created by pumping the mixture 20 times using the GMD before arterial injection. The emulsion was injected into the tumor-feeding artery, followed by embolization using 1-mm gelatin particles (Gelpart; Nippon Kayaku, Tokyo, Japan).

Assessment of treatment effect and adverse events. The treatment efficacy was evaluated by contrast-enhanced computed tomography 1-3 months after TACE using GMD and every 2-3 months thereafter. Based on changes in the maximum diameter of viable lesions, treatment responses were categorized by the modified Response

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Key Words: Hepatocellular carcinoma, transarterial chemoembolization, glass membrane pumping emulsification device.

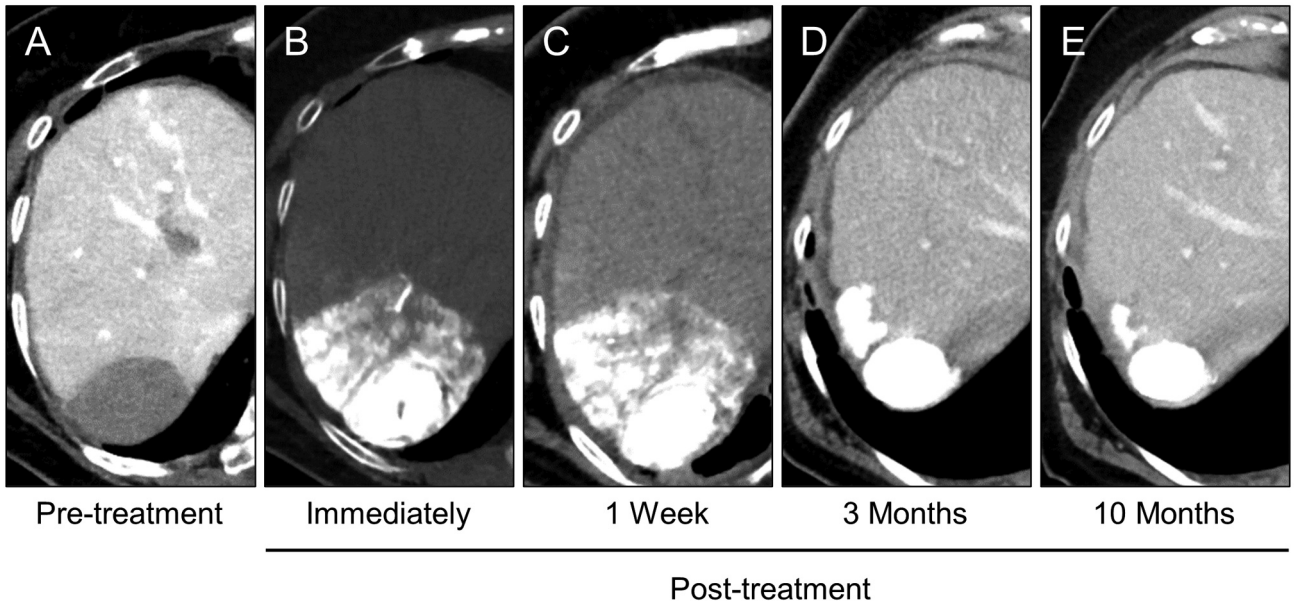

Figure 1. *Representative case of transarterial chemoembolization using a glass membrane pumping emulsification device. A 45 mm hepatocellular carcinoma was treated by transarterial chemoembolization using a glass membrane pumping emulsification device. A total of 4.5 ml of the emulsion was injected into the tumor-feeding artery, followed by embolization using 1-mm gelatin particles. A: Computed tomography (CT) during arterial portography showed contrast defect at segment 7 in the liver. B: Plain CT showed suitable deposition of ethiodized oil surrounding the tumor at the end of the treatment. C: Plain CT also showed ethiodized oil retention 1 week after the procedure. D and E: Contrast-enhanced CT showed complete response in the target nodule at 3 (D) and 10 (E) months after the treatment.*

Criteria in Solid Tumors (7). Briefly, complete response (CR) was defined as the disappearance of any intra-tumoral arterial enhancement; partial response (PR) was an at least 30% decrease in the sum of diameters of viable target lesions; stable disease described cases that did not qualify for either PR or progressive disease; and progressive disease was an increase of at least 20% in the sum of the diameters of viable target lesions. Tumor recurrence was diagnosed when arterial enhancement was observed in or adjacent to the tumor. The safety of TACE was evaluated using the Common Terminology Criteria for Adverse Events version 5.0 (8). Blood examinations were evaluated before and 1 month after each TACE procedure.

Statistical analysis. The local recurrence rate was analyzed by the Kaplan–Meier method. Paired *t*-test was performed to evaluate changes in plasma albumin, bilirubin and prothrombin time as liver function measurements. Statistical significance was defined as $p<0.05$. All statistical analyses were performed using GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA).

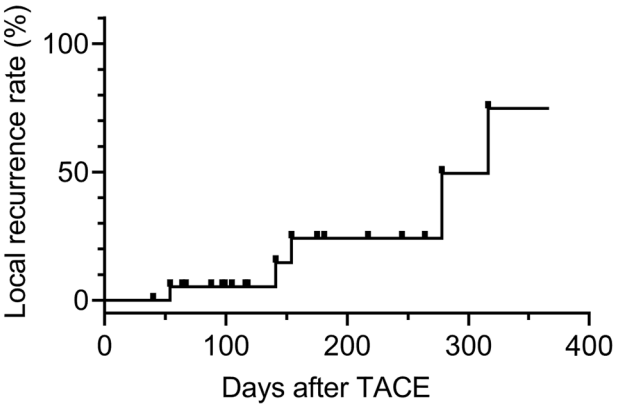

Figure 2. *Local recurrence rates in target nodules after transarterial chemoembolization using a glass membrane pumping emulsification device. The graph shows the local recurrence rate calculated with the Kaplan–Meier method. The rate of local recurrence of target tumors was 5.2% at 100 days, 24.2% at 200 days, and 49.4% at 300 days.*

Results

Patient characteristics. There were 22 males and four females; the median age was 74 years (range=56-85). Child–Pugh scores were A (score 5) in 20 patients, A (score 6) in three patients, and B (score 7) in three patients. The Barcelona Clinic Liver Cancer stages were 0 (very early stage) in seven patients, A (early stage) in 13 patients and B (intermediate stage) in six patients. Overall, 17 patients had a previous history of TACE. The median size of the nodules was 28 mm (range=15-60 mm), and 15 nodules were solitary. Epirubicin was used in all cases, and emulsions were administered

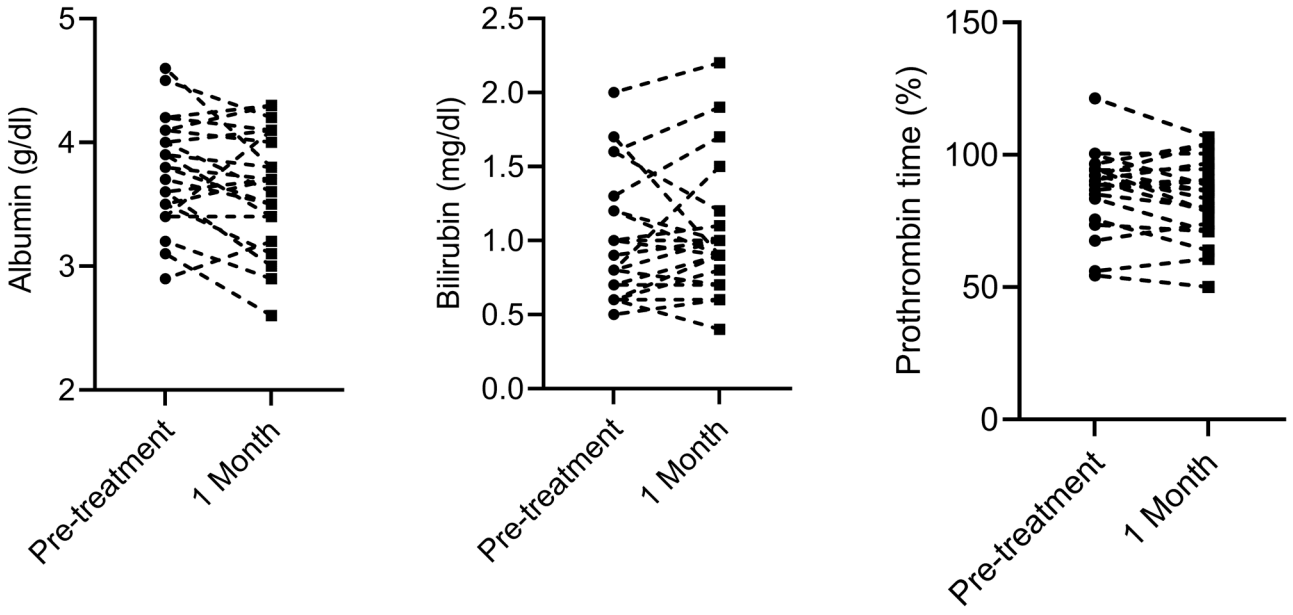

Figure 3. *Changes in liver function. The changes in markers of liver function before and 1 month after transarterial chemoembolization (TACE) using a glass membrane pumping emulsification device were assessed by paired t-tests. Changes were not significantIy different.*

peripherally from the subdistrict branches. The median dosage of GMD-made emulsion was 2.8 ml (range=1.5-6.8 ml). A representative case is shown in Figure 1.

Treatment effects. Treatment response was evaluated in 20 patients at a median of 83 days (range=40-141 days). Overall, 18 (90%) patients experienced CR and two (10%) experienced PR. An objective response (CR plus PR) was obtained in all patients at the first treatment evaluation. The local recurrence rate of target tumors was 5.2% at 100 days, 24.2% at 200 days, and 49.4% at 300 days (Figure 2).

Adverse effects. Grade 3 elevations of liver enzymes were observed in four patients, and grade 4 in one patient. Liver enzyme levels peaked in all cases between 1 and 3 days after the TACE. Liver enzyme elevations were self-limited and no case required additional intervention. Nine (34.6%) patients experienced grade 1 fever and six (23.0%) patients experienced grade 1 anorexia. No other serious side-effects required prolonged hospitalization. In the post-treatment follow-up, one patient was diagnosed with a biloma in the TACE-treated area but no serious subsequent complications were observed.

Changes in liver function. Figure 3 shows the changes in liver function between that before and that at 1 month after the TACE procedures. Paired t-tests revealed no significant differences in albumin concentration, total bilirubin level, or prothrombin time (Figure 3).

Discussion

The results of this study showed that the local tumor control with TACE using GMD for HCC was 75.6% at 6 months without serious complications, indicating that the use of GMD in TACE is a faborable treatment option for locoregional treatment of HCC compared with the 'conventional' emulsification method (9, 10). Ethiodized oil accumulates in HCC by the enhanced permeability and retention effect in solid tumors, and, in combination with embolizing substances, it blocks blood flow not only to the nutrient-supplying vessels of HCC but also to the surrounding sinusoid through the blood sinuses in the tumor, resulting in hemostasis and necrosis of HCC (9). The conventional three-way stopcock pumping method is widely used for emulsification of ethiodized oil with a water-soluble anticancer agent, however, this technique only achieves about 70% water-in-oil emulsion and unstable droplet size and viscosity (11). The GMD connector is a simple device that enables the preparation of a high percentage (97.9%) and stable water-in-oil emulsion (5) and was shown to have a better effect on anticancer drug retention in tumors in the VX2 liver cancer rabbit model (6). Although better TACE treatment outcomes are expected using a GMD, the efficacy in clinical practice is as yet unknown. This study showed a local control rate of 75.6% at 6 months, which is at least comparable with previous reports with TACE using the conventional method (9, 10). Although no serious adverse events were observed in this study, the rates of increased liver enzymes, fever and anorexia

were higher compared with the conventional emulsification method (10). This study has three limitations. Firstly, the number of patients was limited. Secondly, only patients who underwent TACE using GMD were enrolled in this study. Thirdly, this study had a retrospective design and the presence of bias related to the selection of patients for HCC treatment cannot be ruled out. Although a further comparative study is needed to elucidate additional effects of GMD usage, a local control rate of 75.6% at 6 months seems to make it a promising option for locoregional treatment of HCC.

Conclusion

TACE using a GMD is suggested to enable appropriate treatment efficacy without causing serious adverse effects.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

Concept and study design: N. Imai, Acquisition of data: N. Imai, S. Yokoyama, K. Yamamoto, T. Ito, Y. Ishizu, T. Honda, and M. Ishigami, Writing the article: N. Imai. Statistical analysis: N. Imai.

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