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Original article

Transcatheter Arterial Chemoembolization with Hepasphere 30–60 µm for Treatment of Unresectable Hepatocellular Carcinoma

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Abstract:

Background: Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world and second leading cause of cancer related death. Management is mainly accomplished by local ablative therapies that can compete in efficiency with surgical resection. This study aimed to assess the safety and efficacy of the hepasphere 30-60 µm for the treatment of unresectable HCC. **Methods:** This prospective study was conducted on 50 patients with unresectable HCC who were selected for the treatment by transcatheter arterial chemoembolization (TACE) therapy with hepasphere 30 – 60 µm (drug eluting beads), at the Egyptian Liver Hospital, Sherbin, Dakahlia. All studied cases were subjected to laboratory studies and imaging studies including Abdominal ultrasonography and Doppler, abdominal triphasic CT. **Results:** There was highly significant decrease in serum AFP level one, three and six months after treatment compared to pre-treatment level with (P-value < 0.001). There was no insitu recurrence occurred with the first three months after the procedure, but after six months there were five patients (10%) showed insitu recurrence and there was no denovo recurrence occurred till the end of the study. There was a insignificant relation between response and sex (P=0.031), affected hepatic segment number (VI and VIII) (P0.001, 0.027). **Conclusion:** This study suggests of high evidence of efficacy and safety of hepasphere 30-60 µm in treating patient with Unresectable HCC. Tumor response, number of HCC foci, patient age, serum Alpha Fetoprotein level, and complications due to TACE had a significant effect on survival in HCC treated with TACE.

Keywords: Transcatheter Arterial Chemoembolization; Hepasphere; 30–60 µm; Unresectable; Hepatocellular Carcinoma.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy in the world and second leading cause of cancer related death [(1)]. Orthotopic liver transplantation and surgical resection offer the best opportunities to cure patients. However, both options are limited in their application because of the scarce organ availability for transplantation. The size and location of the tumor; associated vascular invasion and thromboses, and the characteristics and severity of the underlying liver disease [(2)]. For these reasons, management is mainly accomplished by local ablative therapies that can compete in efficiency with surgical resection. Moreover, local ablation can be applied to a larger number of patients with more advanced liver disease, with multifocal presentation and other clinical conditions that can represent contraindications for liver surgery [(2)].

Local ablative therapies include catheter-based approaches (transcatheter arterial chemoembolization (TACE)) and locoregional ablative techniques, either chemical, or thermal [(3)]. TACE is the most commonly used method to treat patients with HCC who cannot receive radical treatment [(4)]. TACE can provide high concentrations of chemotherapy drugs to tumor tissues while retaining the surrounding normal liver parenchyma. Embolization agents can cause tumor ischemia necrosis, which slows down the elution of chemotherapy drugs, and evidence has shown that chemoembolization can improve the survival rate of patients with HCC [(5)].

In TACE procedures, HCC nodules are embolized through feeding hepatic artery with embolic agents and anticancer agents, inducing antitumor effects by anticancer effects and ischemic effects. Chemoembolization with drug-eluting bead (DEB)-TACE is technically similar to conventional lipiodol-based TACE (c-TACE), providing similar therapeutic benefits compared with c-TACE [(6)]. DEB-TACE is made from uniform particles and can induce permanent embolization and long-sustaining local concentration of anticancer drugs although c-TACE has a transient embolic effect [(7)]. In addition with those chemoembolic effects, DEB-TACE is shown to be less harmful and to induce mild postembolization syndrome compared with that with c-TACE, from those observations, DEB-TACE is expected as the therapeutic modality for patients with huge HCC or decreased liver function [(8)].

The purpose of this study was to assess the safety and efficacy of the hepasphere 30-60 μm for the treatment of unresectable HCC.

Patients and methods

This prospective study was conducted on 50 patients (36 male and 14 female) their age ranged from 39 to 75 years with unresectable HCC who were selected for the treatment by TACE therapy with hepasphere 30 – 60 μm (drug eluting beads), at the Egyptian Liver Hospital (ELH), Sherbin city, Dakahlia province, Egypt, during the period between 6/2022 and 6/2024.

An informed written consent was obtained from the patients. Every patient received an explanation of the purpose of the study and had a secret code number. The study was done after being approved by the Research Ethics Committee, Faculty of Medicine, Benha University (**Approval code: MD :23-4-2022).**

Inclusion criteria were Child A and B Pough score, patients with HCC not suitable for radiofrequency or microwave ablation (Single nodular-type HCC smaller than 5 cm or as many as 3 HCC lesions) but considered high risk due to location (close to gall bladder, liver hilum, liver capsule, diaphragm or pericardium), surgical resection not an option or refused by the patient, ECOG performance status < 2, Creatinine < 2 mg/dl, and tumor burden <50% of the liver volume.

Exclusion criteria were advanced liver disease (bilirubin >3 mg/dl, and Child Pough's C score or active gastrointestinal bleeding, ascites, or encephalopathy), advanced tumoral disease (Evidence of extrahepatic disease at presentation and evidence of tumor invasion of the hepatic vein or portal vein), and any contraindication for the procedures (Porto systemic shunt, hepato-fugal blood flow, impaired clotting tests (platelets count < 50,000/mm³, prothrombin activity < 50 %), serum Creatinine > 2 mg/dl, and AST and /or ALT > elevated 5 time more than upper limit).

Diagnosis of HCC was confirmed by typical criteria of Triphasic CT and elevated Alfa-fetoprotein.

All studied cases were subjected to the following: Detailed clinical history include: [Presence of predisposing factors as: liver cirrhosis & viral hepatitis, and presenting complaint which may be vague as dyspepsia, abdominal pain, abdominal discomfort or loss of weight and deterioration of the general condition.]. **Laboratory studies include:** [Complete blood picture, liver function tests (serum Bilirubin, transaminases (ALT&AST) & serum albumin), prothrombin time and concentration, Alpha fetoprotein, and kidney function tests]. **Imaging studies include: [**Abdominal ultrasonography and Doppler study of the portal vein, to locate site, size, echo pattern, number of focal lesions and patency of portal vein, abdominal triphasic CT (For all patients as baseline to show the size of lesion, its location, morphology, enhancement pattern, vascular invasion. CT scans were of 3 phases performed on a helical CT scanner. The scans were obtained through the liver in a craniocaudal direction with 5-mm collimation; a 5-mm/s table speed (pitch, 1.0) during a single breath-hold helical acquisition of 20-30 s, depending on the size of the liver; and a 5-mm reconstruction interval. For three phases CT, the hepatic arterial, portal venous and delayed phases were scanned 30, 60 and 180 s respectively after the start of the injection of 120 ml of nonionic iodinated contrast material, via the peripheral vein at a rate of 3 ml/sec by power injector].

Technique:

Embolization was performed percutaneously in the angiography suite, with the patient under conscious sedation. After infiltration of local analgesics, the Seldinger technique is used to gain access to the aorta through femoral artery puncture. A 6-French vascular sheath was placed into the common femoral artery over a 0.035-inch Guidewire. Under fluoroscopic guidance, the 5- French Cobra catheter was advanced into the aorta. An angiographic study of the superior mesenteric artery (SMA), celiac trunk, and common hepatic artery was performed to identify all the vessels feeding the HCC nodule. The arterial branches feeding the tumor were selectively cannulated by microcatheter Progreat 2.7 or 2.4 (Terumo); Renegate HiFlo/Fathom (Boston Scientific); to proceed with TACE and to ensure better preservation of the surrounding non tumoral liver tissue. Hepasphere used were 30 – 60 µm. The injection was done very slowly, and the suspension was diluted. The embolization end point was to achieve complete occlusion of neovascularity. The procedure was considered technically successful when the tumor stain was completely devascularized.

Post procedure care: Good hydration using 1000 ml of intravenous fluids and forced hydration using 40ml Lasix was carried out guided by blood pressure, analgesics, antipyretics , antiemetics, prophylactic antibiotics and proper liver support were prescribed for all patients, the puncture site must be carefully observed for at least 6 hours, bed rest and inform the patient strictly not bending his thigh for 6 hours, vital signs, particularly peripheral pulses, must be taken periodically every two hours up to 24 hours, and after treatment, medications were given (antibiotics, antipyretics and

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analgesics) for 5 days to prevent infection and prophylactic against post –TACE syndrome.

Follow –up and data collection:

All patients were followed up during the first month and every 1, 3 and 6 months after TACE procedure for clinical follow up, laboratory follow up (Liver function tests in 1, 3 and 6 months after procedure, AFP level 1, 3 and 6 months after procedure), and imaging (Triphasic spiral CT was done after one month to assess response and efficacy. The follow up CTs were done 3 and 6 months after the procedure. In each imaging the longest diameter of enhancing viable tumor and percentage of tumor necrosis post-treatment were recorded. Necrosis was defined as a non-enhancing, low-fluid-density intratumoral area).

Tumor response:

Tumor response was measured by contrast-enhancement spiral computed tomography according to EASL (European Associated for the Study of the Liver) consensus amendments for tumor response assessment and according to mRECIST (modified Response Evaluation Criteria in Solid Tumor) criteria. The amendments of the EASL consensus consider that (non-enhanced tumoral areas reflect tissue necrosis after treatment, whereas viable neoplastic cells are recognized by enhanced areas inside the treated lesion). Thus, the definition of response must take into account the extent of tumor necrosis of the total tumor bulk.

Case presentation:

Fifty-three years old male patient with compensated liver cirrhosis Child B score. The sonographic assessment revealed right lobe hypoechoic focal lesion measuring about (5 x 5 cm) in segment VII, Patent portal vein and no ascites. The laboratory investigations were as follows: Pre TACE: the liver function tests included AST (70 U/L), ALT (80 U/L), Bilirubin (1.9 mg/dL), albumin (3.1 mg/dL) and PT (75%), CBC included HGB (11 g/dL), platelets (160000) and TLC (4900), Alpha fetoprotein (1600 ng/dl) and serum creatinine (0.9). At 1 month post TACE: the liver function tests included AST (80 U/L), ALT (95 U/L), Bilirubin (1.8 mg/dL), albumin (3.1 mg/dL) and PT (80%), CBC included HGB (10.5 g/dL), platelets (140000) and TLC (4500), Alpha fetoprotein (960 ng/dl) and serum creatinine (1.2). At 1 month post TACE: the liver function tests included AST (112 U/L), ALT (130 U/L), Bilirubin (1.8 mg/dL), albumin (3 mg/dL) and PT (82%), CBC included HGB (9 g/dL), platelets (105000) and TLC (4500), Alpha fetoprotein (1480 ng/dl) and serum creatinine (1.2). At 3 months post TACE: the liver function tests included AST (125 U/L), ALT (144 U/L), Bilirubin (2.5 mg/dL), albumin (2.8 mg/dL) and PT (61%), CBC included HGB (9 g/dL), platelets (100000) and TLC (12200), Alpha fetoprotein (1820 ng/dl) and serum creatinine (0.4).

Regarding the radiological imaging, triphasic CT before TACE revealed: right lobe hepatic focal lesion showing heterogeneous enhancement at arterial phase, washout at portal and delayed phases. Triphasic CT study after one month of the procedure: Inadequately managed hepatic focal lesion at segment VII with evidence of residual activity. Area of enhancement inside the tumor in arterial phase & washout in portal and delayed phases. The final out-come according to mRECIST criteria revealed that there is a partial response of the target lesion. Figure 1

Statistical analysis:

Data analysis was performed by SPSS software, version 26 (SPSS Inc., PASW statistics for windows version 26. Chicago, USA: SPSS Inc.). Qualitative data were described using number and percentage. Quantitative data were described using mean± standard deviation for normally distributed data after testing normality using Kolmogorov-Smirnov test. Significance of the results obtained was judged at the (0.05) level. Chi-Square,

Fisher exact tests were used to compare qualitative data between groups as appropriate, Student t test was used to compare 2 independent groups for normally distributed data.

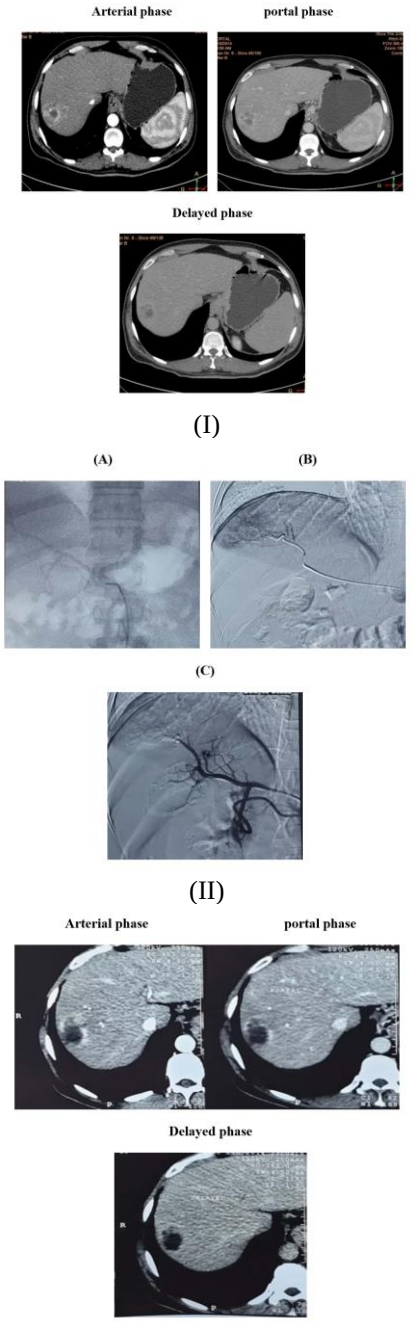

Figure 1: (I) Triphasic CT before TACE, (II) TACE, (A) Celiac arteriogram showing splenic artery, common hepatic artery and gastroduodenal artery, (B) Angiography of the right hepatic artery shows abnormal vascularization of the tumor, (C) Angiography after embolization shows faint abnormal tumor blush. (III) Triphasic CT after TACE

Results

Table 1 shows the age, sex, distribution of lesions in different hepatic lobes and segments, the origin of supplying artery, lesion size, different clinical presentation, and different CT findings.

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Table 1: The age and sex, distribution of lesions, the origin of supplying artery, the size of the lesions, different clinical presentation, and different CT findings

	Total number (50)	**%**
Age / years		
Mean ±SD	60.02±7.85	
(MIN-MAX)	(39-75)	
Sex		
Male	36	72.0
Female	14	28.0
Affected lobe side		
Right	41	82.0
Left	9	18.0
Segment number		
II	2	4.0
III	4	8.0
V	6	12.0
VI	13	26.0
VII	15	30.0
VIII	10	20.0
Origin of supplying artery		
Right hepatic---superior mesenteric	5	10.0
Right hepatic---Celiac	36	72.0
Left hepatic---left gastric	4	8.0
Left hepatic---celiac	5	10.0
Lesion size (largest diameter)		
2 to 4	9	18.0
4 to 6	22	44.0
6 to 8	13	26.0
8 to 10	6	12.0
Lesion size Mean ±SD (MIN-MAX)	4.61±1.41	
Clinical presentation (symptoms)		
Abdominal pain	**22**	44.0
Weight loss	**9**	18.0
Nausea / or vomiting	**4**	8.0
Abdominal enlargement	**8**	16.0
Asymptomatic	**7**	14.0
CT findings		
Lesion definition		
Well defined	**47**	94.0
Ill defined	**3**	6.0
Lesion shape		
Rounded	**37**	74.0
Oval	**9**	18.0
irregular	**4**	8.0
Liver cirrhosis	**50**	100
Portal vein		
Patent	**49**	98.0
thrombosed	**1**	2.0
Ascites	**2**	4.0
Splenomegaly	**42**	84.0

Table 2 shows the response to treatment by TACE using hepasphere 30-60 μm, the effect of hypersphere on frequency and percentages of survival and mortality, and the frequency and percentages of different complications.

There was a highly significant decrease in serum AFP level one, three and six months after treatment compared to pre-treatment level with (P-value < 0.001). There was no insitu recurrence occurred with the first three months after the procedure, but after six months there were five patients (10%) showed insitu recurrence and there was no denovo recurrence occurred till the end of the study. Table 3

There was an insignificant relation between response and sex (P=0.031), affected hepatic segment number (VI and VIII) (P0.001, 0.027), both affected hepatic segment number (VI and VIII) were significantly higher in complete response and males showed higher complete response. There was an insignificant relation between response and age, affected lobe side, affected hepatic segment number (II, III, V and VII) and the origin of supplying artery (right hepatic---superior mesenteric, Right hepatic---Celiac, left hepatic---left gastric, left hepatic---celiac) and lesion size (largest diameter) Table 4.

Table 2: The response to treatment by TACE using hepasphere 30-60 μm, effect of hypersphere on frequency and percentages of survival and mortality, and different complications

Response		**N**		**%**	
Partial		14		28.0	
Complete		36		72.0	
	Criteria				
Overall survival	**6 months**	47		94.0	
Progression free survival	**6 months**	45		90.0	
Complications		**yes**		**No**	
		N	%	N	%
PES (fever ≥ 38C, pain and vomiting)		36	72	14	28
Femoral pseudoaneurysm		1	0	49	98
Decompensations		4	0	46	92

Table 3: Effect of TACE using hepasphere 30-60 μm on AFP level, and frequencies, percentages and results comparison between local recurrence after 1-, 3- and 6-months post-treatment

	Pre-treatment X ± SD	**1month after X ± SD**		**3 months after X ± SD**		**6 months after X ± SD**	
AFP X ± SD	808.11±545.14	268.84 ± 88.3		47.79 ± 82.33		12.18 ± 15.67	
P value		< 0.001		< 0.001		< 0.001	
Significance		H.S		H.S		H.S	
		N	%	N	%	N	%
Total recurrence		0	0	0	0	5	10
Denovo Recurrence		0	0	0	0	0	0
Insitu Recurrence		0	0	0	0	5	10

H.S = highly significant

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Table 4: Relation between response and different parameters

	Response		test of significance	P value
	Partial N=14 (%)	**Complete N=36 (%)**		
Age / years				
Mean ±SD	58.29±7.95	60.69±7.82	t=0.974	0.335
Sex				
Male	7(50.0)	29(80.6)	χ^2=4.67	0.031*
Female	7(50.0)	7(19.4)		
Affected lobe side				
Right	12(85.7)	29(80.6)	χ^2=0.182	0.670
Left	2(14.3)	7(19.4)		
Affected hepatic segment number				
II	2(14.3)	0	χ^{2FET}=5.37	0.07
III	0	4(11.1)	χ^{2FET}=0.096	1.0
V	0	6(16.7)	χ^2=0.043	0.837
VI	8(57.1)	5(13.9)	χ^2=9.80	0.001*
VII	4(28.6)	11(30.6)	χ^2=0.0189	0.891
VIII	0	10(27.8)	χ^2=4.86	0.027*
Origin of supplying artery				
Right hepatic---superior mesenteric	1(7.1)	4(11.1)	χ^{2FET}=0.176	1.0
Right hepatic---Celiac	11(78.6)	25(69.4)	χ^2=0.417	0.519
Left hepatic---left gastric	2(14.3)	2(5.6)	χ^{2FET}=1.044	0.310
Left hepatic---celiac	0	5(13.9)	χ^2=2.16	0.14
Lesion size (largest diameter in cm) Mean ±SD	5.03±1.43	4.44±1.39	t=1.32	0.193

t:Student t test, *statistically significant, χ2=Chi-Square test, FET: Fisher exact test, *statistically significant

Discussion

In our study, we performed TACE with drug eluting beads (hepasphere) 30-60μm produced By Merit Medical, combined with chemotherapeutic agents (Doxorubicin). TACE with drug eluting beads (hepasphere) for large HCC (meaning 5 cm) was promising and proven to lead to extensive tumor necrosis with minimal postprocedural pain.

In 2007, a previous clinical study proved safety and efficacy of drug eluting beads in the transarterial treatment of HCC [(9)].

The study of Padia et al. [(10)] showed that DEB platform extended the release of the drug which led to less adverse events compared to conventional TACE. The beads initially being used ranged from 300-500 μm and 500-700 μm in size, which, compared to smaller sizes, proved less efficient and more toxic. The drawback of even smaller beads is that they could reach more distally into arterial branches and cumulate in higher density which causes extensive necrosis in the tumor mass than beads with the size of 100-300 μm that occlude more proximal arteries.

The aim of this study was to present the 1-, 3- and 6-months clinical results of using Hepasphere 30–60 μm (DEBs) for TACE treatment of patients with unresectable HCC. In this study, the anti-tumoral effect and safety were the endpoints. To achieve this aim, 50 patients (36 male and 14 female, mean age 60.02 years) with HCC were treated by selective TACE using Hepasphere 30–60 μm (DEBs) with chemotherapeutic agents (Doxorubicin).

All our patients were diagnosed with liver cirrhosis with hepatic impairment showed that 15 patients (23%) presented with Child-Pough score A and 35 patients (77%) with Child-Pough score B. Among the treated patients, all patients (100%)

had HCV- related liver cirrhosis and no patients had HBV. The diameter of the treated lesions ranged from 2 to 9.5 cm (mean 4.61±1.41).

In this study, suspension of 30-60 µm hepasphere were used and successfully devascularized the tumors in all patients and achieved intratumoral sluggish flow.

In this study, the angiographic study was done showed the normal variants of the hepatic artery origin, we found that 36 patients (72 %) had hepatic artery arising from the celiac trunk, 5 patients (10%) had artery from SMA, 5 patients (5%) had left hepatic artery arising from celiac trunk, and only 4 patient (8 %) had left hepatic artery arising from left gastric artery

Regarding the end points of our study, we monitor tumor response to demonstrate the efficacy of the hepasphere.

Regarding our choice of monitoring, tumor response was evaluated according to the WHO criteria as modified according to EASL recommendations [(11)], which take into account only residual viable tumor tissue as represented by persistent intratumoral arterial contrast uptake. At 1 month follow up, we observed a high objective response rate (100%) as we recorded complete response in 36 patients (72%), partial response in 14 patients (27 %) and no cases showed stable disease or progression. After 3 and 6 months follow up (which another session was done to the cases of the partial response) the objective response remained high (85%) showed that complete response in 36 patients (72 %), and progression disease occurred in 5 patients (10%), and this showed the good efficacy of the treatment in disappearance of any intratumoral arterial enhancement in all target lesions.

These results showed the good tumor response that occurred between our patients due to the good choice for our patients based on inclusion criteria.

In this study, serological tumor markers such as AFP may be useful in measuring the true degree of response when imaging fails to distinguish residual tumor and necrotic/fibrotic tumor remnants. However, since the sensitivity of this marker is limited, radiological imaging remains the main method of assessing response [(12)].

In this study, the percentage of treatment – related death (within 30 days) was 0%. This ran parallel to the range of 0% to 10% reported in the study review Poon, et al, [(13)] and it was 5% within 6 months after the treatment.

In this study we showed that overall survival after 6 months was 94 %. Three patients died within the study from hepatic encephalopathy at 4th and 5th of months of the treatment. While the progression free survival after 6 months was 90%, as five patients showed Denovo recurrence and received additional treatment.

Conclusion

This study suggests of high evidence of efficacy and safety of hepasphere 30-60 µm in treating patient with Unresectable HCC. Tumor response, number of HCC foci, patient age, serum AFP level, and complications due to TACE had a significant effect on survival in HCC treated with TACE.

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Author contribution

Authors contributed equally to the study**.**

Conflicts of interest

No conflicts of interest

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