

Clinical Research Article

Hepatic Artery Embolization for Palliation of Symptomatic Hypoglycemia in Patients With Hepatic Insulinoma Metastases

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Abbreviations: HAE, hepatic artery embolization; HFS, hypoglycemia-free survival; IV, intravenous; OS, overall survival; PNET, pancreatic neuroendocrine tumor; PRRT, peptide receptor radionuclide therapy; PVA, polyvinyl alcohol; TACE, transcatheter arterial chemoembolization.

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Abstract

Context: Insulinoma is a pancreatic neuroendocrine tumor that causes hyperinsulinemic hypoglycemia. Symptomatic hypoglycemia related to hepatic insulinoma metastases may be addressed with liver-directed therapies such as hepatic artery embolization.

Objective: This work aimed to determine the safety and effectiveness of bland hepatic artery embolization (HAE) for palliation of symptomatic hypoglycemia in patients with hepatic insulinoma metastases refractory to medical management.

Methods: An institutional review board–approved retrospective review was undertaken of all patients with a tissue (n = 18) or imaging (n = 2) diagnosis of hepatic insulinoma metastases and symptomatic hyperinsulinemic hypoglycemia refractory to medical management who underwent bland HAE at a single center between January 1, 1998 and November 1, 2020. Twenty patients (10 women, 10 men; mean age, 56 years; range, 18–84 years) were identified who individually underwent 1 (n = 7), 2 (n = 5), 3 (n = 5), 4 (n = 2), or 5 (n = 1) HAEs, for an overall total of 45 HAEs. Post-HAE hypoglycemia recurrence was defined as onset of adrenergic symptoms (eg, sweating, weakness, tremor), neuroglycopenic symptoms (eg, confusion, loss of consciousness), and/or documented serum glucose of less than 50 mg/dL, in the absence of an alternative explanation. Median time to first hypoglycemia recurrence, hypoglycemia-free survival (HFS), and overall survival (OS) were calculated using Kaplan-Meier method.

Results: Before HAE, all patients experienced adrenergic or neuroglycopenic symptoms alleviated by glucose intake, and 60% (n = 12) of patients had documented serum glucose of less than 50 mg/dL within 1 week of the first treatment. Median post-HAE follow-up was 9.4 months (mean, 26 months; range, 0.1–190 months). Postprocedural hypoglycemic

symptom relief after the first HAE was reported in 100% (n = 20) of patients before discharge or at follow-up. Post-HAE hypoglycemia recurrence occurred in 60% (n = 12) of patients with a median time to first hypoglycemia recurrence of 2 months (mean, 14 months; range, 0.2-60 months). After the first HAE, median HFS was 14.5 months, and median OS was 16 months. One patient experienced labile postprocedure blood glucose levels requiring intensive care unit admission for intravenous dextrose. Otherwise, no major procedure-related complications occurred.

Conclusion: Bland HAE is a safe, effective, and repeatable procedure for palliation of symptomatic hypoglycemia in patients with hepatic insulinoma metastases refractory to medical management.

Key Words: bland hepatic artery embolization, treatment refractory hyperinsulinemic hypoglycemia, polyvinyl alcohol particles, PVA, transarterial chemoembolization, transcatheter arterial

Illustrative Case

A 41-year-old man initially presented with a 6-month history of increasing appetite, episodes of confusion, diaphoresis, and amnesia that tended to respond to juice. A 72-hour fasting study was aborted because of hypoglycemia, and on 2 occasions he was found to have an inappropriately elevated insulin level in the setting of hypoglycemia, initially with an insulin level of 183 mcIU/mL and a blood glucose of 37 mg/dL. An abdominal computed tomography scan demonstrated multiple liver metastases and a large enhancing pancreatic mass (Fig. 1). The patient was initiated on diazoxide, intravenous (IV) dextrose, and transferred to our institution. Liver biopsy demonstrated a metastatic, moderately well-differentiated neuroendocrine tumor. He was deemed inoperable because of vascular involvement. The patient underwent right hepatic artery embolization (HAE) in the morning (Figs. 2 and 3), and overnight blood glucose levels were elevated at 130 to 180 mg/dL while on IV 10% dextrose, which was halved from 50 cc/h to 25 cc/h and discontinued altogether by the afternoon of the next day. The patient developed expected postembolization syndrome with symptoms of right upper quadrant pain and fever. After a negative workup was completed including evaluation for multiple endocrine neoplasia, type 1 with a brain magnetic resonance scan, he was transitioned to a long-acting somatostatin analogue and discharged 6 days after HAE. The patient underwent a second stage treatment of the left hepatic lobe 1 month later without interval recurrence of symptoms. After repeat advanced imaging demonstrated stable metastatic disease, he was initiated on capecitabine and temozolomide approximately 2 months after the first HAE. Imaging obtained approximately 5 months after the initial HAE demonstrated marked progression of left hepatic liver metastases in addition to new retroperitoneal lymphadenopathy in the setting of new abdominal pain. He underwent a third HAE for palliation of abdominal pain without incident. The patient died approximately 1 year and 4 months after the initial diagnosis was made without recurrence of hypoglycemia symptoms.

Insulinoma is a rare, functional, insulin-producing pancreatic neuroendocrine tumor (PNET), with a reported incidence of 1 to 4 cases per million person-years [1]. Unlike nonfunctional PNETs, insulinoma may cause symptomatic hypoglycemia. Hypoglycemia symptoms are broadly categorized as neuroglycopenic or adrenergic. Neuroglycopenic symptoms include confusion, personality changes, dizziness or ataxia, weakness, and vision changes. Adrenergic symptoms are driven by catecholamine release, and may include palpitations, diaphoresis, and tremors [2]. Whipple triad outlines a set of clinical criteria used to identify endogenous hyperinsulinemic hypoglycemia and is defined by symptoms

of hypoglycemia, low circulating glucose, and prompt relief of symptoms after glucose administration [3].

Malignant insulinoma are even rarer, with a reported crude annual overall incidence of 0.0 to 0.27 cases per million person-years [4]. For patients with malignant insulinoma metastatic to the liver with symptomatic hyperinsulinemic hypoglycemia, offered therapies vary widely in treatment intent and discipline, from various combinations of curative to palliative interventions as provided by surgery, medicine, nuclear medicine, and radiology [5]. Liver-directed therapies control tumor burden and address severe associated hypoglycemia symptoms, the

latter of which require vigilance and careful meal timing on an outpatient basis.

Vascular and interventional radiology treatment options include ablation for smaller hepatic lesions and hepatic artery embolization (HAE) of one or both hepatic lobes in a staged approach. Published data regarding HAE for the palliation of hypoglycemia in patients with malignant insulinoma are limited because this group of patients is often included into a broader cohort of patients with metastatic neuroendocrine tumors responsible for an array of endocrine symptoms [6].

The aim of the present study was to determine the safety and effectiveness of bland HAE for palliation of symptomatic hypoglycemia in patients with hepatic insulinoma metastases refractory to medical management.

Materials and Methods

An institutional review board–approved, HIPAA (Health Insurance Portability and Accountability Act)-compliant retrospective review identified 20 patients with hepatic insulinoma metastases and symptomatic hyperinsulinemic hypoglycemia refractory to medical management who underwent bland HAE at a single center between January 1, 1998 and November 1, 2020. Hyperinsulinemic hypoglycemia refractory to medical management was defined as persistent or recurrent hypoglycemia symptoms and/or serum glucose of less than 50 mg/dL while using a somatostatin analogue and/or diazoxide.

Clinical, imaging, laboratory, procedural, and follow-up data were collected from the comprehensive electronic medical record. The clinical record was reviewed for neuroglycopenic (eg, confusion, loss of consciousness) or adrenergic (eg, sweating, weakness, tremor) hypoglycemia symptoms alleviated by glucose intake. Mesenteric angiography and cross-sectional imaging were reviewed for distribution of hepatic metastases. Bilobar hepatic metastases were defined as at least 1 tumor involving the right and left hepatic lobes.

Follow-up

Patients were followed using available clinical encounters and operative notes as documented in the electronic medical record in addition to laboratory values. Specifically, oncology and endocrinology notes were reviewed for hypoglycemic symptom onset and timing before and after HAE. Laboratory information, including serum glucose, insulin, proinsulin, and c-peptide levels, was collected from the institutional database.

Outcome Definitions

Technical success was defined as selective transcatheter HAE facilitated by pretreatment and posttreatment mesenteric angiography. Post-HAE hypoglycemia recurrence was defined on the basis of a modified Whipple triad including documented onset of symptoms (adrenergic or neuroglycopenic), and/or serum glucose of less than 50 mg/dL in the absence of an alternative explanation, such as sepsis or extrahepatic metastases. Whipple triad additionally specifies improvement in hypoglycemia symptoms after administration of glucose, although this information was not available in all patients and therefore was not used in the definition of post-HAE hypoglycemia recurrence. Hypoglycemia-free survival (HFS) was defined to include patients without hypoglycemia recurrence before the date of death. The duration of follow-up for HFS was defined from the date of the first HAE to the date of first hypoglycemia recurrence, date of death, or date the patient was last known to be alive. Overall survival (OS) was estimated for all patients. The duration of follow-up for OS was defined from the date of the first HAE to the date of death or the date the patient was last known to be alive. Complications were categorized based on the proposed Society of Interventional Radiology classification system [7].

Data Analysis

Data were analyzed using Prism 9 (GraphPad Software Inc). Descriptive statistics were generated with continuous variables presented as mean \pm SD and median (range) and categorical variables as counts (proportions). Wilcoxon matched-pairs signed rank test was used to assess the difference in median 24-hour preprocedure and postprocedure glucose levels. Median time to first hypoglycemia recurrence, HFS, OS, and OS stratified by HFS less or greater than 6 weeks were calculated using the Kaplan-Meier method. Two-sided *P* less than .05 was considered statistically significant.

Results

Patient Demographics and Clinical Information

Twenty patients (10 women, 10 men; mean age, 56 years [18-84 years]) who underwent HAE with bland particles were included. Metastatic disease was present at the time of initial diagnosis in 75% (*n* = 15) of patients, at which time all patients had bilobar hepatic metastases. Extrahepatic sites of metastasis included bone (*n* = 3), regional lymph nodes (*n* = 2), lung (*n* = 1), diaphragm (*n* = 1), breast (*n* = 1), and chest wall (*n* = 1). Liver biopsy demonstrating metastatic neuroendocrine carcinoma was performed in

90% (n = 18) of patients. Patients without biopsy-proven liver metastases (n = 2) had primary pancreatic resection with pathology-proven neuroendocrine neoplasm and abdominal MR showing hypervascular liver metastases. Biochemical evidence of an insulinoma, including inappropriately elevated serum insulin or proinsulin in the setting of hypoglycemia, was documented in 85% (n = 17) of patients. No patient in this cohort had documented multiple endocrine neoplasia, type 1.

Before the first hepatic artery embolization, all patients experienced neuroglycopenic or adrenergic symptoms alleviated by glucose intake. The most commonly reported symptoms were diaphoresis (n = 8) and confusion (n = 8), followed by fatigue (n = 7), lightheadedness (n = 6), loss of consciousness (n = 5), tremor (n = 2), nausea (n = 2), and headache (n = 1). Within 1 week before the first treatment, 60% (n = 12) of patients had documented serum glucose of less than 50 mg/dL (median, 47 mg/dL; mean, 54 ± 28.4 mg/dL; range, 15-119 mg/dL).

Insulinoma Treatment History

Standard Whipple and distal pancreatectomy were performed in 1 and 8 patients, respectively, or 45% (n = 9) of patients in total. In 44% of pancreatectomy patients (n = 4), metastases were present at the time of surgery. Hepatic resection was performed in 26% (n = 5) of patients, and 80% (n = 4) of hepatic resections were performed before HAE. One patient without metastases at diagnosis who underwent partial pancreatectomy later underwent open radiofrequency ablation of liver metastases, before HAE.

Chemotherapy was initiated in 60% (n = 12) of patients, 33% of whom (n = 4) started chemotherapy before HAE. In the 8 patients who received chemotherapy after the first HAE, 50% (n = 4) were started after the first recurrence of hypoglycemia.

Medications for hypoglycemia palliation including somatostatin analogues or diazoxide were used in 75% (n = 15) of patients before the first HAE, and in 95% (n = 19) of patients overall. In patients who received medication for hypoglycemia palliation, somatostatin analogues were used in 89% (n = 17) of patients, diazoxide was used in 26% (n = 5) of patients, and everolimus was used in 21% (n = 4) of patients (Table 1).

Hepatic Artery Embolization Procedure

The night before HAE, patients were admitted for blood glucose monitoring. Dextrose infusions were initiated for 85% (n = 17) of patients. One patient's hypoglycemia was initially managed with oral glucose, although ultimately required intravenous (IV) dextrose intraprocedurally.

Table 1. Demographic, surgical, and clinical history in 20 patients with malignant insulinoma, at time of first hepatic artery embolization

Variable	Value
Sex, n (%)	
Male	10 (50)
Female	10 (50)
Age, y, mean ± SD; median (range)	55.6 ± 17.2; 56.5 (18.4-83.8)
Surgery, n (%)	
Partial pancreatectomy	8 (40)
Total pancreatectomy	1 (5)
Hepatic resection	4 (20)
Chemotherapy, n (%)	
Doxorubicin and streptozocin	2 (10)
Streptozocin and 5-FU, then adriamycin	1 (5)
Sunitinib	1 (5)
None	16 (80)
Medications for hypoglycemia palliation	
Somatostatin analogue	9 (45)
Diazoxide	3 (15)
Somatostatin analogue and diazoxide	3 (15)
None	5 (25)
Signs/symptoms, n (%)	
Diaphoresis	8 (40)
Confusion	8 (40)
Fatigue	7 (35)
Lightheadedness	6 (30)
Loss of consciousness	5 (25)
Tremor	2 (10)
Nausea	2 (10)
Headache	1 (5)

Abbreviation: 5-FU, 5-fluorouracil.

The remaining 2 patients were maintained on their home diazoxide and frequent small meals.

HAE was performed in 45 sessions. The right hepatic lobe was treated during the first HAE in 70% (n = 14) of patients, which was at the operator's discretion based on tumor staining at the time of angiography and/or postoperative anatomy. For each patient, a median of 2 HAEs (mean, 2.3 ± 1.2; range, 1-5) were performed. In the 11 patients without prior hepatectomy who underwent at least 2 treatments, 73% (n = 8) underwent treatment of the contralateral hepatic lobe during the second treatment. Medium (250-355 μm) polyvinyl alcohol (PVA) particles were used in 93% (n = 42) of HAEs. Small PVA, large PVA, and Bead Block (300-500 μm) were each used once (Table 2).

Hypoglycemia Control

Postprocedural hypoglycemic symptom relief was reported in 100% (n = 20) of patients before discharge or at

Table 2. Hepatic artery embolization details in 20 patients with insulinoma liver metastases and hyperinsulinemic hypoglycemia

Variable	Value
First treated liver lobe, n (%)	
Right	14 (70)
Left	6 (30)
Second treated liver lobe, n (%)	12 (60)
Right	2 (20)
Left	10 (80)
Total No. of HAEs per patient, n (%)	
1	7 (35)
2	5 (25)
3	5 (25)
4	2 (10)
5	1 (5)
Particle selection per HAE, n (%)	
Small PVA	1 (2)
Medium PVA	42 (93)
Large PVA	1 (2)
Bead Block, 300-500 μ m	1 (2)

Abbreviations: HAE, hepatic artery embolization; PVA, polyvinyl alcohol.

follow-up after the first HAE. The median of the difference between blood glucose levels 24 hours before and after the first HAE was +72 mg/dL ($P = .005$). IV fluids containing dextrose given preprocedurally in 85% ($n = 17$) of patients were stopped either immediately postprocedure, on resumption of oral intake, or before discharge, in all patients after the first HAE. One patient, as detailed later, was discharged home on IV dextrose after the fourth HAE.

Medications for hypoglycemia and/or outpatient management routines in use before the first HAE were generally continued afterward. For example, in the 75% ($n = 15$) of patients on medication for hypoglycemia palliation before the first HAE, 80% ($n = 12$) of patients were maintained on similar medication regimens. Three patients continued to manage hypoglycemia with frequent meals after the first HAE, although one of these patients was initiated on a somatostatin analogue after the third HAE. Quality of life was documented to have improved in several patients. For example, one patient was able to return to work, one patient no longer needed to eat in the middle of the night, and one patient noted higher blood glucose levels between 60 and 80 mg/dL in the morning, improved from 40 to 60 mg/dL.

Hypoglycemia Recurrence and Survival

Median HFS was 14.5 months (Figs. 4 and 5), wherein survival without hypoglycemia recurrence ($n = 1$), date of liver transplantation ($n = 1$), and loss to follow-up ($n = 2$)

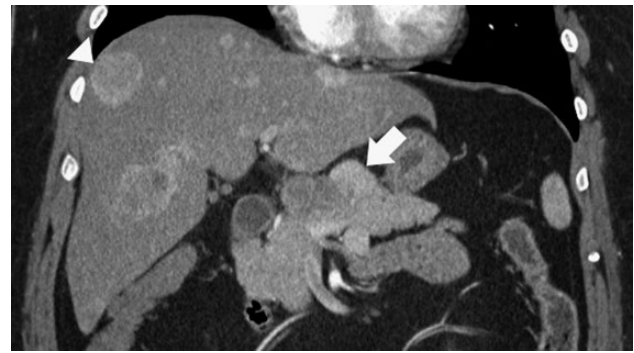


Figure 1. Contrast-enhanced coronal computed tomography of the abdomen demonstrating enhancing hepatic masses (arrowhead) and a hypervascular pancreatic mass (arrow).



Figure 2. Selective celiac angiogram demonstrates numerous hepatic foci of tumor staining (arrowhead) in addition to a hypervascular pancreatic mass (arrow).

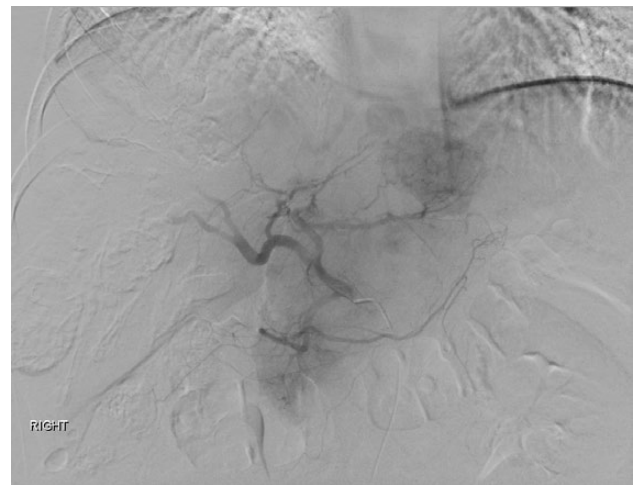


Figure 3. Hepatic artery embolization was carried out from the right hepatic artery to stasis with excellent angiographic result on repeat selective hepatic angiogram.

Table 3. Individual demographic, pathology, and laboratory data, and time to first recurrence and overall survival

Patient	Age at diagnosis, y	Age at HAE 1	Pathology, liver metastasis	Tumor grade	Year of pathology interpretation	Total HAEs	Serum glucose nadirs, mg/dL		Follow-up, mo	Time to first recurrence, mo	Overall survival, mo	
							Within 1 wk before HAE 1	Within 24 h after HAE 1				
1	54	65	Islet cell carcinoma	NS	1994	1	40	70	73	46.3	NA	46.2
2	57	78	None	NA	NA	3	49	47	61	44.2	38.5	44.2
3	18	18	Islet cell tumor	1-2	1998	4	68	92	57	10.8	8.5	11.0
4	84	84	Neuroendocrine tumor	2	2010	1	38	43	NA	2.2	0.8	3.3
5	51	51	Neuroendocrine carcinoma	Low	2000	2	25	156	105	10.2	NA	14.5
6	48	54	Neuroendocrine carcinoma	Low	2006	2	37	100	70	190.2	NA	190.2
7	41	41	Neuroendocrine neoplasm	1	2001	5	119	104	96	53.9	49.0	54.0
8	69	69	Islet cell tumor	NS	2000	4	42	86	25	10.2	3.0	11.1
9	52	53	Neuroendocrine carcinoma	2	2001	1	23	86	43	1.4	1.4	9.1
10	52	62	Neuroendocrine carcinoma	1	2002	1	62	65	NA	1.4	0.7	1.5
11	59	59	Neuroendocrine carcinoma	2	2005	1	58	166	NA	0.1	NA	22.9
12	41	41	Neuroendocrine carcinoma	1	2005	1	114	77	NA	1.0	NA	69.0
13	30	30	Neuroendocrine carcinoma	3	2015	1	15	96	125	65.8	59.8	65.8
14	65	65	Neuroendocrine tumor	3	2013	3	40	80	66	24.0	0.2	24.2
15	40	40	Neuroendocrine neoplasm	3	2016	3	49	81	75	16.6	NA	15.6
16	62	76	Neuroendocrine carcinoma	1	2006	2	61	64	42	6.8	0.6	7.8
17	60	60	Neuroendocrine tumor	NS	2000	3	65	130	59	2.4	1.1	9.3
18	44	44	Neuroendocrine carcinoma	NS	2000	2	96	107	44	3.3	2.7	6.4
19	70	78	None	NA	NA	3	44	74	46	6.4	NA	45.6
20	46	46	Neuroendocrine tumor	3	2020	2	27	41	94	2.0	NA	2.0

Abbreviations: HAE, hepatic artery embolization; NA, data not available; NS, not specified.

were classified as censor events. Median OS after the first treatment was 16 months (Fig. 6). Hypoglycemia recurrence occurred in 60% (n = 12) of patients with a median time to first hypoglycemia recurrence of 2 months (mean, 14 months; range, 0.2-60 months). In the 4 patients who underwent at least 2 HAEs and had a second hypoglycemia recurrence, median time to second hypoglycemia recurrence was 1.1 months (mean, 13 months; range, 0.5-48 months). Individual demographic, pathology, and laboratory data, and time to first recurrence and overall survival are summarized in Table 3.

In patients with recurrent hypoglycemia after the first HAE, 50% (n = 6) recurred within 6 weeks with a median time to recurrence of 0.8 months, and 50% (n = 6) recurred greater than 6 weeks post-HAE with a median time to recurrence of 23.5 months. Recurrence of hypoglycemia within 6 weeks of the first HAE was associated with a median OS of 8.5 months, and recurrence greater than 6 weeks post-HAE was associated with a median OS of 32.6 months ($P = .03$) (Fig. 7). Demographic and therapeutic information stratified by each group is summarized in Table 4.

Follow-up

Median post-HAE follow-up was 9.4 months (mean, 26 months; range, 0.1-190 months). One patient underwent orthotopic liver transplant after HAE without recurrence of hypoglycemia symptoms. Two patients were treated with PRRT after the first HAE, before recurrence of hypoglycemic symptoms. Of the 2 patients treated with PRRT, octreotide radiolabeled with yttrium-90 was used in 1 patient, and lutetium-177 was used in the other. The patient treated with yttrium-90–radiolabeled octreotide had an overall survival of 46.2 months without recurrence of hypoglycemia,

and the patient treated with lutetium-177–radiolabeled octreotide had a first recurrence of hypoglycemia symptoms at 59.8 months. One patient with recurrent hypoglycemia underwent ablation of a flank mass with resolution of symptoms, and therefore was not categorized as having had a recurrence after the first HAE. This same patient later had a recurrence of hypoglycemia symptoms and underwent hepatic artery calcium stimulation testing, which was positive, and subsequently underwent staged bilobar HAEs.

Complications

Out of 45 HAE sessions, there was 1 severe adverse event (2%) wherein the patient experienced labile postprocedure blood glucose levels below 50 mg/dL and above 275 mg/dL, prompting intensive care unit admission for IV dextrose. Of note, insulin levels were 53 mcIU/mL before the procedure, 82 mcIU/mL just after the procedure, and 29 mcIU/mL 5 days after the procedure. This patient's admission was further complicated by hypokalemia requiring parenteral repletion and elevated ammonia levels, which were present on admission, requiring nasogastric tube placement for lactulose in the setting of hepatic encephalopathy. The patient was initially transferred from an outside facility for 2 weeks of hypoglycemia that was difficult to control, and the HAE preceding this event was the patient's fourth treatment. The patient had a 39-day hospital stay in total and was discharged home on IV dextrose where she died 2 days later.

There were 3 mild adverse events in total (7%). Two mild adverse events occurred related to volume overload from periprocedural IV fluids requiring diuretics, which were completed in 1 case on an outpatient basis. One mild adverse event occurred in which a patient experienced flushing after contrast injection, was promptly treated with IV diphenhydramine and methylprednisolone sodium succinate, and underwent HAE without issue.

Postembolization syndrome occurring after transarterial embolization includes symptoms of pain, fever, nausea, and vomiting that begin within 72 hours of solid organ embolization [8]. Postembolization symptoms were common and most frequently included right upper abdominal pain in 80% (n = 16) and fever 40% (n = 8), which were treated with fluids, antipyretics, and/or oral and parenteral opiates, as needed. Steroids were not used in any patient for management of postembolization syndrome.

Discussion

The presented data suggest that patients with malignant insulinoma and hyperinsulinemic hypoglycemia refractory to surgical and medical therapies can derive clinical benefit from bland HAE. Relief from hypoglycemia-related

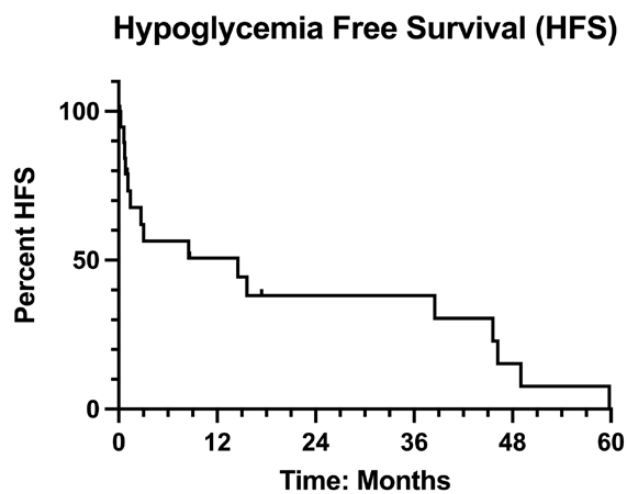


Figure 4. Kaplan-Meier curve of hypoglycemia free survival (months) after the first hepatic artery embolization.

Table 4. Demographic, surgical, and medical history in 12 patients with recurrence of hypoglycemia symptoms fewer or greater than 6 weeks after the first hepatic artery embolization

Variable	Recurrence < 6 wk	Recurrence > 6 wk
Sex, n (%)		
Male	4 (67)	4 (67)
Female	2 (33)	2 (33)
Age, y, mean ± SD; median (range)	62 ± 11.7; 60.7 (51.6-83.7)	47 ± 22.8; 42.4 (18.4-78)
Treatment before first HAE		
Surgery, n (%)		
Partial pancreatectomy	3 (50)	0 (0)
Total pancreatectomy	0 (0)	1 (17)
Hepatic resection	3 (50)	0 (0)
None	3 (50)	5 (83)
Chemotherapy, n (%)		
Doxorubicin and streptozocin	0 (0)	1 (17)
Streptozocin and 5-FU, then adriamycin	1 (17)	0 (0)
None	5 (83)	5 (83)
Medications for hypoglycemia palliation		
Somatostatin analogue	4 (67)	2 (33)
Diazoxide	0 (0)	1 (17)
Somatostatin analogue and diazoxide	1 (17)	0 (0)
None	1 (17)	3 (50)
Treatment before first recurrence		
Surgery, n (%)		
Partial pancreatectomy and Right hepatectomy	0 (0)	1 (17)
None	–	–
None	6 (100)	5 (83)
Chemotherapy, n (%)		
Capecitabine and temozolomide, then FOLFOX and bevacizumab, then Capecitabine and bevacizumab	0 (0)	1 (17)
None	–	–
None	6 (100)	5 (83)
PRRT		
Lutetium Lu 177 dotatate	0 (0)	1 (17)
Medications for hypoglycemia palliation		
Somatostatin analogue	6 (100)	2 (33)
Diazoxide	0 (0)	2 (33)
Everolimus	0 (0)	1 (17)
None	0 (0)	2 (33)
Treatment after first recurrence		
Chemotherapy, n (%)		
Streptozocin and 5-FU	1 (17)	1
Capecitabine and temozolomide	1 (17)	0 (0)
VIP-16 and cisplatin, then Gemcitabine and interferon	0 (0)	1 (17)
None	–	–
Gefitinib	0 (0)	1 (17)
None	4 (67)	3 (50)
Medications for hypoglycemia palliation		
Somatostatin analogue	6 (100)	6 (100)
Diazoxide	0 (0)	1 (17)
Everolimus	1 (17)	1 (17)
Prednisone	1 (17)	0 (0)
None	0 (0)	0 (0)

Abbreviations: 5-FU, 5-fluorouracil; HAE, hepatic artery embolization; PRRT, peptide receptor radionuclide therapy.

Frequency Distribution of Hypoglycemia Free Survival

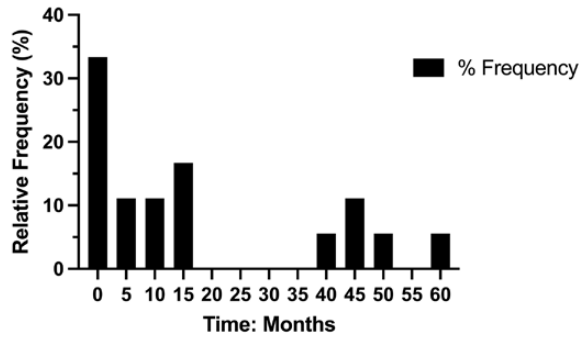


Figure 5. Frequency distribution of hypoglycemia-free survival (HFS) after the first hepatic artery embolization, excluding 2 patients who were lost to follow-up.

Overall Survival (OS)

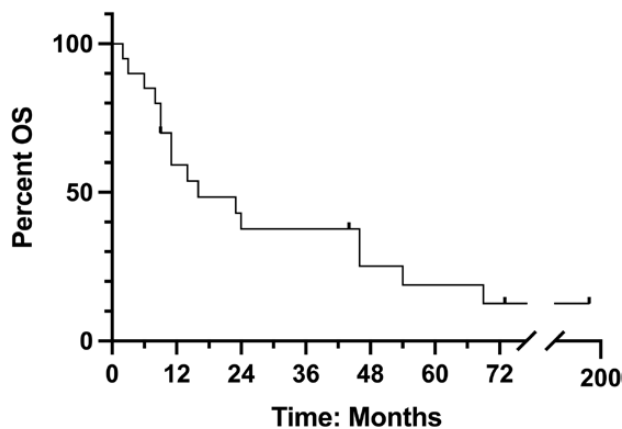


Figure 6. Kaplan-Meier curve of overall survival (OS; months) after the first hepatic artery embolization.

Overall Survival Stratified by 1st Hypoglycemia Recurrence Greater or Less Than 6 Weeks

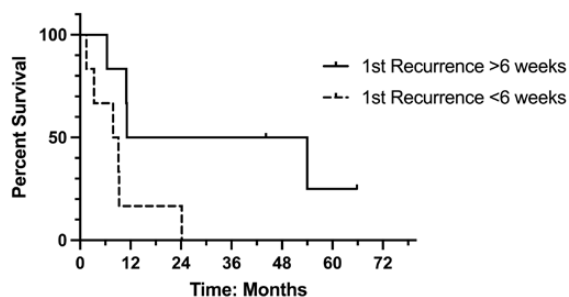


Figure 7. Kaplan-Meier curve of overall survival (OS; months) after the first hepatic artery embolization stratified by first hypoglycemia recurrence occurring greater or less than 6 weeks ($P = .03$).

symptoms was not only reported by all patients before discharge or at follow-up, but also quantitatively observed within the first 24 hours with a significant increase in median blood glucose levels.

Recurrence of hypoglycemia less than 6 weeks after the first HAE was associated with a significantly shorter OS, which suggests that patients with recurrence within 6 weeks of the first HAE may derive less benefit from subsequent HAEs. Unfortunately, owing to the retrospective nature of this study and the long period of time over which these patients were treated, consistent biopsy grading, including Ki-67 index assessment, is not available to correlate response, and heterogeneous imaging modalities across patients precludes comparison of hepatic tumor burden.

In this study, the mean time to first hypoglycemia recurrence of 14 months is greater than a previously reported mean of 7.5 months in a study that more broadly evaluated the use of bland HAE for metastatic carcinoid and noncarcinoid neuroendocrine tumors [9]. This comparison highlights the significant heterogeneity in the current literature both in embolization agent selection and studied neuroendocrine tumor subtypes, although the small number of retrospective studies specific to HAE for malignant insulinoma is likely accounted for by the low incidence of this entity. Available data do suggest at least a palliative effect in the use of HAE in alleviating endocrine symptoms related to not only PNETs, but malignant insulinoma [10].

HAE for the indication of hyperinsulinemic hypoglycemia is primarily performed using medium-sized PVA particles at our institution. The main advantage of PVA particles over other embolic agents for the indication of hyperinsulinemic hypoglycemia is the ability to provide repeat treatments as symptoms recur. At present, no studies have conducted a prospective comparison between the 3 forms of embolotherapy for metastatic neuroendocrine tumor, precluding direct comparisons in progression-free survival, OS, and quality of life [11], and retrospective reviews have not found a statistical difference between transarterial bland and chemoembolization [9, 12]. A recent retrospective review investigated the use of transcatheter arterial chemoembolization (TACE) and radioembolization in 7 patients with malignant insulinoma similarly reported relief of hypoglycemia symptoms in 100% of patients within 1 month of HAE, in addition to a significant increase in daytime random glucose levels [13]. Additionally, Starke et al [14] described the long-term management of 10 patients with malignant insulinoma, which required frequent chemoembolizations with treatment-free intervals between TACE lasting from several weeks to several months, and a 1 month duration of response has been described with the use of gel foam in a patient with malignant insulinoma [15].

There are limitations to this study. It is a single-center, retrospective review with a small sample size, and owing to the palliative nature of the procedure, a control group is not available for comparison. This cohort of patients was also heterogeneous in the surgical and medical management

preceding and following HAE, which is supported by the description of metastatic insulinoma as having a variable natural history [16]. Given these limitations, the presented data focus on areas pertinent to the palliative context, such as subjective hypoglycemic symptom improvement.

Potential additional confounding factors include therapies administered after HAE such as PRRT, variability in medical hypoglycemia palliation including specific somatostatin analogue selection, and chemotherapy. These therapies may have contributed to overestimating the median time to hypoglycemia recurrence. However, the less-stringent, modified Whipple triad criteria used to define hypoglycemia recurrence in this study would be expected to underestimate the median time to first hypoglycemia recurrence because of reliance on provided clinical documentation of subjective patient symptoms. In other words, an event categorized as hypoglycemia recurrence may not necessarily reflect hypoglycemic symptom severity experienced before HAE. This study is also limited by the long study period, although variability in HAE technique over this period was minimal. For example, 49% (n = 22) of the 45 HAEs were performed by a single operator, and 93% (n = 42) were performed using medium-sized PVA.

Overall, bland HAE is a safe, effective, and repeatable treatment option for palliation of symptomatic hypoglycemia in patients with hepatic insulinoma metastases refractory to medical management, especially when considered against the generally well-tolerated nature of the procedure and low adverse event rate. The presented data also suggest that patients with earlier recurrence of hypoglycemia may not derive significant benefit from additional HAEs. Potential avenues of further investigation could include standardized symptom scoring pre-HAE and post-HAE in addition to comparing tumor grade with time to recurrence of hypoglycemia symptoms.

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Additional Information

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