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LABORATORY INVESTIGATION

Evaluation of the Role of Cisplatin-conjugated-soluble Gelatin Sponge: Feasibility Study in a Swine Model

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Abstract
Purpose To evaluate the safety and the delivery function of cisplatin-conjugated-soluble gelatin sponge in a swine model.
Methods Fifteen healthy young swine were assigned into three groups: transarterial cisplatin infusion group, transarterial chemoembolization (TACE) with cisplatin-conjugated 120-min soluble gelatin sponge (TACE-120) group, and TACE with cisplatin-conjugated 360-min soluble gelatin sponge (TACE-360) group. A total volume of 0.8 mL/kg cisplatin in each group and 8 mg/kg soluble gelatin sponge in TACE-120 and TACE-360 groups were injected from the left hepatic artery in small increments for 10 min. Common hepatic angiography and whole-blood sampling via the left hepatic vein were conducted to explore recanalization immediately after the procedure and again at 10, 30, 60, 90, 120, 180, 240, 300, 360, and 420 min later. The area under the plasma concentration curve (AUC) of non-protein-bound platinum was compared among the three groups. Each liver was removed and cut into 10-cm-thick sections for calculating liver-damaged volume ratio.
Results Sequential angiography depicted gradual recanalization of the occluded hepatic artery and total recanalization at 120 and 360 min after embolization in the TACE-120 and TACE-360 groups, respectively. Of the three groups, $AUC_{0–30}$, $AUC_{30–120}$, and $AUC_{120–420}$ were significantly highest in the transarterial cisplatin infusion group ($p < 0.001$), the TACE-120 group ($p < 0.001$), and the TACE-360 group ($p < 0.001$), respectively. The liver-damaged volume ratio in the TACE-360 group was small (8.20 %) but significantly higher than that in the TACE-120 group (2.67 %, $p = 0.014$).
Conclusion Cisplatin-conjugated soluble gelatin sponge functions as a cisplatin carrier and is associated with tolerable liver damage.

Keywords Chemotherapeutic carrier · Cisplatin · Gelatin sponge · Soluble embolic material · Transcatheter arterial chemoembolization

Introduction

Gelatin sponge is commonly used as an embolic material for transcatheter arterial embolization [1–4]. In gelatin sponge commercially available for transcatheter arterial embolization, the gelatin is heated to 150 °C or greater to remove endotoxins and to guarantee bacterial sterilization. The tight heat linkage that occurs during this process results in insoluble gelatin sponge. It is reported that when this insoluble gelatin sponge is injected into an artery, a foreign-body reaction occurs, and the material is gradually absorbed into the arterial wall, resulting in vessel stenosis or occlusion [5–7]. Endotoxin-free gelatin was created in 2008 for regenerative medicine using thin ultrafiltration membranes (regenerative medicine gelatin, RM-gelatin) [8]. Soluble gelatin sponge with weak heat linkages is produced by heating in the temperature range of 110–150 °C. Higher temperatures produce gelatin that remains soluble for a longer time. In other words, we can

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generate gelatin sponge of various soluble times by heating within this temperature range. Takasaka et al. [7] documented that hepatic artery occluded by embolization with RM-gelatin sponge heated at 138 °C brought about recanalization 2 days after the procedure, and that lower heating temperatures produced gelatin sponge that was soluble for a shorter time. It was recently reported that cisplatin conjugates with the gelatin sponge itself by the isoelectricity mechanism [9, 10]. Kanayama et al. [11] reported a conjugated cisplatin volume of 30 mg to RM-gelatin/g, which is approximately twice the conjugation strength previously reported for other gelatins. However, the conjugation between the cisplatin and the gelatin sponge is too tight for the cisplatin to be released easily [12].

This study was conducted under the hypothesis that gelatin sponge with a short soluble time may be suitable for use as a cisplatin carrier. The purpose of this study was to evaluate the safety and the delivery function of cisplatin-conjugated soluble gelatin sponge in a swine liver model.

Materials and Methods

Before initiation of the study, approval was granted by our institutional committee on research animal care.

Fifteen healthy young swine weighing 54.0–62.0 kg (mean 59.5 kg) were used in this study. The swine received intramuscular injection of a combination of 0.08 mg/kg atropine sulfate and 5 mg/kg zolazepam before being intubated. They were then connected to a small whole-body animal anesthesia apparatus, and general anesthesia was maintained with isoflurane inhalation. The right femoral artery and the left femoral vein were surgically exposed and punctured with an 18-gauge needle (Terumo, Tokyo, Japan) under direct inspection, and a 4F cobra catheter (Terumo) was introduced into the celiac artery via a 4F long sheath (Super Sheath; Medikit, Tokyo, Japan). The common hepatic artery was catheterized and angiography was performed with contrast material (Iopamidol 370 mgI/mL; Bracco, Milan, Italy; 6 mL, 1 mL/s). The left hepatic artery was catheterized with a 2.2F microcatheter (Sirabe, Piolax, Yokohama, Japan) and 0.014-inch micro guide wire (Target, Boston Scientific, Natick, MA). A 5F cobra catheter (Terumo) was introduced into the left hepatic vein via a 5F sheath (Medikit) for blood sampling. Thereafter, chemoinfusion or chemoembolization was performed through the microcatheter advanced to the left hepatic artery.

We used low-endotoxin gelatin as the soluble gelatin sponge, with a molecular weight of 50 kDa (regenerative medicine gelatin, RM-gelatin; Jellice, Sendai, Japan). RM-gelatin is made from pigskin, with the gelatin preprocessed by ultrafiltration with a thin membrane to remove antigenicity and endotoxins. It meets the standard for purified gelatin according to the Japanese Pharmacopoeia. Commercially available gelatin sponge is insoluble because the fluid gelatin is sterilized above 150 °C, resulting in tight heat cross-linkage. In contrast, RM-gelatin sponge is guaranteed to be soluble because it is treated at 110–135 °C, resulting in a weaker extent of heat cross-linkage [7]. It is also certified to have a soluble time that increases with increased temperature, enabling the creation of gelatin sponges with various soluble times. In the present study, we used 50 kDa RM-gelatin that was heated at 133 °C for 20 h and at 134 °C for 20 h to form heat cross-linkages. A prestudy trial of swine hepatic artery embolization indicated that gelatin sponge particles treated at these temperatures achieved complete resolution at 120 and 360 min, respectively. It is reported that cisplatin is conjugated with gelatin sponge via an isoelectricity adhesion mechanism [13].

The cisplatin-conjugated-soluble gelatin sponge used in the present study was created as follows: cisplatin solution was made with cisplatin 50 mg (IA-call; Nippon Kayaku, Tokyo, Japan) dissolved in 10 mL saline and 5 mL contrast material (Iopamidol 370 mI/g) warmed at 50 °C; particles of soluble gelatin sponge (500 mg) cut into 1-mm squares were soaked and repeatedly mixed with the cisplatin solution for 5 min with a three-way stopcock. The mixed components were then left for 30 min at room temperature. The free cisplatin was not filtered, and the mixed components were used as the cisplatin-conjugated-soluble gelatin; therefore, cisplatin that was not taken up into the soluble gelatin sponge particles was also present in the mixed components. Table 1 lists details regarding the preparation of cisplatin-conjugated-soluble gelatin as an embolic material and the volumes used. As a control, cisplatin solution was prepared for infusion.

We assigned the swine into three groups: the transarterial cisplatin chemoinfusion (TACI) group as a control; the transarterial chemoembolization (TACE) with cisplatin-conjugated 120-min-soluble gelatin sponge (TACE-120) group; and the transarterial chemoembolization with cisplatin-conjugated 360-min-soluble gelatin sponge (TACE-360) group.

Each swine received the same dose (dose/kg) of cisplatin (Table 1), determined with reference to that previously reported for clinical use [14]. In the TACI group, the five swine were infused with the following solution of cisplatin: cisplatin 50 mg dissolved in 50 mL saline, with a volume of 0.8 mL/kg infused for 10 min.

In the TACE-120 group, the five swine were infused with cisplatin-conjugated 120-min-soluble gelatin sponge. In the TACE-360 group, the five swine were infused with cisplatin-conjugated 360-min-soluble gelatin sponge. In both of these groups, the total volume was scheduled on the basis of a cisplatin dose of 0.8 mg/kg and a total soluble gelatin

Table 1 Technical data for the experimental groups

Pig no.	Procedure	Weight (kg)	Sex	Preparation					Volume used		
				Cisplatin (mg)	Saline (mL)	Contrast medium (mL)	Soluble gelatin sponge	Gelatin volume (mg)	Total volume (mL)	Cisplatin (mg/kg)	Gelatin volume (mg)
1	TACI	62	F	50	50	–	–	–	49.6	0.8	–
2	TACI	54	F	50	50	–	–	–	43.2	0.8	–
3	TACI	58	F	50	50	–	–	–	46.4	0.8	–
4	TACI	62	F	50	50	–	–	–	49.6	0.8	–
5	TACI	58	F	50	50	–	–	–	46.4	0.8	–
6	TACE-120	54	F	50	10	5	RM (50 kDa 133 °C)	500	13.0	0.8	433
7	TACE-120	62	F	50	10	5	RM (50 kDa 133 °C)	500	14.9	0.8	497
8	TACE-120	62	F	50	10	5	RM (50 kDa 133 °C)	500	14.9	0.8	497
9	TACE-120	58	F	50	10	5	RM (50 kDa 133 °C)	500	13.9	0.8	463
10	TACE-120	58	F	50	10	5	RM (50 kDa 133 °C)	500	13.9	0.8	463
11	TACE-360	61	F	50	10	5	RM (50 kDa 134 °C)	500	14.6	0.8	487
12	TACE-360	62	F	50	10	5	RM (50 kDa 134 °C)	500	14.9	0.8	497
13	TACE-360	61	F	50	10	5	RM (50 kDa 134 °C)	500	14.6	0.8	487
14	TACE-360	58	F	50	10	5	RM (50 kDa 134 °C)	500	13.9	0.8	463
15	TACE-360	62	F	50	10	5	RM (50 kDa 134 °C)	500	14.9	0.8	497

TACI Transcatheter arterial chemoinfusion, *TACE* Transarterial chemoembolization, *TACE-120* TACE with cisplatin-conjugated 120-min-soluble gelatin sponge, *TACE-360* TACE with cisplatin-conjugated 360-min-soluble gelatin sponge, *RM* Regenerative medicine

sponge volume of 8 mg/kg. The cisplatin-conjugated gelatin sponge was slowly injected into the left hepatic artery in small increments for 10 min, with no regurgitation observed until the final injection of the total volume. TACE with the total volume of soluble gelatin sponge caused to occlude the left hepatic artery. Angiography was performed after TACE to confirm the extent of the interruption of flow.

Sequential common hepatic angiography and blood sampling via the left hepatic vein were conducted immediately after the procedure and again at 10, 30, 60, 90, 120, 180, 240, 300, 360, and 420 min later to check occlusion of the hepatic artery and to record changes in the cisplatin level. The catheters and sheaths were then withdrawn and the tracheal tube removed.

Of the total platinum in cisplatin, it is the non-protein-bound platinum (N-PBPt) that activates the antitumor effect. We measured N-PBPt with an atomic light absorption method. On the basis of serial data of plasma N-PBPt concentration, an approximate formula was estimated for the time–concentration curve, and the area under the plasma concentration curve (AUC) was calculated for 0–30, 30–120, and 120–360 min after the procedure using the trapezoid rule [15]. $AUC_{0–30}$, $AUC_{30–120}$, and $AUC_{120–420}$ were compared among the three groups.

The swine were euthanized 24 h after TACI and TACE to evaluate adverse effects of embolization on liver tissue. Necropsies were performed and the livers removed. The livers were cut into 10-cm-thick sections and fixed in a 7.5 % neutral formaldehyde buffer. At 7 days after necropsy, we performed macroscopic examination of the liver to assess the extent of liver damage. After photographing each cross section, image data were transferred to a computer for contouring of the liver and damaged areas (Fig. 1) by Lenaraf 200 (Macrosoft, Parsippany, NJ), which is equipped with a tool for measuring length and area. We then calculated liver slice volumes and the volumes of damaged foci using data on the number of pixels and for 10-mm slice thickness. We then calculated the damaged volume ratio for the total slice volume, as described previously [15, 16]. The tissue sections were stained with hematoxylin.

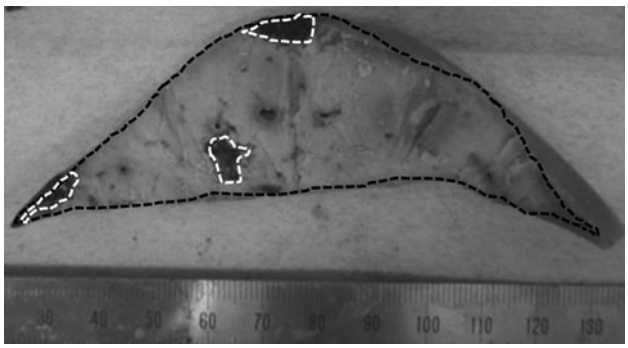

Fig. 1 Macroscopic view of removed liver. Livers were sliced into 10-mm sections, and liver damage after hepatic arterial chemoembolization was evaluated for each cross section. The whole liver (*black dotted lines*) and regions of damage (*white dotted lines*) are shown contoured. Liver damage volume ratios were calculated with the accumulated data

The results of analysis are expressed as mean ± standard deviation. Student's *t*-test was used to compare the mean concentration (μg/mL) of plasma N-PBPt, the values of $AUC_{0–30}$, $AUC_{30–60}$, $AUC_{60–90}$, $AUC_{90–120}$, $AUC_{120–180}$, and $AUC_{180–420}$, and liver damage volume ratio among the groups. Multiple comparisons of the quantitative values among the TACI, TACE-120, and TACE-360 groups were adjusted by Bonferroni's method. For Student's *t*-test and Bonferroni method analysis, significant difference was indicated by $p < 0.05$ and $p < 0.05/3$, respectively.

Results

Sequential Angiographic Changes after TACE-120 and TACE-360

Figures 2 and 3 show sequential angiography of recanalization of the embolized left hepatic artery in the TACE-120 and TACE-360 groups. Briefly, in the TACE-120 group, partial recanalization of the left hepatic artery was observed 30 min after embolization, and total recanalization was observed 120 min after embolization (Fig. 2). In the TACE-360 group, partial recanalization was observed 90 min after embolization, and total recanalization was observed 360 min after embolization (Fig. 3).

Changes in Cisplatin Pharmacokinetics among the TACI, TACE-120, and TACE-360 Groups

The mean concentration (μg/mL) of plasma N-PBPt immediately after the procedure in the TACI, TACE-120, and TACE-360 groups was 1.18 ± 0.12 (1.1–1.35), 0.62 ± 0.084 (0.50–0.70), and 0.42 ± 0.11 (0.3–0.55), respectively, with significant difference found among the groups ($p < 0.05/3$).

In the TACI group, the concentration of plasma N-PBPt fell quickly, to reach a nadir (zero; less than the measurable limit < 0.01 μg/mL) at 90 min after infusion (Fig. 4). $AUC_{0–30}$ in the TACI group (13.9 ± 0.45 μg/mL × min) was significantly greater than those in the TACE-120

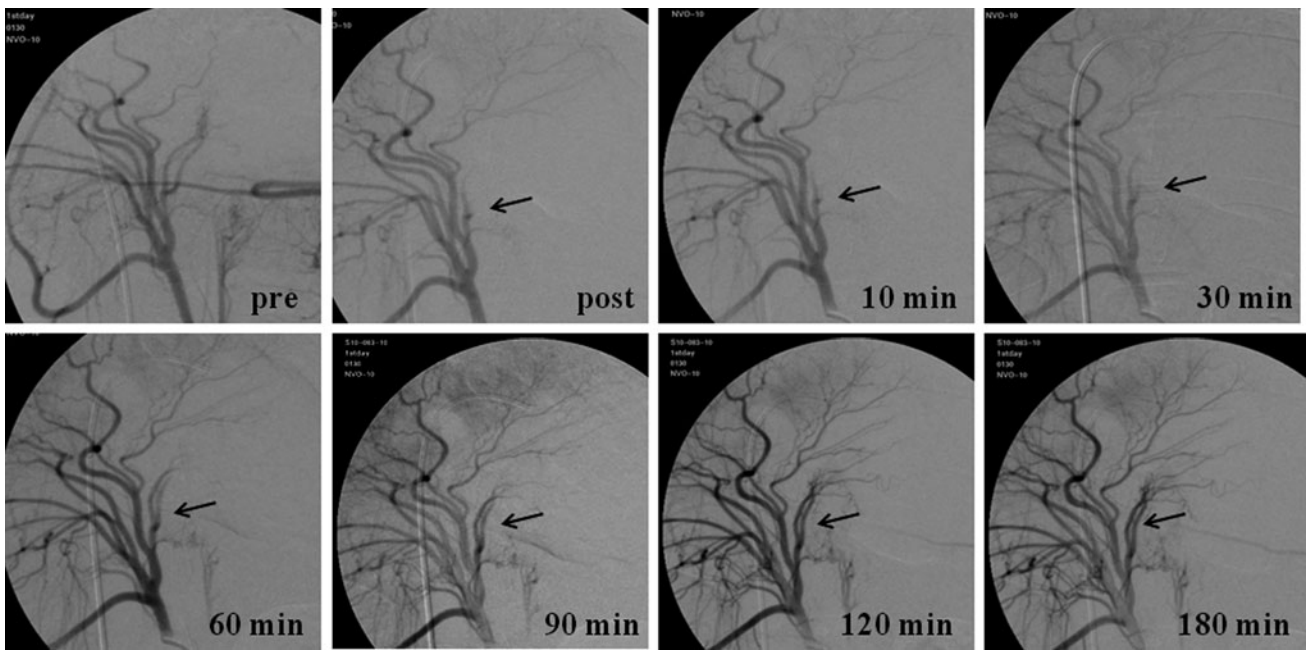

Fig. 2 Sequential common hepatic angiography after transcatheter arterial chemoembolization of the left hepatic artery (*black arrow*) using cisplatin-conjugated 120-min-soluble gelatin sponge particles. Angiography obtained from 30 and 90 min and at 120 min after embolization depicts gradual–partial and total recanalization of the left hepatic artery, respectively

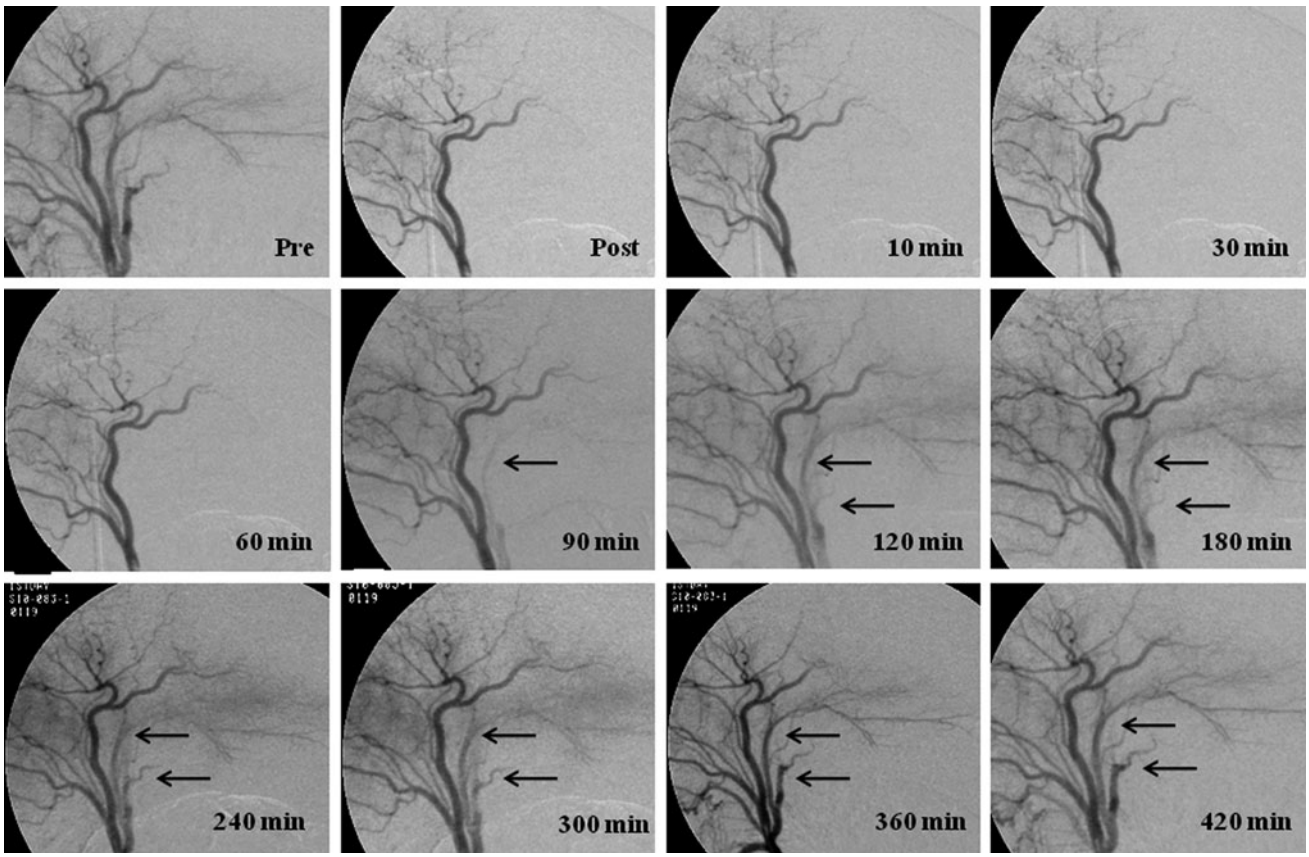

Fig. 3 Sequential common hepatic angiography after transcatheter arterial chemoembolization of the left hepatic artery branches using cisplatin-conjugated 360-min-soluble gelatin sponge particles. Angiography obtained from 90 to 300 min and at 360 min after embolization depicts gradual–partial and total recanalization of the left hepatic artery branch arteries (*black arrows*), respectively

(9.15 ± 1.66 μg/mL × min) ($p < 0.005$) and TACE-360 (6.05 ± 0.93 μg/mL × min) ($p < 0.001$) groups (Fig. 4).

In the TACE-120 group, the concentration of plasma N-PBPt gradually decreased, before dropping suddenly at 120 min after embolization to reach a nadir at 240 min (Fig. 4). $AUC_{30–90}$ in the TACE-120 group was significantly greater than that in the TACI group ($p < 0.001$). $AUC_{60–90}$ in the TACE-360 group was significantly greater than that in the TACI group ($p < 0.001$). $AUC_{30–60}$ and $AUC_{60–90}$ in the TACE-120 group were significantly greater than those in the TACE-360 group ($p = 0.0076$ and $p = 0.0017$, respectively) (Table 2).

In the TACE-360 group, the concentration of plasma N-PBPt was stable between 60 and 360 min, dropping suddenly at 360 min after embolization to reach a nadir at 420 min (Fig. 4). In the TACE-360 group, $AUC_{180–420}$ was significantly higher than that in the TACE-120 group ($p < 0.001$) (Table 2).

Comparison of Pathological Liver Damage among the TACI, TACE-120, and TACE-360 Groups

Comparison of macroscopic liver damage after TACI, TACE-120, and TACE-360 is shown in Table 3. No liver damage was observed in the TACI group. In the TACE-120 and TACE-360 groups, small regions of coagulation necrosis were scattered throughout the liver. Liver damage volume ratios in the TACE-360 group were significantly higher than those in the TACE-120 group ($p = 0.014$). Histological examination of damaged lesions revealed congestion, eosinophilic degeneration, and the disappearance of hepatic cell nuclei.

Discussion

In the present study, we used the technique described by Takasaka et al. [7], using an RM-gelatin sponge heated at 133 and 134 °C, with the expectation of resolution at 2 and 6 h after embolization, respectively. We confirmed complete recanalization of the hepatic artery at 2 and 6 h after embolization, respectively, and found no resulting irregularities or stenosis of the vascular wall. In the in vitro test, RM-gelatin sponge was observed to resolve gradually, leading to final lysis [7]. The sequential angiography performed in the present study revealed gradual recanalization of the occluded hepatic artery, leading to complete

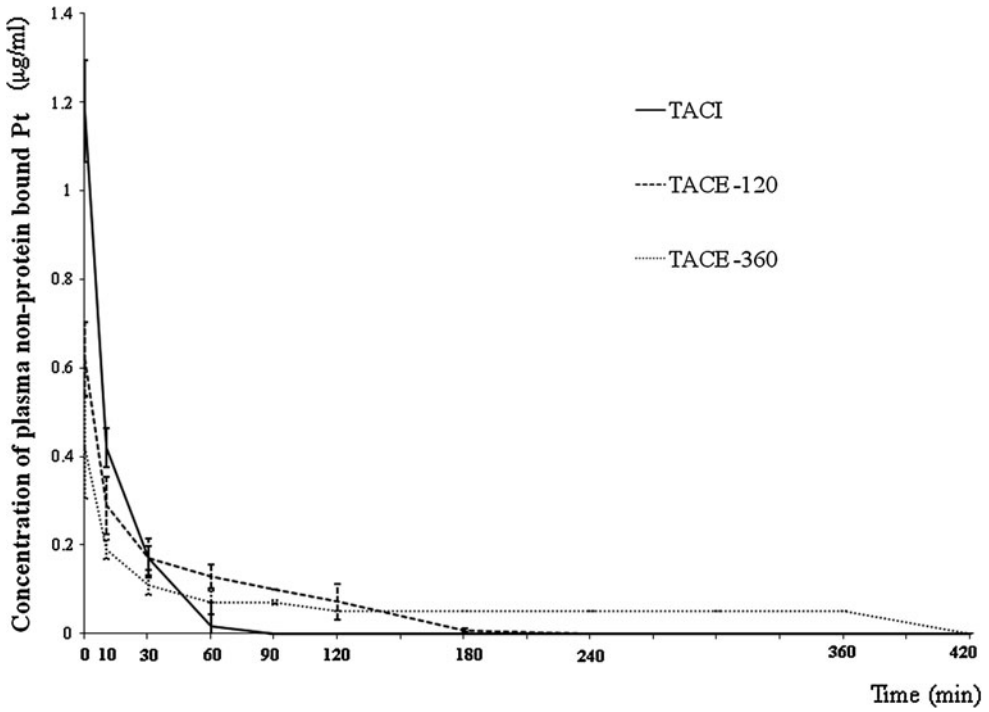

Fig. 4 Time–density curves of left hepatic vein concentration of plasma N-PBPt from 0 to 30 min among the TACI, TACE-120, and TACE-360 groups

Table 2 Comparison of areas under the curve among treatment groups

Procedure	*n*	$AUC_{0–30}$	$AUC_{30–60}$	$AUC_{60–90}$	$AUC_{90–120}$	$AUC_{120–180}$	$AUC_{180–420}$
TACI	5	13.9 ± 0.45	2.79 ± 0.47	0.24 ± 0.08	0	0	0
TACE-120	5	9.15 ± 1.66	4.50 ± 0.91	3.45 ± 0.41	2.28 ± 0.71	2.70 ± 1.71	0.24 ± 0.13
TACE-360	5	6.05 ± 0.93	2.70 ± 0.67	1.85 ± 0.65	1.75 ± 0.56	3.00 ± 0.00	10.5 ± 0.00
p value for:							
TACI vs. TACE-120		<0.001	0.006	<0.001	–	–	–
TACI vs. TACE-360		<0.001	0.81	<0.001	–	–	–
TACE-120 vs. TACE-360		0.0066	0.0076	0.0017	0.23	0.95	<0.001

n number, *AUC* Area under the curve, μg/mL × min, *TACI* Transcatheter arterial chemoinfusion, *TACE* Transarterial chemoembolization, *TACE-120* TACE with cisplatin-conjugated 120-min-soluble gelatin sponge, *TACE-360* TACE with cisplatin-conjugated 360-min-soluble gelatin sponge

Table 3 Comparison of average liver damage volume ratios among the experimental groups after therapy

Group	Liver damage volume ratio (%)
TACI ($n = 5$)	0
TACE-120 ($n = 5$)	2.67 ± 1.81*
TACE-360 ($n = 5$)	8.20 ± 3.54*

TACI Transcatheter arterial chemoinfusion, *TACE* Transarterial chemoembolization, *TACE-120* TACE with cisplatin-conjugated 120-min-soluble gelatin sponge, *TACE-360* TACE with cisplatin-conjugated 360-min-soluble gelatin sponge

* Statistically significant ($p = 0.014$)

recanalization. In other words, RM-gelatin sponge lysis was also confirmed in vivo.

Because cisplatin is a dose-dependent anticancer drug, arterial infusion should be more favorable in terms of cisplatin concentration compared with venous infusion because it has a less diluting effect on the drug. Ohta et al. [12] reported that the absorbed time for cisplatin-conjugated gelatin sponge was approximately 14 days with Gelpart and over 14 days with cisplatin-conjugated gelatin microspheres. When cisplatin-conjugated gelatin sponge is used for TACE, the treatment strategy of scheduled

cisplatin release is preferable to that of release over an unknown period.

In the present study, cisplatin concentration in the TACI group fell sharply compared with the more gradual decline observed in the TACE-120 and TACE-360 groups. That is, N-PBPt concentration in the hepatic vein fell to a level below the limit of zero at 90, 240, and 420 min in the TACI, TACE-120, and TACE-360 groups, respectively.

Sequential measurement results of cisplatin concentration revealed that although $AUC_{0–30}$ was highest in the TACI group, $AUC_{30–120}$ and $AUC_{120–420}$ were significantly the highest in the TACE-120 and TACE-360 groups, respectively. These results imply that cisplatin-conjugated gelatin sponge does function to deliver continuous output of the anticancer drug. To maintain a continuous high concentration for several hours, it may be more favorable to combine TACE-120 and TACE-360, rather than use TACE-120 or TACE-360 alone.

Macroscopic findings showed no damage in livers from the TACI group, while damage was found in livers from the TACE-120 and TACE-360 groups. Microscopically, liver damage was evident as congestion, eosinophilic degeneration, and the disappearance of liver cell nuclei. Although the liver damage volume ratio was higher in the TACE-360 group than in the TACE-120 group, the extent of liver damage was not significant in either group. Because cisplatin volume (0.8 mg/kg) was constant between the groups, the mechanism of liver damage may be related to the duration of ischemia. Sato et al. [17] reported no damage to swine liver after hepatic artery embolization with gelatin sponge alone. In a study by Sahara et al., TACE with higher doses of cisplatin led to greater damage to liver tissue, resulting in necrosis volume ratios of 2.32, 8.05, and 11.83 % for swine livers embolized with 10 mg/mL cisplatin-lipiodol suspension + gelatin sponge, 20 mg/mL cisplatin-lipiodol suspension + gelatin sponge, and 30 mg/mL cisplatin-lipiodol suspension + gelatin sponge, respectively [18]. On the basis of these findings, we consider that the mechanism of liver damage observed in the present study is dependent on both ischemia and the concentration of the anticancer drug.

A limitation of this study is the difference in sensitivity to cisplatin between swine liver and human liver. We only evaluated damage to swine liver without tumor; however, the present data provide a basis on which to consider adverse events in the situation where TACE-120 and/or TACE-360, rather than arterial chemoinfusion, is applied to patients with metastatic liver tumor or hepatocellular carcinoma with portal tumor thrombus. Another limitation is that this material unavoidably causes ischemia, thus limiting the use of this material to relatively ischemia-tolerant organs. Furthermore, we initiated this study to investigate the function of cisplatin-conjugated-soluble gelatin sponge as a cisplatin carrier. However, a carrier should deliver the drug locally to tissues and not into the systemic circulation. Our study merely clarified that the tested soluble gelatin sponges act to limit washout.

In conclusion, although limitations exist, the results of sequential hepatic angiography, cisplatin concentration measurements, and pathological examination after TACI, TACE-120, and TACE-360 revealed that cisplatin-conjugated-soluble gelatin sponge does function as a cisplatin carrier and that it is associated with tolerable liver damage.

Conflict of interest The authors declare that they have no conflict of interest.

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