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Alleviation of gallbladder complications by treatment of hepatic arterial embolization with caerulein

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Summary. Transcatheter arterial embolization (TAE) with the concurrent use of caerulein was assessed for the purpose of preventing gallbladder complications often seen after TAE of hepatic carcinoma. Ninety-six cases with primary hepatic carcinoma, who had undergone TAE in the right hepatic arterial region over the past 4 years, were divided into three groups: 22 cases for which embolization was possible on a selective basis by passing the catheter to the peripheral side beyond the bifurcated region of the cystic artery; 40 cases who had undergone TAE in which caerulein was not administered, from the central side of the bifurcated region of the cystic artery; and 34 cases given 20 µg caerulein 15–30 min before TAE. A comparison was made using the abdominal pain, pyrexia, rate of leukocytosis and the US findings of the gallbladder as the indices of the gallbladder complications. As a result, it become evident that it was possible to prevent or alleviate gallbladder complications if caerulein were administered before TAE in cases where the embolizing substances were infused in the right hepatic artery from the central side of the bifurcated region of the cystic artery. It was conclusively shown that the gallbladder blood flow decreases if the organ is contracted by caerulein, which in turn causes a decrease in the inflow of the embolizing substances whereby complications are alleviated.

Introduction

In treatment using transcatheter arterial embolization (TAE) on hepatic carcinoma, where extirpation is not possible, the selective embolization of only the nutrient artery to the tumor is ideal. However, under actual circumstances, selective embolization is not possible for many cases because there is more than one nutrient artery, nor can the catheter be passed to the artery in question owing to problems of manipulation. Since the embolizing substances must be infused from the central region rather than the nutrient artery (sub-segmental branch), complications of organic infarction resulting from TAE therapy often occur.

Severe complications include hepatic insufficiency [8], splenic infarction [9], acute gastric lesions [11], and gall bladder infarction [4]. It is considered that, of these complications, hepatic insufficiency is avoidable if the operative adaptability is determined by carefully investigating the presence or absence of a portal tumor embolus or by determining the hepatic hemodynamics preoperatively, and that a splenic embolus and acute gastric lesions can be avoided by slowly infusing the embolizing substances into the blood flow.

However, a gallbladder infarction is an unavoidable complication if the embolizing substances have to be infused from the central side of the bifurcated region in the cystic artery during TAE therapy on the right hepatic arterial region because of the tumor site or problems of manipulation. Takahashi et al. [7] reported that the occurrence of abdominal pain and frequent gallbladder lesions was about 70% and 20% respectively.

The authors used TAE concurrently with caerulein in the expectation that TAE therapy could be useful in the prevention of gallbladder complications, noting a general decrease in the blood flow when the smooth muscle is contracted.

This paper compares the frequency of the occurrence of gallbladder complications when TAE therapy is or is not carried out after the administration of caerulein, using the ultrasonographic findings of the gallbladder, abdominal pain, pyrexia and changes in the peripheral leukocyte count as the indices. The authors also present the results of their assessment of whether the blood flow in the gallbladder is reduced by contracting the gallbladder, by measuring the blood flow in the gallbladder wall tissues in patients who had undergone an operation for cholelithiasis.

Subjects and method

The subjects under study were 96 cases with hepatocellular carcinoma, who had undergone TAE therapy on the right hepatic arterial region upon admission to the 3rd Department of Internal Medicine at Ehime University Hospital over the past 4 years (Table 1).

Of these, 22 cases, in which embolization was possible on a selective basis by passing the catheter beyond the bifurcated region of the cystic artery, were designated as the selective embolization group, and 74 cases, in which TAE was carried out from the central side of the bifurcated region of the cystic artery, were designated as the non-selective embolization group. Of the latter group, 40 patients were not given caerulein, while 34 patients underwent TAE with the concurrent use of caerulein (the caerulein

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Table 1. Hepatocellular carcinoma cases which underwent TAE on the right hepatic region

Group	Case no.	Tumor diameter		Blood vessel into which embolizing substance was infused[a]	
		≤3 cm	>3 cm	RHA	PHA or RHA+LHA
Selective embolization group	22	13	9	16	6
Non-selective embolization group					
Caerulein not used	40	6	34	13	27
Caerulein used	34	17	17	28	6

[a] RHA, right hepatic artery; PHA, proper hepatic artery; LHA, left hepatic artery

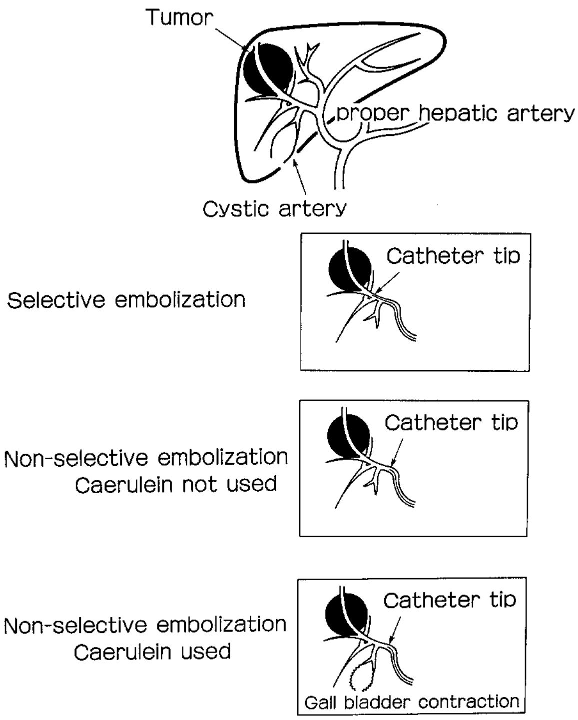

Fig. 1. Position of catheter tip at TAE and use or absence of caerulein (typical diagram). (**a**) Selective embolization (**b**): the embolizing substance is infused from the catheter tip positioned at the distal point at the cystic arterial bifurcation. Non-selective embolization (**c, d**): the embolizing substance is infused from the proximal point at the cystic arterial bifurcation, **c** Caerulein not used; **d** caerulein used

group). Fig. 1 shows the typical TAE method, dividing the 96 patients who underwent TAE on the right hepatic arterial region into three groups. Patients who had undergone cholecystectomy, those treated by TAE in the left hepatic artery, and those with an abnormal bifurcation of the cystic artery were omitted from this study.

Caerulein (20 μg) was administered intramuscularly 15–30 min before TAE. The embolizing substance used was a gelatin sponge (Gelfoam) finely cut into pieces approximately 1 mm^3. The gelatin sponge mixed with 76% Urografin was slowly infused into the artery. The infusion was discontinued when embolization was completed up to the fourth bifurcation counting from the proper hepatic artery. An iodized oil emulsion (lipiodol, 1–2 ml) was added to the gelatin sponge in some of the cases.

Observations were made of abdominal pain, pyrexia, the maximum increase in the leukocyte count during the first week after TAE, the presence or absence of cholecystitis (debris, the thickening of the gallbladder wall and edema around the gallbladder) from US findings and, for the caerulein group, the presence or absence of gallbladder contraction and a change in the gallbladder arterial diameter from angiographic findings.

Caerulein (20 μg) was administered intramuscularly to seven cases of cholelithiasis after laparotomy during cholecystectomy, and the relationship between the gallbladder contraction rate and the change in the blood flow before and 15 min after the administration of caerulein were determined using the electrolytic hydrogen gas clearance method (MT Giken, DHM-3001). To find the approximate value of the gallbladder capacity, the method used was that of Cano et al. [1], in which the capacity of the gallbladder is calculated from the maximum major and minor axes, regarding the organ as a cone.

Statistical tests, including Fischer's exact probability test, Mann-Whitney's *U*-test, the X^2 test or Student's *t*-test, were carried out.

Results

As mentioned previously, the non-selective embolization group was divided into two, the caerulein group and the non-caerulein group, and the abdominal pain, pyrexia and the rate of increase in the leukocyte count were compared (Table 2). The results of the selective embolization group in which, as a rule, the embolizing substance did not flow into the cystic artery, are shown as reference data. The results showed that the severities of abdominal pain and pyrexia were significantly milder and that the increase in the leukocyte count was less in the caerulein group. The results of the former group were about the same as the occurrence rate of complications in the selective embolization group.

However, as seen in Table 1, there was a difference in the tumor diameter and in the blood vessels into which the embolizing substance had been infused between the caerulein group and the non-caerulein group, while the background of the two groups was also different. Then, as a result of investigating to what extent the difference in the blood vessels into which the embolizing substance had been infused is related to the severity of complications, it was found that the difference in the blood vessels was not significant in any group (Table 3).

Since it was considered that complications such as abdominal pain, pyrexia and an increase in the leukocyte count differ not only according to the symptoms but by the size of the tumor embolized, the occurrence rates of complications in cases with a tumor of a diameter of less than 3 cm were compared between the caerulein group and the

Table 2. Abdominal pain, pyrexia, increase in leukocyte count after TAE

Group	Case no.	Abdominal pain[a]				Pyrexia[b]		Rate of increase in leukocytes (%)
		(−)	Mild	Moderate	Severe	Absence	Presence	
Selective embolization	22	17	4	1	0	10	12	66±60.3
Non-Selective embolization								
Caerulein not used	40	12	8	5	15 } a	10	30 } b	129±85.7 } c
Caerulein used	34	28	3	2	1	20	14	61±47.5

[a] Severities of abdominal pain were defined as follows: those not requiring administration of analgesic, mild; those requiring administration of analgesic, moderate; and those requiring narcotic or narcotic-like potent analgesic, severe. Statistical analysis by Mann-Whitney's *U*-test, $P<0.01$

[b] When body temperature was more than 38° C, it was defined as "pyrexia present". Statistical analysis by χ^2 test, $P<0.01$

[c] Statistical analysis by Student's *t*-test, $P<0.01$

Table 3. Blood vessel into which embolizing substance was infused and degree of complications after TAE in non-selective embolization group

Group	Blood[a] vessel	Case no.	Cholecystitis[b] (US)	Abdominal pain[c]				Pyrexia[b]	Rate of increase in leukocytes[d] (%)
				(−)	Mild	Moderate	Severe		
Caerulein not used	PHA or RHA+LHA	27	4/8 } NS	9	6	4	8 } NS	20/27 } NS	12.5±83.3 } NS
	RHA	13	4/7	3	2	1	7	10/13	13.6±93.4
Caerulein used	PHA or RHA+LHA	6	3/6 } NS	4	1	0	1 } NS	3/6 } NS	89.0±40.3 } NS
	RHA	28	3/28	24	2	2	0	11/28	55.0±47.6

[a] PHA, proper hepatic artery; RHA, right hepatic artery; LHA, left hepatic artery

[b] Comparison between groups indicated, not significant (NS) by Fisher's exact probability test

[c] Comparison between groups indicated, NS by Mann-Whitney's *U*-test

[d] Comparison between groups indicated, NS by Student's *t*-test

Table 4. Complications of hepatic carcinoma with diameters less than 3 cm after TAE

Case	Case no.	Cholecystitis (US)	Abdominal pain (right hypochondric region)	Pyrexia (more than 38° C)	Rate of increase in leukocytes (%)
Selective embolization	13	0/10 (0%)	4/13 (30%)	8/13 (62%)	67±64.3
Non-selective embolization			Acute pain		
Caerulein not used	6	5/5 (100%) } a	5/6 (83%) } a	2/6 (33%) } NS	121±45.1 } b
Caerulein used	17	1/17 (6%)	2/17 (11%)	4/17 (24%)	47±46.1

[a] Statistical analysis by Fisher's exact probability test, $P<0.001$

[b] Statistical analysis by Student's *t*-test, $P<0.001$. NS, not significant

non-caerulein group regardless of the blood vessel into which the embolizing substance was infused (proper hepatic artery, proper + left hepatic or right hepatic arteries) (Table 4). The occurrence rates of cholecystitis, abdominal pain and an increase in the leukocyte count were found to be significantly lower in the caerulein group.

The above results indicate that, when the embolizing substance is infused from the proximal point on the bifurcated region of the cystic artery, gallbladder complications can be alleviated if caerulein is previously administered.

The angiographic findings of the gallbladder before and after the administration of caerulein show that, as seen in Fig. 2, there were cases in which the gallbladder, because contracted after the administration of caerulein, and the diameter of the cystic artery became smaller, and that there were cases in which neither underwent a change. From the angiographic findings, both the presence or absence of gallbladder contraction and a change in the cystic artery diameter were observed in 27 out of the 34 cases. Of these, a reduced cystic artery diameter was observed in 7 cases out of the 17 in which gallbladder contraction had been observed, but the reduced cystic artery diameter was observed in only 2 of the 10 cases in which no gallbladder contraction had been observed. For the cases with a contracted gallbladder, the cystic artery also tended to be narrowed. The fact that the ratio of cases with a contracted gallbladder was as low as 10/27 is considered to be the result of the possible redilation of the gallbladder in some of the cases because angiography was carried out 45–60 min after the administration of caerulein.

As a change in the cystic blood flow could not be proved from the angiographic findings, changes in the gallbladder capacity and blood flow 15 min after the intramuscular administration of caerulein were subsequently

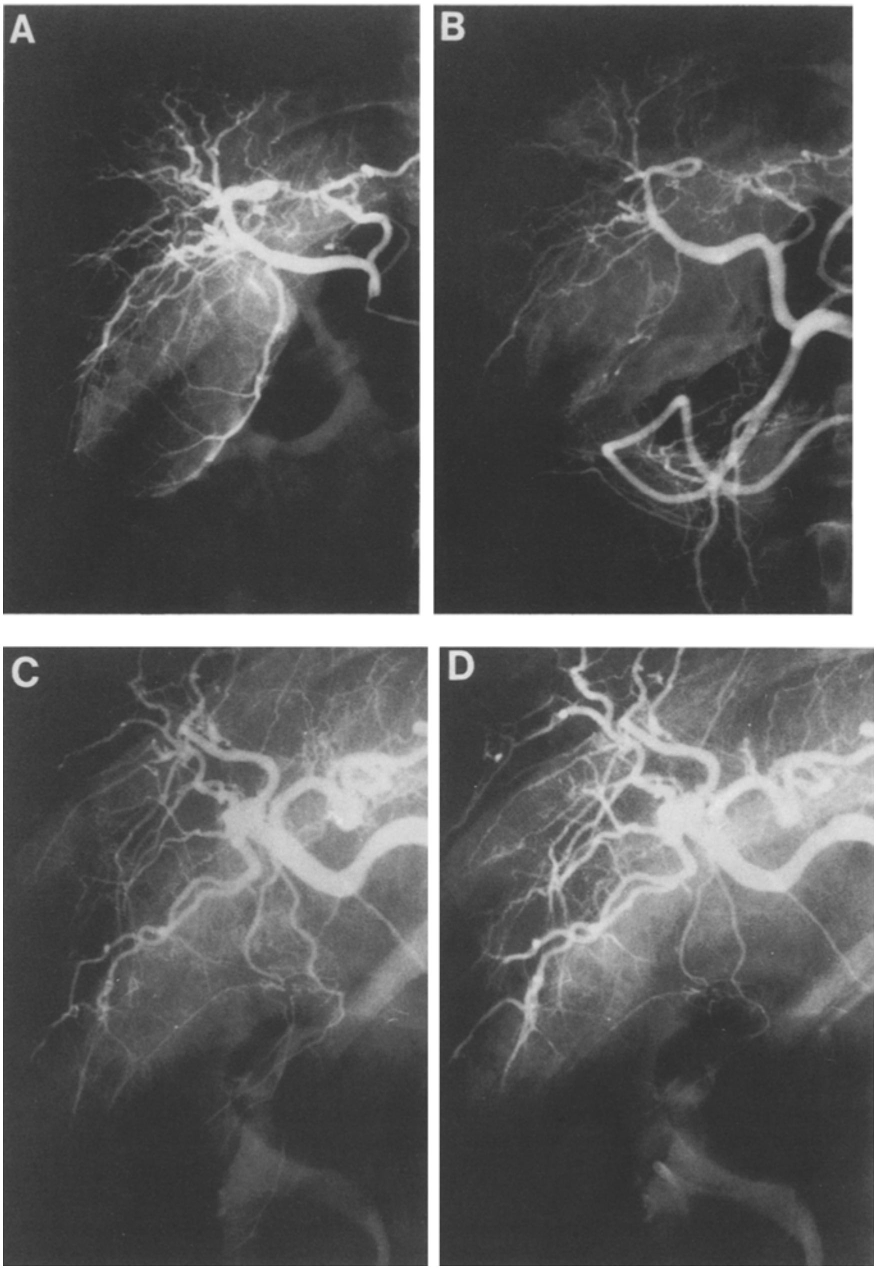

Fig. 2. Change in cystic artery before and after caerulein administration. **A** and **B** show the angiogram before **A** and after **B** administration of caerulein in the same case. After the administration of caerulein, the gallbladder is contracted and raised and the cystic artery diameter narrowed. **C** and **D** are both from another case. In this case, gallbladder contraction did not occur and no change is seen in cystic artery diameter after administration of caerulein, **D**

Table 5. Changes in gallbladder capacity and blood flow before and after administration of caerulein in seven cases of cholelithiasis

Patient	Age	Sex	Gallbladder capacity (cm^3)		Gallbladder contraction rate (%)	Tissue blood in gallbladder wall (ml min^{-1} 100 g^{-1})		Change in tissue blood stream in gallbladder wall
			Before	After		Before	After	
F.I.	67	F	19	17	11	69	69	0
S.K.	30	F	9	8	11	73	45	−38
T.S.	37	M	18	14	22	49	49	0
H.H.	68	M	34	18	47	124	73	−41
Y.M.	46	F	34	17	50	81	32	−60
S.W.	75	F	42	16.5	60	122	72	−40
F.T.	58	M	19	7	63	178	57	−68

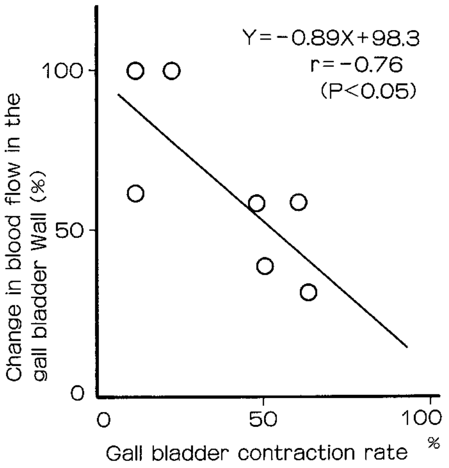

Fig. 3. Contraction rate of the gallbladder and change in blood flow in the gallbladder wall tissue after administration of caerulein.

investigated. In the seven cases of cholelithiasis, the blood flow in the gallbladder wall was measured by means of the electrolytic hydrogen gas clearance method, and the gallbladder capacity was measured during cholecystectomy (Table 5). As a result, it was found that the larger the contraction rate of the gallbladder, the more the decrease in the blood flow there.

Discussion

It has been emphasized that, in TAE treatment, it is necessary to keep the embolizing substance from flowing out of the artery in question to prevent the infarction of other organs, and it it is necessary to prevent the infarction of the cystic artery as much as possible since this [6] causes complications such as severe abdominal pain.

However, though gastric or splenic infarction can be prevented if the embolizing substance is carefully infused under fluoroscopy, there has been no effective method to prevent gallbladder complications in cases where the infusion of the embolizing substance from the central region of the bifurcation of the cystic artery is unavoidable [10].

As is commonly known, symptoms such as abdominal pain, pyrexia, nausea and vomiting are seen in many cases after TAE therapy. Chuang et al. pointed out that ischemia of the gallbladder wall is one of the causes of severe abdominal pain [2], while Jacob et al. reported cases with severe necrosis of the gallbladder wall after TAE therapy and the associated risk of perforation in the gallbladder wall [3]. In fact, a report by Takahashi et al. [7], regarding the recent trend of TAE complications, shows that severe cholecystitis was observed in 8 out of 41 cases when TAE was performed.

Kuroda et al. [5] reported that this gallbladder complication can be cured under strict observation, and our experience also indicates that few cases with acute cholecystitis require an emergency operation. Unfortunately, however, most patients with hepatic carcinoma intended for TAE therapy cannot undergo a curative operation because hepatic carcinoma has already been dispersed in the liver at the time of diagnosis or because cirrhosis, which is a basal disease, is in a progressive state, though the carcinoma itself is small. As a result, the hepatic function is significantly exacerbated. Under these circumstances, the need to suffer severe abdominal pain and pyrexia for several days as a result of TAE therapy, which cannot be termed a radical treatment though it has a life-prolonging effect, is not clear to many patients, particularly as patients are not informed that the symptoms are carcinoma.

The authors carried out TAE with the concurrent use of caerulein anticipating the alleviation or prevention of gallbladder complications and, as a result of carrying out the treatment on clinical cases, found that complications of cholecystitis (US findings) after TAE therapy were reduced and that clinical symptoms such as abdominal pain and an increase in the leukocyte count could be alleviated. As a result of measuring the blood flow in the gallbladder wall tissue before and after the administration of caerulein during a cholelithiasis operation, it was proved that the blood flow was actually reduced when the gallbladder contracted.

From the above results, it is presumed that TAE therapy carried out after the administration of caerulein reduces the amount of embolizing substance flowing into the cystic artery and evidently alleviates infarction of the gallbladder wall, since the contraction of the gallbladder caused by the administration reduces the blood flow in the gallbladder wall tissue.

Conclusion

When TAE is carried out from the central region at the cystic arterial bifurcation in the right hepatic artery, the frequency of gallbladder complications is evidently reduced if the gallbladder is contracted with caerulein before the infusion of the embolizing substance. This mode of reducing complications is ascribed to a decrease in the cystic blood flow due to the contraction of the smooth muscle of the gallbladder wall caused by caerulein.

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