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Effect of caerulein on abdominal pain following transcatheter hepatic arterial embolization in malignant liver cancer patients

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Summary. The severity of pain occurring in the right hypochondrium after transcatheter hepatic arterial embolization carried out in the treatment of malignant hepatic tumors was compared between a caerulein-treated group and a non-caerulein-treated group. The caerulein-treated group and the non-treated group each comprised nine patients Gelfoam powder was used as an occlusive agent. Even though there were no statistically significant differences between the two groups, the caerulein-treated group tended to demonstrate milder pain in the right hypochondricus, less incidence of tenderness and needed fewer administrations of analgesic than did the non-treated group. None of the three patients showing cystic artery contraction after the caerulein administration developed right hypochondricus pain or tenderness, or required the administration of analgesic. It was concluded that caerulein is useful in relieving right hypochondricus pain occurring after transcatheter hepatic arterial embolization

Introduction

Transcatheter hepatic arterial embolization (TAE) has been widely used in the treatment of malignant hepatic tumors, and has been accepted as an established effective technique. Long-survival cases treated with TAE have been reported. However, the treatment causes side-effects in what is termed "the post-embolic syndrome", such as temporary fever and right hypochondricus pain. Acute cholecystitis, caused by the occlusion of the cystic artery, is known as a cause of right hypochondricus pain, and sometimes results in the perforation of the gallbladder in very severe cases.

Caerulein (Ceosunin), which is a stimulant of gallbladder contraction, was combined with TAE, and we compared the severity of right hypochondricus pain between a caerulein-treated group and a group not treated with caerulein. The mechanism of pain relief by caerulein was also investigated by comparing the hepatic angiograms obtained before and after the administration of caerulein. At the same time, the rates of gallbladder contraction were calculated by ultrasonic tomography.

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Material and methods

The caerulein-treated group and the non-treated group each comprised nine patients. Seven patients in the caerulein-treated group and three patients in the non-treated group were suffering from primary liver cancer, while two patients in the caerulein-treated group and six patients in the non-treated group were suffering from metastatic liver cancer (Table 1).

Before angiography was carried out, we first measured the maximum area of the gallbladder with ultrasonic tomography. A catheter was then introduced into the terminal hepatic artery (proximal to the branching region of the cystic artery) or into the right hepatic artery, and then the diameter of the cystic artery was measured through hepatic angiography. Immediately afterwards 20 μg caerulein were injected intramuscularly. The maximum area of the gallbladder was again measured with ultrasonic tomography about 30 min after the injection. Hepatic angiography was again performed in order to remeasure the diameter of the gallbladder in the same manner as that used the first time. TAE was then carried out (Fig. 1).

Embolization was performed on all the patients using Gelfoam powder mixed with anticancer agents until the flow in the main tract of the right hepatic artery ceased.

As for the evaluation of right hypochondricus pain, we examined the patients' complaints, the need for analgesic administration, the occurrence of tenderness and the presence or absence of post-TAE cholecystitis.

Results

Complaints of right hypochondricus pain, analgesic administrations, tenderness and cholecystitis were observed respectively in 44.4% ($^4/_9$), 33.3% ($^3/_9$), 33.3% ($^3/_9$) and 17% ($^1/_9$) of the patients in the caerulein-treated group and in 78% ($^7/_9$), 67% ($^6/_9$), 44.4% ($^4/_9$) and 25% ($^2/_9$) of the patients in the non-treated group (Table 2). All these parameters were more frequently seen in the non-treated group; however, there were no statistically significant differences between the two groups.

The diameter of the cystic artery after the administration of caerulein was reduced in three patients, unchanged in three other patients and enlarged in another three. The three patients with dilatation all complained of right hypochondricus pain and required an analgesic; two of them experienced tenderness. Out of the three patients with an unchanged diameter of the cystic artery, right hypochon-

Table 1. Characteristics of patients in the two treatment groups

Patients treated with caerulein				Patients not treated with caerulein			
Case	Age (years), Sex	Type of liver cancer	Site of lesions	Case	Age (years), Sex	Type of liver cancer	Site of lesions
1	63 M	Primary	Right lobe	1	47 M	Primary	Bilateral lobes
2	67 M	Primary	Right lobe	2	56 M	Primary	Bilateral lobes
3	58 M	Primary	Right lobe	3	75 M	Primary	Right lobe
4	55 M	Primary	Bilateral lobes	4	57 M	Metastatic	Bilateral lobes
5	52 M	Primary	Bilateral lobes	5	37 F	Metastatic	Bilateral lobes
6	75 M	Primary	Bilateral lobes	6	59 F	Metastatic	Bilateral lobes
7	65 M	Primary	Bilateral lobes	7	38 F	Metastatic	Bilateral lobes
8	42 M	Metastatic	Bilateral lobes	8	64 F	Metastatic	Bilateral lobes
9	18 F	Metastatic	Bilateral lobes	9	68 F	Metastatic	Bilateral lobes

Table 2. Frequency of post-TAE disorders

Group	Right hypochondricus pain	Administration of analgesic	Tenderness	Post-TAE cholecystitis
Caerulein-treated patients	4/9 (44.4%)	3/9 (33.3%)	3/9 (33.3%)	1/6 (17%)
Non-treated patients	7/9 (78%)	6/9 (67%)	4/9 (44.4%)	2/8 (25%)

Table 3. Relation between the diameter of cystic artery and pain

Cystic artery	Right hypochondricus	Administration of analgesic	Tenderness	Post-TAE cholecystitis
Dilated	+	+	+	–
	+	+	+	Unknown
	+	+	–	–
Unchanged	+	–	+	Unknown
	–	–	–	–
	–	–	–	–
Contracted	–	–	–	Unknown
	–	–	–	+
	–	–	–	–

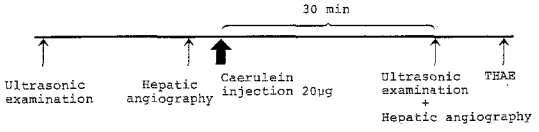

Fig. 1. Methods

Table 4. Diameter of cystic artery and rate of gallbladder contraction

Cystic artery	Rate of gallbladder contraction (%)
Dilated	40
	24
	12
Unchanged	58
	38
	8
Contracted	24
	9
	7

dricus pain and tenderness occurred in one, but could be tolerated without the need for an analgesic. None of the three patients with a contracted cystic artery had hypochondricus pain or tenderness, so they did not require an analgesic. Post-TAE cholecystitis occurred in one patient (Table 3). The degree of relief from right hypochondricus pain seemed to be related to the contraction of the cystic artery.

Table 4 summarizes the state of the cystic artery and the rates of gallbladder contraction examined by ultrasonic tomography after the administration of caerulein. There was no clear correlation between the changes in the cystic artery and the rates of gallbladder contraction.

Discussion

Patients often complain of fever, nausea, vomiting and abdominal pain after transcatheter hepatic arterial embolization (TAE). In particular, severe pain occurring in the right hypochondrium is thought to be caused by ischemic changes in the gallbladder [3]. Takayasu et al. [5] observed the occlusion of the cystic artery in 10 out of 19 patients after they had undergone TAE. In their report, it was not-

ed that 9 of these 10 patients developed necrotizing ulcerative cholecystitis and complained of severe pain in the right hypochondrium after TAE. Kuroda et al. [4] noticed an infarction of the gallbladder in 6 out of 8 patients after TAE, and found the correlation between infarction and the severity of post-TAE abdominal pain. In these two studies, severe ischemic changes in the gallbladder occurred in patients given Gelfoam powder.

In order to achieve an occlusion as peripherally as possible, we have used Gelfoam powder as an occlusive agent in many cases when we carried out TAE for the treatment of malignant liver cancer, after mixing it with anticancer agents. Indeed, quite a few centers utilize Gelfoam powder as an occlusive agent. If we compare Gelfoam powder with Gelfoam pieces, right hypochondricus pain and fever, appear more in patients receiving Gelfoam powder, as our statistics indicate. Although the gallbladder is possibly more extensively damaged through combination with anticancer agents, Carrasco et al. [2] found chemical cholecystitis in only 4 of the 700 patients undergoing hepatic artery infusion with anticancer agents. It cannot, therefore, be said that combination with anticancer agents induces more damage to the gallbladder.

Caerulein, a peptide extracted from the skin of the Austrian hyla (*Hyla caerulea*), has a powerful contractive effect on the gallbladder and a relaxant effect on the sphincter of Oddi. It has been proved that caerulein relieves the pain of biliary colic [1]. In this study, we determined the effect of caerulein combined with TAE on the relief of right hypochondricus pain. In comparison with the group not receiving caerulein, the caerulein-treated group exhibited less right hypochondricus pain, less need for the administration of an analgesic and fewer incidences of tenderness. However, there were no statistically significant differences between the two groups. One patient developed cholecystitis, but this patient complained of no pain immediately after TAE. The diameter of the cystic artery after the administration of caerulein changed in various ways, being enlarged in three patients, unchanged in three other patients and reduced in another three. Although these results failed to define clearly the effect of caerulein on the cystic artery, none of the patients with a contracted cystic artery complained of right hypochondricus pain, none of them required an analgesic, and none suffered from tenderness. This suggests a correlation between the degree of cystic artery contraction and the severity of post-TAE pain. There was no correlation between the rate of gallbladder contraction and the diameter of the cystic artery or the severity of pain.

Although the mechanism of the action of caerulein on the cystic artery still remains unclear, the relief or right hypochondricus pain observed in patients with a contracted cystic artery seems to be partially due to the decreased flow of the occlusive agent into the cystic artery. We felt that there must be other reasons which, however, could not be identified. The combination treatment with caerulein is, however, related to the relief of right hypochondricus pain occurring after TAE. The intraarterial injection of caerulein is worthy of future investigation.

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