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RAPID COMMUNICATION

Ultrasonic interventional analgesia in pancreatic carcinoma with chemical destruction of celiac ganglion

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Abstract

AIM: To detect the therapeutic effects of chemical destruction of celiac ganglion in patients with pancreatic carcinoma with intractable pain.

METHODS: Ninety-seven cases with advanced pancreatic carcinoma received chemical destruction of celiac ganglion-5 mL pure alcohol injection around celiac artery under ultrasonic guidance. The changes of visual analogue scale (VAS), serum substance P (Sub P), β-endopeptide (β-EP) and T-lymphocyte subtypes level were compared between pre- and post-therapy.

RESULTS: Successful rate of puncture was 98.7%, with one failure. No serious complications such as traumatic pancreatitis, pancreatic fistula, abdominal cavity hemorrhage or peritoneal infection occurred. VAS, serum Sub P and β-EP level significantly changed after treatment (8.0 ± 2.3 *vs* 4.6 ± 2.1, 254.1 ± 96.7 *vs* 182.4 ± 77.6, 3.2 ± 0.8 *vs* 8.8 ± 2.1, $P < 0.01$, $P < 0.05$, $P < 0.01$) with complete relief rate 54.2%, partial relief rate 21.9%, ineffective rate 12.5% and recurrent rate 10.7%. The T-lymphocyte subtypes level remarkably increased when compared with that of pre-therapy (46.7 ± 3.7 *vs* 62.5 ± 5.5, $P < 0.01$).

CONCLUSION: Our study suggests that chemical destruction of celiac ganglion under ultrasonic guidance is highly safe, and can evidently relieve cancer pain and improve the cellular immunity in patients with advanced pancreatic carcinoma.

Key words: Pancreatic carcinoma; Analgesia; Chemical destruction; Ultrasonic intervention; Celiac ganglion

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INTRODUCTION

Pancreatic carcinoma (PC) is a hyper-malignant disease. Its onset is insidious but its development is aggressive. The radical excision rate is lower than 25%. About 70% of the patients with PC have obvious symptoms of pain and at the late stage all PC patients suffer from severe and intractable pain. The pain has been the chief complaint of the patients with PC, which has significantly decreased their life quality. Thus, to improve the living quality of patients with PC has become the main task for palliative treatment. In 1998, we began to perform chemical destruction of celiac ganglion by ultrasonic intervention in patients with PC in an effort to reduce cancer pain. The results suggested that this method is effective in alleviating the pain caused by PC and can up-regulate the cellular immune level.

MATERIALS AND METHODS

Patients

Our study included 97 patients, 64 males and 33 females, aged between 38 to 79 years, with body weight ranging from 41 to 78 kg (Table 1). Seventy-two were definitely diagnosed as PC by operation (including 26 by pathological biopsy) and 25 by B-ultrasound, CT or MRI (including 10 combined with the increase of CA19-9 value). All the patients suffered from pain in the abdomen and back, characterized by persistently or intermittently attacking pain. According to visual analogue scale (VAS), 29 had moderate pain, 63 had severe pain, and 5 had mild pain. The duration of pain was between 11 to 67 d. All the patients depended on drugs to alleviate the pain before treatment.

Methods

Instruments and reagents used in the study were color B-ultrasonic diagnostic apparatus Aloka-680EX made in Japan, 3.5 MHz convex probe, puncture shelf Aloka MP-2411B made in Japan, puncture needle CNF2220 made in USA, medical analytical anhydrous alcohol and procaine injection (10 g/L). All the patients were fasted for less

Table 1 General data of 97 PC cases

Location of tumor	Diagnosis					Size of tumor (cm)	Metastasis				
	Patients *n*	Operation	Image+ A19-9	Image			Liver	Lung	Lymph node	Colon	Spinal column
Head of pancrreas	55	46	4	5	4.1 ± 2.3	7	-	15	1	-	
Neck of pancrreas	17	13	-	4	5.5 ± 3.8	2	-	3	1	-	
Body of pancrreas	12	5	3	4	4.7 ± 3.1	-	-	3	-	-	
Tail of pancrreas	7	7	-	-	8.6 ± 3.5	-	-	4	-	-	
Whole pancreas	6	1	3	2	-	-	1	2	-	1	

than 12 h before operation; then they were given procaine skin test and VAS training. They were required to catch how to exactly express the degree of pain with VAS and received the compatibility test of posture and respiration. If the patient felt too nervous, he was given intramuscular injection of 10 mg valium 30 min before operation.

Chemical destruction of celiac ganglion

By B-ultrasonic scanning when the patient was lying, the situation around origin plane of celiac arterial trunk was confirmed as the target region. The point of puncture was accordingly confirmed. Routine sterilization was performed on the abdomen and probe. Puncture was performed after local anesthesia of the insert path of needle. B-ultrasound dynamically supervised the course of puncture until the needle arrived at the target region, which was symbolized with heaving impulse and no blood when the syringe was drawn back. Then the patient was given 10 mL procaine injection (10 g/L). If the patient felt significant alleviation of pain or felt warm on his abdomen, the puncture was considered successful. After that, anhydrous alcohol (15 mL) was given to destroy the ganglion. Post-operational fasting, fluid infusion and anti-infectious treatment were performed. If all procedures were carried out smoothly, the patient could then be given normal diet 24 h after operation.

Criteria of curative effects

We used 5 different terms to describe the curative effects: complete relief (CR), partial relief (PR), mild relief (MR), no relief (NP) and recurrence (RC). Those patients who felt no pain and unnecessary to take pain-killers were described as CR. Those who felt significant alleviation of pain after operation but still needed pain-killers occasionally were described as PR. Those who felt a little alleviation after operation but still needed pain-killers because the pain disturbed their sleep were described as MR. Those who felt no change between before and after operation were described as NR. Those who felt alleviation after operation but the pain recurred soon were described as RC.

Visual analogue scale (VAS)

A direct line of 10 cm in length was used. Its both ends expressed 0 and 10, which stood for no pain and the severest pain, respectively. Patients marked the location of pain by themselves, which was used as the basis of quantification.

Sub P and β-EP

Fasting cubital venous blood (4 mL) was averagely grouped: 2 mL Sub P and 2 mL β-EP blood specimens. Iniprol (1000 U) and heparin (10 g/L, 20 U) were added into the Sub P blood specimen. At the temperature of 4 ℃, centrifugation, at a speed of 3000 r/min was performed for 15 min. The upper plasma was preserved at the temperature of -70 ℃.

The β-EP blood specimen was placed in a plastic tube in which there were EDTA-Na2 (6 mg) and bacitracin (160 μg). Then, low temperature centrifugation was performed and the plasma was preserved at the temperature of -20 ℃. The Sub P and β-EP kits were provided by Neurobiological Department of the 2nd Military Medical University and were assayed with the automatic radioimmunoanalyzer FJ-2008P made in Xi'an The unit of Sub P and β-EP was ng/L and nmol/L, respectively.

Assay of T lymphocyte subtype

Fasting venous blood (5 mL) was sampled. Luminescence immunoassay and flow cytometry were used to determine the level of CD_3^+, CD_4^+, and CD_8^+ (cluster of differentiation) and the results were expressed as the percentage of positive cells. MFITC was used to mark the mcAb rats' anti-human CD_3^+, CD_4^+, and CD_8^+ and FITC was used to mark the IgG of rats. All the reagents were purchased from the American Santa Company. Thirty-eight healthy persons were tested as control group.

Statistical analysis

All data were expressed as mean ± SD. *t* test was used to examine the significance of the difference between before and after the treatment and among the groups. *P* value < 0.05 was taken as significant.

RESULTS

The success rate of puncture was 98.7% (96/97). Puncture failed in one patient, who had PC complicated with portal hypertension and there were many variciform veins along the puncture route. In addition, the patient had poor tolerance to puncture posture. We had to give up puncturing on him because the puncture needle could not safely arrive at the target region. In the other 96 patients with successful puncture, there were no such complications as traumatic PC, abdominal cavity hemorrhage, pancreatic fistula or peritoneal infection. Of them, the pain was

Table 2 VAS, plasma Sub P (ng/L) and β-Ep (nmol/L) pre- and post-operation (mean ± SD)

Operation	VAS	Sub P	β-EP
Pre-	8.0 ± 2.3	254.1 ± 96.7	3.2 ± 0.8
Post-			
1 d	5.2 ± 1.8[b]	231.3 ± 101.3	5.1 ± 1.2[f]
3 d	4.6 ± 2.1[b]	182.4 ± 77.6[c]	8.8 ± 2.1[f]
7 d	4.3 ± 1.3[b]	174.5 ± 90.3[c]	9.2 ± 1.8[f]
15 d	3.7 ± 2.0[b]	154.7 ± 81.2[c]	7.6 ± 2.0[f]
30 d	4.1 ± 1.9[b]	188.2 ± 90.6[c]	6.7 ± 1.6[f]

VAS: [a]$P < 0.05$, [b]$P < 0.01$ *vs* Preoperation; Sub P: [c]$P < 0.05$, [d]$P < 0.01$ *vs* Preoperation; β-EP: [e]$P < 0.05$, [f]$P < 0.01$ *vs* Preoperation.

Table 3 Blood T cell subtypes (%) and β-EP (nmol/L) pre- and post-operation (mean ± SD)

Index	Control (n = 38)	Therapeutic (n = 96)			
		Pre-	Postoperation		
			3 d	7 d	15 d	30 d
CD_3^+	70.3 ± 4.9	46.7 ± 3.7	48.8 ± 5.1	58.7 ± 3.7[b]	62.5 ± 5.5[b]	61.2 ± 6.1[b]
CD_4^+	46.6 ± 5.3	31.2 ± 5.0	33.1 ± 3.8	37.6 ± 4.1[d]	40.6 ± 4.4[d]	39.6 ± 3.1[d]
CD_8^+	23.4 ± 4.1	15.0 ± 2.5	14.7 ± 2.8	20.9 ± 3.0[f]	22.0 ± 2.7[f]	21.4 ± 3.2[f]
β-EP	8.7 ± 2.3	3.2 ± 0.8	8.8 ± 2.1[h]	9.2 ± 1.8[h]	7.6 ± 2.0[h]	6.7 ± 1.6[h]

CD_3^+: [a]$P < 0.05$, [b]$P < 0.01$ *vs* Preoperation; CD_4^+: [c]$P < 0.05$, [d]$P < 0.01$ *vs* Preoperation; CD_8^+: [e]$P < 0.05$, [f]$P < 0.01$ *vs* Preoperation; β-EP: [g]$P < 0.05$, [h]$P < 0.01$ *vs* Preoperation.

completely relieved in 52; partially relieved in 21; slightly relieved in 11 and the puncture had no effect in 12. The longest follow-up time was 104 d. The pain recurred in 9 patients on the d 11-51 after puncture, respectively. The recurrence rate was 10.7%. The statistical analysis showed that there were significant changes in VAS, Sub P and β-EP on d 3 after puncture: significant decrease of VAS and Sub P ($P < 0.01$ and $P < 0.05$, respectively) and significant increase of β-EP ($P < 0.01$). By the dynamic follow-up on d 7, 15 and 30, the level of VAS, Sub P and β-EP kept stable, suggesting the stability of our treatment effect (Table 2).

The results showed that the level of CD_3^+, CD_4^+, and CD_8^+ in patients with PC was significantly lower than that in control group ($P < 0.01$). On the 3rd d after chemical destruction of celiac ganglion, the level of subtype T increased slightly compared with that of preoperation but with no significance. On the 7, 15 and 30 d after operation, the level of CD_3^+, CD_4^+, and CD_8^+ increased significantly compared with that of preoperation ($P < 0.01$). The level of β-EP remarkably increased on the 3rd d after operation and there was significant difference compared with before operation ($P < 0.01$). Moreover, the serum β-EP was kept at a high level at 7, 15 and 30 d during follow-up (Table 3).

DISCUSSION

Mechanism of ultrasonic intervention on the pain caused by pancreatic carcinoma

The pain caused by PC mostly comes from the stimulation on the pancreatic sensory nerve fiber, which is conducted through the visceral sympathetic nerve[1-3]. Although the distribution of pancreatic visceral nerves is very complex, they concentrate in the celiac ganglion, project to relevant spinal segments and reach the nerve center of central nervous system, consequently causing pain. In clinic, excision of celiac ganglion or plexus can significantly inhibit the obstinate pancreatogenic pain[1]. Therefore, blocking of the celiac ganglion can theoretically alleviate the pain caused by PC. However, it is difficult by ordinary image technique to show the situation of celiac ganglion. The celiac ganglion is situated on the wall of celiac artery and the anatomical position is fixed. B-ultrasound can clearly show the celiac arterial trunk and its neighboring structure. Therefore, abdominal B-ultrasound can provide indirect guidance for the localization of celiac ganglion. Local injection of anhydrous alcohol, through its demyelinization to destruct the celiac ganglion, can permanently block the transmission passage of the nerves, resulting in alleviation of the pain.

Evaluation of the analgesic effect

As a subjective feeling, pain is affected by various factors. Therefore, in order to objectively reflect the changes of pain after treatment, apart from VAS, Sub P and β-EP were chosen as the evaluation indexes of efficiency. Sub P is an important nerve transmitter of pain. Its concentration in the blood is directly proportional to the injury stimulation[4]. Therefore, Sub P can objectively reflect the degree of pain. β-EP is the main endogenous opiate peptide in human, which has the same analgesic effect as morphine. Millan[5] found that the secretion of β-EP in patients with chronic or carcinoma pain decreased and that the secretion of β-EP increased after the alleviation of pain. In addition, the secretion of β-EP was negatively related to the degree of pain.

The results of our study showed that the overall effective rate of analgesia of chemical destruction of celiac ganglion was 87.5% and the effectual rate was 76.1%. Three days after the treatment, both VAS and Sub P decreased significantly ($P < 0.01$ and $P < 0.05$, respectively) whereas β-EP increased remarkably ($P < 0.01$). Our follow-up of one month showed that the levels of VAS, Sub P and β-EP kept stable. Thus we may conclude that this method is effective against the pain caused by PC. Nerve destruction can decrease the release of the dolorogenic Sub P and up-regulate the level of β-EP, by which the pain is alleviated. However, in 12 patients pain was not significantly alleviated in our study. We suppose that the pain was related to the incomplete obstruction caused by metastatic cancer of colon in 2 cases and hepatic metastasis in 9 and in the remaining one patient, bone destruction of lumbar spine shown by imaging examination, so we suggested that there might be some somatic nerve injured which was associated with the low effectiveness of simple visceral nerve blockade on the pain.

There were no severe complications in the patients. Diarrhea was the common symptom after treatment and the occurrence rate was about 61.5% (59/96). The reason was that after the destruction of celiac ganglion, the inhibitory effect on intestinal wall neuron decreased while its excitability increased, which led to the accentuation

of peristalsis and secretion. Oral activated charcoal was effective on relieving the symptom.

Relationship between analgesia and immune function of T cells

Kelsen *et al*[2] reported that in 77 PC patients, there was significant difference in the survival time between the pain group and no pain group ($P < 0.01$), whether the patient had received operation or not. The survival time of the patients with pain was significantly shorter than those without pain, indicating that the pain caused by PC was closely related to the prognosis. Melzack *et al*[6] observed that the level of Ts, TH and null lymphocyte in patients with pain caused by cancers decreased significantly in 1983. They concluded that pain caused by cancers might induce "dormancy" of T subtypes. The relation between the pain caused by cancers and the immunity of cells has attracted more attention because cellular immunity plays the main role in tumor immunology and it can inhibit the occurrence and progress of cancers. In addition, Ts can identify the neoantigen and TH can kill the carcinogenic cells by cytotoxic reaction. Ma *et al*[7] reported that in 70 patients with tumors at the intermediate or late stage, the level of CD_3^+, CD_4^+ and CD_8^+ in the pain group was significantly lower than that in no pain group ($P < 0.01$) and after the pain was alleviated the level of CD_3^+, CD_4^+ and CD_8^+ increased significantly ($P < 0.05$). Thus it can be concluded that pain caused by tumors can lead to the decrease of human immunity and influence the prognosis and effective control of pain can improve the activity of T subtypes. Morphine is the commonly used pain-killer. It has been proved that perennially taking morphine can lead to addiction and resistance to drugs. Moreover, repeated use of morphine can result in atrophy of pleura and decrease of the expression of CD_3^+, CD_4^+ and CD_8^+[8-10]. Therefore, analgesia should be reasonable in quantity taking into account of its influence on immune function. Our results showed that the expression of T subtypes in patients with pain caused by PC was significantly lower than that in control group, indicating the necessity to protect the immune function. One week after the destruction of celiac ganglion, the expression of CD_3^+, CD_4^+ and CD_8^+ remarkably increased ($P < 0.01$), indicating that analgesia with chemical destruction of celiac ganglion can improve the immune suppression in patients with PC and increase the expression of T subtypes.

Presently it is not clear about the mechanism of pain treatment regulating the immune function. Studies have been focused on the endogenous opiate peptides. On the one hand, β-EP, as an endogenous opiate peptide, has the inhibitory function on pain by the κ and μ receptor pathway; on the other hand, β-EP, as an immune derived product, is the active substance with close relation to the nerve, incretion and immune systems[11]. Maddle *et al*[12] found that β-EP has an important regulatory activity on immunity. Its up-regulation can promote T-lymphocyte multiplication, antibody polymerization and cytotoxic function of NK. Brown *et al*[13] found that there are opiate receptors on the immune cells and β-EP can take part in the regulation of T subtypes and promote their differentiation and growth through opiate receptors. Our study showed that the level of β-EP in pain group was significantly lower than that in control group ($P < 0.01$), which is consistent with the literature. After analgesic therapy, the level of β-EP increased significantly ($P < 0.01$), with a similar trend to that of T subtypes. β-EP level increased significantly ($P < 0.01$) on the 3rd day after treatment, which was ahead of that of CD_3^+, CD_4^+ and CD_8^+. Therefore, we presume that β-EP might take part in the immune regulation of CD_3^+, CD_4^+ and CD_8^+.

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