

## RESEARCH ARTICLE

# Efficacy of Mannatide Combined with Sodium Cantharidate Vitamin B6 in the Treatment of Malignant Pleural Effusions

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## Abstract

**Objective:** To evaluate the efficacy of mannatide combined with sodium cantharidate vitamin B6 in the treatment of malignant pleural effusions. **Materials and Methods:** Data for 69 patients with malignant pleural effusions who did not receive systemic chemotherapy were collected. Injection into the thorax using mannatide combined with sodium cantharidate vitamin B6 was performed for 37 patients in the experimental group and mannatide combined with cisplatin for 32 patients in the control group. Objective responses, KPS (Karnofsky Scoring) and incidences of side effects between the two groups were compared. **Results:** 13 patients reached CR (complete response) and 11 PR (partial response) in the experimental group, while 12 patients reached CR and 9 PR in the control group, the difference in overall objective responses between the two groups not being significant (66.7% vs 63.6%,  $p=0.806$ ). However, improvement of KPS in the experimental group was greater than in the control group; total side-effect incidences during the period of treatment were 22.2% (8/36) and 54.5% (18/33), respectively ( $p=0.006$ ). **Conclusions:** Regimen of mannatide combined with sodium cantharidate vitamin B6 had better improvement in quality-of-life and symptom relief, with a lower side-effect incidence in treatment of malignant pleural effusions.

**Keywords:** Malignant pleural effusion - mannatide - sodium cantharidate vitamin B6

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## Introduction

Malignant pleural effusion is the serious complication of advanced malignant carcinomas (Sahn, 1997; Yildiz et al., 2011; Zhang et al., 2014). It is characterized by rapid progression and large volume, which can lead to serious consequences including the exacerbation of disease and even death. Effective treatment for malignant pleural effusions is needed urgently in order to improve the quality of life and prolong the survival time of patients. Injection in thorax using mannatide combined with sodium cantharidate vitamin B6 was performed for 69 patients with malignant pleural effusions resulted from several kinds of malignant tumors in our hospital, and treatment method and outcomes were described and analyzed as below.

## Materials and Methods

### Patients

Date of 69 patients with malignant pleural effusion resulted from lung cancer, breast cancer or esophageal cancer treated in Chengde central hospital, Hebei province, China between July, 2013 and August, 2014 were collected

and analyzed. All primary tumors were confirmed by clinicalopathological examination. Pleural effusion was confirmed by chest X-ray and CT (computed tomography) scanning, tumor cells were found microscopically and malignancy was confirmed by biopsy examination.

Of the 69 patients, 37 cases were male and 32 cases were female, their age ranged from 35 to 74 years old with the median age of 52. Unilateral pleural effusion was found in 50 patients and bilateral in 19 patients, massive pleural effusion in 48 patients and medium in 21 patients. All patients were divided into two groups named the experimental group and control group. 36 patients (lung cancer: 20 cases, breast cancer: 10 cases, esophageal cancer: 6 cases) were included in experimental group and 33 patients (lung cancer: 22 cases, breast cancer: 9 cases, esophageal cancer: 2 cases) in control group, which were shown exactly in Table 1.

Blood tests including blood routine, liver and renal function were performed before treatment, and bacteria culture of pleural effusion was also performed routinely and no bacterial colonies were found among the 69 patients. No patients received systemic chemotherapy because of a weak constitution, or any family or economic factors.

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### Treatment method

Puncture point was confirmed by ultrasound localization. Closed thoracic drainage tube was indwelt after disinfecting and local anesthetics, and drainage tube was fixed by aseptic sticking membrane. Injection in thorax using mannate combined with sodium cantharidate vitamin B6 was performed after draining completely (there was no obvious pleural effusion remained which was shown in chest X-ray or CT scanning). The regimen in experimental group: mannate 40 mg plus normal saline 20ml was injected on day1, 3, 5 per week, sodium cantharidate vitamin B6 50ml plus normal saline 20ml on day2, 4, 6 per week, two cycles were applied; regimen in control group: mannate 40mg plus normal saline 20ml and cisplatin 40mg plus normal saline 20ml on day 1 and 4 per week, two cycles were applied. Closed drainage after injection and asked the patient to change position every 30 min. Opened drainage tube at night. Removed the drainage tube when the volume of pleural effusion less than 100ml per day. Blood routine, liver and renal function were performed every three days during the period of treatment and every one week after treatment, chest X-ray and chest ultrasound examination were performed every one week after treatment.]

### Evaluation

WHO criteria was used for evaluating the objective response of pleural effusion to treatment, and the objective response was evaluated 4 weeks after treatment; KPS (Karnofsky Scoring) was used for the evaluation of quality-of-life of patients, and the quality-of-life of patients was evaluated one week before treatment and repeated 4 weeks after treatment. Side effects were recorded during the period of treatment. Response rates, changes of KPS and incidences of side effects between the two groups were compared.

### Statistical analysis

Statistical analyses were performed using statistical software package SPSS version 16.0. A P-value <0.05 was considered to be statistically significant. Categorical variables were analyzed by chi-square test and continuous variables were analyzed by the Student's t test.

## Results

As shown in Table 2, 13 patients reached CR (complete response), 11 PR (partial response) and 8 SD (stable disease) in experimental group; whereas 12 patients reached CR, 9 PR and 10 SD (Table 2) in control group, overall response rate which was defined as the sum of CR and PR was 66.7% (24/36) in experimental group and 63.6% (21/33) in control group, there was no statistically significant in objective response ( $p=0.801$ ), neither in overall objective response ( $p=0.806$ ).

The KPS was  $46.9\pm 12.4$  on average (ranged from 30 to 70) in experimental group and  $46.4\pm 12.5$  (ranged from 30 to 70) in control group before treatment ( $p=0.847$ ), whereas  $62.8\pm 12.1$  and  $55.2\pm 12.8$  in experimental and control groups respectively one month after treatment ( $p=0.013$ ) (Table 3); meanwhile we also found that the

change of KPS in experimental group was obviously significant compared with that in control group, which was shown in Table 4 ( $p<0.001$ ,  $p=0.006$ , respectively).

The total side effect incidences during the period of treatment were 22.2% (8/36) and 54.5% (18/33) in experimental group and control group, and the difference

**Table 1. Comparison of General Parameters Between Experimental and Control Groups**

Parameters	Experimental group (n=36)	Control group (n=33)	P-value
Gender			0.631
Male	18	19	
Female	18	14	
Age, year (mean±SD)	57.4±11.3	58.2±10.9	0.752
Concomitant diseases			0.762
None	10	6	
Cardiovascular system	7	6	
Cerebrovascular system	4	6	
Endocrine system	3	5	
Respiratory system	9	6	
Others	3	4	
Primary lesion			0.364
Lung cancer	20	22	
Breast cancer	10	9	
Esophageal cancer	6	2	
Unilateral/ bilateral			0.293
Unilateral	24	26	
Bilateral	12	7	
Volume			0.309
Massive	23	25	
Medium	13	8	

**Table 2. Comparisons of Objective Response between Experimental and Control Groups**

Parameters	Experimental group (n=36)	Control group (n=33)	P-value
Objective response			0.801
CR	13	12	
PR	11	9	
SD	8	10	
PD	4	2	
Overall objective response (CR+PR)	24	21	0.806

CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease

**Table 3. KPS and Side Effect Comparisons between Experimental and Control Groups**

Parameters	Experimental group	Control group	P-value
KPS			
Before treatment (mean±SD)	46.9±12.4	46.4±12.5	0.847
After treatment (mean±SD)	62.8±12.1	55.2±12.8	0.013
Side effects			
Fever	3	6	0.231
Nausea and Vomiting	2	8	0.028
Anorexia	5	11	0.056
Chest pain	1	6	0.034
Pleurisy	0	2	0.134
Myelosuppression	0	4	0.031
Overall	8	18	0.006

\*KPS, Karnofsky Scoring

**Table 4. Different KPS before and after Treatment in Experimental Group and Control Group**

Parameter	Experimental group		P-value	Control group		P-value
	Before treatment	After treatment		Before treatment	After treatment	
KPS	46.9±12.4	62.8±12.1	<0.001	46.4±12.5	55.2±12.8	p=0.006

\*KPS, Karnofsky Scoring

was significant ( $p=0.006$ ), the incidences of nausea and vomiting, chest pain and myelosuppression in experimental group were obviously lower than that in control group which were shown in Table 3, but similar incidences of fever, anorexia and pleurisy were found between the two groups.

## Discussion

Malignant pleural effusions are common and affect as many as 15% of cancer patients (Sahn, 1997). Considerable symptoms can be caused by malignant pleural effusions, especially breathlessness, and morbidity (Fysh et al., 2014). Patients with malignant pleural effusions have the poor quality of life and prognosis, and effective and timely treatment is urgent. Both of systemic chemotherapy and injection in thorax are recommended routinely. Systemic chemotherapy is sometimes limited by several factors including the weak constitution, family or economic factor and response to chemotherapy. For patients who systemic chemotherapy cannot be delivered to, injection in thorax may be the best choice for the improvement of quality-of-life and prognosis.

Talcum powder (Ahmed et al., 2014; Thomas et al., 2014), cisplatin (Morabito et al., 2013; Zhao et al., 2014), Bleomycin (Gaafar et al., 2014; Rafiei et al., 2014) and so on had been used for the treatment of malignant pleural effusions in different centers, and different incidences of side effects including fever, nausea and vomiting, anorexia, chest pain, pleurisy, myelosuppression and pulmonary fibrosis had been reported.

Nowadays, biological immune regulators has been used for the treatment of pleural effusions (Adams et al., 1989; Strizzi et al., 2001), and mannatide as one kind of biological immune regulators which was developed in China was used in this study. The main function of mannatide is to improve the lymphocyte transformation rate and to increase the number of NK cells. Sodium Cantharidate Vitamin B6 as a new kind of anticarcinogens has been delivered to patients with non-small-cell lung carcinoma (Wang and Cui, 2014) and liver cancer (Shao et al., 2014). Sodium Cantharidate Vitamin B6, as a compound agent, can promote the secretion of IL-2 and reduce the secretion of IL-8, which will lead to the reduction of tumor angiogenesis. Based on our results, we found that patients who received mannatide combined with sodium cantharidate vitamin B6 had the similar overall objective response when compared with mannatide combined with cisplatin; meanwhile, obvious improvement in KPS and side effects were observed. Patients who received mannatide combined with sodium cantharidate vitamin B6 had better tolerance and quality-of-life.

There has not reached consensus on the treatment of

malignant pleural effusions till now (Yildiz et al., 2011; Wang et al., 2013), especially for the patients without the indication of systemic chemotherapy, or patients with weak constitution, for example, KPS less than 50. Without compromising objective response, improvement in quality of life and symptomatic relief, better tolerance and lower side-effect incidence are the key criteria for the choice of regimens. The regimen of mannatide combined with sodium cantharidate vitamin B6 may be one of the alternatives for this kind of patients we think, and of course, randomized and large sample clinical trials are needed.

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