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The clinical efficacy of external application of mirabilite and rhubarb combined with intrathoracic chemotherapy in treating malignant pleural effusion

A prospective, randomized, controlled clinical trial

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Abstract

Background: Malignant pleural effusion (MPE) is one of the commonest causes of an exudative pleural effusion. Breathlessness, dyspnea and other symptoms often seriously distress and affect the quality of life. The external application of mirabilite and rhubarb (EAMR) combined with intrathoracic infusion of cisplatin, as an alternative treatment for MPE, is popular in China. The study aims to assess its effectiveness and safety combined with intrathoracic chemotherapy.

Methods: This study is a prospective, randomized controlled clinical trial. Patient visits were performed at baseline and days 14 and 28 after treatment. Clinical outcomes were measured after chest drain placement using the criterion of efficacy refer to WHO standard, and QLQ-C30 questionnaire.

Results: Database records of patients treated in our institution for MPE between October, 2016 and March, 2019. The study included 84 eligible patients. They were categorized with a randomization schedule into treatment group (N = 42) and control group (N = 42). There is statistical significance in the comparison of the total effective rate between these 2 groups (66.67% vs 54.76%, $P < .05$). Furthermore, there is statistical significance in the comparison of items of Physical (1.95 ± 0.50 vs $2.19 \pm 0.58\%$, $P < .05$), Pain (1.98 ± 0.42 vs 2.07 ± 0.32, $P < .05$), and Global Health (1.23 ± 0.64 vs $1.13 \pm 0.23\%$, $P < .05$) between these 2 groups. None of the patients had adverse reactions such as skin allergy and chest tightness.

Conclusions: The total effective rate of treatment group using extra external application of mirabilite rhubarb powder is significantly higher than that of control group. The improvement of patients' clinical symptoms is greater in treatment group and no adverse reactions is found. Therefore, external application of mirabilite and rhubarb combined with intrathoracic infusion of cisplatin is an effective method for the treatment of MPE, which is worth popularizing.

Abbreviations: EAMR = external application of mirabilite and rhubarb, MPE = malignant pleural effusion, TCM = traditional Chinese medicine.

Keywords: external application, intrathoracic chemotherapy, malignant pleural effusion, mirabilite and rhubarb, RCT

1. Introduction

Malignant pleural effusion (MPE) is one of the commonest causes of an exudative pleural effusion, and its incidence is increasing with increasing cancer prevalence and as more effective cancer therapy that prolongs life. It is the commonest cause of a unilateral massive pleural effusion, although 10% to 13% can be bilateral.[1] Median survival after a diagnosis of MPE depends on

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The study was reviewed by the Longhua Hospital Ethics Committee and ethical approval was waived as written consent was obtained from the patient.

Written patient consent was obtained for publication of all aspects of the case including personal and clinical details and images, which may compromise anonymity.

All authors read and approved the final manuscript and declare that they have no competing interests.

The authors have no conflicts of interests to disclose.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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the underlying malignancy and stage at diagnosis, and varies between 3 and 12 months.[1–3] Most MPEs are secondary to metastases to the pleura from other sites, most commonly lung and breast, which together cause 50% to 65% of all MPE.[4,5] Breathlessness, dyspnea and other symptoms often seriously distress and affect the quality of life (QOL).[4–7]

Most patients can be offered only symptomatic and palliative treatment at this stage of their disease. A chest drain is always recommended for rapidly recurring pleural effusions, as repeat thoracenteses are associated with an increased risk of infection. Cisplatin, as the most frequently used drug for intrathoracic chemotherapy, has been reported to have an effective rate of 54.2% to 66.0%.[8,9] Both antineoplastics (e.g., bleomycin or cisplatinum) and nonantineoplastics (e.g., talc) are used as sclerosing agents for chemical pleurodesis.

In recent years, the external treatment of traditional Chinese medicine (TCM) has played an increasingly important role in the treatment of malignant pleural effusion with its unique advantages.[10,11] It is not only superior to simple use of western medicine, but also has advantages in control of adverse reactions. TCM has certain characteristics and advantages in the treatment of MPE. It can enhance immunity, relieve symptoms, improve life quality, and has little side effects, which is easy for patients to accept.[12,13] Mirabilite is a common TCM which mainly contains sodium sulfate ($Na_2SO_4{\cdot}10H_2O$). It can absorb osmotic solution and eliminate edema. The external application of mirabilite can help patients form a hyperosmotic state locally, and promote the local internal water to be absorbed outside through osmotic pressure. Rhubarb is well known for its bitter taste.[14] Rhubarb is well known for its excellent heat-clearing and detoxifying properties. Studies have shown that rhubarb has purgative, anti-inflammatory, diuretic and other pharmacological effects. The purgation and diuretic effects can effectively remove the water retained in the part of the focus, and the anti-inflammatory effect can inhibit the development of local focus inflammation, so as to achieve the purpose of eliminating edema.

The external application of mirabilite and rhubarb (EAMR) combined with intrathoracic infusion of cisplatin, as an alternative treatment for MPE, is popular in China. Despite its popularity in China, few studies have investigated its effectiveness in the management of MPE. Therefore, this prospective, randomized, controlled clinical trial aims to assess the effectiveness and safety of EAMR combined with intrathoracic chemotherapy after chest drain, and explore whether it could be a potential therapy for symptomatic MPE.

2. Materials and methods

2.1. Subject

This study was a prospective, randomized controlled clinical trial. Institutional review board approval was obtained from our ethics committee to conduct this study. (LH20160876) The participant subjects were tumor patients with MPE admitted to oncology department of our hospital from October, 2016 to March, 2019. Written informed consent was obtained from each patient. We calculated the sample size according to our primary study. We found that primary efficacy parameter of treatment group increased by 4.56, and that of the controlled group increased by 2.34. According to the formula of the rate in completely random design, $n1 = n2 = \frac{[u_{\alpha/2}\sqrt{2\bar{p}(1-\bar{p})}+u_{\beta}\sqrt{p_1(1-p_1)+p_2(1-p_2)}]}{(p_1-p_2)^2}$, among which, n1 and n2 were the number of patients in Shi-style manipulations group and the mechanical traction group respectively, $u_{\alpha/2}=1.96$ when type I error is 0.05, $u_{\beta}=1.282$ when type II error is 0.1 in two-sided tests. We recruited a total of 84 patients with 42 patients in each group. Participants were recruited patients through advertisements, websites and newspapers.

2.2. Patient selection

To be involved in this study, all the patients were required to meet the inclusion criteria as follows:

1. aged 18 to 80 years;
2. definite pleural effusion with medium or above amount confirmed by X-ray or ultrasound;
3. advanced malignant tumor with MPE confirmed by histopathology or cytology;
4. the estimated survival time is more than 3 months;
5. Karnofsky score $\geq$60, ECOG PS score $\leq$2;
6. without serious cardiac, renal, hepatic disease and other treatment contraindications;
7. chemotherapy and intrathoracic drug injection are not performed within 1 month before the treatment;
8. Sign informed consent and agree to receive treatment.

The exclusion criteria were as follows:

1. end-stage patients with cachexia and severe hypoproteinemia, or patients with Karnofsky score <60 and unable to complete 1 course of treatment;
2. Pregnant women, mental disorders and patients who do not cooperate with the treatment;
3. Taking other drugs which may affect the efficacy evaluation during the observation.

2.3. Randomization

After the screening, patients will be randomized into 2 groups with an allocation ratio of 1:1. The randomization will be generated via SPSS 20.0 software by an independent 3rd-party clinical research organization (Institute of Basic Research in Clinical Medicine, China Academy of Chinese Medical Science) and concealed from the researchers by a senior data manager who is not involved in the study.

2.4. Intervention

The real-time ultrasound-guided single-step trocar technique was our standard technique for pleural effusion drainage. The patient was maintained in semisitting, supine, or lateral oblique position according to the amount of pleural effusion and the presence of loculation. The intercostal approach was carried out in the anterior or middle posterior axillary line or in the posterior infrascapular region according to the accessibility of the pleural effusion or empyema. We used the modified Seldinger technique when the trocar technique was not successful or when the intercostal space was too narrow to accommodate the single-step trocar. A postprocedure chest x-ray was obtained for every patient. The catheter output was calculated and the drainage rate was adjusted so that the rate was not more than 1.5L in the first hour to avoid rapid lung-expansion pulmonary edema. 40 to 60 mg cisplatin was infused into patients' chest cavity after thoracic drainage in both groups. The external application of mirabilite (400 g) and rhubarb (100 g) powder (provided by Hehuang

Company) was plastered to the chest wall to the chest wall of the affected side for 28 days (8 h per day) in treatment group. Placebos are made up of simulants that have a 10% efficacy.

2.5. Outcomes

2.5.1. Primary outcome. Patient visits were performed at baseline and days 14 and 28 after treatment. The criterion of efficacy was divided into 4 categories refer to WHO standard.[11] Complete Remission (CR): effusion disappears and symptoms are relieved for at least 4 weeks; Partial Remission (PR): the effusion was reduced by more than 50% compared with that before treatment, and the symptoms were relieved and maintained for at least 4 weeks; Stable (SD): the effusion decreased by less than 50% compared with that before treatment, with no increasing trend, and the symptoms partially relieved; Invalid (PD): effusion grows rapidly. The total effective rate was $(CR + PR)/(CR + PR + SD + PD) \times 100\%$.

2.5.2. Secondary outcome. QLQ-C30 questionnaire: QLQ-C30 was developed the European Organization for Research and Treatment of Cancer (EORTC) in 1986. It is widely used to evaluate the quality of life for patients with oncology. The QLQ-C30 incorporates 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, nausea and vomiting); and a global health and quality-of-life scale. Several single-item symptom measures are also included.[15,16]

2.6. Statistical analysis

All data will be analyzed by the SPSS 20.0 statistical software (SPSS Inc., Chicago, Illinois). Efficacy and safety analyses will be conducted according to the intention-to-treat principle using the "last observation carried forward" rule. Mean standard deviation, median, quartiles and inter quartiles for continuous variables, and frequency for categorical variables will be calculated. Continuous variable followed the normal distribution will be presented as means with standard deviations (SDs) and calculated by an independent sample Student *t*-test, otherwise the data will be expressed as medians with ranges, and nonparametric tests will be used. Categorical variables will be expressed as number (%) and analyzed by χ^2 test or Fisher exact test. A *P* value of less than .05 is defined as statistical significant with 2-sided 90% confidence intervals (CIs).

2.7. Quality control

Prior to the clinical trial, we will carry out unified training to make sure all the physicians, nurses, and assessors involved fully understand the process of the trial, including selecting patient screening and selection, case report form writing and manipulation details. To guarantee the quality of the whole trial, rigorous monitoring will be performed by 3 trained quality supervisors. During the trial, supervisors checked on case report forms and intervention. The standard operating procedures (SOP) will be invariably followed. Drop-outs, withdrawals (and the reasons) and the compliance of all patients were recorded in detail throughout the treatment and follow-up period.

2.8. Safety assessments

All subjects were questioned about adverse events during the treatment at each visit, and all adverse events were analyzed, regardless of the investigators' assessments of causality. Safety was assessed by blood chemistry and complications.

3. Result

Database records of patients treated in our institution for MPE between October, 2016 and March, 2019. Based on the inclusion criteria, our study involved 84 patients who were randomized with randomization schedule into to the treatment group and control group, respectively. (Fig. 1) Figure 2 was the compliant flow diagram. All patients were successfully to complete the prescribed observation period. There were 42 patients in treatment group, including 22 males and 20 females, with 32 cases of lung cancer and 10 cases of breast cancer. The mean age was 63.7 years (range from 41–80 years). There were 42 patients in control group, including 21 males and 21 females, with 33 cases of lung cancer and 9 cases of breast cancer. The mean age was 62.5 years (range from 39–79 years). Table 1 summarizes the demographic and clinical characteristics. All the characteristics had no statistical significance ($P > .05$).

3.1. Clinical effective rate

In treatment group, 7 cases were CR, 21 cases were PR, 8 cases were SD and 6 cases were PD, respectively. In control group, 6 cases were CR, 17 cases were PR, 13 cases were SD and 8 cases were PD, respectively. The total effective rate of the patients in the treatment group (66.67%) is higher than that in the control group (54.76%), and there is statistical significance in the comparison of the total effective rate between these 2 groups ($P < .05$). (Table 2)

3.2. Quality of life questionnaire (QLQ-C30)

In treatment group, the items of Physical, Cognitive, Fatigue, Pain, Nausea, and Vomiting and Global Health were significantly improved compared with those before treatment ($P < .05$), respectively. In control group, the items of Physical, Social, Fatigue and Global Health were significantly improved compared with those before treatment ($P < .05$), respectively. Furthermore, there is statistical significance in the comparison of items of Physical (1.95 ± 0.50 vs $2.19 \pm 0.58\%$, $P < .05$), Pain (1.98 ± 0.42 vs 2.07 ± 0.32, $P < .05$) and Global Health (1.23 ± 0.64 vs $1.13 \pm 0.23\%$, $P < .05$) between these 2 groups. (Table 3)

3.3. Safety assessments

None of the patients had adverse reactions such as skin allergy and chest tightness.

4. Discussion

MPE is mainly caused by lung cancer or other chest malignant tumors. About 50% of lung cancer or breast cancer patients will have pleural effusion in the course of disease. Once MPE appears, it indicates that the primary tumor has local focus or adjacent important organ metastasis, and the chance of radical operation is lost. According to statistics, the median survival time of patients with malignant pleural effusion is only 3 to 12 months. MPE often grows rapidly and aggravates asthma which patients can seldom tolerate. In severe cases, it may be life-threatening. Therefore, for patients with MPE, it is particularly important to prolong their survival period and improve their quality of life.

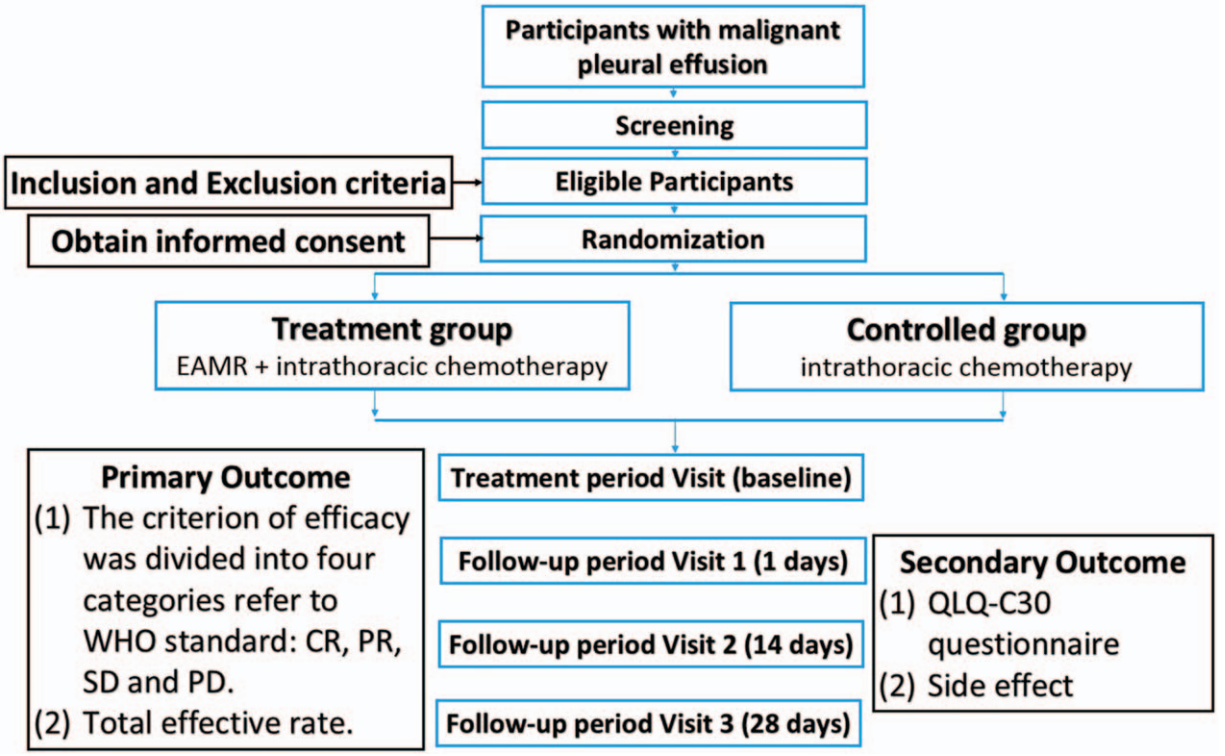

Figure 1. Flow chart.

The treatment of MPE with combination of TCM and western medicine has been widely recognized. It is not only superior to simple use of western medicine, but also has advantages in control of adverse reactions. TCM has certain characteristics and advantages in the treatment of MPE. It can enhance immunity, relieve symptoms, improve life quality, and has little side effects, which is easy for patients to accept. It can be the first choice especially for those who cannot receive chemotherapy. However, there is few relevant clinical report of large cases.[13,17,18]

Drug paste is a topical formulation unique to TCM. Like other topical formations, TCM paste relies on transdermal delivery of bioactive molecules. In recent years, TCM paste has been used to treat cancer patients, and some success has been achieved. However, due to the inefficient absorption of conventional TCM pastes, the therapeutic efficacy of TCM topical applications is limited. Thus, improving transdermal delivery of TCM is one of the important approaches to enhance the efficacy. In this study, the combination of mirabilite and rhubarb has the functions of removing blood stasis, absorbing effusion and eliminating swelling. Modern pharmacological research also confirmed that rhubarb has the effects of anti-inflammatory mainly by inhibiting the synthesis of nucleic acid and protein, sugar metabolism of bacterial cells, and leukotriene B, an important mediator of inflammation. In addition, rhubarb can constrict local damaged blood vessels, reduce capillary permeability and improve microcirculation disorders, so as to play the role of hemostasis. The swelling caused by the early inflammatory exudate can obviously be inhibited by mirabilite. It can form a hyperosmotic state locally while applied to chest, and absorb the plural effusion in the chest through osmotic pressure, thus it has a certain effect on the MPE. The two drugs complement each other to achieve better curative effect.

The general treatment of MPE in modern medicine mainly includes diuretic, fresh plasma and albumin infusion to improve plasma osmotic pressure, intraperitoneal injection of chemotherapy drugs and staphylococcin to promote the regression of plural effusion. However, simple thoracentesis and drainage can only temporarily relieve the symptoms, and the effusion will appear again soon. The use of diuretics will take away serum potassium and sodium, which can easily lead to electrolyte and acid-base balance disorder, and aggravate adverse reactions. Intrapleural chemotherapy is to inject chemotherapy drugs directly into the thoracic cavity, which can inhibit or kill the spread of cancer cells. For solid tumors, the chemotherapy drugs can only penetrate into the tumor by 1 to 3 mm, so the effect for large solid tumors is poor, and adverse reactions such as fever, nausea and vomiting, and myelosuppression will occur. Moreover, patients with MPE are often accompanied with symptoms such as asthenia, chest pain, chest distress, and the above treatment cannot effectively improve chest distress, so MPE is still an intractable disease.

Although there is no research on the treatment of MPE using mirabilite rhubarb powder, a large number of clinical studies have proved the safety and efficacy of it in treating malignant ascites, which provides theoretical and clinical basis for our study. Some author applied rhubarb-mirabilite-borneol externally in the treatment of malignant ascites and achieved good results.[19] Another study found that peritoneum, pelvic effusion and jejunal wall thickness of patients were significantly decreased after using diuretic combined with external application of mirabilite.[6] Another study also indicated that the external application of mirabilite could effectively reduce peritoneum and

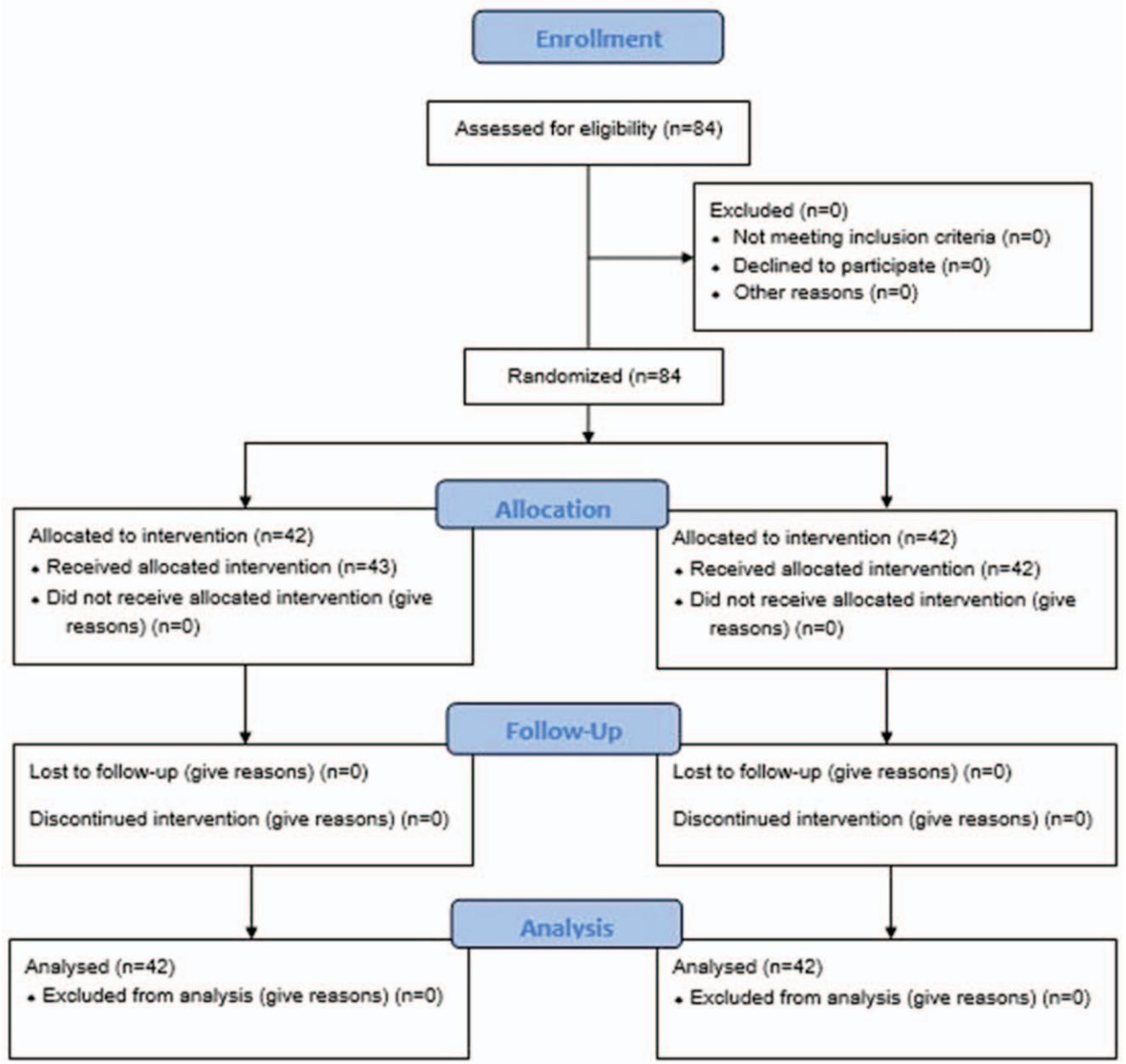

Figure 2. The compliant flow diagram.

weight of the patients with ascites, increase urine volume, and relieve abdominal distention in 8 to 10 days.[17]

The results showed that the clinical effect in treatment group was better than that of control group ($P < .05$). There is statistical significance in the comparison of items of Physical, Pain and Global Health in QLQ-C30 questionnaire between these 2 groups. Thus, the treatment efficacy of mirabilite and rhubarb powder was confirmed. The mechanism of which may be reducing the permeability of capillaries, improving the microcirculation barrier, helping to form hyperosmotic state and absorb the moisture in the chest through osmotic pressure, so as to promote the elimination of MPE.

Clinically, MPE in patients often indicates that the disease has reached a serious stage, and the rapidly increasing pleural effusion mechanically restricts the expansion of the lungs and causes great damage to the respiratory and circulatory system of the patients. Therefore, to actively control the growth of pleural effusion is an important way to prolong the survival time of malignant tumor patients and improve their quality of life. In TCM theory, pleural effusion is classified as "hanging drink". In ancient books of Traditional Chinese medicine, it is often used to "attack evil spirits" by the "water" method. The results of this study show that TCM treatment can play a role of enhancing efficacy and reducing toxicity, effectively regulate the overall physical condition of patients, and enhance patients' ability to resist diseases. Combined application with cisplatin and other chemotherapy drugs can effectively reduce the adverse reactions of drugs.

There are some confounding variables in the study. Firstly, operational process is uniformly trained by researchers.

Table 1

Demographic and Clinical characteristics.

	Treatment Group	Control Group
Age (range), years	63.7 (41–80)	62.5 (38–79)
Gender: Male	28	21
Duration of symptoms (months)	26.55 ± 8.01	25.78 ± 6.60
BMI	20.1 ± 3.12	22.1 ± 2.65
Primary Tumor		
lung	32	33
breast	10	9
Karnofsky score	68.3 ± 3.43	70.4 ± 4.19
Volume of MPE		
Small	11	11
Medium	20	22
Large	11	9
Radiation therapy	9	12
Chemotherapy	32	34
Targeted therapy	12	16

SD = standard deviation.

Table 2

Comparison of clinical efficacy between the 2 groups.

Group	CR	PR	SD	PD	Effective Rate %
Treatment Group	7	21	8	6	66.67*
Control Group	6	17	13	8	54.76

* $P < .05$.

CR = Complete Remission, PD = Invalid, PR = Partial Remission, SD = Stable.

Researchers participating in the scheme should be familiar with and master the difficult positions of the operation, and only those who pass the examination can participate in the clinical study. Secondly, poor dependence and loss of follow-up are main confounding variables. We made patients fully understand and understand the purpose, significance, methods, possible adverse reactions and corresponding treatment measures of the study, respect patients' right to know and other rights, obtain patients' consent and voluntarily sign the informed consent to be included in the clinical study. For the patients included in the clinical study, actively carry out publicity and education work, so that the patients fully cooperate with the clinical study of the diagnosis and treatment routine. Establish a complete follow-up system, such as the establishment of a follow-up clinic or a person in charge, regular follow-up, contact with patients timely, to reduce the loss of follow-up and ensure the smooth completion of the clinical study.

Table 3

Comparison of QLQ-C30 questionnaire between the 2 groups.

	Treatment Group		Control Group	
Item	Pre-	Post-	Pre-	Post-
Physical	2.54 ± 0.48	1.95 ± 0.50*,#	2.38 ± 0.62	2.19 ± 0.58*
Role	1.56 ± 0.42	1.52 ± 0.46	1.67 ± 0.32	1.64 ± 0.28
Cognitive	1.63 ± 0.38	1.55 ± 0.42*	1.53 ± 0.32	1.55 ± 0.43
Emotional	2.72 ± 0.54	2.69 ± 0.62	2.65 ± 0.64	2.67 ± 0.54
Social	1.32 ± 0.82	1.27 ± 0.64	1.56 ± 0.67	1.34 ± 0.52*
Fatigue	1.80 ± 0.78	0.76 ± 0.82*	1.81 ± 0.66	1.63 ± 0.72*
Pain	2.32 ± 0.34	1.98 ± 0.42*,#	2.28 ± 0.44	2.07 ± 0.32*
Nausea and Vomiting	1.32 ± 0.48	1.38 ± 0.54*	1.43 ± 0.67	1.32 ± 0.55
Global Health	1.18 ± 0.53	1.23 ± 0.64*,#	1.09 ± 0.43	1.13 ± 0.23*,

* $P < .05$; Compared with the 2 group.

# $P < .05$.

Compared within the group.

The current study has several limitations which could be altered in some ways to better ascertain the efficacy of this treatment. A limitation of this study is its relatively small sample size. Further expanding our sample population will allow for more meaningful statistical testing on analyzing of the measurements. Another limitation is the relative short period of intervention (28 days), which may cause the bias and less reliability of the result. Therefore, it is necessary to prolong the intervention time properly to reduce the deviation and limitation of the study results. Third, the follow-up time is short. Owing to the lack of a long-term follow-up, its long-term efficacy remains unknown.

5. Conclusion

Based on intrathoracic infusion of cisplatin, the total effective rate of treatment group using extra external application of mirabilite rhubarb powder is significantly higher than that of control group. The improvement of patients' clinical symptoms is greater in treatment group and no adverse reactions is found. Therefore, external application of mirabilite and rhubarb combined with intrathoracic infusion of cisplatin is an effective method for the treatment of MPE, which is worth popularizing.

Author contributions

Conceptualization: Lirong Gao.
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