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Treatment of Hyponatremia Induced by SCLC and SIADH with Wuling San and Tolvaptan

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Abstract

Objective: To observe the efficacy and safety of Wuling San combined with tolvaptan in the treatment of patients with hyponatremia caused by small cell lung cancer complicated by SIADH. **Methods:** A retrospective analysis was conducted on the clinical data of 10 patients with hyponatremia caused by small cell lung cancer complicated by SIADH. One group received tolvaptan alone, while the other group received Wuling San combined with tolvaptan. **Results:** The average patient age was 65.3 ± 6.6 years, with a baseline plasma sodium level of 124.6 ± 2.9 mmol/L. After three days, the Wuling San + tolvaptan group showed a significant increase to 135.2 ± 2.2 mmol/L ($P < 0.05$), with a correction time of 3.4 ± 1.1 days. The tolvaptan-alone group reached 133.1 ± 0.8 mmol/L ($P < 0.05$) in 4.8 ± 0.8 days. The correction time differed significantly between groups. No adverse events occurred in either group. **Conclusion:** Tolvaptan can rapidly improve blood sodium levels and overall physical condition. The addition of Wuling San may further shorten the time required to restore plasma sodium levels and could provide survival benefits for patients.

Keywords Small Cell Lung Cancer (SCLC); Wuling San; Hyponatremia; Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

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1 Introduction

Small cell lung cancer (SCLC) is a highly malignant type of lung cancer that often presents with various complications during disease progression. One of the common complications of SCLC is the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Its primary characteristic is an excessive and inappropriate secretion of antidiuretic hormone (ADH), leading to water retention and dilutional hyponatremia.

Hyponatremia can cause symptoms such as fatigue, nausea, vomiting, and consciousness disorders, severely affecting patients' quality of life and prognosis. Currently, various treatment options exist for hyponatremia associated with SCLC and SIADH. Tolvaptan, a novel antidiuretic hormone receptor antagonist, has demonstrated efficacy in improving blood sodium levels. Traditional Chinese medicine (TCM) also offers unique advantages in disease management. Wuling San, a classic herbal formula, has a long history of application in regulating water metabolism.

This study aims to evaluate the efficacy and safety of Wuling San combined with tolvaptan in treating hyponatremia induced by SCLC and SIADH, providing new insights and therapeutic strategies for clinical practice.

2 Materials and Methods

2.1 General Information

A retrospective study was conducted on 10 patients with small cell lung cancer (SCLC) complicated by syndrome of inappropriate antidiuretic hormone secretion (SIADH)-induced hyponatremia, who were admitted to Shouguang Traditional Chinese Medicine Hospital from January 2023 to January 2024. The patients were divided into two groups: one group received treatment with tolvaptan alone, while the other group received treatment with Wuling San combined with tolvaptan.

2.1.1 Inclusion Criteria

Patients were included if they met the following criteria. They were diagnosed with SCLC through pathological examination and met the diagnostic criteria for SIADH, which include decreased plasma osmotic pressure (<275 mOsm/kgH_2O), increased urine osmotic pressure (>100 mOsm/kgH_2O), and decreased blood sodium concentration (<135 mmol/L). Other causes of hyponatremia were excluded, and all patients provided signed informed consent.

2.1.2 Exclusion Criteria

Patients were excluded if they had severe liver or kidney dysfunction, other serious underlying diseases that prevented them from tolerating treatment, or if they were pregnant or lactating.

2.2 Treatment Methods

2.2.1 Control Group

Patients in the control group received oral administration of tolvaptan tablets (trade name Sumaca, manufactured by Zhejiang Otsuka Pharmaceutical Co., Ltd.). The dosage was 3.75 mg taken orally in the morning.

2.2.2 Treatment Group

Patients in the treatment group received tolvaptan along with Wuling San. The herbal formula consisted of 20 g of *Poria cocos*, 20 g of *Alisma zedoaria*, 20 g of *Atractylodes macrocephala*, and 10 g of *Cinnamomum cassia*. One dose was prepared per day by decocting 400 mL of water, and the solution was consumed warm in two divided doses, taken in the morning and evening.

2.3 Observation Indicators

Plasma sodium levels were measured before treatment and after three days using a fully automated biochemical analyzer. The time required to correct blood sodium levels was recorded, with plasma sodium returning to the normal range (135-145 mmol/L) as the criterion for correction. The occurrence of adverse reactions, including nausea, vomiting, diarrhea, thirst, and fatigue, was observed in both groups.

3 Results

3.1 General Information of Patients

Among the 10 patients, there were 7 males and 3 females, with an average age of 65.3 ± 6.6 years. There was no statistically significant difference ($P > 0.05$) between the two groups in terms of gender, age, and underlying conditions, indicating comparability.(Table 1)

3.2 Changes in Plasma Sodium Levels

Before treatment, the average plasma sodium levels of both groups were 124.6 ± 2.9 mmol/L. After three days of treatment, the average plasma sodium level in the treatment group increased to 135.2 ± 2.2 mmol/L, which was significantly higher than the plasma sodium levels at admission and before treatment in the control group ($P < 0.05$).

In the control group, the average plasma sodium level after three days of treatment was 133.1 ± 0.8 mmol/L, also significantly higher than the levels at admission and before treatment ($P < 0.05$). After three days of treatment, there was a statistically significant difference in plasma sodium levels between the two groups ($P < 0.05$).

3.3 Correction Time for Blood Sodium Levels

The average time for blood sodium correction in the treatment group was 3.4 ± 1.1 days, whereas in the control group, it was 4.8 ± 0.8 days. A significant difference was observed between the

Table 1 Characteristics of 10 patients with SCLC and SIADH

Characteristic	Values (total n=10）
Age (years)	65.3±6.6
Gender: (male/female)	7/3
Height (cm)	169.1±6.6
Weight (kg)	73.5±5.8
ECOG PS	
1/2/3	1/8/1
T stage	
T1/T2/T3/T4	1/4/4/1
N stage	
N0/N1/N2/N3	0/1/7/2
M stage	
M0/M1	1/9
Time to develop SIADH (months)	5.7±2.5
Plasma sodium on admission (mmol/L)	124.6±2.9

two groups ($P < 0.05$). The overall average correction time for both groups was 4.1 ± 1.1 days.

3.4 Adverse Reactions

During the treatment period, no significant adverse events were observed in either group, and all patients demonstrated good tolerance to the treatment.(Table 2)

Table 2 The effect and safety of hyponatremia correction

Characteristic	Values (total n=10）
HTS treatment time(days)	4.9±1.5
Plasma sodium levels in the treatment group after 3 days	135.2±2.2
Plasma sodium levels in the control group after 3 days	133.1±0.8
Treatment group corrects plasma sodium time	3.4±1.1
Control group corrected plasma sodium time	4.8±0.8
The average time for two groups to correct blood sodium levels in total	4.1±1.1
Adverse events	0

4 Discussion

SIADH is a common endocrine disorder in patients with SCLC[1]. Its pathogenesis is primarily due to the ectopic secretion of antidiuretic hormone (ADH) by tumor cells, leading to increased renal water reabsorption, water retention, and dilutional hyponatremia. Hyponatremia can have serious effects on the nervous and cardiovascular systems, reducing patients' quality of life and

even posing a life-threatening risk. Therefore, timely and effective correction of hyponatremia is crucial for improving the prognosis of SCLC patients.

Tolvaptan, a selective V2 receptor antagonist, specifically blocks renal tubular water reabsorption, increases free water excretion, and consequently raises blood sodium levels[2]. Its mechanism differs from traditional treatments such as water restriction and sodium supplementation, offering advantages such as rapid onset and long-lasting effects. In this study, the control group treated with tolvaptan alone showed a significant increase in plasma sodium levels after three days of treatment, confirming its therapeutic efficacy in correcting hyponatremia caused by SCLC and SIADH.

Wuling San, originating from the classical Chinese medical text *Treatise on Cold Damage*, is composed of five medicinal herbs: *Poria cocos*, *Alisma*, *Atractylodes macrocephala*, and *Cinnamomum cassia*. *Poria cocos* promotes diuresis, strengthens the spleen, and calms the heart; *Alisma* facilitates diuresis, dispels dampness, and clears heat; *Atractylodes macrocephala* strengthens the spleen and reduces dampness; and *Cinnamomum cassia* warms the meridians, promotes yang, and facilitates qi transformation[3]. Together, these herbs regulate body fluid metabolism by promoting water infiltration, warming yang, and facilitating qi transformation. Modern pharmacological research has shown that Wuling San possesses diuretic properties, regulates osmotic pressure, and improves kidney function.

In this study, the combination therapy group (Wuling San + tolvaptan) showed superior efficacy compared to the tolvaptan-alone group in terms of increasing blood sodium levels and shortening correction time. This may be due to the synergistic effects of Wuling San in regulating water metabolism and enhancing the therapeutic action of tolvaptan in treating SIADH-induced hyponatremia.

Additionally, no significant adverse reactions were observed in either group during treatment, indicating that the combination of tolvaptan and Wuling San has good safety and tolerability in treating hyponatremia caused by SCLC and SIADH. However, the sample size in this study is relatively small, and the observation period is short. The long-term efficacy and safety of Wuling San combined with tolvaptan require further validation through large-scale, multicenter clinical studies.

5 Conclusion

In summary, tolvaptan can rapidly improve the blood sodium levels and physical status of patients with hyponatremia caused by SCLC combined with SIADH. The addition of Wuling San can shorten the time to recover plasma sodium levels without increasing the incidence of adverse reactions, which may bring survival benefits to patients. This study provides a new and effective treatment for hyponatremia caused by SCLC combined with SIADH, offering certain clinical application value. However, further in-depth research is still needed to clarify its mechanism of action and the optimal treatment plan.

Article History

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