OBSERVATION ON THE EFFICACY OF GLUCOCORTICOID COMBINED WITH SHREZ/6HR IN THE TREATMENT OF PATIENTS WITH TUBERCULOUS MENINGITIS

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ABSTRACT

Objective: *To investigate the effect of glucocorticoids combined with SHREZ/6HR on patients with tuberculous meningitis.*

Methods: *Sixty-eight patients with tuberculous meningitis – admitted into our hospital from April 2016 to April 2019 – were selected as research subjects and randomly divided into a combined group (34 cases) and a control group (34 cases). Patients in the control group were treated using the traditional SHREZ/6HR regimen, and patients in the combination group were treated with glucocorticoids based on the patients in the control group. After 6 months of treatment, the clinical efficacy, adverse reactions, and cerebrospinal fluid indicators of the two groups were compared.*

Results: *The results showed that the number of significant and effective cases in the combined group was more than that in the control group, and the total effective rate of clinical efficacy was 97.06%, which was higher than 82.35% in the control group; this difference was statistically significant (P<0.05). When comparing the adverse reactions (diarrhoea, joint pain, impaired liver function, and gastrointestinal bleeding) between the two groups of patients, no statistically significant difference was found (P>0.05). Before treatment, there was no significant difference in the levels of glucose, chlorides, WBC, and Pro in the cerebrospinal fluid indexes of the two groups of patients (P>0.05). After treatment, the levels of glucose and chlorides in the cerebrospinal fluid index of the two groups of patients were higher than those before treatment, while the contents of WBC and Pro were lower than those before treatment. The difference was statistically significant (P<0.05). The chloride contents were (2.89±0.27) mmol/L and (134.76±5.73) mmol/L, which were higher than those in the control group, (2.26±0.30) mmol/L and (115.35±4.47) mmol/L. WBC and Pro content was (11.70±1.07) × 109/L and (0.36±0.31) g/L, respectively, which was lower than that in the control group, (26.44±2.78) × 109/L and (1.01±0.26) g/L; the difference was statistically significant (P<0.05).*

Conclusion: *A glucocorticoids combined with SHREZ/6HR regimen is effective in treating patients with tuberculous meningitis, and has few adverse reactions. It can clearly improve the cerebrospinal fluid index and promote the rehabilitation of patients. It has potential in clinical applications.*

Keywords: *Streptomycin, isoniazid, rifampin, ethambutol, pyrazinamide, glucocorticoid, tuberculous meningitis.*

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Introduction

Tuberculous meningitis (TBM) refers to the nonsuppurative inflammation of the brain and spinal membrane induced by mycobacterium tuberculosis. About 5–15% of the patients with extrapulmonary tuberculosis will suffer from nervous system damage, of which TBM is the most common, and affects 70% of all patients with nervous system tuberculosis[1, 2]. In recent years, owing to the increasing number of AIDS patients, the difficulties in developing anti-tuberculosis drugs, and the genetic mutation of mycobacterium tuberculosis, the incidence and mortality of TBM is increasing worldwide. At present, conventional antituberculosis treatment schemes are most-often combined with 2-4 kinds of antituberculosis drugs; however, their efficacy is not high enough and drug resistance often appears, which is not conducive to follow-up treatment[3, 4]. Glucocorticoids (GCs) are a type of corticosteroid that have anti-infection and anti-inflammatory characteristics. They can reduce the degree of brain oedema,

improve the functioning of the nervous system, and significantly improve the survival rate of patients with TBM. GCs have been widely used in TBM treatment[5]. Based on this, this study combines the traditional treatment using SHREZ/6HR with GCs to obtain improved effects.

Data and methods

General information

Sixty-eight patients with TBM - admitted to our hospital from April 2016 to April 2019 - were selected as study objects and randomly divided into the combined group (34 cases) and the control group (34 cases).

The inclusion criteria were as follows:

• Meet TBM diagnosis criteria;

• Routine and pathological examination of cerebrospinal fluid (CSF) showed tuberculous lesions, and the skin tuberculin test was positive;

• Patients had recently been diagnosed or just started treatment.

The exclusion criteria were as follows:

• Patients with severe organ dysfunctions, such as in the heart, liver, and kidney;

• Patients with autoimmune diseases or malignant tumours;

• Patients with poor compliance;

• Patients that had received other antituberculosis treatments prior to this treatment or had contraindications to the drugs used in the study;

• Pregnant and lactating women.

In the combination group, there were 16 males and 18 females, aged between 32 and 65 years, with an average age of (45.35±13.73) years; in the control group, there were 15 males and 19 females, aged between 34 and 66 years, with an average age of (45.93±13.69) years. There was no significant difference between the two groups (P>0.05). This study was approved by the ethics committee of our hospital. The family members of the patients were informed and written informed consent was obtained.

Method[6]

Patients in the control group were treated with the traditional SHREZ/6HR regimen. The SHREZ/6HR treatment involved the following - 1 month S: streptomycin (State medical permit H20053988, Jilin Jibang Pharmaceutical Co., Ltd., 4 mL: 0.2 g), intramuscular injection, 0.75 g/time, time/d, H: isoniazid (State medical permit H44020699, Guangdong South China Pharmaceutical Group Co., Ltd., 0.1 g × 100 s), taken orally on an empty stomach, 0.3 g/time, time/d, R: rifampin (State medical permit H44020771, Guangdong South China Pharmaceutical Group Co., Ltd., 0.15 g × 100 s), taken orally on an empty stomach, 0.45 g/time, time/d, E: ethambutol (State medical permit H41025288, Puyang Huiyuan Pharmaceutical Co., Ltd., 0.25 g), taken orally on an empty stomach, 0.75 g/time, time/d, Z: pyrazinamide (State medical permit H44020947, Teyi Pharmaceutical Group Co., Ltd., 0.25 g × 100 s), 1.5 g/time, time/d. After one month of treatment, HR was given for another 6 months. At the end of each month, a sputum smear examination of tubercle bacilli, renal function, liver function, blood routine examination, chest X-rays, and other examinations were carried out. Symptoms appeared and symptomatic treatment was carried out.

The patients in the combined group were treated with GCs on the basis of the patients in the control group. Methylprednisolone (State medical permit H20010098, State Medical Rongsheng Pharmaceutical Co., Ltd., 0.5 g), intravenous drip, 500 mg/d, was administered. After 7 days of impact treatment, it was changed to 80 mg/d, and according to the patient's condition, the dosage was reduced until a later period of oral maintenance dose treatment for a total of 3 months.

Observation indicators

After 6 months of treatment, the clinical efficacy, adverse reactions, and CSF indexes of the two groups were compared.

For clinical efficacy, a significant effect implies that clinical symptoms disappear completely and CSF test indicators are normal; 'effective' implies that clinical symptoms and CSF test indicators improve significantly; and 'ineffective' implies that there is no obvious change in clinical symptoms and CSF indicators remain unchanged. The total effective rate is the percentage of the sum of significant cases and effective cases in the total cases[7].

Adverse reactions include diarrhoea, joint pain, liver damage, gastrointestinal bleeding, etc.

4-5 mL of CSF was collected by lumbar puncture. The glucose content, chloride content, WBC, and Pro in CSF were measured using a glucose test, blood chlorine test, and Pan's test.

Statistical analysis

The data were processed using SPSS 22.0 software. Among them, the count data were expressed by n (%), the inter group by the x^2 test, the measure-

ment data by ($\bar{x}\pm s$), the inter group by the t-test, the clinical efficacy by the Mann-Whitney U test, where P<0.05 indicates that the difference was statistically significant.

Results

Comparison of clinical efficacy between the two groups

The results demonstrated that the number of significant and effective cases in the combined group was more than that in the control group, and the total effective rate of the clinical effect was 97.06%, higher than 82.35% in the control group; the difference was statistically significant (P<0.05), as shown in Table 1.

Group	Cases	Significant effect	Effective	Ineffective	Total effective
Combined group	34	9(26.47)	24(70.59)	1(2.94)	33(97.06)
Control group	34	7(20.59)	21(61.76)	6(17.65)	28(82.35)
Z/χ^2	-	–4.533			3.981
P	-	<0.001			0.046

Table 1: Comparison of clinical efficacy between the two groups n (%).

Comparison of adverse reactions between the two groups

The results showed that there was no significant difference between the two groups in the occurrence of adverse reactions (diarrhoea, joint pain, liver function damage, gastrointestinal bleeding, etc.) (P>0.05), as shown in Table 2.

Group	Cases	Diarrhoea	Joint pain	Liver function damage	Gastrointestinal bleeding
Combined group	34	3 (8.82)	6 (17.65)	5 (14.71)	2 (5.88)
Control group	34	4 (11.76)	8 (23.53)	7 (20.59)	4 (11.76)
$\chi 2$		0.159	0.360	0.405	0.731
P		0.69	0.549	0.525	0.393

Table 2: Comparison of adverse reactions between the two groups.

Comparison of cerebrospinal fluid indexes between the two groups

Before treatment, there was no significant difference in the content of glucose, chloride, WBC, and Pro in CSF between the two groups (P>0.05). After treatment, the content of glucose and chloride in CSF of the two groups were higher than those before treatment, while the content of WBC and Pro were lower than those before treatment; the difference was statistically significant (P<0.05). The content of glucose and chloride in the combined group were (2.89±0.27) mmol/L and (134.76±5.73) mmol/L, respectively, higher than those in the control group, (2.26±0.30) mmol/L and (115.35±4.47) mmol/L. The content of WBC and Pro were (11.70±1.07) × 109/L and (0.36±0.31) g/L, respectively, which were lower than those of the control group, (26.44±2.78) × 109/L and (1.01±0.26) g/L; the difference was statistically significant (P<0.05), as shown in Table 3.

Group	Time	Glucose (mmol/L)	Chloride (mmol/L)	WBC (×109/L)	Pro (g/L)
Combined group	Before treatment	1.25±0.18	108.84±6.41	305.90±35.47	3.31±0.44
	After treatment	2.89±0.27	134.76±5.73	11.70±1.07	0.36±0.31
	t1 value	29.469	17.579	48.342	31.959
	P1 value	<0.001	<0.001	<0.001	<0.001
Control group	Before treatment	1.27±0.20	107.32±4.91	295.51±37.15	3.21±0.61
	After treatment	2.26±0.30	115.35±4.47	26.44±2.78	1.01±0.26
	t1 value	16.010	7.052	42.115	19.346
	P1 value	<0.001	<0.001	<0.001	<0.001
Comparison between groups before treatment	t2 value	0.433	1.098	1.179	0.775
	P2 value	0.666	0.276	0.242	0.441
Comparison between groups after treatment	t3 value	9.102	15.574	28.853	9.368
	P3 value	<0.001	<0.001	<0.001	<0.001

Table 3: Comparison of CSF indexes between the two groups ($\bar{x}\pm s$).

Note: t1 and P1 are the intra-group comparison test values; t2 and P2 are the before-treatment inter-group comparison test values; t3 and P3 are the after-treatment inter-group comparison test values.

Discussion

TBM is a severe nervous system disease induced by mycobacterium tuberculosis[8]. Patients often show signs of positive meningeal stimulation, poor spirit, loss of appetite, general weakness, vomiting, headache, fever, along with several other symptoms. To a certain extent, brain herniation, epileptic attacks, comas, limb paralysis, diplopia, and other symptoms of brain parenchyma and nerve involvement can occur. Imaging examinations show specific inflammatory exudate in the brain. Some patients can experience combined tumour-like lesions or tuberculosis[9]. The treatment of TBM is complex.

If it is not treated in a timely manner, it can cause serious complications such as cerebral infarction, obstructive hydrocephalus, and arachnoid adhesion, threatening the lives of patients[10].

At present, the treatment of the disease often requires early administration of drugs, rational drug selection, combined medication, and systematic treatment. As long as the clinical symptoms, physical signs, and laboratory examination of the patients highly suggest the presence of the disease, anti-tuberculosis treatment should be started immediately; however, there is a lack of a consolidated treatment plan[11]. Drugs that can easily pass through the blood CSF barrier should be chosen, along with those that can maintain a high level in the CSF. At present, the commonly used scheme is SHREZ/6HR (s-streptomycin h-isoniazid r-rifampin e-ethambutol z-pyrazinamide), but because streptomycin and ethambutol pass through the blood CSF barrier quite easily and often come with symptoms such as poor vision and renal function damage, the effect is unsatisfactory[12].

GCs are a type of strong antiviral and anti-infective hormone synthesized and secreted by adrenocortical cells, which can reduce the release of leukocytes and inhibit the secretion of inflammatory factors, weakening the damage to inflammatory cells and improving local/systemic inflammatory response[13]. According to Zhang et al.[14], glucocorticoids can obviously absorb and dissipate the inflammatory exudation in TBM, reduce the degree of brain oedema, reduce the intracranial pressure, and alleviate toxicity.

Wasserman et al.[15] reported that the dynamic observation of the changes in the CSF index is conducive to the early diagnosis and evaluation of the efficacy of TBM. In general, when TBM occurs, owing to the damage to the intracranial blood-brain barrier, its permeability decreases, and some macromolecular proteins (Pro) flow into CSF, resulting in the increase of Pro content in CSF, change its permeability, and decrease the sodium chloride (NaCl) content; therefore, the change in Pro and NaCl content reflects the degree of damage to the blood-brain barrier. In addition, during the onset of TBM, owing to the infection of mycobacterium tuberculosis, the level of leukocytes is increased abnormally, and necrotic cells increase the secretion of glucolytic enzyme, which reduce the glucose content.

The results of this study showed that, in comparison to patients treated with SHREZ/6HR only, patients also treated with GCs had better clinical efficacy, fewer adverse reactions, and better recovery of their CSF index. This shows that GCs can reduce the inflammatory response, reduce the degree of brain oedema, reduce the intracranial pressure, accelerate the repair of the blood-brain barrier, and promote recovery from the disease.

In summary, GCs, in combination with the SHREZ/6HR regimen, have a definitive effect on patients with TBM, and have fewer adverse reactions. This can significantly improve the cerebrospinal fluid index and promote the rehabilitation of patients. It has a high potential for clinical application.

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