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Original Article

Efficacy of aerosol inhalation of dexamethasone and ambroxol hydrochloride in preventing lung infection in patients with severe neurosurgical condition

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Abstract: Objective: This study aimed to investigate the efficacy of aerosol inhalation of dexamethasone and ambroxol hydrochloride (AH) in preventing lung infection in patients with severe neurosurgical condition. Methods: Patients were treated with either inhalation of dexamethasone and AH (study group, n=60) or α-chymotrypsin (control group, n=60). Results: After treatment, patients in the study group had greater levels of arterial blood gas markers and interferon-γ, and total effective rate than the control group (all P<0.05). Furthermore, patients in the study group had lower interleukin-4, interleukin-6, and interleukin-10 levels, shorter time for symptom disappearance, and lower lung infection rate (all P<0.05). Conclusion: Aerosol inhalation of dexamethasone and AH can reduce lung infection rate, decrease inflammatory response, and accelerate improvement of the condition in patients with severe neurosurgical diseases.

Keywords: Aerosol inhalation, dexamethasone, ambroxol hydrochloride, neurosurgical, lung infection

Introduction

Neurosurgery is a field full of high-risk tasks. It often deals with diseases such as intracranial tumor, craniocerebral injury, cerebral infarction, and hemorrhagic stroke. The condition is usually severe in patients and often requires surgical treatment. Due to various invasive operations, incidence of complications is high during patients' hospitalization, and the most common complication is lung infection.

Wu et al. have reported that factors relating to lung infection in neurosurgical patients may include ward environment, nutrition condition, history of smoking, invasive operation, tracheotomy, and age. This complication not only prolongs hospital length of stay and increases medical expenses but also inflict psychological burdens on patients and their family members. Therefore, finding an effective way to prevent lung infection in neurosurgical patients has now become a popular clinic topic [1, 2]. As regular treatments for lung infection, sedation, intracranial decompression, hypothermy, and oxygen therapy are often used in clinic settings. However, there are some limitations to these treatments, as they can only achieve fair results and cannot effectively reduce the incidence of lung infection. In a study by Jin et al., the combined use of dexamethasone and ambroxol hydrochloride (AH) by aerosol inhalation has been reported to have excellent results in treating senile pneumonia [3]. Therefore, in our study, 120 patients were chosen with severe neurosurgical condition who were administered these two agents through inhalation to prevent lung infection. Patients' clinical data were analyzed prospectively with the aim of finding a scientific preventive method against lung infection in neurosurgery.

Materials and methods

Baseline data

The study was approved by the Ethics Committee of the Qingdao Center Hospital, and informed consent was obtained from all patients and their family members. A total of 120 pa-

Table 1. Baseline data

	Study group (n=60)	Control group (n=60)	t	P
Sex (n, %)			0.1389	0.7094
Male	37 (61.67)	35 (58.33)		
Female	23 (38.33)	25 (41.67)		
Mean age (year)	59.6±5.6	59.7±5.6	0.0978	0.9223
Mean sputum volume (mL)	9.26±2.66	9.21±2.96	0.0973	0.9226
Tracheotomy (n, %)			0.1410	0.7073
Yes	36 (60.00)	38 (63.33)		
No	24 (40.00)	22 (36.67)		
Disease type (n, %)			2.7475	0.2532
SAH	18 (30.00)	19 (31.67)		
sTBI	25 (41.67)	23 (38.33)		
Postoperative stroke	17 (28.33)	18 (30.00)		

Note: SAH, subarachnoid hemorrhage; sTBI, severe traumatic brain injury.

tients with severe neurosurgical condition who were treated in Qingdao Center Hospital were chosen for this study. The study period was between June 2015 and June 2018. According to a random number table, patients were assigned to either a study group or a control group of 60 each. In the study group, the female to male ratio was 23:37, the age range was 46-72 years (59.6±5.6 years), and sputum volume was 6.25-12.26 mL (9.26±2.66 mL). Of these patients, 36 underwent tracheotomy while 24 did not. The numbers of cases of subarachnoid hemorrhage (SAH), severe traumatic brain injury (sTBI), and postoperative stroke were 18, 25, and 17 respectively in this group. In the control group, the female to male ratio was 25:35, the age range was 48-70 years (59.7±5.6 years), and sputum volume was 6.38-12.15 mL (9.21 ±2.96 mL). Of these patients, 38 underwent tracheotomy whereas 22 did not. The numbers of cases of SAH, sTBI, and postoperative stroke were 19, 23, and 18 respectively. There were no intergroup differences in the baseline data (all P>0.05), so the results of the two groups are comparable a shown in **Table 1**.

Inclusion criteria: 1) Patients who met the diagnostic criteria for SAH, sTBI, and postoperative stroke as defined by *Neurosurgery* (People's Medical Publishing House Co., Ltd., China, 2014); 2) Patients with Glasgow coma scale (GCS) score ≥6; 3) Patients who were hospitalized for over 2 weeks; 4) Patients who were stabilized.

Exclusion criteria: 1) Patients with GCS score ≤5.9; 2) Patients underwent some relevant treatments before this study; 3) Patients who had liver, kidney, or other organ dysfunctions; 4) Patients who had heart failure or malignant tumor; 5) Women during lactation or pregnancy; 6) Patients with mental illness or communication disorder; 7) Patients who were allergic to the medications in this study; 8) Patients with other lung diseases.

Methods

All participants received symptomatic treatments including sedation, intracranial decompression, hypothermia, and oxygen therapy.

In the control group, patients were given aerosol inhalation of α-chymotrypsin at a dose of 4,000 units (manufacturer: SPH No.1 Biochemical & Pharmaceutical Co., Ltd., China; package: 4,000 units) mixed with 20 mL 0.9% NaCl solution. Patients put their lips and teeth tightly around the mouthpiece and inhaled and exhaled slowly. The oxygen flow rate was 2-4 L/min. The therapy was given 3 times a day, with 15 minutes for each session, and the course of treatment was 7 days.

In the study group, patients inhaled aerosol of 10 mg dexamethasone (manufacturer: Sinopharm Rongsheng Pharmaceutical Co., Ltd., China; package: 1 mL, 5 mg) and 30 mg AH (manufacturer: Chengdu Baiyu Pharmaceutical Co., Ltd., China; package: 4 mL, 30 mg) mixed with 20 mL 0.9% NaCl solution. Patients put their lips and teeth tightly around the mouthpiece and inhaled and exhaled slowly. The oxygen flow rate was 2-4 L/min. The therapy was given 3 times per day, with 15 minutes for each session, and the course of treatment was 7 days.

Outcome measures

Arterial blood gas (ABG) markers: Levels of partial pressure of oxygen (PaO_2), partial pressure of carbon dioxide (PCO_2), oxygenation index (PaO_2/FiO_2), and oxygen saturation (SaO_2) were measured in patients before and after treatment using an automated blood gas analyzer

Table 2. Levels of ABG markers ($\bar{x}$ ± sd)

	Study group (n=60)	Control group (n=60)	t	P
PaO_2/FiO_2 (mmHg)				
BT	182.02±16.25	183.26±15.64	0.4259	0.6710
AT	329.25±12.05####	276.25±9.26####	27.0142	<0.0001
PaO_2 (mmHg)				
BT	44.26±6.28	44.33±6.18	0.0615	0.9510
AT	63.28±8.62####	50.26±7.13####	9.0154	<0.0001
SaO_2 (%)				
BT	80.06±6.25	80.05±6.17	0.0088	0.9930
AT	97.26±2.16####	84.26±1.26####	40.2687	<0.0001
PCO_2 (mmHg)				
BT	33.26±3.25	34.25±3.18	1.6865	0.0943
AT	42.62±2.14####	37.26±3.05####	11.1433	<0.0001

Note: BT, before treatment; AT, after treatment; PaO_2, partial pressure of oxygen; PCO_2, partial pressure of carbon dioxide; PaO_2/FiO_2, oxygenation index; SaO_2, oxygen saturation; ####P<0.0001 vs. the value before treatment within the same group.

(model: GEM; supplier: Nanjing Liaicheng Trade Co., Ltd.).

Serum inflammatory cytokines: Before and after treatment, 5 mL of venous blood sample was taken from each subject who was on an empty stomach. The samples were centrifuged at 3,000 rpm for 5 minutes. The blood serum was then isolated, and values of interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-10 (IL-10), and interferon-γ (IFN-γ) were measured by ELISA. All reagents were provided by Shenzhen iCubio Biomedical Technology Co., Ltd. Tests were performed according to the instruction manuals.

Time taken for symptom disappearance: Time taken for symptom disappearance include time for disappearance of breathing difficulty and disappearance of moist rale in lung.

Clinical effects: After treatment, if patients had no intermittent cough and sputum, and their work and life were not affected, it could be concluded that the treatment was markedly effective; if the cough frequency and sputum volume decreased significantly during the day and night, and patients' work and life were almost not affected, it could be concluded the treatment was effective; if the cough was severe, the sputum volume was large, and patients' work and life were much affected, it could be concluded that the treatment was ineffective. The total effective rate was the sum number of effective treatment and markedly effective treatment divided by the total number of cases [4].

Incidence of lung infection: Criteria for determining lung infection were as follows: patients had symptoms of breathing difficulty, cough, sputum, and fever; moist rale or dry rale appeared in one side or both sides of lung; X-ray result showed a noticeable thickening of lung markings, presence of exudative lesion with or without pleural effusion, and an evident increase in white blood cell ratio [5, 6].

Statistical analysis

Statistical software SPSS 24.0 was applied for data analysis. The measurement data are expressed as mean ± standard deviation; independent t-test was performed for independent samples; before versus after comparison within the group was conducted by paired t-test. The count data are expressed as number or percentage (n, %) and examined by χ^2 test. The α-level was set at 0.05.

Results

Baseline data in the two groups

No intergroup differences were observed in age, gender, sputum volume, disease type, and the number of tracheotomy (all P>0.05, **Table 1**).

Results of ABG test in the two groups

Results of t-test showed that there were no intergroup differences in the levels of ABG markers before treatment (all P>0.05), however, after treatment, values of these markers in the study group were much higher than those in the control group (all P<0.05) as shown in **Table 2**.

Levels of serum inflammatory cytokines in the two groups

Results of t-test showed that there were no differences between the two groups in the levels

Table 3. Levels of serum inflammatory cytokines in the two groups ($\bar{x}$ ± sd)

	Study group (n=60)	Control group (n=60)	t	P
IL-4 (pg/mL)				
BT	84.26±5.16	84.91±5.24	0.6846	0.4949
AT	61.02±3.26####	70.66±4.13####	14.1917	<0.0001
IFN-γ (pg/L)				
BT	45.26±2.25	45.31±2.31	0.1201	0.9046
AT	56.89±3.98####	50.06±2.97####	10.6534	<0.0001
IL-10 (pg/mL)				
BT	8.78±1.26	8.77±1.25	0.0436	0.9653
AT	6.25±0.62####	7.24±0.52####	9.4767	<0.0001
IL-6 (pg/mL)				
BT	65.57±5.17	65.66±5.22	0.0949	0.9246
AT	44.26±3.18####	52.62±3.28####	14.1747	<0.0001

Note: BT, before treatment; AT, after treatment; IL-4, interleukin-4; IL-6, interleukin-6; IL-10, interleukin-10; IFN-γ, interferon-γ; ####P<0.0001 vs. the value before treatment within the same group.

Table 4. Clinical effects in the two groups

	Markedly effective (n)	Effective (n)	Ineffective (n)	Total effective rate (n, %)
Study group (n=60)	24	34	2	58 (96.67)
Control group (n=60)	19	25	16	44 (73.33)
χ^2				12.8105
P				0.0003

of serum inflammatory cytokines before the treatment (all P>0.05), however, after treatment, the study group had much lower levels of IL-4, IL-6, and IL-10 and a much higher level of IFN-γ than the control group (all P<0.05) as shown in **Table 3**.

Clinical effects in the two groups

The total effective rate in the study group was much higher than that in the control group (96.67% vs. 73.33%, P<0.05) as shown in **Table 4** and **Figure 1**.

Time taken for disappearance of clinical symptoms in the two groups

The time taken for disappearance of lung moist rale and breathing difficulty in the study group was much shorter than that in the control group (both P<0.05) as shown in **Table 5**.

Lung infection rate in the two groups

The study group had a much lower incidence of lung infection than the control group (2 cases, 3.33% vs. 18 cases, 30.00%, both p<0.05, χ^2=13.9636, p=0.0002) as shown in **Figure 2**.

Discussion

Compared with healthy normal people, neurosurgical patients often experience some levels of decreased functions in various organs and tissues. The reduced immune function, weakened swallowing function caused by consciousness disorder, and irritation caused by tracheal injury can all markedly increase lung infection rate [7, 8]. Currently, it is believed in clinic that neurosurgical lung infection can be caused by the following reasons. First, surgery increases the excitability of sympathetic nerves, which can lead to an imbalance between β-adrenergic receptor and α1-adrenergic receptor, and fluid exudation, thus causing stress-induced pulmonary edema and increasing lung infection rate. Second, due to weakened cough reflex, long-term bedridden situation, and consciousness disorder in most neurosurgical patients, retention of sputum can occur, which is likely to cause lung infection and respiratory distress syndrome [9-11]. Moreover, patients with lung infection can have reduced pulmonary function and blood oxygen level, and an aggravation of cerebral edema and injury, which forms a vicious cycle [12, 13].

In this study, the total effective rate was higher in the study group than in the control group. This might be due to the fact that dexamethasone is a type of corticosteroid medication with functions against rheumatism, allergy, virus, and infection, and through aerosol inhalation, dexamethasone can effectively relieve symptoms such as mucosal hyperemia, exudation, and edema, which inhibits inflammation to some extent and promotes recovery [14, 15]. The study group had much lower levels of IL-4, IL-6, and IL-10 and a much higher level of IFN-γ than the control group. This result might be caused by the fact that AH can improve ciliary

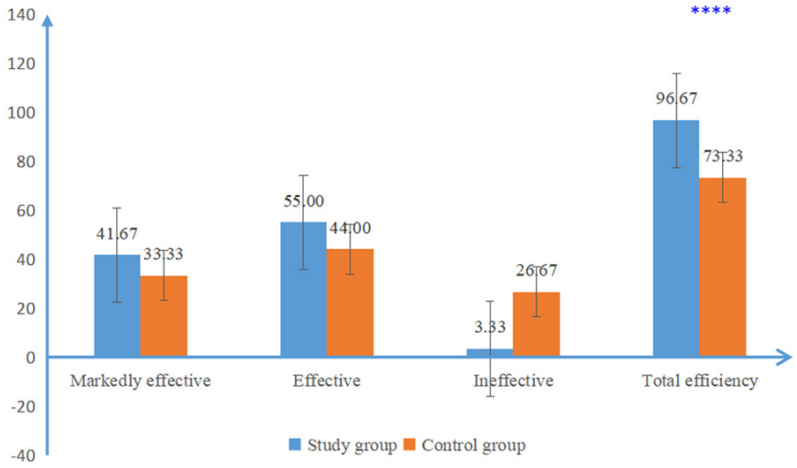

Figure 1. Comparison of clinical effects in the two groups. The difference in total effective rate between the two groups is statistically significant, ****P<0.001.

Table 5. Time taken for disappearance of clinical symptoms in the two groups ($\bar{x}$ ± sd)

	Time for disappearance of breathing difficulty (day)	Time for disappearance of moist rale in lung (day)
Study group (n=60)	1.52±0.26	3.25±0.68
Control group (n=60)	2.68±0.36	5.14±1.26
t	20.2339	10.2249
P	<0.0001	<0.0001

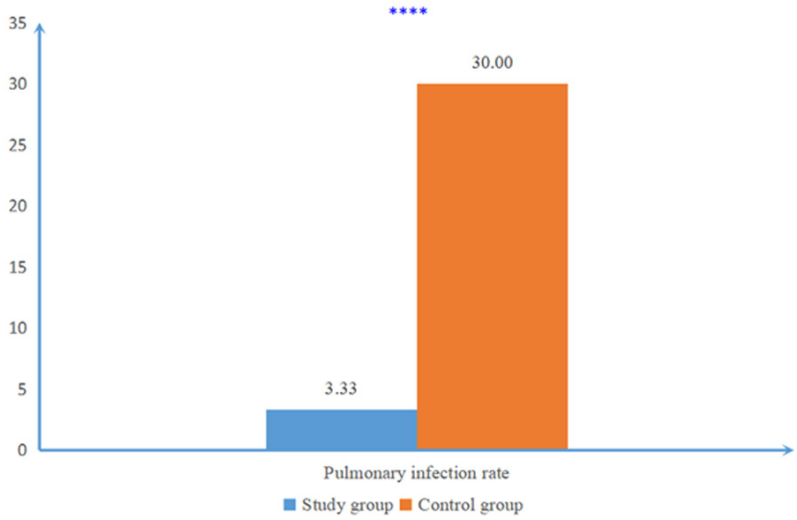

Figure 2. Comparison of lung infection rate in the two groups. The difference between the two groups in lung infection rate is statistically significant, ****P<0.001.

movement and promote synthesis of surface-active materials so that the secretion function of bronchial mucosa can be significantly improved. Also, AH can decrease alveolar surface tension, effectively avoid alveolar shrinkage and oxidative injury in lung, and markedly reduce the inflammatory response in human body [16-18]. Compared with the control group, the study group had much higher levels of ABG markers, shorter time for symptom disappearance, and lower lung infection rate. This outcome may be because aerosol inhalation, as a key administration method for treating neurosurgical patients, can work directly on alveolus pulmonis and terminal bronchiole in the respiratory system, thus increasing the local concentration of the drug. The method is time-saving, easy to operate, and has excellent effects [19, 20]. The combined use of dexamethasone and AH by aerosol inhalation can noticeably relieve bronchospasm, promote expectoration of sputum and respiratory secretion, and improve respiratory ventilation. In a study by Zhang et al., the total effective rate in the study group was much greater than that in the control group (95.3% vs. 65.7%), which is consistent with the result of our study [21]. The findings demonstrated that the combined use of dexamethasone and AH by aerosol inhalation is feasible and effective in preventing lung infection and can be used as a preferred prophylactic treatment.

However, due to the small sample size and short study period, there are still some limitations to this study in terms of evaluating the

long-term effects of the aerosol inhalation of dexamethasone and AH on preventing lung infection in neurosurgical patients. Therefore, a prospective multi-center randomized trial with a larger sample size is necessary for further verification.

In conclusion, the combined use of dexamethasone and AH by aerosol inhalation can effectively prevent lung infection in patients with severe neurosurgical condition, reduce inflammatory response, and decrease the release of inflammatory mediators. Moreover, the aerosol inhalation can avoid the adverse effects caused by other modes of administration including oral administration and intravenous infusion. The aerosol inhalation of dexamethasone and AH is safe and effective, and can be recommended for clinical application.

Disclosure of conflict of interest

None.

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