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Clinical efficacy of treatment with high-dose naloxone in comatose patients in the emergency medicine department

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Abstract: This study examines the clinical efficacy of high-dose naloxone in comatose emergency patients, focusing on its ability to enhance brain metabolism and reduce oxidative stress. A total of 120 patients were randomly assigned to a control group, which received conventional naloxone doses, and a study group, which received higher doses. Key outcomes measured included clinical efficacy, time to awakening, blood gas indices, inflammatory factors, consciousness level, neurological recovery and adverse effects. The study group showed a higher response rate (96.67% vs. 83.33%), regained consciousness more quickly, and had better blood gas indices and glasgow coma scale (GCS) scores ($p<0.05$). Neurological function recovery was superior in the study group, with fewer adverse reactions (6.67% vs. 20.00%, $p<0.05$). These results suggest that high-dose naloxone significantly improves treatment outcomes, enhancing wakefulness, reducing inflammation, and improving prognosis in emergency comatose patients, making it a promising option for clinical use.

Keywords: Emergency medicine, coma, high-dose naloxone, clinical efficacy.

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INTRODUCTION

Coma is a critical and frequently encountered condition in emergency medicine, characterized by the suppression of the brainstem reticular formation and the metabolic capacity of the human cortex, leading to disturbances in sensory or self-consciousness (Won *et al*., 2023; Boursin *et al*., 2018; Smith and Han, 2019). Approximately 4% of emergency department cases involve coma, often resulting from cardiovascular, cerebrovascular, toxic, and other diseases (Gravesteijn *et al*., 2020). Coma patients may exhibit impaired consciousness and unresponsiveness to stimuli while maintaining respiration and heartbeat. Clinically, coma is classified into intracranial and extracranial causes and further divided into mild, moderate, severe and excessive categories based on severity (Qureshi and Qureshi, 2018; Kim KT *et al*., 2022). The high incidence and morbidity associated with coma impose significant economic burdens on families and communities.

The duration of coma correlates with increased mortality and long-term recovery challenges, highlighting the need for effective interventions to prevent irreversible brain damage and promote early patient awakening (Kochanek *et al*., 2019; Iftikhar *et al*., 2020; de Cassia *et al*., 2022). Clinical experience indicates that first aid measures for comatose patients should prevent brain function damage and facilitate early awakening to restore neurological function and improve prognosis (Reznik *et al*., 2020).

Current emergency treatments focus on ensuring open airways, providing oxygen, restoring fluid balance and implementing causative therapy (Jimenez *et al*., 2019). However, these approaches often yield unsatisfactory outcomes. Naloxone, a synthetic opioid receptor antagonist with a molecular composition like morphine, can rapidly penetrate the blood-brain barrier and block central opioid receptors. It achieves peak effects within 1-3 minutes after administration, with a duration of around 45 minutes (Cortinez and Anderson, 2021). Naloxone's rapid metabolism and excretion minimize the risk of accumulation and adverse effects (Skulberg *et al*., 2022).

Additionally, naloxone can improve brain tissue metabolism, reduce oxidative stress, and facilitate the absorption of inflammatory factors (Kohan *et al*., 2021). This study explores the potential of high-dose naloxone in enhancing treatment efficacy for emergency comatose patients, emphasizing the need to balance therapeutic benefits with safety.

MATERIALS AND METHODS

General information

Between September 2022 and November 2023, 120 comatose patients admitted to a hospital emergency department were randomly divided into a control group and a research group, with 60 patients in each group. In the control group, there were 34 individuals aged 26 years old, with women aged 25-74 years and an average age of 49.62±5.17 years. Among them, 6 were in a deep coma, 19 in a moderate coma and 35 in a mild coma. Comas were caused by trauma in 24 cases, carbon monoxide poisoning or alcohol poisoning in 15 cases, cerebrovascular accidents in 7 cases, and other causes in 3 cases. In the study group, there were 32 males and 28 females, aged between 25 to 74 years, with an average

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age of 49.62 ± 5.17 years. Among the 32 women, aged 24 to 75 years, the average age was 49.75 ± 5.23 years. In this group, 7 were in deep comas, 16 in moderate comas, and 37 in mild comas. Causes of coma included trauma in 23 cases, carbon monoxide poisoning or alcohol poisoning in 12 cases, cerebrovascular accidents in 6 cases, and other causes in 5 cases. There was no significant difference in general data between the two groups (P>0.05).

Inclusion and exclusion criteria

Inclusion criteria: (1) patients were comatose on admission, with a Glasgow Coma Score (GCS) score <8 and a duration of coma <12 hours, with an expected survival time of >14 days; (2) patients did not have a history of allergy to naloxone; (3) Patients and their families voluntarily participated in the trial and signed informed consent (Barami K, 2024).

Exclusion criteria: (1) patients with pseudo-coma due to paralysis; (2) Pregnant or lactating women; (3) patients with diseases such as cerebral herniation; (4) patients with infections of urinary diseases; and (5) patients with severe crises after admission.

Methodology

After hospitalization, all patients received routine treatment. Based on the patients' actual conditions, diuretics and antihypertensive drugs were administered to reduce intracranial pressure, and oxygen was provided promptly to minimize intracranial pressure. Disturbances in the body's water and electrolytes were also corrected. The control group was given a regular dose of naloxone injection (Guizhou Jingfeng Injection Co., Ltd.; State Drug Permit H20064965; specification: 2ml: 2mg) for treatment.

The specific method involved administering 0.5-0.6 mg of naloxone combined with 250 ml of 5% glucose injection via intravenous drip, once daily for 14 days. The research team is given a large dose of naloxone. The study group was treated with high-dose naloxone by 1.5~2.0 mg of naloxone combined with 250 ml of glucose injection solution with a concentration of 5%, by intravenous drip, once/d, for 14 d. Approval by the experimental group naloxone at a high dose, is as follows.

Observation indicators

The clinical effects of the two groups were compared. After 3 hours of treatment, the patient's consciousness and perception were normalized and all clinical symptoms disappeared. Laboratory indexes returned to normal, indicating a clear effect. Within three days of treatment, patients showed significant improvements in consciousness and awareness and all clinical symptoms improved markedly, with some indexes returning to normal, indicating effectiveness. However, if within three days of treatment, the patient's consciousness and awareness did not recover and all clinical indexes remained unchanged or even worsened, the treatment was considered ineffective.

To compare the coma duration and blood gas indexes between the two groups, three milliliters of venous blood were drawn from each patient. The arterial partial pressure of carbon dioxide (PaCO2) and arterial oxygen pressure (PaO2) were measured using a blood gas analyzer, following the manufacturer's operating instructions.

The levels of inflammatory factors before and after treatment were compared between the two groups. Five milliliters of venous blood were collected from patients and centrifuged at 3000 r/min for 10 min. After extraction of the supernatant, the levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) were determined by enzyme-linked immunosorbent assay (ELISA).

The state of consciousness before and after treatment was compared between the two groups. The GCS scale (Chen *et al*., 2019) was applied for assessment, including three parts eye-opening response, limb movement, and speech response, and the scoring result was 3-15 points, the higher the scale score, the better the patient's state of consciousness.

Comparison of neurological function recovery between the two groups before and after treatment was assessed using the National Institutes of Health Stroke Scale (NIHSS) (Karpenko and Keegan 2021). The NIHSS evaluates 11 dimensions, including neglect, dysarthria, language, sensation, limb ataxia, lower limb movement, upper limb movement, facial paralysis, visual field, gaze, and consciousness. Higher scores indicate more severe neurological deficits, with a total score of 42. The score classifications are as follows: 0-5 is considered normal, 6-14 is mild, 15-25 is moderate, 26-30 is severe, and 31-42 is severely disabled.

The two groups of side effects were compared, including elevated blood pressure, accelerated heart rate, chest tightness and chills.

ETHICAL APPROVAL

This study was approved by the ethics committee of Shaoxing People's Hospital (2022-R-101). Signed written informed consent was obtained from the patients and/or guardians.

STATISTICAL ANALYSIS

Data analysis was performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation ($\bar{x}$ ± s), while categorical variables were presented as percentages (%). A paired t-test was used to compare continuous variables between groups, while categorical data were analyzed using the chi-square

(χ^2) test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Comparison of the clinical impact of treatment between the two groups

The total effective rate of the control group was 83.33%, while that of the study group was 96.67%. The total effective rate of the study group was significantly higher than that of the control group (P<0.05, table 1).

Comparison of coma awake time and blood gas indexes between the two groups

The coma time and recovery time of the study group were significantly shorter than those of the control group (P<0.05), PaCO2 was significantly lower than that of the control group (P<0.05), PaO2 was significantly higher than that of the control group (P<0.05, table 2).

Comparison of inflammatory factor levels before and after treatment in the two groups

There was no significant difference in the levels of inflammatory factors between the former two groups (P>0.05). However, after treatment, the levels of inflammatory factors in the latter two groups were lower than those in the control group (P<0.05, table 3).

Comparison of state of consciousness before and after treatment in the two groups

Before the GCS score difference of two groups of no statistical significance (P > 0.05). The GCS scores of the latter two groups were higher, and the GCS scores of the study group were higher than those of the control group (P<0.05, table 4).

Comparison of recovery of neurological function before and after treatment in the two groups.

There was no significant difference in the recovery of neurological function between the two groups before treatment (P>0.05). The two groups were improved after treatment, and the effect of the study group was better than that of the control group (P<0.05, table 5).

Comparison of the incidence of adverse effects between the two groups

The total adverse reaction rate of the control group was 20.00%, and that of the study group was 6.67%, significantly lower than that of the control group (P<0.05, table 6).

DISCUSSION

Coma is a severe state of consciousness impairment caused by various etiologies such as brain lesions, metabolic disorders and severe infections, leading to brain failure (Van Skike *et al*., 2019; McDonagh *et al*., 2021). The high mortality rate in comatose patients is often due to the rapid onset and delayed emergency response, particularly in cases like ventricular fibrillation and acute heart failure, where immediate intervention is crucial (Huang *et al*., 2020; Weaver, 2020). Early diagnosis and treatment can significantly improve prognosis by promptly identifying the underlying cause, whether it is due to cerebral diseases or systemic conditions like metabolic imbalances or intoxication (Malik *et al*., 2022; Zhou *et al*., 2019).

In cases of coma induced by metabolic disorders, hypoglycemia is a significant concern, especially in diabetic patients. Rapid correction of low blood glucose levels is essential to prevent irreversible brain damage and improve patient outcomes (Cabre *et al*., 2020; Lacy *et al*., 2020). Emergency treatment strategies for coma include maintaining airway patency, supporting cardiovascular function, and addressing the underlying cause through appropriate interventions like antidotes for poisoning or metabolic correction (Kesapli *et al*., 2018; Steinke *et al*., 2021).

Naloxone, an opioid receptor antagonist, is commonly used in emergency settings to treat comatose patients due to its rapid onset and ability to cross the blood-brain barrier, effectively inhibiting opioid activity and protecting brain function (Xu *et al*., 2022; Dhar *et al*., 2019). Our study demonstrates that high-dose naloxone significantly improves recovery rates and reduces time to regain consciousness compared to standard doses. The enhanced efficacy is attributed to its ability to rapidly restore cerebral metabolism, reduce intracranial pressure, and mitigate inflammation (D'Alessandro *et al*., 2021).

The study showed that patients receiving high-dose naloxone had better outcomes, including improved blood gas levels, and reduced inflammatory markers, suggesting a superior neuroprotective effect compared to traditional doses. This is likely due to its role in inhibiting harmful metabolic pathways and enhancing cerebral oxygenation (Kackell *et al*., 1975; Meskill and O'Bryant, 2020; Saari TI *et al*., 2024).

Adverse reactions to high-dose naloxone were not significantly different from the control group, indicating that it remains a safe option when used judiciously. The rapid recovery of consciousness observed in the study may contribute to minimizing potential side effects, supporting the use of high-dose naloxone as a viable treatment strategy in emergency coma cases (Langham *et al*., 2018; Morgan and Ataras, 2021).

In summary, our findings highlight the efficacy and safety of high-dose naloxone in improving clinical outcomes in comatose patients, providing a valuable tool for emergency medicine practitioners. Future research should further explore optimal dosing strategies to maximize therapeutic benefits while minimizing risks.

Table 1: Comparison of clinical effectiveness of treatment between the two groups [n (%)].

Groups	Number of examples	A conspicuous effect	Efficiently	Null	Overall effectiveness rate
Control subjects	60	19 (31.67)	31 (51.67)	10 (16.67)	50 (83.33)
Research group	60	32 (53.33)	26 (43.33)	2 (3.33)	58 (96.67)
χ^2					5.926
p					0.015

Note: p<0.05 compared to control group.

Table 2: Comparison of coma wakefulness time and blood gas indexes between the two groups ($\bar{x}\pm s$)

Groups	number of examples	Coma awake time (h)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)
Control subjects	60	43.06±5.24	47.83±5.27	72.84±7.05
Research group	60	34.52±4.07	35.06±4.15	90.63±7.71
χ^2		9.970	14.746	13.190
p		0.000	0.000	0.000

Note: *p*<0.05 compared to control group.

Table 3: Comparison of inflammatory factor values between the two groups before and after treatment ($\bar{x}\pm s$).

Groups	Number of	TNF-α (ng/L)		IL-6 (pg/L)	
Control subjects	examples	pre-treatment	post-treatment	pre-treatment	post-treatment
Research group	60	34.27±3.52	22.36±2.15*	121.06±11.43	71.39±7.86*
Groups	60	34.15±3.61	15.37±1.53*#	120.82±11.54	56.35±5.06*#
χ^2		0.184	20.518	0.114	12.463
p		0.854	0.000	0.909	0.000

Note:* p<0.05 compared to pre-treatment; # p<0.05 compared to control.

Table 4: Comparison of state of consciousness before and after treatment in the two groups ($\bar{x}\pm s$, points)

Groups	Number of examples	Pre-treatment	Post-treatment
Control subjects	60	5.06±1.16	10.15±1.53*
Research group	60	5.12±1.21	13.62±2.07*#
χ^2		0.277	10.422
p		0.782	0.000

Note:* p<0.05 compared to pre-treatment; # p<0.05 compared to control.

Table 5: Comparison of recovery of neurological function between the two groups before and after treatment ($\bar{x}\pm s$, score).

Groups	Number of examples	Pre-treatment	Post-treatment
Control subjects	60	26.37±4.26	23.12±2.01*
Research group	60	26.42±4.35	16.49±1.52*#
χ^2		0.064	20.379
p		0.949	0.000

Note: *p<0.05 compared to pre-treatment; #p<0.05 compared to control.

Table 6: Comparison of the incidence of adverse reactions in the two groups [n (%)].

Groups	number of examples	Elevated blood pressure	increased heart rate	chest distress	chills	Total incidence
Control subjects	60	5 (8.33)	2 (3.33)	3 (3.33)	2 (3.33)	12 (20.00)
Research group	60	1 (1.67)	0	2 (3.33)	11.67)	4 (6.67)
χ^2						4.615
p						0.032

Note: p<0.05 compared to control group.

CONCLUSION

In conclusion, high-dose naloxone demonstrates a significant positive effect in the treatment of comatose patients in emergency medicine. It effectively improves clinical treatment efficiency, reduces the time it takes for comatose patients to regain consciousness and enhances both blood gas levels and inflammatory factor levels. Additionally, it promotes the recovery of consciousness and neurological function, while offering a high safety profile. These benefits make high-dose naloxone a promising option for clinical application and worthy of broader implementation in emergency settings.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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