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Original Article

An analysis of the heart rates and the therapeutic effect of aminophylline injections in patients with acute cervical spinal cord injuries and bradycardia

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Abstract: Objective: To investigate the changes in the heart rates and the clinical effectiveness of aminophylline injections in acute cervical spinal cord injury (ACSCI) patients with bradycardia. Methods: This retrospective study was conducted by studying the clinical data of 100 ACSCI patients also suffering from bradycardia admitted to our hospital from June 2019 to June 2020. The patients were randomly placed into a control group (n=50) that was administered atropine therapy and a test group (n=50) that was administered aminophylline injections. The changes in the patients' heart rates and the clinical effectiveness were analyzed. Results: After the treatment, the test group had a significantly higher average heart rate, shorter heart rate recovery times, and a lower bradycardia recurrence rate than the control group (all P<0.05). The systolic blood pressure (SBP) and diastolic blood pressure (DBP) levels in the test group were significantly higher than they were in the control group (all P<0.05). Remarkably higher clinical effectiveness and satisfaction rates and a significantly lower incidence of adverse reactions were observed in the test group compared to the control group (all P<0.05). In addition, the Japanese Orthopaedic Association (JOA) cervical spine scores were similar in the two groups (P>0.05). Conclusion: For ACSCI patients also suffering from bradycardia, aminophylline injections ameliorate the clinical heart rate and have a good clinical effectiveness with few adverse reactions, so the treatment merits clinical promotion and application.

Keywords: Acute cervical spinal cord injury, bradycardia, aminophylline, heart rate, clinical effectiveness

Introduction

Previous studies have demonstrated an association between acute cervical spinal cord injuries (ACSCI) and cardiovascular diseases, such as cardiac arrest, hypotension, and the elevation of bradycardia within 2 h to 24 h after an injury [1-3]. Patients are susceptible to cardiac arrest and reflex bradycardia under hypoxia, which is correlated with the vagus nerve discharge to some extent [4-6]. Trachea stimulation is normally harmless to the sympathetic nerve pathway, and it results in heart rate and blood pressure increases to maintain a complete sympathetic reflex. However, in patients with high-level cervical spinal cord injuries, the parasympathetic nerve is well preserved as the sympathetic nerve pathway is damaged, the imbalance of which leads to bradycardia and even cardiac arrest in severe conditions [7], accounting for the fact that bradycardia and cardiac arrest are common causes of death in patients with ACSCI [8]. Atropine is the main drug for the treatment of ACSCI, the efficacy and dosage of which need to be determined by clinicians based on their relevant experience [9]. Moreover, patients may suffer adverse reactions, a poor prognosis, and a poor quality of life. Aminophylline is a medicine that can effectively relax the airway smooth muscle, enhance myocardial contractility, increase cardiac output, and expand the coronary artery, achieving a promising effect on bradycardia patients [10]. In addition, it can improve the enzymatic activity and the permeability of cell membrane ions, enhance the conductivity and self-discipline of the sinus node, and reduce or even relieve the inhibitory effect of the vagus nerve on the sinus node, thus increasing the heart rate and promoting the influx of calcium

ions to strengthen the autonomy of the atrioventricular node area and speeding up the signal transduction [11-13]. Aminophylline can significantly improve bradycardia in diseases such as acute myocardial infarction and sick sinus syndrome; however, its clinical effectiveness with ACSCI is unclear [10]. Accordingly, this study was conducted to investigate the heart rate changes and the clinical effectiveness of aminophylline injections in patients with ACSCI and bradycardia, aiming to provide a theoretical basis for the clinical treatment of ACSCI and bradycardia.

Materials and methods

General materials

This retrospective study was conducted by studying the clinical data of 100 ACSCI patients also suffering from bradycardia admitted to our hospital from June 2019 to June 2020. The patients were randomly placed into the control group (n=50) that was administered atropine therapy and the test group (n=50) that was administered aminophylline injections. Diagnostic criteria for ACSCI: (1) A clear history of trauma. (2) Neck pain and discomfort, limited mobility, various degrees of sensations in the limbs and trunk, dyskinesia, urinary and fecal dysfunction, as well as positive pathological signs and other upper motor neuron injury bodies. (3) The cervical MRI shows no significant cervical spinal cord compression. The MRIs of the spinal cord show diffuse hyperintensity on T2WI and hypointensity on T1WI, or the spinal cord within the injury segment shows limited hyperintensity on T2WI and hypointensity on T1WI. The patients and their families signed the informed consent forms. This study was approved by the Ethics Committee of the North Hebei Academy (approved No. 2018CD-2323).

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Cervical spinal cord injury without other injuries. (2) No history of aminophylline or β-receptor use before the injury. (3) No serious heart, lung, kidney, liver disease, hypertension, etc. (4) Average heart rate ung, beats/min, lasting for at least 24 h. (5) Hospital stay ≥14 d.

Exclusion criteria: (1) Patients suffering from both brain trauma and consciousness disturbances. (2) Patients also suffering from diseases that require surgical intervention such as syringomyelia and spinal cord or dural vascular malformations. (3) Patients with an unexplained progressive decline in neurological function. (4) Patients with allergies to drugs such as atropine and aminophylline.

Methods

All the patients underwent open venous access and mechanical ventilation after their admission to the ICU. Their invasive arterial blood pressure and their SpO2 levels and their electrocardiograms (ECG) were monitored using multifunctional monitors (GE company, model Dash 2500).

There were 50 patients in the control group, including 26 males and 24 females. The patients were first injected with 0.5 mg atropine (SDFA Approval Number: H20052295, manufacturer: Shenyang Xingqi Pharmaceutical Co., Ltd.), and then intravenously injected with 48 ml solution of 3 mg atropine combined with normal saline at a rate of 2 ml/h for 24 h.

The test group included 25 males and 25 females. First, 0.125 g aminophylline (SDFA Approval Number: H33021655, manufacturer: Hangzhou Minsheng Pharmaceutical Group Co., LTD.) was injected, and then 48 ml solution was prepared by mixing 0.5 g aminophylline with normal saline, which was then injected intravenously at a rate of 2 ml/h for 24 h.

Outcome measures

General clinical data: The patients' genders, ages, injury severity scores, weights, heart rates, causes of injury, and cervical spine injury segments were analyzed and compared between the two groups.

Changes in the heart rates and blood pressure levels: The changes in the heart rates and blood pressure levels after the treatment were analyzed and compared between the two groups. The heart rate recovery times (≥60 beats/min) and the bradycardia recurrence rate within 2 weeks were recorded.

Clinical effectiveness and neurological function: The clinical effectiveness rates in the two

Table 1. General clinical data of the patients in the two groups

Group		Control group (n=50)	Test group (n=50)	T/χ^2	P
Gender	Male	26	25	0.040	0.841
	Female	24	25		
Average age (years old)		44.32±7.24	44.35±7.21	0.021	0.983
Injury severity score (points)		33.89±6.38	34.02±5.73	0.107	0.915
Average weight (kg)		65.23±6.44	65.08±6.37	0.117	0.907
Average heart rate (beats/min)		43.89±5.21	43.75±5.11	0.136	0.892
Cause of injury	Falling accidents	30	29	0.046	0.977
	Car accidents	17	18		
	Collision	3	3		
Cervical spine injury segment	C_3 fracture	10	11	0.234	0.998
	$C_{3, 4}$ fracture	10	9		
	C_4 fracture	8	7		
	$C_{4, 5}$ fracture	10	10		
	C_5 fracture	7	8		
	Simple dislocation	3	3		
	No bone fracture	2	2		

groups were analyzed and compared, with a heart rate tween the two groups. The heart rate recovery times (≥60 beats/min), the JOA scores, which included motor function, and the sensory and bladder function domains, had a total possible score of 17 points. The higher the score, the better the neurological function.

The incidences of adverse reactions and the hospital stay durations: After the treatment, the abdominal distension, vomiting, constipation, and other adverse reactions in the two groups were analyzed and compared. The hospital stay and ICU stay durations were recorded.

Treatment satisfaction: The treatment satisfaction was analyzed in the form of a questionnaire, and the results were into three categories: satisfied, generally satisfied, and dissatisfied. Treatment satisfaction = satisfied + generally satisfied.

Statistical methods

In this study, SPSS 18.0 statistic software was used to process and analyze the research data. The measurement data were expressed as ($\bar{x}$ ±s) and examined using t-tests, while the count data were represented as [n (%)] and examined using Pearson chi-squared tests (theoretical frequency represented by [n (%)]) and examined using chi-squared tests (1≥ theoretical frequency <5). P<0.05 was considered statistically significant.

Results

Analysis of the general clinical data between the two groups

There were no significant differences between the two groups in terms of their general clinical data, such as ages and injury severity scores (P>0.05) **Table 1**.

Analysis of the heart rate changes in the two groups

Before the treatment, the average heart rate in the test group was (43.75±5.11) beats/min, and in the control group it was (43.89±5.21) beats/min, showing no significant difference (T=0.14, P=0.89). After the treatment, the average heart rate in the test group, (72.35±9.42) beats/min, was significantly higher than the average heart rate of (60.25±8.43) beats/min in the control group (T=6.77, P<0.001) **Figure 1**.

Analysis of the time it took for the heart rate to return to normal

In the test group, the heart rate returned to the normal range after (7.98±2.65) h. In the control

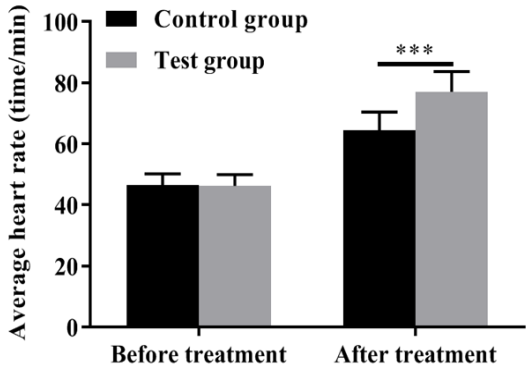

Figure 1. An analysis of the heart rate changes in the two groups. ***indicates P<0.001.

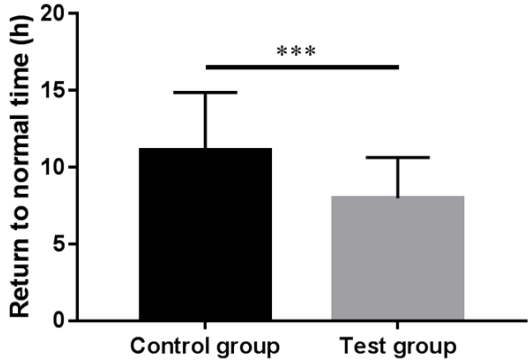

Figure 2. An analysis of the time it took for the heart rate to return to normal. ***indicates P<0.001.

Table 2. Analysis of the bradycardia recurrence rates

Group	Cases	Reoccurred Bradycardia	Bradycardia recurrence rate
Test group	50	1	2% (1/50)
Control group	50	8	16% (8/50)
X^2			5.983
P			0.031

group, the heart rate returned to the normal range after (11.11±3.74) h **Figure 2**.

Analysis of the bradycardia recurrence rates

The bradycardia recurrence rate in the test group was 2% (1/50), which was significantly lower than the 16% (8/50) in the control group (X^2=5.983, P=0.031) **Table 2**.

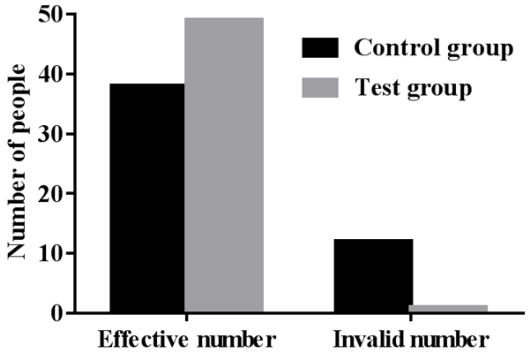

Figure 3. The clinical effectiveness of two groups of patients. Note: The abscissa from the left to the right indicates valid and invalid. The ordinate is the number of people. As shown in this figure, the number of patients experiencing clinical effectiveness in the test group was significantly higher than it was in the control group (χ^2=10.69, P=0.002).

Table 3. The JOA scores in the two groups

	Cases	2 hours after treatment	12 hours after treatment
Control group	50	6.25±1.65	10.68±3.14
Test Group	50	6.79±1.87	11.86±3.49
t		1.531	1.777
P		0.129	0.079

Analysis of the clinical effectiveness and the JOA scores in the two groups

The effective rate in the test group was 98% (49/50), significantly higher than the 76% (38/50) in the control group (X^2=10.69, P=0.002; **Figure 3**). At 2 and 12 hours after the treatment, the two groups had similar JOA scores (P>0.05) **Table 3**.

Analysis of the adverse reactions in the two groups

The incidence of adverse reactions in the test group was 4% (2/50), which was significantly lower than the rate of 20% (10/50) in the control group (X^2=6.061, P=0.028) **Table 4**.

Analysis of the blood pressure changes in the two groups

The systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the test group were sig-

Table 4. The adverse reactions in the two groups

Group	Cases	Ventosity	Vomiting	Constipation	Adverse reaction rate
Test group	50	2	0	0	4% (2/50)
Control group	50	4	3	3	20% (10/50)
X^2					6.061
P					0.028

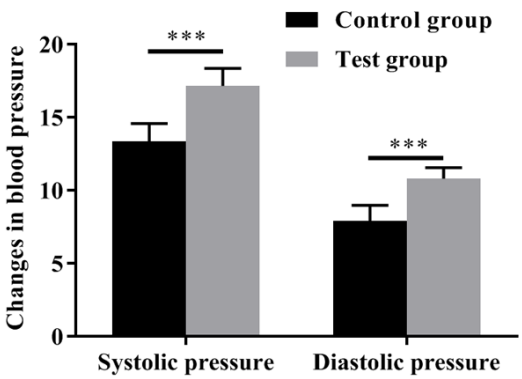

Figure 4. The changes in the blood pressure in the two groups. ***indicates P<0.001.

nificantly higher than those in the control group (16.28±1.69 *vs.* 12.48±1.72 kPa, 10.25±1.05 *vs.* 7.13±1.52 kPa; t=11.143, 11.942, P< 0.001) **Figure 4**.

Analysis of the treatment satisfaction in the two groups

The treatment satisfaction in the test group was significantly higher than the treatment satisfaction in the control group (96% (48/50) *vs.* 78% (39/50); X^2=7.162, P=0.015) **Table 5**.

Discussion

ACSCI impedes the descending sympathetic nerve pathways thereby changing the cardiovascular neuromodulation function in patients, some of whom may suffer significant sinus bradycardia and even sinus arrest in severe cases [14, 15]. Drugs, including β-suprarene receptor agonists, and atropine have been generally adopted to treat bradycardia [16]. If isoproterenol is administered, a pacemaker may be implanted depending on the patient's condition. Atropine has an inhibitory effect on vagal tone and is often used as the first choice for treating bradycardia. However, the side effects of the drug, such as constipation, ventosity, and vomiting, hinder patients' recovery [9].

Generally, bradycardia and its related symptoms may occur in patients seven days after the onset of ACSCI. The peak period of most cases is 4 days after onset, with a duration of about 7 days. The patients' heart rates will return to normal within 14 to 42 days [17]. In this study, the test group had a significantly higher average heart rate, shorter heart rate recovery times, and lower bradycardia recurrence rates than the control group (all P<0.05). Aminophylline is an asthmatic substance commonly used to treat coronary heart disease, which can enhance myocardial contractility and which exerts a positive effect on expanding the coronary arteries and increasing the cardiac output [18, 19]. Relevant clinical evidence has proved that theophylline is a receptor that can improve the intracellular cyclic adenosine monophosphate (cAMP) levels, enzyme activity, and cell ion permeability. It can increase the heart rate, relieve the vagal inhibition of the sinoatrial node, and promote faster conduction [20]. For patients with complete cervical spinal cord injuries, the possibility of bradycardia reaches 100% and the possibility of cardiac arrest is 15%, according to a study by Biering-Sørensen Fin et al. [21]. A previous study pointed out that when the heart rate of the patient is ≤50 beats/min, the cardiac output of the patient will decrease, and so will the blood flow to the tissues and organs, potentially leading to the patient's death [6]. In this study, the test group garnered significantly higher levels of SBP, DBP, a higher treatment effective rate, and a higher satisfaction rate than the control group. Aminophylline can enhance the clinical effect and treatment satisfaction by substantially improving the patient's heart rate and maintaining the patient's blood pressure, which is consistent with the results of a prior study [22]. The limitation of this study lies in its small cohort, short follow-up time, and the absence of an investigation into the effect of aminophylline treatment on patients with atropine resistance, which requires further research in future studies.

In summary, aminophylline injections improve the clinical heart rate and clinical effectiveness

Table 5. The treatment satisfaction levels in the two groups

Group	Cases	Satisfied	Generally satisfied	Dissatisfied	Treatment satisfaction
Test group	50	40	8	2	96% (48/50)
Control group	50	35	4	11	78% (39/50)
X^2					7.162
P					0.015

of ACSCI patients also suffering from with bradycardia, with few adverse reactions, so it merits clinical promotion and application.

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Disclosure of conflict of interest

None.

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