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Research Article
Therapeutic Effects of Naloxone Combined with Edaravone on Elderly Patients with Acute Cerebral Infarction

[1]Yuanyuan Chen, [1]Weiwei Heng, [1]Mengwei Hao, [1]Lechao Li, [1]Meng Xu and [2]Xiaojing Li

[1]Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical University, Xuzhou 221009, Jiangsu, China
[2]The Affiliated Suzhou Science and Technology Town Hospital of Nanjing Medical University, Suzhou 215005, Jiangsu, China

Abstract

Background and Objective: The effects of the combination of naloxone and edaravone on acute cerebral infarction (ACI), a severe cerebrovascular disease, have seldom been referred. This study aimed to assess the therapeutic effects of naloxone combined with edaravone on elderly ACI patients. **Materials and Methods:** A total of 176 ACI patients were randomly divided into control and experimental groups (n = 88) to be administered with edaravone and naloxone combined with edaravone, respectively for 2 weeks. Neurological function was evaluated by the National Institute of Health Stroke Scale (NIHSS) score. Living ability was assessed with the Barthel score. The levels of serum inflammatory factors and related markers were measured. **Results:** The total effective rate of the experimental group (92.05%) exceeded that of the control group (72.73%) ($p<0.05$). Two weeks after treatment, cerebral infarction volume and NIHSS score significantly declined and Barthel score rose in both groups, especially in the experimental group ($p<0.05$). Interleukin-6 (IL-6), IL-8, tumor necrosis factor-α, C-reactive protein, matrix metalloproteinase-9, neuron-specific enolase, S100B, ubiquitin carboxy-terminal hydrolase L1, homocysteine, Fibulin-5, thromboxane B2 and 6-keto-prostaglandin F1α levels reduced in both groups, being lower in the experimental group ($p<0.05$). Superoxide dismutase and vascular endothelial growth factor levels increased in both groups, which were higher in the experimental group ($p<0.05$). **Conclusion:** Naloxone combined with edaravone exerts obvious therapeutic effects on ACI by inhibiting inflammatory cascade and platelet aggregation, reducing cerebral infarction volume, endothelial cell adhesion and blood viscosity, promoting angiogenesis and improving neurological function and daily living ability.

Key words: Naloxone, edaravone, acute cerebral infarction, therapeutic effect, elderly, neurological function, living ability

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Corresponding Author: Xiaojing Li, The Affiliated Suzhou Science and Technology Town Hospital of Nanjing Medical University, Suzhou 215005, Jiangsu, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Acute cerebral infarction (ACI) is a cerebrovascular disease characterized by neurological dysfunction, such as hemiplegia, aphasia and sensory disturbances. Due to various reasons, the obstruction of cerebral arterial blood flow can be caused, leading to hypoxia and ischemia in local brain tissues and cerebral arteriosclerosis, so that stenosis or thrombosis occurs in the cerebral arterial lumen. Ultimately, severer stenosis or even complete occlusion of the artery is caused, thus resulting in brain tissue necrosis and loss of nerve function at the corresponding site[1]. In recent years, the incidence, fatality, disability and recurrence rates of ACI have all shown an increasing and younger trend. Therefore, it is extremely important to find therapeutic regimens with definite efficacy.

The occurrence of ACI involves many factors, including excitatory amino acid toxicity, calcium overload, free radicals, reperfusion injury, oxidative stress, apoptosis and remodelling after nerve injury. Therefore, it is crucial to block multiple links in the pathophysiological process of ACI during treatment and stroke can be well controlled by combining different therapies[2]. Currently, ACI patients are commonly treated by timely thrombolysis or thrombectomy to open blood vessels, anti-platelet aggregation and anticoagulation. Nevertheless, some patients cannot be treated with thrombolysis or thrombectomy, for whom drugs that can improve the circulation and protect nerves based on anti-platelet aggregation are suitable[3].

As an opioid receptor antagonist, naloxone can directly act on nerve cells to improve brain function and it can also activate the physiological arousal system in the human body so that the heart and cerebral vessels of patients with consciousness disorders are in a hyper-functional state, thus promoting the regain of consciousness[4,5]. Naloxone is a derivative of hydroxide hydromorphone that quickly penetrates the blood-cerebrospinal fluid barrier. With a higher affinity than that of morphine, naloxone binds morphine receptors in the brain to inhibit the action of β-endorphin, the most active endogenous opioid. Then it inactivates β-endorphin, relieves transmission failure and reverses neurological dysfunction induced by the ischemic penumbra in brain tissue areas with edema[6]. Meanwhile, naloxone increases blood flow in ischemic areas, inhibits arachidonic acid metabolism, regulates the balance of prostacyclin and thromboxane, improves microcirculation, alleviates reperfusion injury and cerebral oedema and promotes the recovery of ischemic neuronal function[7].

Edaravone is a cerebroprotective agent (radical scavenger). N-acetylaspartic acid is a specific marker of surviving nerve cells and its level plummets at the beginning of cerebral infarction. Administering ACI patients with edaravone can inhibit the decrease of local cerebral blood flow around infarct areas, giving significantly higher N-acetylaspartic acid levels than that of the control group on the 28th day after onset[8]. Edaravone can inhibit oxidative damage in brain cells through scavenging free radicals, so it is often used as a neuroprotective agent in the treatment of ACI[9,10].

Until now, the therapeutic effect and mechanism of the combination of the two drugs have rarely been reported. In the present study, therefore, 176 ACI patients treated in our hospital from May, 2017 to January, 2019 were selected as the subjects and administered with naloxone combined with edaravone and edaravone alone, respectively. Then the efficacy of the two regimens was compared and the mechanism of action was explored.

MATERIALS AND METHODS

Study area: This study was performed in Xuzhou Central Hospital, Xuzhou Clinical School of Xuzhou Medical University from May, 2017 to January, 2019.

Baseline clinical data: A total of 176 ACI patients treated in our hospital from May, 2017 to January, 2019 were selected and randomly divided into an experimental group (n = 88) and control group (n = 88) using a random number table. In the experimental group, there were 47 men and 41 women aged (68.87±1.42) years old on average. In the control group, there were 45 men and 43 women aged (69.25±1.36) years old on average. Inclusion criteria: (1) Patients meeting the diagnostic criteria for ACI and diagnosed by brain CT or Magnetic Resonance Imaging (MRI), (2) Those with new-onset ischemic stroke or a history of stroke without sequelae, (3) Those aged 60-85 years old, admitted to the hospital within 24 hrs after the onset of disease and receiving no treatment related to this study within 1 month before admission, (4) Those without allergic reactions to the drugs used and (5) Those who and whose families voluntarily participated in this study and signed the informed consent. Exclusion criteria: (1) Patients accompanied by cerebrovascular diseases or with a history of intracranial tumors, (2) Those with cerebral embolism caused by brain trauma, cerebral haemorrhage, brain parasites, brain tumors, various heart diseases or metabolic disorders, (3) Those with a neurological deficit score below 4 points or above 25 points, (4) Those who used glucocorticoids or immunosuppressants for a long time, (5) Those with lacunar cerebral infarction, (6) Those complicated with haematological diseases, hepatic dysfunction, severe cardiac insufficiency, chronic kidney disease or respiratory insufficiency, (7) Those participating in other drug trials or (8) Those who died or were transferred to another hospital within 7 days after admission.

This study was approved by the ethics committee of our hospital and family members of all patients signed the informed consent. This study was approved by the ethics committee of our hospital and family members of all patients signed the informed consent.

Methods: All patients were treated with routine treatment based on their specific conditions, including blood glucose and blood pressure control, protection of brain cells, prevention and treatment of complications and symptomatic and supportive treatment. On this basis, the patients in the control group were intravenously injected with edaravone (Sinopharm Group Guorui Pharmaceutical Co., Ltd., NMPN H20080056) twice a day (30 mg/time), based on which those in the experimental group were intravenously injected with 4 mg of naloxone (Sinopharm Group Guorui Pharmaceutical Co., Ltd., NMPN H20093198) added into 250 mL of 0.9% sodium chloride injection once a day. The treatment lasted for 2 weeks in both groups.

Assessment of related scores and therapeutic effects: At the time of admission and discharge, the patients were subjected to head CT examination and the volume of cerebral infarction before and after treatment was calculated using the Pullicino formula:

$$\text{Volume of cerebral infarction} = \text{Number of slices} \times \text{Width} \times \text{Length}/2 \text{ of CT scan}$$

The neurological function of patients was evaluated using the National Institute of Health Stroke Scale Score (NIHSS). The patient's brain nerves, level of consciousness, language and sensation and limb movement were observed and the severer the neurological deficit, the higher the score. The living ability (dressing, washing, eating, defecation and walking) of patients was assessed using the Barthel score and the severer the impairment of living ability, the lower the score. Based on the neurological function and living ability of patients, the efficacy was evaluated. Cured: Decline in NIHSS score by 91-100%, recovery of muscle strength to grade 5 and disability grade 0. Markedly effective: Decline in NIHSS score by 46-90%, recovery of muscle strength to grade 4 and disability grade 1-3. Effective: Decline in NIHSS score by 18-45% and recovery of muscle strength to grade 2-3. Ineffective: Decline in NIHSS score by 0-17% or rise in it and no obvious improvement of muscle strength or even worsening.

$$\text{Total effective rate (\%)} = \frac{\text{Cured cases} + \text{Markedly effective cases} + \text{Effective cases}}{\text{Total cases}} \times 100$$

Detection of serum indices: Fasting venous blood was drawn from every patient in the early morning before and after treatment and then the levels of serum interleukin-6 (IL-6), IL-8, Tumour Necrosis Factor-α (TNF-α), Matrix Metalloproteinase-9 (MMP-9), Vascular Endothelial Growth Factor (VEGF), Neuron-Specific Enolase (NSE), Superoxide Dismutase (SOD), S100B, Fibulin-5 and Ubiquitin Carboxy-Terminal Hydrolase L1 (UCH-L1) were detected via enzyme-linked immunosorbent assay. The levels of Thromboxane B2 (TXB2) and 6-keto-prostaglandin F1α (6-K-PGF1α) were detected via radioimmunoassay. The levels of serum homocysteine (Hcy) and C-Reactive Protein (CRP) were determined using turbidimetric inhibition immunoassay. All operations were performed by the same person in strict accordance with the instructions of the reagents and experimental instruments.

Statistical analysis: The SPSS 19.0 software was used for statistical analysis of experimental data. Quantitative data were expressed as ($\chi \pm s$) and analyzed by t-test. Numerical data were expressed as rate (n (%)) and analyzed by Chi-square Test. The $p<0.05$ was considered to be statistically significant.

RESULTS

Baseline clinical data: The data of the two groups were statistically analyzed. It was confirmed that there were no significant differences in the general data, such as average age, gender, NIHSS score, Barthel score, the incidence of comorbidities and lesion site, between the two groups ($p>0.05$) (Table 1).

Related scores and therapeutic effects: The total effective rate of treatment was 92.05% in the experimental group and 72.73% in the control group and there was a statistically significant difference ($p<0.0001$). The volume of cerebral infarction had no significant difference between the two groups before treatment ($p>0.05$), while it was significantly reduced in both groups after treatment compared with those before treatment ($p<0.0001$), significantly smaller in the experimental group than that in the control group ($p<0.0001$). Moreover, the NIHSS score and Barthel score had no significant differences between the two groups before treatment ($p>0.05$). After treatment, the NIHSS score significantly declined ($p<0.0001$), while the Barthel scores significantly rose in both groups ($p<0.0001$). The experimental group had a lower NIHSS score and a higher Barthel score than the control group and the differences were statistically significant ($p<0.0001$) (Table 2).

Table 1: Baseline clinical data

Clinical data	Control group (n = 88)	Experimental group (n = 88)	χ^2/t	p-value
Average age (year)	69.25±1.36	68.87±1.42	1.813	0.072
Gender			0.091	0.763
Male	45	47		
Female	43	41		
NIHSS score (point)	22.31±6.59	22.48±6.67	0.170	0.865
Barthel score (point)	46.18±6.27	45.83±6.14	0.374	0.709
Comorbidity (n)			0.512	0.916
Hypertension	31	33		
Hyperlipidemia	27	26		
Diabetes	21	18		
Coronary heart disease	9	11		
Lesion site (n)			0.836	0.548
Right temporal lobe	18	19		
Right parietal lobe	12	11		
Right basal ganglia	9	8		
Left temporal lobe	13	14		
Left parietal lobe	15	16		
Left basal ganglia	21	20		

Table 2: Related scores and therapeutic effects

Parameters	Control group (n = 88)	Experimental group (n = 88)	χ^2/t	p-value
Volume of cerebral infarction (cm^3)				
Before treatment	22.06±1.58	21.92±1.63	0.579	0.564
After treatment	13.81±1.17	11.25±0.84	16.673	<0.0001
NIHSS score (point)				
Before treatment	22.31±6.59	22.48±6.67	0.170	0.865
After treatment	13.36±4.15	10.57±3.28	4.948	<0.0001
Barthel score (point)				
Before treatment	46.18±6.27	45.83±6.14	0.374	0.709
After treatment	62.46±6.83	66.79±6.92	4.178	<0.0001
Total effective rate (%)	72.73%	92.05%	12.683	<0.05
Basically cured	18	25		
Markedly effective	22	33		
Effective	24	23		
Ineffective	24	7		

Table 3: Changes in serum inflammatory factors

Parameters	Control group (n = 88)	Experimental group (n = 88)	t-value	p-value
IL-6 (ng L^{-1})				
Before treatment	65.14±19.28	64.89±18.93	0.087	0.931
After treatment	30.35±4.67	21.56±3.41	14.260	<0.0001
IL-8 (ng L^{-1})				
Before treatment	158.74±25.69	161.35±25.87	0.672	0.503
After treatment	131.26±20.91	71.68±17.53	20.483	<0.0001
TNF-α (μg L^{-1})				
Before treatment	49.78±15.56	50.24±15.93	0.194	0.847
After treatment	19.21±3.87	10.85±2.94	16.136	<0.0001
CRP (mg L^{-1})				
Before treatment	55.92±12.75	56.27±12.83	0.182	0.856
After treatment	22.47±4.19	14.66±3.58	13.294	<0.0001
MMP-9 (ng mL^{-1})				
Before treatment	259.86±82.51	262.74±83.29	0.230	0.818
After treatment	218.57±66.35	179.83±61.42	4.019	<0.0001

Changes in serum inflammatory factors: The levels of serum IL-6, IL-8, TNF-α, CRP and MMP-9 had no significant differences between the two groups before treatment ($p>0.05$), while they significantly declined in both groups after treatment compared with those before treatment ($p<0.05$), lower in the experimental group than those in the control group, with statistically significant differences ($p<0.0001$) (Table 3).

Table 4: Changes in related serum markers

Parameters	Control group (n = 88)	Experimental group (n = 88)	t-value	p-value
NSE (μg L^{-1})				
Before treatment	28.07±5.23	27.86±5.15	0.268	0.789
After treatment	23.69±3.58	18.54±2.79	10.644	<0.0001
S100B (μg L^{-1})				
Before treatment	0.89±0.37	0.88±0.35	0.184	0.854
After treatment	0.46±0.18	0.21±0.09	11.653	<0.0001
UCH-L1 (μg L^{-1})				
Before treatment	0.51±0.18	0.49±0.16	0.779	0.437
After treatment	0.35±0.11	0.21±0.09	9.240	<0.0001
Hcy (μmol L^{-1})				
Before treatment	14.05±2.71	13.87±2.59	0.450	0.653
After treatment	11.23±2.35	8.42±1.68	9.125	<0.0001
Fibulin-5 (μg L^{-1})				
Before treatment	119.26±31.42	118.65±30.94	0.130	0.897
After treatment	71.38±4.95	44.12±3.06	43.942	<0.0001
TXB2 (ng L^{-1})				
Before treatment	104.21±43.67	105.18±43.95	0.147	0.883
After treatment	69.48±31.59	47.92±20.76	5.350	<0.0001
6-K-PGF1α (ng L^{-1})				
Before treatment	43.57±20.81	42.86±20.43	0.228	0.819
After treatment	30.62±17.59	22.75±11.38	3.524	0.0005
SOD (nmol L^{-1})				
Before treatment	82.16±18.54	81.78±17.92	0.138	0.890
After treatment	154.35±14.79	186.23±25.57	10.124	<0.0001
VEGF (ng L^{-1})				
Before treatment	165.43±31.96	167.18±32.27	0.361	0.718
After treatment	187.92±37.64	242.35±39.51	9.357	<0.0001

Changes in related serum markers: Before treatment, there were no significant differences in the levels of NSE, S100B, UCH-L1, Hcy, Fibulin-5, TXB2, 6-K-PGF1α, SOD and VEGF between the two groups ($p>0.05$). Compared with those before treatment, the levels of NSE, S100B, UCH-L1, Hcy, Fibulin-5, TXB2 and 6-K-PGF1α significantly declined in both groups after treatment ($p<0.001$) and they were significantly lower in the experimental group than those in the control group ($p<0.001$). After treatment, the levels of SOD and VEGF rose in the two groups compared with those before treatment, with statistically significant differences ($p<0.001$) and they were significantly higher in the experimental group than those in the control group ($p<0.001$) (Table 4).

DISCUSSION

In recent years, the incidence, fatality, disability and recurrence rates of ACI have all shown an increasing and younger trend. It is recognized that hypertension, hyperlipidemia, diabetes and atherosclerosis are closely related to ACI and the disease will develop into progressive cerebral infarction in most patients. The lesions of ACI are formed by the central necrotic area in the brain and its surrounding ischemic penumbra. At the onset of the disease, the brain cells in the necrotic area have died, which is an irreversible lesion. Ischemic penumbra can be restored if the brain tissue-protective drugs can be used as soon as possible to restore brain cell function and blood circulation[11]. Naloxone, with a similar chemical structure to morphine, can competitively bind to opioid receptors to block the binding of morphine-like substances to opioid receptors, thereby exerting its efficacy. In the treatment of ACI, naloxone directly acts on nerve cells to improve their metabolic function, thereby increasing the cerebral blood flow in patients and inhibiting the elevation in cerebral blood pressure. A large number of free radicals such as superoxide anions, fat-soluble free radicals and hydroxyl groups are produced during the process of ACI, so that oxidative damage is caused in intracellular proteins, lipids and nucleic acids, thus inducing brain cell death[12]. Edaravone is a free radical scavenger and its mechanism of action is to alleviate the damage of ischemic cerebrovascular endothelial cells, thus enhancing their tolerance to a hypoxic environment and to inhibit the peroxidation in ischemic cells, thus relieving cerebral oedema and increasing blood flow, ultimately protecting the brain nerve function and reducing the infarction area[13].

In this study, the general data had no significant differences among the subjects ($p>0.05$), so they were comparable. After treatment, the volume of cerebral infarction, NIHSS score, Barthel score and clinical total effective rate were significantly improved in both groups, more significantly in the experimental group, indicating that both naloxones combined with edaravone and edaravone alone have significant efficacy, but drug combination has a better effect. Cerebral ischemia-induced inflammatory cascade during the process of cerebral infarction is an important cause of neuronal damage in the central necrotic area and its surrounding ischemic penumbra[14]. The IL-6 derived from lymphocytes, astrocytes in brain tissue and nerve cells is a multifunctional cytokine involved in immuno-inflammatory responses. It can accelerate cell apoptosis by increasing the level of strong oxidative free radicals in body fluids, thus damaging the blood vessels of the brain. Moreover, it can also increase the level of cell adhesion molecules in the cerebrovascular intima, leading to intima lesions and inducing an inflammatory response[15]. The IL-8 derived from macrophages is a pro-inflammatory factor, which promotes the occurrence and development of cerebral arterial inflammation mainly through inducing secretion of γ-interferon by natural killer cells and lymphocytes. Moreover, it can also increase the levels of other inflammatory factors[16]. In addition, TNF-α produced by cerebral neurons and astrocytes is an important immuno-inflammatory regulator and can cause damage to the blood-brain barrier and facilitate thrombosis, whose mechanism of action is to activate polymorphonuclear leukocytes and increase the expression of cell adhesion molecules[17]. As an acute-phase reactive protein produced by hepatocytes upon the stimulus of cytokines secreted after activation of macrophages, CRP is closely related to the prediction of cardiovascular and cerebrovascular events and the occurrence and development of atherosclerosis[18]. The MMP-9 has an increased expression mainly through activation of Toll-like receptor 4 by TNF-α and IL-8 and it can amplify the inflammatory response, degrade the extracellular matrix, increase the vascular permeability and open the blood-cerebrospinal fluid barrier. As a result, vasogenic cerebral oedema is caused and neurological deterioration is enhanced[19]. The levels of serum inflammatory factors rise in patients with ACI and they are positively correlated with the volume of cerebral infarction[20]. In this study, there was no significant difference in the volume of cerebral infarction between the two groups before treatment and the levels of serum IL-6, IL-8, TNF-α, CRP and MMP-9 were also similar in both groups. After treatment, the volume of cerebral infarction was reduced and the levels of serum inflammatory factors also obviously declined. They were improved more significantly in the experimental group, consistent with the results of previous studies. The above findings suggest that naloxone and edaravone can relieve the inflammatory cascade induced by cerebral ischemia in ACI patients through directly or indirectly inhibiting the secretion and release of inflammatory factors, ultimately alleviating brain tissue damage. The combination of the two drugs had a better effect, possibly because edaravone can scavenge free radicals and inhibit peroxidation and naloxone can directly improve the metabolic function of nerve cells.

The NSE, S100B and UCH-L1 are specific markers evaluating brain neuron damage. Studies have demonstrated that due to ischemia and hypoxia, a large number of oxygen free radicals are produced in brain tissues of patients with cerebral infarction, cell membranes are damaged and blood-brain barrier function is impaired, thus worsening brain tissue damage and leading to the massive release of NSE, S100B and UCH-L1[21]. Edaravone can scavenge free radicals and stimulate the production of prostacyclin to inhibit inflammatory mediators and relieve neuron damage, thereby lowering the levels of NSE, S100B and UCH-L1. The Hcy can enhance platelet aggregation and raise blood viscosity, so the level of TXB2 is increased and thrombosis is caused, ultimately damaging the heart and cerebral vessels and leading to atherosclerosis. Fibulin-5 can bind to integrin to strengthen the adhesion of extracellular matrix and endothelial cells, thereby enhancing the cell adhesion function. Besides, TXB2 is a marker for platelet activation, able to promote platelet aggregation and vasoconstriction, while 6-K-PGF1α can dilate blood vessels. Under normal physiological conditions, there is a dynamic balance between TXB2 and 6-K-PGF1, but the TXB2 level and TXB2/6-K-PGF1α ratio will greatly rise in the case of endothelial cell damage or platelet activation[22]. The SOD can quickly eliminate the toxic superoxide radicals in the human body, exerting its anti-inflammatory effect and protecting the body from immune injury[23]. The VEGF can promote vascular endothelial cell division and vascular growth and it plays an important role in neuroprotection and angiogenesis in the ischemic penumbra in ACI[24]. According to previous literature, the serum levels of NSE, S100B, UCH-L1, Hcy, Fibulin-5, TXB2 and 6-K-PGF1α all markedly increased in patients with ACI[25]. In this study, the levels of NSE, S100B, UCH-L1, Hcy, Fibulin-5, TXB2 and 6-K-PGF1α markedly declined after treatment. It can be seen that naloxone and edaravone can reduce the levels of NSE, S100B and UCH-L1 to relieve brain damage or regulate the TXB2/6-K-PGF1α ratio via reducing Hcy, Fibulin-5 and TXB2, thereby inhibiting platelet aggregation, reducing endothelial cell adhesion and blood viscosity, increasing blood

flow and promoting blood circulation. After treatment, the levels of SOD and VEGF greatly rose. It is speculated that the two drugs may serve as free radical scavengers by increasing the level of SOD and promoting vascular endothelial cell division and angiogenesis in the ischemic penumbra by raising the level of VEGF.

CONCLUSION

In summary, doxofylline combined with budesonide in the treatment of bronchial asthma facilitates the balance of Th1/h2 in the peripheral blood of patients, down-regulates the level of Th17 cells and improve the pulmonary function of patients, with few adverse reactions. Thus, it is worthy of popularizing in clinical practice.

SIGNIFICANCE STATEMENT

This study discovers obvious therapeutic effects of naloxone combined with edaravone on elderly patients with acute cerebral infarction. This study will help the researcher to uncover the critical area of combined drug therapy that many researchers were not able to explore. Thus, a new theory on acute cerebral infarction treatment for the elderly may be arrived at.

REFERENCES

1. Bae, H.W., H.D. Kim, S.W. Choi, N. Han and M.J. Eom, 2016. Acute cerebral infarction as a rare thrombotic event in myelodysplastic syndrome: A case report. Ann. Rehabil. Med., 40: 1144-1148.
2. Yue, C., Z. Lin, C. Lu and H. Chen, 2021. Efficacy of monitoring platelet function by an automated PL-12 analyzer during the treatment of acute cerebral infarction with antiplatelet medicine. Clin. Appl. Thrombosis Hemostasis, Vol. 27. 10.1177/10760296211001119.
3. Wu, L., Y. Sun, G. Ni, B. Sun, X. Ni and S. Cai, 2021. Edaravone combined with clopidogrel is beneficial to improve efficacy, neurological impairment, and life function in acute cerebral infarction patients. Evidence-Based Complementary Altern. Med., Vol. 2021. 10.1155/2021/8030521.
4. Coffin, P.O., E. Behar, C. Rowe, G.M. Santos, D. Coffa, M. Bald and E. Vittinghoff, 2016. Nonrandomized intervention study of naloxone coprescription for primary care patients receiving long-term opioid therapy for pain. Ann. Internal Med., 165: 245-252.
5. McDonald, R. and J. Strang, 2016. Are take home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction, 111: 1177-1187.
6. Ortiz, J.F., C. Cruz, A. Patel, M. Khurana and A. Eissa-Garcés *et al*., 2021. Opioid antagonist in the treatment of ischemic stroke. Brain Sci., Vol. 11. 10.3390/brainsci11060805.
7. Lubo, L., N. Sulin, D. Zhimei and N. Houfa, 2020. Clinical efficacy and CT perfusion of puerarin combined with naloxone in the treatment of traumatic cerebral infarction. Pak. J. Pharm. Sci., 33: 423-428.
8. Watanabe, K., M. Tanaka, S. Yuki, M. Hirai and Y. Yamamoto, 2018. How is edaravone effective against acute ischemic stroke and amyotrophic lateral sclerosis? J. Clin. Biochem. Nutr., 62: 20-38.
9. Zheng, J. and X. Chen, 2016. Edaravone offers neuroprotection for acute diabetic stroke patients. Ir. J. Med. Sci., 185: 819-824.
10. Li, Q., M.J. Bi, W.K. Bi, H. Kang, L.J. Yan and Y.L. Guo, 2016. Edaravone attenuates brain damage in rats after acute CO poisoning through inhibiting apoptosis and oxidative stress. Environ. Toxicol., 31: 372-379.
11. Wo, X., J. Han, J. Wang, X. Wang, X. Liu and Z. Wang, 2020. Sequential butylphthalide therapy combined with dual antiplatelet therapy in the treatment of acute cerebral infarction. Pak. J. Med. Sci., 36: 615-620.
12. Zamani, N. and H. Hassanian-Moghaddam, 2017. Intravenous buprenorphine: A substitute for naloxone in methadone-overdosed patients? Ann. Emerg. Med., 69: 737-739.
13. Chen, Y. and Y. Zhao, 2018. Curative efficacy of penehyclidine combined with edaravone on acute cerebral infarction and their effects on serum TNF-α and NDS score in rats. Eur. Rev. Med. Pharmacol. Sci., 22: 223-228.
14. Wu, L., X. Xiong, X. Wu, Y. Ye, Z. Jian, Z. Zhi and L. Gu, 2020. Targeting oxidative stress and inflammation to prevent ischemia-reperfusion injury. Front. Mol. Neurosci., Vol. 13. 10.3389/fnmol.2020.00028.
15. Wytrykowska, A., M. Prosba-Mackiewicz and W.M. Nyka, 2016. IL-1β, TNF-α, and IL-6 levels in gingival fluid and serum of patients with ischemic stroke. J. Oral Sci., 58: 509-513.
16. Zhu, Y., Y.L. Chai, S. Hilal, M.K. Ikram and N. Venketasubramanian *et al*., 2017. Serum IL 8 is a marker of white matter hyperintensities in patients with Alzheimer's disease. Alzheimer's Dementia: Diagnosis Assess. Dis. Monit., 7: 41-47.
17. Rochfort, K.D., L.E. Collins, A. McLoughlin and P.M. Cummins, 2016. Tumour necrosis factor-α-mediated disruption of cerebrovascular endothelial barrier integrity *in vitro* involves the production of proinflammatory interleukin-6. J. Neurochem., 136: 564-572.
18. Ayas, N.T., A.J.H. Allen, N. Fox, B. Peres and M. Mehrtash *et al*., 2019. C-Reactive protein levels and the risk of incident cardiovascular and cerebrovascular events in patients with obstructive sleep apnea. Lung, 197: 459-464.

19. Guo, P., Z. Jin, H. Wu, X. Li, J. Ke, Z. Zhang and Q. Zhao, 2019. Effects of irisin on the dysfunction of blood-brain barrier in rats after focal cerebral ischemia/reperfusion. Brain Behav., Vol. 9. 10.1002/brb3.1425.
20. Chen, L., Q. Yang, R. Ding, D. Liu and Z. Chen, 2018. Carotid thickness and atherosclerotic plaque stability, serum inflammation, serum MMP-2 and MMP-9 were associated with acute cerebral infarction. Exp. Ther. Med., 16: 5253-5257.
21. Li, K., J. Jia, Z. Wang and S. Zhang, 2015. Elevated serum levels of NSE and S-100β correlate with increased risk of acute cerebral infarction in Asian populations. Med. Sci. Monit., 21: 1879-1888.
22. Guo, S.W., Y. Du and X. Liu, 2016. Endometriosis-derived stromal cells secrete thrombin and thromboxane A2, inducing platelet activation. Reprod. Sci., 23: 1044-1052.
23. Yahfoufi, N., N. Alsadi, M. Jambi and C. Matar, 2018. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients, Vol. 10. 10.3390/nu10111618.
24. Tang, S.C., C.J. Luo, K.H. Zhang, K. Li, X.H. Fan, L.P. Ning and P. Xue, 2017. Effects of dl-3-n-butylphthalide on serum VEGF and bFGF levels in acute cerebral infarction. Eur. Rev. Med. Pharmacol. Sci., 21: 4431-4436.
25. Chen L.L., G.Q. Chen, T. Yang and M.Q. Long, 2016. Effect of alprostadil combined with conventional therapy on serum markers in patients with acute cerebral infarction. J. Hainan Med. Univ., 22: 95-98.