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Original Article

Clinical effects of low molecular weight heparin (LMWH) and edaravone on acute cerebral infarction (ACI) patients with age-dependent differences analysisin hospital

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Abstract: Background: Acute cerebral infarction (ACI) is a common and frequently occurring disease with high risks affecting health. This study aims to evaluate the clinical efficacy and safety of low molecular weight heparin (LMWH) and edaravone in the treatment of ACI and evaluates the effects among different aging groups. Methods: Patients were randomly allocated to the LMWH group, edaravone group, and control group when admitted to our hospital within 24 h of stroke onset. The control group was given conventional treatment, on the basis of therapeutic regimens in control group the LMWH group received LMWH 5000 IU twice per day and the edaravone group received 30 mg edaravone once per day, for continuous 14 days. The levels of catalase (CAT) and S-100 protein of patients were determined and the Chinese stroke scale (CSS) score and Barthel index (BI) were assessed respectively. Results: No significant group difference in baseline clinical characteristics, but both LMWH and edaravone groups had significant higher CAT and S-100 levels after 14 days treatment, moreover, both CSS score and BI score of LMWH and edaravone group showed significant effects intreating ACI patients. However, no significant difference of CSS and BI values was observed between patients >60 years and ≤ 60 years indicates the safety to treat different age patients with LMWH and edaravone. Conclusion: Both LMWH and edaravone have significant clinical effects in ACI patients' treatment compare to conventional treatment, but no significant difference in clinical efficacy among them. Furthermore, these two treatments have similar effects among different-aged patients.

Keywords: Acute cerebral infarction (ACI), edaravone, low molecular weight heparin (LMWH), ages

Introduction

Acute cerebral infarction (ACI) is a common and frequently occurring disease in neurology department, with higher disability rate and case-fatality rate [1]. It is also one of the important diseases threatening middle-aged and elderly people's health, which is the leading cause of death and disability in China [2, 3]. Thrombolysis and neuroprotective therapy are two commonly vital approaches to treating cerebral infarction [4] that aspirin and tissue plasminogen activator have been shown to have a beneficial effect on the outcome. However, the limited efficacy of aspirin, as well as its resistance, and the narrow therapeutic window when using tissue plasminogen activator restrain the treatment [5]. Therefore, intensive clinical research is required to develop more effective interventions, such as low molecular weight heparin (LMWH) and edaravone.

Compare to standard unfractionated heparin, low molecular weight heparin (LMWH) is commonly prescribedto stroke patients to reduce the risk of venous thromboembolism, with no increase in the risk of bleeding, as well as being more bioavailable and simpler to administer [6-8]. Edaravone was first reported to have a beneficial effect in animal models of stroke in the late 1980s [9, 10]. It has been marketed in Japan by Mitsubishi Pharma as the first free

Table 1. Baseline clinical characteristics and treatments of different patients groups

Sectors	Low molecular weight heparin group	Edaravone group	Control group	*P* value
Male	65 (55.6%)	60 (55.0%)	65 (56.5%)	>0.05
Age (years)	62.3±10.3	60.8±5.7	61.5±9.4	>0.05
>60 years	84	74	89	
≤ 60 years	33	35	26	
Systolic pressure (mmHg)	136.25±12.71	135.87±13.17	136.59±12.37	>0.05
Diastolic pressure (mmHg)	75.48±8.27	76.05±8.52	76.37±8.72	>0.05
HDL-C (mmol/L)	0.88±0.25	0.85±0.31	0.87±0.15	>0.05
LDL-C (mmol/L)	3.17±0.78	3.23±0.73	3.25±0.68	>0.05
Treatments for 14 days	Conventional therapy + LMWH 5000 IU 2 times/day	Conventional therapy + 250 mL 12% edaravone 1 time/day	Conventional therapy	Null

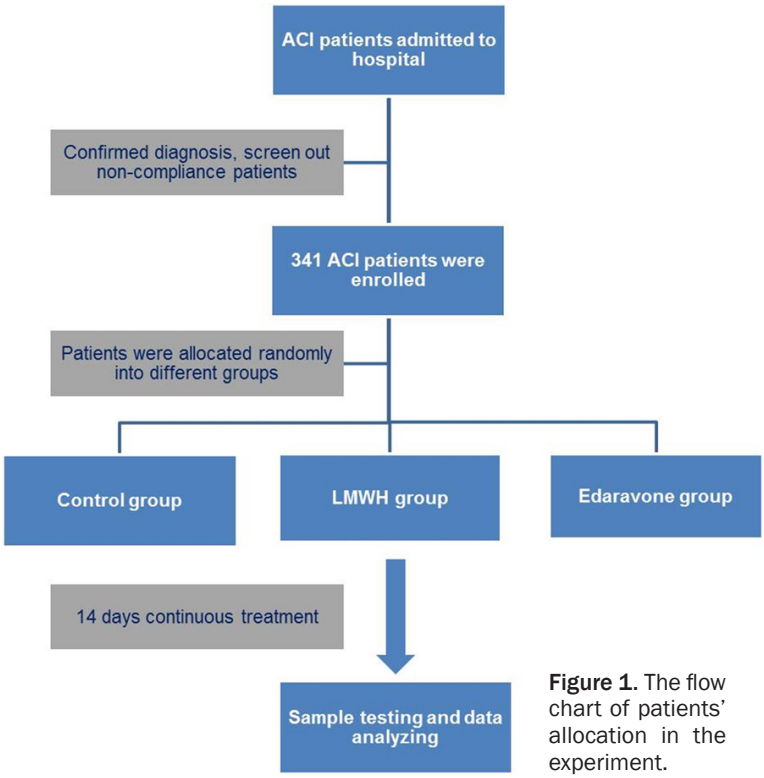

Figure 1. The flow chart of patients' allocation in the experiment.

radical scavenger for clinical use in the management of acute ischemic stroke since 2001 [11]. Researchers indicated thatit has a powerful antioxidant effect on ameliorating ischemia or reperfusion-induced vascular endothelial cell injury and delayed neuronal death, attenuating brain oedema and concomitant neurological deficits [10-13]. However, previous systematic reviews for acute stroke found no conclusive evidence of its efficacy.

Age is an important factor affected the incidence and the prevalence of acute cerebral infarction stroke as well as for its treatments [14-17]. In recent years, new insights intoage-dependent differences in demographics, risk factors and management of ACI patients havebeen gained [18-20]. However, comparisons between younger and older patients with ACI treatments are still limited. Therefore this study aimed to probe theclinical efficacy and prognosis of LWMH and edaravone in the treatment of acute cerebralinfarction with age-dependent differences analysis, providing more effective regimens in the clinical treatment of these diseases.

Materials and methods

Patients

A total of 341 acute cerebral infarction (ACI) patients admitted consecutively to the Shandong Provincial Hospital, between June 2006 and June 2011, were enrolledin this study. All acute cerebral infarction patients admitted within 24 h of ACI symptoms were examined with CT or MRI, and confirmed according to the diagnostic code formulated inthe fourth Chinese national cerebrovascular academic conference (1995), without disturbance of consciousness. All patients with higher diastolic pressure (>110 mmHg) and lower systolic pressure (<200 mmH), subarachnoid haemorrhage, cerebral haemorrhage, brain tumour, cardiogenic cerebral embolism (CCE), thrombocytopenia, allergic history in medicine-

Table 2. Comparisons of CAT and S-100 levels among three groups (U/ml)

Indicators		Low molecular weight heparin group	Edaravone group	Control group
CAT (U/ml)	Before treatment	59.38±2.53	57.14±3.33	60.87±1.98
	After treatment	76.81±7.92*,#	83.21±9.04*,#	69.17±7.58*
S-100 (U/ml)	Before treatment	0.18±0.65	0.18±0.33	0.17±0.98
	After treatment	0.28±0.35*,#	0.26±0.04*,#	0.49±0.11*

*Statistical significance, compared with before treatment (P<0.05); #statistical significance, compared with control group (P<0.05).

Table 3. Comparisons of CSS and BI value among three groups[a]

Indicators		Low molecular weight heparin group	Edaravone group	Control group
CSS	Before treatment	23.84±14.22	22.93±14.03	22.65±13.93
	After treatment	12.54±7.62*,#	12.63±6.92*,#	16.73±6.14*
BI	Before treatment	39.26±10.95	39.71±11.42	39.98±11.33
	After treatment	67.44±11.26*,#	69.23±11.57*,#	44.28±10.87*

[a]CSS- Chinese stroke scale score, BI- Barthel index; *statistical significance, compared with before treatment (P<0.05); #statistical significance, compared with control group (P<0.05).

and within the lactation period when they admitted were excluded (**Table 1**).

Study design and treatments

This study was performed to evaluate the effectsof LMWH and edaravone on ACI patients. Patients were randomly allocated to the LMWH group, edaravone group, and control group when admitted to our hospital within 24 h of stroke onset (**Figure 1**). 115 patients in the control group were given conventional treatment such as infection prevention, used oral antiplatelet agents, intracranial pressure reduction as well as intravenous recombinant tissue plasminogen activator (rt-PA). On the basis of therapeutic regimens in control group, the 117 patients inthe LMWH group were received treatments by injection of the abdominal wall with LMWH 5000 IU (Hainan Unipul Pharmaceutical Group, Haikou, China), twice per day. The edaravone group with 109 patients received 30 mg edaravone (Simcere Pharmaceutical Group, Shanghai, China) diluted with 250 ml of saline, once per day, for continuous 14 days with conventional treatment in control group. The patients were divided into two age periods (>60 years and ≤ 60 years) within different groups, including LMWH group (84 patients >60 years, 33 patients ≤ 60 years), edaravone group (74 patients >60 years, 35 patients ≤ 60 years) and control group (89 patients >60 years, 26 patients ≤ 60 years), and the role of ageing was analysed to the treatment's effects.

Detection and evaluations

The levels of catalase (CAT) and S-100 protein were determined in venousblood samples using commercial fast testing kits (CAT, Nanjing Jiancheng Bioengineering Institute, Nanjing, China; S-100, provided by Laboratory Animal Center of the Fourth Military Medical University, Xi'an, China), respectively, as per the kit instructions. The Chinese stroke scale (CSS) score and Barthel index (BI) were used to assess neurological deficits and activities of daily living, respectively, in the emergency room before and after 14 days treatment [21, 22].

Statistical analysis

SPSS 17.0 (IBM Crop., NY, USA) was used to perform statistical analysis. Categorical variables are presented as frequencies and percentages. For the categorical variables, the statistical differences among groups were analyzed by ANOVA followed by t-tests, patient demographics between groups were presented as means ± SD, P<0.05 was taken to indicate the statistically significant difference.

Results

Clinical characteristics of patients

Of the 341 ACI patients enrolled, 190 were males and 151 were females, the age ranging from 52 to 81 years old and an average age of 61.5±11.2 years old. Baseline clinical characteristics such as sex, age, systolic pressure,

Table 4. Clinical outcome according to age group (>60 years and ≤ 60 years), assessed by CSS and BI values among three groups

Indicators		Low molecular weight heparin group	Edaravone group	Control group
CSS	>60 years	12.03±6.89*	12.97±8.34*	16.89±6.93
	≤ 60 years	12.84±7.03*	11.91±6.41*	16.18±5.97
BI	>60 years	67.94±12.15*	68.94±13.12*	43.39±12.21
	≤ 60 years	66.17±11.93*	69.85±11.37*	47.31±10.01

*Statistical significance, compared with control group (P<0.05).

diastolic pressure, high-density lipoprotein-C (HDL-C) and low-density lipoprotein-C (LDL-C) are listed in **Table 1** and Supplementary Data. There was no significant group difference in any characteristic.

CAT and S-100 levels

Before treatment, CAT and S-100 levels for patients in the three groups indicated no statistically significant difference (P>0.05). After treatment in 14 days, CAT level for patients was distinctly increased in LMWH and edaravone group, showing significant differences compared to control group (P<0.05). Additionally, statistically significant higher in edaravone group compared to patients in LMWH group (P<0.05). After treatment, S-100 level of patients in the three groups indicated are markable increase compared that before treatment. Furthermore, statistically significant difference was shown for patients in LMWH and edaravone group than control group (P<0.05) (**Table 2**).

CSS and BI scores

Among all three groups, comparison of general data for patients has no statistically significant difference such as ages, gender rate, blood pressure and bloodlipid (P>0.05, **Table 1**). Differences in CSS and BI scores for patients before treatment among three groups indicated no statistical significance (P>0.05). However, after treatment, CSS score for patients in all the three groups has a remarkable reduction, and in LMWH group and edaravone group was significantly smaller than that in the control group (P<0.05). The increase of BI score among the three groups indicated the effect of treatment, and BI scores for patients in LMWH group and edaravone group were higher than those in control group (P<0.05), and no statistically significant difference was shown between LMWH group and edaravone group (P>0.05) (**Table 3**).

The CSS and BI values between >60 years group and ≤ 60 years group among both LMWH and edaravone treatments groups were effective. Additionally, included in the control group, there was no significant group difference in clinical effects between >60 years group and ≤ 60 years aged patients (**Table 4**).

Discussion

Acute cerebral infarction is a common and frequently occurring disease in neurology department, if the blood circulation of brain tissues in ischemic regions can be recovered as soon as possible at acute phase, the brain tissue injury in ischemia is ableto obtain a reversal in a certain degree [2, 23, 24]. It is common to treat patients with infection prevention, used oral antiplatelet agents, intracranial pressure reduction and brain cells protection which can reduce the incidence of complications and relieve a certain degree of the disease but with limited efficacy [5, 23, 25]. Moreover, although the thrombolytic therapy could reduce neuronal damage and improve the infarct blood flow, itssafety and long-term efficacy are still been controversial [5, 25, 26]. This study showed that the LMWH treatment is more effective than the control group. In recent years the anticoagulation therapy is considered as an effective treatment that commonly applies unfractionated heparin, however, its short half-life and possibility to induce bleeding to confine the use of this treatment [27]. LMWH is derived from unfractionated heparin by the chemical or enzymatic method of depolymerization, and selectively inhibit the thrombosis process caused by the central part of the Xa, plays a significant effect in inhibiting arteriovenous thrombosis and thrombosis in vitro and in vivo [28]. Anticoagulation with unfractionated heparin or an LMWH is commonly prescribedto stroke patients to reduce the risk of venous thromboembolism, however, it is acontroversial treatment option for acute stroke, as the resultsof clinical trials have been inconclusive [28].

CAT known as catalase, is a hydrogen peroxide reductase which is commonly found in animals

and plants, and with the highest content in liver and kidney in the human body. CAT can quickly remove the toxic metabolise substances produced by hydrogen peroxide [29]. S-100 protein is an acidic calcium-binding protein that mainly exists inglial cells and the corresponding tumour cells ofthe central nervous system and peripheral nervous system, takes around 0.2% of the total brain soluble protein [30]. This clinical effects of edaravone were also confirmed by other researchers that it could inhibit lipid peroxidation and vascular endothelial cell damage in vitro experiment, the research in rat ischemic model shows that edaravone can reduce brain edema and brain tissue damage, delay neuronal death, reduce neurological dysfunction [31]. The significantly higher concentration of CAT in edaravone group than in control group in this research, which indicated that edaravone is able to induce CAT generation, scavenging free radicals and protect the cell membrane, thereby delaying neuronal death and reducing neurological function obstruction to prevent the continued development of cerebral infarction.

The increased content of S-100 protein after treatment could be caused by ischemic necrosis which leads the nerve cells damage andreleased CAT and S-100 protein in theblood [30]. The level of S-100 protein in edaravone patients group was significantly lower than that in the control group, indicating that edaravone scavenging free radicals, protecting the cell membrane and vascular endothelium, and reducing the escape of S-100 protein in neuronal cells, that also protects the nerve system. Indeed, neurones and glial cells are damaged when the ischemic brain is injured, therefore, a lot of cytoplasmic proteins released into the intercellular fluid and help the soluble CAT and S-100 protein transport into the cerebrospinal fluid with intercellular fluid, goes into the blood cycle through the destruction of the blood-brain barrier [32]. Therefore, the presence of S-100 protein in the blood reflects the damage and death of glial cells in the nervous system. Additionally, CAT and S-100 protein levels are also associated with the formation of brain edema, the cell membrane integrity would be destroyed when brain tissue ischemia happens, that enter of sodium into the cells causing cytotoxic edema [33].

The CSS score and BI index were improved after treatment with significant outperformance in both LMWH and edaravone groups than in control group. Compared to the conventional heparin the LMWH has advantages like: (1) has high strength, stable anticoagulant effect; (2) has high efficacy in inhibiting coagulation enzymes that inhibit coagulation and platelet activation, and prevent the occurrence of platelet aggregation and adhesion; (3) could reduce the complications caused by bleeding, and enhance the ability of antithrombotic in vascular endothelial cells without interfering other functions of vascular endothelial cells and the number of platelet [13, 31]; (4) could reduce the non-specific combination with plasma protein and offer the ideal dose effect and bioavailability. Therefore, both LWMH and edaravone have significant effects in treating cerebral infarction than conventional treatment and worthy to apply toclinical treatment.

Although there was no significant difference of CSS and BI values between those two age groups within the LWMH and edaravone treatment groups, the variation among different age individuals, e.g. dyslipidemia, smoking and hypertension, could seriously affect the clinical effects [19, 34]. Therefore, the application of both LWMH and edaravone to different age groups should be identified in the future.

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Disclosure of conflict of interest

None.

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