



Comparative study of neuroprotective effects of ulinastatin versus piracetam treating on acute traumatic craniocerebral injury

Chengyuan Liang^{a,c,*}, Juan Xia^b, Ying Dai^a, Huihui Song^a, Ying Sun^a, Xiaoyun Lei^a,
Zhuangzhuang Feng^a, Junhui Liu^a and Yong Deng^{c,*}

^aDepartment of Pharmacy, Shaanxi University of Science & Technology, Xi'an, China

^bMedical Research Center, Affiliated Hospital of Guangdong Medical College, Zhanjiang, China

^cWest China School of Pharmacy, Sichuan University, Chengdu, China

ABSTRACT

To evaluate the clinical efficacy and feasibility application of a human urinary protease inhibitor (Ulinastatin, UTI) for the patients with acute severe traumatic craniocerebral injury. 90 cases with acute severe traumatic craniocerebral injury were randomly divided into the Ulinastatin treatment group (45 cases) and the control group (45 cases), the control group received piracetam treatment. Ulinastatin conventional therapy in the treatment group based on the intravenous injection of Ulinastatin 200000U, 2 times per day, 12 days a cycle, at the same time, piracetam treatment is based on the intravenous drip piracetam 20ml:4g, 2times/d, 12 days a cycle. The clinical effects was assessed with the GCS and MMSE score sheet at the 12th day and the GOS score sheet at 6 months after craniocerebral injury. Record the side effects and complications such as incidences of alimentary tract hemorrhage, liver damage and renal function injury. Comparing the treatment group with the control group, GCS score and MMSE score had significant difference ($P<0.05$), 6 months GOS score of the neurological function recovery in the treatment group was significantly better than that in the control group ($P<0.05$). Ulinastatin not only appears the effective treatment and promotes the neurological function recovery, but also reduces the risk of death for the patients with severe traumatic craniocerebral injury. Ulinastatin is safe and reliable treating on the patients with acute severe traumatic craniocerebral injury.

Key words: Ulinastatin; Piracetam; Craniocerebral Injury; Neuroprotection; Comparative Study

INTRODUCTION

Traumatic craniocerebral injury, most caused by the external forces acting on the head resulting skull fracture and the deformation of cerebrovascular, meningeal and brain tissue, which has been divided into the local damage and diffuse lesions. Brain injury is the clinical common high mortality and morbidity disease which need complex surgery, meticulous nursing and long coma time.

Ulinastatin (or urinary trypsin inhibitor, UTI) is an acid-resistant protease inhibitor purified from human urine which acts as a trypsin inhibitor. It is released from the high-molecular weight precursor I alpha T₁ or it can be synthetically produced. Proteins of the I alpha T₁ family are composed of two heavy chains (HCs) and one light chain. UTI is composed of two Kunitz-type domains. The inhibitor Ulinastatin shows an apparent molecular mass of 30 kDa. This protein may arise from a gene duplication event of BPTI followed by diversification only within the portion of the gene coding for the functional Kunitz domain. Ulinastatin inactivates many serine proteases such as trypsin, chymo-trypsin, kallikrein, plasmin, granulocyte elastase, cathepsin, thrombin, factors IXa, Xa, XIa, and XIIa[1]. It may be effective in treatment of acute pancreatitis, chronic pancreatitis, toxic shock, Stevens-Johnson syndrome, burn patients, severe sepsis and toxic epidermal necrolysis (TEN) [2-5]. UTI was first launched time

listed was in Japan, 1985, brand name is Miraclid. Currently, UTI is also available in Korea, China and India[6].

The structure or function damage of human body caused by outside agent or force will lead to a large number of the protease inhibitors consumption thus the concentration of UTI will maintain low level along with body recovery and rebound. Former researches indicate that UTI not only has obvious therapeutic effect for acute pancreatitis but also has very significant beneficial effect including anti-shock, antitumor activity and application on surgical infection etc. Recently, the clinical research of UTI has been gradually focused on the treatment of ischemic hypoxic brain injury as well as the nerve recovery of craniocerebral trauma. Between Jan. 2012 and Jun. 2013, 90 patients admitted in emergency room have been divided into control group and the Ulinastatin group ($n=45$ in each group), the control group received piracetam treatment based on conventional therapy and while Ulinastatin group received intravenous drip of ulinastatin based on regular therapy.

Purpose

To assess the neuroprotective therapeutic benefits of a human urinary protease inhibitor (Ulinastatin) on postoperative severe traumatic craniocerebral injuries including its mechanism, a prospective, randomized, clinical study was performed at Affiliated Hospital of Guangdong Medical College, Zhanjiang, P. R. China and Department of Pharmacy, Shaanxi University of Science & Technology, Xi'an, P. R. China

EXPERIMENTAL SECTION

Data Collections

From January 2012 to June 2013, there were 90 neurosurgery patients with acute severe traumatic craniocerebral injury of Affiliated Hospital of Guangdong Medical College were collected in this series. According to the criterion of modern neurosurgery, the diagnosis criteria of patients of all patients were confirmed through physical signs, clinical symptoms, head MRI or CT. They were either treated by Ulinastatin (treatment group, 45 cases) or Piracetam (control group, 45 cases) besides routine managements. All cases were in line with severe brain injury criteria, the performance of more than 1 hour coma, neurological positive signs, skull or brain tissue deformation, cerebrovascular bleeding phenomenon. 24 h adduction hospital in all patients after traumatic brain injury. The causes of injury: 58 cases of car accidents, blunt blow or hit in 22 cases, 8 cases falls, admission GCS (Glasgow) score at 3-8 points. The patients were randomly divided into two with a double-blind study group and the control group, in which the observation group 45 patients (25 males, 20 females), aged 18 to 60 years, mean age 34.3 years, mean GCS score of 5.3 ± 0.34 points, with seven cases with multiple rib fractures, 10 cases of upper and lower extremity fractures, pneumothorax five cases, eight cases of hernia. A control group of 45 patients (19 males, 26 females), aged 17-58 years, mean age 32.8 years, mean GCS score 5.8 ± 0.56 minutes, accompanied by rib fractures in 10 cases, 8 cases of upper and lower extremity fractures, hemopneumothorax six cases, seven cases of hernia. The control and treatment groups were excluded: age under 16 years, 75 years or older; associated with other systems of serious injury and chronic; has a history of neurological infection within 1 year; patients with postoperative cardiopulmonary resuscitation. Two sets of data were not significantly different ($P > 0.05$). Gender, age, cause of the injury and associated symptoms were comparable.

Treatments

Patients admitted to hospital were immediately given relevant examination, inhalation of oxygen, dehydration, blood transfusion, intracranial pressure control, antibiotics and surgical operation. On this basis, the observation group were given Ulinastatin (No. H20040506, 2ml: 10 million units, purchased from Guangdong Techpool Biochem Pharma Company Limited) 200 000 U dilute with normal saline 20 ml, intravenous bolus, 2 times per day. The control group were given Piracetam (No.H23022874, 20ml: 4g, purchased from Heilongjiang Province Gerun Pharmaceutical Co., Ltd.), intravenous drip with 250ml diluted 5% glucose or equivalent 0.9% sodium chloride injection, 4g per day. Both groups were treated for 12 days, according to the the patient's condition, slightly adjustment were made for the appropriate dose. After six months, GCS score, MMSE score, and the GOS score of all cases based on clinical observations were recorded after one course of therapy, compared two groups of patients in stable condition time, All side effects and vital adverse signs including gastrointestinal tract, liver, kidney damage, memory and mental retardation, neurological deficits were also recorded.

Observation and Evaluation Criteria

The Glasgow Outcome Score (GOS), as shown in Table 1, is a scale applies to patients with brain damage such as cerebral traumas can be divided into groups that allow the objective assessment of their recovery degree in five categories. The first description was in 1975 by Jennett and Bond. This allows a prediction of the long-term course of rehabilitation to return to work and everyday life.

All patients were given routine monitoring of blood pressure, heart rate, oxygen saturation, liver and kidney function,

urine and other biochemical indices, recording vital signs returned to normal time and gastrointestinal bleeding, liver and kidney dysfunction and other adverse reactions. Through the six-month follow-up, therapeutic effect were evaluated by Glasgow (GCS) score and concise mental state detection (MMSE) score. Then through the six-month follow-up, carried Glasgow Outcome Scale (GOS), as shown in Table 1. The incidence of adverse drug reactions after treatment were also recorded and compared.

Table 1: Glasgow Outcome Scale table

Score	5	4	3	2	1
Grade	Good recovery Low disability	Moderate disability	Severe disability	Persistent vegetative state (PVS)	Death
Description	Return to normal life, despite the mild defects	No need for assistance in everyday life, employment is possible but may require special equipment.	Severe injury with permanent need for help with daily living	Severe brain damage to a state of wakefulness without detectable awareness.	Severe injury or death without recovery of consciousness

Statistical Method

SPSS 19.0 software were selected for statistical analysis, measurement data were described by ($\bar{X} \pm s$), T-test was utilized for comparing between two groups, χ^2 test was chosen for inner group measurement data comparing, test standard $\alpha=0.05$, $P<0.05$ indicates statistical significance.

RESULTS

The clinical effect of the two groups were compared in Table 2, Table 2 shows that there are obvious differences between the two groups, stable condition of UTI group was achieved about three days earlier than topiramate (Piracetam) small amount group, $P<0.05$. In terms of adverse effects, especially on the liver, kidney and gastrointestinal damage, UTI group was significantly milder than piracetam group, $P<0.05$. This phenomenon confirms that UTI not only has a strong protective effect on internal organs, but also play an important role on rehabilitation of damaged organ.

Under 12 days of UTI or Piracetam treatment MMSE, GCS scores of the two groups have been listed in Table 3. The Statistical data indicate that two sets of GCS score and MMSE scores were somewhat higher, but the increase in the observation group was more significant than that of the control group. The statistical results demonstrated that in terms of the neurological function and memory recovery, patients with mental retardation under the usage of the UTI were more effective than that of piracetam group, there are obvious differences in scores between the two groups, $P<0.01$.

After six months continued rehabilitation Glasgow Outcome Scale score of patients in the observation group was significantly better than the control group, $P<0.05$. The described results indicated UTI also has played a good role in promoting rehabilitation and prognosis

Table 2. The clinical efficacy and side effects of the two groups patients

Grouping	Stable condition (time / d)	Liver dysfunction (The incidence %)	Gastrointestinal bleeding (The incidence %)	Renal victimized (The incidence %)
<i>UTI Group</i>	$9.3 \pm 3.2^*$	5.8*	0*	9.3*
<i>Control Group</i>	12.4 ± 3.5	32	15.6	18.2

Note: * the treatment group and the control group, $P<0.05$

Table 3: GCS and MMSE scores after the first 12 days treatment ($\bar{X} \pm s$, points)

Groups	Number of cases	GCS score		MMSE score	
		Before treatment	After treatment	Before treatment	After treatment
<i>UTI Group</i>	45	5.3 ± 0.34	11.23 ± 0.54	12.78 ± 2.45	$22.36 \pm 3.46^*$
<i>Control group</i>	45	5.8 ± 0.56	10.23 ± 0.55	12.68 ± 2.23	17.36 ± 3.36

Note: *The observation group (UTI) and control group (Piracetam), $P<0.01$

Table 4 Comparison of Glasgow Outcome Scale score between two groups (patients / %)

Groups	Number of cases	Good recovery	Mild disabilities	Severe disability	Vegetative state	Death
<i>UTI Group</i>	45	28 (62.3) *	13 (28.9)	2 (4.4) *	1 (2.2) *	1 (2.2) *
<i>Control group</i>	45	18 (40)	11 (24.4)	8 (17.8)	5 (11.1)	3 (6.7)

Note: *The observation group (UTI) and control group (Piracetam), $P < 0.05$

DISCUSSION AND CONCLUSION

Ulinastatin has previously been used as a drug for patients with acute inflammatory disorders, additionally, the function of protecting cerebral tissue, reducing the incidence of gastrointestinal hemorrhage, improving hepatic and renal function and prognosis of Ulinastatin have been gradually reported by clinical research[7].

The goal of the present study was to investigate the neuroprotective effects of Ulinastatin on acute traumatic craniocerebral injury, and to explore the possible underlying mechanism. Patients were divided into an Ulinastatin treatment group, a piracetam group. The Ulinastatin treatment group had a significantly higher GOS score, MMSE score and GCS score compared with the group with piracetam treatment. Furthermore, Ulinastatin treatment increased the expression of nerve growth factor and brain-derived neurotrophic factor, and protected against oligodendrocyte apoptosis. Thus, Ulinastatin is shown to have a protective effect against severe brain damage to a state of persistent vegetative state (PVS).

Traumatic brain injury (TBI) is a common clinical critical illness caused by changes in the skull, brain and other soft tissues undergoing the strong external force, Parts of the brain that can be damaged include the cerebral hemispheres, cerebellum, and brain stem[8]. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain[9]. Outcome can be anything from complete recovery to permanent disability or death if treatment is not timely or improper[10]. Therefore, appropriate adjunct of UTI has a very important significance in the course of treatment to protect brain tissue and promote nerve repair in improving the therapeutic effect, improving neurological function, promote memory and intellectual function and other aspects of recovery

UTI is a 143 amino acid-containing glycoprotein, has two active region, with a very broad antibacterial spectrum[11]. Recent researches have indicated that Ulinastatin encompass utilities such as reducing inflammation, microcirculation improvement, immune regulation, and protective function of liver, lung, kidney and other organs and tissues[12-16]. In the present study, the incidence rate of side effects in the observation group, for instance, gastrointestinal bleeding, liver and kidney damage is consistent lower than control group. Thus, here is a strong proof of visceral protection due to UTI, $P < 0.05$. In addition, UTI can reduce CRP levels in plasma and plasma endothelin in patients with traumatic brain injury, to a certain extent, alleviate the symptoms of cerebral ischemia, protecting vascular endothelium. These features and the study of 90 cases of severe traumatic brain injury patients after treatment GCS score, MMSE score, and GOS score results are basically the same. All of the statistical tables have verified that Ulinastatin played a good supporting role in the treatment of severe traumatic brain injury, including elevating the nerve function, rehabilitating memory and intelligence, maintaining vital signs, improving life quality and prognosis of patients.

In this comparative study, GOS, GCS, MMSE scores certificated that UTI is superior to piracetam in improving neurological function after severe brain injury. Based on these clinical results, a prudential conclusion can be given as the Ulinastatin is safe and reliable in treating on the patients with acute severe traumatic craniocerebral injury.

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