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Clinical efficacy and CT perfusion of puerarin combined with naloxone in the treatment of traumatic cerebral infarction

Li Lubo[1], Nie Sulin[1], Dong Zhimei[1] and Ning Houfa[2]*
[1]Magnetic Resonance Room, Changyi People's Hospital, Changyi, China
[2]Intervention Room of Affiliated Hospital of Weifang Medical College, Weifang, China

Abstract: Puerarin is an important active ingredient of *Radix puerariae*. Puerarin is an isoflavone compound Z clinical and basic research proves that *S. puerarin* can increase cerebral circulation blood flow; increase cerebral perfusion; reduce blood viscosity and improve microcirculation. The present research was conducted to observe the clinical efficacy of puerarin combined with naloxone in the treatment of traumatic cerebral infarction (TCI). Methods 52 patients with TCI were randomly divided into two groups. The treatment group was treated with puerarin and naloxone and the control group was treated with conventional therapy. Results: The total effective rate was 82% in the treatment group, which was better than 61% in the control group. The difference was statistically significant ($p<0.05$). The efficacy of simple TCI in both groups was significantly better than that of TCI with brain contusion; the effect of intracranial hemorrhage and the effect of TCI alone in the two groups; the treatment group was significantly better than the control group ($p<0.05$). Conclusion: The combination of puerarin and naloxone in the treatment of TCI can improve the curative effect.

Keywords: Puerarin, naloxone, cerebral infarction, traumatic.

INTRODUCTION

Traumatic cerebral infarction (TCI) is one of the complications of traumatic brain injury. The ischemic penumbra after acute cerebral infarction is a dynamic process (Chen *et al.,* 2015). According to the condition of reperfusion, two outcomes can occur. The blood flow in some ischemic areas can be restored to normal brain tissue (Fang *et al.,* 2017; Goldstone *et al.,* 2017). CT perfusion can quickly obtain cerebral perfusion, understand the infarct core and ischemic penumbra volume, quickly quantitatively evaluate the degree of infarction and predict clinical outcome, so as to develop a treatment strategy (Francisco *et al.,* 2018). The concept of "time is the brain" is gradually being replaced by "image is the brain". Some hospitals have used perfusion techniques to guide ultra-early thrombolytic therapy for acute cerebral infarction (Pereira *et al.,* 2018).

The mechanism of TCI is not only the mechanical damage of the cerebrovascular itself, but also the hemorheological changes caused by craniocerebral injury is also an important cause of the disease (Dabash *et al.,* 2015; Daniel *et al.,* 2018). Recent studies have shown that the occurrence and development of ischemic cerebrovascular disease is closely related to the role of adhesion molecules (Beatriz *et al.,* 2018). Leukocyte adhesion molecules participate in the pathogenesis of cerebral ischemia, platelet activation, adhesion and aggregation, and form platelet thrombi (white thrombus) in the diseased vessels (Dindo *et al.,* 2004). Meanwhile, the increase of intercellular adhesion molecules (ICAM-1) and vascular cell adhesion molecules (VCAM-1) from the cell surface mediates the firm adhesion between the inner skin cells and the leukocytes (Cristina *et al.,* 2018). During the period of cerebral ischemia-reperfusion injury, a large number of leukocytes infiltrate into the ischemic group Tissue, through mechanical blockage of microcirculation channels and release of toxic substances, leads to or aggravates nerve cell necrosis (Martins *et al.,* 2018).

Puerarin (isoflavone) is an important active ingredient of *Radix puerariae* (Lohr, 2007). Clinical and basic research has shown that puerarin can increase blood circulation in the brain, increase cerebral perfusion, reduce blood viscosity and improve microcirculation (Gatter *et al.,* 2015; Henkel *et al.,* 2018). The mechanism of puerarin injection to increase blood circulation of cerebral circulation may block the adhesion of leukocytes and vascular endothelial cells, reduce the aggregation and adhesion of leukocytes and prevent micro-emboli formation in capillaries in the ischemic area, reducing microvascular obstruction and contributing to improve microcirculation, reduce brain ischemia and hypoxia, and prevent secondary brain damage (Goldberg *et al.,* 2015; Kanninen *et al.,* 2018). At the same time, puerarin injection can also reduce apoptosis, inhibit superoxide anion radical reaction after cerebral ischemia, increase the activity of super oxide dismutase *in vivo*, reduce neuronal apoptosis, and protect brain cells after cerebral infarction (Ohannessian, 2016). Puerarin injection has been used to treat cerebral infarction and TCI.

MATERIALS AND METHODS

Data

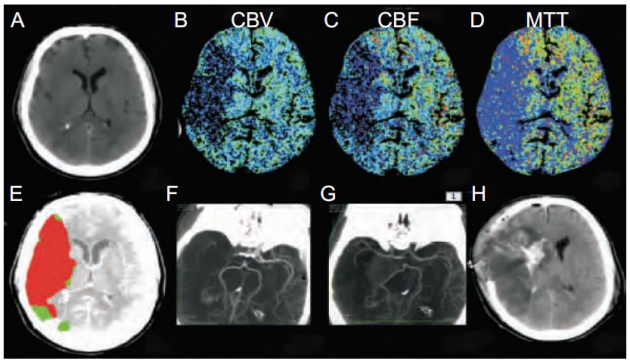
52 patients with TCI were diagnosed by MRI and CT and

**Corresponding author:* e-mail: 15153619853@163.com

were randomly divided into treatment group and control group. There was no significant difference between the two groups of general data (table 1) by statistical treatment (P>0.05), which was comparable.

Treatment Method

In the treatment group, TCI patients were treated with intravenous saline 20ml + naloxone 3.2mg intravenously (intravenous drip) once a day; mass fraction of 5% glucose 20ml + puerarin 0.4g intravenously, once a day. Among patients with cerebral contusion and intracranial hemorrhage, non-surgical patients were treated as described above from the 3 days onset; surgical treatment was treated as described above from 3 days after surgery (Patel 2016).



(A)emergency head CT; (B-D)PCT inmage; (E-H) as CT angiography (CTA)

Fig. 1: A Case of Acute Cerebral Infarction with Poor Prognosis for Intravenous Thrombolysis

In the control group, TCI patients were treated with normal saline 20ml + citicoline 0.5g intravenously once a day; low molecular weight dextran 500ml intravenously, once a day (week for 1 course. Patients with brain contusion, intracranial hemorrhage) Among them, non-surgical treatment patients were treated as described above from the 3 days onset; the surgical treatment was treated as described above from 3 days after surgery. Other treatments in the two groups are similar, such as dehydration, blood pressure reduction, electrolytes and acid-base balance, nutritional support, and prevention of infection (Forero *et al.,* 2018). The patients with severe dehydration often show mental changes, decreased urine volume, hypotension and increased hematocrit. Generally, when the dehydration does not exceed 2% of the body weight, if the patient does not have gastrointestinal disease or consciousness disorder, it is better to correct by oral rehydration (Kohlrausch *et al.,* 2018).

Efficacy judgment standard

Short-term efficacy: The short-term efficacy was evaluated after 4 weeks of treatment. Neurologic deficit scores (NDS) were used, which can be divided into 0-4 points. Basic recovery: NDS score reduced by 91%~100%; significant progress: NDS score decreased by 46%~90%; progress: NDS score decreased by 18%~45%; no change: NDS score decreased by less than 17%; deterioration: NDS score increased More than 18%. Long-term efficacy: Follow-up after 6 months, long-term efficacy was assessed based on the Activity of daily living (ADL) of surviving patients. Level 1: Self-care, independent living, can participate in part of the work; Level 2: Basic independent life, a small number of activities need help; Level 3: Some life activities can take care of themselves, most need help; Level 4: Stand up and walk , but need people to care; Level 5: The patient can only sit on the bed, all life needs people to care; Level 6: Patients can only lie in bed, there is part of the consciousness activities, level 7: Loss of personal awareness.

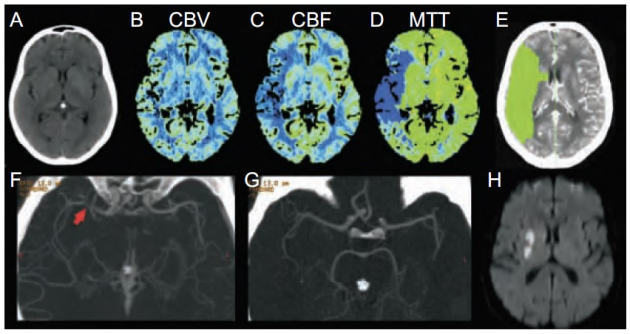


Fig. 2: A Case of Good Prognosis for Acute Cerebral Infarction in Patients with Intravenous Thrombolysis.

Ethical approval

All patients were approved by Ethics Committee of our hospital and signed on the informed consent. Ethical approval number as 17CPHDD-YX.

STATISTICAL ANALYSIS

Data were statistically analyzed using SPSS 21.0 software. Measurement data were expressed as mean ± standard deviation (x ± s), T test was used for comparison; Chi square properly test was used for counting data, x2 value indicates the deviation between the observed value and the theoretical value. P<0.05 was considered statistically significant.

RESULTS

Comparison of the two groups

The clinical efficacy, total effective rate and ADL of the treatment group were better than the control group (P<0.05). The mortality rate of the treatment group was lower than that of the control group, but the difference was not significant.

Comparison of therapeutic effects between TCI alone and TCI combined with cerebral contusion and intracranial hemorrhage

The efficacy of TCI in both groups was significantly better than that in TCI with brain contusion and intracranial hemorrhage (P<0.05). The effect of TCI alone in the two groups was significantly better than that in the control group (P<0.05).

Typical case introduction

Perfusion CT (PCT) can rapidly quantitatively evaluate the degree of infarction and predict clinical outcome, so as to develop a treatment strategy. Fig. 1 shows a case of acute cerebral infarction with poor prognosis for intravenous thrombolysis. No hemorrhagic changes in the emergency head CT, structural disorder in the basal ganglia (A); PCT see the low hemolysis area in the right hemisphere middle cerebral artery supply area as B-D, as shows in fig. 1. MTT detection of cell survival suggests that the ischemic area is large, and the low perfusion area seen by CBV fig. is similar to the MTT size; the software synthetic pseudo-color map (E) indicates that the right middle cerebral artery blood supply area has large infarct (red area), ischemic penumbra (green area); CT angiography (CTA) prompts acute occlusion of the right middle cerebral artery, poor distal collateral circulation (F); intravenous thrombolytic therapy within 180 min according to NINDS criteria; head and neck CTA again after 24 h, prompting right The M1 segment of the lateral middle cerebral artery was recanalized, but the distal collateral circulation was still poor (G). After 2 days, the patient underwent decompressive craniectomy (H) due to large area cerebral infarction with hemorrhagic transformation.

Fig. 2 shows a patient with a good prognosis for acute cerebral infarction. There is no hemorrhagic foci and stroke in the emergency head CT (A); PCT sees the right hemisphere middle cerebral artery in the low-perfusion area (BD), and the MTT suggests a large ischemic area. There was no obvious abnormality in CBV; software synthetic pseudo-color map (E) suggested no acute infarction (no red area), all were ischemic penumbra (green area); head and carotid artery CTA showed acute right middle cerebral artery M1 Occlusion (F, red arrow), distal collateral circulation was good; rtPA 50mg intravenous thrombolysis was given according to NINDS(national institute of neurological disorders and stroke) criteria; after 24 h, NIHSS (National Institute of Health stroke scale) score was 4 points. Review of head and carotid CTA showed right middle cerebral artery (G); 48 hours later, the head MR showed an acute infarct of the basal ganglia with a small lesion range (H); the modified rankin scale (mRS) score of 1 point at 90 days was 1 point.

In the patient of fig. 1, the ischemic penumbra is small and the infarct is large. Although it is in the time window and the intravenous thrombolysis is used to treat the blood vessels, the clinical prognosis is still poor. As shown in fig. 2, the patient was in the time window of thrombolysis and PCT indicated that the infarct core was small and the ischemic penumbra was huge. After intravenous thrombolysis, the blood vessel was recanalized, and the prognosis was better. Therefore, a comprehensive early assessment of acute stroke imaging should provide information on the infarct, ischemic penumbra and vascular occlusion.

Multivariate analysis results

Multivariate logistic regression analysis showed that age was the most important predictor of prognosis. The older the patient, the worse the prognosis (P<0.01). The baseline NIHSS score (P=0.021) and Hyperdense Middle Cerebral Artery CT Sign-HMCACS (P=0.038) and prognosis of patients. Negative correlation, high NIHSS score and positive HMCACS showed poor prognosis; compared with ICA (and M1) occlusion, M1 occlusion had a better prognosis; revascularization was also a significant prognostic factor, the probability of good prognosis after successful recanalization was 6.58 times higher than the prognosis; the infarct core volume obtained by PCT could not accurately predict the prognosis (P=0.145), and the penumbra volume measured by PCT was positively correlated with prognosis. The penumbra is large in volume and has a good prognosis (P=0.044), as shown in table 4.

Table 1: Comparison of General Data between Treatment Group and Control Group

Group	Gender (Example)		Age($\bar{\chi} \pm s$ year old)	State of consciousness (Example)					NDS score($\bar{\chi} \pm s$ score)	TCI type (Example)	
	Male	Female		wide awake	Sleepiness	Light coma	Moderate coma	Deep coma		Simple	Combined brain contusion, intracranial hemorrhage
Treatment group	19	9	38.99±13.4	11	6	5	3	3	25.69±97.58	9	19
Control group	18	6	39.19±17.3	9	5	5	3	2	24.56±98.34	7	17
Test value	$\chi 2$=1.267		t=0.047			$\chi 2$=2.208			t=0.512		$\chi 2$=3.1015
P	>0.05		>0.05			>0.05			>0.05		>0.05

Table 2: Comparison of Therapeutic Effect between Treatment Group and Control Group

Group	Number of cases (example)	Efficacy evaluation (Example)						Total efficiency(%)	Mortality rate(%)	ADL(Example)	
		Basic recovery	Significant progress	Progress	No change	Deterioration	Death			1~3level	4~7level
Treatment group	28	11	8	4	3	1	1	82.14	3.57	23	4
Control group	24	4	5	6	5	2	2	62.50	8.33	12	10
$\chi 2$ test	16.48							6.44	0.02	4.18	
P	<0.05							<0.05	>0.05	<0.05	

Table 3: Comparison of Therapeutic Effects of TCL Alone and TCL Combined with Cerebral Contusion and Intracranial Hemorrhage

Group	Infarct type	Basic recovery	Significant progress	Progress	No change	Deterioration	Death	Total
Treatment group	Simple TCI	7	2	0	0	0	0	9
	TCIcombined bleeding	4	6	4	3	1	1	19
Control group	Simple TCI	2	2	3	0	0	0	7
	TCIcombined bleeding	2	3	3	5	2	2	17

Table 4: Multivariate Logic Analysis Shows Factors Affecting Patient Prognosis

Influencing factor	Constant term	Standard error	Chi square value	P	OR(95%CI)
Constant term	2.6012				
Age	-0.0857	0.0244	12.36	<0.001	1.42(1.16,1.75)
Baseline NIHSS score	-0.0678	0.0642	4.15	0.021	1.87(1.29,2.72)
HMCACS	-0.1851	1.0175	3.98	0.038	1.06(0.98,1.15)
Vascular occlusion =M1	2.197	1.2361	7.9	0.012	1.85(1.24,2.76)
Revascularization or not	3.1648	1.9892	9.12	0.010	6.58(1.55,27.92)
PCTSemi-dark belt volume	0.0261	0.013	3.08	0.044	1.12(1.02,1.23)

*Notes: $P < 0.05$ means significant difference, $P < 0.01$ means extremely significant difference

DISCUSSION

The ischemic penumbra refers to brain tissue surrounding the infarcted area, and its neuronal function is disordered but may be restored (Zapata *et al.,* 2018). Brain PCT is a concept first proposed by Miles *et al* in 1991. Semi-quantitative measurement of blood perfusion of brain tissue effectively reflects changes in brain tissue perfusion, thereby obtaining information on brain tissue function (Ajami *et al.,* 2016). The key to the rescue of the ischemic penumbra is the early treatment of thrombolytic therapy. The study found that PCT can detect the location and extent of cerebral ischemia in the early stage, and can display abnormal lesions immediately after the onset of symptoms (Bartzatt *et al.,* 2010; Cormier *et al.,* 2012). The ischemic penumbra is confirmed from the imaging point of view and can truly reflect the range of cerebral ischemia (Bagatini *et al.,* 2011).

The mechanism of puerarin injection to increase blood circulation of cerebral circulation may block the adhesion of leukocytes and vascular endothelial cells, reduce the aggregation and adhesion of leukocytes, and prevent micro-emboli formation in capillaries in the ischemic area, reducing microvascular obstruction and contributing to improve microcirculation, reduce brain ischemia and prevent secondary brain damage (Bergmann *et al.,* 2016). At the same time, puerarin injection can also reduce apoptosis, inhibit superoxide anion radical reaction after cerebral ischemia, increase the activity of superoxide dismutase (SOD) *in vivo*, reduce neuronal apoptosis, and brain after cerebral infarction (Chtourou *et al.,* 2015). The cells have a protective effect. Clinically, puerarin injection has achieved certain effects in the treatment of cerebral infarction and TCI (Pilar *et al.,* 2018). In order to avoid complications of acute bleeding, we were treated with puerarin injection (Gao *et al.,* 2010).

Zhou *et al* treated naloxone in the treatment of acute ischemic stroke and observed the changes. Based on the table 3-4, the results showed that the naloxone group was significantly better than the control group. Analysis of its mechanism, may be in the cerebral infarction, the ischemic area stimulates the hypothalamus to release a

large amount of g-endorphin, reduce the blood flow in the ischemic area around the infarct, inhibit the electrical activity of neurons, and accelerate the irreversible necrosis of neurons (Ceylan *et al.,* 2016). Naloxone is an opioid receptor antagonist. Recent studies have shown that endogenous opioid peptides in plasma and cerebrospinal fluid after brain injury are involved in pathological processes such as brain and spinal cord injury and cerebral ischemia (Danir *et al.,* 2017). Naloxone inhibits the contraction of central neurons by endogenous opioid peptides, inhibits cerebral vasoconstriction, increases cerebral blood flow and perfusion pressure, improves microcirculation of brain tissue and tissue oxygen supply, and reduces secondary brain damage (Jubie *et al.,* 2012; Fardeau *et al.,* 2014).

This study shows that the infarct core volume obtained by PCT does not accurately predict the prognosis, while the penumbra volume measured by PCT is correlated with prognosis, but the predictive ability is not strong. The reasons for the analysis are as follows: 1. DWI (diffusion weighted imaging) is still the gold standard for the determination of acute infarction. The infarct core obtained by PCT is related to the threshold of CBV (class-based-view), but what kind of threshold can truly reflect the infarct, there is still a lot of controversy; 2. Acute cerebral infarction of the patient is not only related to the final infarct volume, but also related to the involvement of the brain functional area (Ji *et al.,* 2015). In the same infarct volume, the clinical prognosis of patients with cystic or predominant hemisphere involvement is poor; 3. Ischemic penumbra volume does not indicate the size of the final infarct volume. The final infarct volume depends on the size of the infarct core, the relationship between the ischemic penumbra and the recanalization of the blood vessels (Karen *et al.,* 2017). The mechanism of TCI is not only the mechanical damage of the cerebrovascular itself, but also the hemorheological changes caused by craniocerebral injury is also an important cause of the disease. Recent studies have shown that the occurrence and development of ischemic cerebrovascular disease is closely related to the role of adhesion molecules.

CONCLUSION

The data of this group showed that the reduction degree and total effective rate of NDS scores in the treatment group were better than those in the control group, which was consistent with the results reported by Zhou Ling and Xie Ming. The treatment of patients with simple TCI in the treatment group was superior to TCI patients with brain contusion and intracranial hemorrhage. The reason was that brain contusion and intracranial hemorrhage were also important factors influencing the prognosis of patients with TCI. Therefore, for patients with TCI with brain contusion and intracranial hematoma, targeted treatment should be given. If necessary, decompressive craniectomy or surgery should be performed to remove hematoma and inactivated brain tissue, reduce intracranial pressure, and remove cerebral palsy. The cause, relieve vascular compression, ensure effective brain perfusion pressure of normal brain tissue and protect normal nerve cells. On the basis of the above-mentioned corresponding treatment, the combination of puerarin and naloxone was given, and good curative effect was obtained.

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