Multicenter randomized controlled trial of vitamin K1 in the treatment of spontaneous intracerebral hemorrhage

1 Background

1.1 spontaneous intracerebral hemorrhage

1.1.1 Epidemiological of cerebral hemorrhage

Cerebral hemorrhage is a kind of acute onset, rapid change, serious disease, which accounts for about 10%-25% of cerebrovascular disease, disability rate and fatality rate were 70%-80%, 38%-43%, the recurrence rate was about 1 1.8%-11%. Hypertension and amyloid cerebrovascular disease are the main causes of primary spontaneous intracerebral hemorrhage, and hypertension is the most common risk factor for intracerebral hemorrhage. Cerebral hemorrhage not only has a serious impact on patients, but also brings heavy burden to society and family. The treatment of cerebral hemorrhage is complicated , which is one of the stroke which is proved by evidence-based medicine to be effective. Standardized treatment and effective integrated management can significantly reduce the fatality rate and improve the outcome of intracerebral hemorrhage.

Delayed cerebral hemorrhage is one of the important reasons for the aggravation of cerebral hemorrhage . The amount of hematoma in patients with intracerebral hemorrhage is closely related to the secondary injury of nerve function, which directly affects the prognosis of patients. Delayed cerebral hemorrhage is closely related to coagulation dysfunction. The prevention of delayed hemorrhage is an important part in the treatment of cerebral hemorrhage. The blood coagulation is initiated immediately after Acute intracerebral hemorrhage, and the coagulation process is divided into three stages: prothrombin complex formation, prothrombin activation, and fibrin formation. Synthesis of Coagulation factor FX, F II, F VII and F IX are dependent on vitamin K1. Vitamin K1 can cause the formation of prothrombin complex, clot solid, effectively blocking the vascular rupture, so that the amount of bleeding decreased. However, while controlling bleeding, the risk of thrombosis may be induced, and how to effectively control bleeding and avoid thrombosis is often a clinical problem.

1.2 Introduction of vitamin K1 injections

Vitamin K1 is an essential substance in the synthesis of prothrombin in the liver and can cause coagulation disorders when lacking. When the lack of prothrombin in the blood, blood coagulation will appear slow, then add appropriate amount of vitamin K1 can promote liver synthesis of prothrombin, play a role in hemostasis. Vitamin K1 as pharmaceutical formulations, applied to low thrombin disease, vitamin K1 deficiency, the prevention and treatment of neonatal hemorrhage, obstructive jaundice, biliary fistula, chronic diarrhea in clinic, Hypoprothrombinemia caused by coumarin and sodium salicylate etc.. Vitamin also has the effect of relieving pain and relieving bronchospasm, and has obvious effect on colic caused by visceral smooth muscle, colic, spasm of bile duct and spasm of intestine. Vitamin K1 can also be used as an additive for multidimensional foods and livestock feed.

Vitamin K1 indications: 1, low blood coagulation: intramuscular or deep subcutaneous injection, each time 10mg, 1-2 times a day, within 24 hours the total amount of not more than 40mg. 2, prevention of neonatal hemorrhage: 12-24 hours before delivery, intramuscular injection or slow intravenous injection 2 - 5mg. 0.5-1mg can also be injected intramuscularly or subcutaneously after birth, and can be repeated after 8 hours. 3, this product is used in patients with severe static injection, the speed of medication should not exceed 1mg/. 4, can be used for chronic poisoning caused by brodifacoum. Specific usage: (1) intravenous injection of 5 mg / kg vitamin K1, such as the need to repeat 2-3 times, each time interval of 8-12 hours. (2) oral administration of 5 mg / kg of vitamin K1 for 10-15 days. (3) intravenous injecting 200 ml of lemon acidified blood.

1.3 Possible risks

Adverse reactions of vitamin K1: occasionally allergic reactions. Mainly occurs when the intravenous injection is too fast, more than 5mg/ minutes can cause facial flushing, sweating, bronchospasm, tachycardia,

hypotension, etc., serious allergic reactions may endanger life. Intramuscular injection can cause redness and swelling. The newborn may suffer from hyperbilirubinemia, jaundice and hemolytic anemia after the use of the product.

.1.4. Benefits

Cerebral hemorrhage is a common disease in Department of neurosurgery. It is an important measure to reduce the mortality and disability rate in the acute stage. Vitamin K1 may reduce the risk of rebleeding in patients with intracerebral hemorrhage, and the amount of brain bleeding is directly related to prognosis. Effectively reduce the amount of intracerebral hemorrhage, improve the prognosis, reduce the length of stay, reduce the time of admission to ICU and reduce the mortality.

2 Test purpose

The effectiveness and safety of vitamin K1 were mainly targeted at patients with cerebral hemorrhage (non aneurysm or vascular malformations, rupture, bleeding). To observe whether vitamin K1 can effectively avoid the increase of cerebral hemorrhage and improve the prognosis.

3 Test design

The study included spontaneous hypertensive intracerebral hemorrhage at super tentorium of cerebellum patients as the research object, to exclude cerebral aneurysms or cerebral hemorrhage, venous malformation of abnormal liver function, taking anticoagulants or antiplatelet drugs in patients. The study was divided into the experimental group and the control group, and a multicenter randomized controlled trial was conducted. In the use of a etamsylate intravenous infusion of 0.5g of patients admitted to hospital within 8 hours later, the experimental group in the incidence of cerebral hemorrhage within 2 days after the daily intravenous infusion of vitamin K1 20mg, the control group received intravenous saline, all patients were no longer use other hemostatic agents. The efficacy and safety of vitamin K1 in the early onset of cerebral hemorrhage were assessed by the observation between two groups.

A randomized, single blind, positive / placebo parallel control, multicenter, clinical trial design was used. The treatment lasted for 2 days and followed up for 6 months.

4 Subjects recruited and exited

4.1 Diagnostic criteria

4.1.1 Diagnosis of cerebral hemorrhage

Referring to "Surgery" edited by Chen Xiaoping, and published in 2011 by people's Medical Publishing house.

4.1.2 Treatment methods

According to "Neurosurgery of Wang Zhongcheng", conventional cerebral hemorrhage treatment.

4.2 Inclusion criteria

1) Patients with spontaneous intracerebral hemorrhage (enhanced by cerebral arterial CT or cerebral angiography confirmed rupture of non aneurysm or arteriovenous malformation);

3) Age 18-65 years, male or not pregnant female;

4) GCS score at admission;

5) Head CT or MRI examination confirmed cerebral hemorrhage at super tentorium of cerebellum and the amount of bleeding in 10ml-45ml (Duotian formula to calculate the hemorrhage volume);

6)During the hospitalization, no urokinase and other hemostatic drugs were used except for the use of K1 and vitamin D in the project;

7) Informed consent form signed by the patient's family.

4.3 Exclusion criteria

1) CT scan and irregular lobulated hematoma, such as intraventricular hemorrhage (because no accurate measurement of bleeding);

2) Severe liver disease or impaired liver function;

3) Pregnant or lactating women;

4) The usage of anticoagulation or antiplatelet aggregation drug history (including cilostazol, aspirin, dipyridamole, heparin, low molecular weight heparin, hirudin, dabigatran, rivaroxabanand warfarin);

5) Non informed consent.

4.4 Rejection standard

1) The subjects failed to meet the inclusion criteria and were mistakenly included in the trial.

2) The subjects met either of the exclusion criteria.

3) No record of any further visits.

4.5 Exit test standard

4.5.1 The researchers decided to quit

1)During the clinical trial, the subjects experienced other complications, complications,

or special physiological changes, and were not allowed to continue the experiment..

2) Serious adverse events and important adverse events, it is not appropriate to continue to accept the test.

3) The subjects had poor compliance.

4) The test process meets the rejection criteria.

4.5.2 The subjects pulled out of their own accord

1) The subjects were unwilling or unable to continue clinical trials and asked the researchers for an exit test.

2) The subjects were not explicitly asked to quit the trial, but those who were not receiving the medication and the test were lost.

4.5.3 Withdrawal case management

In the case of the withdrawal from the trial, the researchers should actively take measures to complete the final examination as soon as possible to analyze the efficacy and safety. All trial cases should be completed in the case report form and the reasons for the withdrawal.

5 Suspension test standard

The discontinuation test means that the clinical trials have not been completed by the end of the program. The purpose of the suspension test is to protect the rights and interests of the subjects, to ensure the quality of the test and to avoid unnecessary economic losses. Standard for discontinuation of a test:

1) serious safety problems in the test, should promptly stop the test.

2) The trial found that the drug did not have clinical value and should discontinue trials, on the one hand, to avoid delaying the effective treatment of the subjects while avoiding unnecessary economic losses.

3) In the experiment, it was found that the clinical trial program had major errors and

it was difficult to evaluate the effect of the drug; or a well-designed design, which made important deviations in the implementation, and continued, it is difficult to evaluate the effect of the drug.

4) The applicant asked for a suspension (such as funding reasons, management reasons, etc.).

6 Treatment Plans

6.1 Experimental medication

6.1.1 Drug delivery

Test drug: vitamin K1 for injection, specification: 10mg each

Contrast drug: normal saline.

All trials were administered by the investigators in a single blind manner,.

6.1.2 Drug storage and stability

Test drug storage conditions: shading, airtight, cool and dry place to preserve.

6.1.3 Preparation

The study nurse assigned the experimental drug according to the instruction manual in the kit. Before using, add the test medicine to 100ml 0.9% Sodium Chloride Injection and shake it well.

6.1.4 Route of administration

Basic treatment: all subjects according to the routine treatment of cerebral hemorrhage, the use of Phenol ethylamine intravenous 0.5g within 8 hours after admission, another program in accordance with the "Neurosurgery of Wang Zhongcheng", including the surgical removal of hematoma and drainage, conservative treatment, control of intracranial pressure, prevention of complications.

Test group:

Normal saline 100ml+Vitamin K1 20mg, Once a day, intravenous drip, two days in

hospital.

Control group:

Normal saline 102ml, Once a day, intravenous drip, two days in hospital.

6.1.5 Test cycle

Medication for 2 days + followed up for 6 months.

7 Test procedure and plan

7.1 Test program evaluation

①Demographic data: age, sex, and ethnic group.

⁽²⁾History: ask for or collect current and past medical history based on existing medical records.

③Medication history: before taking the test, take the prescription or over-the-counter drugs, and record the generic name, daily total dose, usage and cause of use of the drug.
④The diagnosis of disease was confirmed by CT or MRI, and the amount of cerebral hemorrhage was calculated at the later stage (after the onset of the disease, the examination was not repeated).

⁽⁵⁾Physical examination: vital signs include body temperature (Ye Wen), respiration, heart rate, and blood pressure.

⁽⁶⁾Assessment of biological specimen collection and laboratory: collected blood and urine of Hematology, serum biochemistry, pregnancy test and laboratory examination, biological specimens from all participating units of the laboratory is responsible for collecting, processing, preservation and detection. Prior to the signing of the test drug, the clinical trial participant shall provide the bid with the normal reference range of the laboratory indicators. If there is any change during the test period, the applicant shall be promptly informed of the bid.

⑦Scale evaluation: mRS score.

7.2 Test procedure

Subject to any test procedure, the subjects, legal agents and / or subjects must have read and signed an informed consent letter approved by the ethics committee. The test

procedure shall be carried out within the prescribed time window of the visit, as detailed in the test flow chart.



7.3 Follow-up visit

1 months (+ 3 days) and 6 months (= 3 days) after the onset of intracerebral hemorrhage: the researchers performed a mRS score using telephone follow-up.

7.4 Unscheduled visit

During the trial, unplanned visits should be made if the subject is unwell.

7.5 Test flow chart

			treat	ment		vi	st
Time point	(D0)	D1	50	D7	Discharge	The first	The six
		DI	50	וע	or death	month	month
Collect basic inf	ormation	-	-		_	-	
informed consent	\checkmark						
Inclusion Criteria	\checkmark						
History	\checkmark						
acquisition							
General	\checkmark						
information							
Check item	Γ	ľ	T	T	T	r	1
temperature	\checkmark			\checkmark			
Vital signs	\checkmark			\checkmark			
Cerebral	\checkmark		\checkmark	\checkmark	\checkmark		
hemorrhage							
volume (CT)							
GCS						\checkmark	\checkmark
Drugs and	\checkmark	\checkmark	\checkmark				
dosages							
24h intake and	\checkmark						
output							
Blood routine,	\checkmark		\checkmark	\checkmark	\checkmark		
liver and kidney							
function,							
electrolyte	1	1					
Platelet							1
Coagulation				\checkmark	\checkmark	\checkmark	\checkmark
function	1	1	1		1	1	1
Complications	N	V	N	N	N	N	\checkmark
and adverse							
reactions						1	1
MRS						N	N
ICU total							

	hospital stay
--	---------------

7.5 Concomitant medication and treatment

7.5.1 Basic treatment

Allow the cerebral hemorrhage treated with conventional therapy control of intracranial hypertension, prevention of complications, but it must be the case report form to record the medicine general or other treatment, dosage, reason, use frequency and time etc, so as to summarize, analyze and report.

7.5.2 No medication or treatment

During the period of medication and during the follow-up period, drugs that affect the efficacy of the regimen may not be used, such as antithrombotic or anticoagulant or hemostatic drugs.

7.5.3 Medication and treatment are permitted

(1) The other combined diseases without affecting the curative effect and safety evaluation, can be symptomatic medication, but it must be the case report form to record the medicine general or other treatment, dosage, reason, use frequency and time etc, so as to summarize, analyze and report.

⁽²⁾The follow-up period can use cognitive rehabilitation methods, including occupational therapy, implicit memory rehabilitation, errorless learning, cognitive neuropsychological rehabilitation, rehabilitation and computer assisted cognitive rehabilitation, virtual remote control via the Internet, and the electromagnetic stimulation, should be recorded in detail in CRF.

⁽³⁾The combination drugs used for adverse events during the trial should be recorded in CRF.

8 Therapeutic evaluation standard

Main outcome measures: the amount of intracerebral hemorrhage (0d, 1D, 3D, 7D) at each time after the onset of disease.

Main outcome measures: (1) the amount of the time changes in blood coagulation, platelet levels and GCS scores after the onset (0d, 1D, 3D, 7D); (2) days in ICU; (3) the total hospitalization days; (4) complications including neurological complications, complications, blood coagulation circulatory complications after cerebral hemorrhage; (5) 1m and 6m mRS score.

9 Safety evaluation

9.1 Definition

Adverse events (Adverse, Event, AE): refers to the patient or clinical trial subjects after receiving a drug adverse medical events, but not necessarily have a causal relationship with the treatment.

Serious adverse events (Serious Adverse, Event, SAE): the need for hospitalization, prolonged hospitalization, disability, affecting work ability, endanger life or death, resulting in congenital malformation occurred during the clinical trial.

Important adverse events are any adverse events or laboratory abnormalities that result from the use of targeted medical measures (such as discontinuation, dosage reduction, and / or symptomatic treatment) other than SAE.

Adverse drug reactions (ADR): adverse reactions that occur when prescribed drugs are applied at prescribed doses, not as desired, but are causally related to the use of the drug. In a clinical trial of a new drug or a new drug, when the dose of treatment has not yet been determined, all harmful reactions that are not expected to cause a causal relationship with the use of the drug should be considered adverse drug reactions.

9.2 Background data on safety associated with experimental drugs

The clinical adverse reactions include anxiety, skin itching, rash, nausea and stomachache, which can subside spontaneously after withdrawal. A small number of patients developed mental excitement and abnormal sleep.

9.3 Handling and recording of adverse events

9.3.1 Treatment for adverse events

Inpatient

If the subject has adverse events during hospitalization, follow the following procedures:

Found adverse events in subjects, tube bed doctor or the doctor on duty shall promptly inform researchers, if necessary, can be the first symptomatic treatment, the degree of correlation between classification by research physician preliminary assessment of adverse events and drug test, and give further advice:

- ① General adverse events: can closely observe the outcome of the event or the corresponding symptomatic treatment;
- ② Important adverse events: physicians should promptly inform major researchers, and pause treatment, adjust drug dosage and targeted treatment according to the subjects' condition;
- ③ Serious adverse events: follow "9.4" for processing and reporting.
- ④ According to the patient's treatment, if the subject's injury exceeds the capacity of the research department, the relevant department should be invited to consult and assist in the treatment.

Outpatient

The adverse events that the subjects after the study, physicians should ask detailed subjects at the time of the symptoms and signs and place, the necessary explanation and

guidance on the subjects, and the degree of correlation of adverse events and give preliminary evaluation; as the subjects in the local medical institutions, contact by telephone and reception the doctor, check again the degree of adverse events and give treatment advice:

 General adverse events: initial visit to local hospital and notification of outcome of close observation;

⁽²⁾ Important adverse events: recommend returning to the hospital for treatment or to the local hospital for treatment, and timely notification of the main researchers, such as limited local hospitals, doctors should be sent to the treatment. An emergency envelope is also provided for emergency blind use (if applicable). According to the plan request, adopts the pause treatment, adjusts the medicine dosage and the symptomatic treatment and so on.

9.3.2 Record of adverse events

(1) A physician should perform a record of adverse events, including at least the description of the adverse events, the time of occurrence, the length of the termination, the frequency of attack, and the need for treatment and, if necessary, records of the treatment given.

② In the original record as far as possible with the occurrence and development of SAE records, after the treatment, and record in the CRF table, the SAE track, until we get a proper solution or stable disease or a clear reason to research, clinical drug research institutions ethics committee, unit state food and drug administration, etc. provide a final report.

9.4 Severe adverse events

9.4.1 Treatment of severe adverse events

①In case of SAE, the first visit doctor shall notify the principal investigator or other doctors to be present. If it is serious, he or she shall notify the project leader when subjects are in danger;

② As for the judgment of SAE, according to the clinical manifestations, professional standard and immediate treatment or rescue measures must be taken; if serious toxicity caused by drug overdose, the researchers decided to accelerate the excretion of drugs and take other rescue measures, try to maintain the vital signs of the patients to be as stable as possible, ECG monitoring is necessary, if necessary the first visit doctor can get help from the relevant departments.

③ Outside the hospital subjects were judged as SAE and can't come back, they were advised to timely return to hospital or go to the local hospital. The researchers should immediately notice the person in charge of the project for further treatment; as in the local hospital, made contact with the doctors, to understand the specific situation, treatment advice.

9.4.2 Severe adverse events are reported

Researchers should give immediate rescue to serious adverse events occurred in the test, whether or not it is related to the study drug. The researchers should report to the relevant provinces, autonomous regions and municipalities directly under the drug supervision and administration department and the State Food and Drug Administration in 24 hours, report to the applicant, and ethics committee. The sponsor and researchers should quickly study what happened, and try to take the necessary measures to ensure the safety and interests of subjects and report promptly to administrative departments of health and other researchers involving the same drug. If serious adverse events associated with an experimental drug, the Applicant should undertakes the costs of the rescue and treatment of the patient and the corresponding financial compensation.. The researchers must fill out a "severe adverse event report" which should record when, how, and who are reported. The bidder guarantees to meet all legal requirements.

9.4.3 Hospitalization

Adverse events leading to hospitalization or prolonged hospitalization in clinical trials should be considered as serious adverse events. Any first hospitalized (even shorter than 24 hours). Is according to comply with this standard..

Hospitalization does not include the following circumstances:

• Rehabilitation facility

- Nursing home
- Routine routine emergency room admission
- O day surgery (e.g. outpatient / day / ambulatory surgery)

Hospitalization or prolonged hospital stays unrelated to worsening adverse events are not, in themselves, serious adverse events, for example:

- Because of the original disease, there is no new adverse event, and there is no exacerbation of the original disease.
- Management for reasons of hospitalization (e.g. routine annual examination).
- Clinical setting during the clinical trial (for example, according to the requirements of the test program).
- elective hospitalization with adverse events worsening (e.g., elective cosmetic surgery).
- scheduled treatment or surgery should be performed throughout the trial program.
- admission only because of blood use.

9.5 Grading of adverse events

Mild: mild symptoms can be tolerated, does not affect activities of daily living, symptoms are transient, in the continuing use of drugs during their own relief, without treatment.

Moderate: the symptoms are obvious, affecting the daily activities of the subjects, the symptoms for a long time, can be relieved or symptomatic relief after treatment. It may interfere with the use of investigational drugs, such as reducing drug dosages or stopping medications.

Severe: the subjects suffered from impaired body function, lost normal work and living ability, and had a long duration of symptoms. They had to be stopped and properly treated before they could be relieved

9.6 Adverse events and test drug evaluation

According to the sequence between the occurrences of adverse drug evens and usage of drugs, the type of drug reaction after drug withdrawal reaction is reduced, will disappear or reappear, causality assessment of adverse events related to study drug is certainly relevant, probably, may be related, and certainly can not. The first three were considered to be relevant to the study of the drug, which was evaluated as untoward effect of drug.(ADR).

Adverse events associated with the study of drugs are as follows:

(1)Affirmation: the use of evidence for the study of drugs, the occurrence of adverse events and research, the use of drugs have a reasonable chronological order, adverse events to study drug interpretation, more reasonable than other explanations. The drug withdrawal reaction is positive, and the repeated use (if feasible) is positive.

⁽²⁾Likely related: evidence of the use of research drugs, occurrence of adverse events, and rational timing of drug use in the study. Adverse events are more reasonable in explaining drug explanations than in other explanations. Positive drug withdrawal reaction.

It may be related to the evidence of the use of research drugs, the occurrence and use of adverse events, and the timing of the study of drugs. Adverse events can also be explained by other reasons. Positive drug withdrawal reaction.

③ Perhaps irrelevant: the use of evidence for the study of drugs, the occurrence of adverse events, explained by other reasons is more reasonable. Withdrawal reactions were negative or unclear. (4) Absolutely unrelated: no use of research drugs, or the use of research drugs and adverse events unrelated to the time, or otherwise clearly lead to adverse events.

9.7 Outcome tracking of adverse events

Adverse events at the end of the study or not yet relieved must be followed until one of the following events occurs:

✓ By accident mitigation;

✓ Have stable event;

when it is not possible to obtain other information (subjects or accompanying worker refuse to provide other information to prove after follow-up efforts).

According to the severity of the adverse reactions, the hospital visits, outpatient visits, home visits, telephone calls, communications and other forms can be adopted.