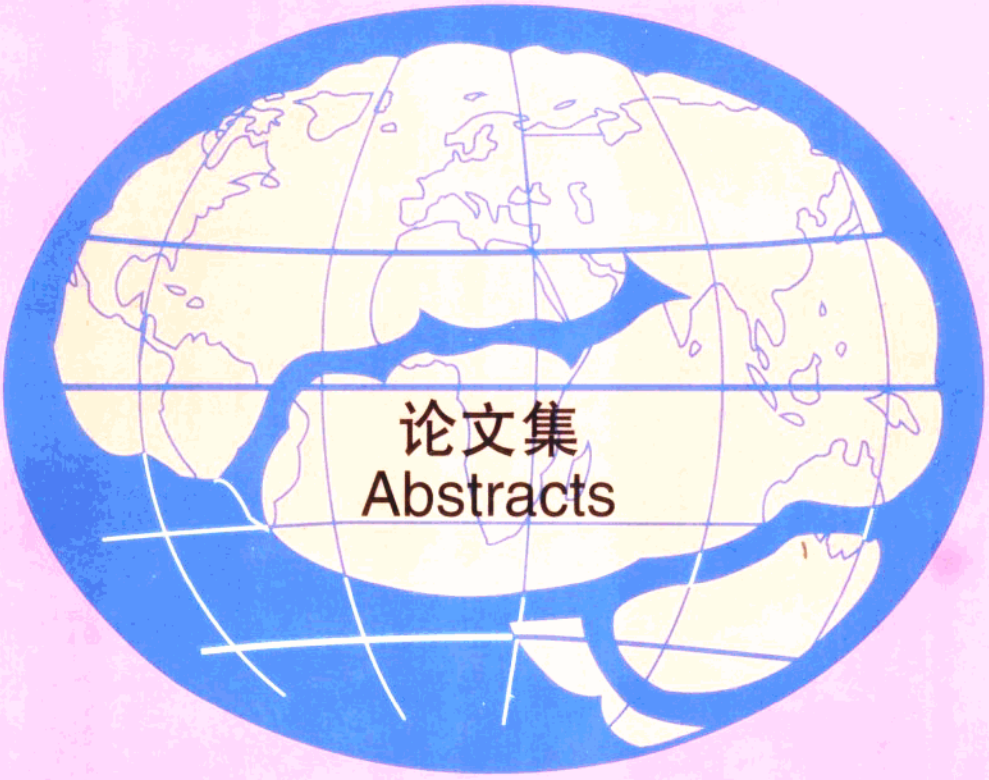
第二届国际临床神经病学学术研讨会

The 2nd International Clinical Neurology Symposium



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第二届国际临床神经病学学术研讨会

The 2nd International Clinical Neurology Symposium

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Conference Chairmen
Prof. Luo Zuming
Dept. of Neurology, West China University
of Medical Sciences, Chengdu, P.R.China
Prof. Charles Warlow
Dept.of Clinical Neurosciences, University

学术秘书组：刘鸣、邹晓毅、唐萍、林川、席静、刘凌、商慧芳
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第二届国际临床神经病学学术研讨会
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第二届国际临床神经病学学术研讨会论文集

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专题报告

001 THE EFFECT THAT RECENT TRIAL RESULTS SHOULD HAVE ON ACUTE STROKE MANAGEMENT

Professor Charles Warlow
Department of Clinical Neurosciences
Western General Hospital
Crewe Road
Edinburgh EH42XU

Tel:0131 537 2082
Fax:0131 332 7886
Email:*cpw@skull.dcn.ed.ac.uk*

Theory alone is not enough; the need for randomised trials

There is a tradition in medicine that treatment decisions can be based on theory, perhaps backed up by animal experiments and clinical anecdotes. But, theories which are said to explain disease and determine clinical outcome, always change with time. Anyway, it is both arrogant and foolish to suppose that we will ever know exactly what causes what in the confusion of real life clinical practice, and certainly not in the context of stroke in the foreseeable future. We must therefore be sure that a treatment which ought to work (on the basis of theory and animal experiments) actually does work in practice, also that any benefits out weigh any risks. Fortunately in medicine we often have the means to do this because we can allocate patients at random to either receive the new treatment, or not. This ensures that the two groups (the treated versus the control or untreated) are equal at baseline in all the factors that we know predict outcome, and in all those that we don't know about as well. Therefore, any definite differences in outcome between treated and control or untreated groups in a randomised trial must be due to the treatment being tested and not because one group would have done better anyway. So, any bias in allocating the new treatment to just the mildly affected patients, who will do well without any treatment at all, is completely avoided.

Systematic reviews and meta-analysis

These days there is so often not just one available randomised controlled trial (RCT), but several trials which have tested the same treatment in the same sort of patients. Therefore, if one wants to get the best evidence about a particular treatment intervention one needs to search out all the properly conducted RCTs and do what is now called a "systematic review". This ensures that firstly, there is no bias in which RCT is selected to review, and secondly that as much information as possible is used to reduce the effect of chance in small trials and so increase the precision of the estimate of the effect of treatment. Therefore, one must search for RCTs in any language, certainly not forgetting Chinese, published in any

journal, as a full paper or just as a letter or an abstract, and even for unpublished trials as well (the last are notorious for being more likely to be "negative", particularly compared with those published in prestigious and so easily accessible journals). However, a superficial search in an electronic database such as Medline is likely to miss half of the releveant RCTs. Fortunately, instead of having to search through countless journals and abstracts of meetings, the reviewer can now go directly to the Cochrane Library (published quarterly on CD-ROM or disc) which is, with 180,000 references to RCTs, the best single available source of trials. Having found all the relevant and available trials, one can now use the robust statistical technique known as meta-analysis This allows one to combine the results of all similar trials and so obtain a "bottom line" estimate of the relative reduction in a poor outcome in the treatment compared with the control group. This provides a more precise and less biased estimate of the treatment effect compared with looking at just one RTC, particularly at just the one with a result which happens to support your prejudice.

From the evidence to clinical practice

To decide what treatment to use in clinical practice one has to make inferences from data collected in previous patients. So which previous patients? The best source must in some way come from patients who are as similar as possible to the one sitting in the clinic waiting for your advice. And better than anecdotal reports on similar patients, and non-randomised case series of similar patients, and even than a single RCT in similar patients, is a well done systematic review of all the RCTs available in similar patients. These are apearing more and more in the literature, and also in the Cochrane Library. Using this principle, what can we say about recent advances in the management of acute stroke?

Aspirin

The Antiplatelet (now Antithrombotic) Trialists' Collaboration has been collating the results of all RCTs of antiplatelet, and more recently anticoagulant drugs, in a wide range of patients for more than 10 years. Now that the results of two very large trials of aspirin are available in about 40,000 acute stroke patients, we have a very precise estimate of its effect. It is not a large effect but it is worth having because the treatment is easy, familiar, non-toxic and cheap, and it can be applied to tens of thousands of patients worldwide every year. Aspirin, 150-300mg oral dily, given within 48 hours of stroke onset, will reduce the risk of recurrent stroke or death in the first two weeks by 11% (standard deviation 3%) (figure 1). This translates into about nine patients out of 1000 treated with aspirin. There is a 5% (standard deviation 2%) reduction in the risk of being dead or dependent after a few months, 13 out of 1000 patients treated avoiding this fate (figure 2). As far as one can work out, from this very large data set, this small but definite effect of aspirin applies to all types of stroke patient (male, female, young, lod etc.), treated at any time up to 48 hours post stroke, and probable even if a CT scan is not done first to exclude intracerebral haemorrhage, at least in Caucasians where most strokes are ischaemic. Provided the patient is not

drowsy, and so unlikely to have an intracerebral haemorrhage of any size, aspirin can be started at once, but stopped if a later CT scan shows haemorrhage.

Heparin

Heparin certainly ought to work in theory (reduced risk of recurrent ischaemic stroke, reduced propagating thrombosis, less venous thromboembolism etc.) but in a way it actually works too well. From the International Stroke Trial, and other smaller trials not yet fully reviewed, the excess risk of early haemorrhagic stroke cancels out the useful effect reducing recurrent ischaemic stroke (1). Moreover, the outcome at six months was almost identical, and rather surprisingly the message was the same for every subgroup examined, even for atrial fibrillation. This is not to say that there might in fact be some patients who would benefit from heparin, but just that we cannot tell who they are. So, routine heparin in acute ischaemic stroke is not indicated.

Thrombolysis

Thrombolysis is likely, in theory, to promote both the haemorrhagic transformation of a cerebral infarct (risk) and recanalisation of the blocked artery and so reduce cell death (benefit). But an estmate of the balance of risk and benefit can only be obtained from RCTs and a meta-analysis is available in print and in the Cochrane Library(2). Clearly both streptokinase and tissue plasminogen activator (tPA) increase the risk of intracranial haemorrhage during the early treatment period, and so early death (figure 3). But, even including this early risk, it seems that thrombolysis may well reduce the risk of death and dependency after a few months (figure 4). The apparent lack of effect of streptokinase may be because the trials were mostly in patients randomised up to six hours post stroke onset, whereas the more promising results in the tPA trials may be because most patients were randomised in under three hours. Very clearly we need much more information from large pragmatic RCTs to sort out more precisely who is at particular risk, and who might gain the most benefit (for example, is this balance different in the old versus the young, those treated with one thrombolytic in a particular dose rather than another, those treated earlier rather than later, severe strokes versus milder strokes, those with hypodensity on brain CT versus not, those with high rather than low blood pressure, etc?). If we can deliver this somewhat risky treatment effectively, and if the meta-analysis turns out to be accurate, then for every 1000 patients treated with thrombolysis we might cause 91 early deaths but prevent 65 deaths and dependent survivors overall.

Stroke Units

Almost no *single* RCT of organised stroke care has shown a better outcome than care in a non-specialised medical ward. However, if *all* the RCTs are put together in a meta-analysis there is then a sufficient sample size (and so sufficient statistical power), to demonstrate that there is a 29% reduction in the risk of death and dependency. For every 1000 patients

treated in such a system, there will be about 50 fewer dead, 180 fewer dead or dependent, and 150 fewer dead or in an institution(3). Moreover, there is no increase in length of hospital stay. Exactly what is responsible for this beneficial effect is not really clear but it may be some combination of working in a multidisciplinary team (doctors, nurses, physiotherapists, occupational therapists, speech therapists etc.), involving the carers in the rehabilitation process, education and training. Although it is not certain that this care should be provided in a defined area of the hospital (i.e. a stroke unit), this is probably the most convenient arrangement. Also it is probably best to admit stroke patients directly to such units for both acute care and then for later rehabilitation.

Conclusions

Stroke patients who need hospital admission should be admitted to an organised stroke unit with easy and quick access to CT scanning (to exclude intracerebral haemorrhage in the first instance) and to a multidisciplinary team for their immediate care and longer term rehabilitation. Anything less is sub optimal. Patients with ischaemic stroke should immediately be given 300mg aspirin by mouth, or nasogastric tube. After a few days the dose can be reduced to 75mg daily for long term secondary prevention of stroke, and of myocardial infarction. There is no obvious place for routine heparin but in ischaemic stroke survivors in atrial fibrillation, long term prevention with warfarin (INR about 3.0) is more effective than aspirin if this treatment can be delivered safely. The exact place of thrombolysis in acute ischaemic stroke is unclear but some highly organised units may well start giving inravenous pTA (0.9mg/kg) to patients seen within three hours of stroke symptom onset. At present there is not enough evidence from RCTs and meta—analysis to support the use of neuroprotective drugs, calcium antagonists, Trental, haemodilution, manipulation of the blood pressure, or osmotic agents, their use would owe everything to theory and nothing to evidence. If we are to be sure that these and other treatments are doing more good than harm, we have to insist and then rely on randomised trials, systematic reviews of those trials, and then competent meta-analyses.

References

1 The International Stroke Trial Collaborative Group (1997) The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both or neither among 19,436 patients with acute, presumed ischaemic stroke. *Lancet* 349 1569-1581

2 Wardlaw, J.M., Warlow, C.P. and Counsell, C. (1997) Systematic review of evidence on thrombolytic therapy for acute ischaemic stroke. *Lancet* 350 : 607-614

3 Stroke Unit Trialists' Collaboration (1997) Collaborative systematic review of the randomised trials of organised in patient (stroke unit) care after stroke. *BMJ* 314 1151-1159

002 Differential Diagnosis of Dementia

Benjamin Seltzer M. D.

Department of Psychiatry and Neurology HC 82 Tulane Univerysity, School of Medicine, 1430 Tulane Avenue, New Or leans, Louisiana 70118 USA

Ⅰ. Definition of the dementia syndrome

Ⅱ. Differential diagnosis of the dementia syndrome

A. Delirium

B. Circumscribed neuropsychiatric syndromes, e.g. aphasia. amnesia.

C. Age—associated memory impairment

D. Subjective memory complaint

E. Depression with cognitive impairment

Ⅲ. Classification of the dementias

A. Clinical symptomatology

1. subcortical dementias

2. cortical dementias

a. anterior (frontal) syndromes

b. posterior (parieto—temporal) syndromes

B. Etiology

1. Secondary dementias

a. infectious, e.g. AIDS, neurosyphilis, Jakob—Creutzfeldt disease

b. traumatic, e.g. subdural hematoma

c. neoplastic

d. toxic and metabolic, e.g. pernicious anemia, thyroid disease

e. Other neurologic diseases, e.g. Parkinson's, Huntington's, multiple sclerosis

f. vascular dementia

g. normal pressure hydrocephalus

h. dementia syndrome of depression

2. primary dementias

a. Alzheimer's disease

b. Pick's disease/frontotemporal dementia

c. diffuse Lewy body disease

d. progressive subcortical gliosis

e. hippocampal sclerosis

Ⅳ. Evaluation of the patient with dementia

A. Clinical history

B. Neurological examination

C. Mental state examination

D. ? Neuropsychological examination

E. Medical evaluation

F. Specific laboratory tests, e.g. serology, thyroid, vitamin B12, HIV, ? ApoE, etc.

G. Neuroimaging, CT vs MRI

H. ? EEG

Up—date on Alzheimer's Disease

Ⅰ. Prevalence and importance of Alzheimer's disease

Ⅱ. Pathology of Alzheimer's disease

A. Neuritic plaques

B. Neurofibrillary tangles

C. Miscellaneous changes

D. Loss of cells and synapses

E. Differentiated from other conditions and normal aging by density and localization of changes

Ⅲ. Current theories on the etiology of Alzheimer's disease

A. Environmental risk factors

1. Aluminum
2. Head injury
3. Electromagnetic forces
4. Solvents/other chemical exposures
5. Viruses/infectious agents
6. Miscellaneous

B. Genetic risk factors

1. Downs syndrome
2. Familial Alzheimer's disease
   a. Chromosome 21 and amyloid precursor protein
   b. Chromosome 14 and presenilin—1
   c. Chromosome 1 and presenilin—2
   d. Others
3. Chromosome 19 and apolipoprotein genotype

Ⅳ. **Current theories of pathogenesis**

A. Neurotransmitter deficiencies

1. Cholinergic hypothesis
2. Other neurotransmitters

B. Oxidative stress and free radical formation

C. Amyloid

D. Other theories

Drug Treatments for Alzheimer's Disease

Ⅰ. **Cognitive symptoms**

A. Older therapies

B. Cholinergic replacement therapies

1. Cholinergic precursors
2. Cholinergic agonists
3. Cholinesterase inhibitors

physostigmine; tacrine; donepezil; rivastigmine; metrifonate; galantamine

C. Other neurotransmitters, including combinations

D. Anti—oxidants; metabolic enhancers

Vitamin E, 1—deperenyl, lazabemide; idebenone

E. Vascular agents

Propentophylline

F. Growth factors (may include estrogens)

G. Membrane stabilizers

H. Anti—excitotoxins

I. Anti—amyloid agents

J. Genetic engineering

Ⅱ. **Design of drug studies**

A. Homogeneity of diagnosis

B. Choice of outcome measures

C. Duration of studies

D. Practical issues

Ⅲ. **Treatment of non—cognitive symptoms**

A. Non—pharmacologic

B. Antidepressants

C. Neuroleptics: traditional, atypical

D. Sedative/hypnotics

E. Other agents for agitation, e.g. beta－blockers, anticonvulsants

003A Thombolytic Therapy in Acute Cerebral Infarctions

Chen Qingtang

Department of Neurology, First Hospital of Beijing Medical University

Abstract

Early in 1958, the thrombolytic therapy for acute ischemic stroke was used in China. But it was noted that the incidence of hemorrhagic transformation and the mortality rate increased because of the indications for thrombolytic therapy and the dosage of thrombolytic drugs were not strictly controlled, the thrombolytic therapy was not continued. In the beginning of 1980s, the thrombolytic therapy in acute myocardial infarctions got great success. It promoted the development of thrombolytic therapy for acute ischemic stroke. Zeumer et al (1984) first began to treat patients with acute cerebral infarctions by thrombolytic drugs. Near 6000 cases had accepted thrombolytic therapy in the world till now. After that, large groups of multicenter, randomized, double blind, placebo controlled clinical trials were established in the United States and European countries. In 1997, FDA approved to recommend rt－PA to be used as a thrombolytic drug in acute ischemic stroke within 3 hours from symptoms Onset.

Streptokinase (SK) was not recommended because the mortality rate and disability rate were significantly higher than the placebo group.

Brain tissue is characterized by high perfusion and high oxygen consumption. As soon as it suffers from ischemia, a cascade of biochemical changes will occur, including energy depletion, accumulation of excitative amino acids (EEA) in the intersynaptic space, opening of calcium channel leading to the overload of Ca^{2+} and delayed neuronal death, the increase of O_2 free radicles, lactic acidosis, and NO toxicity, etc. Neuropathologically, the tissue in the center of the infarction will be necrotic, while the peripheral area, in which the function of the cells is reversible, is called the penumbra. After several hours of ischemia, the central area of the infarction (necrotic area) will enlarge and the penumbra area will reduce. Therefore, the purpose of the thrombolytic therapy is to restore the blood supply before the necrosis of the brain parenchyma. To control the thrombolytic time window, i.e. the time between the onset of the symptoms and the beginning of the thrombolytic therapy is most important, Usually the time window for urokinase (UK) is within 6 hours, for t－PA is within 3 hours (within 90 min is better). Anyway, the time window is shorter, the outcome will be