JOURNAL SCAN

Journal scan

Edited by Jim Wardrope; this scan coordinated by Rob Russell

Thrombolysis for acute ischaemic stroke

Thrombolysis for acute ischaemic stroke remains a controversial area. The National Institute of Neurological Disorders and Stroke study (NINDS)¹ trial reported improved long term neurological function when patients were treated with intravenous tissue type plasminogen activator (iv tPA) within three hours of symptom onset. This benefit was set against an increased risk of intracerebral haemorrhage (ICH). Further studies have produced similar results, although others have not shown any benefit. Doubts remain regarding the safety and efficacy in routine clinical use outside specialist centres. The debate continues in this contentious area and two contrasting papers show different positions and results. It would be a useful postgraduate educational exercise to compare and contrast these studies in detail and try to explain the very different findings in these trials. What are the main conclusions that you draw from this issue? Prize for the best critique that is e-mailed to the Journal scan editor by 22 September 2000.

Use of tissue-type plasminogen activator for acute ischaemic stroke—the Cleveland area experience

I L Katzan, A J Furlan, L E Lloyd, *et al*
JAMA 2000;283:1151–8

Objectives—To assess the rate of tPA use, the incidence of symptomatic ICH, and patient outcomes in a large urban community (Cleveland, Ohio).

Design—Prospective cohort study over one year.

Patients—3948 patients admitted to study hospitals with a primary diagnosis of acute ischaemic stroke.

Methods—Structured chart review of all stroke patients admitted to all of the 29 Cleveland area hospitals.

Outcome measures—Rate of tPA use: occurrence of symptomatic ICH in patients given tPA: proportion of those treated with tPA where treatment varied from national protocols: in-hospital mortality in patients treated with tPA compared with those not thrombolysed, comparison of mortality and length of stay between a case-control matched group.

Results—3948 patients with ischaemic stroke were identified. Altogether 674 were admitted within three hours of symptom onset. Seventy (1.8% of total, 10.4% admitted within three hours) received tPA. Eleven of these (15.7%)

had a symptomatic ICH of which six were fatal. In-hospital mortality was significantly higher among patients receiving tPA ($p < 0.001$). Half of the cases in which tPA was used showed there was at least one deviation from the national protocol governing its use in this situation.

Conclusions—Only a small proportion of patients with acute ischaemic stroke received tPA; there were high rates of symptomatic ICH and deviation from national protocols for the use of this drug. The community experience differs from that of the clinical trial.

Intravenous tissue-type plasminogen activator for treatment of acute stroke—the standard treatment with alteplase to reverse stroke (STARS) study

G W Albers, V E Bates, W M Clark, *et al*
JAMA 2000;283:1145–50

Objectives—To assess safety and efficacy of the routine use of tPA in patients with acute ischaemic stroke.

Methods—A prospective multi-centre study of 389 consecutive patients from 57 different centres. The outcome measures were clinical outcome, adverse events and protocol violations. A control group was not included. The study recruited all its centres from those already involved in another study of thrombolysis and all the principal investigators at each centre were neurologists with experience of thrombolysis for stroke.

Results—30 day mortality rate was 13%. Some 3.3% of patients experienced symptomatic ICH. Thirty five per cent of patients were judged to have a very favourable outcome. Even using experienced investigators, tPA was given to 127 (33%) patients against the advice of national treatment protocols.

Conclusions—Good clinical outcomes and low rates of symptomatic ICH can be achieved.

Critique—These are very different studies but examination of the baseline patient characteristics shows many similarities in the study populations. They contrast the care in a general population base (Cleveland) and a selected population attending hospitals whose previous participation in randomised trials of this treatment must mean that they have experience and expertise in this treatment. One point of agreement would seem the low number of stroke patients who receive this treatment (389 patients from 57 centres in two years compared with 70 patients from 29 cen-

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tres in one year). The findings are very different with one study with a 3.3% rate of symptomatic ICH and one with a 16% rate of ICH. In the Cleveland study the mortality of all stroke patients not treated was 5.1%, for those treated with tPa 16%, and in the other study the mortality of those treated with tPa was 13%. These groups are possibly not comparable and end points for mortality were not the same (hospital discharge versus 30 day). However, these findings raise important questions. How can one explain the differences in mortality? Is it attributable to the experience of the institutions involved? Are there any differences in the type of protocol violations that might explain the differences in ICH? Answers by e-mail please.

Randomised placebo controlled trial of nebulised corticosteroids in acute respiratory syncytial viral bronchiolitis

A Cade, K G Brownlee, S P Conway, *et al*
Arch Dis Child 2000;**82**:126–30

Objectives—To evaluate the short and long term effect of nebulised budesonide in the early treatment of respiratory syncytial virus (RSV) bronchiolitis.

Design—Multi-centre randomised double blind placebo controlled study.

Patients—Infants admitted to hospital with their first episode of RSV bronchiolitis.

Methods—Patients received 1 mg nebulised budesonide or placebo twice daily from admission to two weeks after discharge. Follow up was continued for one year.

Outcome measures—Length of hospital stay; time taken to become symptom free; re-admission rates; GP consultation rates; use of anti-wheeze medication during follow up.

Results—There were no significant differences found between the two groups in any of the outcome measures.

Conclusions—No short or long term clinical benefit was gained from the use of nebulised corticosteroid in the acute phase of RSV bronchiolitis.

Critique—We know nebulised corticosteroids are useful early in croup but there is conflicting evidence of effectiveness in bronchiolitis so this remains an important question. The study had a number of strengths. RSV infection was confirmed by immunofluorescence testing, other trials have not had such a clearly defined group. Most of the exclusion criteria (for example, prematurity, chronic lung disease) are reasonable. The trial was blinded and randomised. The follow up rates were very good, even at one year. The method of randomisation is unclear although it was stratified for sex and study centre and treatment groups were well matched for demographic factors such as breast versus bottle feeding and smoking within the family. Only four patients were excluded after randomisation, two for being RSV negative. The strength of using RSV testing before randomisation gave rise to potential weakness as it caused a delay in randomisation and treatment of up to 12 hours. Compared with a median length of stay of two days, this delay may have been significant. Earlier admin-

istration might have been achieved if it had been acceptable to randomise and treat then test for RSV. However, this would have led to many exclusions and problems with an intention to treat analysis. There was no measure given to describe the severity of the illness at admission. Unfortunately the power calculation suggested that 100 children would be needed in each arm to demonstrate a reduction of coughing or wheezing episodes from 50% to 30%. This was not achieved as the study period (one winter) ended before that number could be reached. It was rightly felt that continuing the study the next winter would not be acceptable as the nature of the virus could change and the environmental conditions would be different. The paper states that all but two children received other drugs while in hospital. The prescribing practices were apparently "broadly similar", however, no analysis of this was given. These drugs included oral and intravenous corticosteroids, a flaw that could give rise to serious confounding of the results. Only just over 50% of patients in each group received the full trial course on returning home. The paper is a useful step in excluding the use of early inhaled corticosteroids in children with bronchiolitis but has too many weak points to allow confidence in this conclusion.

Prevention of infection in multiple trauma patients by high-dose intravenous immunoglobulins

E E Douzinas, M T Pitaridis, G Louris, *et al*
Crit Care Med 2000;**28**:8–15

A prospective randomised double blinded placebo controlled trial of intravenous immunoglobulins in 39 patients with major trauma (ISS>15 and <50) in an intensive care unit. The treatment group suffered significantly fewer pneumonias and non-catheter related infections but mortality and length of stay were not affected. The study also showed significant differences in serum bactericidal activity between the groups. Altogether 156 patients were excluded from the trial indicating a very select patient group. While there were significant reductions in some types of infection the lack of difference in intensive care unit stay does not indicate that this should be routine treatment. There were no deaths in the study, perhaps because of patient selection but would indicate the problems of trying to establish mortality as an end point given this methodology.

Physical treatment of fever

E Purssell

Arch Dis Child 2000;**82**:238–90

This is a review of four studies carried out to determine the efficacy of tepid sponging in reducing fever in children. All of the studies used tepid sponging in addition to anti-fever medication. This review states that none of the studies showed a major additive effect although no information as to sample size, study method or statistical analysis is given. It is suggested that other physical methods of cooling (removal of clothing, fanning) may be equally ineffective as they all rely on heat loss via conduction. Sensibly the paper recommends tepid

sponging if the child finds it relieving, but there is insufficient evidence presented to make a case for or against it.

Carrying passengers as a risk factor for crashes fatal to 16- and 17-year-old drivers

L Chen, S P Baker, E R Braver, *et al*

JAMA 2000;283:1578–82

Canada, New Zealand and some of the United States have introduced graduated driver licensing, whereby newly qualified drivers spend a probationary period with restrictions before obtaining a full licence. These restrictions vary but may include a limit on night time driving and carrying passengers. This incidence study examined three national US databases for information on crashes involving 16 and 17 year old drivers. The relative risk of death increased with each additional passenger under 30 and if the driver or passengers were male, more than doubling for two male passengers. Heightened risk taking behaviour in front of peers is thought to cause this increase. In contrast older drivers had a reduced relative rate of death while carrying passengers. Graduated licensing works as a form of accident prevention and should include passenger restrictions. The take home message is don't let your teenage children travel in cars with multiple passengers if they or another teenager is driving.

Mass psychogenic illness attributed to toxic exposure at a high school

T F Jones, A S Craig, D Hoy, *et al*

N Engl J Med 2000;342:96–100

This is a fascinating account of an episode of psychogenic illness that led to 171 people attending an emergency department on two separate days. The initial event was a teacher noticing a "gasoline-like" smell in her classroom and subsequently developing headache and other non-specific symptoms. Both staff and students throughout the school developed similar symptoms, and 38 were admitted for observation. The paper describes the extensive investigation into possible environmental causes, and analyses the risk factors for developing psychogenic illness in such situations. No cause was found but professionals were reluctant to declare the outbreak to be psychogenic in origin and the media were equally reluctant to accept this explanation.

Effect of out-of-hospital paediatric endotracheal intubation on survival and neurological outcome

M Gausche, R J Lewis, S J Stratton, *et al*

JAMA 2000;283:783–90

This controlled clinical trial compares bag-valve-mask ventilation (BVM) versus endotracheal intubation (ETI) as advanced airway techniques for children in the pre-hospital environment. Treatment groups were determined by using odd/even days. Overall there was no significant difference between the two groups, but BVM was significantly better in three sub-groups: respiratory arrest, non-accidental injury and foreign body aspiration. In the ETI group, there were high failure and complication rates and significantly longer on-scene times. The study used paramedics and an urban environment but does emphasise the point that simple airway maintenance and ventilation with rapid transfer is as good if not better than intubation in a difficult set of patients.

Unstable angina pectoris

Y Yeghiazarians, J B Braunstein, A Askari, *et al*
N Engl J Med 2000;342:101–14

This review article covers the current treatment of unstable angina. It provides a comprehensive review of the treatment of this condition. The section on medical treatment is particularly strong including ticlopidine, clopidogrel and platelet glycoprotein IIb/IIIa receptor antagonists as well as more established drugs. There is also a discussion of risk stratification and selection of management strategies, and a treatment algorithm forms part of the summary. The article is a useful update but unfortunately does not go into the problems of recognising this condition in the undifferentiated chest pain patients attending the accident and emergency department.

Safety and efficacy of Diclofenac ophthalmic solution in the treatment of corneal abrasions

P A Szucs, A H Nashed, J R Allegra, *et al*
Ann Emerg Med 2000;35:131–7

This is a prospective randomised double blinded placebo controlled trial of 49 patients with corneal abrasions. Diclofenac ophthalmic solution is a well established analgesic option in post-ophthalmic surgery. The study is well designed and included a power calculation before the start. Pain scores are significantly reduced in the treatment group with no increased incidence of infection. Topical analgesia for corneal abrasions is a useful addition to the current treatment.

1 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischaemic stroke. *N Engl J Med* 1995;333:1581–7.