Journal Watch: May-July 2012

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Early surgery versus conventional treatment for Infective Endocarditis

DH Kang, YJ Kim, SH Kim *et al*. *N Engl J Med* 2012; **366:** 2455-2473.

The treatment of infective endocarditis remains controversial with differing advice regarding timing of surgery in current guidelines.

This was a prospective, randomised study of 76 patients between 18 and 80 years old with proven left sided native valve infective endocarditis and at high risk of embolism, at two centres in Korea between September 2006 and March 2011. The primary endpoint was a composite of in-hospital death or clinical embolic events occurring within 6 weeks of randomisation. The aim of this study was to determine whether early surgery and valve repair or conventional treatment with antibiotics resulted in more favourable outcomes.

37 patients were randomised to the early-surgery group (undergoing surgery within 48 hours of randomisation), 39 patients underwent conventional treatment of which 30 (77%) required surgery (27 during admission, 3 during follow-up). All patients had definitive diagnosis of endocarditis according to the modified Duke criteria, with native valve vegetation greater than 10mm accompanied by severe left sided valve disease. Patients with moderate-to-severe CCF, infective endocarditis complicated with heart block, right sided lesions, valve abscess, destructive lesion requiring urgent surgery, or fungal endocarditis were excluded.

1 of the 37 patients in the early-surgery group met the primary end point (1 death) versus 9 in the conventional treatment group (1 death, 8 embolic events) (OR 0.10; 95% CI 0.01 to 0.82; P=0.03) at 6 weeks. Comparing embolic events as an endpoint, after 6 weeks the early surgery patients had an embolism rate of 0% compared with 21% in conventional treatment group (P=0.005).

The study concluded that early surgery in patient with large native valve vegetation infective endocarditis significantly reduced the composite end point of in hospital death or embolic event by reducing the risk of systemic embolism.

Although this was a small study, with a number of exclusion criteria, the results of this study show that early surgery is effective in reducing the risk of embolic events, thus reducing the morbidity and mortality rates. Therefore based on the results of this study, on confirming the diagnosis of infective endocarditis in suitable patients on admission to hospital, referral should be made to local cardio-thoracic surgeons to discuss early valve surgery.

Drogtrecogin Alfa (Activated) in Adults with Septic Shock

Ranieri VM, Thompson BT, Baile MD et al. *N Engl J Med* 2012; **366:**2055-2064.

The PROWESS trial showed favourable results of Recombinant Human Activated Protein C, or drotrecogin alfa (activated) (DrotAA), in the treatment of severe sepsis and multi organ failure, with lower mortality in patients at 28 days compared to placebo. This resulted in subsequent licensing for its use in clinical practice, although with set patient criteria.

Its role was believed to be due to antithrombotic, anti-fibrinolytic and anti-inflammatory properties and the inhibition of the activation of cytokines and other pro-inflammatory mediators involved in sepsis. However further studies have failed to confirm this data calling into question the efficacy of this treatment.

This large randomised, double-blind, placebo-controlled, multicentre trial set out to determine what effect if any DrotAA had on patient mortality in severe sepsis. The study was sponsored by Eli Lilly, manufacturers of *Xigris* (trade name for DrotAA).

A total of 1697 patients were recruited into this trial between March 2008 and August 2011. All had clinically defined septic shock requiring fluids and vasopressor support, with 846 patient receiving DrotAA (dose of 24μg/kg/hr) and 834 instead receiving a placebo for a period of 96 hours. Patients with any coexisting illnesses with a higher risk of death (i.e. metastatic cancer) were excluded from the study. Patients were followed until 90 days or death. The primary endpoint was death from any cause within 28 days after randomisation.

The study showed no difference in 28 day all-cause mortality between the two groups, with 26.4% mortality in the DrotAA group and 24.2% in the placebo group (RR in DrotAA group, 1.09;

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Journal Watch: May-July 2012

95% CI 0.92 to 1.28; p=0.31). There was equally no difference in the mortality rates between the two groups at 90 days.

The PROWESS study reported on increased rates of haemorrhage in patients receiving DrotAA, in particular life threatening intra-cerebellar bleeds. Although this study did show an increase in the number of what they defined as 'non-serious' bleeding events between the DrotAA group and the placebo, there was no significant increase in 'serious' bleeding events or intra-cerebellar bleeds.

The findings of this study showed that DrotAA was not of benefit in patients for which it was originally licensed, and therefore from this it could be said that it should not be used in the treatment of septic shock.

On the basis of the results of this trial Eli Lilly have withdrawn *Xigris* from the market in October 2011.

Adverse outcomes after hospitalisation and delirium in persons with Alzheimer's disease.

Fong G, Jones R *et al*. *Ann Internal medicine*. 2012; **156:** 848-856.

Hospitalisation can be a major life changing event for patients with Alzheimer's disease (AD). In this study, patients with AD were assessed during their hospital admission to determine whether delirium was associated with adverse outcome. The study concluded that 1 in 8 patients with AD who developed delirium during their hospital admission had an adverse outcome. The adverse outcomes measured were cognitive decline, institutionalisation and death. Cognitive decline was defined as a decrease of 4 or more points on the Blest information-memory-concentration test score. Delirium was identified by the presence of mental status or behavioural changes by using a method validated against the confusion assessment method.

This was a prospective study of 771 patients with probable or possible AD according to the guidelines from the National Institute of Neurological and Communicative diseases and Stroke and Alzheimer's Disease. Of these 771 patients, 367 (48%) patients were hospitalised and 194 (25%) developed delirium. Hospitalised AD patients who did not have delirium had an increased risk of death (adjusted RR, 4.7 [95% CI, 1.9 to 11.6]) and institutionalisation (adjusted RR, 6.9 [CI, 4.0-11.7]). With delirium the risk of death and institutionalisation was further increased (adjusted RR 5.4 [CI 2.3-12.5] and 9.3[CI, 5.5-15.7] respectively).

In hospitalised patients with AD, 21% of cases with cognitive decline, 15% of institutionalisation and 6% of deaths were associated with delirium.

In patients with AD intervention to prevent delirium and hospitalisation is important as adverse outcomes have been demonstrated. Thus, the prevention of unnecessary inpatient admissions will prevent inpatient morbidity and mortality in this group.

Early administration of intravenous aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised control trial.

Zinstok SM, Roos YB. *The Lancet, Early online publication*, 28 June 2012.

Intravenous alteplase is, at present the only approved thrombolytic treatment for an acute ischaemic stroke. Although this treatment has been shown to be effective, re-occlusion following thrombolysis occurs in 14-34% of patients, and this complication is associated with worse clinical outcomes.

This multicentre, randomised open-label trial with blind-endpoint assessment aimed to see whether early treatment with intravenous aspirin would improve outcomes in acute stroke patients post thrombolysis by reducing the incidence of re-occlusion. The primary endpoint was favourable outcome, defined as a score of 0–2 on the modified Rankin scale at 3 months post randomisation. Intravenous aspirin was chosen to avoid excluding patients with dysphagia and to ensure faster drug uptake.

A total of 642 patients were recruited into the trial between July 2008 and April 2011 at 37 centres across the Netherlands, each with more than 20 thrombolysis cases per year. 322 patients received IV aspirin within 90 minutes of the start of alteplase therapy whilst 320 patients received standard therapy alteplase alone. 24 hours post thrombolysis, both patient groups were commenced on oral antiplatelet therapy.

Patients were eligible if over 18 years old and treated with alteplase for an acute ischaemic stroke. Patients currently receiving antiplatelet therapy, with thrombocytopenia or other contraindications to receiving aspirin were excluded from the study.

This study found no excess benefit in early anti-platelet administration, and the study was terminated due to an excess of symptomatic intracranial haemorrhage (SIAH) on neuro-imaging in the aspirin group (4·3% vs 1·6% 95% CI 0·2–5·4; p=0·04), and these SIAH events were more often the cause of poor outcome in the aspirin group. However, patients only received further neuro-imaging in the case of clinical neurological deterioration, so this rate may not be entirely accurate.

The authors however express caution that the difference noted relies on a small number of patients and that the SIAH rate although higher in the Aspirin group, is similar to the rate found in previous Alteplase only trials. However, they conclude that the results do not support a change of the

current guidelines, and that platelet therapy should continue to be given 24 h after administration of alteplase

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