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Final report summary:

Can a lower dose of clot-busting drug improve outcomes after stroke?

ENCHANTED: Enhanced Control of Hypertension and Thrombolysis Stroke Study

PROJECT CODE: TSA 2012-01
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Why did we fund this research?

Stroke is one of the leading causes of death and disability all over the world. However, other than aspirin which has only modest benefit, emergency clot-busting treatment (thrombolysis) is the only approved treatment for strokes caused by a blocked blood vessel in the brain (acute ischaemic stroke)[1].

Thrombolysis involves the administration of the clot-busting drug 'alteplase' through a stroke patient's vein (intravenously). A dose of 0.9 milligrams (mg) of alteplase per kilogram (kg) of a patient's body weight has been shown to be able to reduce disability if given within 4.5 hours of stroke, with an acceptable risk of bleeding in the brain as a result of the treatment (known as an intracerebral haemorrhage or 'ICH')[1].

Nevertheless, it is vital that research is undertaken to further reduce the risk of ICH, which is the most important and potentially fatal complication of thrombolysis, occurring in 5 to 10% of treated patients[1].

Small non-randomised studies have previously suggested that low-dose alteplase of 0.6 mg/kg of body weight produces comparable outcomes to the standard dose of 0.9 mg/kg, and indeed this dose is approved in Japan[2-4]. However, larger randomised trials are required to confirm this benefit in a wide range of patients, and demonstrate a reduction in bleeding complications (ICH).

The primary aim of the ENCHANTED trial was to show whether low-dose alteplase treatment reduces the risk of death and disability of patients relative to standard dose treatment, with a secondary aim of showing whether risk of ICH is reduced with low-dose treatment.

In addition, currently, only very high systolic blood pressure levels (above 185mmHg) are recommended to be treated during and immediately following thrombolysis. This is despite it being thought that the risk of bleeding into the brain from clot-busting treatment may be increased at systolic blood pressure levels above 150mmHg[5].

Therefore, further aims of the ENCHANTED study are to show whether intensive treatment of blood pressure during and immediately after thrombolysis is better at reducing the risk of ICH, death and disability compared to standard blood pressure management.

It was thought that if the ENCHANTED trial were successful, the findings could influence guidelines for thrombolysis treatment worldwide, change clinical practice and lead to more people being able to receive thrombolysis for stroke, with less risk.

The ENCHANTED trial is being conducted by an international team of researchers, and the Stroke Association has funded the UK contribution to this research.

What did the researchers do?

All patients recruited to the trial have been treated on an acute stroke unit, received regular blood pressure and heart rate monitoring, and active care in accordance with national guidelines.

Dose arm of the trial

Between March 2012 and August 2015, the ENCHANTED trial recruited a total of 3,310 patients across all participating countries; 774 of these patients were recruited in the United Kingdom, the second highest number worldwide after China. Of these, 1,654 were randomly assigned to receive low-dose (0.6mg/kg) alteplase and 1,643 to standard dose (0.9mg/kg) of the drug.

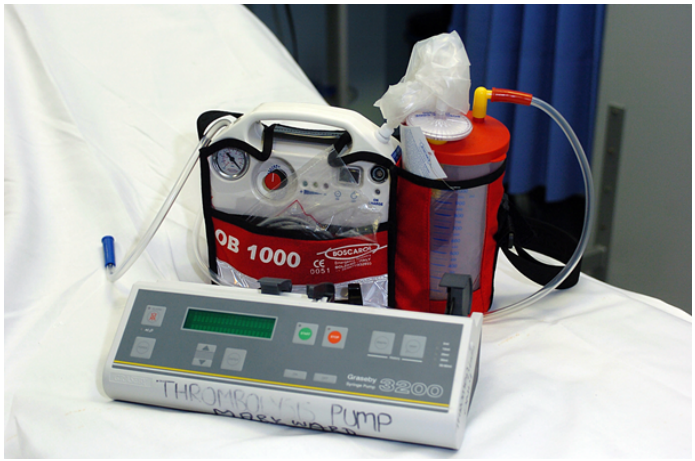
All patients received alteplase treatment for 60 minutes. Delivery of the drug was initially via rapid intravenous injection, followed by slower intravenous infusion through a drip.

The two groups were compared as part of the dose arm of the ENCHANTED trial which completed in August 2015.

Blood pressure lowering arm of the trial

This arm of the trial is ongoing, and is being supported by a further grant from the Stroke Association in the United Kingdom (STAY ENCHANTED).

The aim is to recruit 2,400 patients with a systolic blood pressure of between 150 and 185 mmHg. Half are being randomly assigned to receive intensive blood pressure lowering treatment, defined as lowering the patient's systolic blood pressure to between 140 and 150 mmHg within 30 minutes of receiving thrombolysis, and maintaining this level for 72 hours. The other half of patients are receiving standard guideline-based blood pressure management. From this group, only those patients who have a systolic blood pressure over 180mmHg will receive first line treatment in line with American Heart Association guidelines.



Thrombolysis pump used in emergency stroke treatment

What did the research find?

The primary and some further outcomes from the ENCHANTED trial were published in 2016 in the New England Journal of Medicine[6].

The primary outcome of the ENCHANTED trial was the rate of death and disability at 90 days after stroke, defined by a modified Rankin Scale (mRS) of 2 to 6. The mRS is a seven point scale of death or disability commonly used to describe outcomes after stroke. A score of 0 is 'no symptoms' and a score of 6 is used when a patient has died.

An mRS of 2 to 6 at 90 days after stroke occurred in 855 of 1607 participants (53.2%) in the low-dose group and in 817 of 1599 participants (51.1%) in the standard-dose group. The difference between groups was not a statistically significant result in terms of showing whether low-dose alteplase was as effective as, or safer than the standard dose.

However, an important further outcome of the trial was the risk of fatal ICH within seven days of stroke. A statistically significant reduction was found in the low-dose group (0.5% of patients) when compared to the standard-dose group (1.5% of patients). In addition, all definitions of symptomatic ICH (bleeding associated with neurological or clinical deterioration) were significantly lower in the low-dose arm. The risk of death at seven days after stroke was also reduced in the low-dose group (3.6% versus 5.3% in the standard dose group), however by 90 days after stroke there was no statistically significant difference in the death rates between groups (8.5% in the low-dose group versus 10.3% in the standard-dose group).

All other outcomes that were reported showed no significant differences between the low-dose and standard-dose groups.

The conclusion from these findings, is that whilst the standard guideline dose should still be administered as a rule, there may be circumstances in which the treating doctor may consider using low-dose alteplase to reduce the risk of ICH, whilst accepting that this may also increase the degree of disability a patient may be left with after stroke. This guidance has informed the most recent version of the UK National Clinical Guidelines for Stroke[7].

Further outcomes of the ENCHANTED trial relating to the ongoing blood-pressure lowering arm of the research will be presented and published in early 2019.

What does this mean for stroke patients?

For patients eligible for thrombolysis, the standard guideline dose of alteplase should still be administered as a rule. However, there may be circumstances in which the treating doctor may consider using low-dose alteplase to reduce the risk of a brain bleed, whilst accepting that this may also increase the degree of disability a patient could be left with after stroke.

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