Primary research

Design of the Intravenous Magnesium Efficacy in Acute Stroke (IMAGES) trial

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Abstract

The Intravenous Magnesium Efficacy in Acute Stroke (IMAGES) trial is a multicentre, randomised, placebo-controlled trial of magnesium sulphate ($MgSO_4$) funded by the UK Medical Research Council. When complete, it will be the largest single neuroprotective study undertaken to date. Conscious patients presenting within 12 h of acute stroke with limb weakness are eligible. The primary outcome measure is combined death and disability as measured using the Barthel Index at 90-day follow up. By randomizing 2700 patients, the study will have 84% power to detect a 5.5% absolute reduction in the primary end-point. By April 2000, 86 centres were participating, with representation in Canada, USA, Europe, South America, Singapore and Australia. So far, 1206 patients have been randomised, of whom 37% were treated within 6 h. Overall 3-month mortality was 20% and the primary outcome event rate was 43%. The study is ongoing and centres worldwide are encouraged to participate.

Keywords: acute stroke, IMAGES, magnesium sulphate, neuroprotection

Introduction

Acute ischaemic stroke results in neurochemical and metabolic derangements that contribute to cell death in the ischaemic 'penumbra' surrounding an infarct core. The potential viability of penumbral tissue has been affirmed by the consistent benefit of neuroprotective treatments targeted at a wide variety of metabolic derangements in the penumbra in animal models, which lead to biochemical, histological, radiological and functional recovery. However, an effective neuroprotective treatment for acute stroke in humans remains elusive.

Dose selection for neuroprotective drugs has often been dictated by neurological or cardiovascular toxicity. Parenteral magnesium prevents the death of ischaemic neurones in standard experimental stroke models [1,2] and

ADL = activities of daily living; CT = computed tomography; ICC = IMAGES Co-ordinating Centre; IMAGES = Intravenous Magnesium Efficacy in Acute Stroke (trial); LACS = lacunar syndrome; $MgSO_4$ = magnesium sulphate; MRI = magnetic resonance imaging; OCSP = Oxfordshire Community Stroke Project; PACS = partial anterior circulation syndrome; POCS = posterior circulation syndrome; SAE = serious adverse event; TACS = total anterior circulation syndrome.

other paradigms of ischaemic brain injury [3,4] at concentrations that are known to be well tolerated and safe in humans. Because the magnesium ion is crucial to a large number of cellular processes, the precise mechanism of action is unknown and may be multimodal. Relevant features may be as follows: increased cerebral blood flow after middle cerebral arterial occlusion [5]; antivasoconstrictor actions [6]; antagonism of calcium entry into cells via noncompetitive blockade of the *N*-methyl-D-aspartate receptor [7,8]; calcium antagonism at multiple voltage-gated channels [9]; and enhanced recovery of vital magnesium-dependent cell functions, such as adenosine triphosphate levels and protein synthesis.

Clinical experience with $MgSO_4$ suggests that it is a safe treatment. In acute myocardial infarction, $MgSO_4$ has been administered to over 30,000 patients [10,11] with few side effects. Intravenous or intramuscular $MgSO_4$ is standard treatment for the treatment of eclamptic seizures [12,13], is superior to phenytoin as prophylaxis in pre-eclampsia, and raises cerebrospinal fluid magnesium concentrations significantly (20%) [14].

In a preliminary study of 60 stroke patients [15], $MgSO_4$ had no adverse cardiovascular effects. There was a non-significant trend towards reduction in the proportion of patients dead or disabled at 3 months in the magnesium-treated group (30% versus 40%; $P = 0.07$). A dose-ranging study in 25 stroke patients that compared 8, 12 or 16 mmol bolus doses, followed by a 65 mmol 24-h infusion [16], confirmed that a rapid doubling of serum magnesium concentrations could be achieved. The IMAGES trial was powered to show a potentially real treatment effect. This protocol was piloted in Glasgow, with patients being followed up to 1-month after stroke [17]. That study did not reveal any safety issues. A systematic review of these and an earlier Swedish clinical trial [18] showed a worthwhile reduction in death and disability (modified Rankin Scale <3), but small numbers and wide confidence intervals caution against over interpretation.

Materials and methods

The IMAGES trial is a randomised, double-blind, placebo-controlled, worldwide, multicentre collaborative trial that is designed to test the efficacy of $MgSO_4$ given within 12 h of onset of clinically diagnosed acute stroke (http://www.medther.gla.ac.uk/studies/images/index.htm). The trial is sponsored by the UK Medical Research Council (http://www.mrc.ac.uk). It commenced formally in October 1997, and is expected to be completed by October 2003. In the UK the study has Multicentre Research Ethics Committee approval. Local institutional review boards have approved it in centres across five continents.

The IMAGES Co-ordinating Centre (ICC) at the University of Glasgow is responsible for management of the trial. The trial database is managed by the Robertson Centre for Biostatistics at the same site. The organisation of the trial and scientific conduct are supervised by an appointed Trial Steering Committee.

The Barthel Index, a measure of dependence in activities of daily living (ADL), will be recorded during follow up by telephone or clinic contact. Patients scoring 60 or more will be considered independent and those scoring less than 60 will be considered disabled. The modified Rankin Scale will also be used as an overall measure of handicap. Both scales have been used in a wide variety of interventional stroke trials. Unblinded data have been reviewed by an independent Data and Safety Monitoring Committee consisting of a statistician, a neurologist and a consultant physician. Early trial termination is only recommended if the Data and Safety Monitoring Committee find evidence of an adverse treatment effect or an overwhelming survival benefit with a two-sided *t* test ($P < 0.001$).

Inclusion criteria

Conscious patients aged 18 years or older, who were previously independent, presenting within 12 h of acute stroke with limb weakness are eligible. Patients with a confirmed diagnosis other than ischaemic stroke, those with known renal impairment with a serum creatinine above 200 μmol/l (>2.26 mg/dl), and those who are pregnant or with significant comorbidity are ineligible. To simplify recruitment, brain imaging, formal ADL assessment or serum creatinine levels are not required before randomisation. Stroke onset is considered to have occurred at the time the patient was last known to be well. Patients are considered to have been independent if they had a modified Rankin Score of 2 or less (ie can manage walking, stair climbing, transfer and toileting alone, with a walking stick, hand rail or with minimal assistance). Limb weakness should have been present for at least 1 h and should be present at the time of randomisation. Limb weakness is considered an inability to maintain arm posture for 10 s when held at 90° (sitting) or 45° (supine) or an inability to maintain supine leg position for 5 s when held at 30°. Informed consent is obtained either directly from the patient, from a relative, or, if neither of these is available and subject to local ethical committee approval, from an independent clinician. Patients may withdraw from the trial at any stage.

Exclusion criteria

Patients are ineligible if they do not fulfil the inclusion criteria. Patients are not randomised if they are pregnant, if they are suffering from a severe concomitant illness that is likely to prevent outcome assessment, or if they are participating in another clinical trial that is likely to affect outcome. Patients who are comatose and unable to localise pain are ineligible. Patients with a clear indication or contraindication for magnesium therapy are not eligible.

Routine pretreatment serum magnesium levels are not required. Patients with a computed tomography (CT) or magnetic resonance imaging (MRI) proven diagnosis other than ischaemic stroke are excluded before randomisation.

Randomisation

Patients are randomised via an automated telephone randomisation service (ClinPhone Ltd, Nottingham, UK). Treatment packs are allocated randomly by an algorithm that utilises adaptive techniques to maintain balance on combinations of the prognostic variables patient age, side of stroke, Oxfordshire Community Stroke Project (OCSP) [19] classification, and time to randomisation. The OCSP differentiates stroke presentation into clinical prognostic categories that relate to cerebrovascular territories. Categories include total anterior circulation events (TACS) and partial anterior circulation events (PACS), posterior circulation events (POCS) and lacunar events (LACS). The infusion should be commenced within 30 min of treatment allocation. Three single A4 forms are completed at the time of randomisation and copies are mailed to the ICC; these include one form for patient contact details, which is faxed to the ICC within 3 days of randomisation.

Participation in the study does not inhibit the use of any routine diagnostic investigations, thrombolytic therapy, or therapeutic measures for secondary prevention or treatment of complications. Patients have CT or MRI as soon as possible within 7 days of admission, as recommended by the World Health Organization European guidelines [20], and the results are sent to the ICC. All patients are followed up unless consent is withdrawn.

Study infusion

Each treatment pack contains $MgSO_4$ or placebo (normal saline) supplied as three ampoules prepared by the Sterile Pharmacy Production Unit of the Western Infirmary, Glasgow. The trial solutions are diluted into normal (0.9%) saline and administered via an intravenous cannula using a controlled-rate infusion pump. For patients receiving active treatment, a bolus dose of 16 mmol (4 g) of $MgSO_4$ is infused over 15 min and then a maintenance dose of 65 mmol $MgSO_4$ (16.25 g) is given over 24 h. Blood pressure, heart rate and serious adverse events (SAEs) are monitored at baseline, 15 min, and 12, 24 and 48 h after infusion. Investigators are required to report any serious event occurring up to day 7. Follow up to 48 h is recorded on a single A4 form that is mailed to the ICC.

Follow up

Follow up is undertaken by the ICC in the UK and internationally by a centralised coordinating centre for each country or by a local centre. Surviving patients are contacted by telephone or clinic appointment at 30 ± 3 and 90 ± 7 days after the acute event. Place of residence, modified Rankin Score, Barthel Index, drug therapy and SAE data are routinely collected. A EuroQol EQ-5D health assessment questionnaire is sent to surviving UK patients after 90 ± 7 days.

Study end-points

The primary end-point of the study is the proportion of patients dead or disabled, as assessed using Barthel Index, at 90 ± 7 days. The use of telephone ADL assessment and the dichotomous use of the Barthel score at 60/100 have been validated previously [21,22]. Secondary end-points include overall mortality alone and disability outcome by modified Rankin Score at 90 ± 7 days. Primary end-point subgroup analysis will be undertaken for the 1–6 h subgroup, for primary haemorrhagic and for lacunar versus cortical stroke.

Serious adverse events

SAEs are defined as those events that are fatal, life-threatening, or seriously disabling, or those that prolong/require hospital stay. A single A4 form is completed, and faxed immediately and then mailed to the ICC. All SAE forms are reviewed by the coprincipal investigator. Investigators are required to report all SAEs up to day 7, after which only those events that are fatal and/or unexpected are to be reported. At 30-day and 90-day follow up, only those events that are fatal and/or unexpected are reported. Expected events include the following: deterioration due to initial stroke, further stroke, thrombosis, pulmonary thromboembolism, severe pneumonia, acute myocardial infarction and serious fall/injury. Individual investigators may report any event that they feel is of sufficient importance and related to the trial. Details of supportive investigational evidence for SAEs will help to classify diagnostic certainty. Trial unblinding is discouraged because no specific antidote to magnesium is available and because magnesium-related SAEs are considered unlikely; investigators are able to unblind the treatment allocation independently if toxicity is suspected.

Statistical analysis

The primary analysis will be by intention to treat. Comparisons of proportions of patients suffering events will be by χ^2 tests. Odds ratios and 95% confidence intervals will be calculated using logistic regression. Adjustment for baseline risk factors will be considered.

Sample size

This study of 2700 subjects has a power of 84% at a 5% level of significance to detect an absolute primary end-point reduction of 5.5%, assuming a 40% primary end-point event rate. For the subgroup who receive treatment within 6 h, assumed to constitute one-third of all randomised subjects, or about 900 patients, there would be 80% power at the 5% level of significance to detect an absolute reduction of 9% in death and disability, again assuming a 40% primary end-point event rate. Under

Table 1

IMAGES study patients and centre recruitment (April 2000)

Country	No of centres	No of patients
UK	60	800
Europe (excluding the UK)	5	93
USA	8	38
Canada	3	5
South America	4	19
Singapore	2	225
Australia	4	26
Total	87	1206

these assumptions, the expected number of individuals dead or disabled at 90 days is 1006, and consideration will be given to extending the recruitment to the study until this number of events occurs.

Results

By April 2000, 87 centres worldwide had participated from the following countries: UK (60 centres), South America (4), Europe (5), USA (8), Canada (3), Singapore (2), Hong Kong (1) and Australia (4; Table 1). A total of 1206 patients had been randomised. The mean age was 71 years; 598 patients (50%) were male and 554 (48%) had left-sided weakness.

Stroke risk factors were hypertension (51%), atrial fibrillation (20%), previous stroke/transient ischaemic attack (29%), diabetes mellitus (17%) and ischaemic heart disease (27%). Stroke severity at time of onset was classified for 1196 patients by the OCSP categories TACS, PACS, LACS, POCS and unclassifiable. These were 294 (28%), 383 (36%), 336 (32%), 19 (2%) and 36 (4%), respectively. Of 1016 CT scan reports received, 670 (66%) were reported showing infarct, 162 (16%) were normal, 121 (12%) were haemorrhagic and 63 (6%) were not classified.

Although 50% of patients were randomised within 6 h, review of 984 patients showed that treatment was initiated in under 3 h, 3–6 h and 7–12 h in 37 (4%), 323 (33%) and 624 (63%) of cases, respectively. Six patients did not actually receive medication because of problems at the time of randomisation. Difficulties with treatment administration were reported for 103 patients, but 60% were due to mechanical infusion problems.

A total of 447 adverse events were reported for 351 patients. Three-quarters of these were expected events due to cerebral complications of the initial stroke (23%), pneumonia (19%), infection (6%), further stroke (14%) or other vascular event (13%). Although 182 adverse events were reported during the infusion period, these were mostly due to motor deterioration (40%), reduced level of consciousness (15%) or pneumonia (16%).

All UK and a total of 1096 out of 1103 (99%) 3-month follow ups were complete by April 2000. Internationally, 216/217 (99%) from Singapore, 32/36 (88%) from the USA, 19/19 (100%) from South America, 63/64 (98%) from Europe (excluding the UK), and 23/24 (96%) from Australia were complete. One-month outcomes for 983 patients for death and disability (Barthel Index <60) were 144 (15%) and 358 (36%), respectively. Three-month outcomes for 1030 patients for death and disability (Barthel Index <60) were 209 (20%) and 234 (23%), respectively. The primary outcome measure of combined death and disability at 3 months occurred in 443 out of 1030 (43%).

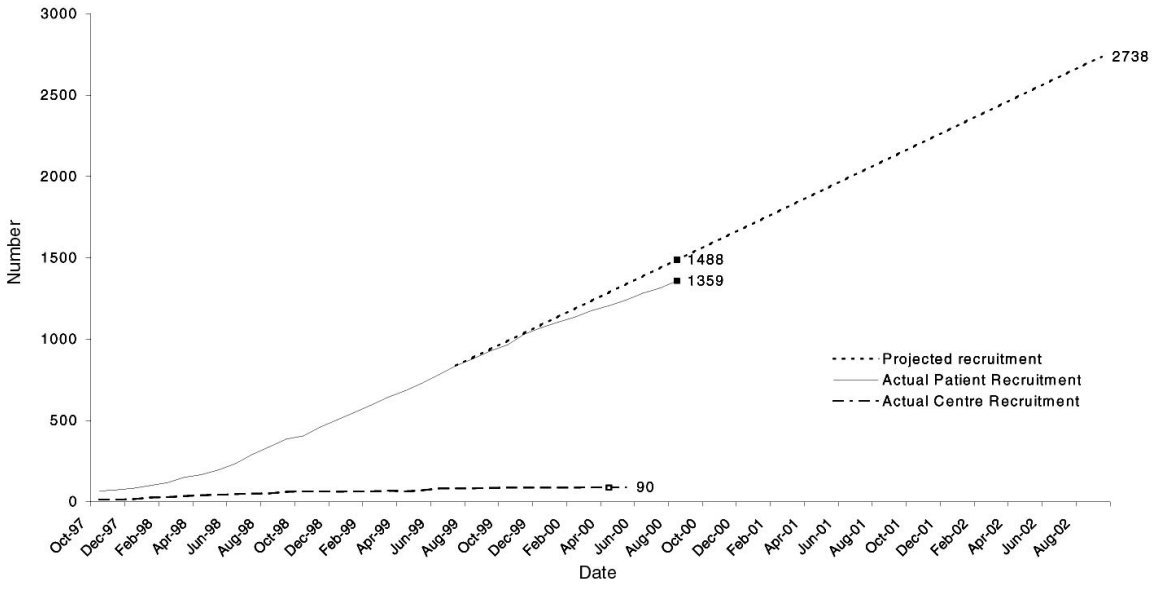
Discussion

Despite the 12-h time window for recruitment of patients with acute stroke with limb weakness, the IMAGES protocol has been implemented in hospitals throughout the UK and worldwide. Although recruitment rates have been slower that expected (Fig. 1), the study has achieved realistic targets. The patient cohort is comparable with those of other large-scale neuroprotective studies. Despite a high randomisation rate from Singapore (225/1206 [18%]), there did not appear to be a disproportionately high rate of intracerebral haemorrhages (121/1206 [10%]), as might be expected in an oriental population.

Power calculations were based on a 40% incidence of primary end-point at 3 months and a recruitment of one-third of patients into the 1–6 h subgroup. So far, 37% were treated within 6 h, and 43% of all patients were dead or disabled at 3 months. Primary outcome at 1 month was 51%, with 20% mortality. Results were similar for secondary end-points of Modified Rankin Scale outcome at 1 and 3 months. These figures are similar to the number of primary outcome events in the Glycine Antagonist (gavestinel) in Neuroprotection (GAIN) international neuroprotective study [23]: 47 and 48% at 1 and 3 months, respectively.

Although 18% of patients experienced an adverse event during the study infusion, conscious level was unchanged in most cases (81%) and improved as often as it deteriorated. Most adverse events were related to cerebral complications of the initial stroke (23%) or pneumonia (19%). The infusion appeared to be safe. This has been confirmed by unblinded analysis of 1000 patients by the Data and Safety Monitoring Committee, who recommended continuation of the study.

Figure 1



Target and actual centre and patient recruitment rate for the IMAGES trial (April 2000).

Age and OCSP classification were predictors of outcome. The original Oxfordshire 543-patient cohort [19] suggested that 6-month mortality outcomes for TACS, PACS, LACS and POCS were 56, 10, 7 and 14%, respectively. These data are comparable with 3-month mortality outcomes from the IMAGES cohort by OCSP classification (31, 25, 7 and 10%, respectively). Both age and OCSP are used in the minimisation algorithm before randomisation, and therefore the two treatment arms are likely to be well matched for these important prognostic parameters.

Extrapolation of current randomisation, averaging 40–50 patients per month, suggests that the study will complete in October 2003. From a total of 87 centres, seven centres have withdrawn because of local funding or staffing issues. A single centre was withdrawn because of poor recruitment rates and protocol violations. More centres are expected to join, including a Chinese collaboration. A number of recruitment strategies have been implemented, including regular visits and distribution of monthly newsletters.

Limited funds when compared to an industry sponsored trial have undoubtedly limited randomisation. Trial participation is based largely on goodwill and scientific interest. Minimal expenses will only cover basic costs of patient randomisation. Participating sites include both district general hospitals and academic centres. Because of the simplicity of the trial, some centres without dedicated research staff have still managed to randomise large numbers of patients. The trial is compliant with the standards of good clinical practice. Many investigators have stated that the trial has highlighted and raised the profile of acute stroke management within their accident and emergency department, acute medical admission ward or dedicated stroke unit.

An additional MRI substudy is underway, and will study treatment effects on the reduction of frequency of infarct growth, as measured from a baseline diffusion-weighted image volume to day 90 T2-weighted MRI volume. The substudy is funded by the US National Institutes of Health, and is coordinated worldwide by the University of Los Angeles, USA. In the UK, the Scottish Chief Scientist's Office has funded national coordination and imaging expenses for 50 patients. Randomizing 150 patients, the substudy will have 80% power to detect a 25% difference in infarct volume growth at a 5% significance level [24].

Conclusion

The IMAGES protocol is sufficiently simple to be undertaken by busy hospital units around the world. Blinded review of the IMAGES database has so far revealed an adequate number of end-points. As expected, the study infusion has remained safe. When complete, IMAGES will be the largest single neuroprotective study. Magnesium is potentially a safe, cheap and effective neuroprotective treatment for acute stroke.

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