Calcium antagonists in stroke
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Citation for published version (APA):
Horn, J. (2001). Calcium antagonists in stroke

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Venus; an Acute Stroke Trial With General Practitioners

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Submitted for publication
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Abstract

Background.

We conducted an acute stroke trial with a neuroprotective agent in a pre-hospital setting. In this manuscript we report on the problems we encountered.

Methods.

In this randomised, double-blind, placebo-controlled trial, stroke patients were randomised by the general practitioner to allow start of treatment within 6 hours after onset of symptoms. Outcome assessment (functional outcome after 3 months) was performed by the trial office. Clear inclusion and exclusion criteria and simple forms were designed. 1800 General practitioners agreed to co-operate, news letters were sent and teaching courses were organised.

Results.

A total of 454 patients were randomised. External validity study showed that only 8% of patients were included, 40% were excluded correctly. 24% Of included patients should not have been randomized, based on exclusion criteria. Neuroradiological imaging was performed in 307 patients, general practitioners diagnosed stroke correctly in 98% of these patients. Of all patients, 52% were admitted in a hospital, elderly patients and patients with severe strokes were admitted statistically significant more often.

Conclusion.

An acute stroke trial in a pre-hospital setting is possible, but difficult. Our trial suffered from a much lower inclusion rate than expected. General practitioners were unfamiliar with randomised controlled trials and asking of informed consent. Sometimes they were too busy and forgot about the trial. Probably, an acute stroke trial with a smaller, more involved group of general practitioners can be more successful.
Introduction

The VENUS trial (Very Early Nimodipine Use in Stroke) was designed to test the hypothesis that early treatment with nimodipine has a positive effect on survival and functional outcome after stroke. Such a positive effect was suggested in a meta-analysis.\(^{{47}}\) To protect neurones in the ischaemic penumbra against the massive calcium influx, treatment has to start as soon as possible. We therefore performed this trial in a pre-hospital setting. No serious adverse events were reported from trials with oral nimodipine,\(^{{45,46}}\) allowing us to start treatment in a pre-hospital setting. In patients with intracerebral haemorrhages an ischaemic area surrounding the haematoma has been identified.\(^{{126,128,129}}\) This suggests that nimodipine is likely to be beneficial for these patients, which were therefore not excluded before randomisation.

To our knowledge, this was the first acute stroke trial in a pre-hospital setting. In this manuscript we report on the problems we encountered.

Methods

In this randomised, double-blind, placebo-controlled trial, patients used 30 mg nimodipine, every 6 hours for 10 days or a similar placebo schedule. Trial medication had to be started within 6 hours after onset of symptoms. Any other concomitant medication, except nimodipine, was allowed. Written, or witnessed oral, informed consent was required. Numbered boxes contained one complete treatment or identical placebo course, and were distributed among participating general practitioners and neurologists. The primary end point was poor outcome, defined as all cause mortality or dependency in daily life (modified Rankin score > 3\(^{{119,120}}\)) three months after inclusion. Outcome was assessed through telephone interview by a trained data manager nurse, blinded for treatment allocation.\(^{{121,122}}\) Information about neuroradiological imaging (CT or MRI scan) was gathered in order to ascertain a definite diagnosis.

Group size

We planned to include 1500 patients, based on the following assumptions: 80% power, two-tailed significance level of 5%, reduction of poor outcome from 40% (placebo group) to 32% (treatment group), requiring 575 patients in each treatment arm. Since pre-hospital trial inclusion by general practitioners can lead to inaccurate diagnosis and drug non-compliance, we substantially raised the estimated sample size with 30%. After inclusion of 454 patients the trial was terminated early, since in our Cochrane Collaboration review on calcium antagonists for ischaemic stroke, the reported positive effects of early administered nimodipine, could not be confirmed.\(^{{123}}\) An interim analysis by an independent committee showed that the assumptions on which the sample size of the trial was based, were unrealistic.
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Exclusion criteria

Ability to raise arm or leg > 10 sec. against gravity; start treatment > 6 hours after stroke; age < 18 or > 85 years; previous participation in this trial; pregnancy; impaired consciousness (does not obey orders and does not open eyes on painful stimuli); other diseases likely to cause death within one year; previous stroke, resulting in serious handicap (modified Rankin scale score >3); dysphagia, excluding oral medication at trial onset; systolic blood pressure < 130 mmHg; heart rate < 50 / min; three or more of the next four conditions: severe headache, vomiting, hypertension (systolic BP >220 mmHg), use of oral anticoagulants.

Randomisation by general practitioner

Co-operating physicians received trial medication and a case record form (CRF) for inclusion of one stroke patient. Included was a small card with all relevant information (inclusion and exclusion criteria, telephone numbers, how to use medication). When a general practitioner encountered an eligible stroke patient he had to explain the trial and ask informed consent. When the patient was unable to write (because of hemiparesis), witnessed oral, or consent by proxy was allowed. Trial medication was started immediately. The general practitioner completed the simple CRF, called the trial office (24-hours service) and sent in the trial forms. Twenty-four hours after start of treatment, blood pressure and heart rate had to be recorded, to detect serious hypotension and bradycardia. After inclusion of a patient, the general practitioner was offered another set of trial medication. The general practitioner received 175 Dutch guilders (79.5 euro) for each included patient.

To assess external validity of VENUS 180 general practitioners (10% of all participants) were asked to report all stroke patients they encountered during six months. They were contacted by phone every month to assess the number of encountered and included stroke patients, and reasons for not including patients (exclusion criteria or other reasons).

Starting VENUS

In September 1994 co-operation of general practitioners was sought. All general practitioners in the Netherlands collaborate in groups, that cover night, holiday, and weekend calls.

Before approaching general practitioners, we asked neurologists in hospitals in the vicinity to continue trial medication after hospital admission of a stroke patient. Some neurologists participated in acute stroke trials, which precluded randomisation by general practitioners in that particular area. After approval from the neurologist, we approached all general practitioners referring to this hospital. Together with the local neurologist a meeting was organised, at which general practitioners were informed about the trial and invited to co-operate. General practitioners who did not attend this meeting were informed by a phone call and, after the study protocol had
been sent, were asked to participate.

In some areas we did not succeed in organising a meeting. We visited general practitioner groups in these areas at one of their regular meetings or we contacted the group by phone.

We aimed at the participation of complete groups of general practitioners in view of the on call hours.

When, in autumn 1995, 1804 general practitioners, in 45 areas, had agreed to co-operate, recruitment stopped. Neurologists of 10 hospitals also agreed to randomise patients at the emergency department. We expected to include all trial patients in less than two years.

In addition, a broader campaign was aimed at media interested in health problems. Several local and national newspapers paid attention to the trial. By increasing knowledge of the general public about the signs and symptoms of a stroke, we tried to diminish patient's delay. We also hoped that publicity would make it easier for the general practitioners to discuss the VENUS study with patients and their relatives and to ask for informed consent.

**Maintaining VENUS**

A Dutch general practitioner with an average patient population encounters approximately 4 stroke patients a year. At such low incidence rates of stroke in general practice, physicians cannot develop expertise in this area, and trial details are unlikely to be remembered. We realised this would endanger the progress of the trial. Newsletters with information about the trial were sent every 2 months. News items on stroke issues, such as therapies, stroke units and trial progress were discussed, advise about how to ask informed consent was given, and the consequences of intention to treat principles were explained. All co-operating physicians were called every 6 to 8 months. We invited questions and reminded the general practitioners of issues mentioned in recent newsletters.

On site audits were not performed in view of the sheer number of general practitioners (1800) and budget limitations. A pharmaceutical company offered help of their sales representatives, who asked participating general practitioners about their experiences with stroke patients and VENUS. We announced these visits to general practitioners in a newsletter.

In the Netherlands, general practitioners are obliged to follow 40 hours a year of post graduate teaching to remain certified. We organised a teaching course on cerebrovascular diseases, free of charge for co-operating general practitioners, and credited for certification.

**Statistical analyses**

Chi-square tests and unpaired T-tests were used to calculate statistical differences between groups.
Results

External validity

Of all approached general practitioners, 117 agreed to co-operate in the external validity study. In six months 73 stroke patients were seen by these general practitioners. Only 6 (8 %) were included in VENUS. Of the remaining 67 patients, 44 were not included because of exclusion criteria (paresis not severe enough (16), existence of symptoms > 6 hours (14), and age > 85 (12), swallowing disturbances (2)). In 23 patients the general practitioner simply forgot VENUS or was uncertain about diagnosis.

In the half yearly telephone calls, three randomised patients who had not been reported by the physician, were retrieved. Trial medication was started, but shortly after onset of medication relevant exclusion criteria were noted.

Of the 454 included patients, 107 (24%) should not have been randomised, because they had the following exclusion criteria: 8 other diagnoses, 74 hemiparesis not severe enough, 8 age > 85 years, 10 swallowing disturbance, 7 other.

Diagnostic accuracy

In VENUS the diagnosis was confirmed by neuroradiological imaging in 307 patients, stroke was diagnosed correctly in 98% of these patients (Table I). In 8 patients the final diagnosis was non stroke etiology (cerebral metastases (2x), primary cerebral tumor (2x), pneumonia, seizure, hyperventilation syndrome, severe hypertension).

Admission

Of all patients randomised, 236 (52%) were admitted to a hospital. Factors influencing general practitioner’s policy towards admission were age (p = 0.003, t-test), and aphasia (p = 0.000, chi-square test). Mean age of admitted patients was 69.4 years, of patients who were treated at home 72.3 years.

Table I. Diagnostic accuracy of family physicians in patients they diagnosed as having suffered a stroke, in whom neuroradiological imaging was performed.

<table>
<thead>
<tr>
<th>Diagnosis after radiological investigations</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic stroke</td>
<td>260 (85%)</td>
</tr>
<tr>
<td>Haemorrhagic stroke</td>
<td>33 (11%)</td>
</tr>
<tr>
<td>Stroke NOS</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Other diagnosis*</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Total number of patients 307.

* Other diagnosis were cerebral metastases (2x), primary cerebral tumor (2x), hyperventilation syndrome.

In 2 patients information of diagnosis after radiological investigation was unavailable.
Of all admitted patients 41% had a poor outcome at the end of follow-up, compared to 17% of patients who were treated at home (p = 0.000, chi-square test). This suggests that patients with a severe stroke are admitted more often.

**Discussion**

The VENUS study was terminated in July 1998 primarily because of doubts about the scientific basis of the study. In our Cochrane Collaboration review on calcium antagonists for ischaemic stroke the positive effects of early administered nimodipine reported before could not be confirmed. This led to an interim analysis by an independent committee, which advised to stop the inclusion of patients.

VENUS suffered from a much lower inclusion rate than expected. Given the number of co-operating general practitioners and the number of stroke patients they encounter, it should have been possible to include all patients within 2 years. The external validity study shows that 117 general practitioners encountered 73 stroke patients in six months, of whom 60% were correctly excluded and 40% were potential participants for the VENUS study. If our sample was representative, the 1800 general practitioners can be expected to have encountered 1124 stroke patients in six months, of whom 450 were eligible for VENUS. Similar disappointing experiences were described by Tognoni et al in their early terminated study on treatment of isolated systolic hypertension and Peto and Coulter in their study on menorrhagia. However, there are important differences between these trials. In the study by Tognoni et al, hypertension did not require immediate intervention and general practitioners had much more time to decide whether a patient was eligible for the trial. Diagnostic uncertainty did not play a major role. General practitioners had to stop anti-hypertensive treatment which they had prescribed before. Tognoni et al suggest that this change from the role of confident and reassuring prescriber to uncertain researcher prevented the general practitioners to randomise patients. In the VENUS trial medication did not have to be interrupted. Instead, general practitioners could start medication whereas in the past they had nothing to offer. But the possibility of placebo medication may have been a problem. Many general practitioners expressed their unfamiliarity with randomised controlled trials and asking of informed consent.

General practitioners only had to hand out a questionnaire to the patient and complete one themselves, in the menorrhagia study by Peto and Coulter. Recruitment rate of patients with this common condition in general practice, was much lower than expected. General practitioners reported they had not seen eligible patients, were too busy and had forgotten about the trial. This last reason has certainly played a role in the VENUS trial, in which a relatively uncommon
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disease in general practice was studied. This might also be an explanation for the high number of incorrectly included patients, despite simple, straightforward inclusion and exclusion criteria, and extensive instructions during the meetings at the beginning of the study.

In the GREAT study (Grampion region early anistreplase trial) the investigators succeeded in performing a pre-hospital based thrombolysis trial in acute myocardial infarction, in which patients had to be treated within 4 hours. In 3 years 29 rural practices included 311 patients with suspected myocardial infarction. Thrombolytic treatment can be considered as far more dangerous than oral nimodipine, but this did not seem to hinder general practitioners in including patients. Of all eligible patients 60% was included. This might be a fine example of the advantages of a small, local group of participating general practitioners in a acute treatment trial.

It has been suggested that a reasonable financial incentive might help general practitioners to randomise patients. For this reason a fair but modest fee was given as compensation for the time the general practitioner spent on including a patient in the VENUS study. The workload for the general practitioners was small, the CRF easy to complete and all follow-up was done by the trial office. Only if patients stayed at home, a check after 24 hours had to be done, but this is a routine visit, performed by general practitioners when stroke patients are not admitted.

We agree with Jonker that general practitioners seem to have little knowledge about trial methodology in general. Trial medication was started, and stopped, in three patients after the practitioner found out that these patients should not have been included because of exclusion criteria. Patients were not reported to the trial office and follow-up was therefore not performed. This clearly shows that basic principles of the intention-to-treat analysis are not widely known.

Critics had doubts about the ability of general practitioners to diagnose stroke. The limited number of stroke patients encountered each year hampers diagnostic accuracy. Schuling reported that general practitioners diagnose stroke (ischaemic or haemorrhagic) in 92% of all cases correctly. Similarly, in the VENUS study the diagnosis appeared not be to a major problem, since in the group of patients in whom the diagnosis could be investigated by CT or MRI, the diagnosis was correct in 98% of the patients.

If early treatment of stroke patients will ever be a critical factor, pre-hospital treatment by general practitioners remains an attractive option. In a next acute stroke trial in general practice we would aim on less general practitioners, focussing on few regions, with much more physician involvement. Such a smaller group will have several advantages. Co-operating general practitioners can easier be trained in trial methodology, in particular the need for strict inclusion- and exclusion criteria and intention to treat principles. Site visits will be possible, which can be done by a trial nurse as suggested by Paterson. It would even be possible for this trial nurse to visit the included stroke patients, which would be a direct benefit for the general practitioners.

A regional group would also benefit from support by the trial office in other aspects. Each
stroke patient encountered could be reported immediately to an on call investigator, who could inform the general practitioner, after some simple questions, whether the patient is eligible or not. With these strategies the number of patients incorrectly included or missed for inclusion might be diminished.

When working with a group of general practitioners of a certain region, it is likely that they feel more responsible for the trial, than in a nation-wide study. This would enlarge the chance for success.¹³⁸

A disadvantage of a small group would be that more time is needed to include all patients. However, if inclusion rate increases and the number of incorrectly included patients diminishes, this increase in time might be moderate.

We assume that with these changes in trial design, acute stroke trials in general practice will be possible. Provided that the distinction between ischaemia and haemorrhage is not required, as is the case in studies with neuroprotective agents, this would enable us to start treatment much earlier than in hospital based trials.

Acknowledgements

We received support from the Dutch Heart Foundation which sent a media announcement about VENUS. ML was a clinical investigator sponsored by the Dutch Heart Foundation. We also want to thank Boehringer Ingelheim for offering the help of their sales representatives.