NEUROPROTECTION IN STROKE RISK PATIENTS

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Because none of the 114 „neuroprotective" compounds in clinical trials have been successful, other approaches should be investigated in the future.

In the first part of the lecture we analyze the results of animal experiments with neuroprotectants (calcium-antagonists, propentofylline, GM-1 ganglioside, glycolipid derivates, NMDA antagonist etc.). Based on the summarized results we conclude: preischemic loading with neuroprotectants reduces more significantly the size of ischemic damage than postischemic application. In the second half of the presentation the authors estimate the necessary sample size for a placebo controlled clinical trial that would investigate the efficacy of a possible new neuroprotective candidate (successful in animal experiment) given for secondary prevention to patients with recent ischemic stroke in reducing mortality and disability of subsequent stroke. In the calculation we set type I error at 0.05, power at 0.8, and allocation ratio between treatment arms at 1:1.

We chose 3-month risk of death or dependence defined as Barthel-scale lower than 60 as the primary outcome of interest. Furthermore, considered 3-month risk of death as secondary outcome. For the placebo arm we estimated these risks based on data from acute stroke trials. We estimated the expected number of strokes during the follow-up based on the incidence rates of strokes reported from secondary prevention stroke trials. Based on the data reported from acute stroke trials we estimated the 3-month risk of death as 20% and the risk of death or dependence as 40%. We assumed an expected stroke rate of 0.06 / year in high-risk patients with recent TIA or non-disabling ischemic stroke.

564 stroke cases needed in each arm to detect a relative risk of 0.8, (20% relative risk reduction, i.e. 32% risk of 3-month death or dependence in the neuroprotective arm; this equals with 8% absolute risk reduction, 12.5 number-needed-to-treat (NNT) with a power of 80%. 564 strokes are expected in 9400 person-years of observation with a stroke rate of 0.06 / year, which requires 5 years follow-up of 1880. This means a study population of 3760 patients.

If we consider 3-month mortality as primary outcome, and would like to be able to detect a 20% relative risk reduction (i.e. 16% 3-month risk in the placebo group, this equals with 4% absolute risk reduction, 25 NNT) with a power of 80%, then we would need 1447 stroke cases on each treatment arm. This would require 24117 person-years of observation, which could be collected with a mean follow-up of 5years of 4823. This means a study population of 9646 patients.

This sample size would provide a possibility to detect with 80% power a relative risk reduction of 13% in the combined outcome of 3-month death or dependence (i.e. 35% 3-month risk in the placebo group, this equals with 5% absolute risk reduction, 20 NNT).