Reviewer’s report

Title: Rational and Design of a Double-blind, Placebo-controlled, Randomized Trial to Evaluate the Safety and Efficacy of Nimodipine Preventing Cognitive Impairment in Ischemic Cerebrovascular Events (NICE)

Version: 1 Date: 4 June 2012

Reviewer: Svetlana Lorenzano

Reviewer’s report:

This manuscript describes the protocol and rationale for a new study, NICE (Nimodipine Preventing Cognitive Impairment in Ischemic Cerebrovascular Events). The study is a multicenter, randomized, double-blind, controlled trial with the aim to evaluate the efficacy of nimodipine in preventing/treating mild cognitive impairment in patients with ischemic stroke, enrolled within seven days from symptom onset.

Some comments:

Major compulsory revisions:

1. The Authors described the rationale and need for the study. However, they should implement the rationale with a little more information of the potential mechanisms of action particularly on vessels and neurons, by which nimodipine could be effective specifically in preventing mild cognitive impairment in patients with acute ischemic stroke.

2. In the paragraph “Rationale”, Authors should rephrase the sentence on the aim of the study, something like this: “The aim of this study is therefore to evaluate clinical efficacy and safety of nimodipine, administered within seven days after an acute ischemic stroke, in the prevention of mild cognitive impairment”.

3. Are patients with prior clinical diagnosis of stroke and patients with prior disability included in the study? How the Authors can exclude that the patients have had a mild cognitive impairment before the index stroke? And moreover, as in this study patients are enrolled within seven days from stroke onset, how much is it reliable evaluating and measuring the presence of a mild cognitive impairment in those patients with acute stroke enrolled for example within 24 hours from the symptom onset when the lesion might not be still stable and in the same patients evaluating the real effects of nimodipine administered during the acute phase on cognitive functions?

4. In the Abstract, in the Table and Figure, Authors should specify if patients are enrolled equal or less 7 days or only less than 7 days after the stroke onset.

5. In the paragraph “Ethics and informed consent”, Authors should specify the
informed consent procedures if the patients is not able to sign the informed consent at the moment of the enrolment due to the acute stroke.

6. In the paragraph “Treatment and Follow-up”, Authors should:
- specify how the randomization is performed, i.e. IVRS;
- specify why they decided to use the ASPECTS score, Fazekas and CHIPS (e.g. in order to have a measure of the baseline infarct size and white matter hyperintensities, respectively), and they should clarify if they are going to use these measurements in the statistical analyses, as these variables together with the location of the infarct could have an influence on the development of cognitive impairment after stroke. Moreover, they should give some references for these scales;
- Moreover, are the Authors going to use an etiopathogenetic classification of the stroke?
- Do the Authors also include in the follow-up assessments a disability scale?

7. In the paragraph “Statistical analysis”:
- Authors should rephrase the null hypothesis;
- Authors should specify how they will consider in the analyses the patients who discontinue and those lost at follow-up.

Minor essential revisions:
8. English quality should be revised all over the manuscript including figure and table, otherwise some information could be not so clear to the readers. Gramatical and typo errors should be cleaned up and some sentences should be better rephrased.

9. In the Abstract, with “…place-controlled…” probably Authors wanted to mean “…placebo-controlled…”, so they should correct the sentence.

10. In the “Background”, Authors should rephrase the sentence: “Cholinesterase inhibitor had controversial roles in treating vascular diseases presented several studies..”, and in the sentence: “…it is in need of more evidence to be…” they should specify the subject.

11. In the paragraph “Rationale”, Authors should
- correct: “It has specific affinity…” instead of “It is…”;
- check if the year of publication of the Reference 31 is correct;
- check the term “…retrogressive …dementia” within this context;
- specify that WMD means Weighted Mean Difference.

12. In the paragraph “Statistical analysis”, does D180 mean day 180? If so, please specify

13. In the paragraph “Conclusion”, Authors probably wanted to mean: “… is to prove the efficacy of nimodipine in the prevention/treatment of mild cognitive
impairment in patients with acute ischemic stroke”.

14. Minor criticism also includes the use of a capital "N" in nimodipine. Nimodipine is the generic name and need not to be capitalized.

Hopefully, the Authors will find these comments helpful.

Best regards,
Svetlana Lorenzano

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.