## Statistical plan - Effect of Sodium Nitroprusside on Cerebral Blood Flow

A power calculation indicated that 14 subjects were required to detect a 15% reduction in CBF by a 40% reduction in MAP by sodium nitroprusside, after correction for changes in $PaCO_2$ (Henriksen and Paulson 1982), assuming a standard deviation of 18% (Lewis et al. 2015) with a 5% significance level and a power of 80%.

Outcomes are predefined in the clinical trials registration. The primary outcome is change in CBF by a 40% reduction in MAP by sodium nitroprusside. Secondary outcomes are 1) change in CBF by a 20% reduction in MAP by sodium nitroprusside, 2) relative reduction in internal carotid artery blood flow by a 40% reduction in MAP by sodium nitroprusside as compared to that of the vertebral artery, 3) the $CO_2$ reactivity of the internal carotid artery as compared to that of the vertebral artery, and 4) comparison of the slope of linear regression of MAP and CBF for the evaluations at baseline and when MAP is reduced by 20% by sodium nitroprusside and that of the evaluations when MAP is reduced by 20% and 40%.

Analysis of skin oxy- and deoxyhaemoglobin concentration and lactate are after logarithmic transformation. Analysis of the time points at baseline and when MAP is reduced by 20% and 40% by sodium nitroprusside was by a repeated measure mixed model, fit by restricted maximum likelihood in a structured covariance model with time as a fixed effect (Proc mixed; SAS 9.4, SAS Institute, Cary, NC, USA) and if the test was significant, changes from baseline are evaluated. Analysis of the time points at baseline and hypo- and hypercapnia is by a repeated measure mixed model, fitted by restricted maximum likelihood in a structured covariance model with time as a fixed effect (Proc mixed) and if the test is significant, changes from baseline are evaluated.

The $CO_2$ reactivity of the internal carotid artery to hypocapnia and to hypo- and hypercapnia is: 100 * change in blood flow / change in $PaCO_2$ * baseline blood flow by individual linear

regression. The $CO_2$ reactivity of the vertebral artery, MCA $V_{mean}$ and cerebral oxygenation is evaluated similarly. The $CO_2$ reactivity to hyper- and hypocapnia is different with higher sensitivity to hypercapnia (Ide et al. 2003, Willie et al. 2012) and CBF, internal carotid and vertebral artery blood flow, MCA $V_{mean}$, and $S_cO_2$ during sodium nitroprusside infusion were corrected for changes in $PaCO_2$ from baseline using the determined $CO_2$ reactivity to hypocapnia. The $CO_2$ reactivity to hypo- and hypercapnia of the internal carotid as compared to that of the vertebral artery is evaluated by a paired *t*-test after logarithmic transformation.

Comparison of the relative reduction in internal carotid and vertebral artery blood flow by a 40% reduction in MAP by sodium nitroprusside is evaluated by linear mixed models, fit by restricted maximum likelihood, with the relative change in blood flow as outcome while the fixed effects are change in MAP and an interaction factor for the difference between the two vessels. Difference in the slope of linear regression of changes in MAP and CBF for the evaluations at baseline and when MAP is reduced by 20% by sodium nitroprusside as compared to that for the evaluations when MAP is reduced by 20% and 40% is by a linear mixed model, fit by restricted maximum likelihood. The outcome parameter is relative change in CBF and the fixed effects are change in MAP and an interaction factor for the difference in two conditions, i.e. changes between baseline and when MAP is reduced by 20% and for changes between when MAP is reduced by 20% and 40%. Values are presented as mean ± SD or median with interquartile range for not normally distributed data and statistical significance was set at $P < 0.05$.

References

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