Nitrous Oxide and Long-term Morbidity and Mortality in the ENIGMA Trial

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Introduction: A plausible pathophysiologic rationale exists for increased long-term cardiovascular morbidity and mortality in patients receiving significant exposure to nitrous oxide. However, this relationship has not been established clinically. The ENIGMA trial randomized 2,050 patients having non-cardiac surgery lasting more than two hours to nitrous oxide-based or nitrous oxide-free anaesthesia. We conducted a follow-up study of the ENIGMA patients to evaluate the risk of cardiovascular events in the longer term.

Methods: The trial case report forms and medical records of all study patients were reviewed. The date and cause of death and occurrence of myocardial infarction or stroke were recorded. A telephone interview was then conducted with all surviving patients. The primary endpoint of the study was survival.

Results: The median follow-up time was 3.5 (range: 0 – 5.7) years. Three hundred and eighty patients (19%) had died since the index surgery, 91 (4.5%) were recorded as having myocardial infarction and 44 (2.2%) had a stroke during the entire follow-up period. Nitrous oxide did not significantly increase the risk of death (hazard ratio = 0.98 (95% confidence interval: 0.80 - 1.20; p = 0.82). The adjusted odds ratio for myocardial infarction in patients administered nitrous oxide was 1.59 (95% confidence interval: 1.01 - 2.51; p = 0.04) and for stroke was 1.01 (95% confidence interval: 0.55 - 1.87; p = 0.97).

Conclusions: The administration of nitrous oxide was associated with increased long-term risk of myocardial infarction, but not of death or stroke in patients enrolled in the ENIGMA trial. The exact relationship between nitrous oxide administration and serious long term adverse outcomes will require confirmation by an appropriately-designed large randomized controlled trial.

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