ONLINE SUPPLEMENT

Prophylactic Edaravone Prevents Transient Hypoxic-Ischemic Brain Injury: Implications for Perioperative Neuroprotection

Yu-Yo Sun, Yikun Li, Bushra Wali, Yuancheng Li, Jolly Lee, Andrew Heinmiller, Koji Abe, Donald G. Stein, Hui Mao, Iqbal Sayeed, Chia-Yi Kuan

Supplemental Table I: Clinical trials and preclinical studies of perioperative protectants.

Study	Design	Results
(Clinical trial) Neuroprotection of the brain during cardiopulmonary bypass: A randomized trial of Remacemide during coronary artery bypass in 171 patients[1]	87 subjects taking reacemide (a NMDA receptor antagonist) every 6 h from 4 days before to 5 days after cardiopulmonary bypass and 84 subjects on the placebo were compared in 9 neuropsychological tests before and 8 weeks after surgery.	The reacemide group showed a trend of reduction in the proportion showing decline of performance above 1 standard deviation (SD) in 2 or more testes (9% vs 12%).
(Clinical trial) Fluvastatin and perioperative events in patients undergoing vascular surgery[2]	250 subjects taking fluvastatin from randomization to at least 30 days after vascular surgery and 247 subjects on the placebo were compared for the onset of myocardial ischemia in 30 days post-operation. The secondary end-point was composite death from cardiovascular causes and myocardial infarction.	The fluvastatin group showed fewer myocardial ischemia (10.8% vs 19%) and fewer deaths from myocardial infarction and cardiovascular causes (4.8% vs 10.1%).
(Clinical trial) Intraoperative magnesium treatment does not improve neurocognitive function after cardiac surgery[3]	198 subjects with magnesium infusion and 191 subjects with the placebo during cardio-pulmonary bypass were assessed for cognitive functions pre-operatively and again at 6 weeks postoperatively.	The incidence of cognitive deficit in the magnesium group was 44.4% compared with 44.9% in the placebo group. Magnesium therapy did not improve neurocognitive function after cardiac surgery.
(Preclinical study) Resolving postoperative neuroinflammation and cognitive decline[4]	C57Bl/6J underwent stabilized tibial fracture were assessed by trace fear conditioning (TFC) for memory functions. Agonists and antagonists of the nicotinic acetylcholine receptor (nAChR) were given to the mice prior to TFC testing.	Tibial fracture decreased freezing behavior, the index for memory retention in the TFC test. Memory deficits were worsened by antagonists of nAChR but prevented by the administration of nAChR agonists.

References:

1. Arrowsmith JE, Harrison MJ, Newman SP, Stygall J, Timberlake N, Pugsley WB Neuroprotection of the brain during cardiopulmonary bypass: a randomized trial of remacemide during coronary artery bypass in 171 patients. *Stroke* 1998;29:2357-2362.

2. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, et al. Fluvastatin and perioperative events in patients undergoing vascular surgery. *New England journal of medicine* 2009;361:980-989.

3. Mathew JP, White WD, Schinderle DB, Podgoreanu MV, Berger M, Milano CA, et al. Intraoperative magnesium administration does not improve neurocognitive function after cardiac surgery. *Stroke* 2013;44:3407-3413.

4. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. *Annals neurology* 2011;70:986-995.