Title: PREVENTION OF INTRA-OPERATIVE MYOCARDIAL ISCHEMIA: A RANDOMIZED TRIAL OF INTRAVENOUS NITROGLYCERIN VS. PLACEBO

Authors: W.A.C. Mutch, M.D., J.D. Culligan, M.D., I.R. Thomson, M.D.

Affiliation: Department of Anesthesia, University of Manitoba, St. Boniface General Hospital, Winnipeg, Manitoba, Canada

Introduction: Intravenous (IV) nitroglycerin (NTG) has been reported to effectively relieve established episodes of intra-operative myocardial ischemia (IMI) during coronary artery surgery,[1] and to reduce the incidence of peri-operative ischemic episodes in patients with angina pectoris undergoing non-cardiac surgery.[2] We employed a double-blind randomized experimental design to compare the efficacy of IV NTG infusion (0.5 ug/kg/min) vs placebo (P) for the prevention of IMI during the pre-bypass period in patients undergoing coronary artery bypass grafting (CABG) under fentanyl/pancuronium/oxygen anesthesia (FOPA). The interaction between IV NTG and FOPA was also evaluated.

Methods: Twenty patients scheduled for elective CABG were studied and randomly assigned to NTG (n=9) or P (n=11) groups. All patients had stable angina and were receiving B-blockers and organic nitrates. Patients with abnormal complexes in leads II or V_5 of their resting electrocardiogram (ECG) were excluded. The study received institutional approval, and informed consent was obtained from each patient. Organic nitrates and B-blockers were withheld from midnight of the evening prior to surgery. Following premedication with diazepam 0.15 mg/kg PO, morphine 0.1 mg/kg IM, and atropine 0.007 mg/kg IM, nasal oxygen (3 l/min) was administered. Upon arrival in the operating room, ECG leads II and CS_5 were recorded by a Del Mar Avionics Holter monitor. Under local anesthesia intravenous, radial artery and thermodilution pulmonary artery catheters were inserted. A separate IV delivery system, shown in vitro to be non-adsorptive for NTG, was used to administer the NTG infusion at 0.5 ug/kg/min (or equivalent volume of P). The investigators did not know whether NTG or P was being infused. After 20 min. of NTG/P infusion anesthesia was induced with fentanyl (3 ug/kg/min) IV. Pancuronium (0.1 mg/kg) IV was administered incrementally to facilitate endotracheal intubation and/or combat rigidity. After fentanyl 25 ug/kg, the trachea was intubated. After a total of 50 ug/kg of fentanyl, surgery commenced. Fluids were administered at the discretion of the anaesthetist. Additional fentanyl was administered (5 ug/kg/min) as required to treat hypertension and tachycardia in response to surgery. The study was terminated when cardiopulmonary bypass was begun. Complete hemodynamic measurements were made at the following intervals: (1) control pre-NTG/P, (2) after 20 min. NTG/P infusion, (3) fentanyl 25 ug/kg, (4) 1 min. post-intubation, (5) 5 min. post-intubation, (6) fentanyl 50 ug/kg, (7) 1 min. post-skin incision, (8) 1 min. post-sternotomy, and (9) pericardium open. Measured and derived variables included heart rate (HR), mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), central venous pressure (CVP), cardiac index (CI), stroke index (SI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), rate pressure product (RPP) and endocardial viability ratio (DPTI/SPTI). The Holter monitor tapes were examined retrospectively and blindly for ECG evidence of myocardial ischemia. Depression of the ST-segment $\geq$ 1 mm. in either lead was considered diagnostic of ischemia. Statistical analysis was performed using Student's t-test for paired or unpaired data, $p \leq .05$ being regarded as significant.

Results: The NTG and P groups did not differ with respect to age, sex, ejection fraction or dose of B-blocker. No significant hemodynamic differences were noted between groups pre-NTG/P infusion. After 20 min. of NTG/P infusion MAP, PCWP and CVP were significantly lower in the NTG group compared to P, and the DPTI/SPTI ratio was higher in the NTG group. No hemodynamic difference was noted between groups at any time period subsequent to the induction of anesthesia. The groups did not differ significantly with respect to total fentanyl dose. Patients in the NTG group tended to receive more IV crystalloid than those in the P group (1.30±.56 1. vs 0.88±.44 1.), although this difference was not statistically significant. No patient exhibited ECG evidence of ischemia immediately pre-induction. Fifty percent of patients subsequently manifested ECG changes of myocardial ischemia. The incidence of ischemia did not differ between groups; 5/9 NTG and 5/11 P patients became ischemic during the pre-bypass period.

Discussion: The patients in the NTG group received a significant dose of NTG which produced hemodynamic effects comparable to those seen after sublingual NTG administration.[3] Despite continuous administration of NTG, these hemodynamic effects were no longer evident following anesthetic induction. Reversal of NTG-induced hemodynamic changes may have been related to differences in fluid administration between groups. Alternatively, FOPA may contribute to the reversal of NTG effects in an unexplained manner. In the absence of sustained changes in systemic hemodynamics, IV NTG was clearly not superior to P for the prevention of IMI. These findings support the hypothesis that beneficial effects of NTG in myocardial ischemia are related to changes in systemic hemodynamics, rather than to direct coronary vasodilator effects. Our findings are also consistent with observations that NTG does not substantially alter the RPP at which patients with coronary disease develop angina pectoris.[4] We conclude that prophylactic IV NTG infusion (0.5 ug/kg/min) does not decrease the incidence of IMI during FOPA in patients undergoing elective CABG.

References:

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