Title: Nitroglycerin Infusion During Rewarming in Cardiac Surgery and Its Effects on Tissue Perfusion and Coagulation

TSGHIRB 1-102-05-049, valid from June 10, 2013 to June 27, 2017.

ClinicalTrials: **NCT01901419**, actual study from July 8, 2013 to June 8, 2017.

Protocol version: May 4, 2016

TEL: 886-2-87923311 ext 10552
FAX:886-2-2793-6049 / 2792-9201
E-mail: tsghirb@ndmctsgh.edu.tw

國防醫學院三軍總醫院
人體試驗審議會

11490 台北市內湖區成功路二段
325 號 醫療大樓五樓 5113 室
No. 325, Sec.2, Cheng-Kung Rd.
Neihu 11490, Taipei, Taiwan, R.O.C

人體試驗計畫同意函

本審議會核准編號：1-102-05-049
計畫名稱：心臟手術回溫過程使用硝化甘油(nitroglycerin)輸注對組織灌流與凝血功能的影響
執行機構：三軍總醫院
計畫主持人：麻醉部林作舟醫師
共同主持人：蔡建松醫師
計畫書版本日期：V2-2016-0504
本會審核通過之其他文件版本及日期：中文摘要：V2-2016-0504
業經本院 2016 年 6 月 17 日人體試驗審議會第一審議會第 231 次會議審查通過變更計畫試驗期限至 2017 年 12 月 31 日、計劃書、中文摘要，該計畫案經評估屬低度風險，(持續審查頻率為每年一次)，有效期限至 2017 年 6 月 29 日，特此證明。
本審議會的運作，遵循藥品優良臨床試驗準則及政府相關法律規章。計畫主持人應於同意函有效期屆滿前二個月，提出展延申請，本案須經本院人體試驗審議會通過後，方可繼續執行。

Letter of Approval

Institutional Review Board, Tri-Service General Hospital

TSGHIRB No.: 1-102-05-049
Protocol title: Nitroglycerin infusion during rewarming in cardiac surgery and its effects on tissue perfusion and coagulation
Research institution: Tri-Service General Hospital
Principle investigator: Tso-Chou Lin
Co-investigator(s): Chien-Sung, Tsai
Protocol version: V2-2016-0504
Other documents: Chinese Abstract : V2-2016-0504

At the 231th meeting on 06/17/2016, the Institutional Review Board 1 of the Tri-Service General Hospital approved the above-named application for amendment. Assessed as Low Risk, the protocol is subject to follow-up review annually. The Board is organized and operated in compliance with International Conference on Harmonization (ICH) / WHO Good Clinical Practice (GCP) and applicable laws and regulations.
This approval is valid for 1 year till 06/29/2017. The principle investigator is required to submit the application for extension 2 months before the expiration date.

三軍總醫院 TSGHIRB 人體試驗審議會

Institutional Review Board
余慕賢 Yu Mu Hsien
Chairman_____.

The Committee is Organized and operates in accordance with ICH6 GCP regulations and guideline.
本審議會組織與運作皆遵守ICH6 GCP規定

Methods

Patients

This study was registered with ClinicalTrials.gov as NCT01901419 after obtaining approval of Tri-Service General Hospital Institutional Review Board (TSGHIRB-1-102-05-049). Patients receiving elective cardiac surgery with cardiopulmonary bypass were recruited and signed the written informed consent. Those with complicated comorbidities were excluded, such as chronic hepatic or renal insufficiency, or acute cardiopulmonary failure requiring mechanical ventilation, intra-aortic balloon pump, or extracorporeal membrane oxygenation. Patients were randomly assigned to receive either NTG infusion 1-5 mcg/kg/min (NTG group), the dose labelled to maintain intraoperative hypotension, or 0-0.1 mcg/kg/min (control group), the dose labelled for acute cardiac insufficiency, during rewarming of hypothermic CPB. Those undergoing normothermic CPB decided by the surgeon intraoperatively were not analyzed.

Anesthesia and cardiopulmonary bypass

Routine physiologic monitoring, including three-lead electrocardiogram, pulse oximetry and an invasive arterial blood pressure monitoring were set up immediately before anesthesia induction. In addition, cardiac output was continuously monitored (FloTrac; Edwards Lifesciences, Irvine, CA, USA). Cerebral oximetry (Fore-Sight oximeter; CASMED, Branford, CT, USA), based on near-infrared spectroscopy technology, was applied on the forehead until the end of surgery.

All patients received general anesthesia with midazolam 5 mg, fentanyl 1.5-3.0 mcg/kg, propofol 0.5-1.5 mg/kg, and cisatracurium 0.1-0.2 mg/kg for induction, as well as sevoflurane or isoflurane for maintenance after tracheal intubation. A pulmonary artery catheter (Swan-Ganz Thermodilution catheter 7.5 Fr; Edwards Lifesciences, CA, USA) was placed through right internal jugular vein for postoperative monitoring. Transesophageal echocardiography

was used to monitor real-time cardiac performance throughout the whole procedure. Minute ventilation was adjusted to maintain end-tidal CO_2 40 ± 5 mmHg, confirmed by serial arterial blood gas analyses. After achieving anticoagulation (activated clotting time >350 seconds) by intravenous administered heparin 300 U/kg prior to cannulation, standard hypothermic CPB (Sarns 8000, Terumo, Ann Arbor, MI) with an extracorporeal membrane oxygenator (Capiox®SX 18, Terumo, Ann Arbor, MI) were carried out in sequence to maintain the body temperature at 26-30 ºC during surgery. The perfusionist adjusted the pump flow to obtain an adequate output of 2.2 l/m^2 of body surface area and adjusted sevoflurane concentration on the vaporizer, to keep mean arterial blood pressure 50-80 mmHg.

Treatment protocol

Before rewarming, the patients were randomly assigned to NTG group with NTG infusion 1-5 mcg/kg/min or control group with 0-0.1 mcg/kg/min. The infusion rate would be tapered if there was profound hypotension (mean arterial pressure <40 mmHg) or cerebral desaturation (absolute saturation value <60 or relative drop to <80% of baseline value each side). Following standard rewarming and deaerating, the pump flow was reduced to 0.5 l/min for release of aortic clamp and was weaned with routine inotropic support, including dopamine 3-8 mcg/kg/min and additional dobutamine, epinephrine, or norepinephrine infusion for acceptable cardiac output. Further intra-aortic balloon pump or extracorporeal membrane oxygenation would be applied for cardiopulmonary support, if needed. Heparin effect was neutralized with protamine sulfate after stop of bypass. All patients were transferred to the cardiovascular surgical intensive care unit (ICU) with endotracheal intubation after the operations were finished. According to the routine criteria, extubation was performed after obtaining oriented consciousness, normothermia (patient rewarmed and shivering controlled), and hemodynamic stability with no uncontrolled arrhythmias and no excessive bleeding (as defined by loss of < 100 ml/h).

Data collection

Arterial blood gas analysis was routinely examined perioperatively, including before incision, after heparin administration, before aortic unclamping, after aortic unclamping, after protamine administration, and immediately upon ICU admission by GEM Premier 3000 (Instrumentation Laboratory, Lexington, MA, USA), including plasma lactate (detectable limit, 0.3 to 20 mmol/L) and glucose (detectable limit, 20-500 mg/dL) levels. The activated clotting (or coagulation) time was tested by ACT Plus (Medtronic, Minneapolis, MN, USA) after heparin administration, during CPB, after protamine administration, and before the end of surgery (if needed). The perioperative variables were collected, including acid-base status, glucose level, and urine output. Postoperative inotropic use, time to extubation, lengths of ICU and hospital stay, and 30-day mortality were also recorded from the hospital's registry database.

Statistical analysis

All values were expressed as mean ± SD or number unless otherwise stated. The Student t-test was applied to compare means of continuous variables. Pearson's Chi-square test or Fisher's exact test was used for categorical variables. All statistical tests were two-tailed, with the level of significance set at *P* values <0.05. Data analysis was performed using the SPSS for Windows.