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Original contribution

Nitric oxide index is not a predictor of cognitive dysfunction following laparotomy

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Abstract
Study Objective: To determine the associations between postoperative cognitive dysfunction (POCD) and plasma concentrations of stable nitric oxide products [nitric oxide index (NOi)].
Design: Prospective study.
Setting: Academic hospital.
Patients: 28 ASA physical status I, II, and III physical status patients undergoing major non-cardiac surgery.
Interventions: Cognitive assessment was performed preoperatively and postoperatively at 4 days (early) and 6 weeks (late).
Measurements: Serial measurements of plasma NOi were recorded.
Main Results: Early POCD with a deficit in one cognitive domain was present in 18 patients (64%), and in 8 patients (28%) with deficits in two or more cognitive domains. Late POCD was evident in three patients (20%) who had a deficit in one domain. Eight patients were lost to late follow-up. There was no difference in baseline or subsequent serum concentrations of NOi between those who showed early and late POCD and those who showed no POCD.
Conclusion: Factors other than nitric oxide-mediated injury is responsible for POCD following major non-cardiac surgery.

1. Introduction

Neuropsychological dysfunction occurs in patients who have undergone major surgery, and ranges in nature from confusion and delirium to early and late cognitive impairment [1-3]. Delirium in hospitalized patients increases the risk of in-hospital mortality by 15% to 30% and is associated with a greater likelihood of permanent cognitive dysfunction and inability to return to independent living [4]. Postoper-

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ative neurological complications in the elderly markedly increase resource consumption [5]. Postoperative cognitive dysfunction (POCD) can manifest as a problem with mental arithmetic or complex planning and, in the case of the elderly, it may result in loss of independence. Research continues into the underlying mechanisms and potential markers for this problem.

A recent study at our institution examined the role of nitric oxide (NO) production as a marker for POCD following laparoscopic cholecystectomy [6]. Plasma NO products [NO index, (NOi)] were consistently elevated over a 48-hour perioperative period in patients who showed POCD (as defined by a deficit in one cognitive domain) at 4 days (40% sample) compared with those who had no POCD. Those who had deficits in two cognitive domains at 4 days (7.5% sample) also had a similar pattern, but over a shorter time, ie, up to 4 postoperative hours. Preoperative NOi was significantly higher in patients who developed POCD, suggesting that they may have had NO-related predisposition.

Laparoscopic cholecystectomy is considered an ambulatory procedure in many centers [7]. In contrast, major surgery is associated with profound changes in endocrine and metabolic function, and a greater inflammatory response [8], resulting in increased expression of mediators such as tumor necrosis factor, interleukin-1β, and glucocorticoids, all known triggers of inducible NO synthetase (iNOS) activity [9]. We hypothesized that a) preoperative NOi predicts POCD following laparotomy, and b) the larger inflammatory response following major surgery produces a greater postoperative NOi in patients with POCD.

2. Materials and methods

With Cork University Hospital institutional review board approval and patients' written, informed consent, 28 ASA physical status I, II, and III patients undergoing major laparotomy were studied. Patients scheduled for surgery lasting more than one hour and which involved an open abdominal cavity (laparotomy), were enrolled. Exclusion criteria included a score of 23 or lower on the mini-mental state examination (MMSE), central nervous system disease, surgery within the preceding 6 months, previous exposure to cognitive testing, severe visual or auditory disorders, alcoholism, active renal or liver disease, and illiteracy. A non-surgical control group was recruited to account for the effects of repeated neuropsychological testing (practice effect). When possible, this group consisted of partners of the study group members.

Patients fasted for at least 6 hours before induction of anesthesia. With the exception of diuretics, which were withheld on the morning of surgery, all regular medication was given. Premedication consisted of oral diazepam 0.1 to 0.15 mg/kg one to two hours prior to induction. General anesthesia was induced with fentanyl one to two μg/kg, propofol one to two mg/kg, and vecuronium 0.1 to 0.15 mg/kg. Each patient's trachea was intubated and anesthesia was maintained with isoflurane 0.2% to 3.0% in oxygen and either nitrous oxide or air. Fraction of inspired oxygen was maintained at 40% to 50% and intermittent positive pressure ventilation was set to ensure normocapnia.

For the purpose of blood sampling, a second intravenous (IV) cannula was placed in the opposite arm to that being used for IV fluid and drug administration.

Analgesia consisted of IV morphine 0.1 to 0.2 mg/kg intraoperatively, with additional dosing of one to two mg boluses given in the recovery room to ensure satisfactory analgesia. Postoperatively, patients received patient-controlled analgesia using a standard regimen consisting of a two mg bolus, 5-minute lockout, and total 4 hourly dose < 40 mg. Diclofenac was also prescribed for postoperative analgesia on an as-needed basis.

Based on a preoperative NOi of 17.1 ± 6.8 μg/mL in a non-cognitive deficit group with a difference of 16 μg/mL in a cognitive deficit group, and based on a likely proportion of 47% showing cognitive deficit at 6 weeks [6], a sample of 28 patients was required where $\alpha = 0.05$ and $\beta = 0.2$. Students *t*-test, Chi square analysis, and Fisher's exact tests were used as appropriate.

2.1. Cognitive testing

A battery of cognitive tests, including those recommended by the Statement of Consensus 1995 [10], were administered at the following perioperative time points: preoperatively, on postoperative day 4, and at 6 weeks postoperatively. Mood was assessed by the Hospital Anxiety and Depression Scale [11]. The MMSE was used to screen for delirium. Patients self-assessed cognitive decline from the short cognitive failures questionnaire (CFQ) [12] both preoperatively and at 6 weeks.

Trained investigators performed each assessment. Domains of cognitive function and the tests used were as follows: *Verbal memory:* the Rey Auditory Verbal Learning Test (ReyAVLT) assesses immediate memory. *Attention:* the Trial-Making Test parts A and B (Halstead-Reitan Neuropsychological Test Battery) assess speed of visual search, attention, and mental flexibility. *Motor speed:* the Purdue Pegboard test examines manual dexterity and fine motor coordination. *Executive function/ Verbal fluency:* the Controlled Oral Word Association Test (COWAT) assesses word fluency. *Psychomotor speed:* the Digit Symbol Substitution Test (DSST) evaluates rapid visual-motor responses as well as sustained attention and concentration.

Using the methodology outlined by Jacobson and Truax [13], a Reliable Change Interval (RCI) was calculated for each neuropsychological measure using the baseline and follow-up data of the control subjects. Each consenting spouse or partner who was within ±10 years of age of a