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ORIGINAL ARTICLE

Dopamine Administration is a Risk Factor for Delirium in Patients Undergoing Coronary Artery Bypass Surgery

Seyhan Yilmaz, MD, PhD, Eray Aksoy, MD *, Adem Ilkay Diken, MD, PhD, Adnan Yalcinkaya, MD, PhD, Mehmet Emir Erol, MD, Kerim Cagli, MD, PhD

Hitit University Corum Education and Research Hospital, Department of Cardiovascular Surgery, Turkey

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Background Delirium is an important morbidity following heart surgery. We sought to determine whether dopamine infusion is associated with increased risk of delirium in patients undergoing coronary artery bypass grafting.

Methods A total of 137 patients (mean age; 61.02±7.83, 105 males) were included in the study. Patients undergoing isolated coronary artery bypass grafting were considered eligible and those with preoperative neurological deficit or significant neurocognitive disorders, dementia or psychiatric disorders were excluded. Primary outcome measure was occurrence of delirium within 72 hours after operation. The diagnosis of delirium was made using confusion assessment method for the intensive care unit questionnaire. Both administration of dopamine as a dichotomised variable and the total amount of dopamine per kg body-weight were included in two different logistic regression models.

Results Delirium occurred in 18 (13.1%) patients. Age adjusted Mantel-Haenszel relative risk for delirium with receiving dopamine was 4.62. Relative risk was 2.37 (0.18 to 31.28, 95% CI, p=0.51) in total doses over 10 mg whereas it was 3.55 (1.16 to 10.89 95% CI, p=0.02) in total doses over 30 mg per kg body-weight. Older age (p=0.03), dopamine administration (OR: 9.227 95% CI, 2.688-32.022, p<0.001) and the amount of dopamine administered (OR: 1.072, 95% CI, 1.032-1.115, p<0.001) were independent predictors for delirium 72 hours after surgery.

Conclusion Along with older age, dopamine infusion - even in low doses but more probably in higher doses - emerged as an independent risk factor for delirium in patients undergoing CABG. Further study is needed to confirm the validity of results presented.

Keywords Delirium • Dopamine • Vasoactive drugs • Coronary artery bypass grafting • Intensive care unit

Introduction

Neurocognitive decline early after coronary artery bypass grafting (CABG) is common and incidence of delirium was reported to range from 4.8% to as high as 44.3%, especially when a specific examination tool was used in diagnosis [1,2]. Several risk factors were suggested to be predictive for delirium after CABG and the common observation was that occurrence of delirium was not only associated with a preoperative neurocognitive decline but also with perioperative risk factors that have already been known to be associated with poor outcomes after surgery. A higher Euroscore, older

*Corresponding author at: Camlik St. No.2 Corum/TURKEY. Tel.: +05336838186; fax: +0 (364) 223 03 23, Email: opdrerayaksoy@gmail.com

age and use of benzodiazepines were among the most commonly reported preoperative risk factors whereas type of surgery or anaesthesia and post-operatively higher rate of transfusion and inadequate mobilisation were reported as modifiable risk factors for occurrence of delirium in cardiac surgical patients [3–5].

Dopamine, an endogenous central neurotransmitter, is the immediate precursor of norepinephrine in the catecholamine synthesis pathway. It has been commonly used in cardiac surgical patients because it weakly binds to β1 adrenergic receptors at intermediate doses (3.00 to 10.00 µg/kg/min), induces norepinephrine release and inhibits its reuptake in sympathetic nerves, thus improving cardiac chronotrophy and contractility [6]. Although the clinical importance of the so-called ''renal dose'' is controversial, as it does not cause a significant increase in glomerular filtration rate [7], even its standard use was proposed to be indicated early after CABG to achieve good renal perfusion [8].

Several theories have been suggested to clarify the pathogenesis of delirium with alteration in neurotransmitter synthesis, function and availability being the most commonly accepted since neurotransmitter imbalance in brain tissue seems to be the final common pathway in delirium occurrence. Dopamine excess is among the most commonly described neurotransmitter imbalance changes in pathogenesis of delirium [9]. To date, there has been no study focussing on whether infusion of dopamine in cardiac surgical patients is associated with an increased risk of delirium, whereas such a relationship has been proposed in patients admitted to general critical care [10]. We conducted the present study to reveal if post-operative administration of dopamine and the amount of dosage given after CABG is associated with an increased risk of delirium.

Material and Methods

The study was approved by local ethics committee (2014-83116987-250). All patients gave informed consent before the operation allowing their clinical information to be used for scientific research. This retrospective study was undertaken in the cardiovascular surgery department of a tertiary university hospital and made up of patients undergoing coronary artery bypass surgery between April 2013 and October 2014. Data included patient counselling charts, operative and intensive care unit (ICU) records, and laboratory parameters and patients' registry information. The ICU where patients were admitted is a newly-established, adequately equipped cardiovascular ICU and optimal indoor measures including air and humidity conditioning and noise and light optimisation is being undertaken. Patients aged 30 to 85 years who were scheduled for isolated CABG were considered eligible for the study whereas those having comorbidities including delirium, preoperative neurological deficit or significant neurocognitive disorders, dementia or psychiatric disorders and those with a clear indication for combined carotid, ascending aorta or valve disease were excluded. Patients with poor cardiac haemodynamics who require emergency operation and those on haemodialysis or mechanic ventilatory support were also excluded. Finally, among a total of 186 patients who underwent cardiac surgery, 137 patients (mean age; 61.02±7.83, male to female ratio 105:32) were included in the study.

Patients were premedicated orally with diazepam 5 mg the night before the operation. All of the operations were performed by the same surgical team. General anaesthesia was induced using thiopental (3 to 4 mg/kg) and fentanyl (2 to 6 g/kg). Tracheal intubation was achieved with pancuronium 0.1 mg/kg and the lungs were ventilated with FiO2 being maintained at 40%. Hydroxyethyl starch 6% and saline were used for fluid management and maintenance. Cardiopulmonary bypass was provided using a Stockert roller pump with an open reservoir with the pump flow being maintained at 2.40 l/min/m2 and mean arterial pressure within 60 to 90 mmHg. Nasopharyngeal temperature was lowered to down to 32 C. Myocardial protection was achieved with intermittent doses (every 20 min) of antegrade normothermic blood cardioplegia combined with retrograde continuous infusion. A routine CABG procedure was performed by use of internal thoracic artery as the preferred graft for left anterior descending artery anastomosis. Proximal anastomoses were performed before removing the cross clamp to avoid repeat clamping.

The primary outcome measure was occurrence of delirium within 72 hours following completion of surgery. Secondary outcome measures were mortality and days of ICU and hospital stay. The diagnosis of delirium was made using ''Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)'' which is a bedside tool consisting of four features including acute change or fluctuating course in mental status, inattention, altered level of consciousness and disorganised thinking [11]. Each one of these features was questioned by following the specific instructions by the developers. Co-existence of feature 1 and feature 2, accompanied by either one of the feature 3 or 4 was deemed as a positive diagnosis for delirium in any given patient. Presence of delirium was not screened routinely but rather CAM-ICU was used to confirm and record the diagnosis upon healthcare staff noticing any level of neurocognitive decline during ICU stay of patients.

Baseline information is given in Table 1. The main indication for dopamine administration was to achieve better renal perfusion. Dopamine infusion was considered as indicated when mean arterial blood pressure < 65.00 mmHg and urine output < 40.00 ml/hour despite adequate volume expansion. For this purpose, dopamine was started at a dose of 3.00 µg/kg/min and the dose was increased up to 7.00 µg/kg/min to achieve adequate urine output. Dopamine administration was regarded as a dichotomous variable and the total amount of its administration (i.e mg per kg of body weight) was also included in analysis. The total amount of dopamine given was obtained by confirming the dosage given in ICU charts with total amount of drug used (Dopamin, Fresenius, 200 mg/5 ml ampoule for