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Original contribution

Effect of remifentanil and fentanyl on postoperative cognitive function and cytokines level in elderly patients undergoing major abdominal surgery

Germano De Cosmo MD (Associate Professor, Director)[a,*], Flaminio Sessa MD (Resident)[b], Federico Fiorini MD (Resident)[b], Elisabetta Congedo MD, PhD (Attending Physician)[c]

[a]*Department of Anesthesia and Intensive Care, Integrated Complex Columbus, Catholic University of Sacred Heart, Rome, Italy*
[b]*Department of Anesthesia and Intensive Care, Catholic University of Sacred Heart, Rome, Italy*
[c]*Department of Anesthesia and Intensive Care, Antonio Perrino Hospital, Brindisi, Italy*

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Abstract

Purpose: Postoperative cognitive dysfunction is a frequent complication occurring in geriatric patients. Type of anesthesia and the patient's inflammatory response may contribute to postoperative cognitive dysfunction (POCD). In this prospective randomized double-blinded controlled study we hypothesized that intraoperative remifentanil may reduce immediate and early POCD compared to fentanyl and evaluated if there is a correlation between cognitive status and postoperative inflammatory cytokines level.

Methods: Six hundred twenty-two patients older than 60 years undergoing major abdominal surgery were randomly assigned to two groups and treated with different opioids during surgery: continuous infusion of remifentanil or fentanyl boluses. Twenty-five patients per group were randomly selected for the quantitative determination of serum interleukin (IL)-1β, IL-6, and IL-10 to return to the ward and to the seventh postoperative day.

Results: Cognitive status and its correlation with cytokines levels were assessed. The groups were comparable regarding to POCD incidence; however, IL-6 levels were lower the seventh day after surgery for remifentanil group (P= .04). No correlation was found between POCD and cytokine levels.

Conclusions: The use of remifentanil does not reduce POCD.

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1. Introduction

The profound social changes that have characterized the last century along with the progress in surgical and anesthetic techniques have made possible the increase of the number of

* Corresponding author at: Department of Anesthesia and Intensive Care, Integrated Complex Columbus, Catholic University of Sacred Heart, 31 G. Moscati Street, 00168, Rome, Italy. Tel.: +39 06 3503899; fax: +39 06 3050101.
E-mail address: gdecosmo@rm.unicatt.it (G. De Cosmo).

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elderly patients safely undergoing surgery. This has given rise to problems that rarely involve young patients, such as postoperative cognitive impairment mainly regarded, for years, a problem associated with cardiac surgery [1].

Alteration in cognitive status in the postoperative period is common after major surgery in the elderly and anesthesia has often been cited as a major cause of this problem [2]. The postoperative cognitive impairment can be classified as postoperative delirium, postoperative cognitive dysfunction (POCD), and dementia. POCD is a neurological mild cognitive disorder characterized by impaired memory, concentration, language comprehension and disturbance of social relations whose diagnosis is made days or weeks after surgery and can result in a lifelong disorder [3].

Despite the extensive research conducted in recent years on the subject, the causes and pathophysiological mechanisms responsible for postoperative cognitive decline remain unclear. With regard to patient-related factors, the so-called predisposing factors, the last studies mentioned old age and low level of education [4,5], the presence of preoperative cognitive impairment, the chronic use of narcotics and/or benzodiazepines, the number of comorbid conditions, the cerebrovascular diseases and the occurrence of postoperative delirium [6]; role of genetic predisposition is not yet clear as the results available are conflicting. Outside of predisposing risk factors, duration of anesthesia, reoperation, infection and postoperative pulmonary complications increase the risk of occurrence of POCD [7]. Similarly, whether the type of anesthesia may influence cognitive status is still subject of debate. Moreover, in the past years, several studies have attempted to assess the effects of systemic inflammation following a surgical insult on neuroinflammation, neurogenesis, and cognitive function postoperatively. In experimental settings involving mice, the postoperative inflammatory response appeared to be more evident in mice with cognitive impairment [8]. However, surgery may not be the only responsible for the neuroinflammatory response as increased levels of inflammation factors such as TNF-α, IL-6 and IL-1β have also been reported after single administration of isoflurane [9].

In order to contribute to the study of pathophysiological mechanisms responsible for postoperative cognitive decline, we want to understand if different methods of analgesia will influence the incidence of early POCD after non-cardiac surgery in the elderly. In particular, we compared two analgesics: remifentanil, an opioid used via continuous infusion for its easy titration and rapid dissipation of clinical effect even after prolonged infusion, and fentanyl that for its pharmacokinetic is administered by bolus. We hypothesized that continuous infusion of remifentanil allows a more constant analgesia that may have a less significant impact on cognitive status. Moreover, we also wanted to understand if patients positive for POCD have inflammatory cytokines more represented and if there was a correlation between inflammatory pattern and type of analgesic used. Therefore, the purpose of this study was to investigate the effects of two different analgesic drugs (continuous infusion of remifentanil versus bolus of fentanyl) during major abdominal surgery on cognitive status of elderly patients at the first and the seventh postoperative day and if there is an association between the level of peripheral inflammatory markers and POCD. The primary aim was to evaluate if there is a difference in postoperative cognitive function in patients receiving remifentanil or fentanyl; secondary aims were to establish if there is an association between the presence or absence of POCD and cytokine levels and if there is a correlation between the two drugs and levels of inflammatory cytokines.

2. Material and methods

This prospective, double-blind, randomized study was performed with approval of the local ethical committee (ref. A/575/CE/2009; registered at ClinicalTrials.gov: NCT01627873). After informed consent, 622 patients older than 60 years, undergoing to major abdominal surgery under general anesthesia in our hospital, ASA I-III, were enrolled from August 2009 to July 2011. Exclusion criteria were: history of allergy to drugs used in the study, Mini Mental Score Examination <24, expected duration of anesthesia less than 1 hour or more than 4 hour, the presence of a cognitive disorder, history of carotid or brain vascular disease, habitual use of anxiolytics or other drugs that affect the Central Nervous System, psychiatric illness, severe hypertension or other vascular disorders, rejection by the patient. Neuropsychological assessment was conducted the day before the surgical procedure to all patients and was designed to assess two cognitive domains: attention (Stroop color word interference test) and memory/learning (Rey Auditory Verbal Learning Test). Patients with Mini Mental Score Examination below 24 were excluded. In the Stroop test the subject was asked to read a random sequence of adjectives, “green”, “red”, “blue” printed in black ink, then he must identify the color of a succession of circles printed in green, red and blue and finally the subject must name the color in which a word is presented and the color and word don’t match (e.g., the word red presented in green). The number of errors that the subject does in reading is a measure of his ability to focus.

In Test of Rey an examiner reads to the patient a list of 15 words at a rate of one per second. Afterwards, the patient has to repeat all the words that he remembers, at any order for five times. Then the examiner presents a list of new 15 words that the patients have to repeat only one time. Following fifteen minutes, the patient is asked to repeat as many words as he remember from the first list. The maximum score of the first phase of the test is an expression of the ability of short-term memory, while the result of the test at a distance of 15 minutes is index of the ability of long-term memory.

Therefore, four variables were used in the calculation of the endpoint of POCD: time and error scores from the Stroop Color Word Interference Test, and cumulative number of words recalled in five trials in 5 minutes that investigates

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