



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

^aDepartment of Anesthesia and Intensive Care, Integrated Complex Columbus, Catholic University of Sacred Heart, Rome, Italy

^bDepartment of Anesthesia and Intensive Care, Catholic University of Sacred Heart, Rome, Italy

^cDepartment of Anesthesia and Intensive Care, Antonio Perrino Hospital, Brindisi, Italy

Received 14 April 2016; revised 19 June 2016; accepted 5 July 2016

Keywords:

Remifentanil;
Fentanyl;
Post operative cognitive
dysfunction;
Analgesia;
Cytokines

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)-1 β , 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.

© 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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).

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-1 β 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: remifentanyl, 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 remifentanyl 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 remifentanyl 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 remifentanyl 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

immediate recall and cumulative number of words recalled after 20 minutes that investigates the delayed recall from the Visual Verbal Learning Test.

Moreover, the day before surgery patients were instructed regarding to the use of visual analogue scale (VAS) for the assessment of the intensity of the postoperative pain (0 = no pain and 10 = worst pain imaginable) and regarding to the use of patient-controlled analgesia (PCA) device by which to manage the administration of tramadol for postoperative pain.

The day of surgery, in the operating room, all patients were monitored with electrocardiogram, pulse oximeter to measure oxygen saturation, blood pressure and non-invasive Bispectral index (BIS) to assess the depth of anesthesia.

Patients were randomized into 2 groups according to the analgesic method: group A and group B. Randomization was performed using a random sequence of numbers generated by software and was implemented through the use of closed envelopes consecutively numbered. In group A anesthesia was induced with propofol (2 mg/kg), intubation was facilitated by administration of cisatracurium (0.15 mg/kg) and analgesia with continuous infusion of remifentanyl at a rate of 0.15 μ g/kg per minute. Maintenance of anesthesia with sevoflurane was obtained in a mixture of oxygen (F_{IO_2} = 0.4) and air. Intraoperative analgesia was maintained with remifentanyl at a rate of 0.15 to 0.25 μ g/kg per minute. Additional boluses of cisatracurium (0.02 mg/kg) were administered as needed during surgery. Sevoflurane and analgesic were administered at a concentration to maintain the BIS between 40 and 60. At the beginning of the closure of the peritoneum was administered a bolus of morphine (0.1 mg/kg) and acetaminophen 1 g. The administration of sevoflurane and remifentanyl was discontinued at the end of the closure of the surgical wound.

In group B anesthesia was induced with propofol (2 mg/kg), fentanyl (2 μ g/kg) and intubation was facilitated by administration of cisatracurium (0.15 mg/kg). Maintenance of anesthesia was performed with sevoflurane in a mixture of oxygen (F_{IO_2} = 0.4) and air. Intraoperative analgesia was maintained with additional boluses of 50 mcg fentanyl according to the clinical needs. Additional boluses of cisatracurium (0.02 μ g/kg) were administered as needed during surgery. At the beginning of the closure of the peritoneum was administered acetaminophen 1 g.

Body temperature of the patients was maintained at or above 35°C to avoid the minimum stress due to major temperature variations. Neostigmine was administered for reversal of neuromuscular block at the end of surgery. Patients in both groups after tracheal extubation, were transferred to the recovery room where an anesthesiologist assessed the pain by the evaluation of VAS score and administered intravenous morphine 2 mg every 5 minutes until a VAS score at rest was less than 3. Afterwards, PCA using an intravenous syringe pump, containing tramadol for 24 postoperative hours, was started. The PCA pump with tramadol at a concentration of 5 mg/ml was planned to deliver boluses of 4 ml with a lock out interval of 7 minutes and a limit represented by a maximum dose in the 8 hours of 150 mg. No other analgesic was

used. The total amount of tramadol and morphine rescue administered, were recorded in 24 hours. The pain, as assessed by VAS at rest (VASr) and after a cough (VASi), was recorded every hour for the first 4 hours and then every 4 hours up to 24 hours postoperatively.

To evaluate the occurrence of postoperative cognitive disorder was administered to the first and seventh day following the surgery the Mini Mental State Examination, the Stroop color word interference test and the Rey Auditory Verbal Learning Test.

Moreover, in the last 50 patients, 25 per group randomly selected, blood samples were collected for the quantitative determination of serum interleukins: IL-1 β , IL-6 and IL-10 as representative of systemic inflammatory mediators. The samples were carried out at the following times: to return to the ward after surgery and at 6 AM of the seventh postoperative day. Determination was made by Multiplex ELISA. Values below 80 pg/mL for IL-1 β , 10 pg/mL for IL-6 and 10 pg/mL for IL-10 were considered non-optimal for a reliable detection.

The patient, the anesthesiologist assigned to collect data and the immunologist dedicated to dose serum cytokines were blinded to the analgesic used.

2.1. Statistical analysis

For statistical analysis of the data collected was used the package WAS 11. To determine the number of patients to be enrolled was carried out the power analysis. Taking into consideration that previous studies have estimated incidence of POCD after 7 days of surgery in elderly patients undergoing non-cardiac surgery of 30% [10] and wanting to find a difference of 50% between the two study groups, selecting as criteria a power of 90% and an α error of 5%, was calculated a total of 290 patients per group. Data were expressed as mean (SD), absolute values or percentages. Differences in the characteristics of patients with and without cognitive disorders, and differences in VAS scores were evaluated by the *t* test or the Mann-Whitney test. To establish the presence of POCD we have applied the definition that has been used previously in other studies; we calculated the change in each individual patient's test scores from baseline (preoperatively) to the tests at 1 day and at 7 days after the operation. The resulting differences were divided by the SD of the corresponding changes in the preoperative test to obtain a Z score for each test according the following formula: $Z \text{ score} = [(Change \text{ Score}) - (Mean \text{ Change Score preoperatively})] / (SD \text{ Change Score preoperatively})$. Patients were defined as having cognitive dysfunction when at least 2 Z scores in individual tests or the average Z score (of all variables) was greater than 1 SD [11]. Difference between the percentages of patients with POCD was calculated using the Pearson χ^2 test. Because of the lack of a control group was not possible to estimate the influence of the effects of learning on neurocognitive assessment. Given the large number of patients to be enrolled, blood samples for analysis of serum cytokines were not performed in all patients but, as already mentioned, in 25 patients in each group. The

differences in cytokine levels in the two subgroups were analyzed by the Kruskal-Wallis test. Variables that were not normally distributed were expressed as median and interquartile ranges. Correlation between the levels of cytokines and the z-score was determined using the Spearman rho test.

3. Results

A total of 622 patients were enrolled. Of these, 30 patients were excluded from the final analysis because they required a postoperative monitoring in the ICU, 21 refused to complete the preoperative neuropsychological tests, therefore a total of 571 patients have been studied and randomized of which 277 belong to the group of remifentanyl and 294 in the fentanyl group. There were no significant differences between the groups regarding to demographic data, length of surgery and type of surgery (Table 1). There were no statistically significant differences with regard to the results of preoperative neuropsychological tests between the two study groups (Table 2).

In the first postoperative day 266 and 247 patients belonging to the fentanyl and remifentanyl group, respectively, have completed neuropsychological tests. Forty-three patients refused to repeat the tests and in 15 cases data were incomplete. In the seventh postoperative day 251 and 231 patients in the fentanyl and remifentanyl group respectively have completed neuropsychological tests. Thirty-one refused to repeat the tests or the data were incomplete. Patients who have refused to perform the tests or whose data were missing were not considered in the analysis. Patients excluded from the evaluation of POCD in the first day because they refused to perform the tests or because data were missing were 9% in the fentanyl group and 10% in the remifentanyl group, while in the seventh day were 14% in the fentanyl group and 16% in the remifentanyl group. This difference was not statistically significant ($P > .05$). A POCD is highlighted in 99 (19.2%) of

513 patients in the first postoperative day and 51 (10.5%) of 482 patients in the seventh postoperative day. In particular, the cognitive impairment was seen in 57 and 28 patients (19.4% and 11.2%) in the group treated with fentanyl in the first and seventh postoperative day and in 42 and 23 patients (15.1% and 10, 2%) in the group treated with remifentanyl in the first and seventh postoperative day (Table 3). The difference in the incidence of POCD is slightly higher in the group treated with fentanyl but did not reach statistical significance in the χ^2 test ($P = .18$ and $P = .6$). Administration of morphine rescue in the recovery room was higher in the remifentanyl group ($P = .05$), while there were no statistically significant differences in the consumption of tramadol administered by PCA device ($P = .06$).

Postoperative pain was well controlled in both groups, as evidenced by the low pain scores, VASr and VASi (Figs. 1 and 2); however, patients who received fentanyl during surgery have lower values of VASr and VASi in the first and second postoperative hour (VASr at first and second postoperative hour: $P = .02$ and $P = .03$; VASi at first and second postoperative hour: $P = .03$ and $P = .04$).

The depth of anesthesia in the two groups was not different and the average BIS during surgery was 48 ± 4 and 47 ± 5 in the remifentanyl and fentanyl group.

Regarding to interleukin records, it was possible to compare only the IL-10 at 1 hour after surgery and IL-6 at 1 hour and 7 days after surgery as the dosages of the other interleukins studied were below the optimum values. Statistical differences between the 2 study groups were found for the levels of IL-6 to the seventh day after surgery; in particular, patients who had received remifentanyl showed significantly lower values compared to those who had received fentanyl (median 10.2 vs 15.3 pg/mL, $P = .04$). POCD was seen in 5 and 0 patients belonging to fentanyl group in the first and seventh postoperative day and in 4 and 0 patients in the remifentanyl group the first and seventh postoperative day. This difference was

Table 1 Demographic data, duration of anesthesia, amount of rescue morphine, postoperative tramadol and level of cytokines in patients belonging to remifentanyl and fentanyl group

	Remifentanyl (Group A) N = 277	Fentanyl (Group B) N = 294	P^a
Age, mean (SD)	68.21 (6.15)	67.81 (5.84)	.5
Men, %	45.4	46.7	.3
BMI kg/m ² , mean (SD)	26 (4.12)	26.5 (4.16)	.24
Education, 0/I/II/III/IV, n	14/85/119/47/12	12/93/124/55/10	.8
Postoperative tramadol mg, mean (SD)	146.87 (75.95)	124.61 (81.3)	.06
Rescue morphine mg, mean (SD)	1.58 (2.61)	0.9 (1.8)	.05*
Duration of surgery minutes, mean (SD)	190 (99)	178 (91.2)	.12
Cytokine levels, pg/mL, median (IQR)			P^b
IL-6 at 1 h	64.3 (13–147)	61.4 (21–180)	.6
IL-6 at 7th day	10.2 (4–16)	15.3 (4–16)	.04*
IL-10 at 1 h	46 (10–50)	50 (10–50)	.5

Data are presented as mean (SD) if normally distributed, absolute values or percentages. Non parametric data are presented as median (IQR).

^a *t* Test or the Mann–Whitney test.

^b Kruskal-Wallis test.

* Statistically significant data.

Table 2 Results of neuropsychological tests before, at 1 day and at 7 days after surgery

	Before surgery		Day 1 after surgery		Day 7 after surgery	
	Fentanyl N = 294	Remifentanyl N = 277	Fentanyl N = 266	Remifentanyl N = 247	Fentanyl N = 251	Remifentanyl N = 231
Memory						
Rey 1–5, no. of words	30.7 (8.45)	30.41 (9.43)	30.08 (8.09)	30.4 (8.85)	33.9 (8.84)	33.24 (10)
Rey 15 min, no. of words	5.50 (2.4)	5.26 (2.58)	5.22 (2.27)	5.25 (2.45)	5.9 (2.56)	5.57 (2.55)
Attention						
Stroop test, part 1, no. of errors	0.003 (0.05)	0.014 (0.18)	0.018 (0.21)	0.027 (0.38)	0.11 (1.34)	0.14 (1.45)
Stroop test, part 1, Time (s)	15.66 (4.98)	15.89 (5.40)	16.43 (4.59)	16.56 (4.94)	16.11 (4.21)	16.87 (4.84)
Stroop test, part 2, no. of errors	0.064 (0.37)	0.057 (0.32)	0.04 (0.23)	0.027 (0.22)	0.04 (0.33)	0.017 (0.15)
Stroop test, part 2, time (s)	16.6 (4.82)	16.9 (5.25)	17.46 (5.87)	17.67 (5.48)	17.20 (5.02)	17.87 (5.07)
Stroop test, part 3, no. of errors	1.7 (2.28)	1.6 (2.3)	1.5 (2.67)	1.5 (2.3)	1.2 (2)	1 (2)
Stroop test, part 3, time (s)	34.2 (12)	33.81 (11)	35.3 (12.6)	34 (9)	34.2 (10)	33.6 (9)

Data are presented as mean (SD).

not statistically significant. Spearman test has not revealed a significant correlation between POCD and levels of IL-6 at 1 hour ($r = 0.08$, $P = .60$) and at the seventh day ($r = -0.25$, $P = 0, 20$), and level of IL -10 at 1 hour ($r = -0.073$, $P = .71$).

4. Discussion

Postoperative cognitive dysfunction (POCD) is a significant social problem occurring in a high percentage of cases in people over 60 years old. The incidence of POCD in our population studied (19.2% and 10.5% in the first and the seventh postoperative day) is lower than that found by other studies present in the literature (30% and 20% of one and 7 days after surgery) [10]. However, to define and diagnose cognitive disorders is still not as simple as shown from the large range of incidence reported in the literature. In fact, the reported incidence varies from 7% to 71% at 7 to 8 postoperative days and 6% to 56% at an interval of 42 to 84 days [12]. The causes of this variability are various. Firstly, there are many risk factors promoting POCD related to patient and to perform a study able to control all variables is very difficult or impossible. Second one, diagnosis of cognitive disorder requires highly sensitive neuropsychological tests that investigate various domains involved in cognitive functions, taking into account that these tests can be difficult to administer in clinical trials in which the sample of the patients studied may be elevated. Moreover, these tests, although correctly performed have many limitations, such as the great variability of the

studied population, the patient’s anxiety present before surgery and the difficulty of administer the tests in the immediate post-operative period, without taking into account of the “effect of learning” when the same test is administered more than once. This difficulty can be overcome by administering the tests in a control group.

Furthermore, one of the main problems of the studies regarding the POCD is the difficulty of using common statistical methods and, consequently, the results cannot be easily compared [11]. In this study we used the same statistical method of the studies ISPOCD 1 and 2, in which the changes in tests of each patient were compared to preoperative baseline values [4,5]. However, unlike the study ISPOCD 1 and 2, we did not use a control group because we were primarily interested in comparing two different analgesic drugs. However, we have calculated the Z score indicative of individual neuro-cognitive changes. In agreement with the study of Hocker and co-workers, our definition of POCD has requested the deterioration of more than 1 SD in 2 or more tests that evaluate the various cognitive domains [13]. The incidence of POCD to seven days was similar to that found by Hocker but lower than that seen in other studies. Among the reasons for the low incidence of POCD in our study, it can be assumed, first of all, the

Table 3 Number of patients with POCD

Day	No. of patients	Remifentanyl patients with POCD (%)	Fentanyl patients with POCD (%)	P^a
Day 1	513	15.1	19.4	.18
Day 7	482	10.2	11.2	.6

^a Pearson χ^2 test.

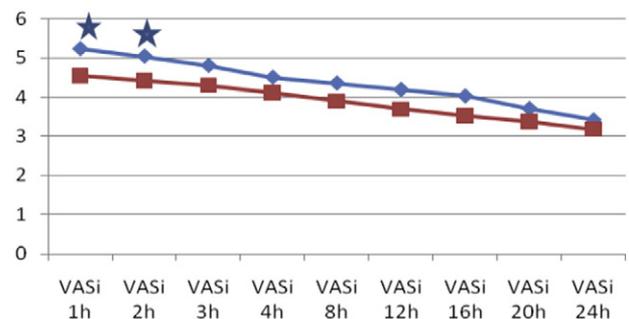


Fig. 1 Values of VASi of patients in group Remifentanyl (A, in blue) and Fentanyl (B, in red). Values are expressed as mean. * $P < .05$.

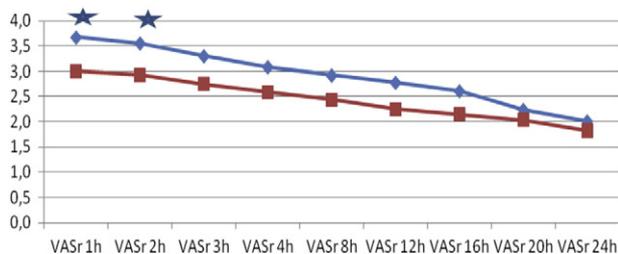


Fig. 2 Values of VASr of Remifentanyl patients in group (A, in blue) and Fentanyl (B, in red). Values are expressed as mean. * $P < .05$.

low sensitivity of neuropsychological tests used and secondly the lack of a control group to overcome the learning effect. Moreover, preoperative tests were carried out the day before surgery, when preoperative stress could already play a fundamental role in modifying the neurocognitive performance.

We did not find a significant difference in the incidence of postoperative cognitive impairment among patients who were treated with intraoperative remifentanyl and fentanyl. However, although not statistically significant the occurrence of POCD is higher in the group treated with fentanyl.

The low incidence of POCD presents in our study makes more difficult the probability to have a statistically significant differences between the 2 study groups. In addition, 58 and 31 patients in the first and the seventh day were deleted from the analysis because they had not completed the tests. Many patients refused to perform or complete neurocognitive tests by stating that they felt tired or could not concentrate. Although, these patients were equally distributed, the lack of these data has probably influenced our results; patients with cognitive disorders may refuse the test, therefore these patients could be considered as affected by POCD. However, in agreement with Rasmussen et al, we have preferred to exclude from the analysis patients with incomplete or missing data by risking to underestimate rather than overestimate the incidence or severity of this disorder in case the lack of data is attributable to deterioration of cognitive domains examined [11]. Regarding to the results, the lowest, although not significant, incidence of POCD in patients treated with remifentanyl might be due to a better control of pain [14]. Fentanyl is administered in boluses, it could cause overexposure or underexposure to the drug and this does not happen with the remifentanyl, which is administered by continuous infusion for its short half-life. This short-acting opioid requires the administration of analgesics at the end of intervention to prevent the onset of severe pain. For this reason, although there were no statistically significant differences in the consumption of tramadol managed by the patient, the administration of morphine rescue doses was higher in the group where the pain was treated with intraoperative remifentanyl despite being given a standard dose morphine towards the end of surgery.

Tramadol is a potent analgesic available to treat moderately-severe pain. Tramadol works by binding to opioid receptors with a mechanism of action similar to morphine and other opioids, but also by inhibiting the uptake of serotonin and

norepinephrine. Recently, Dhaliwal and Hsu in a letter to editor underlined the potential of tramadol patient-controlled analgesia (PCA) infusion contributing to respiratory depression and cardiac arrest in patients who are P450 CYP2D6 ultra rapid-metabolizers. In fact, tramadol is a pro-drug for the active metabolite *O*-desmethyltramadol, which acts by binding mu opioid receptors and inhibiting the reuptake of serotonin and norepinephrine. In patients who are P450 CYP2D6 ultra rapid-metabolizer, the active metabolite *O*-desmethyltramadol increases with important side effects like serotonin syndrome, respiratory depression and cardiac arrest [21]. Moreover, Brouquet et al [22], in their study wherein they investigated the risk factors associated with postoperative delirium in elderly patients, have shown a correlation between tramadol and postoperative delirium [22]. We had no differences regarding the amount of tramadol administered in the postoperative period between the 2 groups.

Despite the postoperative pain was well controlled in both groups, as evidenced by the low pain scores, VASr and VASi, however, patients who received fentanyl have lower values of VASr and VASi in the first and second postoperative hour. This may give the impression that the higher incidence of POCD in patients receiving intraoperative fentanyl cannot be attributed to poor analgesia.

Studies conducted on opioids have shown that these drugs play an important role in the inflammatory response. Immunosuppressive effects of morphine have been well studied and, as reported by various studies, also fentanyl has comparable effects [15]. Moreover, it was demonstrated a strong association between inflammatory cytokines and development of POCD in patients undergoing cardiac surgery with cardio pulmonary bypass [16]. In particular, a relationship was seen among patients who had higher values of IL-6 and IL-8 and postoperative delirium [17]. In this study, differences between the two study groups were found for the levels of IL-6 to 7 days after surgery where patients who had received remifentanyl and that showed a lower incidence of POCD although not significant, showed values of IL-6 significantly lower.

In the subgroup of patients who have been made samples for the determination of serum cytokines, the POCD occurred in 5 and 0 patients at one and seven days after surgery in the fentanyl group and in 4 and 0 patients to one and seven days in the remifentanyl group. Opioids stimulate the cell-mediated immune response through receptors located on various immune cells. Modulation of cytokines through μ receptor agonists has been demonstrated on macrophages, monocytes, natural killer cells and T cells. In both in vivo than in vitro studies, it has been seen that morphine inhibits the proliferation of T cells and significantly reduces the synthesis of IL-2. The exposure to morphine can thus determine the down-regulation of the expression of proinflammatory genes. This is associated with a significant reduction in the expression of mRNA of IL-2 [18]. Moreover, Murphy and colleagues saw that morphine suppresses various components, such as IL-6, CD 11b, of the inflammatory response that is generated during cardiac surgery and cardiopulmonary bypass compared to fentanyl

[19]. Von Dossow and colleagues studied the effect of remifentanyl and fentanyl on the cell-mediated immune response and cytokine release in patients undergoing cardiac surgery and cardiopulmonary bypass. Authors reported that the group treated with remifentanyl presented an attenuated inflammatory response in contrast to the group treated with fentanyl in which there was an increased expression of *SOCS-e* gene and which is rapidly expressed in response to cytokines such as IL-6 and IL-10, and the plasmatic procalcitonin, the second post-operative day, indicating a prolonged activation of the immune system [20]. However, a correlation between IL-6 and POCD has not been demonstrated in our study and we did not find correlation among remifentanyl and a lower postsurgical inflammatory response, with a consequently reduction in POCD incidence. The lack of correlation could be due to the low incidence of POCD highlighted in the group of patients at whom had been executed blood sampling for the detection of serum cytokines. Therefore, future studies that probably use a larger sample for the analysis of cytokines, may definitively answer the question about the effectiveness of the anti-inflammatory and neuroprotective effect of remifentanyl.

The work has been preliminary presented at the SIAARTI Congress in Torino, October 5 to 8, 2011, with the following title "Effects of remifentanyl and fentanyl on Postoperative Cognitive Function in elderly critically ill patients" [23].

References

- [1] Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA, et al. Central nervous system injury associated with cardiac surgery. *Lancet* 2006;368:694-703.
- [2] Tsai TL, Sands LP, Leung JM. An update on postoperative cognitive dysfunction. *Adv Anesth* 2010;28:269-84.
- [3] Krenk L, Rasmussen LS. Postoperative delirium and postoperative cognitive dysfunction in the elderly-what are the differences? *Minerva Anestesiol* 2011;77:742-9.
- [4] Moller J, Cluitmans P, Rasmussen L, Canet J, Rabbitt P, Jolles J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet* 1998;351:857-61.
- [5] Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, Heilman KM, et al. Predictors of cognitive dysfunction after major noncardiac surgery. *Anesthesiology* 2008;108:18-30.
- [6] Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, Korttila K, et al. Postoperative cognitive dysfunction in middle-aged patients. *Anesthesiology* 2002;96:1351-7.
- [7] Abildstrom H, Rasmussen LS, Rentowl P, Hanning CD, Rasmussen H, Kristensen PA, et al. Cognitive dysfunction 1-2 years after non cardiac surgery in the elderly. ISPOCD group. *Acta Anaesthesiol Scand* 2000; 44:1246-51.
- [8] Terrando N, Monaco C, Ma D, Foxwell BM, Feldmann M, Maze M. Tumor necrosis factor- α triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A* 2010;107:20518-22.
- [9] Wu X, Lu Y, Dong Y, Zhang G, Zhang Y, Xu Z, et al. The inhalation anesthetic isoflurane increases levels of proinflammatory TNF- α , IL-6, AND IL-1 β . *Neurobiol Aging* 2012;33:1364-78.
- [10] Bilotta F, Doronzio A, Stazi E, Titi L, Zeppa IO, Cianchi A, et al. Early postoperative cognitive dysfunction and postoperative delirium after anaesthesia with various hypnotics: study protocol for a randomised controlled trial—the PINOCCHIO trial. *Trials* 2011;12:170-6.
- [11] Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, Moller JT, et al. The assessment of postoperative cognitive function. *Acta Anaesthesiol Scand* 2001;45:275-89.
- [12] Ancelin ML, de Roquefeuil G, Ledéser B, Bonnel F, Cheminal JC, Ritchie K. Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry* 2001;178: 360-6.
- [13] Höcker J, Stapelfeldt C, Leindecker J, Meybohm P, Hanss R, Scholz J, et al. Postoperative neurocognitive dysfunction in elderly patients after xenon versus propofol anesthesia for major noncardiac surgery: a double-blinded randomized controlled pilot study. *Anesthesiology* 2009;110:1068-76.
- [14] Kavanagh T, Buggy DJ. Can anaesthetic technique effect postoperative outcome? *Curr Opin Anaesthesiol* 2012;25:185-98.
- [15] Odunayo A, Dodam JR, Kerl ME, DeClue AE. Immunomodulatory effects of opioids. *J Vet Emerg Crit Care (San Antonio)* 2010;20:376-85.
- [16] Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS. Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. *J Anesth* 2011;25:1-9.
- [17] van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *J Am Geriatr Soc* 2008;56:1704-9.
- [18] Eisenstein TK. Opioids and the immune system: what is their mechanism of action? *Br J Pharmacol* 2011;164:1826-8.
- [19] Murphy GS, Szokol JW, Marymont JH, Avram MJ, Vender JS. The effects of morphine and fentanyl on the inflammatory response to cardiopulmonary bypass in patients undergoing elective coronary artery bypass graft surgery. *Anesth Analg* 2007;104:1334-42.
- [20] von Dossow V, Luetz A, Haas A, Sawitzki B, Wernecke KD, Volk HD, et al. Effects of remifentanyl and fentanyl on the cell-mediated immune response in patients undergoing elective coronary artery bypass graft surgery. *J Int Med Res* 2008;36:1235-47.
- [21] Dhaliwal G, Hsu D. Tramadol Ultra Rapid Metabolizers at Risk for Respiratory Depression. *Pain Physician* 2016;19:E361.
- [22] Brouquet A, Cudennec T, Benoist S, Moulia S, Beauchet A, Penna C, et al. Impaired mobility, ASA status and administration of tramadol are risk factors for postoperative delirium in patients aged 75 years or more after major abdominal surgery. *Ann Surg* 2010;251:759-65.
- [23] Congedo E, Sessa F, Fiorini F, Costamagna I, Dottarelli A, De Cosmo G. Effects of remifentanyl and fentanyl on postoperative cognitive function in elderly critically ill patients. *Min Anestesiol* 2011;77 (Suppl 2): P5.