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ORIGINAL ARTICLE

Incidence of postoperative delirium is high even in a population without known risk factors

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Abstract
Purpose Postoperative delirium is a recognized complication in populations at risk. The aim of this study is to assess the prevalence of early postoperative delirium in a population without known risk factors admitted to the ICU for postoperative monitoring after elective major surgery. The secondary outcome investigated is to identify eventual independent risk factors among demographic data and anesthetic drugs used.
Methods An observational, prospective study was conducted on a consecutive cohort of patients admitted to our ICU within and for at least 24 h after major surgical procedures. Exclusion criteria were any preexisting predisposing factor for delirium or other potentially confounding neurological dysfunctions. Patients were assessed daily using the confusion assessment method for the ICU scale for 3 days after the surgical procedure. Early postoperative delirium incidence risk factors were then assessed through three different multiple regression models.
Results According to the confusion assessment method for the ICU scale, 28 % of patients were diagnosed with early postoperative delirium. The use of thiopentone was significantly associated with an eight-fold-higher risk for delirium compared to propofol (57.1 % vs. 7.1 %, RR = 8.0, $\chi^2 = 4.256$; $df = 1$; $0.05 < p < 0.02$).
Conclusion In this study early postoperative delirium was found to be a very common complication after major surgery, even in a population without known risk factors. Thiopentone was independently associated with an increase in its relative risk.

Keywords General anesthesia · Complications · Pharmacology

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Introduction

Delirium is defined as a disturbance of consciousness, accompanied by a change in cognition or the development of perceptual disturbances, with an acute onset and a fluctuating nature, not attributable to preexisting psychiatric disorders or substance-induced states [1]. These symptoms are usually manifested as disorientation, memory impairment, and alteration of mental processes, which can present either as a hyperactive form, a hypoactive form, or a combination of the two [2].

Although often undiagnosed [3], delirium is a recent complication in the intensive care unit (ICU), with a prevalence of 20–80 %, depending on the characteristics of the subpopulation studied [4–7]. Delirium is associated with an increase in the hospital length of stay [8], complication rate, and functional decline [9].

Different studies have investigated risk factors for delirium in ICU patients. Numerous predisposing factors have been identified in the general patient population, including age, baseline comorbidities, and baseline cognitive impairment (host factors), sepsis, hypoxemia, severity of illness, metabolic disturbances (acute factors), anticholinergic medications, and sedative and analgesic medications (iatrogenic factors) [10, 11]. Noxious insults or hospitalization-related factors act as precipitating factors [12], and surgery itself may play a role. Previous studies

have shown that the presence of three or more risk factors increases the likelihood of the development of delirium to approximately 60 % [13], and ICU patients are particularly at risk, usually presenting with more than ten risk factors [14].

Surgery alone has been rarely investigated as an independent risk factor in ICU patients, especially in the population under 65 years of age. Postoperative cardiac surgery patients have been investigated, and the term postcardiotomy delirium (PCD) has been used for the condition occurring after cardiotomy and coronary artery surgery [15]. In this population the reported incidence of PCD varies from 3 % [16] to 72 % [17, 18], depending on the type of procedure. Patients undergoing valve replacement seem to have a higher risk compared to patients undergoing isolated bypass surgery [19]. These studies, however, investigated PCD in a very heterogeneous population, without differentiation according to age, which is a major risk factor. A lower incidence of PCD over the years [20] has been attributed to improved surgical, cardiopulmonary bypass, and anesthesia techniques [21], which suggests that these also represent independent risk factors.

The overall prevalence of delirium has been reported to be about 11 % in patients undergoing major elective surgery [22], whereas orthopedic surgery was associated with a higher prevalence, estimated between 28 % and 52.6 % [23], perhaps related to fat embolism.

The aim of this study is to assess the prevalence of early postoperative delirium in a population of ASA 1 patients admitted to an ICU for postoperative monitoring after elective major surgery, without any known risk factor for this condition. The secondary outcome is to identify independent risk factors among demographic and anesthetic drug variables.

Materials and methods

The study was conducted in a 28-bed intensive care unit of a tertiary care university teaching hospital and major trauma center (Liverpool Hospital, Sydney, NSW, Australia).

Following local ethics committee approval, an observational, prospective study was conducted on a consecutive cohort of patients admitted to our ICU within and for at least 24 h after elective major surgical procedures, defined as laparotomic and thoracotomic procedures lasting more than 1 h (namely, laparotomic hemicolectomies, gastrectomies and intestinal resections, thoracotomic lung resection, and lobectomies). All patients received combined anesthesia induced with either propofol or thiopentone plus fentanil and maintained with either sevoflurane or isoflurane.

Exclusion criteria were any known preexisting predisposing factor for delirium or other potentially confounding neurological dysfunctions, including cardiac surgery, orthopedic surgery, pelvic or long bone fractures, neurosurgery, head traumas, cerebral hemorrhages, history of cerebrovascular diseases, organic or metabolic neuropathies, cerebral tumours, Parkinson disease, diagnosed major depression, dementia, severe sensory deficits, regular use of psychotropic drugs, alcoholism, prolonged hypotension during surgery, massive transfusion during surgery (more than 2 l), documented preoperative anemia, sepsis, renal or hepatic failure, hyperventilation during anaesthesia (documented $PaCO_2 < 30$ mmHg), severe electrolytic alterations, diabetic ketoacidosis, hyper-/hypothyroidism, or regular use of ranitidine, steroids, metoclopramide, and/or anticholinergic drugs. These exclusion criteria have been selected to exclude any known risk factor for delirium to investigate the incidence of this cognitive dysfunction in a population without preexisting risk factors for this condition [8–13].

A power calculation was performed to identify adequate numerosity. Given the wide range of incidences shown by different studies, we assumed an 11 % incidence of delirium after surgery in a general population, as in the study by Litaker et al. [22], as a reference and considered a 5 % reduction in a population without any risk factors as significant, obtaining a numerosity of 73 as adequate (95 % confidence interval). Taking into account compensation for eventual losses at follow-up or exclusion, we however included 100 patients in the follow-up.

Patients were assessed daily using the confusion assessment method for the ICU scale (CAM-ICU) for 3 days after the surgical procedure or until discharge or death. They were evaluated during sedation-free intervals (patients were considered free from sedation if not treated with propofol in the last hour or with midazolam, lorazepam, or diazepam in the past 12 h). Data for each subject including the surgical procedure and the anesthetic drugs used with their relative doses were recorded in an electronic database.

Variability of delirium incidence was than analyzed via a multiple regression model, taking into account demographic data, kind of surgery, and anesthetic drugs used as dependent variables. The following equation describes the model applied: $EPOD = \beta_0 + \beta_1\ age + \beta_2\ Gen + \gamma_i\ Surg + \beta_4\ Ane + \beta_5\ Dos + \varepsilon$, with $SC > 0$. The model includes patient's age (Age), gender (Gen), surgical procedure (Surg), anesthetic drugs (Ane), and anesthetic drug dose (Dos) (where EPOD = early postoperative delirium relative risk).

Data are given as mean ± standard deviation, incidence, risk, and relative risk (RR). Comparison between groups of values was performed by unpaired Student's *t* test for

numeric variables and by χ^2 test for univariate variables. A p value < 0.05 (95 % confidence interval) was considered statistically significant.

Results

During the study period, 346 patients were admitted in the ICU for postoperative monitoring: of these, 100 patients matched the inclusion criteria and were thus included in the study (ASA 1; mean age, 64.5 ± 11.4 years). There were no successive exclusions or losses at follow-up. Population characteristics are summarized in Table 1. The incidence of postoperative delirium in the first 3 days after surgery was 28 %; 86 % of cases occurred on the first day, 14 % on the second day, and no case occurred on the third day of the postoperative period. The most frequent form of delirium was the hypodynamic type (87 %). The risk for developing delirium in patients 65 years old or older was not significantly different from younger subjects (RR = 1.273, $\chi^2 = 0.284$, $df = 1$, $p > 0.5$); gender also did not seem to be a risk factor (RR = 1.406, $\chi^2 = 0.466$, $df = 1$, $0.5 < p < 0.10$). Concerning the induction agent administered, thiopentone was significantly associated with an eightfold-higher risk for delirium compared to propofol (57.1 % vs. 7.1 %, RR = 8.0, $\chi^2 = 4.256$; $df = 1$; $0.05 < p < 0.02$); this increase was not dose related (mean dose in delirium group, 131 ± 108 mg vs. mean dose in control group, 108 ± 48.1 mg, $p = 0.463$, $df = 22$). The use of or type of muscle relaxant eventually used (pancuronium vs. rocuronium) seems to be associated with a risk difference ($\chi^2 = 2.33$, $df = 2$, $0.5 < p < 0.10$). The use of midazolam and fentanyl administered during general anesthesia was not significantly associated with a difference in risk ($p = 0.467$, $df = 38$; $p = 0.484$, $df = 40$). Halogenated anesthetic gases used for maintenance (isoflurane vs. sevoflurane) were compared with no evidence of any difference in risk of developing neurocognitive alterations in the postoperative period ($\chi^2 = 3.201$, $df = 1$, $0.10 < p < 0.05$).

Results, with risks and relative risk values, are shown in Table 2.

Table 1 Patients characteristics

Age (years, mean ± SD)	64 ± 11.4
Gender (M:F)	54:46
ASA status	1
Operation time (min, mean ± SD)	125 ± 65
Anesthesia time (min, mean ± SD)	145 ± 70

Discussion

Postoperative delirium is a common complication in the postoperative period after major surgery, occurring in more than one patient in four, even in patients with any known predisposing factors for this neurocognitive dysfunction. The incidence peak is in the first 24 h after the surgical procedure and the most common delirium observed is the hypoactive form. The age and sex of the subject do not seem to play a role in the development of early postoperative delirium. There was a strong increase in the relative risk for developing postoperative delirium if thiopentone were used as an induction agent, regardless of the dose administered. This correlation persisted even when results were corrected according to the type of surgery performed and demographic variables.

Other studies have investigated the incidence of postoperative delirium in surgical populations, but these often included very heterogeneous populations with known risk factors. To our knowledge, this is the first study to assess early postoperative delirium incidence in a population without any known risk factor and to perform a multiple regression analysis to define in the population an increase in relative risk related to the induction agent administered.

At this stage the formulation of specific contraindications to the use of thiopentone with regard to the development of postoperative delirium is of course still premature. A case–control randomized double-blind clinical trial is in fact advisable to eventually confirm the

Table 2 Results compared: patients with (cases) and without (controls) postoperative delirium

Risk factor	R cases ($N = 28$)	R controls ($N = 72$)	RR	p
Age >65/<65 years	32.8	25.0	1.27	>0.5
Male/female gender	32.2	22.2	1.41	>0.5
Thiopentone/propofol	57.14	7.14	8.0	$0.05 < p < 0.02$
Sevoflurane/isoflurane	50.0	48.6	1.03	$0.5 < p < 0.10$
Pancuronium/rocuronium	53.6	51.4	1.04	$0.5 < p < 0.10$

R cases risk among patients presenting with a given risk factor, *R controls* risk among patients without a given risk factor, *N* total number of patients with and without delirium, *RR* relative risk

preliminary results of this observational study. However, the authors recommend reconsidering the routine use of thiopentone, at least for subjects with known risk factors for this cognitive dysfunction, because the use of this induction agent was shown to be associated with an increased relative risk for developing this condition even in a population without known risk factors.

It is not clear if our results could be related to an intrinsic effect of barbiturates or if it should rather be related to a protective effect of propofol as an induction agent. Propofol postconditioning in fact has been recently attributed to a long-term neuroprotective effect linked to the early-stage formation of PI3K-AMPAR GluR2 subunit complex [24]. These results, if confirmed in humans, could eventually contribute to explain the diminished incidence of neurocognitive dysfunctions observed when propofol was used as the induction agent.

In conclusion, early postoperative delirium seems a frequent complication of major surgery, even in patients without specific known risk factors. Furthermore, in this study thiopentone was associated with an increase in its relative risk.

Conflict of interest None.

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