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Journal of International Medical Research 2010 38: 1225
DOI: 10.1177/147323001003800403

The Journal of International Medical Research
2010; 1225 – 1232 [first published online as 38(4) 10]

Remifentanil Reduces the Incidence of Post-operative Delirium

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A secondary exploratory analysis of data from an observational study was used to study the influence of the opioid used for intraoperative anaesthesia on the incidence of post-operative delirium. Patients who had been admitted to the recovery room following elective general anaesthesia were divided into those who had received fentanyl or remifentanil. For unbiased patient analysis, matched pairs were built with respect to gender, age, physical status, anaesthetic type and surgery duration. In 752 patients, the overall incidence of delirium was 9.9% in the recovery room and 3.8% on the first post-operative day. Compared with the remifentanil group, the fentanyl group had a significantly higher incidence of delirium in the recovery room (12.2% versus 7.7%) and on the first post-operative day (5.8% versus 1.9%). Delirium in the recovery room and on the first post-operative day were both associated with a significantly prolonged post-operative hospital stay. The choice of intraoperative opioid influences the incidence of post-operative delirium. Remifentanil was associated with a lower incidence of post-operative delirium in the early post-operative period.

KEY WORDS: Remifentanil; Fentanyl; Opioids; Analgesia; Delirium; Intraoperative; Outcome

Introduction

Post-operative delirium is a frequent complication observed both in the recovery room and on the ward. The reported incidence of delirium in non-intubated patients after surgery varies between 5% and 52%.[1] Post-operative delirium is considered to be an independent predictor for poor post-operative outcome,[2,3] is associated with a deterioration of cognitive outcome and is considered a risk factor for dementia.[4] In patients with post-operative delirium, mortality may be increased,[5,6] as well as length of post-operative hospital stay and associated healthcare costs.[7]

According to Inouye's multifactorial model,[8] the development of delirium can be regarded as a complex inter-relationship between predisposing factors (such as patient vulnerability) and precipitating factors (hospitalization-related factors or noxious insults, for example). Opioids have already been described as possible influencing factors.[9,10] A previous analysis found that intraoperative opioid use

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influenced delirium on the first post-operative day and showed a tendency for delirium in the recovery room.[11] To clarify the effects of choice of intraoperative opioid on post-operative delirium that were noted in the original observational study, this secondary analysis was carried out to exclude possible bias of confounding factors. Thus, the aim of the present study was to use a matched-pairs technique to investigate the influence of the chosen intraoperative opioid on the incidence of post-operative delirium.

Patients and methods

PATIENTS

This was a secondary analysis from a previously reported observational study that included patients who had been admitted to the recovery room following elective general anaesthesia at the Department of Anaesthesia and Intensive Care, Charité – Universitaetsmedizin Berlin, between November 2006 and April 2007.[11] To account for possible bias, a secondary analysis with a matched-pairs technique was performed; data sets underwent matched-pairs analyses with respect to gender, age (18 – 49 years; > 49 years), American Society of Anesthesiologists (ASA) physical status (PS) classification (I and II; III and IV),[12] duration of surgery (≤ 60 min; > 60 min) and anaesthetic type (inhalational or propofol).

This observational study was approved by the Ethics Committee of the Charité – Universitaetsmedizin Berlin. The requirement for written or verbal consent was waived as this was a retrospective observational study in which no additional data were assembled, including delirium screening, beyond that in routine clinical practice at the Charité – Universitaetsmedizin Berlin.

DIAGNOSIS OF DELIRIUM

All patients were screened by trained research assistants in the recovery room at the time when each patient was formally declared as ready for discharge to the regular ward by the physician in charge of the recovery room. Patients were also screened by trained research assistants on the first post-operative day. Delirium was diagnosed using the Nursing Delirium Screening Scale (Nu-DESC).[13] The Nu-DESC assesses five clinical dimensions (symptoms) in the patient: orientation, behaviour, communication, illusions and psychomotor retardation. Each symptom is rated on 0 – 2 scale of: 0, not present; 1, mild; and 2, severe. A total score ≥ 2 signifies delirium. The symptoms and descriptions of the Nu-DESC are shown in Table 1.

OTHER BASELINE MEASUREMENTS

The following items were recorded: age, body mass index, duration of surgery, gender, physical status (ASA PS 1, healthy patient; ASA PS 2, patient with mild systemic disease; ASA PS 3 and 4, patients with severe systemic disease), pre-existing illnesses, intraoperative heart rate, duration of pre-operative fasting (fluids), choice of intraoperative opioid (fentanyl or remifentanil), length of stay in the recovery room and overall length of post-operative hospital stay. Anaesthesia was provided according to published standard operating protocols.[14]

STATISTICAL ANALYSIS

All statistical calculations were performed using the SPSS® statistical package, version 17.0 (SPSS Inc., Chicago, IL, USA) and StatXact 6® (Cytel Software Corp., Cambridge, MA, USA) for Windows®. Descriptive data analyses were performed for all study variables. Discrete variables were expressed as numbers (percentage) and continuous variables were expressed as means (with 95% confidence intervals [CI]) if

TABLE 1:
Symptoms and descriptions of the Nursing Delirium Screening Scale[13]

Symptom	Description
I. Disorientation	A verbal or behavioural manifestation of not being oriented to time or place, or misperceiving persons in the environment
II. Inappropriate behaviour	Behaviour inappropriate to the place and/or for the person, e.g.: pulling at tubes or dressings; attempting to get out of bed when this is contraindicated
III. Inappropriate communication	Communication inappropriate to the place and/or for the person, e.g.: incoherence; non-communicativeness; non-sensical or unintelligible speech
IV. Illusions/hallucinations	Seeing or hearing things that are not there; distortions of visual objects
V. Psychomotor retardation	Delayed responsiveness, few or no spontaneous actions/words, e.g.: when the patient is prodded, reaction is deferred and or the patient is unarousable

Each symptom is rated on 0 – 2 scale: 0, not present; 1, mild; 2, severe. A total score ≥ 2 signifies delirium.

normally distributed or as medians (with 25 and 75 percentiles) if not normally distributed. Group comparisons in terms of frequencies were tested with the Kruskal–Wallis test. After assessing for normal distribution for continuous variables, the *t*-test was performed for normally distributed continuous variables and the Mann–Whitney *U*-test was performed for non-normally distributed continuous variables. A *P*-value < 0.05 was considered to be statistically significant.

Results

This secondary analysis included 862 patients from a previously reported study who had been admitted to a recovery room following elective general anaesthesia.[11] To account for possible bias, the 862 data sets underwent matched-pairs analysis, resulting in 752 data sets (376 pairs) being generated for further analysis. Baseline characteristics of patients included in the matched-pairs analysis are listed in Table 2.

The overall incidence of delirium in the recovery room was 10.0% (95% CI 8.0 – 12.3) (75 out of 752 patients) and on the first post-operative day it was 3.9% [95% CI, 2.7 – 5.5] (29 out of 752 patients). Significant differences existed between the fentanyl and remifentanil groups for delirium in the recovery room ($P = 0.039$; Fig. 1) and on the first post-operative day ($P = 0.005$; Fig. 2).

Patients who developed delirium in the recovery room or on the first post-operative day showed increased length of post-operative hospital stay. In particular, delirium on the first post-operative day was associated with prolonged post-operative stay (mean ± SD 6.6 ± 8.7 days for patients with no delirium versus 16.2 ± 14.2 days for those with delirium on the first post-operative day; $P < 0.001$). Delirium had no significant influence on the length of stay in the recovery room.

Discussion

The present study used a matched-pairs technique to investigate the influence of the opioid used for intraoperative anaesthesia

TABLE 2:
Baseline characteristics following elective surgery amongst patients who were given intraoperative opioid anaesthesia with either remifentanil or fentanyl and were included in a secondary matched-pairs analysis of delirium episodes

Characteristic	Remifentanil (n = 376)[a]	Fentanyl (n = 376)[a]	Statistical significance[a]
Age (years)	50.7 ± 17.8	50.6 ± 15.9	NS
Body mass index (kg/m²)	25.8 ± 4.8	26.0 ± 4.5	NS
Duration of surgery (min)	74.4 ± 59.4	76.5 ± 56.8	NS
Female gender	173 (46.0)	173 (46.0)	NS
ASA PS			
I and II	281 (74.7)	281 (74.7)	NS
III and IV	95 (25.3)	95 (25.3)	NS
Pre-existing conditions			
Allergies	186 (49.5)	166 (44.1)	NS
Hypertension	61 (16.2)	54 (14.4)	NS
Heart failure	3 (0.8)	4 (1.1)	NS
Coronary artery disease	9 (2.4)	5 (1.3)	NS
COPD	15 (4.0)	9 (2.4)	NS
Renal failure	4 (1.1)	4 (1.1)	NS
Maximum intraoperative heart rate (beats/min)	73.1 ± 13.9	77.9 ± 13.7	$P < 0.001$
Pre-operative fluid fasting (h)	10.21 ± 5.37	10.23 ± 4.99	NS

Data are shown as mean ± SD or as n (%) patients.
[a]P-values calculated using Kruskal–Wallis or Mann–Whitney U-tests as appropriate.
ASA PS, American Society of Anesthesiologists physical status; COPD, chronic obstructive pulmonary disease; NS, not statistically significant ($P > 0.05$).

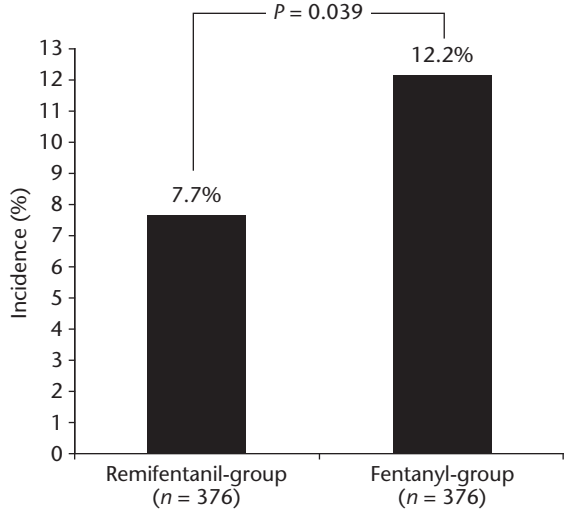

FIGURE 1: Incidence of delirium episodes in the recovery room in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery

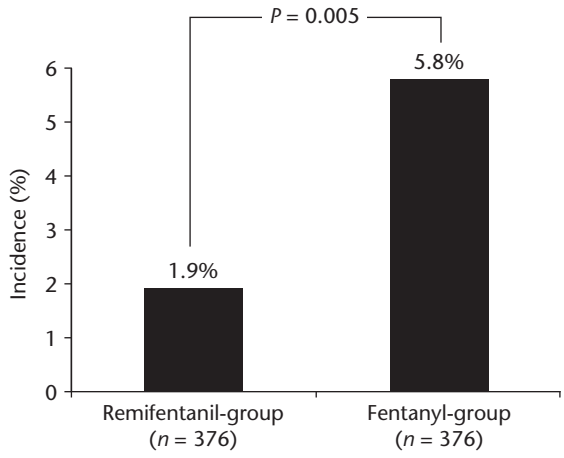

FIGURE 2: Incidence of delirium episodes on the first post-operative day in patients who received either remifentanil or fentanyl intraoperative opioid anaesthesia during elective surgery

on the incidence of post-operative delirium. The most important finding was that the incidence of post-operative delirium in the recovery room and on the first post-operative day differed significantly between patients who had received fentanyl intraoperatively compared with patients who had received remifentanil.

The overall incidence of delirium in the recovery room was 10.0%. A systematic review by Dasgupta and Dumbrell[1] reported a risk of 5 – 52% for post-operative delirium in non-ventilated patients. High-risk groups, such as elderly patients with multiple comorbidities or patients undergoing orthopaedic surgery, showed higher incidences of delirium.[1,5,15] The relatively low incidence of delirium observed in the present study may be explained by the low mean age and low comorbidity rates (as defined by the ASA PS), together with the wide variation in types of surgical procedures mainly covering not only orthopaedic surgical procedures but also general surgical procedures, as well as oral and maxillofacial surgery, ophthalmology, ear, nose and throat surgery, and gynaecological and urological procedures.

Several studies have determined predictors for post-operative delirium,[1,6,16] or have reported an association between opioids and delirium.[10,17 – 19] A systematic review of the role of post-operative analgesia on delirium[20] described the influence of opioids (i.e. meperidine) on cognitive dysfunction. Opioids may be regarded as both predisposing and precipitating factors for post-operative delirium.

In the present study, the choice of intraoperative opioid proved to be relevant for the incidence of delirium. Matched-pairs analysis showed that the intraoperative administration of fentanyl compared with remifentanil led to a significantly higher incidence of delirium, both in the recovery room and on the first post-operative day. This expands on the results of a previous study, which showed a significant influence of opioid choice only on the post-operative ward.[11] The more rigorous matched-pairs analysis undertaken in the present study, which focused on the influence of

intraoperative opioids, also indicated their influence on post-operative delirium in the recovery room and reinforced their influence on delirium on the first post-operative day by eliminating other confounding factors.

The main difference between fentanyl and remifentanil is the metabolism of remifentanil by non-specific esterases and its extremely short, context-sensitive, half-life (3.2 min compared with 47.3 min for fentanyl)[21] Remifentanil may be administered at higher doses than those normally used for fentanyl in order to maintain adequate analgesia until the end of a procedure without the risk of opioid over-dosage.[22] In the present study, the maximum intraoperative heart rate was significantly lower in the remifentanil group, which may indicate greater stress reduction in the remifentanil group. Continuous analgesia with remifentanil compared with intermittent fentanyl administration possibly leads to a superior attenuation of endocrine stress response.[23,24] Decreased stress response is known to be associated with a decreased delirium rate[25] and an improved outcome.[26]

Another important result of the present study was that patients with post-operative delirium had a significantly prolonged length of hospital stay compared with those patients without delirium, which confirms the findings of other studies.[5,6,27]

Delirium had no significant effect on length of stay in the recovery room, possibly because the most common hypoactive form of delirium often remains undetected in routine clinical situations.[28,29] The Nu-DESC was used in the present study and is a sensitive method for detecting delirium[30] that may help to identify patients who are positive for delirium, who would not be diagnosed by the discharging physician, or whom the physician did not consider as having delirium severe enough to be a contraindication for transfer to the ward.

A strength of the present study is that a large number of patients undergoing a wide range of different procedures were included. Secondly, with matched-pairs analysis, other predisposing or precipitating factors for post-operative delirium apart from the type of intraoperative opioids could be largely excluded. One limitation of this study was that it was not a randomized controlled trial; the decision for the type of intraoperative opioid was made by the attending anaesthesiologist, which may have led to selection bias. In addition, as longer-term follow-up of patients was not performed, episodes of delirium after the first post-operative day may have been possible.[31,32]

In conclusion, in this secondary exploratory analysis, the intraoperative choice of opioid anaesthesia had a significant influence on post-operative outcome. Intraoperative remifentanil use may, therefore, be especially recommended for patients at high risk of post-operative delirium.

Acknowledgement

This study was supported by grants from the Charité – Universitaetsmedizin Berlin, Germany.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this manuscript.

• Received for publication 22 January 2010 • Accepted subject to revision 25 January 2010
• Revised accepted 10 May 2010

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