

Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium

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Background and objective Most therapeutic options for postoperative delirium are only symptom oriented; therefore, the best approach remains prevention. The aim of this study was to identify predisposing and precipitating factors for early postoperative delirium.

Methods A total of 1002 patients were screened for delirium in an observational, cohort study. Nine hundred and ten patients were observed in the recovery room and 862 patients on the first postoperative day in the ward at the Charité – Universitätsmedizin, Berlin. Delirium was measured with the nursing delirium screening scale. Risk factors were analysed in a multivariate analysis.

Results Delirium was seen in 11.0% of the patients in the recovery room and in 4.2% of the patients on the ward. Delirium in the recovery room was associated with delirium on the ward (McNemar's test $P = <0.001$). Apart from age and site of

surgery, we found the duration of preoperative fluid fasting to be a modifiable precipitating factor for delirium in the recovery room (odds ratio 2.69, 95% confidence interval 1.4–5.2) and on the ward (odds ratio 10.57, 95% confidence interval 1.4–78.6) and the choice of intraoperative opioid for delirium on the ward (odds ratio 2.27, 95% confidence interval 1.0–5.1).

Conclusion Duration of preoperative fluid fasting and the choice of intraoperative analgesic are risk factors for postoperative delirium, and their modification provides a promising approach to reduce the incidence of postoperative delirium.

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Introduction

Delirium is an acute change in attention and cognition. Transitory confusional states often follow operations under general anaesthesia. Delirium in the early postoperative phase can be a predictor of postoperative delirium on the ward.¹ It is associated with increased morbidity and mortality² and might lead to postoperative cognitive dysfunction.³ Delirium is unpleasant for patients, relatives and staff and is often the first sign of underlying somatic disturbance.⁴ Despite its relevance for patients, as well as healthcare costs, it often goes unrecognized by physicians.² Although the pathophysiology of delirium is not well understood,⁵ the concept of predisposing and precipitating factors introduced by Inouye and Charpentier⁶ is now widely accepted. The aim of our study was to identify modifiable risk factors for delirium in the early postoperative period.

Methods

Study population

We performed this observational, cohort study at the Charité – Universitätsmedizin Berlin, Department of

Anaesthesiology and Intensive Care Medicine, Berlin, Germany. The study was approved by the hospital's Ethics Committee (ref.: EA1/143/07), and the requirement for patient consent was waived. Local data privacy regulations were followed. This study was an exploratory trial to check for influencing factors for delirium and enrolled consecutive patients. Between 13 November 2006 and 6 April 2007, we screened 1002 patients who were admitted to an interdisciplinary recovery room following elective general anaesthesia during regular working hours (9 a.m.–5 p.m.). Because a verbal response was needed for all tests, patients who did not speak the local language were excluded. Further exclusion criteria were age below 18 years ($n=42$), a past medical history of psychiatric or neurological illness or stroke ($n=17$) and a history of drug, alcohol or opioid abuse ($n=14$), as documented by the anaesthetist performing the preanaesthetic evaluation.

A total of 910 adult patients were included in the analysis. Eight hundred and sixty-two patients were available to be seen on the first postoperative day (Fig. 1).

Diagnosis of delirium

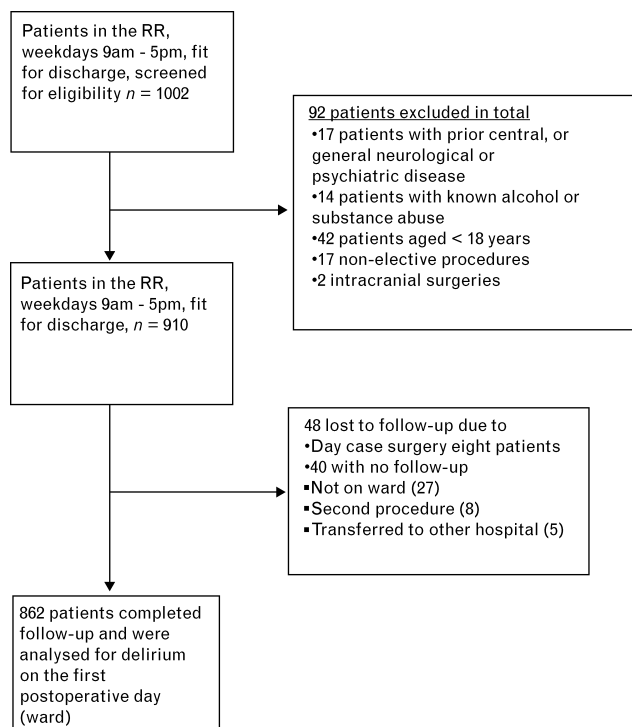
For delirium screening, the nursing delirium screening scale (Nu-DESC,⁷ which assesses five dimensions: orientation, behaviour, communication, illusions and psychomotor retardation; the symptoms are rated on a three-point scale, and a score of 2 or more cumulative points specifies delirium, see Table 1) was chosen because of its high specificity and excellent sensitivity when compared with the gold standard, the Diagnostic and Statistical

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Fig. 1



Flow diagram. RR, recovery room.

Manual of Mental Disorders IV (DSM4) criteria.⁸ In direct comparison to the confusion assessment method (CAM), it displayed the highest sensitivity for detection of early postoperative delirium.⁸

As suggested by Gaudreau *et al.*⁷ (and reaffirmed in our own study⁸), patients with a Nu-DESC score of 2 or more points are considered delirious.

The research team performing the delirium scoring consisted of physicians, medical students and study nurses and were trained and supervised by a psychiatric expert. The programme for staff member training consisted of four steps. First, information about delirium and the

Table 1 The nursing delirium screening scale items, features and descriptions [Symptoms rating (0–2)]

Disorientation	Verbal or behavioural manifestation of not being oriented to time or place or misperceiving persons in the environment
Inappropriate behaviour	Behaviour inappropriate to place and/or for the person, e.g. pulling at tubes or dressings, attempting to get out of bed when that is contraindicated and so on
Inappropriate communication	Communication inappropriate to place and/or for the person, e.g. incoherence, noncommunicativeness, nonsensical or unintelligible speech
Illusions/hallucinations	Seeing or hearing things that are not there; distortions of visual objects
Psychomotor retardation	Delayed responsiveness, few or no spontaneous action/words, e.g. when the patient is prodded, reaction is deferred and/or the patient is unarousable

Nu-DESC was provided (lectures, handouts, literature and video). Second, one-to-one instruction at the patients' bedsides was given. Third, after a pilot phase, each trained staff member had to re-evaluate five patients who were pretested by the delirium expert. Different results in delirium assessment between the trained staff members and the delirium expert were discussed until agreement was reached.

Patients were tested for delirium by the research team at the time they were formally declared to be 'ready for discharge' to the regular ward by the physician in charge of the recovery room. The research team performing the delirium scoring did not intervene in the patients' care or interfere with the usual recovery room protocol. The recovery room physicians and nurses were blinded to the results of the study. The presence of delirium was not diagnosed in any patient by the regular recovery room staff. In addition, the patients were seen on the morning of the first postoperative day.

Other baseline measurements

The following potentially confounding variables were recorded: age, sex, physical status according to the American Society of Anaesthesiologists (ASA PS), duration of preoperative fasting (for clear fluids and for solids in hours), type of anaesthetic agent (inhalational anaesthetics or intravenous anaesthetics), choice of intraoperative opioid (fentanyl or remifentanyl), site of surgery and duration of surgery in minutes (Table 2).

According to our standard operating procedures (SOPs),⁹ general anaesthesia was induced with thiopental, propofol, etomidate or midazolam in combination with fentanyl or remifentanyl, followed by neuromuscular block to facilitate endotracheal intubation. Anaesthesia was maintained by total intravenous anaesthesia (TIVA), using propofol, or inhalation anaesthetics, using one of desflurane, isoflurane or sevoflurane. Patients received nitrous oxide at the discretion of the individual anaesthetist in charge. The anaesthetist was free to use opioid analgesics and muscle relaxants as needed. Typically, for general anaesthesia without regional anaesthesia, intraoperative nonopioid (paracetamol 1 g 100 ml⁻¹ and/or metamizole 1–2 g 100 ml⁻¹) was routinely given 30 min before the end of surgery for postoperative pain management. For major operations such as gastrectomy, partial hepatectomy and thoracotomy and so on, opioid (piritramid or morphine, 0.05–0.1 mg kg⁻¹) was given in combination with nonopioid 30 min before emergence.⁹ In the recovery room, opioid and nonopioid pain medication was administered by nursing staff if the numeric rating scale (NRS) score was above 4; if the NRS score was 3 or 4, pain medication was optional and given if requested by the patient.⁹

Statistical analysis

Results were expressed as arithmetic mean \pm SD or frequencies with percentages. After proof of the distribution

Table 2 Patient characteristics

Characteristic	Recovery room (n = 910)			Ward (n = 862)		
	Delirium (n = 100)	No delirium (n = 810)	P	Delirium (n = 38)	No delirium (n = 824)	P
Age (years)	55.8 ± 16.2	50.1 ± 17.0	0.003	56.4 ± 15.2	50.5 ± 16.9	0.003
Sex						
Female	45 (45.0%)	380 (46.9%)	0.751	15 (39.5%)	388 (47.1%)	0.408
ASA PS			0.019			0.019
1 and 2	66 (66.0%)	623 (76.9%)		22 (57.9%)	625 (75.8%)	
3 and 4	34 (34.0%)	187 (23.1%)		16 (42.1%)	199 (24.2%)	
Preoperative fasting (fluids) (h)			<0.001			<0.001
2–6	11 (11.0%)	209 (25.8%)		1 (2.6%)	201 (24.4%)	
>6	89 (89.0%)	601 (74.2%)		37 (97.4%)	623 (75.6%)	
Preoperative fasting (solids) (h)			0.426			0.210
6–12	36 (10.0%)	325 (90.0%)		11 (3.3%)	322 (96.7%)	
>12	64 (11.7%)	485 (88.3%)		27 (5.1%)	502 (94.6%)	
Anaesthetic			0.525			0.134
Inhalative	56 (56.0%)	423 (52.2%)		25 (65.8%)	433 (52.5%)	
Intravenous	44 (44.0%)	387 (47.8%)		13 (34.2%)	391 (47.5%)	
Opioid			0.011			0.004
Fentanyl	65 (65.0%)	413 (51.0%)		29 (76.3%)	426 (51.7%)	
Remifentanyl	35 (35.0%)	397 (49.0%)		9 (23.7%)	398 (48.3%)	
Fentanyl dosage ($\mu\text{g kg}^{-1} \text{h}^{-1}$)	4.0 ± 3.0	3.9 ± 2.8	0.90	3.5 ± 1.7	4.0 ± 2.9	0.24
Duration of surgery (min)	93.2 ± 63.0	77.5 ± 57.8	0.004	98.0 ± 67.6	78.1 ± 58.5	0.024
Site			<0.001			<0.001
Intraabdominal and intrathoracic	28 (19.2%)	118 (80.8%)		13 (9.6%)	122 (90.4%)	
Other	72 (9.4%)	692 (90.6%)		25 (3.4%)	702 (96.6%)	

Data were expressed as mean ± SD, except for categorical data as number and percentage; *P* values are with respect to χ^2 test or Mann–Whitney *U* test. ASA PS, American Society of Anaesthesiologists physical status.

for normality, differences between the regarded groups in terms of clinical parameters were tested by using the nonparametric Mann–Whitney *U* test. Frequencies were tested by the χ^2 test, McNemar's test or Fisher's test in contingency tables. In case of small samples, greater differences in sample sizes, large but unbalanced groups, datasets containing ties or sparse data, tests were carried out in an exact version. We also performed power analyses to verify the reproducibility of the results obtained. After proof of univariate differences between interesting groups of patients, multiple logistic regression with delirium as the response was conducted in order to confirm the results multivariately and to investigate the impact of further influencing factors. Multiple linear regression analyses were carried out with different outcome variables as the response and the same influencing factors including delirium. Odds ratios (ORs) and regression coefficients with 95% confidence intervals (CIs) were determined in the logistic and linear regression analyses, respectively. Regression analyses were supplemented with a feature selection process using backward elimination. A two-tailed *P* value of less than 0.05 was considered statistically significant. Because of the exploratory character of the study, the statistical tests that were carried out should be seen as constituting hypotheses rather than confirming hypotheses defined in advance. Therefore, no adjustments for multiple testing were made. All numerical calculations were performed with SPSS version 15 (SPSS Inc., Chicago, Illinois, USA) and StatXact 6 (Cytel Inc., Cambridge, Massachusetts, USA). Forest plots were created with Microsoft Excel XP, and forest plots in Excel software

(datasheet) are available from O. Clark and B. Djulbegovic (2001; <http://www.evidencias.com/>).

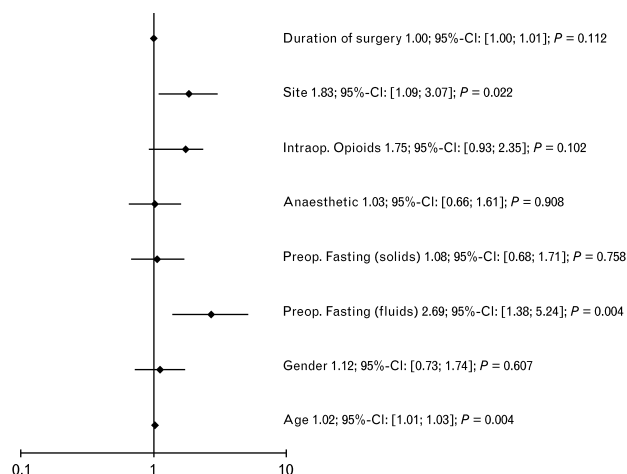
Results

A total of 910 patients were analysed in the recovery room. No follow-up was performed in 48 patients on the first postoperative day (eight patients underwent ambulatory day surgery and 40 patients were not available on the ward). A total of 862 patients were analysed for follow-up on the ward.

Delirium was observed in the recovery room in 100 of 910 patients (11.0%), and on the ward on the first postoperative day in 38 of 862 patients (4.2%). Thirty-two of these 38 patients (84.2%) were already positive for delirium upon discharge from the recovery room (McNemar's test $P < 0.001$).

Basic patient characteristics differed between the groups. Patients with delirium in the recovery room and on the ward were significantly older, were classified as having a higher physical status (ASA PS ≥ 3), experienced longer preoperative fluid fasting, were more often given fentanyl than remifentanyl for intraoperative analgesia and had a longer duration of surgery (Table 2). Preoperative fluid fasting times (>6 versus 2–6 h) were independently associated with an increased frequency of delirium both in the recovery room and on the ward. Additional independent risk factors for postoperative delirium in the recovery room were age and site of surgery [intraabdominal (143 patients) and intrathoracic (three patients) versus neither intraabdominal nor intrathoracic (764 patients)] (Fig. 2). An additional independent predictive

Fig. 2

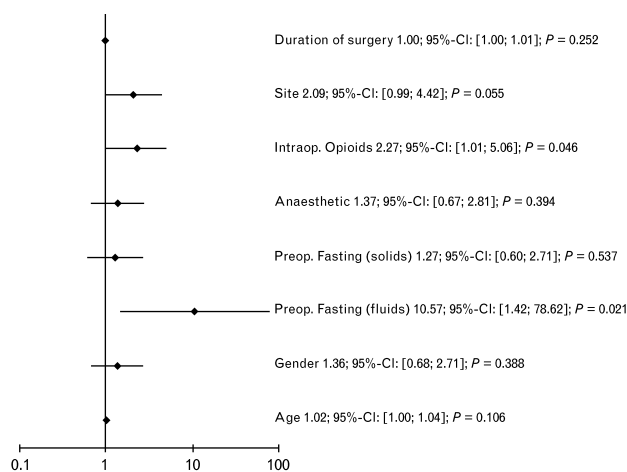


Risk factors for postoperative delirium in the recovery room (multiple logistic regression: odds ratios with 95% confidence interval). Duration of surgery (min); site, intraabdominal and intrathoracic versus other; intraoperative opioids, fentanyl versus remifentanyl; anaesthetic, TIVA versus volatile anaesthetic; preoperative fasting (solids), 6–12 versus >12 h; preoperative fasting (fluids), 2–6 versus >6 h; sex, female versus male; age (years). CI, confidence interval; TIVA, total intravenous anaesthesia.

factor for delirium on the ward was intraoperative opioid use (fentanyl versus remifentanyl) (Fig. 3).

The frequency of delirium was seen more often in longer fluid fasting times than in shorter fluid fasting times (5.0 versus 12.9%, $P < 0.001$) in the recovery room and on the

Fig. 3



Risk factors for postoperative delirium on the ward (multiple logistic regression: odds ratios with 95% confidence interval). Duration of surgery (min); site, intraabdominal and intrathoracic versus other; intraoperative opioids, fentanyl versus remifentanyl; anaesthetic, TIVA versus volatile anaesthetic; preoperative fasting (solids), 6–12 versus >12 h; preoperative fasting (fluids), 2–6 versus >6 h; sex, female versus male; age (years). CI, confidence interval; TIVA, total intravenous anaesthesia.

ward (0.5 versus 5.6%, $P = 0.002$), respectively. With our sample size, the statistical power amounted to 98.2% for the recovery room and 95.7% for the ward. The amount of fluid given during anaesthesia showed no significant difference between patients with regular and prolonged fluid fasting times [cumulative intravenous volume was 21.5 (± 17.4) versus 23.8 (± 24.4) ml kg⁻¹ h⁻¹, $P = 0.132$]. Patients with delirium in the recovery room required significantly longer recovery times [94 (± 40.7) versus 81 (± 43.8) min, $P < 0.001$]. Moreover, a longer length of postoperative hospital stay was observed both in patients with delirium in the recovery room [7.4 (± 8.1) days SD] versus 5.2 days (± 5.9 days SD), $P < 0.001$] as well as in patients with delirium on the first postoperative day [11.9 (± 10.5 days SD) versus 5.2 days (± 5.8 days SD), $P < 0.001$].

Discussion

The most important results were that early postoperative delirium in the recovery room and delirium on the first postoperative day were significantly influenced by potentially modifiable perioperative factors. Age and major surgery are known nonmodifiable risk factors.^{2,10} To the best of our knowledge, this is the first report of prolonged preoperative fluid fasting being an independent risk factor for early postoperative delirium in the recovery room and on the ward, and intraoperative use of a long-acting opioid being a significant predictor for delirium on discharge from the recovery room.

The incidence of early postoperative delirium in the recovery room in this heterogeneous patient group was 11.0%. Other authors have reported that, in specific surgical subgroups, the incidence of early postoperative delirium can be up to 45%.¹ The Nu-DESC is a very sensitive screening tool for delirium. Patients may be positive for delirium that the discharging physician did not diagnose as delirium, or that the physician did not consider as severe enough to be a contraindication for a transfer to the ward.

Intraoperative fentanyl use was an independent risk factor for delirium on the first postoperative day. The average dose of fentanyl, however, did not differ significantly in patients with delirium when compared with patients without delirium neither in the recovery room nor on the first postoperative day. In a systematic review of the role of postoperative analgesia on delirium by Fong et al.,¹¹ an influence of opioids (i.e. meperidine) on cognitive dysfunction was described. However, studies comparing fentanyl with remifentanyl were not available at that time. The main difference between fentanyl and remifentanyl is the metabolism of remifentanyl by non-specific esterases and its extremely short context-sensitive half-time. Remifentanyl may be administered at higher doses than are normally used for fentanyl to maintain adequate analgesia up to the end of a procedure without the risk of opioid overdose.

Preoperative fluid fasting was an independent risk factor for early postoperative delirium. Dehydration is a known risk factor for delirium.¹²

Simini¹³ suggested that the guidelines produced by anaesthetists' associations (e.g. in USA¹⁴ and Norway¹⁵) regarding preoperative fasting should be more widely implemented. Despite the relaxation in guidelines and some success in their implementation into practice, fasting times remain unduly long.¹⁶ The reasons for this include organization of operating rooms in a manner similar to assembly lines, making individualized fasting times impracticable; fear of litigation; difficulty in discarding old habits; and the deep-seatedness of anaesthetists' concerns regarding the risk of aspiration. In order to facilitate more widespread adoption of 'kind' fasting rules, Simini¹⁷ suggested that anaesthetists might prescribe (rather than allow) clear liquids up to 2 h before surgery, making it part of routine 'premedication'. This would reduce preoperative thirst, headache, irritation and discomfort with no added risk, even for anxious or obese patients.¹⁷ However, the author does not recommend a specific amount of fluids to be given. Patient stress through long preoperative fasting times may be regarded as a precipitating factor leading to delirium, according to the model of precipitating and predisposing factors by Inouye and Charpentier.⁶

Early postoperative delirium was predictive of later postoperative delirium on the ward. In total, 32 of 38 (84.2%) patients with delirium on the ward had already been found to have had delirium in the recovery room. Sharma *et al.*¹ have previously described a relationship between early postoperative delirium and delirium on the ward. The authors suggested that the quality of early recovery following surgery might provide an index of functional recovery and functional reserve of the brain during the stress of the perioperative period. Early recognition and treatment of delirium is the key to reducing the duration and severity of delirium and negative outcomes.^{18,19}

In our study, the site of surgery proved to be significantly relevant only for postoperative delirium in the recovery room but not for delirium on the first postoperative day. Olin *et al.*²⁰ observed that patients with a longer lasting postoperative delirium had undergone operations with a higher blood loss than patients with a shorter period of delirium. The authors also noted that those who developed delirium tended to have longer hospital stays and more postoperative complications.²⁰ Age was an independent risk factor for delirium in the recovery room and showed a nonsignificant tendency to predict delirium in the ward. As previously mentioned, Inouye and Charpentier⁶ have described predisposing and precipitating factors for postoperative delirium. The risk of developing delirium increases with each additional risk factor present. Predisposing factors, such as age or comorbidities,

are either by definition nonmodifiable or not realistically modifiable in the perioperative period.

A limitation of this study is that it was not a randomized controlled trial. Therefore, any conclusions will still need to be proven by prospective interventional trials. Other limitations are that we did not investigate why some patients fasted for longer periods, or received intravenous fluids preoperatively, nor did we perform longer term follow-up of the patients. Although we studied a relatively large number of patients, the incidence of delirium was low (4–11%), as evidenced by the large CI for preoperative fluid fasting.

Conclusion

Early postoperative delirium was seen in 11.0% of the patients in the recovery room and in 4.2% on the ward. Early postoperative delirium was predictive of a prolonged length of stay in the hospital. Age, site of surgery and intraoperative use of fentanyl as opposed to remifentanyl were independent risk factors for early postoperative delirium either in the recovery room or on the first postoperative day, whereas preoperative fluid fasting was predictive for early postoperative delirium in the recovery room and on the first postoperative day. Therefore, changes in current practice designed to modify certain precipitating factors, such as better adherence to the fasting guidelines produced by most of the world's anaesthetists' associations, may result in the prevention of delirium in a significant proportion of cases. Interventional studies are needed to confirm an improvement in outcome.

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In an observational study, risk factors for postoperative delirium were analysed. Duration of fluid fasting proved to be an independent predictor for postoperative delirium in the recovery room and on the ward.

F.M. Radtke and M. Franck were involved in data acquisition, interpreted the data and wrote the initial draft of the manuscript; both authors contributed equally. M. MacGuill revised the article for important intellectual content. S. Westhoff examined the patients and collected the data. A. Lütz, M. Seeling and S. Westhoff were involved in data acquisition and critically revised the article for important intellectual content. U. Neumann did the patient acquisition, data interpretation and reviewing of the manuscript. K.D. Wernecke contributed to data analyses and drafting of the article. C.D. Spies conceived the idea and designed the set-up of the study and was responsible for study conception, design, data interpretation, the draft and final reviewing of the manuscript as well as the organizational formal prerequisites for the study and financing. All authors contributed to data interpretation and the final version of the article.

The authors declare that they have no conflict of interest.

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