Pathogenesis of and management strategies for postoperative delirium after hip fracture

A review

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Background Postoperative delirium is a frequent and serious complication in elderly patients following operation for hip fracture, leading to an increased risk of complications. The pathophysiological mechanisms are unresolved, but probably multifactorial. The purpose of this review is to summarize current knowledge about the pathogenesis of postoperative delirium with a view to finding strategies for prevention and management.

Method We conducted an Internet search through the Medline database (1966–March 2003) and supplemented it with a manual search. We included 12 studies which specifically discussed pathogenic factors or interventions against postoperative delirium following operation for hip fracture.

Results 1 823 patients were included with an average incidence of delirium of 35%. We concentrated on pre-, intra-, and postoperative risk factors. Only advanced age and dementia met our fixed criterion of "strong evidence" for a significant association. Hence, from the studies that we reviewed we were unable to find intraoperative or postoperative factors with "strong evidence" for a significant association with delirium.

Interpretation Postoperative delirium is a serious complication. The pathophysiology leading to delirium after hip fracture surgery still remains to be clarified and no single drug or surgical regimen has proven to be preventive. This calls for more detailed investigations of the differential role of different pathogenic mechanisms, as well as an aggressive multimodal approach to enhance recovery and reduce morbidity, as has proven to be successful in a variety of elective surgical procedures. Such multimodal interventional studies represent a major task for orthopedic departments in collaboration with anesthesiologists, geriatricians, physiotherapists and nursing staff.

Postoperative delirium is a frequent complication in elderly patients following operation for hip fracture (O'Keeffe and Ni 1994, Dyer et al. 1995, Holmes and House 2000b), the incidence varying between 16% and 62%. Postoperative delirium is associated with increased morbidity and mortality (Mullen and Mullen 1992, Nightingale et al. 2001) as well as increased length of hospitalization, resulting in increased suffering and cost. The multifactorial pathophysiological mechanisms behind postoperative delirium are unresolved. Several theories have been put forward, including impairment of cerebral metabolism (metabolic encephalopathy), intoxication by drugs and polypharmacy (especially drugs with anticholinergic effects), hypoglycemia, surgical stress responses, perioperative hypoxemia, and hypotension. Moreover, it has been suggested that the type of anesthesia, administration of opioids, sleep deprivation, and unrelieved pain may play a role in the development of postoperative delirium (Flacker and Lipsitz 1999, Trzepacz 2000). Recent efforts to improve postoperative recovery have therefore made use of a multimodal approach to enhance rehabilitation (Kehlet and Wilmore 2002), but these data come from elective surgical procedures.

The purpose of this review is to describe current knowledge about the pathogenesis of postoperative

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Table 1. Diagnostic criteria for delirium (adapted from DSM-IV (American Psychiatric Association 1994)

Disturbance in consciousness (impaired ability to focus, sustain, or shift attention).
Change in cognition (memory impairment, disorientation, or language disturbance) or perceptual disturbance (misinterpretations, illusions, or hallucinations).
The disturbance develops over a short period of time and fluctuates during the course of the day.
There is laboratory or clinical evidence that the delirium state is caused by the direct physiological consequences of a general medical condition.

delirium after surgery for hip fracture, in order to define future strategies for prevention and management.

Clinical features and diagnosis

Over the past few years, several reviews have been published on delirium in general (Meagher 2001), postoperative delirium in the elderly (Parikh and Chung 1995), and psychiatric illness in patients treated for hip fracture (Holmes and House 2000b). These reviews have described in detail the clinical features which characterize the diagnosis of delirium, and emphasize the fact that much of the methodological confusion has been due to inconsequent nomenclature. At present there seems to be consensus on the use of the classification of delirium by the American Psychiatric Association, which is described in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (1994). DSM-IV diagnostic criteria for delirium are given in Table 1.

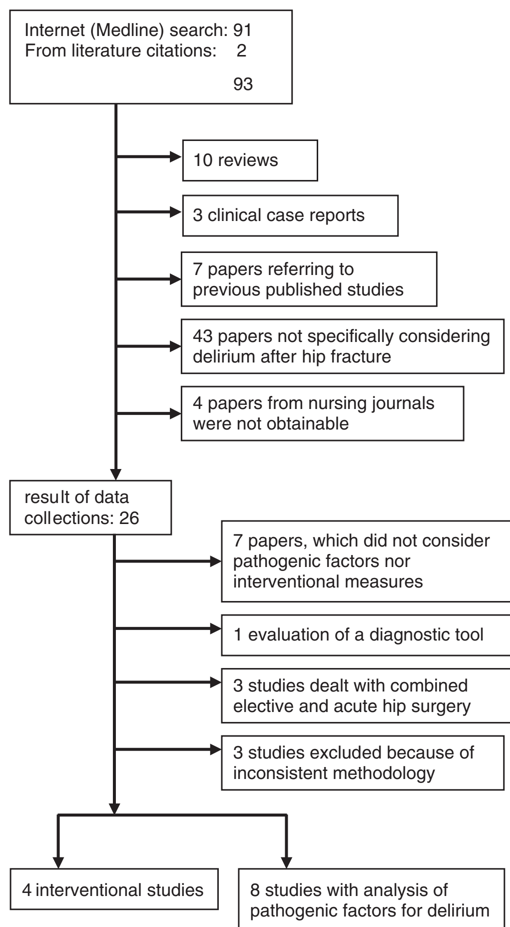

Figure. Outcome of the literature search from the Internet and citations.

Methods

We searched Medline (1966–March 2003) to identify potential articles for this review. The key words “delirium”, “confusion”, “postoperative cognitive dysfunction”, “hip fracture”, and “femoral neck fracture” were incorporated and used in relevant combinations. This was supplemented by a manual search from citations and reference lists. We only included original papers in English-language publications, and papers which specifically discussed pathogenic factors or interventions against postoperative delirium following operation for hip fracture. Papers not presenting data for hip fracture separately were thus excluded.

Results

The Internet search provided us with 91 references and the manual search from the bibliographies gave 2 additional references (Figure). 10 of the 93 references were reviews (4 of which dealt with medical care, 2 with anesthesia, 1 with psychiatric illness, 2 with surgical management, and 1 of which was a review of previously published studies with emphasis on nursing intervention and organization). All of the reviews were on hip fracture patients, but in general pathogenic factors for delirium were rarely described. 3 studies were

Table 2. Data from the 12 studies that were included: number of patients involved, incidence of delirium, exclusion criteria, diagnostic instruments, diagnostic criteria, and study method

Source	n	Incidence of delirium, %	Exclusion criteria	Diagnostic instruments [a]	Diagnostic criteria	Study method [b]
Morrison et al. 2003	541	16	Delirious at the initial interview	CAM and review of medical records	Ns (presumably DSM)	DPC
Zakriya et al. 2002	168	28	Dementia or delirium on admission	CAM	Ns (presumably DSM)	DPC
Marcantonio et al. 2001	126	50 vs. 32 [c]	< 65 yr, metastatic cancer or life expectancy < 6 mo	MMSE, DSI, MDAS and CAM	Ns (presumably DSM)	PRBS
Edlund et al. 2001	101	48 [d]	< 65 yr	MMSE, OBS-scale	DSM-IV	DPC
Milisen et al. 2001	120	23 vs. 20 [e]	Multiple trauma, concussion of the brain, pathological fractures, surgery < 72 h after admission, aphasia, blindness, deafness, < 9 yr of education	CAM, MMSE	Ns (presumably DSM)	LPBAD
Andersson et al. 2001	267	20	< 65 yr, diagnosis of mental disease, confusion at admission, patients with difficulty in communicating	OBS scale	DSM-IV	DPC
Marcantonio et al. 2000	126	41	< 65 yr, life expectancy < 6 mo	Daily interviews, MMSE, DSI, CAM	Ns (presumably DSM)	DPC
Edlund et al. 1999	54	28	None	Daily observation, OBS-scale	DSM-III-R	DPC
Lundstrom et al. 1999	49	31	Ns	OBS-scale	DSM-III-R	IS/DPC
Gustafson et al. 1991a	103	48	< 65 yr	OBS-scale	DSM-III	IS
Gustafson et al. 1988	111	62	< 65 yr	OBS-scale	DSM-III	DPC
Berggren et al. 1987	57	44	Not fully lucid , < 64 yr	OBS-scale	DSM-III	PRBS

Ns Not stated.
[a] Diagnostic instruments: CAM confusion assessment method, DSI delirium symptom interview, MDAS memorial delirium assessment scale, MMSE mini-mental state examination, OBS-scale organic brain syndrome scale.
[b] Study methods: DPC descriptive prospective cohort, IS interventional study, LPBAD longitudinal prospective before/after design, PRBS prospective randomized blinded study.
[c] A randomized trial; the incidence of delirium in the usual-care group and the intervention group was 50% and 32% respectively.
[d] 30% were delirious on admission or developed delirium before surgery, 19% developed delirium postoperatively.
[e] The incidence in the non-intervention cohort and in the intervention cohort was 23% and 20%, respectively (difference not significant).

clinical case reports, and 7 publications referred to previously published studies. Of the remaining studies, 43 did not specifically consider delirium in hip fracture patients and 4 studies, all from nursing journals, were not available. Thus, from the initial data collection, we found 26 studies suitable for more detailed analysis (Billig et al. 1986, Berggren et al. 1987, Furstenberg and Mezey 1987, Gustafson et al. 1991a, b, 1988, Krasheninnikoff et al. 1993, Bowman 1997, Edlund et al. 1999, Lundstrom et al. 1999, Brauer et al. 2000, Clayer and Bruckner 2000, Duppils and Wikblad 2000, Holmes and House 2000a, Marcantonio et al. 2000, 2001, 2002, Sato et al. 2000, Andersson et al. 2001, Edlund et al. 2001, Galanakis et al. 2001, Milisen et al. 1998, 2001, 2002, Zakriya et al. 2002, Morrison et al. 2003).

Of the 26 papers identified, 14 were excluded: 7 papers did not deal with any pathogenic factors; nor was there any interventional aspect (Billig et al. 1986, Furstenberg and Mezey 1987, Milisen et al. 1998, Gustafson et al. 1991b, Holmes and House 2000a, Sato et al. 2000, Milisen et al. 2002), 1 study was an evaluation of a diagnostic instrument

(Marcantonio et al. 2002), and 3 additional studies dealt with elective and acute hip surgery, where the hip fracture patients were not analyzed separately (Clayer and Bruckner 2000, Duppils and Wikblad 2000, Galanakis et al. 2001). Finally, 3 studies were excluded because of inconsistent methodology (Krasheninnikoff et al. 1993, Bowman 1997, Brauer et al. 2000). Thus, the final number of studies meeting our inclusion criteria was 12.

Descriptive parameters for the studies and the patients involved

Exclusion and inclusion criteria for patients (Table 2)

The criteria for exclusion of patients varied. 3 studies (Edlund et al. 1999, Zakriya et al. 2002, Morrison et al. 2003) included patients regardless of age. In the remaining studies, the general criterion for inclusion was age above 65 years. In addition to age, the most common exclusion criterion was cognitive dysfunction at admission, presenting as delirium and/or dementia. Furthermore, 4 studies (Marcantonio et al. 2000, 2001, Andersson et al. 2001, Milisen et al. 2001) excluded patients with severe co-morbidities other than delirium or dementia, including metastatic cancer, pathological fractures, and a life expectancy of less than 6 months.

Diagnostic criteria (Table 2)

Where mentioned, the diagnostic criterion for delirium was the one compiled by the American Psychiatric Association, the DSM (1994). In 5 of the reviewed studies (Marcantonio et al. 2000, 2001, Milisen et al. 2001, Zakriya et al. 2002, Morrison et al. 2003) the criteria for the diagnosis were not explicitly stated, but the diagnostic instrument was based on the DSM criteria.

Diagnostic instruments (Table 2)

All of the studies under review used standardized mental tests as their case-finding instrument. In general, the case-finding instruments are designed to recognize the crucial features of delirium as outlined in Table 1. The most widely used diagnostic tests were the Confusion Assessment Method (CAM) (Inouye 2002), the Mini-Mental State Examination (MMSE) (Folstein et al. 1975), and the Organic Brain Syndrome scale (OBS scale) (Berggren et al. 1987).

Confusion assessment method (CAM)

The CAM is a structured interview with the patient. It is derived from the DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, third edition revised) and designed to focus on the most prominent clinical features of delirium: acute change in mental status with a fluctuating course, inattention, disorganized thinking, and altered level of consciousness. Of these, the first and second features must be present, and the patient must be showing symptoms of either the third or the fourth clinical feature in order to make the diagnosis of delirium.

Mini-mental state examination (MMSE)

The MMSE was originally conceived as short (5–10 min) clinical instrument for detecting cognitive impairment. It is designed to test abilities in orientation, memory, attention, naming objects, following verbal and written commands, writing a sentence spontaneously, and in copying a complex polygon (Folstein et al. 1975, Tombaugh and McIntyre 1992, Smith et al. 1995). When using the test to screen for delirium as opposed to dementia, it only has relevance if the clinician has as baseline value, or knows by some other means, that the patient was cognitively intact prior to the current testing.

Organic brain syndrome scale (OBS scale)

The OBS scale is composed of two parts, a disorientation subscale based on an interview with the patient, and a confusion subscale based on observations of the investigator or nursing staff. The former describes orientation ability regarding time, place and own identity, whereas the latter subscales test different cognitive, perceptual, emotional, and personality changes, physical and practical disabilities, and fluctuations in the clinical state. Each of the questions in both parts are rated on a 4-point scale, with an accurate description of each scoring level (Berggren et al. 1987, Jensen et al. 1993). Other tests have been designed to differentiate between different types of delirium or to measure the severity of the delirium state (Marcan-

Table 3. Preoperative risk factors for postoperative delirium

Preoperative factors	Studies which showed an association between a given factor and delirium	Studies which showed no association betwen a given factor and delirium	Evidence for association with delirium [a]
Advanced age	Marcantonio 2000, Edlund 1999, Andersson 2001, Gustafson 1988, Gustafson 1991a, Morrison 2003	Berggren 1987, Edlund 2001, Zakriya 2002	++
Male sex	Morrison 2003 [b], Edlund 2001, Gustafson 1991a	Edlund 1999, Marcantonio 2000, Gustafson 1988, Zakriya 2002	+
Impaired sight	Andersson 2001	None	–
Impaired hearing	None	None	–
History of cerebrovascular disease	Gustafson 1988	None	–
History of cardiovascular disease	Gustafson 1988, Morrison 2003	Zakriya 2002	+
History of stroke	None	Zakriya 2002	–
History of congestive heart failure	Zakriya 2002, Morrison 2003	None	+
Abnormal fluid and electrolyte parameters	Zakriya 2002	Morrison 2003, Gustafson 1988	–
Endocrine diseases	None	Zakriya 2002	–
Dementia	Morrison 2003, Edlund 2001 Gustafson 1988, Marcantonio 2000, Edlund 1999, Andersson 2001	None	++
Depression	Edlund 1999, Gustafson 1988, Berggren 1987	Edlund 2001	+
Reduced ADL [c]	Morrison 2003 [d], Marcantonio 2000	None	+
Alcohol abuse	None	Zakriya 2002	–
Medicine abuse	None	None	–
Prolonged waiting time for operation	Edlund 1999	Morrison 2003, Gustafson 1988, Gustafson 1991a	–
Anticholinergic drugs	Gustafson 1988, Edlund 1999, Berggren 1987	None	+
Neuroleptic drugs	Berggren 1987, Gustafson 1988	None	+
Benzodiazepines	Gustafson 1988	None	–
Antidepressants	Gustafson 1988, Berggren 1987	None	+
Type of fracture	None	Morrison 2003, Marcantonio 2000	–

[a] High evidence (positive evidence in > 3 studies): ++, some evidence (positive evidence in 2–3 studies): +, no convincing evidence (positive evidence in 0–1 study): –.
[b] Only for patients who were cognitively impaired on admission.
[c] Activities of Daily Living.
[d] Independent predictor for cognitively intact subjects only.

tonio et al. 2002), but the clinical implications of these tests are still somewhat unclear and beyond the scope of this paper.

Study method and general results (Table 2)

Most of the 12 studies were prospective, descriptive studies. 2 studies were prospective, randomized and performed blind (Berggren et al. 1987, Marcantonio et al. 2001) and 4 studies had interventional measures (Gustafson et al. 1991a, Lundstrom et al. 1999, Marcantonio et al. 2001, Milisen et al. 2001).

1 823 patients were included in the 12 studies, with an average of 152 patients in each cohort (range 49–541 patients). On average, delirium occurred in 35 (16–62)% of the patients included.

Pre-, intra-, and postoperative risk factors for delirium

A general overview of risk factors involved in postoperative delirium requires a consideration of these risk factors in 3 categories: preoperative, intraoperative, and postoperative (Tables 3, 4, and 5).

Table 4. Intraoperative risk factors for postoperative delirium

Intraoperative factors	Studies which showed an association between a given factor and delirium	Studies which showed no association between a given factor and delirium	Evidence for assocation with delirium [a]
Morphine as premedication	None	None	–
Benzodiazepine as premedication	None	None	–
General anesthesia	None	Berggren 1987	–
Spinal and epidural anesthesia	Gustafson 1988	Berggren 1987	–
Anticholinergic drugs	None	None	–
Hypoxia	Gustafson 1991a	None	–
Hypotension	Gustafson 1991a, Edlund 2001, Gustafson 1988	Berggren 1987	+

[a] High evidence (positive evidence in > 3 studies): ++, some evidence (positive evidence in 2–3 studies): +, no convincing evidence (positive evidence in 0–1 study): –.

Table 5. Postoperative risk factors for postoperative delirium

Intraoperative factors	Studies which showed an association between a given factorand delirium	Studies which showed no association between a given factorand delirium	Evidence for assocation with delirium [a]
Pneumonia	Edlund 2001	None	–
Urinary infection	Gustafson 1988	Edlund 2001	–
Elevated temperature	Gustafson 1988	None	–
Hypoxia	Berggren 1987 [b]	None	–
Treatment with large doses of opioids	None	None	–
Inadequate analgesia	Morrison 2003 [c]	None	–
Inadequate nourishment	Gustafson 1988	None	–
Postoperative fluid therapy	None	None	–

[a] High evidence (positive evidence in > 3 studies): ++, some evidence (positive evidence in 2–3 studies): +, no convincing evidence (positive evidence in 0–1 study): –.
[b] In patients treated with halothane, there was a significant association between postoperative delirium and a decrease in arterial oxygen tension after anesthesia,
[c] Less than 10 mg parenteral morphine sulphate equivalents/day.

Preoperative factors (Table 3)

Acetylcholinergic functions are involved in consciousness and attentiveness (Blass and Gibson 1999, Flacker and Lipsitz 1999) and a loss of nicotine binding in the brain is seen in the normal aging process (Picciotto and Zoli 2002). Accordingly, when looking at the preoperative factors, advanced age and dementia were consistent predictors of postoperative delirium. In addition, there was some evidence that preoperative treatment with anticholinergic drugs and depression may be positively associated with delirium.

A history of cerebrovascular disease (Gustafson et al. 1988), cardiovascular disease (Gustafson et al. 1988), stroke, and congestive heart failure (Zakriya et al. 2002) showed no convincing association with postoperative delirium. One study described an association between abnormal serum sodium and development of postoperative delirium (Zakriya et al. 2002). In another study, delayed operation was associated with postoperative delirium (Edlund et al. 1999).

Administration of long-acting benzodiazepines may be a pathogenic factor (Marcantonio et al. 1994), but only 1 study supported this in hip frac-

ture (Gustafson et al. 1988). Treatment with neuroleptic drugs was found to be linked to delirium in 2 studies (Berggren et al. 1987, Gustafson et al. 1988). Surprisingly, none of the studies indicated an association between postoperative delirium and abuse of alcohol and/or drugs. This contrasts with the non-surgical literature (Blass and Gibson 1999), where alcohol withdrawal and intoxication with sedatives are predisposing factors for delirium.

Intraoperative factors (Table 4)

Hypotension, defined as a drop in perioperative systolic blood pressure to ≤ 80 mmHg (Gustafson et al. 1991a), or severe drop in peroperative blood pressure (Gustafson et al. 1988), was associated with postoperative delirium. In the study by Edlund and Lundstsröm (2001), it was found that patients with postoperative delirium had a fall in mean peroperative blood pressure of around 31%, in contrast to the lucid patients who experienced a fall of around 23%.

No significant difference between epidural/spinal and general anesthesia has been found (Berggren et al. 1987).

Postoperative factors (Table 5)

Postoperative hypoxia was found to be associated with delirium in 2 studies (Gustafson et al. 1991a, Berggren et al. 1987). Other trials have also shown an association (Krasheninnikoff et al. 1993, Clayer and Bruckner 2000), but none of them applied known standardized mental tests. One study showed an association between delirium and inadequate postoperative analgesia (Morrison et al. 2003). Postoperative delirium has often been associated with postoperative complications such as pneumonia, urinary infections or sepsis, but this does not appear to be a general risk factor, even though Gustafson et al. (1988) found an association in their study. Surprisingly, none of the articles dealt with the cerebral side effects of opioids, nor was there any information in the literature examined describing whether fluid therapy, malnutrition, and immobilization may play a role in postoperative delirium.

Interventional studies

4 studies were interventional: 2 were nurse-led studies (Lundstrom et al. 1999, Milisen et al. 2001) and 2 were geriatric and geriatric-anesthesiological studies (Gustafson et al. 1991a, Marcantonio et al. 2001) (Table 6). A common theme in the 2 nurse-led intervention programs was staff education. In addition, Milisen et al. (2001) focused on postoperative pain management, screening of cognitive status, and providing expertise by specially trained nurses. The result showed a non-significant reduction in the incidence of delirium. Lundstrom et al. (1999) focused their intervention on geriatric and orthopedic cooperation as soon as possible after operation, regional anesthesia, prevention of hypoxemia, and early rehabilitation. It showed a significant reduction in the incidence of delirium from 61% and 48% in controls, to 31% in the interventional cohort.

The geriatric intervention study by Marcantonio et al. (2001) randomized the patients to proactive geriatric consultation and "usual care". Patients receiving proactive care were visited daily by a geriatrician who made recommendations based on a structured protocol. The recommendations most frequently given were: transfusion to keep hematocrit > 30%, discontinuation of urinary catheter, and conservative use of benzodiazepines. The overall adherence rate by the orthopedic team was 77%. The authors documented a non-significant reduction in delirium. The geriatric-anesthesiologic interventional study by Gustafson et al. (1991a) demonstrated a significant reduction in delirium from 61% to 48%, when patients were operated as soon as possible, when patients were treated with O_2 1 L/min, from admission until at least the first postoperative day, and received spinal anesthesia. For a more thorough description of the interventional measures and outcome (Table 6).

Discussion

Delirium in the postoperative period after surgery for hip fracture is a common complication among the elderly. No single drug or surgical regime has proven to be preventive, and the exact pathophysiology remains to be clarified. From the studies available, it is evident that there is no common pathway leading to postoperative delirium. More likely, postoperative delirium is a product of cere-

Table 6. Interventional measures and their outcome

Study [a]	Intervention	Results of intervention
Milisen et al. 2001 Design: LPBAD n=120 Incidence of delirium: 20% (intervention cohort) vs. 23% (control study)	Education of nurses in delirium, depression, and dementia Systematic screening of cognitive status. Consultative services by specially trained nurses. Effective postoperative pain control (loading dose of iv tramadol 6 mg/kg, maintenance infusion of tramadol 6 mg/kg/24 h and iv propacetamol 120 mg/kg/24 h during the first 48 postoperative h). Tramadol and acetaminophen were given orally after the first 48 postoperative h until 5. post-operative day.	Non-significant reduction in the incidence of delirium (from 23% in the non-intervention group to 20% in the intervention group (p=0.8). Shorter duration of delirium. Fewer severely delirious patients.
Lundstrom et al. 1999 Design: DPC Intervention cohort compared with historical cohorts from the same and different hospitals n=49 (intervention cohort only) Incidence of delirium: 31% (intervention cohort) significantly lower than historical cohorts	Education of staff. Orthopedic surgeons and geriatricians cooperate 48 of 49 patients were operated under spinal anesthesia. Operation as soon as possible. Prevention of hypoxemia with O_2. Treatment with PEEP bottle. Rehabilitation starts as soon as possible. Assessment and treatment of complication in delirious patients. Administration of pain-reducing pills to ensure training. Physiotherapists and occupational therapists participate in rehabilitation. Focus on nutrition.	Lower incidence of delirium. Shorter duration of delirium. Better outcome of rehabilitation. Fewer complications.
Marcantonio et al. 2001 Design: PRBS n=126 Incidence of delirium: 32% (intervention cohort) vs. 50% (usual-care cohort)	Patient evaluation: pre-fracture self-care function, post-fracture cognitive function, and symptoms of delirium. Daily proactive geriatrics consultation with targeted recommendations. The 5 most frequently given recommendations were: Transfusion to keep hematocrite > 30%, discontinuation of urinary catheter, minimizeing of benzodiazepines, anticholinergic medicines, and antihistamines, bowel movement, and out of bed on postoperative day 1 and several h daily.	Lower incidence of delirium (although non-significant after adjustment for imbalance between the consultation and usual-care group).
Gustafson et al. 1991a Design: DPC intervention cohort, n=103, compared with historical cohorts from the same orthopedic department, n=214 Incidensce of delirium: 48% (intervention cohort) vs. 61% (control study)	Operation as soon as possible. Preoperative examination by a physician. Thrombosis prophylaxis. Treatment with O_2 (1 L/hr) from admission until first postoperative day. Morphine s.c. for pre-medication (200–100 µg/kg body weight, depending on age). Spinal anesthesia (15–20 mg isobaric bupivacaine hydrochloride). Hypotension was treated with crystalloids and and phenylephrine. Postoperative assessment and treatment by specialist in geriatrics.	Shorter time between admission and operation. Fewer patients experienced hypotension. Lower incidence of delirium. Fewer with severe delirium. Duration of delirium shorter. Incidences of postop. urinary retention, decubital ulcers, and severe falls were lower. More patients were given blood transfusions. Mean stay in orthopedic ward was significantly shorter.

[a] Study methods: DPC descriptive prospective cohort, LPBAD longitudinal prospective before/after design, PRBS prospective randomized blinded study.

bral abnormalities, the surgical and environmental stress applied in the perioperative period, and adverse effects of drug therapy.

Descriptive parameters for the studies and for the patients included

A significant dilemma when reviewing the literature has been the varied exclusion criteria applied in the different studies. Many studies excluded patients with cognitive dysfunction on admission (Berggren et al. 1987, Andersson et al. 2001, Zakriya et al. 2002, Morrison et al. 2003) and serious co-morbidities other than delirium and dementia (Marcantonio et al. 2000, 2001, Andersson et al. 2001, Milisen et al. 2001), whereas other studies included patients regardless of cognitive function and co-morbidities (Gustafson et al. 1988, 1991a, Edlund et al. 1999, 2001). The delirium state is difficult to diagnose among patients with cognitive dysfunction on admission, but when excluding the most vulnerable patients, the incidences of delirium reported may only represent a minimum risk given that high-risk patients have been excluded. Consequently, a study that includes all patients regardless of age, cognitive and physical state must give the most accurate description of perioperative risk factors for postoperative delirium and also demonstrate that one of the risks of the operation is to aggravate a preexisting delirium state.

The variable inclusion criteria also reflect the large differences in the incidences of delirium, but one could also suspect that the different diagnostic instruments were responsible. However, all studies implicitly applied the DSM criteria for delirium. This is a methodological strength when comparing the studies, but it also demands that the patients be interviewed daily and in many cases that medical charts have to be reviewed retrospectively in order to identify important aspects of the diagnosis, such as its fluctuating course. Hence, unless the staff is specially trained in making the diagnosis of delirium, this could be a methodological weakness since it is often overlooked or misinterpreted (Gustafson et al. 1991b, Milisen et al. 2002).

The 3 clinical instruments, MMSE, CAM, and OBS scale all have their advantages and disadvantages. Essentially, they all screen for clinical features of delirium, both the CAM and the OBS scale including an evaluation of whether or not the state has evolved acutely, and whether there are signs of perceptual disturbances, psychomotor agitation, and an altered sleep-wake cycle. Still, these two instruments require a certain amount of clinical experience and cannot be completed just from a bedside interview. In contrast, the MMSE requires little instruction, and can be completed without the aid of medical charts, but it lacks descriptions of key clinical features of delirium. However, we are of the opinion that this can be compensated for in most cases by a thorough preoperative examination to obtain preoperative cognitive status, which should be followed by regular postoperative testing. It should be emphasized that preoperative testing is essential, regardless of which test the clinician chooses, in order to obtain a baseline value and a postoperative standard of reference (Rasmussen et al. 2002).

Most of the studies reviewed here were prospective, descriptive studies. A common denominator in these studies was the lack of comprehensive description of perioperative care principles such as pain management, fluid therapy, anesthesia, general pharmacological treatment, nutrition, physiotherapy etc., thereby limiting interpretation of the relative importance of the pathogenic mechanisms involved.

Pre-, intra-, and postoperative risk factors for delirium

This review has primarily focused on the pre-, intra-, and postoperative factors for postoperative delirium after hip fracture. A substantial number of the preoperative risk factors, which had a positive association with postoperative delirium, were factors that were essentially unadjustable, i.e. causes such as age, gender, dementia, depression, and concomitant diseases.

Intraoperative and postoperative risk factors for delirium were sparsely documented, and only hypotension in the intraoperative period (Gustafson et al. 1988, 1991a, Edlund et al. 2001) showed an association with postoperative delirium. Since neuroaxial anesthesia reduces postoperative morbidity (Rodgers et al. 2000) it may also be expected to reduce delirium, although there is limited data to support this (Urwin et al. 2000).

Interventional studies

In the nurse-led interdisciplinary intervention program by Milisen et al. (2001), there was no preoperative evaluation of the mental status of the patients. Furthermore, possible risk factors such as prolonged waiting time and also medication, type of anesthesia, treatment or prevention of hypoxia and hypotension, nutritional considerations, and fluid therapy were not mentioned, thereby limiting interpretation.

The nursing and medical intervention study by Lundstrom et al. (1999) intervened broadly, which may account for the substantial reduction in the incidence of delirium in comparison to the control studies, but again the lack of information on perioperative care regimens would make reproduction of the study impossible.

In the study by Marcantonio et al. (2001), accurate documentation of pre- and postoperative cognitive and self-care functions are provided, but not treatments provided by the orthopedic team independently of geriatric recommendations. Thus, although proactive geriatric consultation may decrease the incidence of delirium, the exact mechanisms remain unresolved.

The geriatric-anesthesiologic intervention study by Gustafson et al. (1991a) has great strength in the fact that the interventional measures (surgical policy, preoperative assessment and thrombosis prophylaxis, oxygen therapy, anesthetic technique, and postoperative assessment and treatments) and cognitive function pre- and postoperatively were well documented. On the other hand, the study lacked information on pre- and postoperative pain management, nutrition, fluid therapy, and mobilization.

In conclusion, all 4 interventional studies dealt with relevant measures to avoid postoperative delirium, but in general the studies approached the problem either with intervention regarding a limited number of possible risk factors or, in the case of broader intervention, the reproducibility of the study was low because of lack of description of the many factors involved in the perioperative care.

Management strategies

As mentioned in the introduction to this review, recent progress in surgical management has been focused mainly on elective surgical patients, where a multimodal approach to enhancing recovery and reducing morbidity has been very successful in a variety of surgical procedures (Kehlet and Wilmore 2002).

Although it is debatable whether regional anesthesia *per se* will reduce the incidence of delirium in hip fracture patients (Urwin et al. 2000), it reduces surgical stress and thus morbidity and mortality in major orthopedic surgical patients (Rodgers et al. 2000). Thus, the anesthetic technique of choice should be spinal or epidural, unless there are significant contraindications.

To date, there has been no randomized trial on whether early vs. late operation has any association with morbidity, but the consequences of prolonged waiting time for surgery may be inadequate nutrition and fluid intake, immobilization, and pain, all of which may contribute to delirium in an elderly patient.

In general, patients admitted to hospital for hip fracture have many co-morbidities and therefore receive a wide variety of drugs. This issue is two-sided. There is a chance that these drugs may be discontinued unintentionally, resulting in increased morbidity (Noble and Kehlet 2000), but also that the drugs or their metabolites may produce side effects such as delirium due to acetylcholinergic antagonism (Tune and Egeli 1999). Every effort should therefore be made to adjust concurrent medications to avoid side effects and abstinence syndromes.

Rational fluid therapy for this category of patient is often complicated by the fact that on admission patients are often dehydrated. On the other hand, intra- and postoperative fluid therapy frequently causes fluid excess, which may contribute to heart and lung complications (Holte et al. 2002). It is therefore essential to avoid both dehydration and fluid excess in the perioperative period.

Although inconclusive, a recent Cochrane review on nutritional supplementation for hip fracture patients (Avenell and Handoll 2003) has provided some evidence for reduced postoperative complications and mortality, when oral multi-nutrient feeding was instituted. Opioid-reduced analgesia and prophylaxis for postoperative nausea and vomiting should increase the likelihood of early institution of oral nutrition, as has been demonstrated in abdominal surgery (Kehlet et al. 1999). Hence, a

multimodal analgesia represents a prerequisite for postoperative mobilization and physiotherapy, and therefore a potential reduction of morbidity.

We hypothesize that the principles applied in this multimodal approach to enhance recovery (Kehlet and Wilmore 2002) will prove to be valuable when dealing with hip fracture patients. The main goal is fast recovery, in order to minimize expenditure of human and economic resources. Accordingly, such a multimodal approach to this vulnerable category of patients may decrease morbidity, including delirium, and increase patient satisfaction as supported in preliminary studies (Rasmussen and Kristensen 2002).

Future studies should aim to clarify whether or not an aggressive and multimodal approach to hip fracture patients can reduce the incidence of delirium and overall morbidity and mortality.

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American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edn.Washington, DC: American Psychiatric Association, 1994.

Andersson E M, Gustafson L, Hallberg I R. Acute confusional state in elderly orthopaedic patients: factors of importance for detection in nursing care. Int J Geriatr Psychiatry 2001; 16: 7-17.

Avenell A, Handoll H H G. Nutritional supplementation for hip fracture aftercare in the elderly (Cochrane Review). In: The Cochrane Library, Issue 1, 2003 Issue 1, Oxford: Update Softwear.

Berggren D, Gustafson Y, Eriksson B et al. Postoperative confusion after anesthesia in elderly patients with femoral neck fractures. Anesth Analg 1987; 66: 497-504.

Billig N, Ahmed S W, Kenmore P, et al. Assessment of depression and cognitive impairment after hip fracture. J Am Geriatr Soc 1986; 34: 499-503.

Blass J P, Gibson G E. Cerebrometabolic aspects of delirium in relationship to dementia. Dement Geriatr Cogn Disord 1999; 10: 335-8.

Bowman A M. Sleep satisfaction, perceived pain and acute confusion in elderly clients undergoing orthopaedic procedures. J Adv Nurs 1997; 26: 550-64.

Brauer C, Morrison R S, Silberzweig S B, et al. The cause of delirium in patients with hip fracture. Arch Intern Med 2000; 160: 1856-60.

Clayer M, Bruckner J. Occult hypoxia after femoral neck fracture and elective hip surgery. Clin Orthop 2000; (370): 265-71.

Duppils G S, Wikblad K. Acute confusional states in patients undergoing hip surgery. A prospective observation study. Gerontology 2000; 46: 36-43.

Dyer C B, Ashton C M, Teasdale T A. Postoperative delirium. A review of 80 primary data-collection studies. Arch Intern Med 1995; 155: 461-5.

Edlund A, Lundstrom M, Lundstrom G, et al. Clinical profile of delirium in patients treated for femoral neck fractures. Dement Geriatr Cogn Disord 1999; 10: 325-9.

Edlund A, Lundstrom M, Brannstrom B, et al. Delirium before and after operation for femoral neck fracture. J Am Geriatr Soc 2001; 49: 1335-40.

Flacker J M, Lipsitz L A. Neural mechanisms of delirium: current hypotheses and evolving concepts. J Gerontol A Biol Sci Med Sci 1999; 54: B239-46.

Folstein M F, Folstein S E, McHugh P. Mini Mental State Examination (MMSE). J Psych Research 1975; 12: 189-98.

Furstenberg A L, Mezey M D. Mental impairment of elderly hospitalized hip fracture patients. Compr Gerontol (B) 1987; 1: 80-5.

Galanakis P, Bickel H, Gradinger R, et al. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. Int J Geriatr Psychiatry 2001; 16: 349-55.

Gustafson Y, Berggren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. J Am Geriatr Soc 1988; 36: 525-30.

Gustafson Y, Brannstrom B, Berggren D, et al. A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. J Am Geriatr Soc 1991a; 39: 655-62.

Gustafson Y, Brannstrom B, Norberg A, et al. Underdiagnosis and poor documentation of acute confusional states in elderly hip fracture patients. J Am Geriatr Soc 1991b; 39: 760-5.

Holmes J, House A. Psychiatric illness predicts poor outcome after surgery for hip fracture: a prospective cohort study. Psychol Med 2000a; 30: 921-9.

Holmes J D, House A O. Psychiatric illness in hip fracture. Age Ageing 2000b; 29: 537-46.

Holte K, Sharrock N E, Kehlet H. Pathophysiology and clinical implications of perioperative fluid excess. Br J Anaesth 2002; 89: 622-32.

Inouye S K. Confusion Assessment Method Instrument (CAM). Ann Intern Med 2002; 113: 941-8.

Jensen E, Dehlin O, Gustafson L. A Comparison between three psychogeriatric rating scales. Int J Geriatr Psychiatry 1993; 8: 215-29.

Kehlet H, Wilmore D W. Multimodal strategies to improve surgical outcome. Am J Surg 2002; 183: 630-41.

Kehlet H, Werner M, Perkins F. Balanced analgesia: what is it and what are its advantages in postoperative pain? Drugs 1999; 58: 793-7.

Krasheninnikoff M, Ellitsgaard N, Rude C, et al. Hypoxaemia after osteosynthesis of hip fractures. Int Orthop 1993; 17: 27-9.

Lundstrom M, Edlund A, Lundstrom G, et al. Reorganization of nursing and medical care to reduce the incidence of postoperative delirium and improve rehabilitation outcome in elderly patients treated for femoral neck fractures. Scand J Caring Sci 1999; 13: 193-200.

Marcantonio E R, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. JAMA 1994; 272: 1518-22.

Marcantonio E R, Flacker J M, Michaels M, et al. Delirium is independently associated with poor functional recovery after hip fracture. J Am Geriatr Soc 2000; 48: 618-24.

Marcantonio E R, Flacker J M, Wright R J, et al. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001; 49: 516-22.

Marcantonio E, Ta T, Duthie E, et al. Delirium severity and psychomotor types: their relationship with outcomes after hip fracture repair. J Am Geriatr Soc 2002; 50: 850-7.

Meagher D J. Delirium: optimising management. BMJ 2001; 20: 322: 144-9.

Milisen K, Abraham I L, Broos P L. Postoperative variation in neurocognitive and functional status in elderly hip fracture patients. J Adv Nurs 1998; 27: 59-67.

Milisen K, Foreman M D, Abraham I L, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc 2001; 49: 523-32.

Milisen K, Foreman M D, Wouters B, et al. Documentation of delirium in elderly patients with hip fracture. J Gerontol Nurs 2002; 28: 23-9.

Morrison R S, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A Biol Sci Med Sci 2003; 58: 76-81.

Mullen J O, Mullen N L. Hip fracture mortality. A prospective, multifactorial study to predict and minimize death risk. Clin Orthop 1992; (280) : 214-22.

Nightingale S, Holmes J, Mason J, et al. Psychiatric illness and mortality after hip fracture. Lancet 2001; 357: 1264-5.

Noble D W, Kehlet H. Risks of interrupting drug treatment before surgery. BMJ 2000; 321: 719-20.

O'Keeffe S T, Ni C A. Postoperative delirium in the elderly. Br J Anaesth 1994; 73: 673-87.

Parikh S S, Chung F. Postoperative delirium in the elderly. Anesth Analg 1995; 80: 1223-32.

Picciotto M R, Zoli M. Nicotinic receptors in aging and dementia. J Neurobiol 2002; 53: 641-55.

Rasmussen S, Kristensen B B, Foldager S, et al. Accelerated recovery programme after hip fracture. Ugeskr Laeger 2002; 165: 29-33.

Rodgers A, Walker N, Schug S, et al. Reduction of postoperative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. BMJ 2000; 321: 1-12

Sato N, Sanuki M, Matsumoto C, et al. Perioperative temporal profile of cognitive function in elderly patients undergoing hip surgery. J Geriatr Psychiatry Neurol 2000; 13: 206-9.

Smith M J, Breitbart W S, Platt M M. A critique of instruments and methods to detect, diagnose, and rate delirium. J Pain Symptom Manage 1995; 10: 35-77.

Tombaugh T N, McIntyre N J. The mini-mental state examination: a comprehensive review. J Am Geriatr Soc 1992; 40: 922-35.

Trzepacz P T. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. Semin Clin Neuropsychiatry 2000; 5: 132-48.

Tune L E, Egeli S. Acetylcholine and delirium. Dement Geriatr Cogn Disord 1999; 10: 342-4.

Urwin S C, Parker M J, Griffiths R. General versus regional anaesthesia for hip fracture surgery: a meta-analysis of randomized trials. Br J Anaesth 2000; 84: 450-5.

Zakriya K J, Christmas C, Wenz J F, Sr, et al. Preoperative factors associated with postoperative change in confusion assessment method score in hip fracture patients. Anesth Analg 2002; 94: 1628-32.