

Relationship Between Pain and Opioid Analgesics on the Development of Delirium Following Hip Fracture

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Background. Delirium and pain are common following hip fracture. Untreated pain has been shown to increase the risk of delirium in older adults undergoing elective surgery. This study was performed to examine the relationship among pain, analgesics, and other factors on delirium in hip fracture patients.

Methods. We conducted a prospective cohort study at four New York hospitals that enrolled 541 patients with hip fracture and without delirium. Delirium was identified prospectively by patient interview supplemented by medical record review. Multiple logistic regression was used to identify risk factors.

Results. Eighty-seven of 541 patients (16%) became delirious. Among all subjects, risk factors for delirium were cognitive impairment (relative risk, or RR, 3.6; 95% confidence interval, or CI, 1.8–7.2), abnormal blood pressure (RR 2.3, 95% CI 1.2–4.7), and heart failure (RR 2.9, 95% CI 1.6–5.3). Patients who received less than 10 mg of parenteral morphine sulfate equivalents per day were more likely to develop delirium than patients who received more analgesia (RR 5.4, 95% CI 2.4–12.3). Patients who received meperidine were at increased risk of developing delirium as compared with patients who received other opioid analgesics (RR 2.4, 95% CI 1.3–4.5). In cognitively intact patients, severe pain significantly increased the risk of delirium (RR 9.0, 95% CI 1.8–45.2).

Conclusions. Using admission data, clinicians can identify patients at high risk for delirium following hip fracture. Avoiding opioids or using very low doses of opioids increased the risk of delirium. Cognitively intact patients with undertreated pain were nine times more likely to develop delirium than patients whose pain was adequately treated. Undertreated pain and inadequate analgesia appear to be risk factors for delirium in frail older adults.

DELIRIUM is the most frequent medical complication observed in the 350,000 Americans hospitalized annually with hip fracture (1). The prevalence of delirium following hip fracture ranges from 13% to 61% (2–5), and delirium has been associated with delayed recovery, increased mortality, and poorer physical, cognitive, and affective function 6 months postfracture (2–4,6).

Although risk factors for the development of delirium have been well described in the medically ill and patients undergoing elective noncardiac surgery (7–9), extrapolating the results of these studies and applying previously developed prediction rules to hip fracture patients is problematic. Hip fracture patients are typically older, have poorer baseline functional status, more comorbid medical conditions, and a higher prevalence of dementia than patients previously studied. Indeed, recent data suggest that delirium following hip fracture results from different causes and follows a different clinical course than other delirium syndromes (10). Hip fracture also is associated with considerable pain (11), and undertreated pain has been demonstrated to be an independent risk factor for delirium in healthy older adults undergoing elective surgery (12,13).

This study was performed to examine the relationship among pain, opioid analgesic prescribing, and other risk factors on the development of delirium in frail older adults with hip fracture.

METHODS

Study Cohort

We reviewed daily admissions to four New York City metropolitan hospitals for patients admitted with intertrochanteric or femoral neck fracture and without evidence of delirium from July 1997 to August 1998. Of 620 eligible subjects, 571 (87%) consented to participate, and 541 of these subjects (94%) did not have delirium at admission and were enrolled.

Diagnosis and Detection of Delirium

Within 48 hours of admission, a research nurse interviewed all subjects by using the Confusion Assessment Method (CAM)—a standardized algorithm for the detection of delirium (14). Subjects who were found to be delirious by the CAM at the initial interview were excluded. Subjects were assessed with the CAM on a daily basis, 5 days a week (Monday–Friday) until discharge. Additionally, the research assistant reviewed the medical records daily and spoke to hospital staff to supplement the CAM observations. The medical record was reviewed for the key words “delirious/delirium,” “agitated/agitation,” “changed/altered mental status,” or “new/increased/more confused/confusion” for patients without a diagnosis of dementia and for the key words

“delirious/delirium,” “changed/alterd mental status,” or “new confusion” for patients with a history of dementia. These criteria were used because the fluctuating nature of delirium limits the sensitivity of once-daily interviews and because subjects were not interviewed on weekends. Delirium was considered to be present if either the CAM or chart criteria were met. The use of these chart criteria in combination with the CAM to diagnose delirium has been previously validated (7). Patients were not assessed postoperatively on the day of surgery because of the difficulty of distinguishing true delirium from residual effects of anesthesia (7). Although subjects were not interviewed on weekends, patients who developed delirium over the weekend would not have been expected to clear their delirium by Monday, given the reported duration of delirium (3).

Collection of Delirium Risk Factors

Risk factors were collected from medical records, patient or proxy interviews, nursing staff interviews, and patient observation. Selection of risk factors was based on previous studies of delirium (2,7–9,13) and on clinical relevance and experience. Risk factors were grouped into nine variable sets: patient demographic or background characteristics, cognitive status, functional status, biomedical factors, abnormal laboratory or clinical findings on admission, medical complications, nonoperative process variables, operative process variables, and pain-related variables (Table 1). For the cognitive status variable, patients were classified as cognitively intact if they had no diagnosis of memory impairment or a dementing illness and were able to give correct answers to a four-item screen that contained questions about their orientation (place and time), circumstances of their fracture (place, time, and circumstances of their fracture), immediate recall of the nature and purpose of the research study, and recall of the name or position of the person administering the informed consent. Patients were classified as cognitively impaired if they had a diagnosis or history of memory impairment or a dementing illness or if they made one or more errors in answering the four-item screen.

Functional status was determined by using the motor component of the Functional Independence Measure (FIM-Motor). The FIM-Motor includes 13 items—eating, grooming, bathing, dressing (both upper body and lower body), toileting, bladder and bowel control, bed to chair transfer, toilet transfer, tub to shower transfer, walking, and climbing stairs (15–17). Scores on the FIM-Motor range from 13 (dependent in all items) to 91 (completely independent in all items). Biomedical factors included a modification of the RAND comorbidity score, the Acute Physiology, Age, and Chronic Health Evaluation (APACHE II) score without the Glasgow coma score, a history of weight loss, and type of fracture. Eleven criteria that assessed abnormal clinical and laboratory findings on hospital admission were derived from previous research in delirium (Table 1). Major medical complications were defined as events that pose a threat to life or bodily function and that are typically treated with parenteral medications, a procedure, or intensive monitoring (venothromboembolic events, infection, cardiopulmonary

events, surgical complications, hemorrhagic complications, or miscellaneous). We counted a complication as a risk factor if it occurred before the episode of delirium or through postoperative Day 3 for nondelirious subjects.

Nonoperative process variables included time spent in the emergency department, time spent without oral intake (NPO), and sedative or hypnotic medication use. Days spent NPO were counted as a risk factor if they occurred before the episode of delirium or through postoperative Day 3 for nondelirious subjects or hospital Day 5 for nondelirious subjects who received nonoperative management. The operative process variables included surgery more than 24 hours after admission, surgical repair technique, type of anesthesia, and duration of anesthesia.

We collected data on pain and opioid analgesic intake in morphine sulfate equivalents through postoperative Day 3.

Patients were interviewed on a daily basis and asked to report the average amount of pain that they experienced at rest over the previous 24-hour period on a 1 (no pain) to 5 (very severe) scale. As patients were not interviewed over the weekend, patients interviewed on Monday were asked to rate their average pain at rest over the preceding 48 hours on the same 1–5 scale. Pain was included as a risk factor if the subject had a pain at rest score of 4 or 5 (severe to very severe pain) within 48 hours before the episode of delirium or through postoperative Day 3 for nondelirious subjects.

We calculated the total daily opioid dose in parenteral morphine sulfate equivalents for the 24 hours preceding the delirious episode and the highest 24-hour cumulative opioid dose for the first 3 postoperative days for nondelirious subjects. Doses of all opioids (including continuous infusions and patient-controlled analgesia) were converted into parenteral morphine sulfate equivalents by using the AHCPR equianalgesic dosing guidelines (18). As meperidine has been associated with an increased risk of delirium in previous studies, we also examined whether the use of meperidine increased the risk of delirium (19). Meperidine was considered a risk factor if it was administered within 24 hours of a delirious episode or at any time during postoperative Days 1–3 for nondelirious subjects. Finally, we created a dichotomous variable to indicate whether opioid administration increased immediately following an episode of severe pain prior to a delirious episode or at any time during the first 3 postoperative days for nondelirious subjects. This variable was included in an effort to determine whether it was pain or an increase in the analgesic dose in response to pain that was associated with delirium.

Statistical Analysis

Risk factors known prior to surgery.—Logistic regression was used to identify risk factors for delirium. The first model examined the effects of risk factors that are known to the medical team at hospital admission. All variables with $p < .15$ in univariate comparisons were entered into the model. However, if a variable set from Table 1 (e.g., biomedical factors) did not contain a variable that was significantly associated with delirium, one or more representative variables from the missing set(s) were entered on

Table 1. Risk Factors for the Development of Delirium Following Admission for Hip Fracture ($N = 541$)

Risk Factor	No. (%)	No. with Delirium (%)	Delirium p Value
Patient characteristics			
Age (y)			.02
<70	49 (9)	4 (8)	
70–79	141 (26)	15 (11)	
80+	351 (65)	68 (19)	
Sex			.11
Male	99 (18)	21 (21)	
Female	442 (82)	65 (15)	
Residence			.08
Nursing home resident	64 (12)	15 (23)	
Lives at home	477 (88)	71 (15)	
Delay to hospital presentation			.15
≥6 h from fracture to hosp.	306 (60)	56 (18)	
<6 h from fracture to hosp.	207 (40)	28 (14)	
Cognitive status			<.001
Cognition intact	244 (45)	14 (6)	
Cognition impaired	297 (55)	72 (24)	
Functional status			.001
FIM score 13–67	171 (32)	40 (23)	
FIM score 68–88	174 (32)	30 (17)	
FIM score 89–91	196 (36)	17 (9)	
Biomedical factors			
APACHE w/out Glasgow coma score 0–1	155 (29)	26 (17)	.52
APACHE w/out Glasgow coma score 2–3	125 (23)	16 (13)	
APACHE w/out Glasgow coma score 4–12	261 (48)	45 (17)	
Modified RAND score 0–1	163 (30)	15 (9)	.01
Modified RAND score 2–3	152 (28)	27 (18)	
Modified RAND score 4–12	226 (42)	45 (20)	
Type of fracture			.17
Intertrochanteric	273 (51)	49 (18)	
Femoral neck	268 (49)	38 (14)	
Weight loss			.17
History of recent loss	399 (76)	60 (15)	
No weight loss	129 (24)	26 (20)	
Abnormal clinical and laboratory findings			
Abnormal BP	93 (17)	20 (20)	.12
Normal BP	448 (83)	67 (15)	
Abnormal heart rhythm	23 (4)	8 (35)	.01
Normal heart rhythm	518 (96)	79 (15)	
Substernal chest pain	12 (2)	6 (50)	.001
No chest pain	529 (98)	81 (15)	
Heart failure	108 (20)	31 (29)	<.001
No heart failure	433 (80)	56 (13)	
Respiratory compromise	52 (10)	7 (13)	.59
Normal resp. status	489 (90)	80 (16)	
Coagulation disorder	41 (8)	7 (17)	.86
Normal coagulation	500 (92)	80 (16)	
Electrolyte abnormality	49 (9)	9 (18)	.64
Normal electrolytes	492 (91)	78 (16)	
Hyperglycemia	1 (0.2)	1 (100)	.02
Normal glucose	540 (99)	86 (16)	
Fluid imbalance	41 (8)	8 (20)	.53
Normal fluid status	500 (92)	79 (16)	
Anemia	4 (1)	0 (0)	.38
Normal blood count	537 (99)	87 (16)	
Fever/pneumonia	40 (7)	7 (18)	.80
No evidence of active infection	501 (93)	80 (16)	
Medical complications			
None	61 (11)	10 (16)	.94
1 or more	480 (89)	77 (16)	

Table 1. Risk Factors for the Development of Delirium Following Admission for Hip Fracture ($N = 541$) (Continued)

Risk Factor	No. (%)	No. with Delirium (%)	Delirium p Value
Nonoperative process measures			
Time in emergency department			.47
>12 h in the department	27 (5)	3 (11)	
≤12 h in the department	514 (95)	84 (16)	
Time spend NPO			.65
>24 h	79 (15)	14 (18)	
≤24 h	458 (85)	72 (16)	
Operative process measures*			
Surgical delay			.16
>24 h delay until surgery	388 (70)	65 (17)	
Surgery ≤24 h	166 (30)	21 (13)	
Type of anesthesia			.35
Regional	304 (58)	54 (18)	
General	219 (42)	32 (15)	
Duration of anesthesia			.38
>3 h	81 (15)	16 (20)	
≤3 h	442 (85)	70 (16)	
Surgical repair			.28
Pin/plate	167 (31)	34 (20)	
Complete/hemiarthroplasty	357 (66)	52 (15)	
Nonoperative management	16 (3)	1 (6)	
Pain-related variables			
Total opioid dose/d (parenteral morphine sulfate equivalents/d)			<.001
<10 mg	204 (38)	56 (28)	
10–30 mg	192 (36)	21 (11)	
>30 mg	145 (27)	10 (7)	
Received meperidine	129 (23)	27 (21)	.04
Pattern of opioid use in cognitively intact patients			.21
Increase in dose w/in 48 h prior to delirium	134 (55)	4 (4)	
No increase or decrease in dose w/in 48 h prior to delirium	108 (45)	10 (7)	
Self-reported pain for cognitively intact patients			.01
Severe pain at rest	51 (21)	6 (12)	
None to moderate pain	187 (79)	5 (3)	

Notes: FIM = Functional Independence Measure; APACHE = Acute Physiology, Age, and Chronic Health Evaluation; BP = blood pressure; NPO = without oral intake. Abnormal clinical and laboratory findings included the following: abnormal BP (systolic BP >180, diastolic BP >110, or systolic BP ≤90); abnormal heart rhythm (electrocardiogram that included atrial fibrillation, a supraventricular tachycardia, ventricular tachycardia, third-degree heart block, or sinus rhythm with a rate >130 or <50); heart failure (chest radiograph finding of congestive heart failure such as interstitial edema or pleural effusion or a normal chest radiograph in the setting of dyspnea, an abnormal lung exam, and the presence of an S3); respiratory compromise (arterial blood gas findings of a $p\text{CO}_2$ >46 mmHg, a $p\text{O}_2$ <60 mmHg, or oxygen saturation <90%); coagulation disorder (INR >1.4); electrolyte abnormality (serum sodium <126 or >155, serum potassium <2.5 or >5.6, or serum bicarbonate <18 or >35); hyperglycemia (serum glucose >450); fluid imbalance (serum blood urea nitrogen >40 or serum creatinine >2.1 in the absence of dialysis-dependent renal disease); anemia (hemoglobin <8); fever or pneumonia (temperature >38.5°C, physical exam findings of pneumonia, or infiltrate on chest radiograph).

*Relationship is for delirium developing after surgery.

the basis of clinical relevance. The amount of missing data from patients with a diagnosis of dementia who could not self-report their pain (over 30% of subjects) precluded the pain variable being entered into the overall model.

Table 2. Independent Risk Factors for the Development of Delirium Following Admission for Hip Fracture That Were Included in the Multiple Logistic Regression Model ($N = 541$)

Risk Factor	Adjusted RR (95% CI)	p Value
Age (y)	1.0 (0.97–1.0)	.8
Women	0.6 (0.3–1.1)	.08
Residence in a nursing home	1.3 (0.6–2.8)	.5
Cognitive impairment	3.6 (1.8–7.2)	<.001
FIM score 68–88*	1.0 (0.5–1.9)	.98
FIM score 89–91	.7 (0.3–1.5)	.4
RAND score 2–3†	1.2 (0.6–2.3)‡	.5
RAND score 4–15†	1.1 (0.6–2.4)‡	.7
Abnormal BP on admission	2.3 (1.2–4.7)	.01
Abnormal heart rhythm on admission	1.7 (0.6–4.9)	.3
Chest pain on admission	1.9 (0.5–8.2)	.4
Heart failure on admission	2.9 (1.6–5.3)	.001
Medical complication	0.6 (0.2–1.4)	.2
Parenteral morphine sulfate equivalents/d‡		
10–30 mg	1.4 (0.6–3.3)	.4
<10 mg	5.4 (2.4–12.3)	<.001
Received meperidine	2.4 (1.3–4.5)	.004

Notes: RR = relative risk (for postadmission delirium); CI = confidence interval; FIM = Functional Independence Measure; BP = blood pressure.

*Reference is a FIM score of 13–67.

†Reference is RAND < 2.

‡Reference is >30 mg of parenteral morphine sulfate equivalents/d.

Risk factors known at the time of surgery.—A second regression model examined the association of risk factors on postoperative delirium. The postoperative model was created by entering the operative and postoperative process variables that were associated with the development of delirium following surgery at a significance level of $p < .15$ into the regression equation, along with the variables previously included in the postadmission delirium model just described.

Delirium in cognitively intact patients and cognitively impaired and dementia patients.—As patients with cognitive impairment were at increased risk of developing delirium as compared with cognitively intact patients, and because pain was not reliably reported in cognitively impaired patients, we performed separate analyses examining risk factors for the development of delirium in (a) cognitively intact and (b) cognitively impaired patients. Model development proceeded as just described. We included the pain self-report variables in models for the cognitively intact patients.

Goodness of fit was assessed for all models by using the area under the receiver operating characteristic (ROC) curve and the Hosmer–Lemeshow statistic (20). Analyses were performed by using STATA (College Station, TX).

RESULTS

Table 1 lists patient characteristics. Eighty-seven of 539 patients (16%) developed delirium after admission, and 71 of 525 patients (14%) who were not delirious at the time of surgery developed delirium postoperatively. Only 12 of 87 delirious subjects (14%) developed delirium after postoperative Day 3. Fourteen of 242 cognitively intact subjects (6%) developed delirium, compared with 72 of 297 patients with cognitive impairment (24%; $p < .001$). Patients

without a formal diagnosis of dementia who could not successfully complete the cognitive screen had a similar incidence of delirium to those patients with a formal diagnosis of dementia (23% vs 26%; $p = .6$). Very few patients received sedatives or hypnotics.

Risk Factors for Delirium for All Patients

Table 1 lists univariate associations for the possible risk factors for delirium following hospital admission. Table 2 lists the multiple logistic regression analysis results. Independent predictors of new delirium following hospital admission were as follows: evidence of cognitive impairment (relative risk, or RR, 3.6; 95% confidence interval, or CI, 1.8–7.2), abnormal blood pressure on admission (RR 2.3, 95% CI 1.2–4.7), heart failure on admission (RR 2.9, 95% CI 1.6–5.3), meperidine use (RR 2.4, 95% CI 1.3–4.5), and receiving very low doses of opioid analgesia (RR 5.4, 95% CI 2.4–12.3) for patients receiving <10 mg of parenteral morphine sulfate equivalents per day and RR 1.4, 95% CI 0.6–3.3 for patients receiving 10–30 mg of parenteral morphine sulfate equivalents per day compared with patients receiving <30 mg of morphine sulfate equivalents). Among all subjects, independent predictors of postoperative delirium were identical to those for postadmission delirium, and no operative process variables were independently associated with delirium. Too few patients received benzodiazepines or other sedatives or hypnotics for meaningful analyses to be performed. The area under the ROC curve for the post-admission delirium model was 0.80.

Risk Factors for Delirium for Cognitively Intact and Cognitively Impaired Patients

In cognitively intact subjects, independent predictors of delirium included the presence of an episode of severe pain at rest (RR 9.0, 95% CI 1.8–45.2), functional impairment (RR 0.05, 95% CI 0.004–0.7–100 for FIM scores of 68–88 and RR 0.2, 95% CI 0.02–1.3 for FIM scores of 89–91 compared with FIM scores under 68), and receiving very low doses of opioid analgesia (RR 25.2, 95% CI 1.3–493.3 for patients receiving <10 mg of parenteral morphine sulfate equivalents per day and RR 4.4, 95% CI 0.3–68.6 for patients receiving 10–30 mg of parenteral morphine sulfate equivalents per day compared with patients receiving <30 mg of morphine sulfate equivalents) (Table 3). For cognitively impaired patients, independent predictors of delirium included female sex (RR 2.8, 95% CI 1.4–6), abnormal blood pressure on admission (RR 2.3, 95% CI 1.1–5.0), heart failure on admission (RR 2.4, 95% CI 1.2–5.0), meperidine use (RR 3.4, 95% CI 1.6–6.9), and receiving very low doses of opioid analgesia (RR 4.0, 95% CI 1.6–10.2 for patients receiving <10 mg of parenteral morphine sulfate equivalents per day and RR 1.1, 95% CI 0.4–2.7 for patients receiving 10–30 mg of parenteral morphine sulfate equivalents per day compared with patients receiving <30 mg of morphine sulfate equivalents) (Table 4). The areas under the ROCs curves were 0.92 for the cognitively intact model and 0.77 for the cognitively impaired model.

Table 3. Independent Risk Factors for Delirium Following Admission for Hip Fracture That Were Included in the Multiple Logistic Regression Models for Cognitively Intact Patients (N = 242)

Risk Factor	Adjusted RR (95% CI)	p Value
Age (y)	1.1 (0.97–1.2)	.2
FIM score 68–88*	0.05 (0.004–0.7)	.02
FIM score 89–91*	0.2 (0.02–1.3)	.08
RAND score 2–3†	5.9 (0.9–40.3)	.07
RAND score 4–15‡	1.8 (0.2–19.3)	.6
Heart failure on admss.	3.1 (0.6–17.0)	.2
Severe pain prior to delirium	9.0 (1.8–45.2)	.01
Parenteral morphine sulfate equivalents/d‡		
10–30 mg	4.4 (0.3–68.6)†	.3
<10 mg	25.2 (1.3–493.3)†	.03
Received meperidine	2.6 (0.4–15.8)	.3
Increase in opioid dose after episode of severe pain	2.6 (0.5–18.1)	.2

Notes: RR = relative risk (for postadmission delirium); CI = confidence interval; FIM = Functional Independence Measure.

*Reference is a FIM score of 13–67.

†Reference is a RAND score < 2.

‡Reference is >30 mg of parenteral morphine sulfate equivalents/d.

Relationship Between Delirium Risk Factors and Analgesic Prescribing

To assess whether clinicians were reducing opioid doses in patients they perceived to be at greater risk for delirium (and hence accounting for the observed relationship between opioid dosing and risk of delirium), we compared the mean daily dose of opioid administered to patients at increased risk of delirium (i.e., those having one or more significant delirium risk factors as determined by the multivariate analyses) with that administered to patients at low risk of delirium (i.e., those having no significant delirium risk factors) for all patients, cognitively intact patients, and cognitively impaired patients. Patients with one or more delirium risk factors received an average of 10.0 mg of morphine sulfate equivalents, whereas patients with no delirium risk factors received 11.2 mg of morphine sulfate equivalents ($p = .4$). Cognitively intact patients with one or more delirium risk factors received an average of 16.8 mg of morphine sulfate equivalents, whereas patients with no delirium risk factors received 11.2 mg of morphine sulfate equivalents ($p = .93$). Cognitively impaired patients with one or more delirium risk factors received an average of 6.5 mg of morphine sulfate equivalents, whereas patients with no delirium risk factors received 9.0 mg of morphine sulfate equivalents ($p = .3$).

DISCUSSION

Delirium is the most common complication observed following hip fracture. Understanding risk factors that predispose hip fracture patients to delirium is important, given the projected increase in the incidence of this disease (21) and because of the association of delirium with poorer functional outcomes following hip fracture (2–5). Our data suggest that patients at increased risk for delirium can be identified at hospital admission by using readily available variables and that undertreated perioperative pain signifi-

Table 4. Independent Risk Factors for Delirium Following Admission for Hip Fracture That Were Included in the Multiple Logistic Regression Models for Cognitively Impaired Patients (N = 297)

Risk Factor	Adjusted RR (95% CI)	p Value
Women	2.8 (1.4–6.0)	.01
>6 h delay to emergency department presentation	0.8 (0.4–1.6)	.6
Femoral neck fracture	1.9 (1.1–3.6)	.03
Medical complication	0.5 (0.2–1.4)	.2
FIM score 68–88*	1.1 (0.6–2.3)	.7
FIM score 89–91*	0.6 (0.2–1.5)	.3
RAND score 2–3†	0.9 (0.4–1.9)	.8
RAND score 4–15‡	0.8 (0.4–1.8)	.6
Abnormal BP on admss.	2.3 (1.1–5.0)	.03
Congestive heart failure on admss.	2.4 (1.2–5.0)	.02
Chest pain present on admss.	3.1 (0.6–15.7)	.13
Parenteral morphine sulfate equivalents/d‡		
10–30 mg	1.1 (0.4–2.7)	.9
<10 mg	4.0 (1.6–10.2)	.004
Received meperidine	3.4 (1.6–6.9)	.001

Notes: RR = relative risk (for postadmission delirium); CI = confidence interval; FIM = Functional Independence Measure; BP = blood pressure.

*Reference is a FIM score of 13–67.

†Reference is a RAND score < 2.

‡Reference is >30 mg of parenteral morphine sulfate equivalents/d.

cantly increases the risk of developing delirium in frail older adults.

Data from this study suggest that undertreated pain is a significant contributor to the development of delirium. Furthermore, our data demonstrate that opioids, with the exception of meperidine, do not precipitate delirium in patients with acute pain and that avoiding opioids or administering very low doses of opioids is associated with an increased risk of delirium. A major barrier to the treatment of pain in older adults has been the fear that opioids cause delirium. In the subgroup of cognitively intact adults in this study, severe pain was associated with a ninefold risk of developing delirium. Receiving no opioid analgesia or a very low dose of an opioid increased the risk of developing delirium for both cognitively intact and cognitively impaired patients. Our data also confirm previous findings that meperidine is associated with an increased risk of delirium (19)—perhaps because of the action of its neuroexcitatory metabolite normeperidine—and thus should not be administered to geriatric patients. Doses of meperidine were significantly higher than those of other opioids, providing evidence that the association of delirium with meperidine was not the result of meperidine being administered at lower equivalent doses as compared with other analgesics.

Although it is possible that clinicians may have identified patients at increased risk of delirium and thus altered their analgesic prescribing practices (i.e., administering lower doses of analgesia to patients at high risk of delirium), we believe that this is unlikely. We found no evidence that doses of opioids were reduced in the immediate 48 hours preceding an episode of delirium, and we did not observe significant differences in opioid prescribing between patients with and without other delirium risk factors. Studies in relatively healthy older adults undergoing elective surgery have revealed similar findings with respect to the

relationship between pain and delirium, further supporting our data (12,13).

Although this study cannot determine whether improved pain management will reduce the incidence and duration of delirium, it provides evidence to support future studies of intensive pain management in older adults. Two studies employing geriatric consultation, targeting known delirium risk factors, and providing recommendations for pain management have recently demonstrated reductions in the incidence (22) and duration of delirium (23) following hip fracture. However, the studies could not distinguish the independent effect of enhanced analgesia on the prevention of delirium, and compliance with the analgesic recommendations was poor.

This study has limitations. We observed patients for 5 days of every week the patient was hospitalized, and subjects were observed once per day; as a result, some episodes of delirium might have been missed. Nevertheless, we supplemented our observations with chart notations that were previously shown to be relatively sensitive and with specific markers for delirium (7), and, given the duration of delirium observed in this cohort and other studies (10,24), it is unlikely that we missed a substantial number of cases. We were unable to include pain as a variable in our overall or subanalysis of cognitively impaired patients because of missing data in dementia patients unable to self-report their pain. Thus, we do not know whether untreated pain is a risk factor for delirium in the cognitively impaired.

The findings from this study both extend previous research on delirium and provide new insights into this complicated medical syndrome in hip fracture patients. This study suggests that hip fracture patients at increased risk for delirium can be identified at admission on the basis of a limited number of variables and that untreated pain and underuse of opioid analgesics are important contributors to its development. Our data will help guide studies of interventions aimed at improving pain management and preventing the development of delirium in high-risk patients hospitalized with hip fracture.

ACKNOWLEDGMENTS

This project was supported by Grant U18HS09459-0 from the Agency for Healthcare Research and Quality. Dr. Morrison is a Paul Beeson Faculty Scholar in Aging Research, an Open Society Institute Project on Death in America Faculty Scholar, and the recipient of Mentored Clinical Scientist Development Award K08AG00833-01 from the National Institute on Aging. Dr. Siu is the recipient of a Midcareer Investigator Award in patient-oriented research from the National Institute on Aging.

We gratefully acknowledge the invaluable assistance of our project manager, Stacey Silberzweig, and of our research assistants, Camille Cohen, Linda Dutcher, and Sameh Samy.

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REFERENCES

1. Agency for Health Care Policy and Research. *Hospital Inpatient Statistics 1996*. Washington, DC: US Dept of Health and Human Services; 1999. AHCPR publication 99-0034.

2. Edlund A, Lundstrom M, Lundstrom G, Hedqvist B, Gustafson Y. Clinical profile of delirium in patients treated for femoral neck fractures. *Dement Geriatr Cogn Disord*. 1999;10:325-329.
3. Marcantonio ER, Flacker JM, Michaels M, Resnick NM. Delirium is independently associated with poor functional recovery after hip fracture. *J Am Geriatr Soc*. 2000;48:618-624.
4. Dolan MM, Hawkes WG, Zimmerman SI, et al. Delirium on hospital admission in aged hip fracture patients: prediction of mortality and 2-year functional outcomes. *J Gerontol Med Sci*. 2000;55A:M527-M534.
5. Gustafson Y, Berggren D, Brannstrom B, et al. Acute confusional states in elderly patients treated for femoral neck fracture. *J Am Geriatr Soc*. 1988;36:525-530.
6. Rockwood K. Delays in the discharge of elderly patients. *J Clin Epidemiol*. 1990;43:971-975.
7. Marcantonio E, Goldman L, Mangione C, et al. A clinical prediction rule for delirium after elective noncardiac surgery. *JAMA*. 1994;271:134-139.
8. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;275:852-857.
9. Inouye S, Viscoli C, Horwitz R, Hurst L, Tinetti M. A predictive model for delirium in hospitalized elderly medical patients based on admission characteristics. *Ann Intern Med*. 1993;119:474-481.
10. Brauer C, Morrison RS, Silberzweig SB, Siu AL. The cause of delirium in patients with hip fracture. *Arch Intern Med*. 2000;160:1856-1860.
11. Morrison RS, Siu AL. A comparison of pain and its treatment in advanced dementia and cognitively intact patients with hip fracture. *J Pain Sympt Manage*. 2000;19:240-248.
12. Duggleby W, Lander J. Cognitive status and postoperative pain: older adults. *J Pain Sympt Manage*. 1994;9:19-27.
13. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg*. 1998;86:781-785.
14. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. *Ann Intern Med*. 1990;113:941-948.
15. Hamilton BB, Laughlin JA, Granger CV, Kayton RM. Interrater agreement of the seven-level functional independence measure (FIM). *Arch Phys Med Rehabil*. 1991;72:790.
16. Dodds T, Martin D, Stolov W, Deyo R. A validation of the functional independence measure and its performance among rehabilitation inpatients. *Arch Phys Med Rehabil*. 1993;74:531-536.
17. Mauthe R, Haaf D, Hayn P, Krall J. Predicting discharge destination of stroke patients using a mathematical model based on six items from the functional independence measure. *Arch Phys Med Rehabil*. 1996;77:10-13.
18. Agency for Health Care Policy and Research. Management of cancer pain: adults. Cancer Pain Guideline Panel. Agency for Health Care Policy and Research. *Am Fam Physician*. 1994;49:1853-1868.
19. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272:1518-1522.
20. Hosmer D, Lemeshow S. *Applied Logistic Regression*. New York: Wiley; 1989.
21. Barrett-Connor E. The economic and human cost of osteoporotic fracture. *Am J Med*. 1995;98:3S-8S.
22. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49:516-522.
23. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc*. 2001;49:523-532.
24. Levkoff S, Evans D, Liptzin B, et al. Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. *Arch Intern Med*. 1992;152:334-340.

Received July 23, 2002

Accepted August 8, 2002