Original article

Delirium Risk Factors in Elderly Patients Suffering from Femoral Neck Fractures

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SUMMARY

Delirium is a common complication in hospitalized elderly patients suffering from hip fractures. Considering the growing incidence of delirium, understanding the risk factors for this condition is of great importance. The preoperative prevalence of delirium is approximately 4.4–35.6%, while postoperative prevalence is even higher - 4–53.3%. Various studies have shown the multifactorial etiology of delirium arising from a combination of predisposing and precipitating factors.

The aim of this study was to explore these factors, which can contribute to delirium in patients with femoral neck fractures. This case control study included 62 patients diagnosed with femoral neck fractures, with 31 cases and 31 controls. Results have shown that the use of sedatives, especially benzodiazepines, and smoking increase the risk of delirium by five and sixteen times, respectively.

Key words: hip fracture, delirium, risk factors

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INTRODUCTION

Delirium is a very common medical complication among hospitalized elderly patients, covering approximately 30% of this population (1). It is defined as a neuropsychiatric syndrome characterized by reduced ability to focus and maintain attention, the occurrence of some cognitive changes such as memory loss, disorientation, slurred speech, and the development of perceptual disturbance (DSM- IV) (2). Delirium has an acute onset and fluctuating course. Recent studies have reported a prevalence of 10-31% on hospital admission and an incidence of 3-29% during hospitalization (3). Both prevalence and incidence are somewhat higher among surgical patients, especially in patients undergoing cardiothoracic surgery, urgent orthopedic procedures and cataract surgery, and in intensive care unit patients. The preoperative prevalence of delirium in patients with hip fractures is 4.4–35.6%, while postoperative incidence is somewhat higher, ranging from 4 to 53.3% (4, 5). Elderly patients with delirium have a higher risk of mortality after hip fracture (6-8). Considering the growing incidence of delirium, understanding the risk factors for this condition is of great importance (9). As delirium is very common in patients suffering from hip fracture and as it is associated with multiple adverse outcomes, further research is essential in reducing its incidence (3, 10, 11). To this end, some risk factors can be prevented and properly managed.

PATIENTS AND METHODS

This retrospective, clinical, observational case control study was conducted at the Department of Orthopedics, General Hospital Užice, from April 2014 to December 2014. The study population comprised patients potentially diagnosed with hip fracture who were hospitalized at the department and examined by a consultant psychiatrist because they developed cognitive impairment and exhibited perceptual disturbances during hospitalization. Patient inclusion criteria for the study were hip fracture and delirium, as diagnosed by a psychiatrist (for cases). Patient exclusion criteria included psychosis, major depression, bipolar disorder, psycho - organic syndrome or dementia on hospital admission, as well as cognitive deficit with no specific diagnosis made on admission. The study population initially included patients with delirium diagnosed by a psychiatrist right after hospital admission, in the period from April 2014 to December 2014. During the study period, a total of 43 patients were diagnosed with delirium. Twelve patients were excluded from the study. The control group consisted of patients without delirium admitted to the Orthopedics Department during the study period. Study data were collected from patients' medical records. Data from nursing admission charts included patient demographic data (age, gender), mental state on admission, symptoms of pain, visual and hearing impairments, previous habits (smoking and alcohol consumption), comorbidities (cardiovascular diseases, previous psychiatric diseases, diabetes mellitus), cognitive deficit, patient's drug compliance, psychiatric report, laboratory test results, operative and anesthesiology reports, type of anesthesia, therapy administered during and before hospitalization, and clinical outcome. Twelve non-eligible patients with confirmed diagnoses other than hip fracture were excluded from the study population (43 patients). During the same study period, 31 controls without delirium were obtained from the database of the Orthopedics Department. Cases and controls were matched by age and gender. Standard descriptive statistics was used for all continuous variables, described as means and standard deviations. Categorical variables were presented as percentages. T-test for independent samples compared continuous variables between two groups (with and without delirium), and the Chi-square test was used for assessing the significance of difference in categorical variables between the two study groups. Associations between delirium and erythrocytes, haemoglobin, senility, former benzodiazepine use, smoking and age were analyzed using a logistic regression. The Backward Wals with Stepwise Deletion approach was used.

RESULTS

During the study period, a total of 125 patients diagnosed with hip fracture (dg. ICD - 10; S72.0; S72.1) were hospitalized at the Orthopedics Department. Of this number, thirty-one patients were examined by a psychiatrist as they had delirium symptoms (disorientation, agitation and hallucination) (n1). Delirium incidence was 25%. The mean age of patients with delirium was 81.8 ± 6.1 (45% were males and 55% females). In the group of patients without delirium (n2 = 31), mean age was 79.8 ± 5.8 (45% men and 55% women). The results on continuous variables are shown in Table 1. A statistically significant difference between groups was found for the levels of plasma erythrocytes (p - 0.019) and hemoglobin (p - 0.048).

Most patients had concomitant diseases, such as hypertension − 46 (62), cardiomyopathy 29 (62) and diabetes mellitus 9 (62). Frequency was similar in both groups of patients. Statistical significance between groups was also found in former benzodiazepine use (p - 0,019) and senility (p - 0,001) (Table 2).

Variables including erythrocytes, hemoglobin, senility, gender, former use of benzodiazepines and smoking were analyzed using the logistic regression model. Table 3 presents variables which greatly contribute to the incidence of delirium: erythrocyte level (OR = 0.18; 95% CI = 0.04 – 0.75), smoking (OR = 16.48; 95% CI = 1.43 – 189.82) and former use of benzodiazepines (OR = 5.13; 95% CI = 1.47 – 17.87). The occurrence of delirium was not correlated with gender, hemoglobin level, and senility.

DISCUSSION

Delirium has a multifactorial etiology, arising from a combination of predisposing and precipitating factors (12). The most common predisposing factors for delirium are age, male gender, dementia, depression, hearing and vision impairments, dehydration, malnutrition, polypharmacy (with psychoactive drugs), alcohol addiction, and comorbidities (13, 14). In the present study, the associated diseases (hearth insufficiency, hypertension and diabetes) did not lead to delirium, probably due to low statistical power.

The most common precipitating factors include comorbidities (e.g. infections), iatrogenic complications, metabolic disturbance, some neurological conditions (acute stroke), surgery, drugs (benzodiazepines, narcotic analgesics, drugs with anticholinergic activity) (15). Uncontrolled pain is an another potential precipitating factor (16). Side factors such as admission to the ICU, physical activity restriction, and bladder catheterization are additional precipitating factors (17). Various studies have shown the multifactorial background of delirium.

Apart from age, previous cognitive defects are the most frequently confirmed risk factors (18-21). The pathophysiology of delirium is still unknown, although there is some evidence indicating delirium as a condition of neurotransmission interruption, inflammation, and acute stress reaction (1).

Smoking is among variable risk factors for delirium. The explanation for the smoking effect lies in acute nicotine suspension following admission to hospital or ICU (22, 23). Studies have suggested that neurotransmitter secretion disorder is an underlying cause of delirium. This disorder is due to various factors such as systemic inflammatory response, acute stress reaction, metabolic disorders and psychoactive substance abuse (24). Another mechanism supposed to contribute to delirium is acetylcholine deficiency in the central nervous system (25). The relative deficiency of nicotine also plays an important role as chronic exposure to nicotine causes down-regulation and desensitization of nicotine acetylcholine brain receptors, leading to a withdrawal syndrome (26).

Nicotine withdrawal and delirium share some characteristics, such as confusion, agitation and irritability. Moreover, symptoms during nicotine withdrawal are most intense in the first week, and can last for 2-4 weeks, thus overlapping with the onset of delirium, which is diagnosed after hospital admission or a few days after surgery (27, 28). Some clinical trials have been conducted to investigate whether smoking is a risk factor for delirium.

Table 1. Results on continuous variables

Variable	Patients with delirium (n_1=31)	Patients without delirium (n_2=31)	p-value (*t* test)
Age (median ± SD)	81.8 ± 6.1	79.8 ± 5.8	0.204
Leukocytes (median ± SD)	9.7 ± 2.5	9.7 ± 2.8	0.942
Erythrocytes (median ± SD)	4.0 ± 0.4	4.3 ± 0.4	0.019
Hemoglobin (median ± SD)	117.1 ± 2.9	125.2 ± 2.9	0.048
Hematocrit (mediana ± SD)	36.5 ± 4.5	37.9 ± 4.3	0.217
Urea (median ± SD)	8.6 ± 3.8	8.6 ± 3.5	0.943
Creatinine (median ± SD)	78.3 ± 35.6	80.1± 31.7	0.837
Glycemia (median ± SD)	7.2 ± 3.0	7.3 ± 2.1	0.892
Sodium (median ± SD)	141.2 ± 5.7	135.2 ± 25.3	0.206
Potassium (median ± SD)	4.4 ± 0.5	4.1± 0.9	0.136
Hospital stay (median ± SD)	13.2 ± 5.3	13.2 ± 4.3	0.979

Table 2. Statistical difference between groups

Variable		Patients with delirium (%)	Patients without delirium (%)	*p*-value (Pearson Chi-Square test)
Gender	male	14 (45%)	14 (45%)	1.000
	female	17 (55%)	17 (55%)	
Fracture AGE! on admission day	first 24h	24 (78%)	27 (87%)	0.555
	24h-72h	6 (19%)	3 (10%)	
	more than 72h	1 (3%)	1 (3%)	
Pain	present	27 (87%)	27 (83%)	0.722
	not present	4 (13%)	3 (10%)	
Vision	normal	21 (68%)	21 (70%)	0.849
	defected	10 (32%)	9 (30%)	
Hearing	normal	21 (68%)	24 (80%)	0.425
	defected	10 (32%)	6 (20%)	
Smoking	no	24 (77%)	29 (97%)	0.065
	yes	7 (23%)	1 (3%)	
Alcohol consumption	yes	7 (22%)	3 (10%)	0.327
	no	24 (78%)	27 (90%)	
Admission state of awareness	no disorder	28 (90%)	29 (93%)	0.641
	disorder	3 (10%)	2 (7%)	
Senility	present	7 (22%)	2 (6%)	0.001
	not present	16 (52%)	29 (94%)	
	no data	8 (26%)	0 (0%)	
Cardiovascular diseases	none	6 (19%)	2 (6%)	0.320
	hypertension	6 (19%)	11 (36%)	
	hypertension and cardiomyopathy	15 (49%)	14 (45%)	
	other cardiovascular diseases	4 (13%)	4 (13%)	
Former use of benzodiazepines	yes	17 (55%)	7 (23%)	0.019
	no	14 (45%)	24 (77%)	
Previous minor psychiatric diseases	yes	6 (19%)	1 (3%)	0.108
	no	25 (81%)	30 (97%)	
Polypharmacy	no therapy	6 (19%)	1 (3%)	0.028
	< 3 drugs	11 (36%)	10 (32%)	
	3 - 5 drugs	1 (3%)	8 (26%)	
	> 5 drugs	13 (42%)	12 (39%)	
Operation	yes	28 (90%)	31 (100%)	0.237
	no	3 (10%)	0 (0%)	
Anesthesia	none	3 (10%)	0 (0%)	0.180
	regional spinal	20 (65%)	24 (77%)	
	general anaesthesia	8 (25%)	7 (23%)	
Outcome	recovered	10 (32%)	30 (97%)	0.000
	partly recovered	17 (55%)	0 (0%)	
	death	4 (13%)	1 (3%)	

Table 3: Variables highly contributing to delirium

Variable	unadjusted OR	95% CI	adjusted OR	95% CI
Erythrocyte level	0.25	0.0 7- 0.83	0.18	0.04 – 0.75
Smoking	8.45	0.97 – 73.63	16.48	1.43 – 189.82
Former use of benzodiazepines	4.16	1.38 – 12.50	5.13	1.47 - 17.87

Different results have been reported. In a meta-analysis, it was hypothesized that active smoking is an independent risk factor for delirium in hospitalized and intensive care unit patients (29). The analysis covered 14 cohort studies involving the study population of surgical and ICU patients. Delirium incidence was 9-52%, while the prevalence of active smoking was 9-44%. In one of six studies, smoking was an independent risk factor for delirium in patients undergoing coronary bypass surgery (OR = 4.19, 95% CI = 1.35–13.05; p = 0.019) (30). A recent study testing patients with knee or hip arthroplasty has found no significant effect of the presence of smoking on the onset of delirium (31). The results of the present study have shown that smoking is a significant risk factor (OR = 16.48, 95%CI = 1.43– 189.82), with wide confidence intervals.

Benzodiazepines affect delirium probably through their basic action mechanism. These drugs potentiate the inhibitory activity of GABA in the central nervous system, thus inducing slow-wave sleep disorders and, hence, nervous system depression and delirium.

In the literature, there are a few studies which have evaluated the correlation between benzodiazepine use and delirium (32-37). Significance was found in only four studies. In one of them, an increased risk of delirium was strongly correlated with the daily benzodiazepine dosage in the range of 1.83 – 14.75 mg (OR= 3.3, 95% CI = 1.31–8.04). (38). In the second study, results were similar (OR = 2.1, 95% CI = 1.26 – 3.53) (39). The findings of the third and fourth study have shown an increased risk associated with the use of long-acting and short-acting benzodiazepines. Results were as follows: OR = 2.6, 95% CI = 1.1–6.5 for long-acting drugs (37) in the third study, and OR = 0.53, 95% CI = 0.32–0.89 for short-acting drugs and OR = 0.12, 95% CI = 0.03–0.50 for long-acting benzodiazepines in the fourth study (36, 40). Given the abovementioned results, benzodiazepines are not recommended for patients who are at risk of delirium (40). The same results were obtained in this study (OR = 5.13, 95% CI = 1.47 -17.87).

Although less frequently confirmed, anemia is another risk factor for delirium (41). Accordion to WHO definition, anemia is considered when hemoglobin level is less than 130g/l for men and less than 120g/l for women (42). Hematocrit level can also be used to define anemia (39% for men and 36% for women) (43). In addition to causing delirium, anemia can lead to many other side effects, such as increased blood transfusion requirement, decreased physical activity, increased risk of infections, longer hospital stays, and increased mortality. The main reason for delirium risk is that anemia reduces the oxygenation of the central nervous system. The prevalence of anemia in patients with hip fracture is 50% (43). In critical condition and trauma patients, anemia is the result of two fundamental processes: shortening of the life span of erythrocytes in the circulation and reduced production of red blood cells. Causes of shortened erythrocyte life span are hemolysis, phlebotomy losses, leakage at the site of injury, invasive procedures, gastrointestinal bleeding. Reduction in erythrocyte synthesis occurs due to nutrient deficiencies and systemic inflammation. Systemic inflammation involves the secretion of various pro-inflammatory cytokines which reduce both erythropoietin production and the ability of erythroblasts to incorporate iron (42, 44, 45). Not many studies have dealt with the correlation between erythrocyte levels and delirium. The results of the present study have suggested that patients with delirium have significantly lower erythrocyte levels compared with patients without delirium (OR = 0.18, 95% CI = 0.04 – 0.75). Further research is needed to confirm the effect of low erythrocyte levels on delirium in patients with hip fracture.

CONCLUSION

This study has shown that the main risk factors for delirium in patients with hip fracture are smoking, former use of benzodiazepines, and low erythrocyte levels. Considering the high incidence of this complication in hospitalized patients and the multitude of risk factors, further investigation is needed in order to overcome the limitations of this study and provide the most valid data about delirium in this vulnerable population.

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Faktori rizika za nastanak delirijuma kod starih bolesnika sa prelomom vrata butne kosti

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SAŽETAK

Delirijum je veoma česta medicinska komplikacija kod starijih hospitalizovanih bolesnika. Posle preloma kuka je jedna od najčešćih, sa rastućom prevalencijom preoperativno 4,4%-35,6% i incidencijom postoperativno 4-53,3%. Različite studije su pokazale multifaktorijalnu prirodu delirijuma kao kombinaciju predisponirajućih i precipitirajućih faktora. Cilj studije bio je da istraži navedene faktore koji utiču na pojavu delirijuma kod bolesnika sa prelomom vrata butne kosti. Ova studija tipa slučaj/kontrola je uključila ukupno 62 bolesnika sa prelomom vrata butne kosti, od kojih je 31 razvio delirijum. Pokazalo se da prethodna upotreba benzodiazepina i pušenje povećavaju rizik od nastanka delirijuma za 5, odnosno 16 puta.

Ključne reči: **prelom kuka, delirijum, faktori rizika**