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Original article

Delirium risk factors analysis post proximal femur fracture surgery in elderly

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Abstract. *Background and aim:* The increase in the average-age and in the percentage of elderly people implies an exponential increase in fractures of the proximal femur. A common consequence of hip fracture in elderly patients is delirium, characterized by cognitive confusion or a lethargic-type condition. Predisposing factors have been identified, but risk factors assessment useful for managing clinical intervention, has not received unanimous consent. This work aims to identify the potential risk factors for delirium in the elderly operated for hip fracture. *Methods:* In this prospective observational study, we included 83 patients aged ≥65 years. Patients undergoing osteosynthesis of the femur and hip replacement for fractures were included. Patients already delusional in the pre-operative period were excluded. At the time, deadlines T0 (pre-operative), and T1,T3,T7 post-operative day, delirium, hematic parameters, blood transfusions, were assessed. *Results:* Level of delirium was assessed obtaining 80% not delusional and 20% delusional. Glycemia and hemoglobin were not found to be risk factors, although they are known to influence cognitive status; we hypothesize they should be considered predisposing factors. Comorbidities such as atrial fibrillation and Chronic Obstructive Pulmonary Disease were found associated with delirium. The most advanced age, anxiolytic drugs, the use of benzodiazepine as anaesthetic, the time surgical waiting, were found significantly associated with delirium. *Conclusions:* Taken together, findings of this prospective observational study showed that environmental and metabolic risk factors might contribute to make elderly susceptible to develop postoperative delirium following hip surgery. Thus, these patients should be adequately assessed and monitored. (www.actabiomedica.it)

Key words: delirium; femur; hip; fracture; cognitive status; hospitalization.

Introduction

One of the major health problems in elderly is represented by hip fracture, that represent an important orthopedic trauma able to increase morbidity and triggering mechanisms of functional decline. Because the average age and the prevalence of "older adults" (> 80 years-old) within the population increased, there was an exponential increase in fractures of the proximal femur, make it a primary emergency in the elderly wellness (1).

A major complication in elderly patients following hip fracture is represented by postoperative delirium (2-4), for which has been estimated an incidence

rate varying from 13.0% to 70.0% (5), being the high variability, the consequence of measurement methods and criteria used to diagnose it, and patients' susceptibility.

Delirium is an acute and complex disorder that can develop in hours or over a few days, it produces a significant decline in the initial cognitive, perceptual and consciousness / attention state of the subject (6).

There are two main forms of delirium: hyperactive, in which the patient is agitated at a motor level, disoriented in space and time and subject to visual and auditory hallucinations; hypoactive, or lethargic state, in which the patient does not show any of the previous symptoms, but rather apathy, drowsiness and above all the absence of communication and response to stimuli of various kinds (6). Postoperative delirium is associated with poor outcomes, such as impaired functional and cognitive recovery, increased hospital length of stay (7,8), becoming the major obstacle to successful rehabilitation treatment of these patients (9), and a serious cause of morbidity and mortality, being associated with a 2 to 5 times higher mortality risk (10).

The importance of limiting the adverse event of postoperative delirium have leaded physicians to analyze risk factors to prevent it (11). Authors stated that in the general geriatric population, 30% to 40% of the delirium episodes could be prevented by treatment of the risk factors (12).

However, analysis of the risk factors remains complex and the link between the hip fracture (orthopedic lesion) and delirium (neurological processes alteration) remains rather enigmatic. In several studies delirium has been associated with a large variety of predisposing factors, including older age (13,14), male gender (15), dementia (16), multiple medical comorbidities (17) and polypharmacy (18). But several studies remain weak and not able to offer sufficiently clear procedural indications. Indeed, the complex anamnestic situation that frequently elderly patients showed, may be considered the main difficulty in organizing and analysing the risk factors.

Risk factors can be divided into predisposing and precipitating. The predisposing factors are present at the time of hospitalization and represent the patient's basic vulnerability. The precipitating factors are harmful events or factors related to hospitalization that contribute to the development of delirium (19,20). Patients with a high basic vulnerability can develop delirium if subjected to even single precipitating factor of a mild degree (19).

In elderly people, predisposing factors to an increased risk of developing delirium can be considered psychiatric comorbidities (21) or a high number of other comorbidities, often occurring with aging (3,11). Whereas precipitating factors may be considered: hospitalization time before surgery (22); narcotics (23,24); functional dependence (25,26), waiting time for surgery (27), pain and problems with pain management (28,29). All factors that may induce alteration of the physiological homeostasis of the subject, known that elderly have a reduced ability to respond to metabolic or environmental stress.

Furthermore, dementia is associated with other predisposing factors for postsurgical delirium and could be considered a "confounding factor" leading to false conclusions about the longitudinal association between the candidate precipitating factor (es.: age), accident and delirium (30). The focusing adopted by authors on very elderly patients (age > 80 years) also, could induce a non-correct evaluation or an over-estimation of risk factors.

Therefore, by the present study, we sought to investigate the potential risk factors for post-operative delirium in elderly operated for fracture of the proximal femur.

Materials and methods

Study participants

We have performed a prospective observational study enrolling 123 patients aged ≥ 65 years, hospitalized with a diagnosis of proximal femur fracture (intra and extracapsular) at the Department of Orthopedics and Traumatology of the "Maggiore della Carità" University Hospital of Novara from 1 May 2019 to 15 September 2019.

All patients were informed about the study, and all included consented to participate. Patients undergoing fracture osteosynthesis or hip replacement surgery were included, excluding non-operated patients.

This study was performed in accordance with the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) Guidelines. All the study participants were asked to carefully read and sign an informed consent,

obtaining the written permission for any third-party materials you have included. The researchers provided to protect the privacy and the study procedures according to the Declaration of Helsinki.

Intervention

All enrolled patients underwent osteosynthesis or prosthetic replacement surgery for fracture of the proximal femur, divided as follows: 35/83 (42%) fixation with Gamma 3 locked intramedullary nail (Stryker Howmedica), 13/83 (16%) fixation with long Gamma nail (Stryker Howmedica), 26/83 (31%) bi-polar cemented hip hemiarthroplasty, 6/83 (7 %) Total Hip Arthroplasty (THA), 4/83 (4%) fixation with three cannulated screws.

In the 24 hours before surgery (T0) the delirium level of all patients in the sample was assessed by administering the Delirium Rating Scale (DRS) test (31): patients with scores higher than 10/32 points at T0 were excluded as they were considered already delusional.

Enrolled patients were evaluated with the DRS and for each patient several parameters were taken in account: serum-blood levels of hemoglobin (Hb), hematocrit (Ht) and glucose, comorbidities and drug therapies, the ASA (American Society of Anesthesiology) classification, the use of pre-anesthesia, the quantity (number of bags of concentrated erythrocytes) and the time of blood transfusions: 24 hours before surgery (T0), on the 1st postoperative day (T1), 3 and 7 days after intervention (T3 and T7, respectively).

The mental state and the other parameters indicated were reported on a Case Report Form for each patient and then on a dedicated database for statistical analysis.

Statistical analysis

The characteristics of the sample were described by calculating the percentages or mean values with standard deviation of the quantifiable parameters.

The distribution of the continuous variables in the two groups were analyzed with the chi-square test. The categorical variables analyzed in the two groups of patients (Delusional vs Non-delusional) was instead evaluated with the Student's t-test for independent samples. Furthermore, a logistic regression analysis was performed to assess whether there were any risk factors for delirium. All the results of the statistical analyses were carried out with the SW STATA 13 (StataCorp LP, College Station, TX, USA); $p<0.05$ was considered as statistically significant.

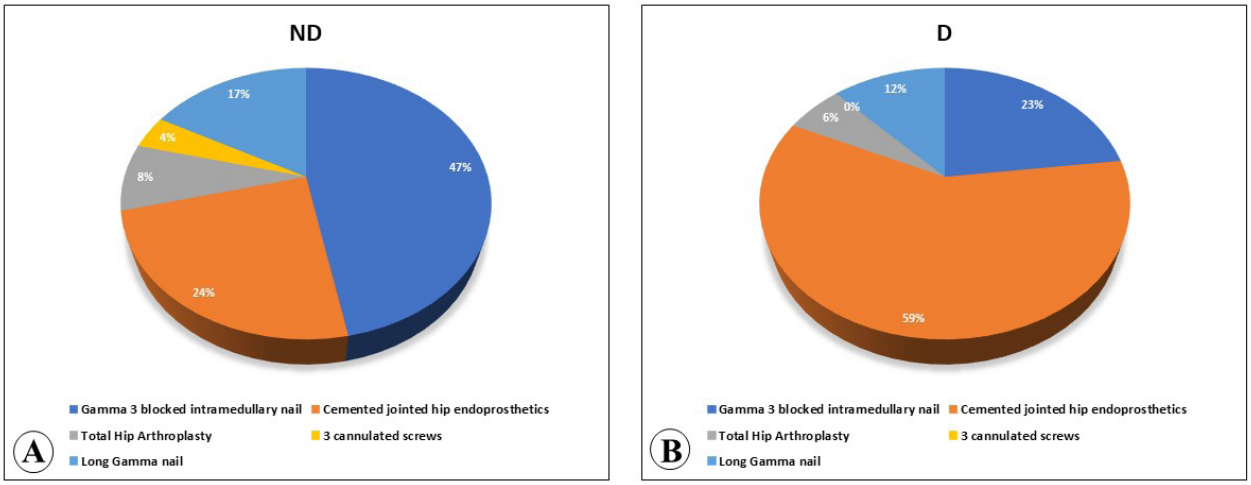

Figure 1. Distribution of the several surgical interventions in Not Delusional (ND) (Fig.1A) and Delusional (D) group (Fig.1B) studied.

Results

The study considered 123 patients, 40 of whom were excluded because already delusional at the time of admission. Of the 83 patients included in the study, 57 (69%) were female and 26 (31%) were male, respectively.

All patients enrolled before surgery were classified by the anesthesiologist according to the American Society of Anesthesiology (ASA Class) obtaining the following distribution: 1/83 (1%) ASA I, 12/83 (14%) ASA II, 43/83 (52%) ASA III, 27/83 (33%) ASA IV

In the postoperative period 17/83 (20%) of patients were delirious (D) while 66/83 (80%) were not delirious (ND). ND patients were represented by 44/66 (67%) females, and 22/66 (33%) males; D patients were 13/17 (76%) female and 4/17 (24%) male.

ASA class ND patients: 1/66 (1%) ASA I; 10/66 (15%) ASA II; 34/66 (52%) ASA III; 21/66 (32%) ASA IV. ASA class D: 0/17 (0%) ASA I; 2/17 (12%) ASA II; 9/17 (53%) ASA III; 6/17 (35%) ASA IV.

The breakdown by type of surgery among ND and D patients was displayed in Figure 1.

The prevalence of comorbidities in the ND and D patients were displayed in Figure 2 A and B; in concomitance with the comorbidities, the corresponding therapies for the ND and D patients were displayed in Figure 2 C and D.

Hemotransfusions performed in the 1st post-surgery day, 3rd post-surgery day and 7th post-surgery day resulted in ND and D patients were resumed in Figure 3A; the level of delirium assessed with the DRS scale among ND and D patients was displayed in Figure 3B, where is described that patients with a DRS score < 10 in T1 were not found delusional at T3 and T7.

The values of glycemia, hemoglobin and hematocrit have showed no changes along the post-surgery days monitoring; any statistical difference of the values has been detected between delusional and not delusional group (data not shown).

Comparing the several variables occurring in ND and D patients, comorbidity, therapy, and pre-anesthesia were found with sufficient statistical significance. No statistical significance was found related to gender (see Table 1 for further details).

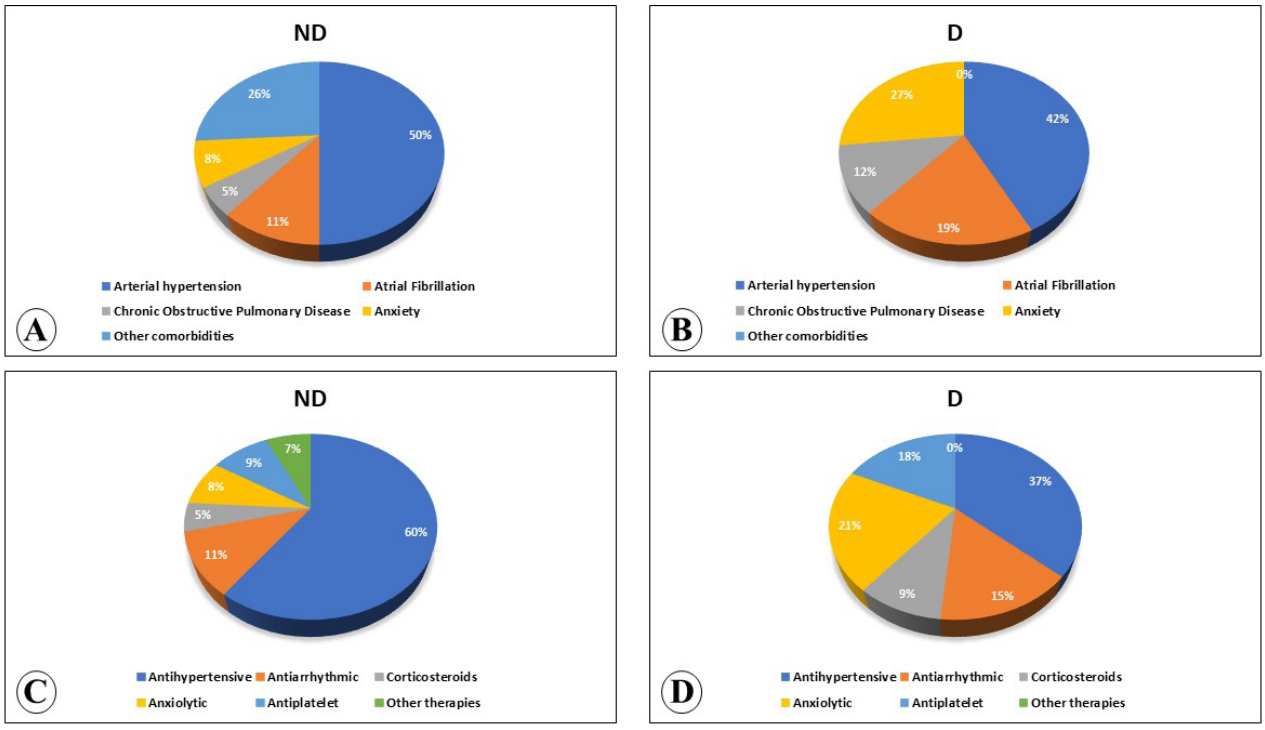

Figure 2. Distribution of several comorbidities (A, B) and pharmacological therapy (C, D) in Not Delusional (ND) and Delusional (D) group studied.

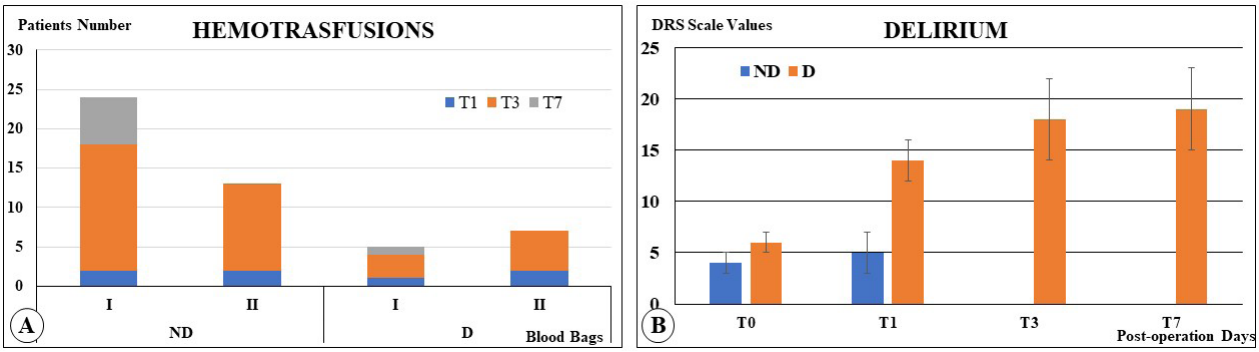

Figure 3. Bar-graphs illustrating the hemotransfusions administered in Not Delusional (ND) and Delusional (D) group studied during the several postoperative days taken in consideration (A), and DRS scale detection of delusional level (B).

Table 1. Statistical analysis by Chi-Square test, of variables occurring in Not delusional and Delusional group. Significance p< 0.05

	Not Delusional	Delusional	Statistic (p)
Gender			
Male	22	4	0.437
Female	44	13	
Comorbidities			
Hypertension	33	11	0.279
NO-Hypertension	33	6	
Atrial fibrillation	7	5	0.049
NO-Atrial Fibrillation	59	12	
BPCO	3	3	0.063
NO-BPCO	63	14	
Anxiety	5	7	0.000
NO-Anxiety	61	10	
Terapy			
Antihypertensive	33	12	0.129
NO- Antihypertensive	33	5	
Antiarrhythmic	7	5	0.049
NO- Antiarrhythmic	59	12	
Corticosteroids	3	3	0.063
NO- Corticosteroids	63	14	
Anxiolytic	5	7	0.00
NO-Anxiolytic	61	10	
Antiplatelet	6	6	0.006
NO- Antiplatelet	60	11	
Preanesthetic			
No use	31	5	
Midazolam 0.5	30	4	0.000
Midazolam 1.0	8	8	

In delusional patients prevail Atrial Fibrillation (29% D vs 11% ND), anxiety (41% D vs 8% ND), antiplatelet drugs (35% D vs 9% ND), antiarrhythmics (29% D vs 11% ND) and anesthetic premedication with benzodiazepine (71% D vs 53% ND) (see Table 1 for further details).

The distribution of the continuous numerical variables Glycemia, Hb, Htc, Age in the two groups of subjects evidenced that only the most advanced age was significantly associated with delirium (see Table 2 for further details).

To evaluate any predictive factors of delirium, the continuous numerical variables were inserted one by one in a univariate logistic model. From these models only the age variable, among those considered, could constitute a prognostic factor of delirium, as depicted by Table 2.

Discussion

The literature demonstrates the beneficial effects of an intervention program focused on the recognition

Table 2. Statistical analysis by t-test and Logistic Regression, of continuous variable detecting in Not delusional and Delusional group. Significance p< 0.05.

	Not Delusional	Delusional	t-test (p)	Logistic Regression (p)
Glycemia (mg/dl)	123 ± 22	124 ± 27	0.9261	0.925
Hb (g/dl)	11 ± 1	11 ± 1	0.6496	0.645
Htc (%)	31 ± 4	31 ± 3	0.6385	0.651
Age (years)	84 ± 8	89 ± 7	0.0222	**0.027**

and early treatment of delirium in elderly patients with proximal femur fracture (11,32). Early geriatric care can reduce the incidence, severity, and duration of delirium; these interventions focus on adequate oxygen supply, maintenance of electrolyte balance, pain treatment, elimination of unnecessary drugs, regulation of cardiocirculatory and renal function, adequate nutrition and early mobilization and rehabilitation (11,32). However even if in elderly patients the above listed parameters are all generally important into assuring a correct control of patients' homeostasis, not all of them can be considered effective risk factors for postoperative delirium insurgence following hip surgery and the literature at today has not reach unanimous consent.

In our work the gender and the type of surgery did not result to be risk factors for delirium. Similarly, the difference between the two groups of delusional and non-delusional ones, regarding the comorbidities of hypertension and chronic obstructive pulmonary disease, have not reached statistical significance.

Although parameters such as Glycemia, Hb and Htc has been considered important to influence brain function and the cognitive status of the elderly (11,33,34), in our research they have not reached the statistical significance to be considered effective risk factors. On the contrary, Mosk et al., (11) have indicated low postoperative Hb levels as a risk factor for delirium. We hypothesize that these parameters should be considered precipitating factors, the influence of which has become important only in very elderly patients (> 80 years-old), in whom physiological homeostasis can be considered compromised. In our sample the presence of subjects < 70 years old may explain the discrepancy with the Mosk et al. results, in support to the hypothesis that hematic parameters should be considered precipitating factors, only in very elderly patients.

It is relevant that about half (52%) of patients was blood transfused after surgery and in particular almost all of these (42% of the total) in the 3rd postoperative day. The use of blood transfusion has been observed more frequent in delusional patients than in non-delusional, but our results are not enough significative to promote blood transfusion as risk factors, even if transfusion *in sè* is a procedure not totally exempt from risks (35). However, in the present study all days of hospitalization were not systematically considered, but fixed evaluation times were chosen, therefore the evaluation of blood transfusions may be not precise, and we could underestimate them. We hypothesize that a dangerous condition arises behind the blood transfusion, in which low cerebral blood flow predisposes patients to impaired brain function that can develop into delirium.

Regarding the level of delirium, it should be noted that already in the preoperative period (T0) the patients who subsequently have experimented delirium started from higher DRS values that gradually increased during subsequent days. These findings evidence that these patients were somehow predisposed to delirium and that surgery is not the only cause.

Atrial fibrillation and anxiety can be considered risk factors properly associated with delirium as well as antiarrhythmics, antiplatelet drugs, anxiolytics, and pre-existing psychiatric pathologies. However, these findings represent the evidence of an existing neuropathological susceptibility.

In the present work the use of anesthetic premedication with benzodiazepine has been confirmed to represent a risk factor for postoperative delirium, as elsewhere evidenced (23). This finding once more claims attention on the anesthetic protocols to be used during surgery in elderly patients.

Other environmental and metabolic parameters such as dependence in activities of daily living before the fracture, the stay living in care structure, long waiting times for surgery, high number of comorbidities or organ disease, have been recognized as risk factors to develop postoperative delirium in elderly patients (11,32). However, these parameters are indicative of an occurrence of compromised physiopathological status. This dysfunctional status could be considered as a disturbance in both peripheral and central neurotransmitter system, leading patients at risk of post-operative delirium and at risk of falling, that could lead to another fracture (36,37). The long waiting times for surgery may also represent a risk of developing postoperative delirium following proximal fracture of the femur (27), remarking that an altered response to environmental stress occurs in the elderly patients. Therefore, we should consider that the heterogeneity and complexity of the delirium issue, particularly in the older patients

operated for fracture of the proximal femur, suggests the need for multidisciplinary management (38).

Conclusions

Taken together, our findings showed several environmental and metabolic variables contribute to make elderly patients susceptible to develop postoperative delirium following hip surgery. However, the logistic regression model has given age only, as predictive factor for delirium in particular, we have found that the most advanced age was significantly associated with delirium. It is our opinion that the occurrence of numerous variables precipitating the event might make a condition of susceptibility *in sè*, rather than a risk factor. Therefore, further studies are warranted to prevent post-operative delirium, starting from a careful determination of environmental situations particularly in very older patients.

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