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
duration, the consequence of measurement methods
and criteria used to diagnose it, and patients’ suscep-
tibility.

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 associ-
ated with poor outcomes, such as impaired function-
al 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 asso-
ciated with a 2 to 5 times higher mortality risk (10).

The importance of limiting the adverse event of
postoperative delirium have led physicians to ana-
lyze 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 com-
plex 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 con-
sidered 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 harm-
ful 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 in-
creased 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: hos-
pitalization time before surgery (22); narcotics (23,24);
functional dependence (25,26), waiting time for sur-
gery (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 oth-
er 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-es-
timation of risk factors.

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

Materials and methods

Study participants

We have performed a prospective observational
study enrolling 123 patients aged ≥ 65 years, hospital-
ized with a diagnosis of proximal femur fracture (intra
and extracapsular) at the Department of Orthopedics
and Traumatology of the “Maggiore della Carità” Uni-
versity 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 under-
going fracture osteosynthesis or hip replacement sur-
gery 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 2A and B; in concomitance with the comorbidities, the corresponding therapies for the ND and D patients were displayed in Figure 2C 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.
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 of delirium.
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 sé 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 pre-medication 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 se, 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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