Gerontology And Geriatric Research
ISSN# 2834-3476

Research Article

Effectiveness of Ultra-Micronized Palmitoylethanolamide /Luteolin (PEALut) in Reducing Postoperative Delirium in Elderly Patients with Hip Fracture

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ARTICLE INFO

Received Date: December 06, 2023
Accepted Date: December 18, 2023
Published Date: December 18, 2023

KEYWORDS

Hip fracture; Delirium; Orthogeriatrics; Surgery; Neuroinflammation; Palmitoylethanolamide

Citation for this article: Emilio Martini, Giulio Pioli, Giorgio Cocuzza and Maria Lia Lunardelli. Effectiveness of Ultra-Micronized Palmitoylethanolamide /Luteolin (PEALut) in Reducing Postoperative Delirium in Elderly Patients with Hip Fracture. Gerontology And Geriatric Research. 2023; 5(1):135

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ABSTRACT

Postoperative Delirium (POD), a common complication in elderly patients after surgery for hip fracture, is associated with negative outcomes including functional decline, mortality, prolonged in-hospital stay and institutionalization. The literature highlights the relation between neuroinflammation and delirium. The co-ultramicronized association of Palmitoylethanolamide and Luteolin (PEALut) is known to reduce the production of pro-inflammatory cytokines, thus interrupting the spread of inflammation from the periphery to the Central Nervous System (CNS). This study, which included 80 elderly patients admitted to the hospital for hip fracture surgery, aimed to investigate the efficacy of PEALut in the management of POD. PEALut 700/70 mg was administered to 40 patients twice daily starting within 12 hours from admission up to 3 days after surgery. The presence and severity of delirium were assessed with the Confusion Assessment Method (CAM) and the Delirium-O-Meter (DOM) scale, the duration was measured in days. Incidental POD was observed in a total of 28 participants, with a significantly lower presence in PEALut-treated patients, compared to the controls (p =0.019). Mean duration of POD was shorter, albeit not significantly, and POD was significantly less severe in PEALut group (p=0.045). The administration of PEALut to elderly hip fracture patients seems to prevent the onset of POD and attenuate symptoms intensity and duration.

INTRODUCTION

Postoperative Delirium (POD) is a common complication occurring with an incidence of up to 50% in elderly patients undergoing surgery after hip fracture, appearing mainly within five days after surgery. POD is associated with several negative outcomes including functional decline, mortality, prolonged in-hospital stay, and institutionalization [1]. Therefore, the prevention of delirium is a primary issue in managing elderly patients admitted to hospital with hip fracture.

The pathogenesis of delirium is still poorly understood. Acute systemic inflammation related to peripheral insults such as infection, trauma or surgery can lead to an inflammatory cascade with acute release of inflammatory mediators into the bloodstream and propagation of the inflammatory process within the Central Nervous System (CNS) via blood-brain barrier disruption and microglial activation (Neuroinflammatory Hypothesis of Delirium) [2]. Microglial cells and astrocytes in the brain are suggested to play a key role in the behavioral changes due to systemic

inflammation. These cells, especially in elderly age and in neurodegenerative diseases, can change from a resting state into an activated state called 'primed microglia'. Primed microglia cells produce high amounts of cytokines transmitting and amplifying the peripheral inflammatory stimulus at CNS level. These exaggerated central nervous system inflammatory responses to peripheral stressors may be implicated in delirium onset [3].

Some studies found a relationship between cytokine levels in serum or cerebrospinal fluid and the occurrence of delirium. In a group of elderly hip fracture patients developing POD, the circulating levels of pro-inflammatory interleukin (IL)-6 and IL-8 were higher than in patients without POD, as well as significantly higher levels of IL-8 and IL-1 have been found in cerebrospinal fluid of patients with delirium after hip fracture [4]. Moreover, there is evidence that proinflammatory cytokines such as IL-1b can inhibit acetylcholine release and cholinergic-dependent memory function, thus these inflammatory mediators may be a key determinant of cognitive dysfunction during episodes of delirium [5].

The treatment of delirium requires a multicomponent strategy aimed at both optimizing preventative measures in addition to pharmacological management. Pain control, nutritional support, early mobilization, reorientation, normalization of electrolytes, adequate hydration, oxygenation, control of constipation, a reduced and correct management of the bladder catheter, drug monitoring with review of the psychoactive drugs, have been found to be useful in reducing incidence, duration and intensity of delirium [6]. Among pharmacological therapies, antipsychotic drugs have been used in the treatment of agitation and psychotic symptoms in course of delirium, but have not proven to be effective in preventing it and have been associated with numerous side effects [7]. Similarly, acetylcholinesterase inhibitors have proved to be ineffective [8], as well as melatonin and melatonin agonists have shown promise for prevention of delirium in elderly surgical patients but the optimal dosage, formulation and treatment duration remain unclear [9]. Other agents such as benzodiazepines [10], histamine antagonist [11] and statins [12] have been suggested as pharmacological treatments, but lacking of the evidences supporting their use in delirium prevention.

The recent acquisitions about the role of neuroinflammation in delirium open up new possible therapeutic targets supporting the use of anti-inflammatory substances in the prevention and treatment of POD. Palmitoylethanolamide (PEA) is an endogenous molecule that modulates inflammation response at the level of the nervous tissue by the indirect interaction with the membrane cannabinoid type 2 (CB2)-like receptor and the direct activation of the nuclear receptors of the family of peroxisome proliferator–activated receptors (PPAR)-alfa. PEA exerts a modulatory control on mast cells degranulation [13] and it has been associated with a reduced astrocytes activation, a lower recruitment of mast cells in the areas of damage, and a reduction of microglial cells activation [14]. Luteolin, a plant-derived flavonoid, exerts antioxidant action at the level of CNS and has been shown to reduce inflammatory mediators, oxidative stress and neuronal death in experimental models [15]. Based on these evidences, the aim of this study was to test the effect of a co-ultramicronized association of PEA and Luteolin (co-ultra-PEALut or just PEALut) on the onset of POD in elderly hip fracture patients.

MATERIALS AND METHODS

Study participants

This study involved 80 elderly hip fracture patients. Patients of both sexes were eligible if they were ≥ 75 years and had a primary diagnosis of low trauma hip fracture, while patients with recent head injury, severe dementia, delirium at admission to the hospital, receiving antipsychotic drugs and not scheduled for surgery within 48 hours, were excluded from the investigation. The study was planned and conducted in agreement with Declaration of Helsinki about ethical principles for medical research involving human subjects and according to the guidelines of Good Clinical Practice (GCP). Ethical approval was obtained on 13/09/2016 from the Ethical Committee of the S.Orsola, Malpighi University Hospital in Bologna (code CE 156/2016/O/Sper). Informed consent was obtained from all patients. Trial reporting will comply with CONSORT guidelines.

Study design

The present interventional, randomized, single-blind, monocentric, prospective trial was carried out at the Orthogeriatric Unit of the IRCCS University Hospital in Bologna, Italy, from December 2018 to May 2019. Eighty patients were

randomized into two groups (control or PEALut) in a 1:1 ratio. The randomization list was generated by the statistician via computer, in random blocks of 4. The randomization sequence was blinded for the investigators and eligible subjects were assigned to the lowest available randomization number after their admission to the Orthogeriatric Unit.

A commercial oral formulation composed by co-ultramicronized association of 700 mg PEA and 70 mg of luteolin (Food for Special Medical Purposes, Glialia®, Epitech Group SpA, Saccolongo, Italy) was administered to each patient of the treatment group twice daily at 12 hours intervals (8:00 am and 8:00 pm) starting within 12 hours from admission, up to 3 days after the surgery. The administration of PEALut was carried out and controlled by the Orthogeriatric Unit nursing staff to ensure treatment adherence.

Non-pharmacological strategies to address the range of risk factors associated with POD were applied to all patients of both control and PEALut groups. Key elements of this multicomponent intervention were i) quick treatment of the major triggering clinical factors (dehydration, electrolyte imbalances, infections, postoperative anemia, etc.); ii) effective control of pain, early surgery, physiotherapy rehabilitation starting from the first postoperative day; iii) early removal of the bladder catheter; iv) promotion of the presence of the caregiver during the hospital stay.

A complete review of the home drug therapy was performed by physicians upon admission to the Orthogeriatrics Unit. Therapies with anticoagulants/antiplatelet agents, antihypertensive and non-essential drugs were suspended, while blood-active vitamins were prescribed to limit anemization and transfusion requirements. Acetaminophen 1000 mg was administered every 8 hours to all patients for pain control. A further dose of analgesic was administered upon requested of the patient or if considered necessary by the physician. Administering a placebo to the control group was deemed unnecessary, as nurses dispensed PEALut simultaneously with the other drug therapy, therefore the elderly patients were unaware of the treatment received. The physician who performed the established assessments was blinded of which drug therapy the patients were being given. The main outcome of the study was to evaluate the incidence of POD, while the severity and duration of delirium were registered and analyzed as secondary outcomes.

Delirium assessment

Patients underwent delirium assessment at least three times daily by the same physician who was comprehensively trained for questionnaires administration and data collection.

All patients were subjected to the following assessments:

1) Diagnosis of delirium by the 4-items short form Confusion Assessment Method (CAM) [16], a screening instrument consisting of four 'cardinal' criteria (acute onset and fluctuating course, inattention, disorganized thinking and altered level consciousness) where the presence of both first and second and either the third or fourth criteria are compatible with a delirium diagnosis [17];

2) Severity of delirium by means of the Delirium-O-Meter (DOM) scale [18], a behavioral scale with 12-items, each of which scored on a four-point scale (0 = absent, 1= mild disturbance, 2= moderate, 3 = severe) allowing to obtain a total score ranging from 0 to 36 [17];

3) Duration of delirium, registered in total number of days from the first to the last occurrence.

Patients' health status and disability assessment

On admission all patients underwent a Comprehensive Geriatric Assessment (CGA): a process focused on determining a frail older person's medical, functional, mental, and social capabilities and limitations [19].

The following further standardized tools were performed:

1) Cumulative Illness Rating Scale (CIRS) [20], a comorbidity index consisting of 14 items exploring impairment regarding different organ and systems. Each item rated from 1 (no impairment) to 5 (extremely severe impairment). The CIRS Severity Index (CIRS-SI) is calculated as the average of all the CIRS items, while CIRS Comorbidity Index (CIRS-CI) score is based on the count of the organ system with moderate to more significant impairment (score ≥ 3) [21];

2) American Society of Anaesthesiology (ASA) score [22], an assessment of patient's overall health based on five classes: I) completely healthy fit patient, II) patient with mild systemic disease, III) patient with severe systemic disease that is not incapacitating, IV) patient with incapacitating disease that is a constant threat to life, V) moribund patient who is not expected to live 24 hours with or without surgery [23];

3) Short Portable Mental Status Questionnaire (SPMSQ), an assessment of the mental functioning status consisting of 10 questions, where a poor performance (higher number of incorrect answers) is correlated with the presence of cognitive disorders [24];

4) Geriatric Depression Scale (GDS) [25] in its five-item version, a scale scored from 0 to 5 points, for the assessment of depressive symptoms, in which a score ≥ 2 points is indicative of depression [26];

5) Mini Nutritional Assessment Short Form (MNA-SF) [27], a six-item instrument with scores ranging from 0 to 14 points which categorized patients into 3 groups: with a normal nutritional status (12 – 14 points), at risk of malnutrition (8 – 11 points), or malnourished (0 – 7 points) [28];

6) Katz Index (ADL) and Lawton Index (IADL) to evaluate the prefracture functional status in basic and instrumental activities of daily living, respectively [29,30]. The six-item Katz index assess with a unique yes/no question the performance in the functions of bathing, dressing, toileting, transferring, continence and feeding. A score of 6 indicates full function, 4 moderate impairment and 2 or less indicates severe functional impairment [31]. The eight-item IADL scale consists of 8 domains, with a summary score ranging from 0 (low function, dependent) to 8 (high function, independent) [32];

7) Numeric Pain Rating Scale (NPRS), a 11-point scale scored from 0 to 10 where 0 indicates 'no pain' and 10 corresponds to 'the most intense imaginable pain' [33]. Patients presenting NPRS score ≥ 7, indicative of postoperative severe pain [34], were considered patients with 'poor control of pain'.

Laboratory data collection

Patients were subjected to routine laboratory tests, serum albumin, hemoglobin and vitamin D level analyses. Blood samples were collected in the morning under fasting conditions, within 24 hours of hospital admission.

Peri- and postoperative assessments

All patients underwent the following evaluations during the in-hospital observation period:

1) type of fracture, surgical procedure, time to surgery (from admission to hospital), type of anesthesia performed;

2) length of in-hospital stay and incidence of in-hospital mortality;

3) postoperative complications.

Safety assessments

Blood chemistry analyses, postoperative assessments, and patients' monitoring for possible occurrence of adverse events were used for safety treatment evaluation.

Sample size calculation and statistical analysis

Assuming a delirium incidence of 50% in the control group and a reduction to 20% incidence in PEALut group, the power analysis (beta= 0.20 and alfa= 0.05) revealed that a sample of 36 subject per group was needed, which was rounded to 40 to handle possible drop outs.

Categorical variables were expressed in percentages, while continuous variables were reported as mean ± Standard Deviation (SD). One-way analysis of variance, Pearson's chi-square test, and the Mann–Whitney U test were used to examine differences in patients' baseline characteristics between the groups. The occurrence of delirium and the differences in its severity and duration were compared between PEALut and control groups according to the intention-to-treat principle. Moreover, a multiple logistic regression analysis was carried out on the whole sample to identify the independent effect of treatment for delirium occurrence including all variables known to affect the incidence of delirium as covariates. Odds ratios (OR) and 95% confidence intervals (95% CIs) were calculated using standard formulae. Significance was set at $p<0.05$. Statistical analysis was performed using SPSS 22.0 for Windows.

RESULTS

Patients' baseline characteristics

During the period of the study, 127 patients with hip fracture were admitted to the hospital, 47 were excluded as they did not meet the inclusion criteria, 80 patients (70 women and 10 men) with an average age ± SD of 87.3 ± 5.4 years were enrolled. Patients' treatment adherence was 100% and all enrolled patients completed the study. Control and PEALut groups were homogeneous in terms of the patients' mean age, percentage of female participants, average number of drugs taken and in the analyzed laboratory parameters, whereas the rate of subjects living in nursing home was statistically higher ($p=0.04$) in the control group (15%) compared to PEALut group (3%) (Table 1).

Table 1: Patients' baseline characteristics.

	PEALut Group N=40	Control Group N=40	p
Age, mean years ± SD	87.2 ± 5.2	87.3 ± 5.6	0.98
Female, %	82.5	92.5	0.17
Living in nursing home, %	3	15	0.04
Number of drugs, mean number ± SD	5.4 ± 2.4	4.8 ± 2.6	0.27
Hemoglobin on admission, mean g/dL ± SD	12.0 ± 1.4	11.6 ± 1.7	0.33
Albumin level on admission, mean g/dL ± SD	35.5 ± 3.1	35.2 ± 3.1	0.60
Vitamin D level on admission, mean ng/mL ± SD	9.1 ± 6.7	10.1 ± 8.4	0.42

Patients' clinical assessment

Control and PEALut-treated patients showed similar clinical features with no significant differences except for CIRS severity index score that was slightly higher in the PEALut group (1.9 ± 0.3) compared to controls (1.7 ± 0.2) (p=0.02). However, most of the participants had several comorbid disorders (mean comorbidity index 4.1 ± 1.4) including mainly hypertension (77.5%), pulmonary diseases (37.5%), hearth diseases (59%), previous diagnosis of dementia (21%) and auditory or visual deficit (35%).

The evaluation of ASA score showed that patients' overall health was comparable between control (3.1 ± 0.3) and PEALut-treated (3.2 ± 0.4) patients, as well as the depression symptoms evaluated by the GDS score (1.6 ± 1.5 in controls compared to 1.4 ± 1.2 in PEALut group) exhibited by 42% of all patients. The cognitive status evaluation showed that PEALut and control patients had similar SPMS questionnaire scores. Seventeen participants were diagnosed with Alzheimer or vascular dementia, and about 40% showed cognitive impairment at the screening test. The independence in activities of daily living showed similar basic (ADL) and instrumental (IADL) scores in the control and PEALut groups, with the majority of patients (65%) fully independent in ADL and almost 70% who needed help in 2 or more IADL.

Patients nutritional profile detected by MNA-SF showed no statistically different results between the two groups. However, more in-depth evaluation showed that only 44% of patients had a normal nutritional profile and 15% reported a state of severe malnutrition (Table 2).

Table 2: Patients' clinical characteristics.

	PEALut Group N=40	Control Group N=40	p
CIRS comorbidity, mean score ± SD	4.4 ± 1.5	3.8 ± 1.2	0.07
CIRS severity, mean score ± SD	1.9 ± 0.3	1.7 ± 0.2	0.02
SA, mean score ± SD	3.2 ± 0.4	3.1 ± 0.3	0.16
GDS, mean score ± SD	1.4 ± 1.2	1.6 ± 1.5	0.41
SPMSQ, mean score ± SD	2.9 ± 2.1	2.9 ± 2.4	1.0
Katz index (ADL), mean score ± SD	4.7 ± 1.6	4.5 ± 1.6	0.68
Lawton index (IADL), mean score ± SD	4.0 ± 2.7	4.5 ± 3.2	0.47
MNA-SF, mean score ± SD	10.5 ± 2.7	10.6 ± 2.8	0.84

CIRS: Cumulative Illness Rating Scale; SPMSQ: Short Portable Mental Status Questionnaire; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living; GDS: Geriatric Depression Scale; MNA-SF: Mini Nutritional Assessment Short Form; ASA: American Society of Anaesthesiologist

Surgical characteristics

Based on fracture type, no statistically significant difference was found between the two groups. On a total of 40 PEALut-treated patients, 11 (27.5%) had an intracapsular fracture, while the remaining 29 (72.5%) presented an extracapsular fracture. Similarly, in the control group 13 (32.5%) patients had intracapsular fracture compared to 27 (67.5%) with extracapsular fracture. Control and PEALut groups underwent similar surgical procedure with no significant differences in the type of anesthesia performed (spinal anesthesia for all patients), in time-to-surgery evaluation and in the number of patients which underwent osteosyntheses procedure, as shown in (Table 3). In particular, overall, 21 patients underwent hemiarthroplasty, 54 osteosynthesis with intramedullary nail and 5 osteosynthesis with cannulated compression screw.

Table 3: Patients' surgical characteristics

	PEALut Group N=40	Control Group N=40	p
Fracture type, %	Intracapsular 27.5 Extracapsular 72.5	Intracapsular 32.5 Extracapsular 67.5	0.62
General anaesthesia, %	0	0	na
Surgical procedure, osteosyntheses %	72.5	75	0.80
Time to surgery, mean hours ± SD	41.9 ± 7.8	40.1 ± 12.7	0.45

Postoperative assessment

The distribution of the postoperative complications was comparable between the groups: the rate of patients developing one or more medical complication was 52.5% in controls and 50% in PEALut patients. In particular, controls and PEALut patients showed similar incidence rate of postoperative cardiological problems such as heart failure, myocardial infarction and new detected atrial fibrillation which were observed in 12.5%, 0%, 10% controls and 7.5%, 2.5%, 0% PEALut patients, respectively for each complication. Similarly, acute kidney failure was observed in 12.5% controls compared to 7.5% PEALut patients, and infectious complications such as pneumonia and urinary tract infections were reported in 2.5% and 10% controls and in 5% and 12.5% patients treated with PEALut. In neither group, no patients experienced thrombosis, thromboembolism and only one patient in PEALut group suffered from sepsis. Gastrointestinal bleeding was not experienced in any patients, while intestinal subocclusion was reported by 3 (7.5%) control patients and by no patient treated with PEALut. The number of patients experiencing 'poor control of pain' was similar between the two groups: 7 (17.5%) patients had an NPRS≥7 in the control group and 10 (25%) in the PEALut group. No differences were observed in perioperative death within 30 days after surgery (1 patients in both control and PEALut groups) and in the number of blood transfusions required by control (1.03 ± 1.45) and PEALut-treated patients (0.98 ± 1.09). Also, the mean in-hospital stay was comparable between the two groups (8.7 ± 2.4 and 8.9 ± 3.4 for PEALut and control groups, respectively) (Table 4).

Table 4: Patients' postoperative complications.

	PEALut Group N=40	Control Group N=40	p
Medical postoperative complications, n (%)	20 (50)	21 (52.5)	0.823
Heart Failure, n (%)	3 (7.5)	5 (12.5)	0.456
Myocardial infarction, n (%)	1 (2.5)	0 (0)	0.314
Atrial Fibrillation New Finding, n (%)	0 (0)	4 (10)	0.040
DVT/PTE, n (%)	0 (0)	0 (0)	
Acute kidney injury, n (%)	3 (7.5)	5 (12.5)	0.456
Pneumoniae, n (%)	2 (5)	1 (2.5)	0.556
UTI, n (%)	5 (12.5)	4 (10)	0.723
Sepsis, n (%)	1 (2.5)	0 (0)	0.314
Gastrointestinal bleeding, n (%)	0 (0)	0 (0)	
Intestinal subocclusion, n (%)	0 (0)	3 (7.5)	0.077
Poor control of pain, n (%)	10 (25)	7 (17.5)	0.412
Perioperative death (30 days from surgery), n (%)	1 (2.5)	1 (2.5)	1.000
Transfusions, mean blood unit ± SD	0.98 ± 1.09	1.03 ± 1.45	0.859
In-hospital stay, mean days ± SD	8.7 ± 2.4	8.9 ± 3.4	0.780

DVT: Deep Vein Thrombosis; PTE: Pulmonary Thromboembolism; UTI: Urinary Tract Infection

Delirium assessment

The incidence of postoperative delirium, evaluated by the CAM scale, was observed in a total of 28 (35%) patients. Among the controls, POD incidence was observed in 19 (47.5%) patients, while only 9 (22.5%) PEALut patients had a diagnosis of delirium, showing a statistically significant difference between the control and PEALut groups (p =0.019).

The delirium severity, assessed through the DOM scale, was significantly lower in the PEALut group (p=0.045): the mean DOM score in control patients was 12.7 ± 3.3, while in PEALut-treated patients the mean score was 10.1 ± 2.6.

The results of the mean duration of POD showed a shorter duration of delirium in the PEALut group, as demonstrated by the mean duration of 1.44 ± 0.5 days compared to 2.16 ± 1.7 days of the control patients, but the difference between the two groups did not reach the statistical significance (Figure 1). Importantly, 21% of control patients required additional sedative therapies to treat severe clinical manifestations of POD, while none of PEALut-treated patients required these types of parenteral interventions.

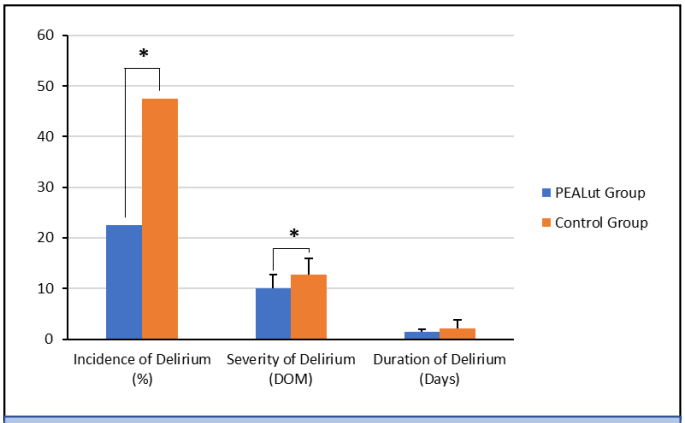

Figure 1: Primary and secondary study outcome: PEALut was effective in reducing POD incidence (p=0.019), POD severity (p=0.045), POD duration (p=0.227) (ns). *: p<0.05.

The results of multiple logistic regression, which used the occurrence of delirium as binary outcome, showed that PEALut treatment reduced about 4 times the risk of delirium (OR: 0.25 [0.08-0.73]; p=0.011) even after adjusting for age, comorbidity, cognitive impairment, postoperative infection and independence in activities of daily living (Table 5).

Table 5: Multiple logistic regression analyses.

	OR	95%CI -	p
PEALut group	0.247	0.084-0.729	0.011
Age, years	0.964	0.864-1.073	0.501
SPMSQ	1.215	0.946-1.561	0.128
CIRS-severity score	1.584	0.195-11.909	0.688
Katz index	0.889	0.623-1.268	0.516
Postoperative infections	2.589	0.803-8.344	0.111

DISCUSSION

The impact of postoperative delirium on elderly patients' lives represents an important challenge as this common complication is associated with postoperative neurocognitive disorder, increased other postoperative complications, prolonged hospital stays, and poor survival rates [35].

To date, many pharmacological approaches have been proposed in the prevention of delirium, but none of them have shown significant effectiveness. Therefore, since there are no consistent data to support a widespread use of pharmacological treatment [36], the best evidence-based approach for the prevention of POD is a multicomponent non-pharmacological intervention [6,37]. Recent acquisitions regarding the role of neuroinflammation in delirium opened new scenarios and new hypothetical therapeutic strategies through the use of anti-inflammatory drugs in the prevention of POD. Ultra-micronized PEA-based FSMPs may be deservedly considered part of a new and promising nutritional approach to disorders sustained by neuroinflammation such as postoperative delirium.

The present interventional, randomized, single-blind, monocentric prospective trial evaluated whether treatment with the antineuroinflammatory compound PEALut, administered up to 3 days after surgery as POD usually occurs between postoperative days 2–5, can reduce the incidence, severity, and duration of postoperative delirium in elderly patients with hip fracture. Our results showed that patients treated with PEALut perioperatively and up to 3 days after surgery had a significant reduction in both primary and secondary outcomes.

Our sample was characterized by a very high average age, higher than in most elderly hip fractures studies. Older age is a known risk factor for the development of POD and, as a result, our study population had a high vulnerability to develop POD. Furthermore, about a third of study participants had additional risk factors for POD onset such as previous diagnosis of dementia, depressive symptoms, deficit in the basal activities of daily living with different levels of impairment, auditory or visual deficit and malnutrition. These factors explain the high mean incidence of POD (35%) recorded in these patients, which, however, is similar to that reported in other studies (20-50%) [4]. Importantly, the incidence of delirium, assessed in all the patients by a physician who was comprehensively trained in the administration of the screening instrument used for the diagnosis of delirium, was significantly lower in patients treated with PEALut compared to that observed in the control group. Multiple logistic regression showed that treatment with PEALut reduced about 4 times the risk of delirium even after adjusting for age, comorbidity, postoperative infection, and mental and functional status. These results have an important clinical impact as POD is one of the main risk factors for unfavorable outcome after hip fracture such as increased mortality, high risk of developing dementia or worsening of the symptoms of pre-existing dementia, increased risk of perioperative complications, and poor functional recovery.

The statistical analysis also showed a reduction in the severity of POD in the group of patients treated with PEALut, in which the severity was indeed mild and none of the patients required parenteral sedative therapies unlike the control group, where 21% of patients had severe clinical manifestations of POD that required additional sedative therapies. This aspect is of great importance since the reduction in the use of neuroleptics or other sedatives avoid exposing patients to the multiple side effects associated with this class of drugs. Low intensity of delirium also allows better awareness of himself/herself and the surrounding environment, thus reducing the trauma of experiencing delirium. Moreover, the length of delirium in PEALut group was about one-half that in the control group even if not statistically significant. The reduction of length of delirium is an important goal as high duration of delirium has been related to an increased mortality at 6 months [38].

PEALut proved to be a safe and well-tolerated treatment, as demonstrated by the results of postoperative evaluation, which showed that PEALut did not increase the rate of patients

developing one or more medical complications and by the evaluation of adverse events which, at the end of the study, were not reported by any patient. However, this study has some limitations. The main ones are the relatively low number of patients enrolled, which could limit the transferability of the results to the general population, and the single-blind design. Furthermore, the study participants were recruited from a single hospital, so selection bias may be existed. The importance of these findings shows that larger-scale multicentric studies, with placebo, a double-blind design and longer follow-up, are needed to evaluate patients' long-term survival and cognitive decline, thus confirming the usefulness of PEALut in POD prevention, also in other types of surgery.

CONCLUSIONS

The results obtained from this study demonstrate that a timely administration of PEALut seems to be able to prevent the onset of postoperative delirium and to attenuate the intensity of the symptoms and their duration.

ACKNOWLEDGMENTS

In memory of Dr. Pioli, for his passionate dedication to scientific research. The authors thank Epitech Group SpA for kindly provided the food supplement.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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