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Adam Wysokiński[1], Krzysztof Socha[2], Bartłomiej Konrad Sołtysik[2], Iwona Kłoszewska[1], Tomasz Sobów[3], Tomasz Kostka[2]

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Platelet count in elderly patients with unipolar depression – case control analysis

Liczba płytek krwi u pacjentów w podeszłym wieku z depresją jednobiegunową – analiza typu *case control*

[1] Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Łódź, Poland
[2] Department of Geriatrics, Medical University of Lodz, Łódź, Poland
[3] Department of Medical Psychology, Medical University of Lodz, Łódź, Poland
Correspondence: Dr hab. n. med. Adam Wysokiński, Klinika Psychiatrii Wieku Podeszłego i Zaburzeń Psychotycznych, Uniwersytet Medyczny w Łodzi, ul. Czechosłowacka 8/10, 92-216 Łódź, tel.: +48 42 675 73 72, fax: +48 42 675 77 29, e-mail: adam.wysokinski@umed.lodz.pl
Adam Wysokiński, MD, PhD, Department of Old Age Psychiatry and Psychotic Disorders, Medical University of Lodz, Czechosłowacka 8/10, 92-216 Łódź, Poland, tel.: +48 42 675 73 72, fax: +48 42 675 77 29, e-mail: adam.wysokinski@umed.lodz.pl

Abstract

Aim: While the effect of antidepressants on platelet functions is relatively well studied, there are few studies comparing platelet parameters, such as platelet count, between elderly patients with unipolar depression and non-depressed elderly subjects. Therefore, the aim of the study was to determine if there are differences in platelet count in elderly patients with unipolar depression (DEP) compared with non-depressed elderly patients (nonDEP) using case-control analysis. **Methods:** We measured platelet count in 582 (DEP: n = 291, nonDEP: n = 291) Caucasian in-patients aged ≥60. The mean age of the study subjects was 77.2 years, there were 243 (83.5%) women in both study groups. **Results:** The mean platelet count was significantly (p = 0.02) lower in the DEP group (241.6 ± 82.0) compared with the nonDEP group (263.6 ± 107.2). We also found that platelet count was not correlated with age. **Conclusions:** Compared with non-depressed controls, elderly patients with depression have decreased number of platelet cells. This, combined with the known effect of antidepressants on platelet agreeability, may translate into an increased risk of bleeding complications in the course of antidepressive treatment in elderly patients. Careful monitoring of platelet parameters is therefore recommended in the clinical population of elderly depressed patients.

Keywords: platelet count, depression, elderly, old age psychiatry

Streszczenie

Cel: O ile wpływ leków przeciwdepresyjnych na funkcje płytek krwi jest stosunkowo dobrze zbadany, o tyle niewiele jest badań porównujących parametry płytek krwi (takie jak liczba płytek krwi) u osób w podeszłym wieku z depresją jednobiegunową i bez depresji. Celem badania było określenie, czy istnieją różnice w liczbie płytek u pacjentów w podeszłym wieku z depresją jednobiegunową (DEP) w porównaniu z pacjentami w podeszłym wieku (nonDEP), za pomocą metody analizy *case control*. **Metody:** Oceniono liczbę płytek krwi u 582 (DEP: n = 291, nonDEP: n = 291) pacjentów rasy kaukaskiej w wieku ≥60 lat. Średni wiek badanych wynosił 77,2 roku, w obu grupach było 243 (83,5%) kobiet. **Wyniki:** Średnia liczba płytek krwi była istotnie statystycznie mniejsza (p = 0,02) w grupie DEP (241,6 ± 82,0) w porównaniu z grupą nonDEP (263,6 ± 107,2). Stwierdzono ponadto, że liczba płytek krwi nie korelowała z wiekiem. **Wnioski:** W porównaniu z grupą kontrolną u pacjentów w podeszłym wieku z depresją liczba płytek krwi była mniejsza. Fakt ten, w połączeniu ze znanym wpływem leków przeciwdepresyjnych na agregację płytek krwi, może przełożyć się na zwiększone ryzyko wystąpienia powikłań krwotocznych w trakcie leczenia przeciwdepresyjnego u pacjentów w podeszłym wieku. Zaleca się ostrożne monitorowanie parametrów płytek w populacji klinicznej u pacjentów w podeszłym wieku.

Słowa kluczowe: liczba płytek, depresja, podeszły wiek, psychogeriatria

INTRODUCTION

Platelets, also called "thrombocytes," are the smallest of the three major types of blood cells. They are 2.5 μm in average normal diameter and have a discoid shape. Platelets have no nucleus, they are fragments of cytoplasm, which are derived from the megakaryocytes of the bone marrow, and then enter the circulation (Machlus et al., 2014).

The principal function of platelets is to prevent bleeding. Platelets contribute to the haemostatic process in two different ways. First, through their adhesive and cohesive functions platelets form a haemostatic plug. Second, they activate coagulation mechanisms through the exposure of a phospholipidic surface, acting as a catalytic site for coagulation and the consolidation of the haemostatic plug. To promote correct haemostasis, platelets should ideally retain their adhesive and procoagulant properties. Furthermore, platelets possess important secretory functions. During the process of activation, platelets express internal membrane proteins and release adhesive proteins, coagulation and growth factors. Some of the proteins facilitate the cross-talk of platelets with leukocytes and endothelial cells (Rodgers, 1999). Thus, platelets play an important role in inflammatory and proliferatory events and play a critical role for tissue remodelling and wound healing (Wagner i Burger, 2003). Platelet concentration is measured either manually using a haemocytometer, or by placing blood in an automated platelet analyser using electrical impedance. Usually, the normal range (99% of population analysed) for platelets in healthy Caucasians is 150–400 × 10^3 per mm^3 (Ross et al., 1988). Platelet concentration is often informally referred to as the platelet count (PLT) without stating the units.

Depression is the leading cause of disability worldwide and is a significant contributor to the global burden of disease. It affects millions of people worldwide and is associated with great human and economic costs (stigma, limited activity, decreased life expectancy, raised health care costs). The World Health Organization (WHO) estimates that in Europe depression is responsible for 6% of total DALYs (disability-adjusted life years) caused by all diseases. The total annual cost of depression in Europe was estimated to be 118 billion Euros in 2004 (Sobocki et al., 2006), which makes depression the most costly mental disorder in this region of the world. The relation between platelet parameters and mental disorders has long been recognized. Studies show that patients with various mental disorders have elevated PLT (Ragolsky et al., 2013; Seidel et al., 1996). Also, the relationship between schizophrenia, major depression and increased platelet activity has been previously confirmed by several studies (Canan et al., 2012; Lee et al., 2014; Semiz et al., 2013). Other psychiatric conditions that have been reported to affect platelet activity are bipolar disorder (Soares et al., 1999) and anxiety disorders (Gurguis et al., 1999). Moreover, treatment with antidepressants may significantly affect platelet agreeability, which may translate into increased risk of bleeding complications, while age is one of the strongest risk factors for these complications (Wysokiński et al., 2015).

There are few studies comparing platelet parameters PLT between elderly patients with unipolar depression and non-depressed elderly subjects. Therefore, the aim of the study was to determine differences in PLT in elderly patients with unipolar depression compared with non-depressed elderly patients using case-control analysis.

METHODS

This was a retrospective, cross-sectional, case-control study. Databases of two clinical hospital units (old age psychiatry and geriatrics) were searched for complete blood count examinations, from which PLT was extracted. Data for all patients with depression admitted to the hospital from 2011 to 2014 were included in the analysis. This is a routine blood test done for every patient admitted. Only the first entry for each patient was used for analysis. Usually, the first blood tests are done the next day after admission. Thus, we have assumed that most patients that we included in the study were in the acute phase of depression. We focused on patients aged ≥60 years, with unipolar depression (all severities). For the diagnosis of depression the following codes were used: ICD-10: F32/F33, DSM-IV: 296. In our units diagnosis is based on the ICD-10 criteria, DSM-IV codes were given as reference. To every patient, an age- and sex-matched subject without depression was assigned. The control group consisted of 202 patients admitted to the hospital unit of geriatrics from 2011 to 2014, aged ≥60 years with excluded mental disorders. In both groups patients hospitalized due to acute somatic conditions (e.g. malignant diseases, infections, acute or chronic inflammatory diseases, renal disorders, myocardial infarction) were excluded from the analysis. Also, only non-demented patients, screened using Mini-Mental State Examination (MMSE) with a score ≥24 (Crum et al., 1993), were included into the analysis. Therefore, from the initial number of patients (n = 976; 411 subjects with depression, 465 subjects without depression), results for 582 Caucasian patients were finally included in the study. We have assessed depression severity using the 15-item version of the Geriatric Depression Scale (GDS-15) (scores of 0–4 are considered normal, 5–8 indicate mild depression, 9–11 indicate moderate depression, and 12–15 indicate severe depression), assuming that higher scores indicate higher depression severity (Marc et al., 2008). The protocol for the research project has been approved by a suitably constituted Ethics Committee of the institution within which the work was undertaken and it conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Tokyo, 2004).

Blood samples were drawn for all patients between 8 and 9 a.m. after 12 hours of overnight fast. Immediately after collecting the blood samples, complete blood count was determined using Sysmex XS-1000i TM Automated

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Hematology Analyzer (Sysmex, USA). From the result we extracted PLT (expressed in $\times 10^3/mm^3$). Reference range used in the analysis was $130–400 \times 10^3/mm^3$.

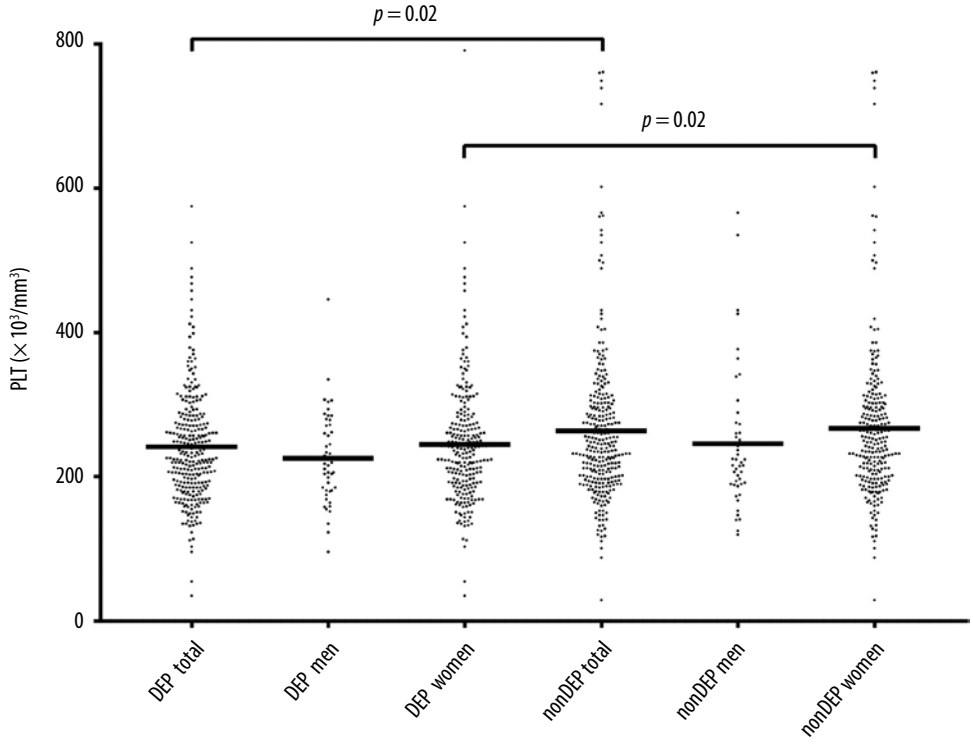
Statistical procedures were performed with STATA 14.1 (StataCorp, USA). Simple descriptive statistics (means ± standard deviations) were generated for continuous variables. For discrete variables, the number of patients and percentages are given. Normality of distribution was tested with Shapiro–Wilk test. PLT did not follow normal distribution, even after transformation of this variable, therefore differences were analysed using the Kruskal–Wallis and the Mann–Whitney tests. The difference between proportions was analysed with the chi-square test. Associations were tested by Spearman's correlation coefficients. The level of significance was set at $p < 0.05$.

RESULTS

The proportions of women in the depression (DEP) and non-depressed (nonDEP) groups ($n = 291$ and 291 in both groups) were 83.5% ($n = 243$ and 243 in both groups). The age of the whole study group and in the both subgroups was 77.2 ± 8.3 years.

The mean PLT in the study groups was: DEP 241.6 ± 82.0 (median: 231), nonDEP 263.6 ± 107.2 (median: 243) and the difference was significant ($p = 0.02$). PLT in men with and without depression were 225.7 ± 63.1 and 245.8 ± 95.6, respectively ($p = 0.61$). PLT in women with and without depression were 244.7 ± 85.0 and 267.1 ± 109.2, respectively ($p = 0.02$). There was a significant difference between men and women for PLT in the whole study group (235.8 ± 81.2 vs. 255.9 ± 98.4, $p = 0.02$), but not in the DEP group ($p = 0.20$) or the nonDEP group ($p = 0.06$). The summary of PLT in the study groups is shown in Fig. 1. As expected, depressed patients had significantly higher score in GDS-15 (8.4 ± 3.6 vs. 4.1 ± 3.1, $p < 0.001$), but there was no correlation between GDS-15 score and PLT in the DEP group, in the nonDEP group or in the whole study group.

Tab. 1 presents the distribution of PLT ranges in two study groups. The overall rate of being in the low PLT range (<130) was 2.4% for patients with depression and 3.4% for non-depressed patients, while the overall rate of being in the high PLT range (>400) was 4.1% for patients with depression and 7.6% for non-depressed patients. Evaluation of the low, moderate and high PLT ranges revealed no significant differences between the two groups with regard to PLT categories ($X^2 = 3.79$, $p = 0.15$). There were no differences in the distribution of PLT categories according to sex performed separately in the DEP and nonDEP groups (Tab. 1).



DEP – elderly patients with unipolar depression; **nonDEP** – non-depressed elderly patients.
Vertical bars represent means.

Fig. 1. PLT in the study groups

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Group	PLT category, *n* (%)			*p*†
	Low (<130)	Moderate (130–400)	High (>400)	
Depression: • Men • Women	7 (2.4) 2 (4.2) 5 (2.1)	272 (93.5) 45 (93.7) 227 (93.4)	12 (4.1) 1 (2.1) 11 (4.5)	$X^2 = 1.32$ $p = 0.52$
Non-depressed: • Men • Women	10 (3.4) 2 (4.2) 8 (3.3)	259 (89.0) 42 (87.5) 217 (89.3)	22 (7.6) 4 (8.3) 18 (7.4)	$X^2 = 0.15$ $p = 0.93$
† Chi-square test for sex vs. CRP-categories, performed separately in the DEP and the nonDEP groups.				

Tab. 1. Distribution of PLT ranges in the study groups

Analysing the association between age and PLT we have found the correlation to be non-significant for the DEP group ($r = 0.02$, $p = 0.69$), the nonDEP group ($r = -0.03$, $p = 0.55$) and the whole study group ($r = -0.01$, $p = 0.88$). Also, we have found no significant correlations between PLT and age in men or women in the DEP group (men: $r = -0.14$, $p = 0.35$; women: $r = 0.05$, $p = 0.47$), in the nonDEP group (men: $r = -0.12$, $p = 0.42$; women: $r = -0.02$, $p = 0.70$) and in the whole study group (men: $r = -0.13$, $p = 0.21$; women: $r = 0.01$, $p = 0.81$). Next, we have analysed differences in PLT between three age categories: <70 years, 70–80 and >80 years. The mean PLT in age categories for depressed and non-depressed patients are shown in Tab. 2. In both study groups there were no differences between PLT in age categories. Also, there were no sex differences for PLT in different age categories (Tab. 2).

DISCUSSION

The aim of this study was to investigate if there are any differences in platelet parameters between elderly depressed and non-depressed patients. Using case-control analysis, we have found that compared with non-depressed controls, elderly patients with depression have decreased number of platelets.

Since the study sample was not population-based, our results reflect possible associations with mental disorders and alterations in platelet parameters. The results from the large ($n = 4{,}978$) National Health and Nutrition Examination Survey (NHANES) include distribution of PLT values in the general population of non-Hispanic white population (geometric mean: 260; median: 271) (Segal i Moliterno, 2006). In depressed subjects in our study group, the mean PLT values were lower, while non-depressed subjects had comparable PLT values. On the other hand, results by Msaouel et al. (2014) for general non-Hispanic white European population ($n = 8{,}853$, mean age 74 years) showed the mean PLT to be 230, which is lower to our results.

In general, studies show that patients with various mental disorders have elevated PLT (Ragolsky et al., 2013; Seidel et al., 1996) and increased platelet activity (Canan et al., 2012; Lee et al., 2014l Semiz et al., 2013). Lazier et al. (2001) reported mean PLT value in 60 subjects with schizophrenia to be 282.5±66.7. Also, they found that in a 22q11 deletion syndrome subtype of schizophrenia, low PLT is a common feature. In another study, which assessed the effect of treatment with antipsychotics on platelet volume, Semiz et al. (2013) found in 35 patients treated with antipsychotics that platelet volume was increased.

Furthermore, in our study PLT values in patients with depression were lower compared with those reported by Canan et al. (2012), who studied platelet parameters in two age-matched groups: healthy controls ($n = 575$) and patients with depression ($n = 84$). In their study, the mean PLT value for depression group was 267.7 ± 69.4, which is significantly higher compared with elderly depressed patients from our study ($p = 0.008$). Again, our group of subjects with depression was much larger and probably better reflects

Group	Total	Age category			*p*†
		<70 (DEP: *n* = 63 nonDEP: *n* = 63)	70–80 (DEP: *n* = 111 nonDEP: *n* = 111)	>80 (DEP: *n* = 117 nonDEP: *n* = 117)	
Depression (all): • Men • Women • *p*‡	241.6 ± 82.0 225.7 ± 63.1 244.7 ± 85.0 *z* = 1.28 *p* = 0.20	247.8 ± 90.8 229.3 ± 56.2 252.6 ± 97.6 *z* = 0.22 *p* = 0.82	234.5 ± 64.9 234.2 ± 66.9 234.6 ± 64.8 *z* = 0.09 *p* = 0.93	244.9 ± 91.4 212.9 ± 65.7 250.0 ± 94.1 *z* = 1.63 *p* = 0.10	H = 0.89, *p* = 0.64 H = 0.99, *p* = 0.61 H = 1.33, *p* = 0.51
Non-depressed (all): • Men • Women • *p*‡	263.6 ± 107.2 245.8 ± 95.6 267.1 ± 109.2 *z* = 1.84 *p* = 0.06	254.3 ± 101.2 255.1 ± 113.5 254.1 ± 99.0 *z* = 0.81 *p* = 0.41	270.1 ± 107.8 244.9 ± 82.0 275.3 ± 112.0 *z* = 1.30 *p* = 0.19	262.4 ± 110.3 239.4 ± 100.6 266.1 ± 111.8 *z* = 1.11 *p* = 0.27	H = 1.19, *p* = 0.55 H = 0.20, *p* = 0.90 H = 1.04, *p* = 0.59
† Kruskal–Wallis test for age subgroups, performed separately in DEP and nonDEP groups; ‡ Mann–Whitney test for men vs. women within a given age-category, performed separately in the DEP and the nonDEP groups.					

Tab. 2. Mean PLT according to age groups

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platelet parameters in this sub-population of patients. Also, patients in the study by Canan et al. (2012) were younger compared with our sub-group with depression (mean age 40.9 vs. 77.2, respectively), and it is well documented that PLT is inversely correlated with age (Balduini and Noris, 2014). However, we did not confirm such a correlation between PLT and aging.

For patients with mental disorders, the importance of platelet parameters results from their role in the development of cardiovascular diseases. Cardiovascular diseases and associated mortality due to these conditions are more frequently encountered in psychiatric patients when compared with the general population (Correll et al., 2006). The mean platelet volume (MPV) is a surrogate biomarker of platelet activity and a useful prognostic test in cardiometabolic diseases. It has been shown that platelet size (measured as MPV) correlates with their reactivity (Yetkin, 2008). There is an increasing interest in MPV as an independent risk factor of atherosclerotic disease. Several studies have documented its association with acute myocardial infarction (Cameron et al., 1983) and its prognosis (Kiliçli-Camur et al., 2005) with coronary atherosclerosis (Martin et al., 1991), as well as the presence, short-term prognosis and long-term risk of stroke (Greisenegger et al., 2004). High MPV values have been reported in patients with hypertension (Ordu et al., 2010), hypercholesterolemia (Pathansali et al., 2001), and history of smoking (Kario et al., 1992). Therefore, the role of MPV as a risk proxy for cardiovascular disorders should be validated in further studies.

There might be several reasons why patients with mental disorders have changed platelet parameters. Alterations in PLT and reactivity may be caused by treatment with psychotropic medications. Therefore, the number of platelet should be determined prior to treatment and monitored in the course of therapy. Atypical antipsychotics may affect blood platelet structure, namely, increase their volume (Semiz et al., 2013). Also, anti-aggregatory properties of atypical antipsychotics have been described (Dietrich-Muszalska et al., 2010). An increased risk of thrombotic events in schizophrenic patients treated with antipsychotics has also been reported (De Clerck et al., 2004; Thomassen et al., 2001; Zornberg and Jick, 2000), and it may be one of the mechanisms responsible for an increased risk of cardiovascular morbidity associated with antipsychotic treatment (De Hert et al., 2011).

Assessment of platelet number is particularly important in patients with affective disorders, since many antidepressants (of serotonergic mechanism of action) may inhibit platelet activation and lead to bleeding complications, particularly in elderly patients (van Walraven et al., 2001). There are several reports pointing out the antiplatelet effect of antidepressant medications, particularly selective serotonin reuptake inhibitors (SSRI), including escitalopram (Ataoglu and Canan, 2009; Song et al., 2012), paroxetine (Musselman et al., 2000), sertraline (Serebruany et al., 2001) and fluoxetine (Lainé-Cessac et al., 1998). Non-SSRI antidepressants, such as bupropion (Piletz et al., 2000), and mirtazapine (De Berardis et al., 2003) seem to have no effect on platelet activity. In patients with bipolar disorder, thrombocytopenia may develop during treatment with valproic acid (De Berardis et al., 2003) and carbamazepine (Tohen et al., 1991). Careful monitoring of platelet parameters is therefore recommended in this clinical population.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could adversely affect the content of the publication or claim rights thereto.

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