RESEARCH ARTICLE

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The Effect of Polypharmacy on Procalcitonin Levels in the Intensive Care Admission of Geriatric Patients with Sepsis

ABSTRACT
Objective: Majority of intensive care unit(ICU) patients are elderly with sepsis and polypharmacy due to chronic diseases. Procalcitonin(PCT) is a biomarker used in early diagnosis of sepsis and gaining more value day by day. The aim of this study was to determine the effect of polypharmacy on PCT levels of elderly patients pre-diagnosed with sepsis in admission to ICU.
Methods: Data of the elderly patients such as demographic features like age and gender, sepsis-related laboratory results, SOFA and APACHE-II scores, medications they used who admitted to ICU due to sepsis were recorded.
Results: The median age of patients(n=227) is 77 years(70-84 years). The percentage of young-old, middle-old, and very-old patients was %41%, 35.7%, and 23.3%, respectively. 39.8% of young-old patients were polypharmacy(+) where 60.2% were polypharmacy(−). In middle-old patients, the rates are 56.8%–43.2%, and in very-old patients are 58.5%–41.5%, respectively. There is a significant difference in the prevalence of polypharmacy between young-old group and the other age groups. For polypharmacy group, level of PCT was significantly lower compared to the non-polypharmacy group. In the patients with severe infection and the risk of sepsis (PCT>5ng/mL), PCT levels were significantly different between polypharmacy and non-polypharmacy(p<0.05).
Conclusions: PCT levels were significantly lower in elder age who admitted to ICU, especially those with severe infection sepsis risk and polypharmacy compared to those without polypharmacy. Care should be taken in the diagnosis and follow-up of sepsis in elderly patients with polypharmacy and PCT levels should be evaluated together with clinical findings.
Keywords: Geriatrics, Intensive Care Units, Polypharmacy, Sepsis, Procalcitonin

Yoğun Bakıma Kabul Edilen Sepsisli Geriatrik Hastalarda Polifarmasinin Prokalsitonin Değerlerine Olan Etkisi

ÖZET
Amaç: Yoğun bakım (YB) hastalarının önemli bir kısmı sepsisli ve kronik hastalıkları nedeniyle polifarmasi maruziyeti olan yaşlılardır. Prokalsitonin (PCT) klinikte sepsis ön tanısında kullanılan, değeri gittikçe artan bir biyobelirteçtir. Çalışmamızla sepsis ön tanılı 65 yaş üstü hastaların yoğun bakıma kabulünde polifarmasinin PCT düzeylerine olan etkisi incelenmiştir.
Gereç ve Yöntem: Sepsis nedeniyle yoğun bakım kabulü yapılan yaşlı hastaların demografik özellikleri, sepsisle ilişkili laboratuvar sonuçları, SOFA ve APACHE II skorları, kullandıkları ilaçlar kaydedildi.
Bulgular: Toplam 227 hastanın olduğu çalışmada medyan yaş 77 (70-84)'dir. Hastaların %41'i genç-yaşlı, %35.7'si orta-yaşlı, %23.3'ü ileri-yaşlıdır. %49.8 hastada polifarmasi varken, %50.2'sinde yoktur. Genç-yaşlıların %39.8'i polifarmasi(+), %60.2'si ise polifarmasi(−)'dir. Orta-yaşlılarda oranlar sırasıyla %56.8 ve %43.2 iken ileri yaşlılarda %58.5 ve %41.5'dir. Yaş gruplarına göre polifarmasi görülme açısından genç-yaşlılarla diğer gruplar arasında anlamlı fark vardır (p<0.05). Ortalama 5.7±2.4 farklı ilaç kullandığı saptanan hastalarda sıkça kullanılan ilaçlar sırasıyla antihipertansifler, proton pompası inhibitörleri, steroid olmayan antiinflamatuarlardır. Ortalama PCT değeri polifarmasi(+) grupta, polifarmasi(−) gruba göre anlamlı şekilde farklı çıkmıştır. Ciddi enfeksiyonlu ve sepsis riski taşıyan polifarmasili yaşlılarda, 5ng/mL'nin üzerindeki PCT değerleri polifarmasi gözlenmeyenlere göre anlamlı şekilde düşüktür (p<0.05). 5ng/mL'nin altındaki lokal enfeksiyonlu ve olası sepsis riski taşımayan yaşlı hastalardaysa gruplar arasında PCT düzeyleri açısından bir anlamlılık yoktur.
Sonuç: Yoğun bakıma kabul edilen sepsisli yaşlılarda yaş ilerledikçe polifarmasi görülme oranları artmaktadır. Yoğun bakıma kabul edilen özellikle ciddi enfeksiyonlu ve sepsis riski taşıyan polifarmasili yaşlılarda PCT değerleri polifarmasi gözlenmeyenlere göre anlamlı şekilde düşüktür. Polifarmasili yaşlılarda sepsisin tanı ve takibinde dikkatli olunmalı, PCT değerleri mutlaka klinik bulgularla birlikte değerlendirilmelidir.
Anahtar Kelimeler: Geriatri, Yoğun Bakım Ünitesi, Polifarmasi, Sepsis, Prokalsitonin.

INTRODUCTION

Intensive care patients are individuals with multi-diseases, requiring interventional procedures and in need of hospitalization for a long time. Almost all of these patients are older than 65 years old, with significant physiological changes such as age-related immune system weakness and failing of liver and kidney functions. Taking chronic drug treatment due to their chronic conditions also increases the number of medications used (1-4). Studies show that when these patients are admitted to intensive care unit (ICU), they use an average of 5 different drugs, these increases to about 13 on the first day, and over 20 different drugs are used per patient during the entire intensive care hospitalization period (5). Although different definitions are available from literature, polypharmacy is often described as the simultaneous use of five and more drugs at the same patient (1,6). It has become an increasingly important health problem, especially in ICUs. Although the use of a large number of drugs do not always mean inappropriate and unnecessary use of drugs, it is a fact that it brings with it many risks related to drugs. Primarily, in this situation, which increases drug side effects and pharmacoeconomic cost, it also opens up important different interactions such as non-compliance with treatment, drug-drug or drug-disease interactions (1,7). Also, it is known that many drugs can affect most laboratory parameters. This probability increases correlation with the increasing number of drugs used (8). Although a wide range of guidelines on drug management, which are prepared to reduce the possible harm of polypharmacy, has been recommended in the literature, these are not sufficient in terms of number and evidence-based, especially for ICUs.

Currently, a dysregulated systemic reaction to a severe infection defined as sepsis. The condition can worsen within hours, rapidly becoming life-threatening. It is the most common cause of admission to an ICU. However, the symptoms of sepsis are not specific, making it difficult to obtain an early diagnosis, which can result in a delay of proper therapy. A delay in the diagnosis and the treatment of sepsis may cause to significant organ failure and can be accorded with elevated mortality rates. When sepsis is not treated early, severe septic conditions may occur, with a reported mortality rate of about 29% (9,10). A prompt antibiotic therapy and a potential reduction in mortality can be possible in sepsis with early diagnosis and effective management. High procalcitonin (PCT) levels can provide high sensitivity and specificity for diagnosing infections. In the systemic production of PCT, several inflammatory cytokines and especially bacterial endotoxins induce it in various tissue types. PCT that evaluated in a present systemic bacterial infection are normally higher than levels in most non-infectious inflammatory states and patients that has infections of fungal or viral etiology (11-13). In addition to demonstrating the presence and severity of infections, it is also one of the most important predictive biomarkers used in the clinic as a valuable tool for diagnosis and management of sepsis, determination, and guidance of antibiotic therapy, and reduction of antibiotic resistance (12,14,15). For these purposes, it has an increasing use in emergency and ICUs. In those who will be admitted to ICU, distinguishing the difference in whether the patient has a serious bacterial infection or local bacterial or viral infection has critical importance. Indeed, delaying the treatment of a serious bacterial infection can cause unfavorable results. Low PCT levels are very valuable while eliminating possible bacteraemia and have a powerful diagnose accuracy in distinguishing (12,15). Apart from all PCT tests that are used in clinical practice make an accurate and qualified evaluation, the importance of carefully evaluating the identified cut-off values according to patient groups with different types of infection and clinical evaluations have showed. Serum PCT level can consist of many different clinics such as cardiogenic shock, heat shock, severe pancreatitis, rhabdomyolysis, kidney failure, liver and autoimmune diseases (16). Furthermore, drugs able to have an influence on PCT levels. The drugs that have been found to typically increase or decrease serum PCT levels are drugs that cause an endogenous rise of cytokines (17,18). Also, it should be kept in mind that lipemic, icteric and hemolysis serums may cause problems such as low or excessive evaluation in laboratory results due to interference (18,19). Recent studies have demonstrated that there is an inverse correlation between vitamin D and PCT, that giving vitamin D to the patients or vitamin D deficiency in patients can significantly alter PCT results (20).

There are very few studies in the literature on whether PCT levels vary according to drug use (18). In this study, it is aimed to investigate whether polypharmacy causes any change in PCT levels in the intensive care admission of elderly patients with the usage of a large number of drugs and pre-diagnosed as sepsis

MATERIAL AND METHODS

The study is a retrospective, cross-sectional, descriptive study. This study began after its approval by the Health Sciences University Izmir Bozyaka Training and Research Hospital Ethics Committee for Non-Interventional Research (protocol number is: 11.03.2020-01) and was performed in accordance with the Declaration of Helsinki. In the period between 01.01.2018 and 31.12.2019, data of patients admitted to the Health Sciences University Izmir Bozyaka Training and Research Hospital Internal Medicine ICU with the

early-diagnosis of sepsis were recorded. The demographic characteristics such as age and gender of sepsis pre-diagnosed patients with sepsis-associated main laboratory results (White blood cells count (WBC), C-reactive protein (CRP), sedimentation, calcium, PCT, albumin, blood urea nitrogen (BUN), sequential organ failure assessment data such as (SOFA) score, acute physiologic assessment and chronic health evaluation (APACHE) II score, vitamin D and vitamin B12) and drugs used by patients were recorded. Patients with five or more drugs used are divided into patients with polypharmacy. Patients with a history of the use of drugs (immunosuppressive drugs, chemotherapeutics, corticosteroids, etc.) that directly disrupt the immune response in their treatment are excluded from the study. Patients older than 65 years were divided into young-old (65-74 years), middle-old (75-84 years), and very-old (85 years and older) groups. Serum PCT test were analysed by immunoassay method (Radiometer, PCT Test Kit, 942-964) with the AQT90 FLEX analyzer (Radiometer Medical ApS, Bronshoj, Denmark) in the Medical Biochemistry Laboratory, and the results are expressed in ng/mL.

Statistical Analysis: The results were defined as mean±standard deviation, frequencies (n) and percentages (%) or medians and interquartile ranges. The mean and median are compared using the t-test and Mann–Whitney U-test, as applicable, after checking normality using the Kolmogorov–Smirnov test. Test results with P values <0.05 are determined to be statistically significant. Statistical analysis of the data was conducted using the SPSS 17.0 software package (SPSS Inc., Chicago, IL, USA).

RESULTS

In this study, a total of 227 patients are evaluated. The median ages of all patients are 77 years (70-84 years). While 41% (n=93) of the patients are composed of young-old patients, 35.7% (n=81) of the patients are middle-old, and 23.3% (n=53) of the patients are very-old patients. While 55.5% (n=126) of all patients are women, 44.5% (n=101) are men. While the median age of women is 78 years (71-85 years), the median age of men is 75.5 years (69-82 years).

Polypharmacy is not present in 114 patients (50.2%), while in 113 patients (49.8%) polypharmacy is present. In the group with polypharmacy, distribution of men are 41.5% (n=47) and distribution of women are 58.5% (n=66). In the group with non-polypharmacy, the distribution of men is 47% (n=53) and the distribution of women is 53% (n=60). There is no statistical difference in terms of gender between the groups with and without polypharmacy (p>0.05). The median age in patients with polypharmacy is 78 years (71.5-85.5 years), whereas the median age in the group with non-polypharmacy is 75.5 years (69-82.3 years), and both groups. There is no statistically significant difference stated in terms of age (p>0.05). While polypharmacy is not present in 60.2% (n=56) of young-old patients, 39.8% (n=37) is stated present. While polypharmacy is not present in 43.2% (n=35) of middle-old patients, in 56.8% (n=46) of middle-old patients polypharmacy is present. While polypharmacy is not present in 41.5% (n=22) of very-old patients, polypharmacy is found to be present in 58.5% (n=31). According to age groups, there is a significant difference in terms of existing polypharmacy between the young-old groups and the other groups (p<0.05).

The first three drug groups used in elderly patients with polypharmacy, which it's found to be an average of 5.7±2.4 different drugs, are antihypertensive drugs, proton pump inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs), these followed by antihyperlipidemic drugs and other drugs from different drug groups (respectively antihistamines, Ginko biloba different herbal products for anti-aging and sedation, fish oil and vitamin preparations, etc.). The distribution of all the drugs used by the patients by groups is given in Figure 1.
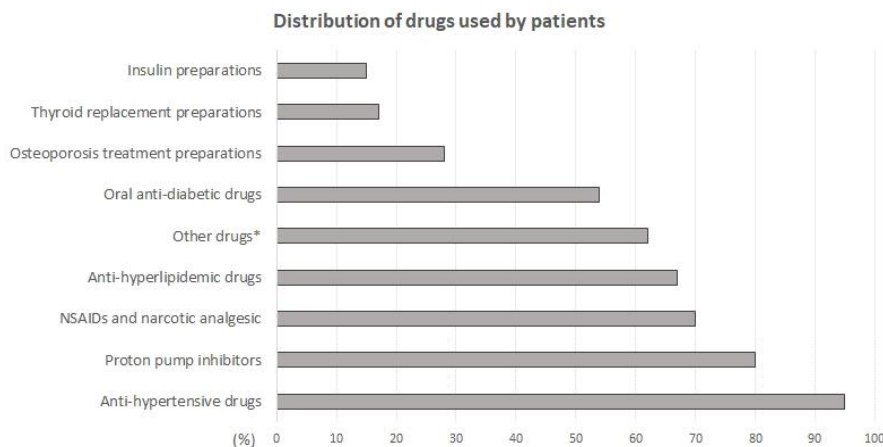

Figure 1. Distribution of drugs used before admission to the intensive care unit by groups. * Refers to drugs that cannot be included in the drug groups on the chart.

In the elderly patients with and without polypharmacy, the main laboratory parameters frequently requested and statistical significance between these groups are given in Table 1.

PCT levels grouped according to the clinical status of all elderly patients with and without polypharmacy are given in Table 2.

Table 1. Comparison of laboratory parameters, SOFA score, and APACHE II score between with polypharmacy and non-polypharmacy patients.

Parameters	Non-polypharmacy	Polypharmacy	P value
WBC, x1000 µL	10.9±6.6	10.3±6.2	NS
CRP, mg/L	121.9±112.1	103.7±81.2	NS
Sedimentation, mm/h	63.3±31.1	56.7±27.5	NS
Blood urea nitrogen, mg/dL	7.7±33.5	7.4±41.8	NS
Calcium, mg/dL	8.4±1.0	8.2±0.9	NS
Procalcitonin, ng/mL	9.5±12.6	6.5±9.8	p<0.05
Albumin, g/dL	2.6±0.6	3.0±3.0	NS
SOFA Score,	10.6±2.5	10.0±2.8	NS
APACHE II Score,	22.7±4.3	22.1±4.3	NS
Vitamin D, ng/mL	18.5±13.2	17.2±13.5	NS
Vitamin B12, pg/mL	625.3±461.2	459.6±362.7	p<0.05

NS; Not significant.

Table 2. Comparison of procalcitonin levels according to the clinical situation in patients with polypharmacy and non-polypharmacy.

Procalcitonin Levels According to Clinical Condition					
Systemic infection, Sepsis is suspected (0-2 ng/mL)		Local infection, Possible sepsis (2-5 ng/mL)		Septic shock (5+ ng/mL)	
Polypharmacy (n) No(39)	Yes(49)	No(37)	Yes(38)	No(38)	Yes(26)
Procalcitonin level 0.7±0.6	0.6±0.5	4.2±2.2	4.1±2.4	23.7±12.6	17.4±10.3
P value	0.272		0.405		**0.038**

* t-test and Mann-Whitney U test were used, p<0.05 was considered significant.

DISCUSSION

In the study, which consisted of all patients with intensive care patients over the age of 65, it is observed that the majority of the patients are young-old and middle-old, while the very-old patients are higher compared to the literature (2,3). Many chronic diseases such as hypertension, diabetes, vision and hearing disorders, circulatory and respiratory system diseases, joint and rheumatic diseases cause elderly patients to use a large number of drugs and therefore causing to polypharmacy. When we look at the drugs used by elderly patients in the study, it is noteworthy that drugs for this type of the chronic disease are included. Studies show that polypharmacy rates are higher in patients over 65 years of age compared to age groups under 65 years of age, but more in women. Also, it is stated that the prevalence rates of polypharmacy is increasing in directly proportional to aging in patients over 65 years of age. In the study, the presence of polypharmacy in very-old and middle-old patients is significantly higher compared to young-old patients, confirming this information (1,4,6). Furthermore, the average number of drugs used by elderly patients before admission to the ICU is compatible with the literature. Although there are different values in

different studies, it is emphasized that the average number of drugs used in elderly patients admitted to the ICU in the studies of Bell et al. can reach up to 12 (3,5,21). Besides, although the number of elderly female patients is partially high in both groups with and without polypharmacy in the study, there is no significant difference in terms of both age and gender. Although it is looked for coronary intensive care, in a similar study, it is emphasized that there is no significant difference between gender, but the risk of polypharmacy increases as the average age increases (22).

When the laboratory tests requested to confirm the diagnosis in elderly patients who are hospitalized in the ICU with an early diagnosis of sepsis are examined, a significant decrease in the PCT test especially in patients with polypharmacy is noticeable. As a matter of fact, the average laboratory levels decreased slightly in those with polypharmacy in all parameters except albumin. Considering the appreciation the PCT gains in management of the treatment and the diagnosis of sepsis in recent years, the importance of this significant decrease in PCT levels in patients with an early diagnosis of sepsis can be better understood. Even a small change in PCT levels

used for the diagnosis of sepsis is vital, especially in patients with immune deficiency or is immunosuppressed, in patients that has exacerbation of chronic obstructive pulmonary disease and septic shock that is treated with systemic corticosteroids (14). Of course, PCT is not a substitute for an attentive history and physical examination, and alone is not a complete criterion for determination of the hospitalization and administration of antibacterial treatment (12). However, it should not be forgotten that it is one of the few reliable tests that are frequently applied in intensive care when the subject is sepsis.

The findings indicate that in elderly patients with local infection and without the risk of possible sepsis, admitted to ICU there is no significant difference in PCT levels between polypharmacy and non-polypharmacy groups. However, what is clinically more meaningful to physicians in the intensive care day-to-day practice is that PCT levels in patients with severe infection above 5ng/mL and with polypharmacy at risk of sepsis are significantly lower than those without polypharmacy. This situation brings the risk of experiencing problems in the diagnosis and follow-up of sepsis in elderly patients with polypharmacy if it is overlooked; it also reduces the diagnostic value of PCT in elderly patients.

The absence of any significant difference in other laboratory parameters, SOFA score and APACHE II score in patients with polypharmacy, suggests that a mechanism specific to PCT may have been affected. PCT expression is tissue-specific in the absence of any infection and PCT is suppressed in non-neuroendocrine cells except in the parafollicular cells of the thyroid glands. As for bacterial infections, it is known that PCT is clear that many tissue types (liver, lung, kidney, adipose tissue, and muscle, etc.) can release intact PCT during bacterial infection. The increase in PCT levels specific to bacterial infections occurs directly due to lipopolysaccharide-structured bacterial endotoxins or through a variety of proinflammatory cytokines upregulation of the CALC-14 gene (13,16,20). It is possible that this complex gene regulation during the expression of PCT can be affected by various drugs and polypharmacy may increase this possibility even more. Kutz et al. claim that age and male gender may be one of the pre-analytical factors that can cause a decrease in PCT levels (23). Although it may come to mind that partial weakening of the immune response in the elderly with the advancement of age may also affect this system, the median age averages of elderly patients exposed and not exposed to polypharmacy are found to be close to each other, and there is no statistical difference stated in terms of age and gender. Nevertheless, adverse reactions such as drug adverse reactions, drug-drug interactions, malabsorption, and weight loss that may develop due to most drugs used in the elderly may also

disrupt reduced immunity (6). Indeed, the fact that the levels of vitamin B12 which its role in immunological response is important, are significantly low in elderly patients with polypharmacy, support this view. Insufficient immunological response may have caused a decrease in PCT levels. Similarly, studies are claiming that NSAIDs that cause inhibition in cyclooxygenase activity can indirectly affect immunity negatively (24). These drugs that are frequently prescribed and used in the geriatric period are among the most important drugs of polypharmacy and theoretically, have the power to cause a change in PCT levels despite few studies (23). Also, recent studies have shown that vitamin D has new functions such as differentiation, cellular proliferation, regulation of hormone secretion, and taking a role in the immunity. Chen et al. revealed that there is an inverse relationship between vitamin D and PCT levels in septic patients and that they increase PCT levels in vitamin D deficiency. Based on this, it has been claimed that vitamin D supplementation in septic patients can decrease PCT levels (16,20). Although findings show that vitamin D levels decreased slightly in the elderly group with polypharmacy compared to the group without polypharmacy, this decrease is not significant. However, it should be remembered that the use of vitamin D and other vitamin preparations that can alter the immune response, which is often overlooked by elderly patients, can affect PCT levels. Patients with immunosuppressant, chemotherapeutic and corticosteroid drug use, which directly disrupt the immune response, are not included in the study. Because, although studies are claiming that PCT is a useful marker in patients with such drug use history (12), PCT levels of these patients are often confusing in the clinic (23). These patients are excluded from the study because of their capability of affecting the study results and to provide reliability.

Although less likely, most biochemical analysis methods are known to interfere with drugs or other laboratory parameters (albumin, bilirubin, cholesterol, hemoglobin, triglycerides, etc.), drug molecules in serum may affect the correct evaluation of the test (8). A similar situation is also valid for PCT, and possible drugs, laboratory parameters and interference values are determined by the kit manufacturer by the PCT test. For example, it is reported that the interference value determined for trimethoprim can exceed 10% (18). In another study comparing the methods of two different devices, it is stated that there may be high bias values in icteric serum samples ranging from 6.6% to 28.6% (19). This list is constantly expanding with similar new studies. In a study in which Kutz et al. researched pre-analytical factors affecting tests including PCT in community-borne pneumonia patients coming to the emergency room, some drugs are shown to directly affect the PCT

levels. In particular, antibiotics and steroid therapy may cause a decrease in PCT levels (23). Considering that polypharmacy in elderly patients will automatically increase the possibility of interference, this issue should also be taken into consideration in the evaluation of test results in this group of patients.

In conclusion, findings show that PCT levels are significantly lower in the elderly who are admitted to intensive care, especially in the elderly with severe infection and at risk of sepsis, compared to those without polypharmacy. While this situation requires vigilance in the diagnosis and follow-up of sepsis in elderly patients with polypharmacy, overlooking this may decrease the diagnostic value of PCT in elderly patients.

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