ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI:10.5336/pharmsci.2022-94331

Evaluation of Potential Drug Interactions with Proton Pump Inhibitors: A Retrospective Study

Proton Pompası İnhibitörleri ile Potansiyel İlaç Etkileşimlerinin Değerlendirilmesi: Retrospektif Bir Çalışma

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ABSTRACT Objective: Proton pump inhibitors (PPIs) are the most prescribed gastrointestinal system medications and are often prescribed together with other medications. This may lead to drug interactions. In our study, it was aimed to determine the possible interactions of PPIs. **Material and Methods:** This retrospective study was conducted between January 1, 2021 and March 31, 2021. A prescription review was conducted in a community pharmacy in İstanbul and potential drug interactions were evaluated using the Medscape and Lexicomp databases. **Results:** A total of 114 prescriptions were reviewed. The mean age of the patients was 55.1±14.8 years, and the mean duration of PPIs use was 5 months. It was determined that the one who prescribed PPIs the most was the family physician and it was prescribed most frequently with the indication of gastroesophageal reflux disease. The total number of interactions in the prescriptions was determined as 248 in the Medscape database and 295 in the Lexicomp database ($p<0.05$). Pantoprazole was found to be the most interacting PPIs in both databases. Levothyroxine was found to be the drug that interacted most with PPIs in both databases. Age and duration of PPIs use were found to be positively significantly correlated ($p<0.05$). **Conclusion:** In our study, the number of potential drug interactions in prescriptions containing PPIs was found to be high. We think that the possible interactions and duration of use of drugs used due to comorbid diseases should be considered in prescriptions containing PPIs.

Keywords: Proton pump inhibitors; drug interactions; clinical pharmacy; prescriptions

ÖZET Amaç: Proton pompası inhibitörleri (PPI) en çok reçete edilen gastrointestinal sistem ilaçları olup, diğer ilaç gruplarıyla birlikte sıklıkla reçete edilmektedir. Bu durum, ilaç etkileşimlerine yol açabilmektedir. Çalışmamızda PPI ilaçlarının olası etkileşimlerinin belirlenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu retrospektif çalışma 1 Ocak 2021 ile 31 Mart 2021 tarihleri arasında yapılmıştır. İstanbul'da bir serbest eczanede reçete incelemesi yapılmış ve ilaç etkileşimleri Medscape ve Lexicomp veri tabanları kullanılarak değerlendirilmiştir. **Bulgular:** Toplam 114 reçete gözden geçirilmiştir. Hastaların yaş ortalaması 55,1±14,8 yıl, ortalama PPI kullanım süresi 5 ay olarak tespit edilmiştir. En sık PPI yazan hekimin aile hekimi olduğu ve en sık gastroözofageal reflü hastalığı endikasyonu ile reçete edildiği belirlenmiştir. Reçetelerdeki toplam etkileşim sayısı Medscape veri tabanında 248, Lexicomp veri tabanında 295 olarak belirlenmiştir ($p<0,05$). Pantoprazol, her iki veritabanında da en çok etkileşime giren PPI olarak bulunmuştur. Levotiroksin, her iki veri tabanında da PPI'lar ile en çok etkileşime giren ilaç olarak bulunmuştur. PPI kullanım süresi ile yaş arasında pozitif yönde anlamlı bir ilişki bulunmuştur ($p<0,05$). **Sonuç:** Çalışmamızda PPI içeren reçetelerdeki ilaç etkileşimlerinin sayısı yüksek bulunmuştur. PPI içeren reçetelerde komorbid hastalıklar nedeniyle kullanılan ilaçların olası etkileşimlerinin ve kullanım sürelerinin dikkate alınması gerektiğini düşünüyoruz.

Anahtar Kelimeler: Proton pompa inhibitörleri; ilaç etkileşimleri; klinik eczacı; reçeteler

Proton pump inhibitors (PPIs) are weak base drugs with lipophilic structures and can pass through the parietal cell membrane. Since PPIs target the extracytoplasmic luminal area of the proton pump, it must reach the acidic space inside the parietal cell. For this reason, PPIs are administered in the form of a prodrug which is activated in an acidic environment. PPIs are protonated in the acidic environment and bind covalently to the H+/K+-ATPase enzyme, irreversibly inhibiting the acid secretion of the pro-

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Peer review under responsibility of Journal of Literature Pharmacy Sciences.

Received: 14 Nov 2022 ***Received in revised form:*** 13 Feb 2023 ***Accepted:*** 15 Feb 2023 ***Available online:*** 22 Feb 2023

ton pump.[1] PPIs are a group of medicines used with high success in the treatment of various acid-peptic disorders, including gastroesophageal reflux, peptic ulcer, and gastropathy induced by nonsteroidal anti-inflammatory drugs.[2] Due to their widespread use, PPIs are often used together with other drug groups, thus increasing the potential for drug interactions. The increased availability of over-the-counter PPIs products has led to self-medication practices in public.

A drug interaction occurs when two or more drugs react with each other.[3] Pharmacokinetic and pharmacodynamic interactions are the basis of the drug interaction mechanism. While synergistic and antagonist interactions are the underlying mechanisms of pharmacodynamic interactions; pharmacokinetic interactions occur via the interaction of two drug molecules at the absorption, distribution, metabolism, excretion, and drug transport mechanisms.[4] Although some drug interactions may cause serious consequences, not all drug interactions are clinically significant.[5]

The classification of drug interactions in drug databases may vary. Lexicomp classified interaction levels into 5 categories (A, B, C, D, and X): A: No known, B: No action needed, C: Monitor therapy, D: Consider therapy modification, X: Avoid combination. The interaction levels X, and D potential drug interactions and being very important therapeutically and clinically significant, necessitating the modification of drugs and dosages or the avoidance of combinations. Medscape database categorizes the severity into 4 levels (contraindicated, serious, monitor closely and minor).

PPIs; affect drug absorption by changing the pH in the gastrointestinal tract, they also affect drug metabolism and elimination by inhibiting the cytochrome p450 and p-glycoprotein pathways.[6,7] While PPIs may reduce the plasma concentration of several anti-retroviral agents, such as dabigatran, mycophenolate mofetil; they may increase the plasma concentrations of some other drugs such as calcineurin inhibitors, methotrexate, and metformin.[8]

Potential drug interactions become an important factor in prescribing decisions, especially in patients who use more than one concomitant medication (such as elderly patients) or who take drugs with a narrow therapeutic window.[6] In pharmacies, which is the last step of healthcare for patients before using the prescriped drugs, more time can be spared for prescription control, the patient's medication history can be accessed, and detailed health history can be taken from the patient. The pharmacist can determine and intervene in potential drug interactions. Our study aims to determine the possible interactions in prescriptions containing PPIs.

MATERIAL AND METHODS

This was a retrospective descriptive study. The study was approved by the Marmara University Faculty of Medicine Research Ethics Committee (date: November 23, 2020, no: E-70737436-050.01.04-2000313206). Our study was conducted in accordance with the principles of the Declaration of Helsinki.

The patients over the age of 18 visiting a community pharmacy in İstanbul with a prescription containing PPIs between January 1, 2021, and March 31, 2021, were included in the study. Sample size was calculated by taking into account the number of prescriptions containing PPIs in the medula system of the pharmacy (during the 12-month period) where the study was conducted. Information on prescriptions [age, gender, name of PPIs, indication compatibility of International Classification of Diseases (ICD) codes, and other drugs in the prescription] was obtained. Potential drug interactions were evaluated using the Medscape and Lexicomp databases. Drug interactions classified as "contraindicated, serious, and monitor closely" from the Medscape database and C, D, and X classes from Lexicomp database were evaluated in our study.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences v. 15.0 (SPSS Inc., Chicago, IL, USA) program was used for the analysis. The information on prescription registration forms was expressed as "%". The relationship between demographic characteristics, the data in the prescription information, and potential drug interactions data were analyzed with the chi-square test or Fisher exact test and correlation analy-

sis. Significance was considered as $p<0.05$ with a 95% confidence interval.

RESULTS

A total of 114 prescriptions of 108 patients were reviewed. The mean age of the patients was 55.1±14.8 (25-87) years, of which 57% were female. The mean duration of PPIs use of patients was 5.0±0.4 (1-12) months.

It was determined that pantoprazole was one of the most prescribed PPIs with a rate of 40.4%. It was observed that the most frequently prescribed health institution was the family health center. When the prescriptions were examined, it was determined that the branch that prescribed the most PPIs was the family physician. When the indications in the prescriptions were grouped according to the "ICD" diagnostic codes, it was observed that 50% of the prescriptions had an indication for gastroesophageal reflux disease (GERD) (n=57) (Table 1).

The mean number of drugs excluding PPIs in 114 prescriptions examined during the study was found to be 2.3±0.2. The average number of interactions in the prescriptions was 2.2±0.4 in the Medscape database and 2.6±0.4 in the Lexicomp database, with a statistically significant difference ($p<0.0001$). Table 2 presents the average interaction degrees in the two databases.

When the active ingredients of PPIs were compared with the mean of potential drug interactions, pantoprazole was found to be the most interacting active ingredient but, no significant difference was found ($p>0.05$) (Table 3).

The total number of drugs in prescriptions was determined as 377. No significant correlation was observed between the number of drugs prescribed and the number of interactions in both databases (Medscape database: Spearman's rho 0.05 p=0.61; Lexicomp database: Spearman's rho 0.07 p=0.46).

It was observed that the drug that interacted most with PPIs was levothyroxine according to the Medscape and Lexicomp databases (Figure 1A, Figure 1B).

According to the Medscape database, pantoprazole was the most interacting drug among PPIs. Also, pantoprazole was found to be the "monitor closely" category with the highest rate (Figure 2A). According to the Lexicomp database, the most interacting drug was pantoprazole, with the highest degree of interac-

TABLE 1: Characteristics of the prescriptions.

	n	%
PPI		
Pantoprasole	46	40.4
Esomeprazole	33	28.9
Lansoprazole	20	17.5
Rabeprazole	14	12.3
Omeprazole	1	0.9
Prescribed in the health institution		
Public hospital	29	25.4
Family health center	68	59.6
Private hospital	17	14.9
Prescribed by specialist of cardiovascular surgery		
Internal medicine	2	1.8
Family medicine	14	12.3
Physical therapy and rehabilitation	71	62.3
Emergency medicine	4	3.5
General surgery	2	1.8
Obstetrician and gynecology	6	5.3
Cardiology	4	3.5
Rheumatology	4	3.5
Other*	2	1.8
	5	4.5
Indications for PPI		
No indication	16	14
Gastroesophageal reflux	57	50
Gastritis	11	9.6
Cholecystitis	4	3.5
Dyspepsia	12	10.5
Peptic ulcer	14	12.4

*Neurology, urology, gastroenterology, psychiatry and orthopedics;
PPI: Proton pump inhibitor.

TABLE 2: Total number of potential drug-drug interactions per prescription

Drug interaction database	Level of drug interaction	$\bar{X}$±SE
Medscape (n=248)	Serious (n=33)	0.3±0.1
	Monitor closely (n=215)	1.9±0.4
Lexicomp (n=295)	C (n=250)	2.2±0.4
	D (n=40)	0.4±0.1
	X (n=5)	0.04±0.02

$\bar{X}$±SE: Mean and standard error; n=Total number of drug interactions;
C: Monitor therapy; D: Modify regimen; X: Avoid combination.

TABLE 3: Number of potential drug interactions by PPI active ingredients.

PPI	Number of drug interactions ($\bar{X}$±SE) Medscape*	Lexicomp**
Pantoprazole	2.9±0.9 (n=135)	3.2±0.9 (n=147)
Esomeprazole	1.5±0.4 (n=51)	2.6±0.7 (n=86)
Lansoprazole	2.2±0.9 (n=44)	2.3±0.9 (n=45)
Rabeprazole	1.1±0.3 (n=16)	1.1±0.5 (n=16)

n=Total number of drug interactions; *Serious, and monitor closely categories; **C, D and X categories (C: Monitor therapy; D: Modify regimen; X: Avoid combination; PPI: Proton pump inhibitor; X±SE: Mean and standard error.

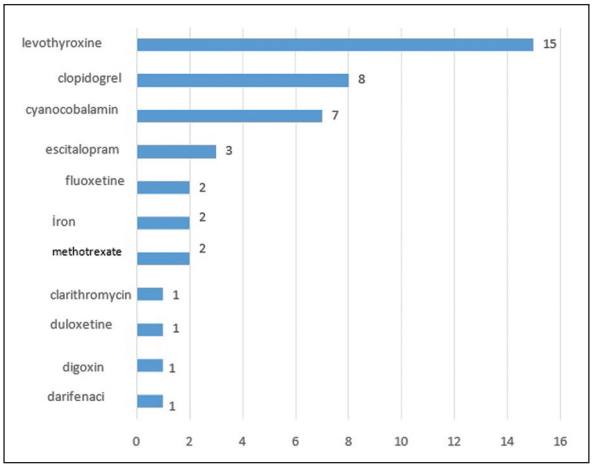

FIGURE 1A: The frequecy of drugs that interact most with proton pump inhibitor drugs (Medscape database).

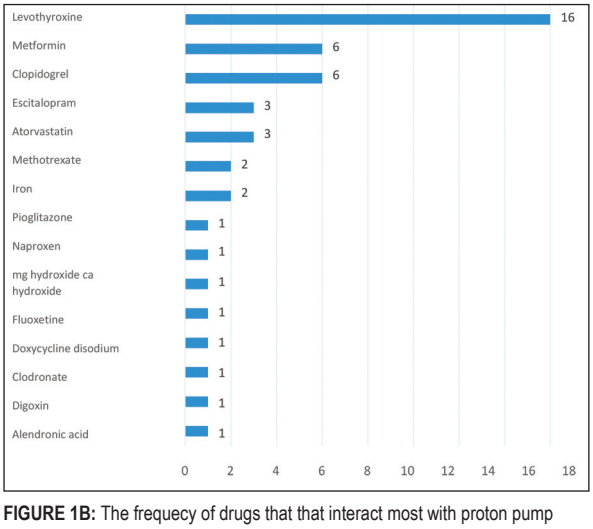

FIGURE 1B: The frequecy of drugs that that interact most with proton pump inhibitor drugs (Lexicomp database).

tion observed as degree "B (no action needed)" (Figure 2B).

It was observed that as the duration of PPIs use and the age of the patients increased, the number of potential drug interactions increased significantly according to both databases ($p<0.05$) (Table 4).

DISCUSSION

As one of the gastrointestinal system drugs, PPIs are frequently prescribed together with other drug groups. This may lead to potential drug interactions with PPIs, and may also lead to inappropriate long-term use of PPIs, especially when prescribed by different doctors. In this study, prescriptions containing PPI in a community pharmacy were examined retrospectively. The prescribing patterns and potential drug interactions of PPIs were evaluated.

When the patient profile in the prescriptions was evaluated, it was determined that 75% of the patients were women. Similarly, in a study on the PPIs prescribing habits of family physicians in Sakarya, the rate of female patients using PPIs were found to be 61%.[9] In the same study, it was determined that the majority of the patients were between the ages of 41 and 60. In our study, the mean age of the patients was found to be 55 years old.

The average duration of PPIs use was found to be 5 months in our study. In a similar study conducted in a hospital, it was found that 50% of the patients were prescribed PPIs for 1-3 months.[10]

In our study, it was determined that 81% of prescriptions were prescribed by family physicians. In a retrospective study conducted on outpatients, it was found that 80% of prescriptions were prescribed by an internal medicine specialist.[11] In another study, it was determined that 63% of the doctors who prescribe PPIs were internal medicine specialists.[12] Since the pharmacy where our study was conducted was located just across from the family health center, we think that the prescriptions containing PPIs in our study were mostly written by family physicians.

In our study, the most commonly prescribed PPIs active ingredients were pantoprazole (40%) and esomeprazole (29%). In a study conducted in the United Arab Emirates, the most prescribed PPIs drug was found to be pantoprazole with 87%, which is consistent with our study.[13] In a study conducted

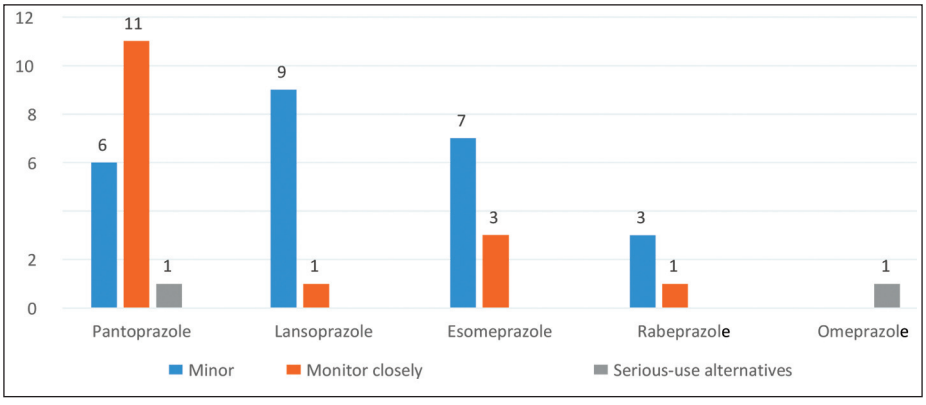

FIGURE 2A: Proton pump inhibitor-potential drug interaction degrees in the Medscape database.

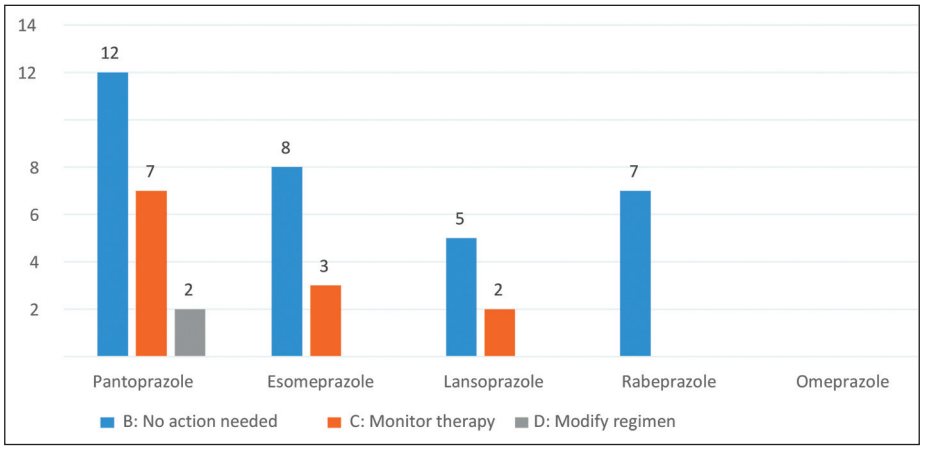

FIGURE 2B: Proton pump inhibitor-potential drug interaction degrees in the Lexicomp database.

TABLE 4: Evaluation of potential drug interactions by age and duration of PPI drug use.

	Number of potential drug interactions	
	Medscape database (Correlation coefficient)	Lexicomp database (Correlation coefficient)
PPI use (months)	0.32 p<0.0001*	0.39 p<0.0001*
Age	0.26 p=0.004*	0.38 p<0.0001*

*Statistical significance, Spearman's correlation analysis was performed;
PPI: Proton pump inhibitor.

in Sakarya, it was observed that esomeprazole (35%) was the most prescribed PPIs by family physicians.[9]

In a study conducted in Saudi Arabia, it was reported that the most commonly prescribed PPI drug was omeprazole (85%). In the same study, the rate of pantoprazole was found to be 15%.[10] In another study conducted in Saudi Arabia, esomeprazole was determined as the most commonly prescribed PPIs drug with a rate of 75%. In the same study, this rate was determined as 11% for omeprazole.[12] A study conducted in Ireland found that the most commonly prescribed PPIs in the hospital was esomeprazole (54%).[14] In a study conducted in Italy, the most commonly prescribed PPIs drug was found to be omeprazole.[15] These differences may be due to physicians' prescribing habits and changes in the brand's marketing strategy. Some physicians' believe that the older drug is safer and they continue to prescribe omeprazole to their patients.[16]

Investigating the compatibility of indications in prescriptions containing PPIs, it was found that PPIs were mostly prescribed for GERD with a rate of 50%. It was observed that 14% of these prescriptions did

not have a suitable indication for PPIs. In a study conducted in a hospital in Saudi Arabia, peptic ulcer was found to be the most common indication for the use of PPIs.[10] It was observed that 6.5% of the prescriptions with PPIs did not have any indications approved in the guidelines. In another study conducted in Sakarya, GERD indication was found to be the most common reason for prescribing PPIs with a rate of 83%, which is similar to our study.[9] In another study conducted in Slovakia, GERD (25%) was the most preferred indication for prescribing PPIs at hospitalization, which was found to be consistent with the results of our study.[17]

According to a study conducted on outpatients in Indonesia, 79% of the indications of PPI therapy used were found to comply with the guidelines. A potential PPIs interaction risk with other drugs was found in 324 prescriptions (81%) out of 475 (Drug interactions were traced using Micromedex Solutions (IBM Micromedex Solutions. Truven Health Analytics, Inc. Ann Arbor, Michigan) and based on Stockley's Drug Interaction 8th edition, Drug Interactions by Hansten, Drug Interaction Facts, 5th edition, and related journals). Of all interactions, 42 were considered major interactions, 138 moderate interactions, and 295 minor interactions.[11] In this study 14 drugs that can potentially interact with PPIs such as mycophenolate mofetil, clopidogrel, cilostazol, warfarin, iron, levothyroxine, propranolol, cyclosporine, simvastatin, atorvastatin, cyanocobalamin, sucralfate, theophylline, and antacids have been identified and show similar findings with our study.[11]

In our study, 114 prescriptions containing PPIs were examined and it was determined that the drug that interacted most with PPIs was levothyroxine (n=15 and n=16) according to Medscape and Lexicomp databases respectively. In a study conducted in a community pharmacy with 100 patients in İstanbul, it was determined that levothyroxine was the most interactive drug with PPIs in 16 patients similar to our study.[18] In a study conducted with 1,288 patients discharged from the hospital in Italy, the highest interaction rate was found between omeprazole- clopidogrel.[15] Long-term use of PPIs may increase the risk of interactions in patients with chronic conditions.[19]

There were 114 prescriptions in our study, and the total number of drugs in these prescriptions was found to be 377. No significant correlation was found between the number of drugs prescribed and the number of interactions. (Medscape database: Spearman's rho 0.05 p=0.61 Lexicomp database: Spearman's rho 0.07 p=0.46) This is inconsistent with the view that polypharmacy increases drug interaction. The most interacting PPIs with prescription drugs was found to be pantoprazole but no statistically significant difference was found. In another study, healthcare professional who works in the intensive care unit were trained on the interactions of PPIs.[20] Before and after the training, the number of drug interactions and the rates of PPIs side effects were evaluated and it was found that the number of interactions decreased from 66% to 54% and the side effects from 44% to 25%.[20] With similar studies to be carried out, possible drug interactions can be evaluated by increasing the consciousness and awareness of healthcare professional.

LIMITATIONS

Since our study was conducted during the pandemic period, the number of prescriptions examined is low. In addition, access to pharmacies was limited to one person and patient-pharmacist interaction was kept at a very low level. For this reason, only the prescriptions could be examined and the sociodemographic characteristics of the patients could only be obtained through the system.

CONCLUSION

In conclusion, it was observed in our study that PPIs were mostly prescribed by the family physician and the most commonly prescribed PPIs was pantoprazole. The most interacting PPIs with prescription drugs was found to be pantoprazole but no statistically significant difference was found. In our study, different degrees of drug interactions were detected in the prescriptions of patients with using other pharmacologic agents for comorbid conditions, and the most common PPIs-drug interaction was found to be with levothyroxine. However, this drug interaction can be managed properly if patients take levothyrox-

ine one hour before PPIs. Since the potential drug interactions are extremely important in pharmacy practice, we think that concomitant diseases and all regularly used drugs should be considered in the evaluation process of prescriptions containing PPIs. In order to generalize the results of our study, studies with more prescriptions are needed.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Songül Tezcan, Beyza Nur Bayuk, İzel Dede;* ***Design:*** *Songül Tezcan, Beyza Nur Bayuk;* ***Control/Supervision:*** *Songül Tezcan, Beyza Nur Bayuk;* ***Data Collection and/or Processing:*** *Songül Tezcan, Beyza Nur Bayuk, İzel Dede;* ***Analysis and/or Interpretation:*** *Songül Tezcan, Beyza Nur Bayuk;* ***Literature Review:*** *Songül Tezcan, Beyza Nur Bayuk;* ***Writing the Article:*** *Songül Tezcan, Beyza Nur Bayuk, İzel Dede;* ***Critical Review:*** *Songül Tezcan, Beyza Nur Bayuk, İzel Dede.*

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