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ANXIETY AND ASSOCIATION WITH COVID-19 VACCINATION-RELATED HEADACHE SYMPTOMS

COVID-19 AŞISINDAN SONRA YAŞANAN BAŞ AĞRISI SEMPTOMLARININ KAYGI DÜZEYİ İLE İLİŞKİSİ

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Abstract

Objective: To prevent the pandemic, widespread vaccination work continues in Turkey. We aimed to determine the level of pain, headache, and anxiety among the neuropsychiatric symptoms after the vaccination was given to the healthcare workers.

Methods: Healthcare workers who have received the COVID-19 vaccine were given a questionnaire through the internet after the second dose of the vaccination. A form consisting of 34 questionnaire questions about their demographic characteristics, whether they experienced pain or headache after vaccination and the Beck Anxiety scale was to be filled.

Results: The data of 484 participants were examined in our study. 31.1% of the participants reported experiencing a headache after the vaccination. In the analysis using a single variable model, it was found that individuals with mild anxiety symptoms had a 2.6-fold increased risk of experiencing headaches. For those with moderate anxiety symptoms, the risk was 4.5 times higher, while individuals with severe anxiety symptoms faced a 7.2-fold increased risk. Additionally, the study observed that patients with a history of previous headaches had a 2-fold higher risk compared to those without such a history in the single variable model.

Conclusion: We suggest that the assessment of anxiety levels during vaccination after COVID-19 vaccination can be an important indicator in predicting the development of headaches. Further studies on this will be important in optimizing vaccination programs and ensuring social immunity.

Keywords: Anxiety, COVID-19, Headache, SARS-CoV-2, Vaccine

Öz

Amaç: Pandemiyi önlemek amacıyla Türkiye'de yaygın aşılama çalışmaları devam etmektedir. Bu çalışmada sağlık çalışanlarına aşı yapıldıktan sonra nöropsikiyatrik semptomlardan ağrı, baş ağrısı ve anksiyete düzeylerinin belirlenmesi amaçlandı.

Yöntem: COVID-19 aşısı olan sağlık çalışanlarına aşının ikinci dozundan sonra internet üzerinden anket verildi. Demografik özellikleri, aşı sonrası ağrı ya da baş ağrısı yaşayıp yaşamadıkları ve Beck Anksiyete Ölçeği ile ilgili 34 sorudan oluşan bir form doldurulması istendi.ve mikroskobik görüntüler değerlendirilmiştir**.**

Bulgular: Çalışmamızda 484 katılımcının verileri incelenmiştir. Katılımcıların %31,1'i aşılamadan sonra baş ağrısı yaşadığını bildirdi. Tek değişkenli modelde hafif kaygı belirtileri 2,6 kat, orta düzeyde kaygı belirtileri 4,5 kat ve şiddetli kaygı belirtileri 7,2 kat daha yüksek baş ağrısı riski taşıyordu. Benzer şekilde, önceden baş ağrısı olan hastaların tek değişkenli modelde olmayanlara göre 2 kat daha fazla risk taşıdığı gözlendi.

Sonuç: COVID-19 aşısı sonrası aşılama sırasındaki kaygı düzeyinin değerlendirilmesinin baş ağrısı gelişimini öngörmede önemli olduğu gözlenmiştir. Bununla ilgili ileri çalışmalar aşılama programları sonrası baş ağrısının yönetilmesi ve toplumsal bağışıklığın sağlanması açısından önemli olacaktır.Anahtar

Anahtar Kelimeler: Anksiyete, COVID-19, Baş Ağrısı, SARS-CoV-2, Aşı

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Introduction

The severe acute respiratory failure syndrome caused by SARS-CoV-2, the COVID-19 pandemic, has been on a large scale not seen since the 1918 influenza pandemic. Although the predominant clinical picture is associated with respiratory disease, neurological signs are increasingly recognized.[1]

Clinical evidence from COVID-19 patients indicates that the virus causes damage to endothelial cells in various organs, including the lungs, heart, kidneys, liver, and intestines. This multi-organ involvement sets COVID-19 apart from other viral infections such as the H1N1 influenza and SARS, which primarily affect the lungs.[2]

SARS-CoV-2, the virus that causes COVID-19, demonstrates neurotropism, meaning it has an affinity for the nervous system. This is attributed to the presence of ACE2 receptors in endothelial cells, which are also found in the brain, including glial cells and neurons. Consequently, the virus can potentially target and affect the nervous system. The neurotropic nature of COVID-19 aligns with the wide range of neurological, psychiatric, and psychological symptoms and syndromes observed in individuals throughout the course of the infection. [2,3]

Moriguchi et al. observed viral RNA in the cerebrospinal fluid of a patient with aseptic encephalitis, and Paniz-Mandolfi et al. reported the presence of SARS-CoV-2 viral particles in neuronal and capillary endothelial cells in the frontal lobe tissue in a postmortem study. Therefore, SARS-CoV-2 neuroinvasion, neuroinflammation, and impairment of the blood-brain barrier (BBB) have been suggested to be responsible for neurological symptoms. [4-6]

To prevent the pandemic, vaccination studies have gradually commenced in Turkey. Priority is accorded to healthcare workers and most of them have received the second dose of vaccination. The vaccine, administered in Turkey, is inactivated with Beta-propiolactone and contains alum adjuvant. It belongs to Sinovac and is of Chinese origin. Looking at the side effect profile, it resulted in a low side effect rate - no different from a placebo. [7-9]

A study conducted in Turkey in 2021 involving 780 healthcare workers revealed that 62.5% of them experienced at least one side effect following COVID-19 vaccination. The most frequently reported side effect was injection site pain, which was reported by 41.5% of the participants. Fatigue was experienced by 23.6% of the individuals, and headache was reported by 18.7%, making them the next most common side effects.[10]

Vaccines are successful in providing immunization, despite being inactive. Due to COVID-19's ability to affect the nervous system, cause neuroinflammation, and potentially disrupt the blood-brain barrier, it is expected that neuropsychiatric symptoms may arise following vaccination. Our objective is to assess these symptoms, particularly pain, headache, and anxiety. To achieve this, we have planned to administer a questionnaire on headache and pain, as well as an anxiety scale, to healthcare professionals after they have received the full vaccine dosage.

Methods

The study complies with the Helsinki Declaration requirements and received local ethics committee approval (Sakarya University, Ethics Committee Decision Letter No E-71522473-050.01.04-14843/122). For the survey for the assessment of pain, headache, and anxiety in healthcare professionals after the COVID-19 vaccination in 2020, the healthcare workers who completed the 2nd vaccination program and who willingly participated in the study were given a questionnaire form and Beck Anxiety Scale prepared on the internet. The vaccination program applied to healthcare workers in Turkey is in the form of two doses at a one-month interval. Our questionnaire form consisted of two parts and a total of 34 questions. In the first part, there were 24 questions, demographic data such as age, gender and duty, vaccination, and whether they experienced pain in general, and if they experienced pain, the region and severity were questioned. The pain experience location question has multiple-choice options. In the second part of the study, only patients with headaches were included. They were asked about the duration, characteristics, analgesic requirements, and severity of their headaches. Additionally, the Beck Anxiety scale was administered online as a continuation of the questionnaire. Participants who chose to take part in the survey provided informed consent. Individuals under the age of eighteen and those who did not complete the necessary data form were excluded from the study. Our study is an observational questionnaire study conducted in a cross-sectional manner.

Statistical analysis

The data were evaluated by uploading it to the computer environment via SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as mean (±) standard deviation, median (minimum-maximum), frequency distribution, and percentage. The conformity of the variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk Tests). To predict treatment response using defined sociodemographic and clinical data, a logistic regression model with a retrospective elimination method was applied. The statistical significance level was accepted as $p < 0.05$.

Results

In our study, the data of 484 participants were examined. It reported that 443 of its participants had completed two doses of the vaccine. The mean age of the participants was 40.1±8.9, 76.6% were women and 60.3% were working as doctors. The sociodemographic characteristics of the study group are given in Table 1.

Table 1. Sociodemographic features

Study Parameters		n (%) (n=443)
Gender	Male	103 (23.3%)
	Female	340 (76.7%)
Education	High School	4 (0.9%)
	University	252 (56.9%)
	Doctorate / Specialist Physician	187(42.2%)
Job	Doctor	267 (60.3%)
	Dentist	88 (19.9%)
	Nurse	47 (10.6%)
	Staff	20 (4.5%)
	Anesthesia Technician	12 (2.7%)
	Medical secretary	9 (2.0%)
Working place	University Hospital	136 (30.7%)
	Training and Research Hospital	118 (26.6%)
	Public Hospital	87 (19.6%)
	Freelance	31 (7.0%)
	Other Public Institutions	25 (5.6%)
	Family Health Center	24 (5.4%)
	Private Hospital	22 (5.0%)

Table 2. COVID-19 and vaccine-related data

Study Parameters		n (%)
Have you had COVID-19 before?	Yes	67 (14.9)
	No	376 (85.1)
How long has it been if you've had COVID-19?	1 month and less	5 (1.1)
	2-4 months	37 (8.4)
	5-6 months	7 (1.6)
	More than 6 months	17 (3.8)
	I did not have the disease	376 (84.9)
How long ago did you get the first dose of COVID-19 vaccine?	21-35 days	49 (11.1)
	36- 45 days	224 (50.6)
	More than 45 days	170 (38.4)
Have you had any pain after the first COVID-19 vaccine?	Yes	195 (44.0)
	No	248 (56.0)
How long ago did you get the second dose of COVID-19 vaccine?	10-20 days	323 (72.9)
	21-35 days	115 (26.0)
	36- 45 days	3 (0.7)
	More than 45 days	2 (0.5)
Did you have any pain after the second COVID-19 vaccine?	Yes	203 (45.8)
	No	240 (54.2)
Did you feel the need to use painkillers after the COVID-19 vaccine?	Yes	109 (24.6)
	No	210 (47.4)
	No Pain	124 (28.0)
Did your pain that started after the COVID-19 vaccine worry you about getting the disease?	Yes	52 (11.7)
	No	391 (88.3)
Have you applied to the health institution regarding your pain that started after the COVID-19 vaccine?	Yes	6 (1.4)
	No	437 (98.6)
In which area did the pain occur?	Vaccinetion site	140 (31.6)
	Head	138 (31.1)
	Arms	67 (15.1)
	Neck	54 (12.0)
	Chest	32 (7.2)
	Back	29 (6.5)
	Legs	23 (5.2)
	No pain	248 (56.0)

Notably, 44% of the participants (n: 195) reported any pain after the first vaccine and 45.8% (n: 203) after the second vaccine. 24.6% (n: 109) of them used painkillers due to this pain. In addition, 1.4% (n: 6) stated that they applied to a health institution after the vaccination due to pain. Table 2 shows data related to COVID-19 and vaccines.

According to the findings of our study, 31.1% of the participants reported having a headache after vaccination, and 21.0% used painkillers for the headache. When the duration of pain was questioned, the highest rate (11.1% in the whole group) reported that the pain lasted for 2-4 hours, and when they scored it out of 10, the median score was 4 (Q1:2-Q3:6). 24.2% of the participants reported that they were diagnosed with a headache-related disease before vaccination. Table 3 shows headache-related data.

Table 3. Headache data

Study Parameters		n (%)	(n:443)
Have you had a headache after the COVID-19 vaccine	Yes	138 (31.1)	138
	No	305 (68.8)	305
Have you used painkillers for your headache?	Yes	93 (21.0)	93
	No	45 (10.0)	45
	No headache after vaccination	305 (68.8)	305
How long was the headache without taking painkillers?	<2 hours	17 (3.8)	17
	2-4 hours	49 (11.1)	49
	4-24 hours	42 (9.5)	42
	24-72 hours	24 (5.4)	24
	More than 72 hours	6 (1.4)	6
	No pain	305 (68.8)	305
How was the headache severity?	Mild	16 (7.0)	16
	Moderate	75 (16.9)	75
	Severe	47 (10.6)	47
	No headache after vaccination	305 (68.8)	305
Is there a migraine, tension type or other headache previously diagnosed by a doctor?	Yes	107 (24.2)	107
	No	336 (75.8)	336

Upon the examination of the Beck Anxiety scale scores, it was observed that the median score of the participants was 5 (Q1: 2-Q3: 11). According to the classification, 20.1% (n: 89) had mild anxiety, 5.4% (n: 24) reported moderate anxiety and 2.0% (n: 9) reported severe anxiety.

The forecast the occurrence of headaches within the entire group of participants (n: 443), a model was developed using the backward elimination method. The significant variables included gender, previous COVID-19 history, previous headache-related diagnosis, and anxiety classification (Chi-square: 25.832, p: 0.001). This model explained 39% of the variance (Nagelkerke R2: 0.398) and achieved a 70% correct classification rate. In the univariable model, individuals with mild anxiety symptoms had a 2.6 times higher risk of experiencing headaches, while those with moderate anxiety symptoms had a 4.5 times higher risk, and those with severe anxiety symptoms had a 7.2 times higher risk (Table 4).

Additionally, patients with previous headaches were twice as likely to be at risk in the univariable model compared to those without.

Table 4. Multivariable Logistic regression model to predict having headache after vaccination

		Multivariable Model			
		B	**S.H.**	**p**	**OR**
Beck Anxiety Inventory	No worries (0-7)	Reference category			
	Mild Level (8-15)	0.648	0.253	0.010	1.912
	Moderate Level (16-25)	1.262	0.441	0.004	3.532
	Severe (26-35)	1.656	0.725	0.022	5.237
Having previously been diagnosed with a headache-related disease	No	Reference category			
	Yes	0.551	0.239	0.021	1.736

*In Step 1, the variables of Age, Gender, Beck Anxiety Classification, Previous COVID and Previous headache-related diagnosis were entered. Step 4 shown in the table.

Discussion

This study shows that participants who have anxiety symptoms tender to have headaches after vaccination. In addition, previous headache is important for post vaccination headache. Sekiguchi et all also showed that patients with pre-existing headaches were more likely to suffer from headaches after COVID-19 vaccination. Both migraine and non-migrainous headache groups were found to have significantly higher rates of headaches after vaccination. But they mentioned that the majority of their participants were women so caution shouldn't be missed when applying results to the general population.[11] Similarly our participants were more likely women and it is one of our study's key limitations. Göbel et all studied headache characteristics after vaccination BNT162b2 mRNA. Their results showed that this type of headache was similar to neither migraine nor tension type. If there is a pre-existing primary headache such as migraine, the hyperexcitability of trigeminovascular neurons can increase pain as the reason for the long duration and intensity of pain in patients with post-vaccine headaches. Also, post-vaccine headaches can be triggered by the immune responses of the protein. The pathomechanisms of headaches after vaccination against COVID-19 are not yet understood. [12]

Regardless of the precise mechanisms by which SARS-CoV-2 enters the central nervous system (CNS) and how sensitively it exerts its pathogenetic effects, a wide variety of neuropsychiatric symptoms have been reported in COVID-19 patients affecting both the CNS and the peripheral nervous system (PNS).[13] Early neurological symptoms include loss of sense of smell and taste, as well as body aches, headache, and myalgia. Anosmia, fever, and myalgia are considered the strongest independent predictors of positive SARS-CoV-2 tests. At the same time, the percentage of patients suffering from these complications varies widely between different studies, assessment time points, and geographic locations even though the involvement of both CNS and PNS is now well documented. [2,14]

Another fundamental aspect of SARS-CoV-2 infection in the (CNS) is the induction of high levels of systemic inflammation and disruption in the blood-brain barrier (BBB). This high inflammation promotes neuroinflammation in conditions such as sepsis, which ultimately significantly impairs brain homeostasis and leads to neuronal apoptosis. [15,16] Interestingly, in one study, the total blood lymphocyte counts were significantly lower in patients with CNS-related (eg headache, dizziness, ataxia) or muscular (eg, myalgia) symptoms. Immunological findings were in the same line in COVID-19 patients with neurological symptoms. [17] A study from Wuhan noted that 36% of the patients admitted to a hospital for SARS-CoV-2 infection had neurological features, mostly mild symptoms such as dizziness and headache, but these symptoms may be more specific neurological syndrome than a systemic disease. [18,19]

Whittaker et al. conducted a comprehensive review of existing published literature and found that headache and anosmia are frequently observed neurological symptoms associated with SARS-CoV-2. [20] In the study conducted by Mao et al. in Wuhan, neuronal complications were found at a rate of 36.4%, and headache at a rate of 13.1% [19]. Currently, world science is focused on the development of a vaccine against SARS-CoV-2. The need to develop vaccines during pandemic periods poses a major challenge to science and medicine. [21,22]

The Sinovac Biotech vaccine, used in Turkey, is based on a platform initially developed for pre-SARS-CoV-1. It involves growing the virus in Vero cells and then inactivating it using beta-propiolactone. Two versions of this inactivated vaccine, adjuvanted with alum or CpG108, have been developed. In a Phase II human trial involving 600 healthy adults (NCT04352608) aged 18-59 years, the vaccine demonstrated 90% seroconversion after the second dose, with the presence of neutralizing antibodies. Interestingly, the production method for the virus differed between the Stage I and II trials, which may have contributed to increased immunogenicity. The study, which included a placebo control group, did not observe any side effects such as headache. [7-9]

In a study in which side effects after Moderna and Pfizer-Biontech vaccinations in the USA were published,

headache was found at a rate of 22.4% and it was one of the most frequently mentioned side effects. [23] In the review made by Maury et al., it was stated that one of the most common symptoms in COVID-19 patients was a headache at a rate of 20.4%. [24]

In the BNT162b2 mRNA COVID-19 vaccine Safety and Efficacy study by Polack et al., the most frequently reported systemic events were fatigue and headache (after the second dose, 59% and 52% among young vaccines; 51% and 39% among older ones, respectively). However, fatigue and headaches have also been reported by many people taking a placebo. (After the second dose, 23% and 24%, respectively, among the young vaccines; 17% and 14% among the older ones).[25]

The most common adverse events were found to be injection site pain, headache, and fatigue following each vaccination in both age groups in the preliminary report of a randomized controlled phase 2 trial on the safety and immunogenicity of the MRNA-1273 SARS-CoV-2 vaccine. After the first vaccination, the most common adverse events were headaches in young adults 50 mg (29%) and 100 mg (25%), placebo in young, and placebo in older adults.[26]

In the first human study of Zhu et al.'s recombinant adenovirus type-5 vectored COVID-19 vaccine, the most common side effects were found to be fever, fatigue, and muscle pain, whereas the most common headache rate was at 39%. [27] In the rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine study conducted for two different forms of lyophilized and frozen in Russia, the most common side effects were stated as pain in the vaccine area, hyperthermia and headache (42%). [28] In a study in which symptoms were evaluated after vaccination in India, the headache was found at a rate of 28% in the population where different types of vaccines were used. [29]

In our study, headache was observed with a rate of 31.1%. Looking at the pain areas, it was seen that the most common site of pain was the arm where the vaccine was administered and the headache. In a review by Tolebeyan et al., it was stated that headache is one of the most common neurological manifestations in SARS-CoV-2 patients and its prevalence varies between 6-71%. One meta-analysis noted that 12.1% of patients with SARS-CoV-2 reported headaches or dizziness. In another meta-analysis of 38 studies of patients with SARS-CoV-2 infection, the prevalence of headache was reported in 15.4% of all patients. [30,31] The consistency of headache prevalence following vaccination was observed across multiple studies. It would have been valuable to compare the prevalence of headaches after different vaccines, such as Pfizer and Janssen. However, at the time of our study, only the Sinovac vaccine was available in Turkey.

While the efficacy of a vaccine primarily relies on factors related to the vaccine itself, it is crucial to consider the individual characteristics of the vaccinated person. Psychological, social, and behavioural factors can have a notable impact on the immune response triggered by the vaccine. Glaser et al. conducted studies suggesting that the response to vaccination might be influenced by conditions such as depressive disorder or stress anxiety. Participants exhibiting higher levels of depressive symptoms were found to have elevated levels of IL-6 both before and following vaccination compared to those reporting fewer symptoms. They stated that humoral or cellular immunity may change with stress levels after vaccination. [32-34] In their review of the effects of stress on antibody response by Cohen et al., [35] in contrast to the relative lack of evidence for the primary immune response, promising evidence was found for an association between stress and secondary immune response. A lower secondary antibody response was found among patients with chronically high-stress levels. This situation was more pronounced in the elderly. Furthermore, it was observed that individuals who reported acute stress or negative affect showed a diminished secondary immune response. However, this association was specifically observed in studies measuring secretory immunoglobulin A (sIgA) antibodies, where psychological factors and antibody levels were closely linked over time.

In a study by Szmyd et al., it was stated that anxiety about the side effects of vaccination such as headache and depressive symptoms decreased the desire for vaccination in healthcare workers.[36] In addition, they reported that there was a significant relationship between concerns before vaccination and post-vaccination side effects and that the side effects increased.[36] In a study by Zarobkiewicz et al., healthcare workers were found to have significantly less anxiety about vaccination. It has been suggested that this may be due to more knowledge and realization in this field acquired during the training process. However, healthcare professionals also reported concerns about short-term side effects such as fever or malaise. [37] Therefore, this anxiety situation will increase the possibility of a headache that may occur after vaccination. In our study, in addition to the above studies, we found that severe anxiety increased the probability of a headache by 7.2 times, moderate anxiety increased that probability by 4.5 and mild anxiety by 2.6 times in predicting people with post-vaccination headaches.

Our study had several limitations. Firstly, we did not collect data on past medical histories, such as alcohol or smoking habits, and comorbidities like Diabetes Mellitus or Hypertension. Additionally, the type of headache experienced before vaccination and the type of pain after vaccination could have provided valuable information, but we were unable to categorize the headaches as participants self-reported their pain without evaluation by a clinician. Moreover, the majority of our participants were women, and it is known that women are more prone to anxiety disorders, which could have influenced our findings. Another limitation is that we only included participants who had completed the second dose of the Sinovac vaccine, and we did not compare the first and second doses. Furthermore, at the time of our study, only the Sinovac vaccine was available in Turkey, so we were unable to compare the effects of different vaccines. We

also did not analyse or correlate pain in other parts of the body with headaches and anxiety. These limitations should be considered when interpreting our findings.

In conclusion, our study suggests that assessing anxiety levels during COVID-19 vaccination can be an important indicator for predicting the development of headaches. Therefore, providing information about headaches and addressing vaccination concerns may help prevent neuropsychiatric symptoms associated with vaccination. Neuropsychiatric manifestations potentially caused by vaccination can encompass a wide range of serious conditions. Headaches can also be influenced by subjective factors. Post-vaccine headaches following COVID-19 vaccination may represent a distinct headache type, and its characteristics will be important for classification. Diagnostic criteria should be carefully defined. Anxiety could act as a trigger or comorbidity and may vary depending on the vaccine type.

There is a need for more extensive research on post-vaccine headaches and anxiety levels. Further studies investigating neuropsychiatric symptoms associated with COVID-19 vaccination are crucial for optimizing vaccination programs and ensuring community immunity.

Compliance with Ethical Standards

The study complies with the Helsinki Declaration requirements and received local ethics committee approval (Sakarya University, Ethics Committee Decision Letter No E-71522473-050.01.04-14843/122).

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

Authors contributed equally to this work.

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