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Post-Vaccination Side Effects After the First Dose of Inactive CoronaVac® in Healthcare Personnel in Türkiye

Mustafa Bayraktar[1], Esra Cinar Tanriverdi[2*], Zulal Ozkurt[3], Pinar Gursoy Guven[4]

[1]Department of Family Medicine, Faculty of Medicine, Atatürk University, Erzurum, Türkiye, Türkiye
[2]Department of Medical Education, Faculty of Medicine, Atatürk University, Erzurum, Türkiye
[3]Department of Infectious Disease, Faculty of Medicine, Atatürk University, Faculty of Medicine, Erzurum, Türkiye
[4]Department of Family Medicine Clinic, City Hospital, Erzurum, Türkiye

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[*]***Corresponding Author***
Esra Cinar Tanriverdi
Department of Medical Education
Faculty of Medicine
Atatürk University, Erzurum, Türkiye
Phone: +90 5333233047
E-mail: esracinart@yahoo.com

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Authors' ORCIDs
Mustafa Bayraktar
https://orcid.org/0000-0001-8486-9915
Esra Cinar Tanrıverdi
https://orcid.org/0000-0001-8857-3986
Zulal Ozkurt
https://orcid.org/0000-0001-5554-8768
Pinar Gürsoy Guven
https://orcid.org/0000-0002-8782-8403

Abstract: This study aimed to investigate the side effects observed in healthcare personnel who were the first to receive the first dose of inactivated CoronaVac® vaccine in Türkiye. Healthcare personnel vaccinated for the first time with the inactivated CoronaVac® vaccine between February and March 2021 during the initial administration of COVID-19 vaccines were asked to respond to an online questionnaire to investigate local and systemic side effects they observed after vaccination. Of the 2601 participants included in the study, 72.5% (n=1886) were female, and 27.5% (n=715) were male. The mean age was 37.6±11.7 years. Regarding side effects, 39.9% had at least one local side effect, and 54.4% had at least one systemic side effect. These side effects lasted for 4.0±2.6 days on average. The three most common local side effects were local pain (38.1%), swelling (1.9%) and redness (1.5%), whereas the most common systemic side effects were weakness (28.4%), headache (27.9%), fatigue (26%), myalgia (18.2%), and arthralgia (11.8%). Systemic side effects were significantly more common in females, nurses and midwives, younger age groups, and people without a history of chronic disease (P<0.05). Myalgia and fever were significantly more common in people without a previous history of COVID-19, but localized redness was found more often in people with previous COVID-19 (P<0.05). This comprehensive study reveals the potential side effects expected due to CoronaVac®, as healthcare personnel are more conscious of observing their symptoms. It is worth noting that severe or long–term side effects were not detected. ©2025 NTMS.

Keywords: COVID-19; Vaccination; Side Effect; Inactivated Vaccine; CoronaVac.

1. Introduction

Novel coronavirus disease 2019 (COVID-19) was first detected on 31 December 2019 in Wuhan, China. Later, it spread worldwide and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. By the end of 2022, 650 million positive cases were seen worldwide, and deaths reached more than 6.5 million [2]. Although some measures have been suggested and implemented to protect against COVID-19, the most important preventive measure that will end the pandemic has been the development of the vaccine and its application to the population. The rapid development of COVID-19 vaccines within the scope of combating the pandemic and the issuance of emergency use permits for early use have caused

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doubts in the community as to whether they are safe. Therefore, it is a scientific necessity and a social responsibility to determine the side effects after vaccinations and present them to the public.

The first COVID-19 vaccine brought to Türkiye with emergency use approval was the CoronaVac® vaccine belonging to the Chinese Sinovac® company. Health workers were determined to be the first to be vaccinated because of their high–risk level. Within the scope of the vaccination program in Türkiye, the healthcare workers started to be vaccinated with the CoronaVac® vaccine as of January 2021, and first data was obtained at that time. WHO recommends that particularly vulnerable, at-risk, and elderly patients be vaccinated annually with the seasonal flu vaccine and the COVID–19 vaccine [3], which will be the future target perspective for combining the two vaccines in one vaccine. Unlike other novel COVID–19 vaccines, CoronaVac® is a conventionally produced inactivated type vaccine and may have the advantage of being combined with other inactivated vaccines, especially influenza vaccine. This highlights the need to identify the side effects of CoronaVac® before the development of combined vaccines.

Healthcare workers are expected to be conscious about identifying and monitoring postvaccination symptoms. In this context, we aimed to investigate the postvaccination side effects of the CoronaVac® vaccine administered to healthcare personnel of our university.

2. Material and Methods

2.1. Study Design

This study was an observational and descriptive study, conducted in the form of an online questionnaire.

2.2. Ethical Approval

Prior to the study, necessary permission was obtained from the Scientific Research Platform of the Ministry of Health of the Republic of Türkiye, and ethical approval was obtained from the Erzurum City Hospital Clinical Research Ethics Committee (Ethics Committee Approval number: 15.02.2021; 2021/04-83). During the study, the Helsinki Good Clinical Practice criteria were complied with. The voluntary participation of the participants in the study was questioned and their online consent was obtained.

2.3. Setting

The study was conducted in a tertiary university hospital and faculty of dentistry of a university in Erzurum, in eastern Türkiye.

2.4. Participants

The eligible participants of the study consisted of the healthcare personnel working at the university hospital and the Faculty of Dentistry, or the 4th, 5th and 6th grade students of the Medical Faculty, and the 4th and 5th grade students of the Dentistry Faculty, who required and received first dose CoronaVac® vaccination due to the risk of COVID–19 in their jobs or in their clerkships. During the COVID-19 pandemic in Türkiye, all universities switched to online education and students (including lower-class medical and dental students) were not required to come to campus, but 4th, 5th and 6th grade interns had to continue working in the hospital (or in the Faculty of Dentistry). Moreover, last year intern students in faculties of medicine and dentistry are accepted as healthcare workers and are paid monthly salaries. Therefore, as these students, like all other health staff, are easily accessible in the hospital or in the Faculty of Dentistry, the research was conducted in two centers to reach health professionals and students of medicine and dentistry.

2.5. Sample Size and Response Rate

The total number of health personnel in the hospital and faculty of dentistry is 2648 and 823, respectively. The total number of intern students in the 4th, 5th and 6th grades in the Faculty of Medicine is 792, and the total number of intern students in the 4th and 5th grades in the Faculty of Dentistry is 308. Therefore, the population size of our study consists of a total of 4571 people. In terms of sample size, since this was a convenience sample, the aim was to include all vaccinated people in the study.

The study questionnaire form was delivered to all study population via official online links. According to the responses received, the number of participants who had the first dose of CoronaVac® vaccine and voluntarily answered the questionnaire was determined as 2607. Due to missing answers, 6 people were excluded from the study. As a result, 2601 people were included and the participation rate was found as 56.9%.

2.6. Questionnaire

The online questionnaire method was adopted to prevent the risk of contact and transmission of COVID–19, and the questionnaire created in Google® Forms was delivered to healthcare workers online. As healthcare personnel, voluntary participation to be vaccinated with the first dose of CoronaVac® (Sinovac®, Beijing, China) vaccine was accepted as the inclusion criteria. The participants' sociodemographic characteristics and postvaccination local and systemic side effects were questioned. The study was carried out between 17 February and 02 March 2021.

2.7. Statistical Analysis

The obtained data were analyzed with the SPSS 23.0 (IBM®, NY, USA) program. Categorical data are presented as frequencies and percentages, and numerical data are presented as the mean and standard deviation. The normal distribution of numerical data was investigated with the Kolmogorov–Smirnov test. In the analysis of two independent variables, Student's t–test was used if there was a normal distribution, and the Mann–Whitney U test was used if not distributed normally. In analyzing three or more independent variables, one-way ANOVA was used if there was a normal distribution. The Kruskal–Wallis test was used

if not distributed normally. The chi–square test was used in the analysis of categorical data. $P<0.05$ was considered statistically significant.

3. Results

Of the 2601 participants, 72.5% (n=1886) were female, and 27.5% (n=715) were male. The mean age was 37.6±11.7 years. The most participating occupational groups were nurses, midwives and emergency medical technicians, with 822 people (31.6%), and doctors, with 697 people (26.8%). The demographic properties of the participants are presented in Table 1.

Table 1: Sociodemographic features of the participants.

		Frequency	Percent
Gender	Male	715	27.5
	Female	1886	72.5
Occupation	Doctor	697	26.8
	Assistant doctor	63	2.4
	Nurse, midwife, emergency technician etc.	822	31.6
	Dentist	218	8.4
	Pharmacist	41	1.6
	Health co–worker	289	11.1
	Student (medicine, dentistry)	471	18.1
Chronic Disease	Yes	615	23.6
	No	1986	76.4
Smoking	Yes, still smoking	787	30.3
	No, never	1396	53.7
	Yes, but quitted	418	16.1
Alcohol Usage	Yes	460	17.7
	No	2141	82.3
COVID-19 History	Yes	431	16.6
	No	2170	83.4
Previous COVID-19 Severity	Mild	180	6.9
	Moderate	198	7.6
	Severe	51	2.0
Allergy History	Yes	612	23.5
	No	1989	76.5
Total		2601	100.0

Regarding postvaccination side effects, 1037 (39.9%) of the participants stated that at least one local side effect developed after vaccination. The remaining 1564 people (60.1%) did not describe any local side effects. While the majority (n=979) of the participants with local side effects expressed only a single side effect, two local side effects were detected in 54 people, and three or four side effects were detected in two people (Figure 1).

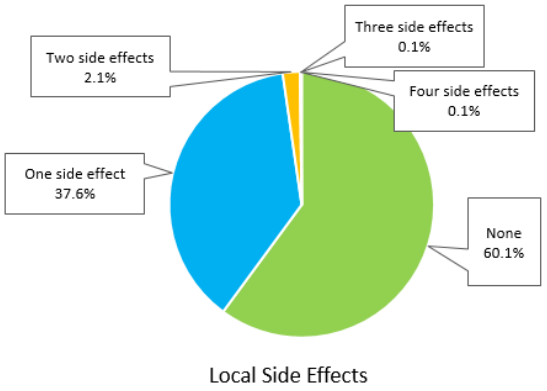

Figure 1: Distribution of number of local side effects.

Among the local side effects, 991 (38.1%) had local pain, 50 (1.9%) had swelling, 38 (1.5%) had redness, six (0.2%) had itching, four patients (0.2%) reported abscess, eight (0.3%) had more than normal bleeding, three (0.1%) had tingling and numbness in the arm, and one person had bruising (Table 2).

Table 2: Postvaccination local and systemic side effects.

		Frequency	Percent	95%C.I.
Local Side Effects	Local pain	991	38.1	36-40
	Swelling	50	1.9	1-2
	Redness	38	1.5	1-2
	Itching	6	0.2	0-0
	Abscess	4	0.2	0-0
	Bleeding more than normal	8	0.3	0-1
	Numbness and tingling in arm	3	0.1	0-0
	Bruise	1	0.0	0-0
Systemic Side	Weakness	739	28.4	27-30
Effects	Headache	725	27.9	26-30
	Tiredness	675	26.0	27-35
	Myalgia	474	18.2	17-20
	Arthralgia	308	11.8	11-13
	Nausea	141	5.4	5-6
	Fever	121	4.7	4-5
	Runny nose	111	4.3	3-5
	Sore throat	96	3.7	3-4
	Cough	71	2.7	2-3
	Shaking	57	2.2	2-3
	Dyspnea	31	1.2	1-2
	Elevation of blood pressure	27	1.0	1-1
	Allergy	23	0.9	1-1
	Loss of taste	21	0.8	0-1
	Swelling in lymph nodes	12	0.5	0-1
	Vertigo	9	0.3	0-1
	Metallic taste in mouth	9	0.3	0-1
	Loss of smell	5	0.2	0-0
	Sleepiness	4	0.2	0-0
	Itching	2	0.1	0-0
	Vomiting	2	0.1	0-0
	Diarrhea	2	0.1	0-0
	Herpes labialis	2	0.1	0-0

In terms of systemic side effects, 1416 people (54.4%) stated that they developed at least one systemic side effect, while 1185 (45.6%) did not observe any systemic side effects.

Of them, 470 participants had one side effect; two side effects were reported in 358 people, three side effects in 228 people and four side effects in 139 people (Figure 2). Six people had 20 different systemic side effects.

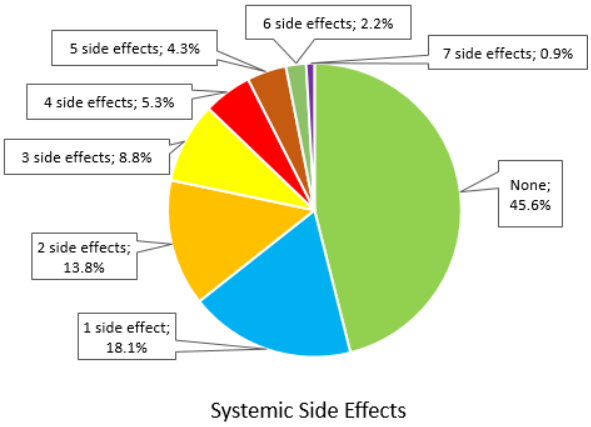

Figure 2: Distribution of the number of systemic side effects.

When systemic side effects were examined, 739 people (28.4%) had a weakness, 725 people (27.9%) had a headache, 675 people (26%) had fatigue, 474 people (18.2%) had myalgia, 308 people (11.8%) had arthralgia, 141 (5.4%) had nausea, 121 (4.7%) had fever, 111 (4.3%) had a runny nose, 96 (3.7%) had a sore throat, 71 people (2.7%) reported cough, 57 (2.2%) had shivering, 31 (1.2%) had shortness of breath, and 27 (1%) had hypertension. Other systemic side effects included systemic allergy in 23 (0.9%), taste loss in 21 (0.8%), swelling in the lymph nodes in 12 (0.5%) and a metallic taste in the mouth in nine (0.3%) (Table 2).

Table 3: Association of local side effects with demographic variables.

	Age	Gender	Occupation	Chronic Disease	COVID History	Allergy History	Smoking	Alcohol Usage
Local Pain	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.987	**0.003**	0.161
Swelling	0.754	0.129	0.055	0.782	0.154	0.797	0.650	0.287
Redness	0.998	0.350	0.384	0.125	**0.039**	0.982	0.066	0.160
Itching	1.000	0.748	0.434	0.172	0.995	0.571	0.757	0.315
Abscess	**0.002**	0.911	0.548	0.949	0.650	0.945	0.515	0.701
Bleeding more than normal	**0.001**	0.342	0.264	0.458	0.207	0.351	0.782	0.189
Numbness, Tingling in Arm	0.961	0.286	0.773	0.079	0.440	0.689	0.363	0.422
Bruise	1.000	0.538	0.904	0.578	0.656	0.579	0.649	0.643

It was determined that the side effects developed after vaccination lasted 4.0 ± 2.6 days on average.

The relationship between the local side effects and the participants' demographic data are given in Table 3. Accordingly, local pain was significantly higher in young participants who had no chronic disease, had a previous COVID-19 history, had never smoked and were students in the health field. The local redness was significantly higher in participants with a history of COVID-19 (P<0.05). While abscess and bleeding more than normal were found to be related to age (respectively P=0.002 and P=0.001), local pain was found to be related to gender (P<0.001).

The systemic side effects and the participants' demographic data are presented in Table 4. Systemic side effects such as arthralgia, increased blood pressure, weakness, and fatigue were found to be significantly more common in younger participants (P<0.05). When systemic side effects were compared according to gender, it was found that many side effects, such as fatigue, headache, myalgia, and high blood pressure, were significantly more common in women. Regarding the participants' occupations, systemic side effects such as fatigue and joint pain were significantly more common in nurses and midwives, who were primarily female.

When systemic side effects were evaluated according to whether there was a chronic disease, many systemic side effects, such as joint pain and muscle pain, were more common in those without chronic disease. At the same time, only high blood pressure was found to be significantly more common in those with chronic disease. While alcohol consumption did not cause any side effect differences (P>0.05), fatigue, headache, and joint pain were significantly higher in nonsmokers. Shaking was associated with gender, ocupation and presence of chronic disease, loss of taste was associated with presence of chronic disease, and runny nose was associated with gender and ocupation (P<0.05 for all).

In terms of a previous history of COVID-19, only myalgia and fever were significantly more common among systemic side effects in people without previous COVID-19. In terms of known allergy history, many side effects, such as weakness, fatigue, and headache, were more common in those without a history of allergy. In contrast, taste loss, lymph node swelling and postvaccine allergy development were significantly higher in individuals with an allergic constitution (P<0.05).

Table 4: Association of systemic side effects with demographic variables.

	Age	Gender	Occupation	Chronic Disease	COVID History	Allergy	Smoking	Alcohol
Weakness	**0.002**	**<0.001**	**<0.001**	**0.023**	0.053	**0.001**	**0.041**	0.593
Headache	**0.008**	**<0.001**	**<0.001**	**0.026**	0.297	**0.002**	**0.018**	0.750
Tiredness	**0.039**	**<0.001**	**<0.001**	**0.022**	0.606	**<0.001**	0.600	0.921
Myalgia	**0.018**	**<0.001**	**<0.001**	**<0.001**	**0.048**	**<0.001**	0.693	0.411
Arthralgia	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.074	**0.003**	**0.028**	0.694
Sleepiness	0.988	0.218	0.120	0.949	0.650	0.945	0.417	0.701
Cough	0.387	**0.005**	0.056	**0.009**	0.171	**0.001**	0.217	0.861
Dyspnea	0.629	0.067	**0.001**	**0.001**	0.061	**0.015**	0.362	0.819
Allergy	0.180	0.119	**0.001**	**<0.001**	0.915	**<0.001**	0.497	0.970
Swelling in lymph nodes	0.878	**0.045**	0.083	**0.031**	0.442	**0.004**	0.619	0.926
Shaking	0.383	**0.001**	**0.001**	**<0.001**	0.603	0.078	0.304	0.280
Itching	1.000	0.384	0.885	0.431	0.203	0.433	0.422	0.512
Loss of taste	0.811	0.064	0.311	**0.038**	0.370	**<0.001**	0.604	0.682
Elevation of blood pressure	**<0.001**	**0.005**	**0.010**	**<0.001**	0.198	**0.010**	0.656	0.694
Runny nose	**0.040**	**<0.001**	**<0.001**	**0.046**	0.497	0.116	0.519	0.728
Fever	0.903	0.273	**0.007**	0.458	**0.006**	0.579	0.320	0.733
Sore throat	0.227	**0.002**	**0.001**	0.250	0.800	**0.021**	0.454	0.582
Metallic taste in mouth	1.000	0.064	0.252	0.095	0.181	0.926	0.084	0.605
Nausea	0.146	**0.002**	**0.004**	0.249	0.397	0.710	0.168	0.989
Vomiting	0.970	0.384	0.475	0.431	0.203	0.377	0.360	0.231
Diarrhea	0.970	0.384	0.475	0.431	0.203	0.377	0.360	0.231
Vertigo	0.827	0.064	0.779	0.375	0.181	0.487	0.451	0.605
Loss of smell	**0.008**	0.531	0.820	0.848	0.159	0.385	0.189	0.892

4. Discussion

The side effects observed after inactive CoronaVac® vaccination were investigated with the broad participation of individuals working in the health field. While the rate of people with local side effects was 39.9%, the rate of people with systemic side effects was 54.4%. In other words, half of the participants had no systemic side effects and the vast majority had no local side effects. Pain was described as the most common local side effect, and among the systemic side effects, weakness, headache and fatigue were commonly detected.

It is known that prospective controlled trials are a better approach to evaluate the safety of a vaccine. Therefore, with this survey-based research, we cannot easily detect rare events, the population surveyed is not representative of the population at large (i.e. predominantly women and healthcare professionals), and a prospective design may be superior. However, a major purpose of this study was to identify relatively minor side effects that may deter vaccination. According to the data obtained, local side effects that may cause non-vaccination or hesitancy in vaccination were not observed in the vast majority of the study group. This result can be emphasized when informing people about the safety of the vaccine in order to overcome possible barriers to vaccination.

Another important aspect of our study is that the study was conducted on health professionals, and therefore it is possible to obtain more realistic and accurate results with this study group that is aware of, monitors and defines post-vaccine side effects. Another advantage is the lack of prior knowledge and prejudices, since this study population was vaccinated in the first place in our country with the acquisition of the vaccine, and any possible side effects were not known yet at the time of vaccination. Thus, a more objective result was obtained.

There is still a lack of studies regarding side effects after the CoronaVac® vaccine. Acute asthma exacerbation was reported in one case report [4]. Another postvaccine side effect after CoronaVac® was described as petechial rash on the skin [5].

In a study conducted on 780 people questioning the side effects after the CoronaVac® vaccine in healthcare personnel, the most common local side effect was reported as pain (41.5%). The most common systemic side effects were weakness (23.6%), headache (18.7%) and muscle pain (11.2%) [6]. Our study was conducted with more participants than this study. When the results of the study were compared, although the complaints of

local pain and weakness were similar, headache and fatigue were more common in our study. Another common result of this study and our study was that the incidence of side effects increased due to female sex and young age. However, our study found fewer side effects in patients with chronic diseases.

In another study, pain at the injection site (48.6%) was the most common local side effect that developed after vaccination, and itching outside the injection site (2.3%) was the most common systemic finding. In addition, they found that such side effects were more common in patients with a history of allergic disease [7]. Wan et al. investigated the safety of the CoronaVac® vaccine in people over 60 years of age and did not find an increase in the incidence of serious events. However, they found that the incidence of anaphylaxis increased after the second dose of the vaccine [8].

In the current study, all local and systemic side effects were higher than those reported in the first clinical trial studies investigating the safety and efficacy of vaccines involving 809 and 743 people [9-11]. In the study of Riad et al., the side effects were found to be high, similar to our study [6]. We think that this difference is due to methodological differences. Considering that our study numerically represents a large cross-section, we think that our findings reflect real-life data.

Although there were various local and systemic side effects in our study, these were acceptable side effects that were commonly seen in other vaccines, lasted for 4-5 days and improved over time.

A study comparing the efficacy and safety of four different COVID-19 vaccines showed that CoronaVac® had fewer side effects and no serious side effects compared to other vaccines [12]. Other studies have also found that CoronaVac® is a safe vaccine, has fewer local and systemic side effects than other vaccines and is well tolerated [13-16] .Our study found no life-threatening serious or permanent side effects, and it was determined that CoronaVac® is a safe inactivated vaccine.

5. Conclusion

In this study, postvaccination side effects of the inactive CoronaVac® vaccine were investigated with a large-participation study conducted on healthcare workers. A valuable result has been obtained since healthcare professionals are more conscious and can describe side effects more accurately. In this study, the CoronaVac® vaccine was evaluated as a safe inactivated vaccine with no serious life-threatening side effects other than acceptable effects. Future studies should be continued to monitor the safety and tolerability of the vaccine in real-world settings. This will be important for ensuring that the vaccine is safe for widespread use and for identifying any rare or serious side effects that may not have been observed in clinical trials.

Limitations of the Study

One strength of this study is that it can provide valuable information on the safety and tolerability of the Inactive CoronaVac® vaccine in a real-world setting. This may be particularly important for at-risk individuals who are at high risk of exposure to COVID-19 but cannot tolerate the risk of serious post-vaccine side effects. In addition, this study, which was conducted with a relatively large number of people, may provide more descriptive information due to the examination of post-vaccine side effects in healthcare personnel who are more conscious of describing the side effects. However, the study may not have a control group, making it difficult to determine if the side effects observed were caused by the vaccine or other factors. Additionally, there may be some missing, rare but serious side effects that are overlooked and not thought to be related to vaccination. It is also essential to note that the study is focused on a specific region and may not be generalizable to other parts of the world.

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Conflict of Interests

The authors have no conflicts of interest to declare.

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Author Contributions

Concept – ECT, ZO, PGG; Design - ECT, ZO,PGG; Supervision - ZO; Resources - ECT, ZO; Materials - ECT, ZO; Data Collection and/or Processing - ECT, ZO, PGG, MB; Analysis and/or Interpretation – MB; Literature Review - ECT, MB, ZO,PGG; Writing – ECT, ZO, PGG; Critical Review – MB, ECT, ZO, PGG

Ethical Approval

The study was approved by the Erzurum City Hospital Clinical Research Ethical Committee (Date: 15.02.2021; Number: 2021/04-83).

Data sharing statement

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Consent to participate

No consent to participate is required for this study.

Informed Statement

Participation in the study was voluntary. Informed consent was obtained from participants online.

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Sonographic features and perinatal outcomes in fetuses with ductus venosus agenesis: Single center experience

Verda Alpay[1*], Selçuk Atalay[2], Fırat Ersan[1], İzel Günay[3]

[1]Department of Obstetrics and Gynecology, Division of Perinatology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye
[2]Department of Obstetrics and Gynecology, Division of Perinatology, Ordu University Training and Research Hospital, Ordu, Türkiye
[3]Department of Obstetrics and Gynecology, Başakşehir Çam and Sakura City Hospital, Istanbul, Türkiye

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****Corresponding Author***
Verda Alpay
Department of Obstetrics and Gynecology
Division of Perinatology
Başakşehir Çam and Sakura City Hospital
Istanbul, Türkiye
Phone: +90 5332523100
E-mail: verda_alpay@yahoo.com

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Authors' ORCIDs
Verda Alpay
https://orcid.org/0000-0002-5937-0220
Selçuk Atalay
https://orcid.org/0000-0001-7702-5773
Fırat Ersan
https://orcid.org/0000-0001-5337-0169
İzel Günay
https://orcid.org/0009-0007-5650-5998

Abstract: The purpose of this study is to evaluate the prenatal sonographic features and postnatal outcomes in fetuses with ductus venosus agenesis (DVA) in a tertiary center. We performed a retrospective study of 15 consecutive cases of DVA diagnosed in our perinatology department between January 2020 and October 2023. All clinic records, fetal echocardiograms, any accompanying anomalies, obstetrical ultrasounds, and postnatal echocardiograms were reviewed. Of the 15 cases detected, umbilical vein had extrahepatic type connection in 8 fetuses (53.3%) and intrahepatic type connection in 7 fetuses (46.7%). 11 patients had associated anomalies including hydrops (n=3, 20%), cardiac (n=6, 40%), extracardiac structural (n=7, 46.7%) and chromosomal anomalies (n=3, 20%). In our patient group, only 4 cases (26.7%) presented with isolated DVA, of which 3 had intrahepatic type connection. Prenatal genetic testing including karyotype and microarray was performed in 8 patients (53.3%) and 3 (20%) of them had abnormal results. 4 women (26.7%) underwent legal termination of pregnancy. There were 2 (13.3%) neonatal deaths, and the remaining 9 cases (60%) were alive at last follow-up. DVA is associated with cardiac, extracardiac, and genetic anomalies independent of the site of umbilical venous connection. Postnatal outcomes in cases with DVA depend on the presence of additional anomalies. Fetuses with DVA and extrahepatic connection have additional risk for cardiac failure, hydrops and portal venous system agenesis which worsen the outcomes. DVA cases with intrahepatic connection associated with no or minor anomaly tend to have more favorable outcomes. ©2025 NTMS.

Keywords: Ductus Venosus Agenesis; Portosystemic Shunt; Intrahepatic Drainage; Extrahepatic Drainage; Hydrops.

1. Introduction

Human fetal circulation depends on three physiological shunts which are specific to fetal life and essential for the adaptation of fetal circulation throughout intrauterine life: the ductus arteriosus, the foramen ovale and the ductus venosus (DV)[1]. The first two have been extensively studied over time but DV has recently become a subject of interest with the improvement of ultrasound techniques such as Doppler ultrasound which led a more detailed examination of fetal venous circulation, even in the first trimester[2]. DV is an

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hourglass-shaped structure between umbilical vein and inferior vena cava and plays a key role in the redistribution of fetal blood flow by directing 20-30% of highly oxygenated blood to the systemic circulation[3,4]. Abnormal ductus venosus blood flow is found to be associated with chromosomal abnormalities and congenital cardiac defects[5,6]. Furthermore, observation of typical triphasic flow pattern over the DV may be used for the surveillance of wellbeing in growth restricted fetuses[7].

Ductus venosus agenesis (DVA) is a recently described group of anomalies in which the common characteristic is the absence of normal connection between umbilical vein-portal system and inferior vena cava[8]. The evaluation of DV in the late first trimester as a part of routine ultrasonography led to an increase in the number of DVA cases published in the literature. Despite this and common use of better technologies, DVA is a rare condition, and the true prevalence is unknown[2]. There are several classifications of this anomaly, to simplify we use the one that divides the cases into two large subgroups according to the drainage site of the umbilical vein: intrahepatic and extrahepatic[8,9]. In the intrahepatic type, umbilical vein drains into portal sinus without giving rise to the DV and the blood circulation occurs passing through the liver. In the extrahepatic type, umbilical vein bypasses the liver, does not connect to portal system, and drains to superior vena cava, inferior vena cava, iliac veins or directly to right atrium[9,10]. While extrahepatic type DVA is more often associated with congestive cardiac failure, portal system agenesis and hydrops, intrahepatic type DVA tends to show better neonatal outcomes as it is rarely associated with major structural anomalies compared with extrahepatic type[10,11]. In cases presenting with DVA as an isolated finding, the prognosis is usually good[4,12]. Here, we present prenatal features, association with other structural and genetic abnormalities and postnatal outcomes of 15 cases of DVA followed up in our institution.

2. Material and Methods

This was a retrospective study of a series of cases with DVA diagnosed prenatally in Başakşehir Çam and Sakura City Hospital perinatology department between January 2020 and October 2023. All patients referred in our department for tertiary review of suspected fetal anomalies have a detailed morphology scan, fetal echocardiography, and Doppler flow studies, as appropriate. The DV is evaluated in all patients referred for suspected anomalies, detailed morphological scan and as a part of fetal wellbeing assessment, using color or power Doppler in transverse or sagittal plane. If DV is not visualized at its insertion between portal system and vena cava inferior, the diagnosis of DVA is confirmed and then the site and type of umbilical venous drainage is determined. All ultrasound examinations were performed on ARIETTA 850 (Hitachi Medical Corporation, Tokyo, Japan) device (3.5 mHz abdominal transducer). All clinic records, including fetal echocardiograms, obstetrical ultrasounds and postnatal echocardiograms were reviewed. Fetal echocardiographic data included site of connection of the umbilical vein, any accompanying structural or functional cardiac anomalies and presence of hydrops. Results of genetic testing (both pre- and postnatal if present), the outcomes of pregnancies and for live births, status of the baby at last follow-up were recorded. Patients' characteristics and clinical features were summarized using standard descriptive statistics. Statistical analyses were performed using IBM SPSS statistical software, version 21 (IBM, SPSS Corp., Armonk, NY, USA). This study was approved by Istanbul Başakşehir Çam and Sakura City Hospital Clinical Research and Ethics Committee (ethical approval no: 2023/522, date: 25.10.2023) and was conducted in accordance with the World Medical Association's Declaration of Helsinki (including the 2013 amendments). In addition, informed consent was obtained from all participants before the enrollment.

3. Results

During the study period, a total of 15 cases with prenatally diagnosed DVA were collected. The gestational age at diagnosis ranged from 12 to 33 weeks. In 2 cases, the reason for referral was cystic hygroma in the first trimester and DVA was the accompanying finding. 8 of the cases were referred to our tertiary center for suspected anomalies or intrauterine growth restriction and DVA was detected during targeted ultrasound. In the remaining 5 cases, DVA was an incidental finding during routine second trimester ultrasound scan. The prenatal findings and postnatal outcomes of the cases are summarized in Table 1. Prenatal ultrasound studies revealed intrahepatic type connection in 7 cases (46.7%) and extrahepatic type connection in 8 fetuses (53.3%). Among 8 cases with extrahepatic connection, umbilical vein drained directly to inferior vena cava in 5 cases (62.5%), into right atrium in 2 cases (25%) and to vena azygos in 1 case (12.5%). In our patient group, only 4 cases (26.7%) presented with isolated DVA. 3 of 4 fetuses with isolated DVA had intrahepatic type connection with clearly detectable left portal vein, they were all survivors and reported to be healthy at discharge. However, the remaining fetus with isolated DVA had extrahepatic type connection with umbilical vein draining directly into inferior vena cava. The patient delivered at 25 weeks of gestation due to preterm premature rupture of membranes and the newborn died at day 3 because of extreme prematurity. 11 patients had associated anomalies including hydrops (n=3, 20%), cardiac (n=6, 40%), extracardiac structural (n=7, 46.7%) and chromosomal anomalies (n=3, 20%). Cardiac anomalies constitute the most common associated group of structural anomalies in our study. The majority of cardiac diagnoses were ventricular septal defects. Two cases presented with pericardial effusion, one of them had confirmed Turner syndrome. Other detected cardiovascular anomalies were tricuspid

atresia, total anomalous pulmonary venous connection and left persistent vena cava superior. Extracardiac structural anomalies were present in 7 patients (46.7%) including cystic hygroma, unilateral renal agenesis, cleft lip, ventriculomegaly, hepatosplenomegaly, ileal atresia, and intrauterine growth restriction. Except the patient with co-existing ileal atresia, all cases with extracardiac anomalies were extrahepatic type DVA cases. In the case with hepatosplenomegaly, there was also hepatic calcifications, and, in this case, umbilical vein had an extrahepatic course draining directly into vena azygos. In one case with intrahepatic type DVA, the only associated anomaly was single umbilical artery. In our series, there were 3 cases presented with hydrops, all of them had DVA with extrahepatic type connection and all of them had termination of pregnancy due to associated anomalies. Prenatal genetic testing including karyotype and microarray was performed in 8 patients (53.3%) and 3 (20%) of them had abnormal results. Confirmed genetic diagnoses were Noonan syndrome, Turner syndrome and 3p deletion syndrome. The remaining 5 cases had normal karyotype and microarray results. 4 women (26.7%) underwent legal termination of pregnancy, all of them had extrahepatic type DVA and multiple structural anomalies, two of them were diagnosed with confirmed genetic anomalies (Noonan syndrome and 3p deletion syndrome). In our study group there were 2 (13.3%) neonatal deaths, one at day 3 due to extreme prematurity and the other at day 10 due to prenatally diagnosed tricuspid atresia, pulmonary stenosis and coarctation of aorta. The remaining 9 cases (60%) were alive at last follow-up (follow-up duration between 2 months and 2 years). 6 of these survivors had intrahepatic type DVA prenatally, the diagnosis is confirmed, and varying degrees of portal system components are demonstrated in the postnatal period, none of them had portal agenesis. The other 3 survivors had extrahepatic type DVA with co-existing structural anomalies, all detected sonographic findings in the prenatal period are confirmed postnatally. One of them has co-existing total anomalous pulmonary venous connection and is waiting to be operated at 3 years old. The other one with co-existing hepatosplenomegaly was thought to have portal agenesis in the prenatal period, hepatosplenomegaly is still present, and the infant is following up by pediatric haemato-oncology due to pancytopenia. However, portal system was partially visualized in the postnatal period.

Table 1: Prenatal features, associated anomalies, and outcomes in 15 fetuses with ductus venosus agenesis (DVA).

Cases	Gestational age at diagnosis	Type of DVA-Umbilical vein insertion	Cardiac anomalies	Associated extracardiac findings	Hydrops	Prenatal genetic testing-Karyotype	Outcome
1	12	Extrahepatic-Inferior vena cava	None	Cystic hygroma, polyhydramnios	Yes	CVS / AS Noonan syndrome	TOP at 28 weeks
2	23	Extrahepatic-Inferior vena cava	None	None	No	N/A	PPROM at 25 weeks Neonatal death at day 3 due to extreme prematurity
3	22	Intrahepatic-Left portal vein	Pericardial effusion, ventricular septal defect	None	No	AS Turner's syndrome (45,X)	Live birth at 38 weeks Alive at 1,5 years
4	22	Intrahepatic-Portal system	None	None	No	AS Normal	PROM at 32 weeks Live birth at 32 weeks 5 days Alive at 16 months old
5	20	Extrahepatic-Inferior vena cava	Total anomalous pulmonary venous connection	Left renal agenesis, hydroureteronephrosis in the right kidney	No	N/A	Live birth at 38 weeks Alive at 14 months old Postnatal karyotype normal
6	22	Intrahepatic-Left portal vein	None	Single umbilical artery	No	N/A	Live birth at 38 weeks Alive at 9 months Postnatal karyotype normal Postnatal ultrasound: Portal system visualized.

7	22	Extrahepatic-Right atrium	None	Early onset fetal growth restriction, bilateral anophthalmia, ascites	Yes	AS 3P deletion	TOP at 25 weeks
8	22	Intrahepatic-Portal system	Tricuspid atresia, ventricular septal defect, pulmonary stenosis, coarctation of the aorta	None	No	N/A	Live birth at 40 weeks Neonatal death at day 10
9	24	Extrahepatic-Right atrium	None	Fetal growth restriction, severe ventriculomegaly, non-visualization of stomach, esophageal atresia, cleft lip, interruption of inferior vena cava, azygos continuation, single umbilical artery, bilateral talipes, lumbosacral hemivertebrae	No	N/A	TOP at 25 weeks
10	21	Intrahepatic-Left portal vein	None	None	No	AS Normal	Live birth at 37 weeks Alive at 8 months Postnatal ultrasound: Left portal vein visualized; right portal vein thin. Postnatal diagnosis: Abernethy type 2 syndrome Operation will be planned.
11	22	Extrahepatic-Vena azygos	Pericardial effusion, left persistent superior vena cava	Hepatosplenomegaly, non-visualization of portal system in the liver, diffuse calsifications in the liver, interruption of inferior vena cava, azygos continuation	No	AS Normal	Live birth at 39 weeks Alive at 8 months Postnatal ultrasound: Portal system partially visualized, hepatosplenomegaly. Pancytopenia detected, close follow-up by pediatric hematology-oncology.
12	22	Intrahepatic-Portal system	None	None	No	N/A	Live birth at 39 weeks Alive at 3 months
13	33	Extrahepatic-Inferior vena cava	Tricuspid atresia, hypoplastic right heart	None	No	N/A	Live birth at 37 weeks Alive at 1,5 months Operated once due to cardiac anomaly, waiting for the second operation.

14	22	Intrahepatic-Left portal vein	Ventricular septal defect	İleal atresia	No	AS, Normal	Live birth at 38 weeks Alive at 2 weeks
15	13	Extrahepatic-Inferior vena cava	None	Cystic hygroma	Yes	CVS Normal	TOP at 13 weeks

CVS: chorion villus sampling, AS: amniocentesis, TOP: termination of pregnancy, N/A: not assessed, PROM: premature rupture of membranes.

4. Discussion

The ductus venosus is located between umbilical vein and inferior vena cava and plays a critical role in the redistribution of blood flow by shunting placental oxygenated blood in the fetal systemic circulation[13]. 20-30% of highly oxygenated blood in the umbilical vein directly reaches the left atrium through ductus venosus. The remaining oxygenated blood in the umbilical vein is dispersed to the left lobe of fetal liver via left portal vein and overall portal blood flow is directed to the right lobe of the liver[14]. In cases of fetal hypoxia or reduced placental return, the percentage of blood flow shunted through ductus venosus is increased[15]. Embryologically, the right umbilical vein obliterates at day 33-34 while the left umbilical vein persists and gives rise to left portal vein and DV in the liver[3]. The etiology of the fetal venous system anomalies is not clearly defined, but failure of development of these primitive veins is thought to be associated with anomalies of umbilical-portal circulation, as well as DVA[8,14]. Another possible explanation of DVA may be secondary occlusion of already formed vessel due to thromboembolism or a systemic event[16]. Whichever is the etiopathogenesis, in case of DVA, umbilical vein which carries the blood returning from the placenta takes an alternative route to fetal heart[8]. The lack of flow regulation in this alternative route may contribute to fetal cardiac volume overload, congestive heart failure and eventually hydrops fetalis[17].

Although the definite incidence of DVA in the general population is unknown, the estimated prevalence varies between 1/556 and 1/2500[18,19]. However, in high-risk populations such as fetuses referred to maternal-fetal units with cardiomegaly, hydrops, cardiac or extracardiac anomalies, the prevalence increases up to 6/1000 cases[20]. The prognosis of DVA depends on site of connection, associated malformations, and chromosomal anomalies[11].

In our study, most cases of DVA were diagnosed in the second trimester during anatomical screening or in association with other malformations. Only 2 cases (13.3%) were diagnosed in the first trimester, and they were both associated with cystic hygroma. One of these cases was diagnosed with Noonan syndrome after prenatal genetic testing. Iliescu et al. have evaluated the potential of first and second trimester screening in the diagnosis of DVA. In 6114 consecutive low risk pregnancy, they identified 11 cases of DVA and 10 of these cases (91%) were identified during first trimester screening[19]. This proves the need for a careful and detailed examination in the first trimester as the early the detection of DVA is possible and may have an important impact during follow-up.

In our cohort, a total of 15 cases of DVA were detected, out of which 7 fetuses (46.7%) had intrahepatic venous drainage without liver bypass and 8 (53.3%) had extrahepatic venous drainage with liver bypass. In a similar study, Dhingra et al. presented 8 cases of DVA, out of which 2 (25%) with intrahepatic and 6 (75%) with extrahepatic drainage[12]. They suggested that DVA with intrahepatic shunt may be a more common condition but is less frequently reported as it requires a more rigorous examination particularly with color flow mapping of the fetal portal venous system. Extrahepatic shunt is more easily noticed due to abnormal course of intraabdominal umbilical vein which can also be detected on gray scale mode. Berg et al. reported 19 cases of DVA with intrahepatic connection and only 4 cases of DVA with extrahepatic connection. The authors explained this high rate of intrahepatic type connection by the Doppler assessment of the DV which is an integral part of routine fetal examination in their institution[21]. According to the recent literature about DVA, intrahepatic type connection occurs more frequently, but more easily escapes diagnosis even in the presence of coexisting anomalies due to the need of Doppler examination[9]. In our institution, Doppler examination of DV is a routine part of fetal assessment in the second trimester anatomical screening or in fetuses referred to our center due to suspected anomalies and fetal growth restriction. This may explain the relatively high proportion of DVA cases with intrahepatic connection in our series.

Irrespective of the type of connection, DVA is significantly associated with cardiac, extracardiac structural and chromosomal anomalies[12,21]. In our study, 4 fetuses had isolated DVA (26.7%) and 11 fetuses (73.3%) had associated chromosomal anomalies and major or minor structural malformations including cardiac, skeletal, gastrointestinal, central nervous and genitourinary system. Cardiac anomalies were the most common associated malformations and comprised ventricular septal defects, total anomalous pulmonary venous connection, tricuspid atresia, pulmonary stenosis, and aortic coarctation. Genitourinary system anomalies included unilateral renal agenesis and hydronephrosis. Gastrointestinal malformations included ileal atresia, esophageal atresia, and hepatosplenomegaly. The only central nervous system anomaly detected in our cohort was severe ventriculomegaly. Musculoskeletal system malformations comprised spinal deformities, hemivertebrae and bilateral clubfoot. Other vascular

anomalies including interruption of vena cava inferior and vena azygos continuity, single umbilical artery and left persistent vena cava superior along with facial anomalies such as cleft lip and palate were also diagnosed. Although a wide range of malformations occur in association with DVA, none of these anomalies is disease specific. In our series, among 8 fetuses with extrahepatic connection, 7 (87.5%) had associated anomalies, whereas among 7 fetuses with intrahepatic connection, 4 (57%) had associates minor or major anomalies and 3 fetuses (43%) had isolated DVA. Contratti et al. suggested that particularly fetuses with extrahepatic connection have higher incidence of complex malformations, chromosomal anomalies, and hydrops[14]. Additionally, fetuses with extrahepatic drainage and liver bypass tend to develop congestive heart failure which unfavorably affects the outcome even if the fetal anatomy is normal[21]. The exact mechanism triggering heart failure in the fetus is not well established, the possible explanation is that the umbilical vein bypassing the liver and draining directly into the heart may cause an increased preload, progressive cardiac decompensation, and high central venous pressure[3]. The leading clinical sign in this situation is cardiomegaly and the chronic volume overload may lead to fetal hydrops[22,23]. In a meta-analysis of 35 cases of DVA draining directly into the heart, a higher incidence of cardiomegaly and hydrops was detected[24]. It may also occur in form of edema restricted only to one compartment, such as pericardial, pleural spaces or subcutaneous tissue[2]. Nevertheless, these signs are usually not observed in DVA with intrahepatic drainage, in the presence of connection between umbilical vein and portal system[4,8]. In our study, 3 of the 4 cases (75%) with hydrops/effusions had DVA with extrahepatic connection. The remaining case presenting with pericardial effusion had DVA with intrahepatic connection, was diagnosed with Turner's syndrome in the prenatal period and we linked the presence of pericardial effusion to Turner's syndrome rather than DVA. None of our cases presented with cardiomegaly. DVA without liver bypass seems to have a better prognosis especially if it is not associated with other malformations and chromosomal anomalies[21]. The association with other abnormalities may be the most important prognostic factor in DVA[8,25].

DVA is known to be associated with chromosomal abnormalities with a reported incidence between 17-24%[14,23]. Abnormal connection of the umbilical vein into the inferior vena cava has been reported to increase the risk trisomy 21[26]. However, according to the literature, most frequent chromosomal abnormalities associated with DVA are Turner's syndrome and Noonan syndrome[3,18,23]. Additionally, DVA has been reported in the context of various syndromes such as VACTERL, Beckwith-Wiedemann syndrome, Jacobsen syndrome, Pierre Robin sequence, Pallister-Killian syndrome, Smith-Lemli-Opitz syndrome and Wolf-Hirschhorn syndrome[10,27]. However, genetic abnormalities associated with DVA are thought to be underdiagnosed using conventional cytogenetic studies[28]. Advanced genetic studies, namely chromosomal microarray (CMA) and exome sequencing (ES) allow more detailed analysis of fetal genome and thus, enhance prenatal diagnosis of genetic abnormalities in cases of DVA[27,28]. In our study, 8 out of 15 cases (53%) had invasive genetic testing. In total 20% of cases (3/15) and 37.5% of tested cases (3/8) received a genetic diagnosis thought to be associated with DVA. Confirmed abnormal results were as follows: Turner's syndrome (1), Noonan syndrome (1) and 3p deletion syndrome (1). Genetic abnormalities detected in our series are consistent with the literature. McBrien et al. reported results of 14 cases with DVA and in their series, the incidence of genetic abnormalities was 43% in total and genetic diagnoses were trisomy 21, PHACE syndrome and RASA1 related disorder beside Noonan syndrome[25]. Therefore, fetal genetic assessment including CMA and ES must be indicated in fetuses with prenatally diagnosed DVA especially in the presence of associated anomalies[11,28,29].

Prenatal diagnosis of DVA is strongly linked with high rate of pregnancy termination due to the presence of associated malformations which impact pregnancy outcomes and parental decision making[17]. In our series, 4 women (26.7%) underwent legal termination of pregnancy, all these fetuses had DVA with extrahepatic connection and associated major structural anomalies. Two fetuses had abnormal genetic results (Noonan syndrome and 3p deletion syndrome). Decision for termination of pregnancy should be based upon associated structural or chromosomal anomalies. The prognosis for cases of isolated DVA is usually good, independent of the type of umbilical vein connection site[17]. This information is extremely important and should be emphasized during parental counseling even if precise outcome prediction is challenging. In case of continuation of pregnancy, possibility of rapid deterioration of cardiac status and in utero fetal demise for DVA cases with liver bypass should be kept in mind and close follow-up should be planned for these fetuses until delivery[17].

Our findings are consistent with the literature suggesting that fetuses with intrahepatic connection with no or minor malformation have better outcomes compared to fetuses with extrahepatic connection[12]. In our series, among 7 cases with intrahepatic connection, 5 cases presented with minor or no associated anomalies, all these fetuses survived, all diagnoses were confirmed in the sonographic imaging of portal system during neonatal period, none of them had portal agenesis, various degrees of portal venous system components were demonstrated, and no short-term sequelae was observed. 1 case with DVA and intrahepatic connection had also ventricular septal defect and pericardial effusion, invasive genetic testing resulted as Turner's syndrome, the infant is 1,5 years old and otherwise healthy, her portal system was visualized in the sonography. Similarly, Berg et al.

found that all 13 fetuses with isolated DVA without liver bypass survived and none had long-term sequelae[21].

Extrahepatic connection of umbilical vein is associated with portal agenesis which may unfavorably affect long-term outcomes in 24% of fetuses with DVA and liver bypass[21]. This may cause severe postnatal complications such as congestive heart failure, pulmonary edema, focal nodular hyperplasia, and hepatic tumors[30,31]. In all cases with DVA and extrahepatic connection, agenesis of portal system should be ruled out, as it is the main prognostic factor[9]. However, according to the literature, prenatally suspected cases of portal agenesis may recover in the postnatal period[32]. Presence of portal venous system may predict favorable outcomes if there are no associated anomalies[17]. DVA with intrahepatic connection is associated with portosystemic shunts, rather than portal agenesis[32]. In this condition, intrahepatic portal venous system is normally developed, but there is a connection between portal and hepatic veins, also known as portosystemic shunt[32]. This group of anomalies require postnatal sonographic evaluation because a precise sonographic determination of portal system components in the prenatal period is difficult and that makes parental counseling more challenging[3]. In case of DVA with extrahepatic connection, if the possibility of portal agenesis cannot be ruled out, then long-term sequelae cannot be predictable, and parents must be informed about possible poor prognosis. During the counseling process, the family must be informed about the type of malformation, associated anomalies, postnatal complications, and possible surgical correction. It should also be kept in mind that intrahepatic shunting may be associated with metabolic consequences, potential neonatal hepatic dysfunction and hyperammonemic encephalopathy in the neonate[17,20]. If an intrahepatic shunting is suspected on prenatal ultrasound, the neonate should be monitored for hiperammonemia and liver and followed up until the closure of the shunt is confirmed[9,33]. Once DVA is diagnosed, care must be taken to rule out coexisting venous system anomalies including umbilical, hepatic, portal or caval venous systems since defects in the venous systems can either occur in isolation or in combination[11]. In our opinion, evaluation of an anatomically normal DV should be an integral part of detailed anatomy screening and in case of non-visualization, a thorough assessment of hepatic and portal veins is mandatory. However, some anomalies of portal venous system such as partial portal agenesis or portosystemic shunts can occur even if DV is present and precise diagnosis is not possible during prenatal period[9].

Our study provides significant data about prenatally diagnosed DVA cases to the literature and thus, may help promote antenatal management approaches, parental counseling and decision-making processes keeping in mind that clinical decision should always be made on a case-by-case basis. One strength of our study is that there is no lack of data during follow-up due to centralization of cases in a tertiary referral unit. The retrospective design and limited data on long-term outcomes are among our study limitations. Further studies with larger number of cases and with long-term outcomes are needed to confirm our results.

5. Conclusion

DVA is a rare anomaly, and the routine use of Doppler ultrasound has enabled the diagnosis of DVA as early as 11-14 weeks. Our study results are consistent with the findings and short-term outcomes previously reported about DVA. DVA is significantly associated with cardiac and extracardiac structural malformations, hydrops, and genetic abnormalities. The presence of additional anomalies is the main prognostic factor and may lead to poorer fetal outcomes. Fetuses with DVA and extrahepatic connection have additional risk for cardiac failure, hydrops and portal venous system agenesis which worsen outcomes, even if the fetal anatomy is normal. On the other hand, DVA with intrahepatic connection tend to have more favorable outcomes especially if it is not associated with other malformations and counseling can be reassuring. Detailed anatomical assessment, fetal echocardiography and genetic testing modalities of the current modern era including CMA and ES are recommended when DVA is detected. Ongoing fetal surveillance should be targeted on fetal signs of hydrops and cardiac failure, especially in cases of DVA with extrahepatic connection.

Limitations of the Study

The retrospective design and limited data on long-term outcomes are among our study limitations.

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None.

Conflict of Interests

No conflict of interest was declared by the authors.

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Author Contributions

Idea/Concept: VA. Design: SA, VA. Data Collection/Processing: SA, İG. Analysis/Interpretation: İG, VA. Literature Review: FE. Drafting/Writing: VA, FE. Critical Review: all authors

Ethical Approval

This study was approved approved by Istanbul Başakşehir Çam and Sakura City Hospital Clinical Research and Ethics Committee (ethical approval no: 2023/522, date: 25.10.2023).

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author.

Consent to participate

Informed consent was obtained from all participants before the enrollment.

Informed Statement

None.

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Evaluation Of Preoxygenation At Three Different Altitudes Using Blood Gas Results: A Multicenter Prospective Observational Study

Özgür Özmen[1,6], Elzem Şen[2], Muhammet Ahmet Karakaya[3], Merve Ümran Yılmaz[4], Canan Atalay[1,2], Ayşenur Dostbil[1,6], Mehmet Aksoy[1,6], İlker İnce[5,6]

[1]School of Medicine, Department of Anesthesiology and Reanimation, Ataturk University, Erzurum, Türkiye
[2]School of Medicine, Department of Anesthesiology and Reanimation, Gaziantep University, Gaziantep, Türkiye
[3]Department of Anesthesiology and Reanimation, Acıbadem Ataşehir Hospital, İstanbul, Türkiye
[4]School of Medicine, Department of Anesthesiology and Reanimation, Koç University, İstanbul, Türkiye
[5]Department of Anesthesia and Perioperative Medicine, Milton S. Hershey Medical Center, Penn State University, Pennsylvania, USA
[6] Anethesiology Clinical Research Office, Atatürk University, Erzurum, Türkiye

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****Corresponding Author***
Özgür Özmen
School of Medicine
Department of Anesthesiology and Reanimation
Ataturk University, Erzurum, Türkiye
Phone: +90 5424002477
E-mail: dr.ozgurozmen@yahoo.com.tr

Doi:10.56766/ntms.1598661

Authors' ORCIDs
Özgür Özmen
https://orcid.org/0000-0003-2014-0468
Elzem Şen
https://orcid.org/0000-0003-3001-7324
Muhammet Ahmet Karakaya
https://orcid.org/0000-0001-8026-4783
Merve Ümran Yılmaz
https://orcid.org/0009-0007-4754-8056
Canan Atalay
https://orcid.org/0000-0002-4859-4616
Ayşenur Dostbil
https://orcid.org/0000-0002-7167-901X
Mehmet Aksoy
https://orcid.org/0000-0003-0867-8660
İlker İnce
https://orcid.org/0000-0003-1791-9884

Abstract: Protecting patients from hypoxia during anesthesia induction is crucial for those undergoing coronary artery bypass surgery. High altitude does not change the inspired O2 concentration (%21), but reduced barometric pressure leads to decreased partial alveolar pressure and arterial PaO2. We aim to evaluate the effects of preoxygenation in the operating room at three different altitudes. After obtaining ethical approval, patients aged 40 and above, living in the same city for at least 10 years, and scheduled for coronary artery bypass surgery will be included in the study. A total of 60 patients will be divided into three groups: Group 0, Group 800, and Group 1900, with 20 patients in each group corresponding to three different altitudes. Before anesthesia induction, patients will receive 12 L/min of 80% O2 for 3 minutes via a face mask. During preoxygenation, arterial blood gas values will be recorded at the 0th, 1st, 2nd, and 3rd minutes. PaO2 values from arterial blood gas results will be evaluated at these time points across the three altitudes. There were no statistically significant differences between the groups regarding height, weight, age, and ASA classifications. There were no statistically significant differences in PaO2 values between the 0th, 1st, 2nd, and 3rd-minute blood gas measurements across all groups ($p>0.05$). Preoxygenation before anesthesia induction for coronary artery bypass surgery patients produced similar results at all three altitudes. ©2025 NTMS.

Keywords: Blood Gas; Preoxygenation; Different Altitudes.

1. Introduction

Preoxygenation is an important technique that delays the development of hypoxia and increases oxygen reserves during anesthesia. In particular, adequate oxygenation is critical in minimizing complications and

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accelerating the recovery process in cardiovascular surgeries. Preoxygenation aims to reduce the risk of hypoxia by increasing patients' oxygen levels before anesthesia, especially in major surgeries like coronary artery bypass grafting (CABG) [1,2].

This study aims to evaluate the effects of preoxygenation in the operating room on patients undergoing coronary artery bypass grafting (CABG) surgery at three different altitudes. In recent years, the ability of high-fraction inspired oxygen (FiO2), or preoxygenation, to delay the onset of arterial oxyhemoglobin desaturation due to apnea before anesthesia induction and tracheal intubation has gained significant importance. Preoxygenation replenishes the body's oxygen reserves and increases functional residual capacity, which is crucial for maintaining oxygenation during surgery.

Although the inspired oxygen concentration (%21) remains unchanged at high altitudes, the decreased barometric pressure reduces partial alveolar pressure and arterial PaO2. For instance, PaO2, normally around 100 mmHg at sea level, decreases to 74 mmHg at 2000 meters. As altitude increases, PaO2 declines exponentially [3]. Despite the known effects of altitude on oxygenation, to our knowledge, no study has specifically addressed the impact of altitude on preoxygenation efficacy.

Considering the importance of protecting patients from hypoxemia, optimizing the duration of preoxygenation based on altitude is crucial for improving patient safety, especially in environments with varying atmospheric pressures. This study aims to fill the gap in the literature and evaluate how preoxygenation, depending on the altitude, can contribute to maintaining adequate oxygenation during surgery.

2. Material and Methods

The study was initiated after obtaining approval from the Faculty of Medicine, Clinical Research Ethics Committee, Ataturk University (protocol number: B.30.2.ATA.0.01.00/8, date: 05.11.2020). The study was supported by the Scientific Research Projects Coordination Unit, Ataturk University (04.03.2021, Project Number: TAB-2021-9143, ID: 9143). The study will include adult patients aged 40 and above who have been living in the city where the surgery is performed (altitude) for at least 10 years and are scheduled for coronary artery bypass grafting (CABG) surgery. Preoperative assessment will include patients with ASA II-III physical status, and the study is planned to be conducted on at least 80 patients. Patients with pneumonia or other signs of infection, hemodynamic instability, respiratory distress, FEV1 < 60%, FEV1/FVC < 60%, VC < 50% before surgery, BMI ≥ 40, patients who have received a blood transfusion before surgery, and patients who refuse or are unable to decide to participate in the study will be excluded.

The study will begin when patients are admitted to the operating room for elective CABG surgery without premedication. Upon entering the operating room, patients undergo heart rate measurements, peripheral oxygen saturation (SpO2), and non-invasive arterial blood pressure using a 5-electrode electrocardiogram (ECG). Continuous invasive blood pressure measurements will be obtained using a radial artery catheter. Immediately before anesthesia induction, patients will receive 12 L/min of 80% oxygen via a face mask for 3 minutes. During the anesthesia phase, preoxygenation will be applied using a face mask that perfectly fits the patient's face to prevent gas leakage. During this period, patients will be instructed to breathe normally (tidal volume) for 3 minutes with the face mask (Baillard et al.). The fraction of inspired oxygen (FiO2) and expired oxygen (FiO2) will be measured with a calibrated gas analyzer on the ventilator during preoxygenation.

The study will be conducted in operating rooms in three cities with different altitudes (1900 m—Erzurum, 800 m—Gaziantep, 0 m—Istanbul). During preoxygenation, arterial blood gas values will be recorded at the 0th, 1st, 2nd, and 3rd minutes. Among these arterial blood gas measurements, PaO2 (partial arterial oxygen pressure) values will be evaluated at the three different altitudes. The data obtained will allow the examination of how the effects of preoxygenation change depending on environmental conditions.

2.1. Statistical Analysis

Analyzes were made with IBM SPSS 20 statistical analysis program. Data will be presented as mean, standard deviation, median, minimum, maximum, percentage and number. Normal distribution of continuous variables will be examined with Shapiro-Wilk test, Kolmogorov-Simirnov test, Q-Q plot, skewness and kurtosis. In comparing continuous variables with more than two independent groups, the ANOVA test will be used if the normal distribution condition is met, and the Kruskal Wallis test will be used if it is not met. Chi square test will be used for comparisons between categorical variables. The statistical significance level will be set at $p < 0,05$.

3. Results

There were no statistically significant differences in the patient's demographic characteristics, such as age, gender, height, weight, and ASA classifications, between the groups ($p>0.05$). Table 1 presents the demographic data regarding the patient's age, gender, height, weight, and ASA classifications (Table 1).

3.1. Blood Gas Values

There were no significant differences in the PaO2 values measured at 0, 1, 2, and 3 minutes between the groups ($p>0.05$). The detailed SpO2, PaO2, and PaCO2 values measured for each groups ($p> 0,05$) (Table 2, Table 3, Table 4, Table 5).

The data presented in the tables above show that there were no significant differences in PaO2 and PaCO2 values between the groups during the 0th, 1st, 2nd, and

3rd minutes of preoxygenation. The results indicate that preoxygenation had similar effects across the three groups, suggesting that altitude did not significantly impact the preoxygenation process.

Table 1: Demographic Data.

	Group 0	Group 800	Group 1900	P
Age (years)	60.42	61.75	61.12	0.22
Gender (M/F) (n)	15/5	17/3	16/4	0.42
Height (cm)	168	170.2	169.4	0.68
Weight (kg)	74	72.6	75.8	0.44
ASA (II/III) (n)	2/18	3/17	4/16	0.45

All data are represented as n (number). Chi square test and ANOVA test.

Table 2: Blood Gas Values at 0 Minute.

	Grup 0	Grup 800	Grup 1900	P
SpO2 (%)	94.45±1.7	93.66±0.9	92.88±1.1	0.21
PaO2 (mmHg)	77.6±6.42	75.4±5.47	76.5±7.35	0.15
PaCO2 (mmHg)	35.4±4.01	33.1±3.47	34.9±2.45	0.33

Data are represented as mean ± standard deviation. ANOVA test.

Table 3: Blood Gas Values at 1 Minute.

	Grup 0	Grup 800	Grup 1900	P
SpO2 (%)	99.2±0.21	99.3±0.07	99±0.15	0.42
PaO2 (mmHg)	172.25±21.4	176.4±20.3	169.41±18.6	0.66
PaCO2 (mmHg)	35.5±1.14	36.45±2.11	34.6±1.75	0.43

Data are represented as mean ± standard deviation. ANOVA test.

Table 4: Blood Gas Values at 2 Minutes.

	Grup 0	Grup 800	Grup 1900	P
SpO2 (%)	100	99.4±0.33	99.6±0.32	0.47
PaO2 (mmHg)	211.4±27.54	220.47±24.4	215.43±28.43	0.13
PaCO2 (mmHg)	37.8±2.7	39.5±3.5	40.4±2.24	0.18

Data are represented as mean ± standard deviation. ANOVA test.

Table 5: Blood Gas Values at 3 Minutes.

	Grup 0	Grup 800	Grup 1900	P
SpO2 (%)	100	100	99.5±0.14	0.65
PaO2 (mmHg)	224.32±21.21	232.23±24.30	226.47±22.14	0.54
PaCO2 (mmHg)	36.4±1.45	38.4±1.37	38.2±2.02	0.33

Data are represented as mean ± standard deviation. ANOVA test.

4. Discussion

This study aimed to investigate the effects of preoxygenation at different altitudes (0 m, 800 m, 1900 m) on arterial blood gas values in patients undergoing elective coronary artery bypass grafting (CABG) surgery. Despite the differences in altitude, no significant differences were found in PaO2 values between the groups during the 0th, 1st, 2nd, and 3rd minutes of preoxygenation. These findings suggest that the impact of altitude on preoxygenation, at least in terms of PaO2 and PaCO2, is minimal in the context of elective CABG surgeries.

Preoxygenation is a crucial intervention that replenishes the body's oxygen reserves and increases functional residual capacity [4,5]. This process is particularly important in patients undergoing coronary surgery, where protecting against hypoxemia is essential for optimal outcomes. It is well-established that high altitude does not alter the inspired oxygen concentration (21%), but the reduced barometric pressure decreases both partial alveolar pressure and arterial PaO2. For instance, PaO2, which is normally around 100 mmHg at sea level, has been reported to decrease to 74 mmHg at 2100 meters above sea level.

As altitude increases, PaO2 declines exponentially [6-8]. In our study, while we observed no significant differences in PaO2 levels across the different altitudes (0 m, 800 m, 1900 m) during preoxygenation, the impact of altitude on oxygenation remains a significant consideration in clinical practice. Although the preoxygenation procedure may offer some protective effect in maintaining oxygen levels, it is crucial to recognize that at higher altitudes, the body's ability to compensate for reduced oxygen availability may be limited, particularly in patients with comorbidities or those undergoing high-risk surgeries like CABG.

Preoxygenation is a critical step in anesthesia, providing oxygen reserve to delay the onset of hypoxia in patients undergoing surgery. Studies have shown that preoxygenation effectively increases oxygen reserve in healthy individuals and those with various underlying conditions. In high-altitude areas, the lower atmospheric pressure could theoretically reduce the oxygen available to the patient, potentially affecting the efficacy of preoxygenation. However, our study suggests that preoxygenation had comparable effects on arterial oxygen levels within the altitudes considered (Erzurum at 1900 m, Gaziantep at 800 m, and Istanbul at 0 m). It is well established that altitude can affect oxygen partial pressure and the ability to maintain adequate oxygen levels in tissues. However, it has been shown that the body adapts to hypoxic conditions over time through increased red blood cell production and improved tissue oxygen utilization [9,10]. This adaptation may explain why this study found no significant difference in PaO2 despite varying altitudes. It is important to note that this study included patients with ASA II-III physical status, which may have limited the influence of altitude on preoxygenation [11]. In healthy individuals, the effects of altitude may be more pronounced, especially in those with pre-existing respiratory or cardiovascular conditions. Our exclusion criteria, which ruled out patients with significant respiratory or hemodynamic instability, ensured that the results were not confounded by these factors.

The study's methodology, including using a calibrated gas analyzer to measure FiO2 and FiO2 during preoxygenation, provided accurate data on oxygen levels and allowed for precise comparisons across different altitudes. The findings suggest that preoxygenation, even in higher altitudes, does not lead to significant changes in PaO2, indicating that this practice remains effective across varying environmental conditions. However, this study has some limitations. The sample size was relatively small, and the findings might differ with a larger cohort, especially considering the inclusion of patients with different comorbidities or those undergoing more complex surgeries. Additionally, the focus was solely on arterial oxygen levels, and other factors such as tissue oxygenation or recovery time were not evaluated. Further research is needed to investigate these aspects and to determine whether altitude has a more significant impact on other physiological parameters.

This study optimized preoxygenation duration based on altitude to protect patients from hypoxemia. To our knowledge, no study specifically addresses the effects of preoxygenation performed before anesthesia induction at different altitudes on patients' PaO2 values. Our study compared preoxygenation techniques applied at three different altitudes and found no significant differences in PaO2 values between the groups. Based on these results, we conclude that the preoxygenation technique and duration applied are suitable and effective across all altitudes.

These findings are particularly relevant in patients undergoing coronary surgery, where adequate oxygenation is critical. Although the effects of altitude on oxygenation, particularly PaO2, are well-documented, our results suggest that preoxygenation, when performed appropriately, can mitigate the potential impact of altitude on arterial oxygen levels. Given that preoxygenation did not significantly alter PaO2 levels at any altitude in our study, this supports the notion that the current preoxygenation protocol can be safely applied to patients, regardless of the altitude at which the surgery is performed.

However, it is important to note that this conclusion is based on the specific patient population in this study, which included individuals with ASA II-III physical status undergoing elective CABG surgery. Further studies with larger sample sizes, including patients with varying comorbidities and from different surgical backgrounds, are needed to confirm these findings and to explore the broader implications of preoxygenation in diverse clinical settings.

5. Conclusion

Preoxygenation before anesthesia induction for coronary artery bypass surgery patients produced similar results at all three altitudes.

Limitations of the Study

There are some limitations to the study. The study can be done on a larger population. Time and conditions for blood gas samples to reach the laboratory.

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Conflict of Interests

The authors declare that they have no conflict of interest to disclose.

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Author Contributions

Conception, ÖÖ , EŞ , AD and İİ; Design, CA and AD; Supervision, MAK and MA; Materials, ÖÖ; Data collection and processing, ÖÖ , EŞ , MAK and MÜY; Analysis and interpretation ,ÖÖ , EŞ, CA; Literatüre Rewievn , ÖÖ, MA , İİ; Writing, ÖÖ , MAK, EŞ; Critical rewiev, CA , AD..

Ethical Approval

Clinical Research Ethics Committee, Ataturk University (protocol number: B.30.2.ATA.0.01.00/8, date: 05.11.2020).

Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent to participate

Consent was obtained from the patients participating in the study.

Informed Statement

Informed consent was obtained from all subjects involved in the study.

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Antibiotic Resistance in COPD Patients in the Intensive Care Unit: A Review of Recent Developments

Özgür Özmen[1,2*]

[1]School of Medicine, Department of Anesthesiology and Reanimation, Ataturk University, Erzurum, Türkiye
[2]Anethesiology Clinical Research Office, Atatürk University, Erzurum, Türkiye

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[*]***Corresponding Author***
Özgür Özmen
School of Medicine
Department of Anesthesiology and Reanimation
Ataturk University, Erzurum, Türkiye
Phone: +90 5424002477
E-mail: dr.ozgurozmen@yahoo.com.tr

Doi:10.56766/ntms.1586539

Authors' ORCIDs
Özgür Özmen
https://orcid.org/0000-0003-2014-0468

Abstract: Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality globally, and it remains a leading contributor to hospital admissions, particularly in the elderly. In the past decade, COPD has been identified as one of the leading risk factors for infection-related complications, including pneumonia, bronchitis, and ventilator-associated pneumonia (VAP). Antibiotics are a cornerstone of therapy for COPD exacerbations caused by bacterial infections. However, inappropriate antibiotic use in this patient population has led to an increasing burden of antibiotic resistance. The overuse of broad-spectrum antibiotics is especially problematic in ICU settings, where empirical antibiotic treatment is often initiated without adequate microbiological testing. The relationship between COPD and antibiotic resistance is multifaceted. On the one hand, COPD patients are more likely to require antibiotics due to recurrent infections, leading to frequent antibiotic courses. On the other hand, the repeated exposure to antibiotics can promote the selection of resistant bacterial strains. The management of antibiotic resistance in COPD patients, particularly those in the ICU, is a complex and growing challenge. Strategies such as antibiotic stewardship programs, rapid microbiological diagnostics, and the use of narrow-spectrum antibiotics have been shown to reduce the emergence of resistant organisms and improve patient outcomes. However, the problem of antibiotic resistance in COPD patients remains significant, particularly in the context of multidrug-resistant pathogens. ©2025 NTMS.

Keywords: Intensive Care Unit; Chronic Obstructive Pulmonary Disease; Antibiotic Resistance.

1. Introduction

1. COPD and Infection Risk in Intensive Care

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality globally, and it remains a leading contributor to hospital admissions, particularly in the elderly. COPD is characterized by persistent airflow limitation and an increased susceptibility to respiratory infections. Exacerbations of COPD are commonly triggered by bacterial or viral infections, leading to hospitalization and, in severe cases, the need for intensive care unit (ICU) admission [1]. The intensive care setting further complicates the management of these patients due to comorbidities, advanced age, and frequent mechanical ventilation needs.

In the past decade, COPD has been identified as one of the leading risk factors for infection-related complications, including pneumonia, bronchitis, and ventilator-associated pneumonia (VAP). Notably, patients with severe COPD often have compromised immune defenses, including impaired mucociliary clearance and altered airway microbiota, which predispose them to frequent infections. Furthermore,

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the use of corticosteroids and other immunosuppressive treatments in COPD exacerbations may further increase the risk of opportunistic infections. This compromised state creates a vicious cycle, where infections exacerbate COPD and vice versa, leading to an increased need for hospitalization and prolonged ICU stays [2].

The COVID-19 pandemic further exacerbated this issue by increasing the incidence of co-infections in critically ill COPD patients, particularly in those requiring mechanical ventilation. Studies have shown that these patients often receive broad-spectrum antibiotics as empirical treatment, which significantly contributes to the rise of antibiotic resistance [1,3].

2. Antibiotic Use and Antibiotic Resistance in COPD Patients

Antibiotics are a cornerstone of therapy for COPD exacerbations caused by bacterial infections. However, inappropriate antibiotic use in this patient population has led to an increasing burden of antibiotic resistance. Recent studies highlight that a significant proportion of antibiotics prescribed in COPD exacerbations are either unnecessary or poorly targeted. A study by found that ICU patients with COPD are frequently prescribed broad-spectrum antibiotics before microbiological confirmation of infection, which leads to increased pressure on bacterial populations to develop resistance mechanisms [1,4].

The overuse of broad-spectrum antibiotics is especially problematic in ICU settings, where empirical antibiotic treatment is often initiated without adequate microbiological testing. This practice increases the risk of multi-drug resistant (MDR) infections, particularly from pathogens like *Pseudomonas aeruginosa, Acinetobacter baumannii, and Klebsiella pneumoniae*, which are notorious for their resistance to multiple classes of antibiotics [4]. Notably, these pathogens are commonly associated with hospital-acquired infections, including VAP and catheter-related bloodstream infections, which are common in mechanically ventilated COPD patients.

A study conducted in Nseir et al. demonstrated a significant increase in the prevalence of MDR pathogens in ICU patients with COPD, correlating antibiotic overuse with poorer outcomes, including longer ICU stays and higher mortality rates. The authors also highlighted that despite the growing body of evidence pointing to the overuse of antibiotics, there remains a gap in the implementation of effective antibiotic stewardship programs (ASPs) in many healthcare settings, particularly in developing countries [5].

The emergence of extensively drug-resistant (XDR) organisms has further complicated the management of infections in COPD patients. These organisms are resistant to almost all available antibiotics, leaving clinicians with few therapeutic options. A recent study by Ullah et al. reported that the number of XDR infections in ICU patients with COPD has increased over the past five years, leading to an urgent need for new antibiotic classes and innovative therapeutic strategies [6].

3. The Impact of COPD on Antibiotic Resistance

COPD patients, particularly those with severe or very severe forms of the disease, are at an elevated risk of developing infections due to several factors inherent to the disease. The chronic inflammation associated with COPD results in structural changes to the airways, such as goblet cell hyperplasia and mucus plugging, which impair the natural defense mechanisms of the respiratory tract. Additionally, the frequent use of corticosteroids, which are commonly prescribed to manage COPD exacerbations, further suppresses the immune response, making patients more susceptible to both bacterial and viral infections[2-4].

The relationship between COPD and antibiotic resistance is multifaceted. On the one hand, COPD patients are more likely to require antibiotics due to recurrent infections, leading to frequent antibiotic courses. On the other hand, the repeated exposure to antibiotics can promote the selection of resistant bacterial strains. This is particularly concerning in the ICU, where patients are often treated with broad-spectrum antibiotics empirically while awaiting culture results. As a result, bacterial populations are increasingly exposed to antibiotic pressure, leading to the development of resistance over time [3,4].

A study by Günay et al. examined the impact of frequent hospital admissions on the development of antibiotic resistance in COPD patients [7]. The study found that patients who experienced multiple hospitalizations for COPD exacerbations over a two-year period had a significantly higher rate of colonization with resistant pathogens compared to those with fewer hospital admissions. This highlights the importance of carefully managing antibiotic use in hospitalized COPD patients to prevent the development of resistance.

Furthermore, the use of mechanical ventilation in COPD patients has been linked to an increased risk of acquiring hospital-associated infections, including VAP, which is particularly challenging to treat due to the involvement of resistant organisms. Ventilated COPD patients are often exposed to a range of antibiotics during their ICU stay, leading to a greater likelihood of developing resistance. Studies have shown that the duration of mechanical ventilation is directly correlated with the risk of acquiring multidrug-resistant pathogens [7,8].

4. Strategies to Mitigate the Burden of Antibiotic Resistance

To address the growing challenge of antibiotic resistance in COPD patients, especially those in the ICU, several strategies have been proposed and implemented. Antibiotic Stewardship Programs (ASPs) have gained widespread recognition as an essential tool in reducing inappropriate antibiotic use. The main

objective of ASPs is to ensure the appropriate selection, dosage, and duration of antibiotic therapy, thereby minimizing the emergence of resistant organisms. Suzuki et al. demonstrated that the implementation of an ASP in ICU settings resulted in a significant reduction in the use of broad-spectrum antibiotics and a corresponding decline in the prevalence of resistant pathogens [9]. This study further emphasized the need for ongoing education and training of healthcare staff on the principles of antimicrobial stewardship to achieve sustainable improvements in antibiotic prescribing practices [9].

One of the key elements of effective antibiotic stewardship is the use of rapid microbiological diagnostics, which allows for more targeted therapy. Recent advancements in molecular diagnostics, such as polymerase chain reaction (PCR)-based tests, enable clinicians to quickly identify the causative pathogen and its resistance profile. This approach has been particularly beneficial in ICU settings, where time is of the essence in selecting the appropriate antibiotic therapy[10]. Rapid identification of pathogens such as Methicillin-resistant Staphylococcus aureus (MRSA) and Pseudomonas aeruginosa has led to faster de-escalation of antibiotic therapy and improved patient outcomes.

Additionally, the use of narrow-spectrum antibiotics is a critical component of antibiotic stewardship. Studies have consistently shown that the use of broad-spectrum antibiotics should be reserved for cases where the causative pathogen is unknown or when the patient is critically ill. As soon as microbiological results are available, therapy should be narrowed to target the specific pathogen, which helps minimize the risk of resistance. A 2020 meta-analysis found that the use of narrow-spectrum antibiotics in ICU patients with COPD was associated with lower rates of MDR infections and reduced hospital stays [11].

5. Emerging Directions and Future Research

The fight against antibiotic resistance requires ongoing research and the development of new therapeutic approaches. The emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) pathogens highlights the urgent need for novel antibiotics. Recent advancements in drug development have focused on the creation of new antibiotic classes, including beta-lactamase inhibitors and cephalosporin combinations, which have shown promising results in treating resistant pathogens [2-5].

Furthermore, immunomodulatory treatments for COPD patients are being explored as a potential way to enhance the host's ability to fight infections and reduce the need for frequent antibiotic use. Research into agents that can modulate the immune system, such as interleukin inhibitors and toll-like receptor agonists, has shown promise in reducing the frequency of exacerbations and infections in COPD patients. These therapies may provide an adjunct to antibiotics in the management of respiratory infections, particularly in patients with severe COPD who are at high risk of recurrent infections[12].

In addition to pharmacological interventions, non-pharmacological strategies such as vaccination and pulmonary rehabilitation may play a key role in reducing the incidence of infections in COPD patients. The use of vaccines against pneumococcal infections and influenza has been shown to reduce the frequency of COPD exacerbations, thereby potentially reducing the need for antibiotics [13].

2. Conclusion

The management of antibiotic resistance in COPD patients, particularly those in the ICU, is a complex and growing challenge. Strategies such as antibiotic stewardship programs, rapid microbiological diagnostics, and the use of narrow-spectrum antibiotics have been shown to reduce the emergence of resistant organisms and improve patient outcomes. However, the problem of antibiotic resistance in COPD patients remains significant, particularly in the context of multidrug-resistant pathogens.

Future research into novel antibiotics, immunomodulatory therapies, and non-pharmacological interventions will be critical in addressing this issue. In the meantime, clinicians must continue to prioritize appropriate antibiotic use, ensure effective infection control measures, and remain vigilant in the face of emerging resistance.

Limitations of the Study

Limitation of our study; antibiotic resistance could be evaluated in the intensive care spectrum rather than in a single disease group.

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Conflict of Interests

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None.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Medication-Related Osteonecrosis of the Jaw: Risk Factors, Management and Prevention in Dental Practices

Osayd Alawawda[1*], Gelengül Urvasızoğlu[2], Funda Bayındır[1]

[1]Department of Prosthodontics, Faculty of Dentistry, Ataturk University, Erzurum, Türkiye
[2]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Atatürk University, Erzurum, Türkiye

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[*]***Corresponding Author***
Osayd Alawawda
Department of Prosthodontics
Faculty of Dentistry
Ataturk University, Erzurum, Türkiye
Phone: +90 5466357397
E-mail: osayd33540@gmail.com

Doi:10.56766/ntms.1528563

Authors' ORCIDs
Osayd Alawawda
https://orcid.org/0009-0008-3954-6373
Gelengül Urvasızoğlu
https://orcid.org/0000-0003-1628-7571
Funda Bayındır
https://orcid.org/0000-0001-5699-2879

Abstract: Medication-related osteonecrosis of the jaw (MRONJ) constitutes a considerable clinical challenge, particularly for individuals undergoing antiresorptive therapy for osseous malignancies and osteoporosis. This review seeks to investigate the risk factors, management approaches, and prophylactic strategies pertaining to MRONJ, emphasizing the implications of tooth extraction, implant therapy, oral surgical interventions, periodontitis, and inadequately fitting removable dentures. An exhaustive literature review was performed to assess the prevalence of MRONJ, concentrating on the specific drug type, method of administration, and dental interventions. Particular emphasis was placed on the hazards linked to intravenous bisphosphonate therapy, tooth extractions, dental implants, and various oral surgical procedures. Investigations examining the potential protective function of dental implants in contrast to alternative interventions were also scrutinized. Data regarding collaborative preventive strategies involving dental practitioners, medical professionals, and patients were incorporated. The review elucidated that the incidence of MRONJ is contingent upon the specific drug and procedure utilized, with intravenous bisphosphonates presenting a heightened risk. Tooth extraction is identified as a principal local risk factor for MRONJ, whereas the evidence regarding dental implants is inconsistent, with certain studies indicating a diminished risk. Prophylactic measures, encompassing pretreatment assessments, enhanced oral hygiene practices, and minimally invasive procedures, were recognized as vital for mitigating the incidence of MRONJ. The prevention and management of MRONJ necessitate a multidisciplinary framework, which includes comprehensive dental assessments, patient education initiatives, and meticulous treatment planning. Interdisciplinary collaboration among healthcare providers is imperative for optimizing clinical outcomes. Additional research is warranted to elucidate the pathophysiological mechanisms underlying MRONJ and to devise targeted therapeutic interventions that enhance safety and quality of life for patients receiving antiresorptive therapy. ©2025 NTMS.

Keywords: Medication-Related Osteonecrosis of the Jaw (MRONJ); Antiresorptive Therapy; Dental Implants; Tooth Extraction; Bisphosphonates (BPs).

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1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a significant clinical problem, particularly in patients receiving antiresorptive therapy for primary or metastatic bone malignancies or osteoporosis[1]. The incidence of MRONJ is reported to be between 1% and 10% in patients receiving intravenous (IV) bisphosphonates (BPs), whereas this rate is 0.001% to 0.01% in patients taking oral BPs[2]. MRONJ is considered a multifactorial disease with an incompletely defined pathophysiology. It is characterized by the complex interplay of systemic and local risk factors that sustain a continuous cycle of necrosis, leading to bone necrosis and soft tissue destruction. The disruption of soft tissue integrity exacerbates the condition, highlighting the need for ongoing preclinical and clinical research to understand the fundamental factors and modifiers of disease development, severity, progression, and healing [1].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) updated the widely used definition of MRONJ in a 2022 position paper. The 2014 criterion of "current or previous treatment with antiresorptive or antiangiogenic agents" was revised to "current" or "previous treatment with antiresorptive therapy, either alone or in combination with immunomodulators or antiangiogenic drugs"[3,4]. Despite ongoing research, the underlying mechanism of MRONJ remains unknown, and systematic and targeted therapies are not yet available. Since the etiology of MRONJ is not fully understood, specific targeted treatment is currently unavailable[5].

Tooth extraction, implant treatment, oral surgery, periodontitis and poorly fitting removable dentures have been identified as triggers and associated risk factors that directly or indirectly influence the development of MRONJ[6]. Since MRONJ is mostly limited to the maxillofacial region[7], dentists have a crucial role in its prevention. They must take preventive measures to reduce the risk factors associated with drug-induced osteonecrosis. If prevention is not entirely possible, it is important to delay the start of MRONJ. Dentists are responsible for a comprehensive assessment of risk factors and developing effective strategies to mitigate or eliminate them[8].

The expert panel encourages the development of predictive tools for the development of MRONJ, such as bone turnover markers and genetic markers[9]. These tools would help dentists identify at-risk patients and adapt preventive measures more effectively. By understanding and addressing these risk factors, dentists can significantly reduce the incidence and impact of MRONJ.

MRONJ is a potentially serious condition, and its development generally requires a combination of systemic and local oral risk factors. It is relatively common in cancer patients receiving antiresorptive therapy (2-5%) and rare in patients with osteoporosis (0.01-0.03%). Therefore, the most common systemic risk factor is the use of antiresorptive drugs [10]. The number of patients with MRONJ is expected to increase over the next decade [11]; which underscores the urgent need for further research to develop effective prevention and treatment methods.

The aim of this study is to evaluate the risk factors, management strategies, and preventive measures for MRONJ in patients receiving antiresorptive therapy, focusing on dental procedures like tooth extractions and implants to improve prevention and treatment outcomes.

Antiresorptive Agents and Risk Factors

There are several types of antiresorptive drugs including Bisphosphonates (BPs), Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL)and Antiangiogenic drugs. Bisphosphonates (BPs) are classified as nitrogen-containing (zoledronic acid, pamidronate, alendronate) or non-nitrogen-containing (etidronate, clodronate, tiludronate). RANKL inhibitors include denosumab and romosozumab. Antiangiogenic drugs include bevacizumab, imatinib, and sunitinib [12]. The risk of developing MRONJ after implantation is much lower in patients with osteoporosis treated with denosumab[13].

Studies confirm that ibandronate is less effective than zoledronic acid in the treatment of MRONJ in malignancy. While the risk of alendronate is lower compared to intravenous bisphosphonates, the risk of intravenous ibandronate is lower than that of pamidronate and zoledronic acid [14]. The overall risk of MRONJ is higher in some classes of antihypertensive drugs because the total dose is higher. Drugs like alendronate can remain in circulation for up to 10 years. The risk of MRONJ is higher in those who have used these drugs for more than four years, and the risk is highest in those who have used the treatment for more than five years [3]. The AAOMS reported that the risk of developing MRONJ is highest when oral antihypertensive drugs are used for more than two years [4].

It is confirmed that malignancies increase the risk of developing MRONJ when exposed to antihypertensive, antiresorptive, or antiangiogenic drugs. Cumulative doses of intravenous drugs contribute to the development of MRONJ15. Saad and colleagues reported that the incidence of MRONJ in cancer patients treated with zoledronate or denosumab was 0.5 to 0.8 percent in one year and 1.0 to 1.8 percent in two to three years [16].

The incidence of MRONJ has been reported to be 1-25% with concurrent antiangiogenic and antiresorptive agents and 1-11% with antiresorptive agents alone. The frequency of MRONJ was found to be 6% when antiangiogenic and antiresorptive drugs were used together [17]. Compared to pamidronate or zoledronate alone, an increased incidence of MRONJ was observed with sequential pamidronate-zoledronate therapy. Similarly, patients who switched from bisphosphonates

to denosumab had a higher incidence of MRONJ compared to those who received bisphosphonates or denosumab alone [18].

The risk of MRONJ is shown to be higher with denosumab than with bisphosphonates, being 3.77% in patients treated with denosumab, compared to 2.13% in patients treated with zoledronic acid [19]. The type of antiresorptive drug leads to a higher risk with BPs compared to denosumab or antiangiogenic agents; this is due to the mechanism of action of BPs and their longer half-lives [13].

Antiresorptive drugs alone do not cause bone necrosis; however, when combined with trauma such as tooth extraction or inflammation/infection resulting from periodontal or periapical disease, bone necrosis can occur[1] .Surgical interventions pose significant risks for patients on high-dose denosumab, especially those with cancer, periodontitis, denture use, BP history, or current BP use, as well as those who are immunosuppressed due to chemotherapy, rheumatoid arthritis, diabetes, Sjogren syndrome, or steroid treatment. Comorbidities such as diabetes and autoimmune diseases further increase the risk of MRONJ [3]. The general health status of patients also contributes to MRONJ development. Dentoalveolar surgery, particularly tooth extraction, is a major risk factor, with 52-61% of MRONJ cases reporting tooth extraction as the precipitating event [20] Low doses of antiresorptive drugs are used for osteoporosis treatment, while high doses are for cancer patients with bone metastases. It is crucial to assess antiresorptive side effects in implant therapy, including fixture installation, bone augmentation, and late complications [21]. Cancer patients typically receive a ten-fold higher cumulative antiresorptive dose than those with osteoporosis, and the addition of local oral risk factors significantly increases MRONJ incidence[10]. The mandible has a higher risk of MRONJ than the maxilla. Factors such as pre-existing inflammation, rather than just high-dose antiresorptive use before or after tooth extraction, are significant MRONJ risk factors. Key factors include root amputation, immunosuppressive therapy, extraction of mandibular teeth, teeth with pre-existing inflammation, and longer high-dose antiresorptive duration (≥ 8 months) [22]. Clinical signs like pain and infection, along with the duration of antiresorptive medication, are significantly related to early necrotic bone biopsy results[23]. Necrotic bone can cause loss of soft tissue integrity, leading to clinical MRONJ, with surgical interventions further complicating the disease. A combination of antiresorptives, trauma, and/or inflammation/infection is necessary for MRONJ development [1]. MRONJ is more common in cancer patients (1.8–5% incidence) than in those with osteoporosis (0.01–0.03% incidence). Local oral risk factors include tooth extraction, inflammatory dental disease, trauma from removable prostheses, and dental implants. Identifying and managing these risk factors is crucial to minimizing MRONJ risk in susceptible patients.(24)Other significant risk factors include chemotherapy, corticosteroids, smoking, medical conditions, cardiovascular diseases, targeted therapies, inflammatory diseases, and oral trauma[25].While bisphosphonates and denosumab are well-known causes of MRONJ, other biologic agents, notably antiangiogenics like vascular endothelial growth factor antagonists and tyrosine kinase inhibitors, have also been implicated [26]. The evidence is of very low certainty. In a study of 24 cancer types, osteoporosis was the most common non-malignant condition associated with MRONJ, accounting for 23% of cases. The primary dental risk factor was tooth extraction (45%), followed by periodontal disease (10%) [27]. Several studies have concluded that the risk of MRONJ varies among different types of cancer, with the highest incidence reported in prostate cancer patients[19].

A case study highlighted MRONJ development in a patient treated with IV zoledronate for sacral plasmacytoma, who also underwent radiotherapy and chemotherapy. The MRONJ was noted in the mandible after 13 months of orthodontic treatment [28].

Overall, recognizing and managing MRONJ risk factors such as the duration of bisphosphonate intake and local infections is crucial [29].

Radiographic tests are essential for diagnosing and staging MRONJ, with approximately 75% of cases affecting the mandible [12].

The rate of MRONJ in BP patients using glucocorticoids is higher compared to those not using them. Patients receiving corticosteroid and immunosuppressive therapy carry a risk of MRONJ even with short-term BP use [14,29]. Some results indicate that male BP patients have significantly more MRONJ cases compared to females [14]. However, MRONJ is generally reported to occur in elderly female patients [12].

Management and Treatment Strategies

Surgical interventions pose a heightened risk for patients actively receiving high-dose denosumab due to the increased trauma to the bone. In contrast, nonsurgical therapies are considered lower risk [2]. Denosumab-econdary MRONJ surgery was successful in 16 of 20 patients (80.0%). This success rate is similar to the 80-90% reported for bisphosphonates [30]. Alveoplasty is emphasized as a crucial preventive measure to minimize trauma [14]. Furthermore, understanding the pathophysiological mechanisms underlying MRONJ is vital for developing targeted interventions that can reduce its incidence and improve patient outcomes.

Physicians and dentists should prioritize the prevention of MRONJ in patients with malignancies receiving antiresorptive therapies [15]. The importance of a collaborative approach involving dentists, physicians, and pharmacists cannot be overstated, as it is critical for preventing MRONJ development [31]. Increased awareness of MRONJ among dental professionals has led to a rise in cases where extractions were avoided, potentially allowing MRONJ to develop despite the

need for intervention [32]. Therefore, there is a critical imperative to enhance the awareness, education, and training of dentists in effectively managing patients prescribed antiresorptive drugs [33].

Optimizing oral and dental health before starting treatment with antiresorptive medications is mandatory. Patients should be strongly reminded to promptly report any early signs and symptoms of MRONJ. When infection is detected, treatment should begin immediately with less traumatic procedures [29]. Evidence from a 2022 Cochrane review suggests that various preventive strategies, including regular dental checkups, oral care instructions, antibiotics, and special wound closure techniques, can reduce the risk of MRONJ in cancer patients receiving antiresorptive drugs [7]. One retrospective study found a significantly higher risk of MRONJ in antibiotic-naïve patients. The QUIPS tool showed a moderately high risk of bias. The validity of antibiotics remains to be determined [34].

Development of management recommendations using algorithms to guide healthcare professionals in the prevention, diagnosis and treatment of MRONJ in different clinical scenarios. Preventive strategies should be adopted to avoid MRONJ, which is a rare but important complication that can compromise patients' quality of life. These strategies must also take into account the prevention of fragility fractures associated with untreated osteoporosis, which not only affects the quality of life but also increases mortality [35].

During treatment with antiresorptive medications, close follow-ups and meticulous oral hygiene routines should be maintained by patients. The management of MRONJ is generally challenging, and a well-established treatment strategy is yet to be developed. Therefore, prevention remains more effective than management [12]. According to the 2022 position papers of the American Association of Oral and Maxillofacial Surgeons (AAOMS), nonoperative therapy is effective for treating any stage of MRONJ [3], while surgery also plays a crucial role in its management, as indicated by a multicenter study conducted in Europe [36].

Among patients with osteoporosis treated with antiresorptive medications and undergoing tooth extraction, radiographic signs of chronic dental infection can predict MRONJ onset. Greater pathology development has been observed in sites with furcation involvement, root remnants, or untreated dentinal or pulpal caries lesions. ARDs induce bony changes visible in diagnostic images commonly used in dental practice. Postoperatively, these bony changes, such as the persistence of the alveolar socket and lamina dura, are noteworthy [37].

Development of MRONJ in Pediatric Populations

While much is known about the risks and prevalence in adult populations, particularly the elderly, It is well-documented that increased age is a significant risk factor for the development of MRONJ. Patients over the age of 65 are particularly vulnerable [3,4]. The incidence and implications in pediatric populations remain relatively understudied. There are compelling reasons to believe that MRONJ may not significantly affect children, particularly those with genetic conditions that influence bone formation. To date, no cases of MRONJ have been reported in children or adolescents in the literature, suggesting that the risk of developing MRONJ in this demographic is negligible. For instance, patients with secondary osteoporosis undergoing long-term bisphosphonate treatment should be closely monitored from adolescence into adulthood, as the risk becomes more pertinent with age [38]. The presence of MRONJ in the child and youth population treated with antiresorptive drugs has been noted to be very low, further supporting this observation [39]. A position paper has stated that there have been no reports of MRONJ or Drug-Related Osteonecrosis of the Jaw (DRONJ) in bisphosphonate-treated children with conditions like osteogenesis imperfecta [40]. This lack of evidence highlights the rarity of such occurrences in pediatric patients. However, there has been a notable case report, which is, as far as the authors are aware, the first known instance of MRONJ in a child following dental extractions. This case underscores the importance of recognizing the unusual and slow presentation of MRONJ in younger patients, which necessitates careful follow-up and monitoring [41]. Given the current evidence, longitudinal studies are required to assess the long-term implications for children treated with bisphosphonates as they transition into adulthood. These studies are crucial to evaluate the potential risks posed by the cumulative doses of past bisphosphonate therapy on the development of MRONJ later in life. Until more data is available, primary prevention of oral and dental pathologies in adulthood remains a critical strategy. Pediatric dentists play a pivotal role in maintaining the oral health of these patients during their growth, thus potentially mitigating the future risk of MRONJ [42].

Impact of Dental Implants on (MRONJ) Risk in Patients with Antiresorptive Therapy

Recent studies have explored the relationship between dental implants and the risk of Osteonecrosis of the Jaw (ONJ) in patients undergoing antiresorptive therapy, such as bisphosphonates (BPs) and denosumab, with varying results. In a systematic review of 31 failed implants due to MRONJ, 36% were in the maxilla and 65% were in the mandible, mostly posteriorly (85%). 23% of implants failed after postresorptive therapy, and 83% of these failures were due to MRONJ. The average time from the start of antiresorptive medications to the start of MRONJ was 34 months. 65% of the implants that received MRONJ were in the mandible, mainly in the posterior part. 80% of MRONJ cases were stage 2 and limited to the alveolar bone 43. Contrary to initial concerns, dental implants did not increase the risk of ONJ. In fact, they may reduce the risk even in patients with a history of bisphosphonates, steroids, periodontitis, or tooth extraction. Implant surgery did not show a higher MRONJ risk compared to those

without implants, suggesting implants might lower the MRONJ risk [44]. Ryu et al. [45] found that osteoporosis patients with dental implants had a lower risk of MRONJcompared to those without implants, suggesting that dental implants may be safely considered in patients with a history of antiresorptive therapy.

A recent systematic review Despite some limitations, implant-assisted rehabilitation in patients with previous surgical treatment of MRONJ showed a low incidence of biological complications, reduced disease recurrence for implants, and satisfactory implant survival. However, the strength of the evidence supporting these results is considered "very low"[46]. Despite these encouraging findings, other studies present a more nuanced picture. Pichardo et al. [47] reported an increased risk of MRONJ in patients with dental implants taking antiresorptive medications, including bisphosphonates. They observed that short-term (<2 years), low-dose oral bisphosphonate therapy for osteoporosis did not significantly impact implant success rates. Gelazius et al. [48] conducted a systematic review revealing a higher success rate for implants in patients receiving oral bisphosphonate therapy (98.8%) compared to those receiving intravenous treatment (91%). This underscores the potential for favorable outcomes in bisphosphonate-treated patients, offering reassurance to clinicians and patients. Conversely, Sulaiman et al. [49] showed that implants in bisphosphonate-treated patients had a higher failure risk compared to non-treated patients. Papadakis et al. [50] introduced a critical caveat, noting the challenges in making definitive claims about the impact of antiresorptive medication on dental implant success rates due to limitations in many studies, such as small sample sizes, absence of control groups, and short follow-up periods. Consequently, establishing the precise success rate of dental implants in patients undergoing antiresorptive medication remains challenging. Sher et al. [13] found that patients with a history of bisphosphonates were not at increased risk of implant failure compared to healthy patients but emphasized the risk of developing MRONJafter implant placement. Systematic reviews have also reported mixed results, with some indicating high success rates for implants in patients receiving bisphosphonate therapy, while others highlighted an elevated risk of bisphosphonate-related osteonecrosis of the jaw (MRONJ) and implant failure [51]. Specifically, Granate-Marques et al. [51] identified an increased risk of MRONJ associated with dental implants placed in the posterior jaw of patients on long-term bisphosphonate therapy, particularly those concurrently receiving systemic corticosteroids. Close collaboration between oral surgeons and prescribing physicians, individualized treatment planning, regular post-implant maintenance, and vigilant monitoring are essential for achieving successful outcomes in bisphosphonate-treated patients [52]. Evidence suggests that low-dose oral bisphosphonate intake for osteoporosis generally does not compromise implant therapy [13]. These patients do not lose more implants nor experience more implant-related complications or failures compared to implant patients without bisphosphonate intake. However, high-dose bisphosphonate intake for managing malignancies, long-term oral bisphosphonate use, and the presence of comorbidities may increase the risk of MRONJ [21]. Studies by Abtahi et al. [53] evaluated patients over a five-year follow-up period and reported that marginal bone loss increased over time in both bisphosphonate-coated and uncoated implant groups. However, results were satisfactory, with the bisphosphonate-coated implants showing 0.20 mm of marginal bone loss compared to 0.70 mm for the control group. There was a significant decrease in the incidence of MRONJin the dental implants group compared with the no dental implants group. Inserting dental implants before intravenous BP administration was not a risk factor. Dental implants were not risk factors; they were associated with lower MRONJratios [45]. Holzinger et al. [54] noted that the development of osteonecrosis in conjunction with dental implants might be a side effect of treatment with oral or intravenous BPs. Conversely, javed and Almas [55] showed that the incidence of implant failure was minimal in patients using oral and intravenous bisphosphonates, concluding that dental implants in patients undergoing bisphosphonate therapy can osseointegrate and remain functionally stable. In general, the majority of reported implant losses in antiresorptive patients occur within a short time post-installation/post-loading (i.e. early losses), Low-dose oral BP intake for osteoporosis treatment does not compromise implant therapy, indicating these patients do not lose more implants or experience more complications compared to those without BP intake [21]. Nisi et al. [56] included 90 patients with MRONJ caused by various reasons, with only 9 cases attributed to implant placement. Indicating that implant surgery might trigger MRONJ development. The presence of peri-implantitis during surgery was found to potentially affect implantation success adversely [45].

Systematic review suggested that patients with a history of bisphosphonates for osteoporosis treatment are not at increased risk of implant failure in terms of osseointegration compared to those without such medications [13]. However, studies reported significant differences in success and survival rates of dental implants between bisphosphonate-treated and control patients [57]. The overall evidence from the systematic review suggests that patients taking BPs present a higher risk of implant failure than patients not taking BPs [49]. This evidence has prompted new research suggesting that long-term use of antiresorptive drugs is contraindicated for implant treatment [58].

In a related case report, a patient with a history of bisphosphonate use for osteoporosis underwent dental implants. Follow-up visits were scheduled at 1-month intervals, during which no pathology was detected. After prosthesis placement, the patient was evaluated clinically and radiographically at 1, 3, and 6 months.

During this evaluation, no complications were observed in the jaw or in the implant [59].

Tooth extraction

Tooth extraction has been identified as a major risk factor for the development of MRONJ, particularly in patients receiving antiresorptive and antiangiogenic agents. It is reported that among patients with MRONJ, 52 to 61% attribute tooth extraction as the precipitating event [20]. The most reported dental risk factor was tooth extraction (45%), followed by periodontal disease (10%) [27].

The extraction of a tooth with preexisting infection has been suggested as one of the risk factors for antiangiogenesis agents [2]. The risk is especially pronounced in those undergoing high-dose bisphosphonate therapy for cancer treatment [22], with the duration of intravenous bisphosphonate therapy exceeding 11 months being a significant risk factor [60].

The risk of MRONJ after tooth extraction is influenced by several factors, including the duration of medication use, the presence of pre-existing inflammation, and the patient's overall health status. Furthermore, root amputation, immunosuppressive therapy, extraction of mandibular teeth, extraction of teeth with pre-existing inflammation, and longer duration of high-dose BMA (≥ 8 months) were all significantly associated with the development of MRONJ. Additionally, extractions in patients with pre-existing inflammation, such as periodontal disease or infection, are more likely to lead to MRONJ. A study found that 90.2% of all MRONJ cases had pre-existing inflammation, underscoring the importance of addressing infection before extraction [22].

For patients exposed to oral bisphosphonates, the risk is approximately 0.5%, whereas intravenous bisphosphonates elevate this risk to about 14.8% [52]. For cancer patients exposed to BPs, the risk of developing MRONJ after tooth extraction ranges from 1.6 percent to 14.8 percent (3), with some studies reporting rates as high as 51.9% [62]. The risk is directly proportional to the duration of medication use and the patient's age [62].

A significant relationship between tooth extraction frequency and increased MRONJ risk has been observed in various studies. For example, the incidence of MRONJ after tooth extraction was found to be lower in the group of osteoporotic patients with dental implants compared to those without implants [45].

The control of inflammation should be the first step, and wound-healing-compromising diseases and medications should be considered for osteoporotic patients. The older osteoporotic Korean patients who underwent tooth extraction had a six times higher risk of developing MRONJ, with rheumatoid arthritis and bisphosphonates also associated with a significantly higher risk [45]. This suggests that pre-existing inflammation is a significant risk factor for MRONJ development post-extraction.

Invasive dental procedures, such as tooth extraction, can disrupt the delicate mucosal and periosteal barrier between the teeth and bones, increasing the susceptibility to the development of MRONJ [52].

To minimize the risk of MRONJ, several preventive measures and surgical techniques have been recommended. These include minimally traumatic extraction techniques, removal of any bone edges, and mucosal wound closure [63]. The SPP muco-periosteal flap has been demonstrated to be markedly superior to the EPP mucosa flap for primary wound closure after surgical tooth extractions in cancer and osteoporosis patients undergoing or after antiresorptive treatment [23].

In terms of clinical management, it is advised that infected teeth, which cannot be salvaged through nonsurgical endodontic therapy, be extracted to prevent the progression of the infection and potential MRONJ development [2]. Prophylactic antibiotics before tooth extraction may be necessary despite their limited efficacy in reducing MRONJ risk (63). Experts have noted that the risk of developing MRONJ after a periodontal surgical procedure that requires bone manipulation is comparable with the risk associated with a dental extraction. Nonsurgical therapy should not be considered high risk because of the relatively lower level of trauma to the bone [2]. Furthermore, early dental examinations and preventive care are recommended to decrease the risk of MRONJ, especially in older osteoporotic patients [45].

Tooth extraction may also be attributable to the success of dental implants. The dental implant is closely related to tooth extraction, which happens before the surgery in most cases. Patients who had complications after extraction should be excluded from dental implantation. Only patients with insignificant problems can undergo this surgery. The incidence of MRONJ after tooth extraction was lower in the group of osteoporotic patients with dental implants than in the no-implants group [45].

Despite the high risk associated with tooth extraction, successful outcomes have been reported with the use of atraumatic surgical protocols and careful postoperative management. For example, no postoperative bisphosphonate-associated osteonecrosis of the jaw was observed in a study group of 700 patients who underwent 1,480 extractions using minimally traumatic techniques. No patients with steroid therapy had problems during healing time or developed MRONJ, and all OPTs performed showed normal alveolar bone healing following the extractions. At the last visit of the follow-up, all patients had intact mucosa and displayed no additional signs of inflammation [64].

Additionally, factors such as root amputation, the extraction of a single tooth, the presence of bone loss or severe tooth mobility, and an unclosed wound were all significantly associated with the development of MRONJ. Therefore, it is essential to consider these factors and adopt minimally traumatic extraction techniques to minimize the risk of MRONJ [63].

Tooth extraction in patients undergoing or after antiresorptive treatment cannot be considered the major risk factor for MRONJ; however, it might be the major

triggering event when not performed with preventive measures [23].

Drug holiday

The effectiveness of a drug holiday in reducing the incidence of Medication-Related Osteonecrosis of the Jaw (MRONJ) remains inconclusive; since bisphosphonate (BP) therapy has a long-term effect due to its incorporation into bone, a drug holiday of a few months is unlikely to significantly alter this risk (22, 63), although recent systematic reviews support the benefits of a drug holiday [65].

For patients undergoing procedures involving bone tissue, such as tooth extractions or dental implant installations, there is a consensus to suspend BP medication three months before and after the intervention. However, evidence supporting the efficacy of this short-term pharmacological interruption in reducing osteonecrosis risk is lacking [23]. Some studies have suggested that a preoperative drug holiday, combined with serum CTx level control, could allow safe osseointegrated implant installation without MRONJ development [66]. Despite these isolated findings, new guidelines highlight the lack of high-quality evidence supporting the effectiveness of interrupting antiresorptive drug therapy to mitigate MRONJ risk [3.9.35.67]. Overall, current evidence does not support the routine implementation of drug holidays to minimize MRONJ risk. Larger, well-designed prospective studies and randomized controlled trials are needed to draw definitive conclusions [68, 69]. A two-month holiday period did not show significant differences in osteonecrosis development [37], although some animal studies reported a 50% reduction in MRONJ incidence with a drug holiday [70].

2. Conclusion

In conclusion, the management of patients on antiresorptive therapy represents a significant challenge in dentistry, especially in relation tooth extraction, implant treatment, oral surgery, periodontitis and poorly fitting removable dentures. The development of MRONJ remains critical due to the multifactorial nature of the disease, which includes both systemic and local risk factors. Dental implants have historically been considered a risk factor for MRONJ, but recent studies have shown conflicting results. Some evidence suggests that dental implants may not significantly increase the risk of MRONJ and may even decrease it compared to other dental procedures. However, the success rate of implants in patients receiving antiresorptive therapy can vary, and factors such as duration and dose of medication play a critical role. Tooth extraction remains an important local risk factor for MRONJ, with a significant proportion of MRONJ cases attributable to this procedure. Extraction-related trauma, especially in patients with underlying disease such as periodontitis or high-dose antiresorptive therapy, requires careful planning and preventive measures. Preventive strategies including careful oral hygiene, regular dental checkups and the use of less traumatic dental procedures are important to minimize the risk of MRONJ. Collaboration between dentists and other healthcare providers is essential to optimize patient outcomes and develop effective treatment strategies for those at risk for MRONJ. Increasing awareness of MRONJ among dentists and patients is essential. A better understanding of risk factors, early signs and appropriate treatment strategies can significantly reduce the incidence of MRONJ. Continuing education and research in this area allows dentists to implement better preventive measures and improve patient care. Future research should continue to focus on understanding the pathophysiology of MRONJ, developing targeted therapies, and improving preventive strategies to improve the quality of life of patients receiving antiresorptive therapy. In addition, it is very important to implement oral measures as soon as antiresorptive therapy begins. Before starting treatment, patients should receive a thorough dental evaluation and appropriate treatment. To reduce the risk of developing MRONJ, continuous oral care and preventive measures such as maintaining excellent oral hygiene and scheduling regular dental checkups should be prioritized. Dentists must work closely with other healthcare providers to ensure a holistic approach to a patient's overall health and treatment plan.

Limitations of the Study

The limitations of this study warrant careful consideration. Variability in data sources and methodologies introduces inconsistencies, while the lack of large-scale, high-quality studies restricts the generalizability of the findings. Additionally, the incomplete understanding of MRONJ's multifactorial etiology and pathophysiology presents challenges in establishing definitive prevention and management strategies. The study’s focus on cancer and osteoporosis patients receiving antiresorptive therapy may overlook other at-risk groups. Lastly, the potential for publication bias and the evolving nature of research in this field could limit the broader applicability of the conclusions.

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The data that support the findings of this study are available from the corresponding author upon reasonable request.
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