e-ISSN: 3023-655X

Ankyra Medical Journal

Volume: 3 Issue: 1 Year: 2024

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Hello,

We have published the first issue of the new year. This year, we went down the path of name change in the journal. As it is known, the first name of the journal was "**Journal of Translational and Practical Medicine**." The purpose of publishing this journal was to include and publish articles in the fields of translational medicine and general medicine. Translational medicine is an important field that constitutes the pioneer of many innovations. When it was realized that there was a lack of articles in the field of translational medicine within a two-year period, it was decided to continue only in the field of general medicine, which was our second goal, and to make a name change in accordance with this. "**Ankyra Medical Journal**" has been adopted as the new name.

The aim is to publish high-quality articles that are indexed by important scientific article citation platforms. We would like to thank all the authors who contributed their articles to the publication of the journal, the reviewers who meticulously carried out the peer review process, valuable scientists who worked on the editorial board, and the journal publishing house.

We wish to meet you for many years.

Prof. Mehmet ÇITIRIK
Editor-in-Chief

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ORIGINAL ARTICLES

REVIEW

Ankyra Medical Journal
ORIGINAL ARTICLE
DOI: 10.51271/ANKMJ-0001

The relationship between sodium glucose co-transporter 2 inhibitors and diabetic ketosis/infection: single center retrospective experiences

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Cite this article: Tan B, Çifci A. The relationship between sodium glucose co-transporter 2 inhibitors and diabetic ketosis/infection: single center retrospective experiences. *Ank Med J.* 2024;3(1):1-5.

Received: 01.01.2024 ◆ **Accepted**: 26.01.2024 ◆ **Published**: 31.01.2024

ABSTRACT

Aims: Diabetes is a serious social problem in our country and around the world. Beyond hyperglycemia, it causes common and potentially life-threatening complications in all systems. For this reason, beyond the regulation of blood glucose, a holistic approach and combating complications are important in diabetes management. Sodium glucose co-transporter 2 (SGLT2) inhibitors are a type of antidiabetic medication that effectively regulate blood glucose levels and provide cardiac and renal protection, regardless of the decrease in blood glucose. Despite its strong effectiveness, it is seen as risky in terms of diabetic ketosis and infection, which limits its use. We aimed to investigate the legitimacy of concerns by examining the relationship between SGLT-2 inhibitors and diabetic ketosis or infection.

Methods: Our study was designed single-center and retrospectively. 152 patients over the age of 18 who were treated as inpatients in our clinic with diabetic ketosis between January 2020 and June 2023 were included in the study. In these patients, ketosis and the severity of the infection clinic, if any, were examined through various parameters among type 2 diabetic patients using SGLT-2 inhibitors, type 2 diabetic patients not using SGLT-2 inhibitors, and type 1 diabetes patients. These parameters were determined by the patient's blood and urine biochemistry tests at admission and discharge, the duration of ketosis treatment, the duration of intravenous antibiotic use, and the duration of hospitalization.

Results: Within the scope of the study, type 2 diabetic patients using SGLT-2 inhibitors were compared with type 2 diabetic patients not using SGLT-2 inhibitors and type 1 diabetic patients. In patients using SGLT-2 inhibitors, the leukocyte count in urine, an indicator of urinary tract infection, was found to be significantly higher ($p<0.002$). When the blood biochemistry tests of the patients at the time of admission were compared in terms of ketosis severity, no significant difference was detected between the groups. No significant difference was detected in terms of ketosis treatment duration, intravenous antibiotic use duration, or hospitalization duration.

Conclusion: We believe that we have obtained data showing that ketoacidosis and infection complications associated with SGLT-2 inhibitors are manageable and controllable. Based on this, we recommend that further research be conducted on the side effects of SGLT-2 inhibitors, emphasizing their additional systemic benefits, and that the place of these agents in diabetic treatment should be discussed.

Keywords: Diabetes mellitus, diabetic ketosis, diabetic ketoacidosis, sodium glucose co-transporter 2 inhibitors, infection, antibiotics

INTRODUCTION

Diabetes mellitus (DM), with its increasing momentum in recent years and all the problems it causes, threatens life all over the world and in our country and is seen as a global health crisis.[1,2] In a study, it was predicted that the number of diabetic patients living in the world in 2045 will reach 783.2 million.[3] The situation in our country is not much different from that of other societies. In the TURDEP-2 study conducted in 2011, it was found that the prevalence of DM in our country was 16.5%.[4]

Patients must meet certain criteria to be diagnosed. 1) Plasma fasting glucose level of 126 mg/dl and above after roughly 8 hours of fasting; 2) DM is diagnosed when randomly measured plasma glucose levels are 200 mg/dl or more at any time and symptoms are present; 3) Glycated hemoglobin A1c (HbA1c) levels are 6.5% (48 mmol/L) or more; and 4) plasma glucose levels are 200 mg/dl or more at 2 hours after oral ingestion of 75 grams of glucose solution.[5] DM is categorized under 4 main headings according to the pathophysiology of development: type 1 DM, type 2 DM, gestational diabetes, and other specific types.[6] Among the diabetes types, type 2 DM has the highest prevalence and accounts for approximately 90% of all diabetes cases.[7]

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Metformin is the most commonly used drug as a first-line treatment for DM due to its safety, cost-effectiveness, and cardioprotective properties.8 According to current American Diabetes Association (ADA) guidelines, sodium glucose co-transporter-2 (SGLT-2) inhibitors are recommended as second-line treatment immediately after metformin in patients with atherosclerotic cardiovascular history, heart failure, and chronic kidney disease.[9,10] They act by inhibiting glucose reabsorption from the proximal renal tubules and increasing glucose excretion through the urinary system; these agents, which act through insulin-independent pathways, have many advantages, such as having no risk of hypoglycemia, having diuretic and blood pressure-lowering effects, causing weight loss, and being cardioprotective.

In addition to their advantages, SGLT-2 inhibitors also have side effects related to their mechanism of action. The first of these is that they cause more genitourinary infections than other agents in relation to the glycosuria pathway.[11,12] Another side effect is that they predispose to diabetic ketoacidosis (DKA) with increased lipolysis and free fatty acid formation in adipose tissue and increased ketone body formation in plasma after a series of reactions.[13-15]

METHODS

Ethics

For this specialty thesis study, permission was obtained from the Kırıkkale University Non-interventional Researches Ethics Committee with decision number 2023.09.07 on 06.09.2023. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

In this retrospective cross-sectional study, 152 patients over the age of 18 who were hospitalized with a diagnosis of diabetic ketosis or ketoacidosis between January 2020 and June 2023 at Kırıkkale University Faculty of Medicine Hospital were identified and included in the study by scanning through the hospital information management system.

Patients who did not meet the criteria for diabetic ketoacidosis and ketosis at the time of hospitalization, those who subsequently developed diabetic ketoacidosis or ketosis while being followed up in the hospital for any other reason, patients younger than 18 years of age, and patients with incomplete clinical and laboratory records were not included in the study.

Some clinical parameters were defined to evaluate the clinical severity and course of the patients.

- **Ketosis treatment duration:** It includes the time between the start and end of the treatment of diabetic ketoacidosis, or ketosis, in our clinic.
- **Duration of intravenous antibiotics:** It is calculated for patients who received antibiotics and indicates how many days intravenous antibiotics were administered.
- **Length of hospitalization:** The number of days the patient was hospitalized. It is calculated to include the day the patient was hospitalized and the day the patient was discharged.

The first blood and urine tests of the patients included in the study were analyzed at admission. These tests included urea, serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, magnesium, phosphorus, calcium, and albumin in the blood; pH, CO_2, HCO_3, lactate in venous blood gas; a hemogram includes leukocytes (white blood cells; WBC), hemoglobin (Hgb), platelets (Plt), neutrophils, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). Glucose, ketone, density, and leukocyte values in urinalysis were included in the study.

Statistical Analysis

The categorical variables in the study were presented as frequency (n) and percentage (%) and analyzed by Pearson Chi-square and Fisher's exact test. The Shapiro-Wilk test determined whether the data adhered to a normal distribution. In the analysis of the difference between the continuous variables of two independent groups, the Mann-Whitney U test was used when the data did not conform to the normal distribution, and an independent t-test was used when the data did conform to the normal distribution. Data analysis was performed with the IBM SPSS 23.0 package program (IBM Corp., Armonk, NY). p values less than 0.05 were considered statistically significant.

RESULTS

Of the 152 patients included in the study, 38 had type 1 DM and were defined as type 1 (group 1). The medication use of 114 type 2 DM patients was analyzed, and 42 patients using SGLT-2 inhibitors were divided into a group called SGLT-2 inhibitors (group 2), and the remaining 72 patients not using SGLT-2 inhibitors were divided into another group called non-SGLT-2 inhibitors (group 3).

Gender, whether the patients were followed up in the intensive care unit or not, and the DK/DKA during hospitalization were analyzed for each group; 22 (57.9%) in the type-1 group, 29 (29%) in the SGLT-2 inhibitors group, and 39 (54.2%) in the non-SGLT-2 inhibitors group were female. The rate of patients requiring intensive care unit follow-up was 23.7% (9 patients) in type-1, 27.6% (5 patients) in SGLT-2 inhibitors, and 8.3% (6 patients) in non-SGLT-2 inhibitors. The DKA rate was 42.1% in the type-1 group, 16.7% in the SGLT-2 inhibitors group, and 15.3% in the non-SGLT-2 inhibitors group.

Age, number of days of hospitalization, duration of IV antibiotic use, duration of ketosis treatment, and history of DM were analyzed. The disease duration was considered to be 0 years for patients diagnosed at admission. The mean ages, duration of hospitalization, rates and duration of IV antibiotic treatment, duration of IV antibiotic treatment, and duration of diabetes for the type-1, non-SGLT-2 inhibitors group, and SGLT-2 inhibitors group are given in Table 1.

The mean, standard deviation, minimum and maximum values were determined by analyzing the last blood biochemistry tests of the patients at admission and before discharge within the groups (Table 2).

There was no significant difference between patients with and without SGLT-2 inhibitors in terms of IV antibiotic initiation rate, initial CRP, ESR, WBC, PLT, neutrophil, and TIT nitrate values. In contrast, there was a significant difference between the two groups in terms of urine leukocyte values at admission ($U=1122.50$; $p<.05$). In particular, when the arithmetic mean of both groups was analyzed, it was observed that the urine leukocytes at admission of patients who used SGLT-2 inhibitors (M=1.02) were higher than those who did not use SGLT-2 inhibitors (M=.50).

Table 1. Rates and duration of initiation of IV antibiotic treatment in patients with ketosis and ketoacidosis; duration of diabetes

	Type-1			Non-SGLT-2 inhibitors			SGLT-2 inhibitors		
	Mean	SD	Min-Max	Mean	SD	Min-Max	Mean	SD	Min-Max
Age[1]	31.82	11	19-55	52.07	14.88	18-86	61.50	12.78	35-81
Days of hospitalization[1]	6.13	3.03	2-17	7.28	6.67	2-36	5.38	2.90	1-14
AB* usage[2]		28.94 (%)			34.72 (%)			47.71 (%)	
IV AB* duration[1] (days)	7.73	5.04	2-20	9.04	5,51	2-20	6.07	2.97	1-10
Ketosis treatment duration[1] (hours)	28.00	32.39	1-168	23.60	26.54	2-168	31.24	34.66	3-173
Disease duration[1] (years)	9.50	7.73	0-30	8.22	8.40	0-28	14.63	8.02	1-30

1 Except for the antibiotic use parameter, parameters are expressed as Mean (Mean), Standard deviation (SD), Minimum value (Min), Maximum value (Max). 2 Intravenous antibiotic use parameter is expressed as a percentage (%) only. *AB: Antibiotic

Table 2. The laboratory parameters of the patients at admission and before discharge

	Type-1			Non-SGLT-2 inhibitors			SGLT-2 inhibitors		
	Mean	SD	Min-Max	Mean	SD	Min-Max	Mean	SD	Min-Max
sGlucose	398.61 160.35	162.90 60.43	191-821 72-342	355.47 171.43	105.07 75.29	149-705 80-472	322.31 154.64	135.78 55.87	97-652 59-283
Urea	37.18 26.89	27.04 19.44	11-134 12-123	36.32 28.97	21.50 14.76	10-164 11-95	39.71 31.15	21.30 15.65	12-117 12-92
sCrea	0.98 0.74	0.48 0.31	0.6-2.67 0.4-2.27	0.90 0.75	0.31 0.27	0.19-1.9 0.32-1.63	0.92 0.73	0.35 0.21	0.52-2.35 0.43-1.5
GFR	97.57 113.93	32.76 30.35	23-141 5.5-179	88.04 101.43	26.63 29.94	37-163 34-219	76.48 91.43	26.55 20.45	11-116 44-148
ALT2	17.19	10.73	6-58	21.68	14.83	5-74	15.80	7.45	4-38
AST2	18.68	7.46	9-42	22.36	15.17	8-106	17.37	6.85	4-35
Sodium	132.95 137.34	4.88 3.21	118-140 130-147	135.00 138.22	5.01 3.02	122-157 131-147	135.98 138.54	3.95 3.35	127-144 131-148
Potassium	4.72 4.23	0.72 0.46	3.9-7.86 3.19-5.27	4.55 4.20	0.71 0.47	2.6-6.6 3.2-5.2	4.54 4.36	0.67 0.48	3.5-5.9 3.3-5.4
Calcium	9.35 9.22	0.67 0.45	7.2-11,3 8.4-10.1	9.38 9.18	0.66 0.73	7.8-10.9 7.4-10.8	9.59 9.37	0.76 0.63	7.9-11.3 8.3-10.9
Phosphorus	3.38 3.93	1.16 1.06	1-6.1 1.24-5.9	3.23 3.76	1.24 0.87	1.1-9.2 0.9-5.9	3.74 3.66	0.79 0.78	2.2-5.6 1.5-5.2
Albumin	4.38 3.94	0.53 0.47	3.6-5.6 2.9-4.9	4.07 3.77	0.55 0.51	2.6-5.2 2,8-5.1	4.18 3.91	0.57 0.57	2.5-5 1.9-4.7
Magnesium	1.96 1.97	0.25 0.29	1-2.4 1.3-2.8	1.98 1.95	0.34 0.26	1-3.4 1.3-2.5	2.02 1.93	0.28 0.25	1.5-2.84 1.4-2.6
CRP2	28.86	56.49	0.1-239	59.22	96.01	0-380	36.88	60.25	0-237

[1]Mean: Mean, SD: Standard Deviation, Min-Max: Refers to Minimum and Maximum Values.
[2]Only ALT, AST and CRP statistics are generated from and represent the values at the time of application. All parameters, with the exception of these three parameters, are calculated from the values at admission in the first (top) row of the block and from the last values before discharge in the second (bottom) row and represent these measurements.
[3]The units of the defined parameters are as follows: sGlucose: Serum glucose: mg/dl, Urea: mg/dl, sCrea: Serum creatinine, mg/dl, GFR: Glomerular filtration rate, ml/min/1.73m2 (CKD-EPI), Alanine aminotransferase: ALT: U/L, AST U/L, Sodium: mmol/L, Potassium: mmol/L, Calcium: mg/dl, Phosphorus: mg/dl, Albumin: g/dl, Magnesium: mg/dl, CRP: mg/L

There was no significant difference between the duration of ketosis treatment, days of inpatient stay, and days of IV antibiotics in participants who used SGLT-2 inhibitors and participants who did not use SGLT-2 inhibitors ($p>.05$). In other words, the hypothesis that patients on SGLT-2 inhibitors have a more persistent ketosis clinic and require longer treatment than patients following other treatment regimens is rejected.

Venous blood gas pH, CO_2, HCO_3, lactate; urine ketone, glucose, and density were analyzed to examine whether the ketosis clinic was worse at presentation in patients using SGLT-2 inhibitors. No significant difference was found between patients using SGLT-2 inhibitors (group 3) and patients not using SGLT-2 inhibitors (group 2).

DISCUSSION

Although diabetes occurs in all age groups in society, the elderly are more affected by diabetes and its complications. In our study, in a similar way to society, patients with type 2 DM had a higher average age, additional diseases, and chronic complications. It is important to protect these patients from cardiovascular and renal complications and not to confront them with infection or DK/DKA. With this study, we believe we have made meaningful findings about the adverse effects of SGLT-2 inhibitors on patients with diabetes.

There was no difference between the groups in terms of CRP, ESR, WBC, and neutrophils on admission; however, we found a significant difference between the leukocyte values in urine ($U=1122.50$; $p<.05$). This data was in line with the existing opinions. In our study, 58.8% of patients who used SGLT-2 inhibitors were started on IV antibiotics, whereas this rate was 35.3% in patients who did not use SGLT-2 inhibitors. There was no statistically significant difference between these rates. The mean duration of IV antibiotic use was 6.07 days in SGLT-2 inhibitor users and 9.04 days in non-SGLT-2 inhibitor users. The duration of IV antibiotic use in patients using SGLT-2 inhibitors was not significant compared to the others.

Uitrakul et al.[16] reported that patients using SGLT-2 inhibitors had an increased risk of urinary tract infections. In a study examining SGLT-2 inhibitors against DPP-4 inhibitor drugs, it was reported that SGLT-2 inhibitors caused a risk in terms of genital infections, but no difference was found in terms of urinary tract infections.[17] Obviously, considering that SGLT-2 inhibitors act by causing glycosuria, it is not difficult to predict that they may pose a risk for infection in any part of the urinary tract.[18]

In a study conducted by Jeon et al.[19] examining DKA cases in terms of SGLT-2 inhibitors, it was found to be the precipitating cause of infection in 3 (20%) of 15 patients using SGLT-2 inhibitors and 131 (26%) of 508 patients not using SGLT-2 inhibitors and was not statistically significant ($p=0.77$).

Despite the high percentage of antibiotic use, the fact that the mean duration of antibiotic use in patients using SGLT-2 inhibitors was less than 1 week and did not differ statistically against other treatment regimens led us to think that these infections were easy to manage and uncomplicated cases. On the other hand, as a limitation of our study and as an opposing view, it should be noted that while our cases were discharged in a week, cases with a highly complicated course may be followed up with gangrene or abscess in surgical clinics a few steps away from our clinic, and we may be unaware of this situation. Therefore, we think there is a need for long-term and more comprehensive studies on this subject.

SGLT-2 inhibitors have always been blamed for DKA, and there are well-defined theories for how DKA occurs in patients.[20] Liu et al.[21] pointed out that SGLT-2 inhibitor use may increase the risk of DKA. Hamblin et al.[22] found data showing that the risk of developing DKA in inpatients increased with SGLT-2 inhibitor use ($p<0.0001$). On the other hand, a systematic review published by Yang et al.[23] concluded that SGLT-2 inhibitor use did not lead to an increased risk of DKA. Our study is not suitable to contribute to this controversial literature by design. However, we can put this controversy aside and reveal whether SGLT-2 inhibitor treatment is an additional burden to patients by examining the duration of ketosis treatment and hospitalization.

DK/DKA treatment lasted an average of 31.24 hours in patients on SGLT-2 inhibitors and 23.59 hours in type 2 DM patients not on SGLT-2 inhibitors. In type 1 DM patients, this time was 28 hours, noting the higher presence of DKA. Despite the significant difference between the averages, we found that the use of SGLT-2 inhibitors did not cause a statistically significant difference in type 2 DM patients. This lack of differentiation continued in terms of the length of hospitalization. The duration of hospitalization was 7.27 days in patients who did not use SGLT-2 inhibitors, but 5.38 days in those who did. These data were statistically insignificant.

In a study in which patients with type 2 DM and DKA were analyzed separately according to SGLT-2 inhibitor use, the results were similar to our data. In this study, a total of 55 cases, 17 of which used SGLT-2 inhibitors, were retrospectively analyzed. The duration of DKA treatment was 23 hours in SGLT-2 inhibitor users and 20.8 hours in nonusers and was not statistically significant (p .544).[24]

Based on these statistics, we would like to think that DKA and other clinical conditions associated with the use of SGLT-2 inhibitors have roughly no impact on the time patients have to spend in the hospital and do not impose an additional burden on patients and hospitals.

Apart from these parameters, we aimed to obtain information about the severity of the patients' clinical conditions at the time of admission by examining some laboratory parameters at the time of admission. No difference was observed between the patient groups in terms of pH, CO_2, HCO_3, lactate values in venous blood gas, ketone, glucose, and density values in urine. When we reviewed the literature, we found that there were studies supporting our findings. If we compare it with the study conducted by Jeon et al.[19] mentioned above; the mean pH was 7.17, HCO_3 was 8.4 mmol/L, and CO_2 was 20 mgHg in the venous blood gas at admission in patients using SGLT-2 inhibitors. In patients followed up with other treatment regimens, these values were 7.19, 4.8 mmol/L, and 14 mmHg, respectively, and were not statistically different. Although statistical insignificance is common, it is noteworthy that these figures are quite different from our data. Unlike the aforementioned study, in our study, in addition to DKA cases, there were also cases of diabetic ketosis without acidosis, so it is expected that the averages would be much different. Therefore, when comparing these studies, it would be a more accurate approach to examine the statistical difference, not the numbers.

In a two-year retrospective study by Papanastasiou1 et al.[25] cases of DKA directly related to SGLT-2 inhibitors were analyzed against cases of DKA due to other causes, and they reached important data in our opinion. This study reported no difference in the severity of DKA between the two groups based on the levels of venous blood gas samples. However, there was a statistical difference in the resolution of DKA, or, in other words, the duration of DKA treatment, against SGLT-2 inhibitors (39 hours versus 19 hours, $p<0.001$). In addition, the duration of hospitalization also showed a result against SGLT-2 inhibitors (11 days versus 5.5 days).

Compared to our study, despite the similarity in blood picture, this difference in treatment and discharge times led us to think about this study, and we think we have found an explanation for this difference. In the aforementioned study, it was noted that more intravenous fluids were used in the treatment of the SGLT-2 inhibitor group (14L vs. 5.5L, $p=0.013$) and in our study, to remind you again, there were not only DKA cases but also DC cases. We know that SGLT-2 inhibitors cause glycosuria and fluid loss, and we know the importance of fluid in the development and resolution of DKA. According to our hypothesis, we treated not only severely dehydrated DKA cases but also relatively less dehydrated and early diabetic ketosis cases, and these early cases were easily treated, causing the statistical difference between the studies.

There is a national cohort study on DKA in Korea.[26] In this study, SGLT-2 inhibitors versus DPP-4 inhibitors were examined in terms of DKA. It was reported that there was no difference in the risk of hospitalization for DKA between the two groups, but the risk was increased in patients with microvascular complications of diabetes or those taking diuretics.

Based on these data, we may think that SGLT-2 inhibitors increase the risk of complications for patients with fluid balance problems and that the DKA clinics that will develop in these patients will be persistent and more dangerous. If this is correct, the main idea to be drawn from this is that the same importance given to the renal function and HBA1c of the patients when deciding to use SGLT-2 inhibitors should also be given to the evaluation of the fluid volume of the patients. Only in this way can we offer the right patients additional cardiac and renal protection through SGLT-2 inhibitors without putting them at risk, and at-risk patients can be easily identified and protected from DKA caused by these agents.

CONCLUSION

Based on the available evidence, we think the following question needs to be asked: Are we forcing patients to live in the hospital and suffer the pain of infection while desiring potential benefits, or are we withholding a drug that promises cardiac and renal protection from patients for nothing?

Considering the mechanism of action of these agents, it can be easily predicted that they may pose a risk in terms of

infection and ketosis. Indeed, many studies in the literature have drawn attention to these risks and presented strong data; however, as in our study and many similar studies, there are also data in the literature showing that the risks of SGLT-2 inhibitors are not different from others. According to our analysis, the management of these SGLT-2 inhibitor-related complications is not more challenging and does not produce worse hospital outcomes. In addition to this, we consider SGLT-2 inhibitors to be an important family of drugs for DM management with additional systemic benefits. There is a need to define parameters that can predict complications associated with the use of SGLT-2 inhibitors and to determine the importance of risk factors in order to prescribe these agents correctly to the right patients in the clinic. For the holistic management and healthier lives of diabetic patients, we believe that comprehensive and long-term research on SGLT-2 inhibitors is essential to resolving the uncertainties about this family of drugs.

ETHICAL DECLARATIONS

Ethics Committee Approval

This thesis study was initiated with the approval of the Kırıkkale University Faculty of Medicine Non-interventional Clinical Researches Ethics Committee (Date: 06.09.2023, Decision No: 2023.09.07).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Ankyra Medical Journal
ORIGINAL ARTICLE DOI: 10.51271/ANKMJ-0002

Healthcare-associated infections: prospective rotational surveillance data of a training and research hospital

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Cite this article: Çekli Y, Çavuşoğlu Ş. Healthcare-associated infections: prospective rotational surveillance data of a training and research hospital. *Ank Med J.* 2024;3(1):6-12.

Received: 01.01.2024 ◆ **Accepted**: 28.01.2024 ◆ **Published**: 31.01.2024

ABSTRACT

Aims: The monitoring and prevention of healthcare-associated infections (HAIs) are considered to be among the key measures to improve the effectiveness and quality of healthcare services. This study aimed to ascertain the prevalence of HAIs in various hospital departments and identify the causative bacterial profile, risk factors, and associations with mortality.

Methods: This prospective study included 3117 patients who were monitored in various departments of a training and research hospital. The identified HAI cases were monitored using an active, prospective, rotational surveillance method. Patient data on HAIs were recorded daily with pre-established tracking forms.

Results: The mean hospital stay of the patients was 9.9±7.5 days. The HAI prevalence was 4.5% and the HAI rate was 5.5%. The HAI rate showed no difference between internal medicine and surgical departments (5.7% vs 5.5%, p>0.05), but it was higher in intensive care units (ICUs) (p<0.001). The majority of the isolated agents (65.2%) were gram-negative bacteria. Advanced age, intrinsic risk factors such as malignancy, and invasive procedures (use of central, peripheral, and urinary catheters) were associated with the development of HAIs. The frequency of HAIs was higher among deceased patients compared to survivors (25.4% vs 4.1%, p<0.001).

Conclusion: HAIs remain a major concern in hospital settings, particularly in ICUs, and they strongly correlate with intrinsic risk factors and invasive procedures. Optimized infection control measures for these risk factors can make a significant contribution to improving patient outcomes.

Keywords: Healthcare-associated infection, intensive care unit, surveillance, mortality

INTRODUCTION

Healthcare-associated infections (HAIs) affect hundreds of millions of patients worldwide and are among the most common causes of mortality and morbidity in hospitals.[1] Furthermore, they increase hospital costs due to additional medication use and prolonged patient hospital stays.[2,3]

Many studies have shown that the hospital environment may be responsible for the transmission of significant nosocomial pathogens to patients.[4,5] Bacteria isolated from hospital settings differ from those originating from the community. Troublesome bacteria such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA) more frequently cause HAIs.[6-8] Infections caused by these bacteria with high resistance rates typically require the use of broad-spectrum antibiotics, resulting in significant costs and an increase in antimicrobial resistance. The spread of resistant pathogens within and between hospitals can be mitigated with effective infection control measures. One of the most crucial components of these measures is effective surveillance methods.[9,10] Monitoring and preventing HAI cases are considered key measures to enhance the effectiveness and quality of healthcare services. In this context, providing accurate and sufficient information about HAI cases is essential for initiating effective prevention programs in hospitals.

In this study, by implementing an active, prospective, rotational surveillance method, we aimed to determine the frequency of HAIs in our hospital's wards and ICUs, the distribution of cases across wards, the bacterial profile responsible for HAIs, risk factors in HAI cases, and the impact of HAIs on mortality.

METHODS

The study was approved by the Gülhane Military Medical Academy Haydarpaşa Training Hospital Clinical Researches Ethics Committee (Date: 08.08.2001, Decision No: 0530-63-01/264). All patients were informed about the details of the research prior to the beginning of the study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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This prospective study was conducted at Gülhane Military Medical Academy Haydarpaşa Training Hospital Hospital between March 2002 and November 2003, utilizing an active, prospective, rotational surveillance method with the aim of monitoring hospital infections.

During the study period, a total of 3117 patients were monitored in various departments and ICUs. All cases were actively monitored using a prospective, rotational surveillance method. Cases from the department of psychiatry, dermatology, pulmonary diseases and tuberculosis, endocrinology, hematology, and oncology of our hospital were not included in the surveillance data. Cases from the departments included in the study were monitored in three phases (Table 1). Information pertaining to patients who developed HAIs was recorded with pre-established patient tracking forms, and all collected data were recorded daily.

Inclusion criteria for the study were as follows: patients admitted to any department or ICU of the hospital included in the study who were hospitalized for more than 48 hours and were present in the department when data collection began, and, if they had undergone any surgery, they returned within a week with signs of infection or, in the event of a foreign body/prosthesis during surgery, within a year with infection symptoms. Patients who had stayed in the department or ICU for less than 48 hours, who died or were transferred to another hospital within the first 48 hours, who showed early infection symptoms during outpatient visits or at the time of admission, whose laboratory and culture results did not support the clinical findings, or who were not suspected of HAI were not included in the study.

The rates and frequencies of HAIs were calculated using the formulas below based on the criteria set by the Centers for Disease Control and Prevention (CDC) and the National Nosocomial Infection Surveillance System (NNIS):

$$\text{Incidence}=\left(\frac{\textit{Number of HAIs}}{\textit{Number of hospitalized patients}}\right)\times 100$$

$$\text{Device-associated infection rate}=\left(\frac{\textit{Number of infections associated with a specific device}}{\textit{Number of device days}}\right)\times 1000$$

Surgical site infection data were evaluated using surgical wound classification and the American Society of Anesthesiologists (ASA) scoring system.[11,12]

Statistical Analysis

All data were analyzed with SPSS 11.0 for Windows (SPSS Inc., Chicago, IL, USA). Numerical data determined to be normally distributed based on the results of Kolmogorov-Smirnov tests are given as mean±standard deviation, while non-normally distributed variables are given as median (min-max). For comparisons between two groups, the Student t-test and Mann-Whitney U test were used in line with the normality of the considered distribution. For comparisons between three or more groups, ANOVA and Kruskal-Wallis tests were used in line with the normality of the considered distribution. Categorical variables are given as numbers and percentages, and inter-group comparisons were conducted with chi-square and Fisher exact tests. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

Table 1. Services included in the study and surveillance dates

Services	Bed Capacity	PERIODS									
		I			II			III			
		01-31 March 2002	01-30 April 2002	01-31 May 2002	01-31 December 2002	01-31 January 2003	01-28 February 2003	01-31 October 2003	01-30 November 2003		
Physical Therapy	34	X				X			X		
General Surgery Clinic	74	X				X		X			
General Surgery Intensive Care Unit	8	X				X		X			
Urology	27	X				X		X			
Gastroenterology	41	X				X		X			
Plastic Surgery	26	X				X		X			
Burn Unit	10	X				X		X			
Anesthesia and Reanimation Intensive Care Unit	10	X				X		X			
Orthopedics	70		X				X		X		
Otorhinolaryngology	31		X				X		X		
Ophthalmology	40		X				X		X		
Cardiovascular Surgery Clinic	18		X				X	X			
Cardiovascular Surgery Intensive Care Unit	8		X				X	X			
Nephrology	29		X				X		X		
Pediatrics	26		X				X		X		
Neonatology	6										
Cardiology Clinic	53		X			X			X		
Cardiology Intensive Care Unit	6		X				X		X		
Neurosurgery Clinic	54			X	X			X			
Neurosurgery Intensive Care Unit	6			X	X			X			
Neurology Clinic	55			X	X			X			
Neurology Intensive Care Unit	6			X	X			X			
Internal Medicine Clinic	30			X	X			X			
Internal Medicine Intensive Care Unit	12			X	X			X			
Obstetrics and Gynecology	25			X	X				X		
Infectious Diseases and Clinical Microbiology	42			X	X				X		
Underwater and Hyperbaric Medicine	18			X	X			X			

RESULTS

The age range of the patients was 1-100 years (mean: 36.7±23.2 years), 72% of them (n=2245) were male, and 28% (n=872) were female. The hospitalization duration was determined to range from 2 to 31 days, with a mean of 9.9±7.6 days. In the first period, 778 patients were monitored, while 1166 were monitored in the second period and 1173 in the third period. The distributions of gender, age, and hospitalization duration showed no differences between the periods (p>0.05) (Table 2).

Table 2. Demographic characteristics of patients according to periods

Periods	Gender		Total	Age, years (Mean±SD)	Length of hospitalization, day (Mean±SD)
	Male n (%)	Female n (%)			
First period	599 (77)	179 (23)	778	33.4±22.6	9.6±7.6
II. period	804 (69)	362 (31)	1166	37.0±23.3	10.8±7.8
III. period	842 (71.8)	331 (28.2)	1173	38.6±23.1	9.1±6.6
Total	2245 (72)	872 (28)	3117	36.7±23.2	9.9±7.6

Abbreviations: SD, standard deviation

Patients were monitored in surgical and internal departments. Of the analyzed cases, 59.8% were in surgical departments, while 40.2% were in internal departments. In terms of patient density, the top three services in the surgical departments were general surgery (11.9%), orthopedics (10.9%), and urology (6.5%). In internal departments, the top three were neurology (5.7%), gastroenterology (5.3%), and physical medicine and rehabilitation (5.2%).

From among the 3117 patients monitored, 173 HAIs were identified to have occurred in 141 patients (4.5%). The HAI rate was determined to be 5.5% or 5.6 per 1000 patient days. In internal medicine departments, these rates were respectively 5.7% or 5.4 per 1000 patient days, while in surgical departments, they were 5.5% or 5.8 per 1000 patient days (p>0.05). From the internal medicine departments, in the Underwater and Hyperbaric Medicine Service, where severe cases such as diabetic foot, osteomyelitis, and necrotizing fasciitis are monitored, the HAI rate was identified as 31.3% or 19.6 per 1000 patient days (Table 3).

The HAI rate in the ICUs was found to be higher compared to the general services (p<0.001). In the anesthesia ICU, the HAI rate was 180% or 117.4 cases per 1000 patient days. Meanwhile, the neurology ICU had rates of 82.3% and 44.7/1000 patient days, the neurosurgery ICU had rates of 58.8% and 39/1000 patient days, the burn unit had rates of 50% and 34.8/1000 patient days, the general surgery ICU had rates of 33.9% and 24.9/1000 patient days, and the internal medicine ICU had rates of 18.9% and 27.9/1000 patient days.

The most common cause of HAI was bloodstream infection (30.1%), followed by urinary tract infection (UTI) at 28.3%, surgical site infection (SSI) at 23.6%, skin and soft tissue infection at 11.6%, and pneumonia at 6.4%. In the first period, UTIs and SSIs were the most prevalent infections, while in the second and third periods, bloodstream infections and UTIs were most frequently observed. However, no significant difference was found between these periods (p>0.05).

The most frequently encountered intrinsic risk factors among the cases were malignancy (4.7%), diabetes mellitus (4.4%), and H2 receptor blocker usage (4.1%). Medical care-related risk factors were predominantly peripheral catheter (41.7%), urinary catheter (8.9%), and central catheter usage (4.9%) (Table 4).

Table 3. Distribution of healthcare-associated infections rates by services

Section	Services	Number of inpatients	Number of HAI patients	HAI rate (%)	HAI rate (per 1000 patient days)
Surgical					
	Anesthesia Intensive Care	15	27	180	117.4
	Burn Unit	17	10	58.8	34.9
	General Surgery	425	28	6.6	6.7
	Plastic Surgery	110	7	6.4	5.6
	Neurosurgery	190	10	5.3	4.7
	Orthopedics	341	18	5.3	4.1
	Urology	203	2	1	1.9
	Obstetrics and Gynecology	191	0	0	0
	Otorhinolaryngology	151	0	0	0
	Ophthalmology	134	0	0	0
	Cardiovascular Surgery	93	0	0	0
	TOTAL	1870	102	5.5	5.8
Internal					
	Underwater and Hyperbaric Medicine	32	10	31.3	19.6
	Internal Medicine	202	19	9.4	11.2
	Neurology	194	17	8.8	6.8
	Nephrology	116	8	6.9	6.1
	Neonatology	70	2	2.9	4.6
	Cardiology	106	3	2.8	2.6
	Physical Medicine and Rehabilitation	161	4	2.5	1.9
	Pediatrics	120	3	2.5	5.2
	Gastroenterology	166	4	2.4	1.8
	Infectious Diseases and Clinical Microbiology	80	1	1.3	1.4
	TOTAL	1247	71	5.7	5.4
TOTAL		3117	173	5.5	5.6

Abbreviations: HAI, healthcare-associated infections.

Table 4. Presence of intrinsic and medical care-related risk factors

Risk Factors	Total		Periods		
			I	II	III
	n	%	%	%	%
Intrinsic					
Malignancy	145	4.7	6.2	3.9	4.4
Burns	11	0.4	0.4	0.7	0
Liver failure	17	0.5	0.4	0.5	0.7
General body trauma	0	0	0	0	0
Diabetes mellitus	137	4.4	1.7	4.5	6.1
AIDS/HIV infection	0	0	0	0	0
Loss of consciousness	19	0.6	0.4	0.5	0.9
H2 receptor blocker	127	4.1	4.1	3.9	4.2
Immunosuppression	3	0.1	0.4	0	0
Transplantation	0	0	0	0	0
Respiratory failure	21	0.7	0.5	0.8	0.7
Neutropenia	0	0	0	0	0
Kidney failure	70	2.2	2.6	1.7	2.6
Transfusion	75	2.4	2.8	2.3	2.2
Medical care-related					
Urinary catheter	278	8.9	8.8	9.1	9.1
Peripheral catheter	1301	41.7	53.1	62.6	61.5
Central catheter	154	4.9	5.4	5	4.6
Intubation	80	2.6	3.1	2.7	2.1
Mechanical ventilation	53	1.7	1.2	2.7	1.1
Arterial cannula	47	1.5	1.4	1.3	1.8
Nasogastric tube	109	3.5	1.9	4.7	3.3
Tracheostomy	20	0.6	0.8	0.8	0.4
Peritoneal dialysis	1	0.01	0	0.01	0
Hemodialysis	14	0.5	1.7	0.09	0
Drainage catheter	93	3	4.8	2.2	2.6
Prosthesis/foreign body	125	4	6.7	3.1	3.2
Other interventions	51	1.6	2.2	1.6	1.3

Abbreviations: AIDS, acquired immune deficiency syndrome; HIV, human immunodeficiency virus

The incidence of HAIs in the first period was 5.8%, in the second period was 3.8%, and in the third period was 4.4% (p=0.110). The incidence of HAIs was higher among female patients compared to male patients (7.1% vs 3.5%, p<0.001). Intrinsic risk factors associated with the development of HAIs included the presence of malignancy, burns, diabetes mellitus, altered consciousness, anti-acid usage, respiratory failure, and renal failure requiring transfusion therapy (p<0.001). Additionally, it was found that other invasive procedures, excluding peritoneal dialysis (p=0.828), were also associated with the development of HAIs (p<0.001) (Table 5).

It was determined that advanced age (p<0.001), prolonged hospital stay (p<0.001), and the duration of invasive procedures (p<0.001) influenced the development of HAIs, but there was no statistically significant relationship between ASA scores and the development of HAIs (p=0.263) (Table 6).

During the study period, a causative agent was isolated in 155 of 173 HAI cases (89.5%). In 18 cases (10 SSI and 8 pneumonia) where the causative agent could not be isolated, the diagnosis of HAI was made based on clinical symptoms. The majority of the isolated agents were gram-negative bacteria (65.2%), followed by gram-positive bacteria (31%) and *Candida* species (3.8%). The most common bacterium causing HAIs was *Escherichia coli* (25.2%), followed by *staphylococci* [coagulase-negative *staphylococci* (CoNS) 16.1%, *Staphylococcus aureus* 8.4% (with 98% methicillin resistance)], *Klebsiella* spp. (14.2%), and *Pseudomonas aeruginosa* (13%) (Table 7).

Regarding bloodstream infections, the most prevalent pathogens were CoNS (44.2%), followed by *Pseudomonas aeruginosa* (13.5%) and *Acinetobacter* spp. (13.5%). In cases of UTIs, *Escherichia coli* (40.7%), *Pseudomonas aeruginosa* (12.2%), and *Enterococcus* spp. (12.2%) were the primary pathogens. Among SSIs, the leading pathogens were *Escherichia coli* (35.5%), *Staphylococcus aureus* (19.4%), and *Klebsiella* spp. (16.1%) (Table 8).

During the study period, a total of 59 patients died. The HAI rate was higher among deceased patients compared to survivors (25.4% vs 4.1%, p<0.001).

Table 5. Relationship between the prevalence of healthcare-associated infections and risk factors/invasive interventions

Risk factors		HAI		p
		n	%	
Gender	Male	79	3.5	0.001
	Female	62	7.1	
Period	First period	45	5.8	0.111
	II. period	44	3.8	
	III. period	52	4.4	
Malignancy	Yes	18	12.4	0.001
	No	123	4.1	
Burn	Yes	5	45.5	0.001
	No	136	4.4	
Liver Failure	Yes	0	0	0.368
	No	141	4.5	
Diabetes Mellitus	Yes	25	18.2	0.001
	No	116	3.9	
Unconsciousness	Yes	9	47.4	0.001
	No	132	4.3	
H2 Receptor Blocker	Yes	40	31.5	0.001
	No	101	3.4	
Immunosuppression	Yes	1	33.3	0.016
	No	140	4.5	
Respiratory Failure	Yes	15	71.4	0.001
	No	125	4.0	
Renal Insufficiency	Yes	11	15.7	0.001
	No	130	4.3	
Transfusion	Yes	25	33.3	0.001
	No	116	3.8	
Urinary Catheter	Yes	87	31.3	0.001
	No	54	1.9	
Peritoneal Dialysis	Yes	0	0	0.828
	No	141	4.5	
Hemodialysis	Yes	7	24.1	0.001
	No	134	4.3	
Intubation	Yes	24	30.0	0.001
	No	117	3.9	
Mechanical Ventilation	Yes	26	49.1	0.001
	No	115	3.8	
Tracheostomy	Yes	18	90.0	0.001
	No	123	4.0	
Central Catheter	Yes	51	33.1	0.001
	No	90	3.0	
Peripheral Catheter	Yes	136	10.5	0.001
	No	5	0.3	
Drainage Catheter	Yes	20	21.5	0.001
	No	121	4.0	
Prosthesis	Yes	20	16.0	0.001
	No	121	4.0	
Nasogastric Tube	Yes	45	41.3	0.001
	No	96	3.2	
Arterial Cannula	Yes	22	46.8	0.001
	No	119	3.9	

Abbreviations: HAI, healthcare-associated infections.

Table 6. Relationship of healthcare-associated infections development with age, hospitalization duration, ASA score, and duration of invasive procedures

Variables	HAI	n (%)	Mean±SD	p
Age, years	Yes	141 (4.5)	54.9±24.5	0.001
	No	2976 (95.5)	35.8±22.7	
Length of stay, day	Yes	141 (4.5)	18.9±8.7	0.001
	No	2976 (95.5)	9.4±7.2	
ASA score	Yes	44 (4.6)	2.1±0.5	0.263
	No	908 (95.4)	2.0±0.1	
Duration of urinary catheter, day	Yes	87 (31.2)	17.1±9.2	0.001
	No	191 (68.8)	8.1±7.3	
Duration of intubation, day	Yes	24 (30)	12.1±9.4	0.001
	No	56 (70)	2.8±3.5	
Duration of central catheter, day	Yes	51 (33.1)	14.6±8.9	0.001
	No	103 (66.9)	5.7±5.4	
Duration of peripheral catheter, day	Yes	138 (10.6)	18.4±8.7	0.001
	No	1163 (89.4)	6.4±5.6	

Abbreviations: HAI, healthcare-associated infections; SD, standard deviation.

Table 7. Distribution of healthcare-associated infections agents by periods

HAI agents	Periods						Total	
	I		II		III			
	n	%	n	%	n	%	n	%
Gram (+) bacteria	11	26.8	20	37.1	17	28.3	48	31.0
CoNS	3	7.3	11	20.4	11	18.3	25	16.1
Staphylococcus aureus	5	12.2	5	9.3	3	5.0	13	8.4
Enterococcus spp.	3	7.3	4	7.4	3	5.0	10	6.5
Gram (-) bacteria	29	70.7	31	57.4	41	68.3	101	65.2
Escherichia coli	8	19.5	14	26.0	17	28.3	39	25.2
Klebsiella spp.	11	26.9	4	7.4	7	11.7	22	14.2
Pseudomonas aeruginosa	4	9.6	8	14.8	8	13.3	20	13.0
Acinetobacter spp.	2	4.9	2	3.7	6	10.0	10	6.5
Proteus spp.	2	4.9	3	5.5	3	5.1	8	5.1
Enterobacter spp.	2	4.9	0	0	0	0	2	1.3
Candida spp.	1	2.5	3	5.5	2	3.4	6	3.8
Total	41	100	54	100	60	100	155	100

Abbreviations: CoNs, Coagulase-negative *staphylococci*; HAI, healthcare-associated infections; spp, species.

DISCUSSION

In Turkiye, the HAI rate is generally reported to be between 1% and 16.5%, and in ICUs, it ranges from 5.3% to 65.3%.[13-16] Based on these studies, the HAI rate in our research (5.5%) is comparatively low. This variation could be attributed to differences in hospital bed capacities, the types of patients, distinct risk factors, and the non-inclusion of certain departments where HAIs are more prevalent, such as hematology, oncology, and transplantation, in our study.

In our study, the HAI rates identified in the ICUs, ranging from 18.9% to 180%, were higher compared to those of general services. In the period in which our study was conducted, HAI rates in the reanimation units of university hospitals in our country were reported to range broadly between 5.3% and 171.8%.[17,18] The HAI rate of 180% obtained for the resuscitation unit in our study was slightly higher than the upper limit of the studies mentioned above. The reason for this might be that our hospital's resuscitation department admits patients with severely deteriorated general conditions due to ease of patient care. Compared to other departments, patients might stay longer in this unit and experience multiple HAI episodes. Additionally, the combination of fewer patients staying for extended periods and experiencing multiple HAI events diminishes the denominator in incidence calculations, resulting in an elevated rate.

The types of HAIs observed in ICUs vary according to the type and capacity of the particular ICU. In our study, bloodstream infections were the most common cause. This was followed by UTIs, SSIs, skin and soft tissue infections, and pneumonia, respectively. In studies conducted in ICUs during the same period in different countries, similar HAI rates were found, excluding the rates for pneumonia.[18,19] The low rate of hospital-acquired pneumonia in our study might be due to reduced utilization of equipment such as ventilators that heightens infection risk and the complexities of diagnosis during the period in question. However, in a recent study, it was reported that 83.7% of HAIs were lower respiratory tract infections, while only 2.9% were bloodstream infections.[20] It was also reported that the preventive and control measures taken in response to the COVID-19 pandemic reduced the rate of nosocomial infections in almost all departments excluding ICUs, and particularly respiratory, gastrointestinal, and oral infections. However, no difference was observed in rates of bloodstream infections and catheter-related infections before and after the COVID-19 pandemic.[6]

Ventilators, endotracheal tubes, catheters, and surgical wounds are identified as the most common risk factors contributing to the development of HAIs.[8,21] Furthermore, there is a positive correlation between the type of procedure and the resulting HAI. In ICUs where urinary catheter usage is high, UTIs are more frequent. Likewise, when central or peripheral catheter usage is involved, catheter infections or bloodstream infections are commonly observed. Invasive procedures, excluding peritoneal dialysis, were found to be associated with the development of HAIs. In cases where HAIs developed, the durations of intubation and central catheter, urinary catheter, and peripheral catheter usage were longer compared to cases without HAIs, and, in parallel, there was an elevated risk of HAIs.[21,22]

Table 8. Distribution of isolated agents according to the type of healthcare-associated infections

Agents	Bloodstream Infections		Urinary Tract Infections		Surgical Site Infections		Skin Infections		Pneumonia	
	n	%	n	%	n	%	n	%	n	%
Klebsiella spp.	6	11.5	5	10.2	5	16.1	6	30	0	0
Escherichia coli	3	5.8	20	40.7	11	35.5	5	25	0	0
Pseudomonas aeruginosa	7	13.5	6	12.2	2	6.5	4	20	1	33.3
Staphylococcus aureus	3	5.8	1	2.1	6	19.4	2	10	1	33.3
CoNS	23	44.2	0	0	2	6.5	0	0	0	0
Acinetobacter spp.	7	13.5	2	4.1	0	0	0	0	1	33.3
Enterobacter spp.	0	0	1	2.1	1	3.2	0	0	0	0
Candida spp.	1	1.9	5	10.2	0	0	0	0	0	0
Enterococcus spp	1	1.9	6	12.2	2	6.5	1	5	0	0
Proteus spp.	1	1.9	3	6.1	2	6.5	2	10	0	0
Total	52	100	49	100	31	100	20	100	3	100

Abbreviations:CoNs, coagulase-negative *staphylococci*.

Bacteria isolated from hospital environments differ from those originating from the community, and specific problematic bacteria are the primary causes of HAIs.[23,24] The isolated agents vary according to the types of HAIs. In previous studies, it was reported that the most frequently isolated agents in cases of catheter-related bloodstream infection were CoNS and *Staphylococcus aureus*, while in cases of UTIs, the agents were *Escherichia coli*, other gram-negative bacteria, *Pseudomonas aeruginosa*, and CoNS. In cases of ventilator-associated pneumonia, the reported agents were *Pseudomonas aeruginosa*, *Acinetobacter* spp., and other gram-negative bacteria. In cases of burn-related infections, *Staphylococcus aureus* is typically identified as the causative agent in the initial 7 days, whereas in later stages, *Pseudomonas aeruginosa* and other gram-negative bacteria are found to be responsible.[6-8,18-20] In our study, we found that CoNS were the predominant agents in bloodstream infections, while *Escherichia coli* was responsible for UTIs and SSIs.

In addition to negative impacts such as prolonged hospitalization and economic losses, the most significant consequence of HAIs is a high rate of mortality. Among cases that ended in death, the HAI prevalence was greater than that observed among survivors. The general health of the patient, comorbidities, duration of ICU stay, surgeries undertaken, invasive methods, the nature of the infection, and the causative agent's type and sensitivity to antibiotics are all risk factors directly influencing the prognosis.[12]

CONCLUSION

In hospitals, HAIs are among the significant causes of increased morbidity and mortality. Although their development might be viewed as inevitable, various strategies can be implemented to mitigate this risk, including conducting active surveillance in hospitals, emphasizing education, promoting hand hygiene habits, strictly adhering to asepsis and antisepsis rules, avoiding unnecessary diagnostic and therapeutic interventional procedures, monitoring invasive interventions closely, preventing the colonization of pathogenic bacteria, regulating antibiotic use in the hospital to maintain low levels of microbial resistance, and using broad-spectrum antibiotics only for treatment purposes rather than prophylactically. The implementation of these controls and precautions can be beneficial in preventing and reducing HAIs.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki and was approved by the Gülhane Military Medical Academy Haydarpaşa Training Hospital Ethics Committee (Date: 08.08.2001, Decision No: 0530-63-01/264).

Informed Consent

The need for informed consent was waived with the approval of the Gülhane Military Medical Academy Haydarpaşa Training Hospital Ethics Committee due to the study's retrospective design.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Ankyra Medical Journal
ORIGINAL ARTICLE
DOI: 10.51271/ANKMJ-0003

Approach to mediastinal masses: a comparison of open surgery and uniportal video-assisted thoracoscopic surgery techniques

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Cite this article: Gülmez G, Hasdiraz L, Önal Ö. Approach to mediastinal masses: a comparison of open surgery and uniportal video-assisted thoracoscopic surgery techniques. *Ank Med J.* 2024;3(1):13-18.

Received: 02.01.2024 ◆ **Accepted**: 30.01.2024 ◆ **Published**: 31.01.2024

ABSTRACT

Aims: This study aimed to compare perioperative and postoperative outcomes in patients who underwent uniportal video-assisted thoracoscopic surgery (U-VATS) and open surgery for mediastinal mass resection.

Methods: A total of 62 patients who underwent mediastinal mass resection in the thoracic surgery clinic were included. The patients were separated into the open surgery group (n=30) and the U-VATS group (n=32). The groups were compared in terms of perioperative and postoperative outcomes including operative time, blood loss, chest tube removal time, drainage volume, pain, and hospital stay.

Results: The distributions of age and gender were similar between the groups. Median operation time (120 vs. 180 minutes, P<0.001), median intraoperative blood loss (50 vs. 100 mL, P<0.001), median time of chest drain removal (4 vs. 6 days, P<0.001) and median postoperative drainage volumes were lower in the U-VATS group than the open surgery group. The U-VATS group exhibited a lower VAS score, return time to daily activity (1 vs. 4 days, P<0.001) and length of hospital stay (4 vs. 6 days, P<0.001). A postoperative myasthenic crisis was not observed in all cases. One thymoma patient in the open surgery group had a recurrence, but not in the U-VATS group.

Conclusion: The U-VATS approach had better intraoperative safety and lower postoperative outcomes than open surgery. U-VATS, which has the potential to enhance postoperative recovery and quality of life, may be a safe and effective treatment option for patients with mediastinal mass resection.

Keywords: Mediastinal lesions, minimally invasive surgery, sternotomy, thymoma, video-assisted thoracoscopic surgery

INTRODUCTION

Mediastinal masses are a diverse group of lesions, including bronchogenic cysts, thymomas, neurogenic tumors, and thyroid tumors, and account for approximately 3% of thoracic lesions.[1] Thymomas are tumors that arise from thymic epithelial cells and are located in the anterior mediastinum, while bronchogenic cysts are derived from the embryonic foregut and can be found in the middle or posterior mediastinum.[2] Neurogenic tumors arise from neural crest cells and are most commonly located in the posterior mediastinum, while thyroid tumors can be located in the anterior or middle mediastinum.[3] The location and origin of the mediastinal mass can sometimes provide important clues about the nature of the lesion and influence the choice of surgical approach.[4]

Traditionally, open surgical procedures such as median sternotomy, posterolateral thoracotomy, and hemi-clamshell sternotomy have been the preferred approaches for resection of mediastinal masses.[5] However, these procedures are associated with substantial surgical trauma and morbidity. Video-assisted thoracoscopic surgery (VATS) is a minimally invasive surgical technique that involves the use of a thoracoscope and specialized instruments to access and remove the mediastinal mass through small incisions in the chest wall.[6] As a result of advancements in thoracoscopic instruments and surgical techniques and the evolution of minimally invasive concepts, the requirement for ports in VATS has been gradually reduced from three or four to just one.[7]

The VATS technique has been shown to be effective and safe for the resection of mediastinal masses, with a lower rate of morbidity and a shorter hospital stay compared to open procedures.[8,9] However, there are few studies on the effectiveness of uniportal VATS (U-VATS) for mediastinal mass resection. In these studies, the postoperative outcomes are in favor of the U-VATS, while the perioperative outcomes are inconsistent. Thus, further research is required to investigate the efficacy of U-VATS. This study aimed to compare perioperative and postoperative outcomes in patients who underwent U-VATS and open surgery for mediastinal mass resection.

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METHODS

Following the principles set forth in the Declaration of Helsinki, this prospective study was conducted at the Erciyes University Faculty of Medicine Department of Thoracic Surgery from January 2018 to January 2020. The study received approval from the Erciyes University Faculty of Medicine Ethics Committee (Date: 12.2017, Decision No: 2017-548). All participants provided their written informed consent.

A total of 74 patients planned for mediastinal mass resection between the years of the study were evaluated for eligibility. Cases with significant cognitive difficulties (vision, hearing, and mental disabilities) (n=1), preoperative chronic pain syndrome (n=3), use of opioid pain relievers (n=3), and history of thoracotomy or sternotomy (n=5) were excluded from the study. Finally, 62 cases were included in the study, and no cases were excluded during the follow-up period.

The arterial blood gas, electrocardiography, pulmonary function tests and posteroanterior chest radiographs (PAAG), thorax computed tomography (CT) (**Figure 1**), and positron emission tomography with CT (PET/CT) were performed in all cases. Histopathological diagnoses for the patients were obtained with transthoracic needle aspiration (TTNA), endobronchial ultrasonography (EBUS), fiberoptic bronchoscopy (FOB), and endosonography (EUS). Mediastinal and distant metastases were evaluated with PET/CT. Oral intake of patients was discontinued for 24 hours before the operation. Following the cessation of oral intake, patients with chronic renal failure and diabetes mellitus were hydrated with neutralizing fluid, and their blood sugars were controlled. All patients were evaluated preoperatively by the anesthesiology and reanimation department, while patients over the age of 65 were consulted preoperatively by cardiology. The patients were divided into two groups based on the surgical procedure, which was either open surgery or U-VATS.

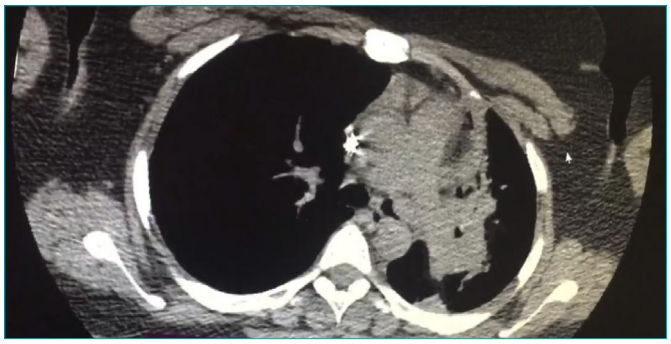

Figure 1. The thorax computed tomography image of the patient who underwent open surgery due to suspicion of mediastinal invasion

Surgical Procedure

Under general anesthesia, patients undergoing open surgery were intubated with a single-lumen endotracheal tube, while those undergoing U-VATS procedures were intubated with a double-lumen tube to facilitate access and management of lesions on the contralateral side. In myasthenic patients, a central venous catheter was placed in the subclavian vein or the internal jugular vein. Invasive arterial monitoring was provided. All patients undergoing U-VATS were placed in the posterolateral thoracotomy position, while those undergoing open surgery were placed in both the posterolateral thoracotomy (n=6) and sternotomy positions (n=24), and a thoracotomy pillow was utilized.

A uniportal incision was made on the anterior axillary line through the 4th or 5th intercostal space. From this range, a high-resolution thoracoscope, which has a 30° optic with a 10-mm diameter, and 5-mm angled hand tools such as staple systems and endoscopic polymer clips, which allow work in the thoracic cavity, were used. Postoperatively, a single drain was placed in the same incision.

Patients who underwent open surgery with muscle-sparing posterolateral thoracotomy in the lateral decubitus position had their serratus anterior muscle preserved. Patients who underwent sternotomy were placed in the supine position. After surgery, a chest drain was placed in the thoracic cavity. In patients undergoing thoracotomies, a costa retractor was used.

After surgery, the patients were transferred to the intensive care unit. Every 4 to 6 hours, hemograms were monitored, and PAAG was performed daily. The patients' fluid intake and output were monitored hourly. When the daily drainage fell below 200 ml and the air leak ceased, the chest tube drain was removed. These patients were discharged after a control PAAG, which was evaluated 24 hours later.

Postoperative Pain Evaluation

The VAS scale was used for the evaluation of postoperative pain. The pain intensity is expressed on a scale from 0 (not painful) to 10 (extremely painful). A single physician explained each patient on how to properly score their level of pain. At the 4th, 8th, 12th, 24th, 48th, and 72nd hours after surgery, each patient completed a pain evaluation.

In both open and minimally invasive surgical techniques, the same pain management strategy was employed. This involved administering analgesic medication to all patients in equal dosages and at the same intervals postoperatively, regardless of the surgical approach used. Patients with pain were given paracetamol first, while nonsteroidal anti-inflammatory drugs were given if the pain started again. Analgesics were administered at 8-hour intervals. Opioid analgesics were not used.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) for Windows 23 (IBM SPSS, Chicago, IL, USA). The extent to which the data followed a normal distribution was evaluated using the Shapiro-Wilk test. Numeric variables with and without a normal distribution were plotted as mean±standard deviation and median (min-max), respectively. The student-T test or Mann-Whitney U test was used for the comparison of numeric variables between the two groups according to the distribution of normality. Categorical variables were indicated as numeric and percentile values. Chi-square, Yates correction and Fischer's exact tests were used for the comparison of categorical data. A p-value of less than 0.05 was considered significant in statistical analyses.

RESULTS

The mean age of the 62 cases with mediastinal masses included in the study was 49.2±15.4 years, and the majority of them had additional diseases (77.4%). The demographic and clinical characteristics of the cases are presented in

Table 1. The mean age, rates of females and smokers were similar in the open surgery group compared to the U-VATS group. The rates of hypertension, coronary artery disease and Myasthenia gravis were higher in the open surgery group compared to the U-VATS group. Mass localization had a similar distribution in both groups.

Table 1. Demographic and clinic characteristics of the study population

Variables	All patients	Open surgery	U-VATS	P value
	n=62	n=30	n=32	
Age, years	49.2±15.4	48.1±15.2	50.2±15.8	0.609
Gender, n (%)				0.585
Male	27 (43.5)	12 (40.0)	15 (46.9)	
Female	35 (56.5)	18 (60.0)	17 (53.1)	
Smoking, n (%)	17 (27.4)	10 (33.3)	7 (21.9)	0.312
ASA grade, n (%)				0.261
I	6 (9.7)	3 (10.0)	3 (9.4)	
II	48 (77.4)	21 (70.0)	27 (84.4)	
III	8 (12.9)	6 (20.0)	2 (6.3)	
Comorbidities, n (%)				
Hypertension	19 (30.6)	17 (56.7)	2 (6.3)	<0.001
Coronary artery disease	10 (16.1)	9 (30.0)	1 (3.1)	0.004
Rheumatoid arthritis	7 (11.3)	3 (10.0)	4 (12.5)	0.756
Myasthenia gravis	7 (11.3)	6 (20.0)	1 (3.1)	0.036
Asthma	6 (9.7)	4 (13.3)	2 (6.3)	0.346
Diabetes mellitus	6 (9.7)	4 (13.3)	2 (6.3)	0.346
Mass localization, n (%)				0.485
Anterior	33 (53.2)	16 (53.3)	17 (53.1)	
Middle	12 (19.4)	6 (20.0)	6 (18.7)	
Posterior	17 (27.4)	8 (26.7)	9 (28.2)	

Data are mean±standard deviation or median (min-max), or number (%). ASA, American Society of An-esthesiologists; U-VATS, Uniportal video-assisted thoracoscopic surgery.

Cyst tumor excision was performed in the majority of cases (60%) who underwent open surgery, while mass excision was performed in the majority of cases (65.6%) who underwent U-VATS. Median operation time (120 vs. 180 minutes, P<0.001) and median intraoperative blood loss (50 vs. 100 mL, P<0.001) were lower in the U-VATS group compared to the open surgery group. In all of the cases that underwent U-VATS, the procedure was completed without additional port incisions or conversion to a thoracotomy / sternotomy. Median pathological mass size was lower in the U-VATS group compared to open surgery (8 vs. 4 cm, P<0.001). In terms of pathological findings, the rates of malignant lesions and lymph nodes did not differ significantly between the groups (Table 2). The histopathological diagnosis distributions were as follows: 18 cases of thymoma, 8 cases of bronchogenic cyst, 7 cases of pericardial cyst, 7 cases of schwannoma, 6 cases of hydatid cyst, 4 cases of thymic hyperplasia, 3 cases of teratoma, 2 cases of enteric cyst, and one case each of cystic thyroid, hemangiopericytoma, and granulomatous events. A malignant neurogenic tumor was not detected. The rate of patients with thymoma was similar in both surgical groups. Three of the patients with thymoma were Stage II and above.

The median time of chest drain removal (4 vs. 6 days, P<0.001) and median postoperative drainage volumes were lower in the U-VATS group compared to the open surgery group. During the postoperative 72 hours, the U-VATS group exhibited lower postoperative VAS scores compared to the open surgery group (Figure 2). Median return time to daily activity (1 vs. 4 day, P<0.001) and median length of hospital stay (4 vs. 6 days, P<0.001) were lower in the U-VATS group compared to the open surgery group (Table 3).

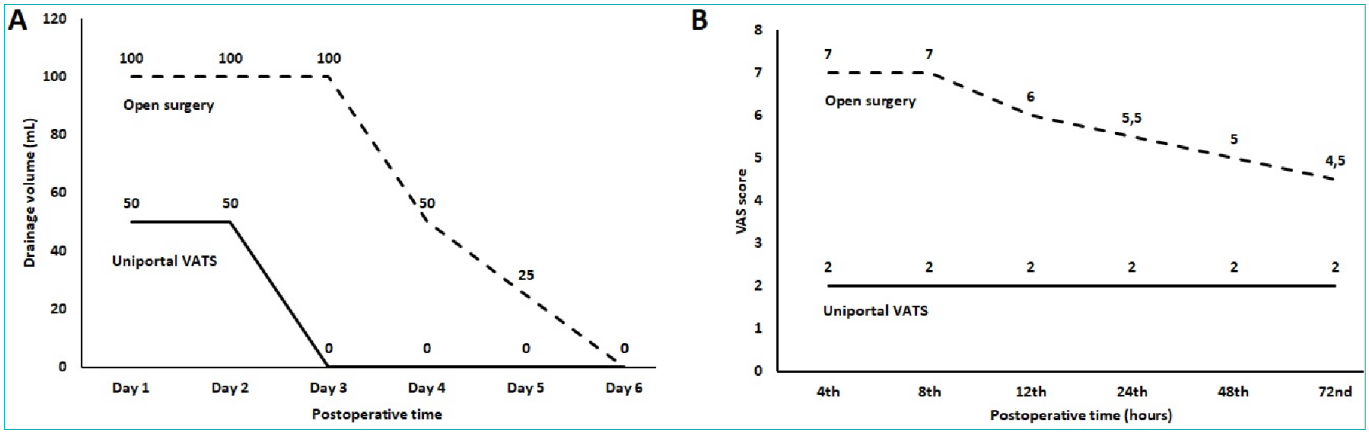

Figure 2. Variations in postoperative drainage volume (A) and VAS score (B) by surgical group

Table 2. Perioperative and histopathological findings

Variables	All patients	Open surgery	U-VATS	P-value
	n=62	n=30	n=32	
Type of surgery, n (%)				<0.001
Cyst tumor excision	18 (29.0)	18 (60.0)	0	
Mass excision	23 (37.1)	2 (6.7)	21 (65.6)	
Maximal thymectomy	21 (33.9)	10 (33.3)	11 (34.4)	
Operation time, minutes	165 (60-260)	180 (120-260)	120 (60-240)	<0.001
Intraoperative blood loss, mL	50 (20-200)	100 (30-200)	50 (20-80)	<0.001
Wound length, cm	3.5 (2.5-16.9)	15.5 (8-16.9)	3.0 (2.5-3.5)	<0.001
Pathological mass size, cm	5.5 (1-22)	8 (2-22)	4 (1-12)	<0.001
Thymoma, n (%)	18 (29.0)	10 (33.3)	8 (34.4)	0.579
Capsule invasion, n (%)	5 (8.1)	3 (10.0)	2 (6.3)	0.067
Metastatic lymph node, n (%)	1 (1.6)	0	1 (3.1)	0.974

Data are mean±standard deviation or median (min-max), or number (%). U-VATS, uniportal video-assisted thoracoscopic surgery.

Table 3. Postoperative findings

Variables	All patients n=62	Open surgery n=30	U-VATS n=32	P-value
Chest drain removal, day	5 (3-7)	6 (5-7)	4 (3-5)	<0.001
Drainage volume, mL				
Day 1	100 (50-150)	100 (50-150)	50 (50-100)	<0.001
Day 2	80 (0-150)	100 (50-150)	50 (0-100)	<0.001
Day 3	50 (0-350)	100 (50-350)	0 (0-100)	<0.001
Day 4	0 (0-150)	50 (0-150)	0 (0-50)	<0.001
Day 5	0 (0-100)	25 (0-100)	0	<0.001
Day 6	0 (0-100)	0 (0-100)	0	0.009
Day 7	0	0	0	1.000
VAS score				
4th hours	4 (1-10)	7 (5-10)	2 (1-4)	<0.001
8th hours	3.5 (2-10)	7 (4-10)	2 (2-4)	<0.001
12th hours	3 (2-10)	6 (2-10)	2 (2-3)	<0.001
24th hours	3 (2-9)	5.5 (2-9)	2 (2-3)	<0.001
48th hours	2 (1-8)	5 (2-8)	2 (1-2)	<0.001
72nd hours	2 (1-8)	4.5 (2-8)	2 (1-3)	<0.001
Return time to daily activity, day	2.5 (1-6)	4 (3-6)	1 (1-3)	<0.001
Length of hospital stay, day	6 (3-9)	8 (6-9)	5 (3-7)	<0.001

Data are mean±standard deviation or median (min-max), or number (%). U-VATS, uniportal video-assisted thoracoscopic surgery; VAS, visual analogue scale.

In the U-VATS group, partial pneumothorax developed in one patient who underwent thymectomy after drainage was terminated. This patient underwent clinical follow-up with nasal oxygen therapy and the air in the thorax was resorbed without the need for additional intervention. A postoperative myasthenic crisis was not observed in all cases. The median follow-up period for the patients was 18 months, ranging from 1 to 25 months. In the group undergoing open surgery, a patient with thymoma had a recurrence, while there were no recurrences in the U-VATS group.

DISCUSSION

This study of mediastinal masses, which is frequently observed in thoracic surgery, showed that when compared to open surgery, U-VATS was associated with better outcomes in terms of perioperative blood loss, postoperative drainage volumes, postoperative pain, return to daily activities, and length of hospital stay. The findings of this study indicated that VATS is safe and feasible for the resection of mediastinal masses.

Although surgical treatment is usually the first option for mediastinal lesions, technological advancements have increased the trend toward minimally invasive approaches in recent years.[10] Increasing evidence indicates that minimally invasive surgeries involving the use of smaller incisions are equivalent to open surgery.[11] Previous studies have reported that minimally invasive surgery provides better outcomes than open surgery because of reduced blood loss, chest tube time, and hospital stay.[12,13] On the other hand, traditional thoracoscopic surgery has several restrictions. The procedure necessitates 3–4 ports, which result in many scars and severe intercostal discomfort. In addition, there are some unique challenges with the technology, such as the two-dimensional field, limited processing capacity in a small location, and sewing difficulties.14 In VATS, the number of ports that are required has been decreased to a single incision as a result of technological advancements, and this approach has shown comparable perioperative and postoperative outcomes compared to other approaches.

In a study that compared the median sternotomy with the multiportal VATS in the treatment of early-stage thymoma, the duration of the operation and the amount of blood loss were partially lower in the multiportal VATS.[10] Two different meta-analyses involving patients with non-small cell lung cancer and spontaneous pneumothorax reported that there was no difference between U-VATS and multiportal VATS in terms of perioperative outcomes such as operative time, blood loss amounts, and conversion rate.[15,16] Another study evaluating patients who underwent minimally invasive mediastinal lesion resection demonstrated similar perioperative outcomes.[17] However, there are studies reporting more favorable outcomes for U-VATS.[18,19] These results indicate that U-VATS does not extend the duration of operation. Besides, the incision size was smaller in the U-VATS group compared to the open surgery group, which was consistent with previous studies.[20] Theoretically, a smaller incision could make surgery more challenging and lengthen the duration of the procedure. This may also depend on the experience of the surgeons. Since 2014, our clinic has utilized the U-VATS approach, which has been linked to superior perioperative results as compared to open surgery.

The difficulty of applying the single-port technique to mediastinal masses is observed in tumors larger than 5.0 cm in diameter. In these cases, an extended thymectomy may be required. A larger mass may impede the surgeon's vision, necessitating the opening of the mediastinal pleura. There is also a risk of vascular injury and compression and proximal vessel control are required to control bleeding.[21] In different cohorts, the rate of conversion to thoracotomy in VATS varies widely, from 1% to 43%.[22] In the present study, clinical and pathological mass sizes were consistent in patients who received U-VATS, and the mass size was less than 5 cm in the majority of patients. Despite the fact that several patients had masses larger than 5 cm, thoracoscopic surgery was effectively performed without the need for further port incisions or conversion to a thoracotomy/sternotomy. This suggests that single-port surgery is a safe and practical procedure for the removal of mediastinal masses.

This study also supports that maximal thymectomy can be performed safely with a single port incision in thymic pathologies. Thymoma was detected in 29% of patients with mediastinal masses, and the proportion of these patients did not differ significantly between surgical groups. In cases of early-stage thymoma, the survival rate with surgery alone is over 80% at a 10-year follow-up. The efficacy of postoperative prophylactic radiotherapy in patients with stage II disease has not yet reached consensus.[23] In the U-VATS group, 3 of 8 thymoma patients were Stage II or higher. Two of these patients received chemotherapy plus radiotherapy in the postoperative period, while the remaining patient received chemotherapy alone. Although surgical procedures and the presence of thymoma are important factors for myasthenic crises,[24] no postoperative myasthenic crises were detected in the present study.

The U-VATS approach has been linked to superior post-operative outcomes in the resection of mediastinal masses

when compared to open and traditional thoracoscopic surgeries.[8,9,25] Previous research indicates that U-VATS is associated with earlier removal of chest drainage, lower drainage volume, pain intensity, and length of hospital stay compared to open surgery.[10] Several comparative studies between U-VATS and multiportal VATS demonstrated that U-VATS was partially more effective at the duration of chest drainage removal and drainage volume. However, post-operative pain and hospital stay duration favored U-VATS.[26,27] Multiportal VATS may cause further injury to the intercostal nerves and more residual neurologic symptoms such as paresthesia and postoperative pain.[28] In the present study, in the post-operative period, patients returned to their daily activities on day 1, chest drainage was removed on day 4. Besides, they had less pain in the first four hours after surgery and were discharged earlier compared to open surgery. The intercostal nerves may be affected less by a small wound incision, resulting in less postoperative pain. However, pain, which is a subjective evaluation, can be affected by a number of factors, such as the length of the surgical procedure, the size of the drainage tube, and the postoperative analgesic regimens.[29]

Limitations

This study has several limitations. Firstly, the sample size was modest. Secondly, the superiority of U-VATS over multiportal VATS cannot be determined as this study evaluated only U-VATS among minimally invasive techniques. Thirdly, the long-term survival results of the patients could not be evaluated. A larger, randomized, controlled trial design that incorporates these factors could shed more light on the clinical significance of U-VATS.

CONCLUSION

The U-VATS approach had better intraoperative safety and lower postoperative out-comes than open surgery. U-VATS, which has the potential to enhance postoperative recovery and quality of life, may be a safe and effective treatment option for patients with mediastinal masses.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the Erciyes University Faculty of Medicine Ethics Committee (Date: 12.2017, Decision No: 2017-548).

Informed Consent

A written informed consent form was obtained from all patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Ankyra Medical Journal
ORIGINAL ARTICLE DOI: 10.51271/ANKMJ-0004

Effect of adipose tissue-derived stromal vascular fraction on the viability of random-pattern skin flaps: an experimental study

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Cite this article: Kul Z, Özsoy Z. Effect of adipose tissue-derived stromal vascular fraction on the viability of random-pattern skin flaps: an experimental study. *Ank Med J.* 2024;3(1):19-23.

Received: 04.01.2024 ◆ **Accepted**: 30.01.2024 ◆ **Published**: 31.01.2024

ABSTRACT

Aims: Random pattern skin flaps are still widely used in plastic surgery. However, necrosis in distal flap sections resulting from ischemia is a serious problem, increasing the cost of treatment and hospitalization. The aim of this study was to test the effects of adipose tissue derived stromal vascular fraction (SVF) on random pattern skin flaps in rats.

Methods: In this experimental study conducted on Wistar rats, three groups were formed using the simple random sampling technique. Group 1 consisted of rats with a raised flap and a subcutaneous SVF injection. Group 2 comprised rats that underwent a flap operation with no additional treatment. Group 3 included rats with a raised flap and a subcutaneous saline injection. Tissue necrosis and level of survival area was detected with planimetric method and histopathologic examination was performed for detect of level of vascular density. On the 7th day post-operation, the viability assessment was calculated based on the ratio of the living flap area to the total flap area.

Results: The mean viability rate in Group 1 was higher compared to other groups, while there was no significant difference between Group 2 and Group 3 (Group 1=79.2±4.9 % vs. Group 2=41.0±5.9 % vs. Group 3= 39.2±2.7 %, p<0.001). The mean vascular densities of the flaps were higher in Group 1 compared to the other groups, while it were similar between Group 2 and Group 3 (Group 1=29.8±1.2 vs. Group 2=8.4±4.6 vs. Group 3=9.3±1.8, p<0.001).

Conclusion: The use of fat tissue-derived SVF injections has been found to be advantageous in improving the survival of random pattern flaps, frequently utilized in plastic and reconstructive surgery.

Keywords: Adipose tissue, flap viability, rat, stromal vascular fraction

INTRODUCTION

Random pattern skin flaps are a cornerstone in reconstructive plastic surgery, offering the ability to cover defects and improve aesthetic outcomes. However, their effectiveness is frequently marred by the occurrence of necrosis, particularly in the distal sections, which is primarily a consequence of inadequate blood supply or ischemia.[1] This ischemic necrosis not only affects the success of surgical outcomes but also elevates healthcare costs and extends hospital stays.[2] Thus, finding solutions to enhance the survival of these flaps is of paramount importance in the field of plastic surgery.

Recent studies have demonstrated that (SVF) derived from adipose tissue possesses significant potential in tissue regeneration and repair.[3,4] SVF, is particularly rich in mesenchymal stem cells (MSCs), but also includes a variety of other cell types such as endothelial progenitor cells, pericytes, fibroblasts, and immune cells. The diversity of cell types within SVF contributes to its broad range of regenerative capabilities.[5] In the context of plastic surgery, the utility of SVF in enhancing the viability of skin flaps is of significant interest. The ability of SVF to promote angiogenesis could potentially address the critical issue of ischemia in flap surgeries. Enhanced blood supply facilitated by the growth factors within SVF could improve the survival rates of skin flaps, thereby reducing the incidence of necrosis.[6,7]

We hypothesized that the injection of SVF obtained from adipose tissue could enhance the viability of random pattern skin flaps in Wistar rats. This study aimed to investigate the effect of injecting adipose tissue-derived SVF, containing stem cells, endothelial cells, and preadipocytes, on the viability of random pattern skin flaps in rats.

METHODS

This experimental study was conducted on Wistar rats in February 2006 at the Vakıf Gureba Training and Research Hospital's Plastic, Reconstructive and Aesthetic Surgery Clinic. The study protocol received approval from the İstanbul University Experimental Medicine Research Center Ethics Committee (Date: 08.08.2001, Decision No: 0530-63-01/264).

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Thirty female Wistar rats, each weighing between 300-350 grams on average, were utilized. During the experiment, these animals were kept under identical laboratory conditions (standard room temperature and natural daylight) and were nourished with rat feed and tap water. All surgical procedures were performed under general anesthesia. Anesthesia was achieved with an intramuscular injection of ketamine hydrochloride (65 mg/kg) and xylazine hydrochloride (0.65 mg/kg).

Formation of the SVF

Through an incision made parallel to each of the inguinal creases, two samples of fat tissue, each with dimensions of 1×1×1 cm, were surgically excised from the inguinal fat pads. The excised fat tissue was then transferred into a sterile container containing 1 cc of physiological saline. As previously described in the literature,[8] the fat tissue, which was converted into a suspension by manual crushing, was transferred to a centrifuge tube and centrifuged at 1500 rpm for 5 minutes. After centrifugation, the triglycerides collected in the upper layer and the mature fat cells in the middle layer were removed from the tube. The stromal vascular fraction accumulated at the bottom of the suspension was then aspirated into 1 cc insulin syringes, and a 30 gauge needle was used for injection.

Surgery Procedure

Using an electric shaver, the animals' backs were shaved, followed by a cleaning with Betadine solution. Subsequently, 3×10 cm caudal-based dorsal skin flaps were removed using the Khouri-modified McFarlane flap model (Figure 1).[9] Once the flap had been raised, it was re-sutured to the area where it was removed (since no other suturing was performed beforehand), using a 4/0 silk suture with a sharp needle.

Figure 1. The McFarlane flap was planned to be 3x10 cm-sized with a caudal base.

Experimental Groups

Using a simple random sampling technique, the animals were divided into three groups, each consisting of 10 rats. Group 1 consisted of rats with a raised flap and a subcutaneous SVF injection. Group 2 comprised rats that underwent a flap operation with no additional treatment. Group 3 included rats with a raised flap and a subcutaneous saline injection.

In Group 1, a suspension containing 1 cc of SVF was injected subcutaneously at six quadrants on each flap. Flaps in Group 2 were sutured directly to the area from which they were lifted without any injection. In Group 3, a total of 1 cc of saline solution was injected into the subcutaneous tissue of the flaps in 6 quadrants (Figure 2). At the end of the operation, to prevent the animals from damaging each other's flaps, each animal was placed in a separate cage and monitored for 7 days.

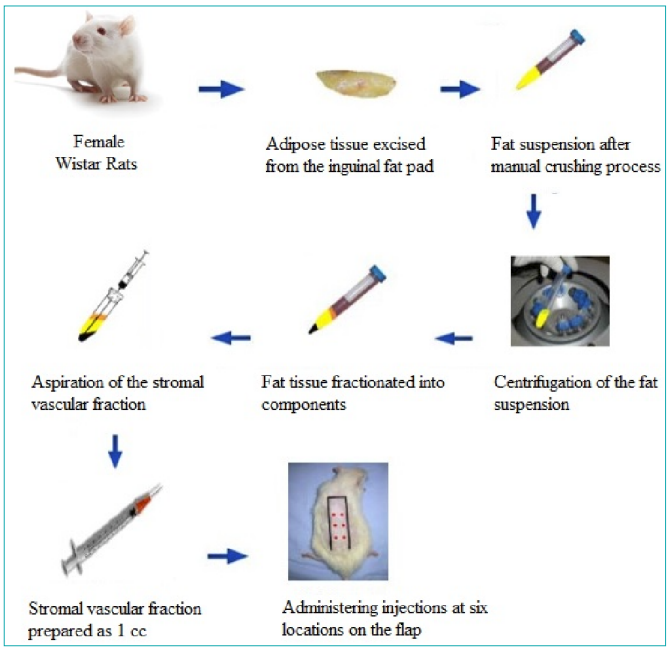

Figure 2. Schematic summary of the experimental stages

Viability Assessment

On the 7th postoperative day, flap viability percentages were calculated using Sasaki's paper template method.[10] For this purpose, the animals were re-anesthetized, and the flap sizes and necrosis lines were copied onto transparent acetate paper using a colored acetate pen. From the obtained shapes, the area of the entire flap was calculated first, followed by the area representing only the living skin. The resulting values were then ratioed and expressed as a percentage of viability. Additionally, the flap areas of all animals were photographed from an equal distance using an M-307 Hp-photosmart digital camera, these images were then graphically processed in Microsoft Paint version 5.1.

Measurement of Capillary Density

On the 10th postoperative day, full-thickness tissue samples measuring 0.5×0.5 cm were taken from the ischemic transition zones of the flaps in all three groups. After staining with Hematoxylin Eosin, the capillary count within a 1 mm^2 area was identified under a light microscope.

Statistical Analysis

All analyses were conducted using IBM SPSS Statistics for Windows 14.0 (SPSS Inc., Chigaco, IL, USA) software. The normal distribution of numerical variables was assessed using the Kolmogorov-Smirnov test and they presented as mean±standard deviation. Comparisons between groups were conducted using the Kruskal-Wallis test (post-hoc test: Mann-Whitney U with Bonferroni correction). Significance was accepted at P-value<0.05 (*) for all statistical analyses.

RESULTS

On the 7th day post-operation, the viability assessment was calculated based on the ratio of the living flap area to the total flap area. Accordingly, the mean viability rate in Group 1 was higher compared to other groups, while there was no significant difference between Group 2 and Group 3 (Group 1=79.2±4.9% vs. Group 2=41.0±5.9% vs. Group 3=39.2±2.7%, p<0.001). **Figure 3A** illustrates the necrosis and viable parts of the McFarlane flap's distal portions in the groups, while **Figure 3B** presents the viability rates of these flaps. Additionally, **Figure 3C** depicts the digital images of the necrotic and surviving areas within the groups' flaps.

The mean vascular densities of the flaps were higher in Group 1 compared to the other groups, while it were similar between Group 2 and Group 3 (Group 1=29.8±1.2 vs. Group 2=8.4±4.6 vs. Group 3=9.3±1.8, p<0.001) (**Figure 4A**). The microscopic examination of the tissue samples taken from the ischemic transition zones of the flaps belonging to the groups, in terms of capillary density, is shown in **Figure 4B**.

DISCUSSION

Random pattern skin flaps are widely used in plastic surgery. When the length of the flap is excessive, necrosis can develop at the distal end of the flap, which poses a significant problem for both the patient and the surgeon. The viability of these types of flaps primarily depends on the flap maintaining sufficient blood flow. Previous studies have shown that vasoconstriction, edema formation, and leukocyte activation and accumulation play significant roles in flap necrosis.[11-13] Eliminating or reducing these factors can positively impact the viability of the flap.[12,14] Numerous studies have shown that stem or endothelial cell precursors in the peripheral circulation contribute to neovascularization in ischemic tissues.[15-17] Endothelial progenitor cells, also known as angioblasts, are abundantly present in the adipose tissue-derived SVF, and these cells are precursors for new blood vessel formation.[18] In the process of new blood vessel formation, VEGF is recognized as a key cofactor. In vitro models have indicated that the viability of ischemic skin flaps is directly related to the formation of new endothelial cells and that VEGF is the primary mediator in this process.[19]

Previous studies have demonstrated that neovascularization in ischemic tissues can be achieved through the intravenous infusion of endothelial progenitor cells.[20] However, local injection has certain advantages over intravenous infusion. Firstly, it can increase the local density of endothelial progenitor cells in the target tissue. Secondly, it guards against the systemic adverse effects of the cells, including their role in promoting angiogenic diseases.[21,22] Hence, our study employed the local injection approach.

In a study conducted on athymic rats, a limited amount of stem cells was harvested from the bone marrow, and the allo-injection method was used to increase the number of cells to be injected into the vein.[23] Histological examinations of this mentioned study have shown that the increased granulation tissue in the injected flaps contained a dense microvascular network newly formed due to the effect of vascular endothelial progenitor cells.[23] In a study conducted on Sprague Dawley rats with a pedicled fascial flap combined

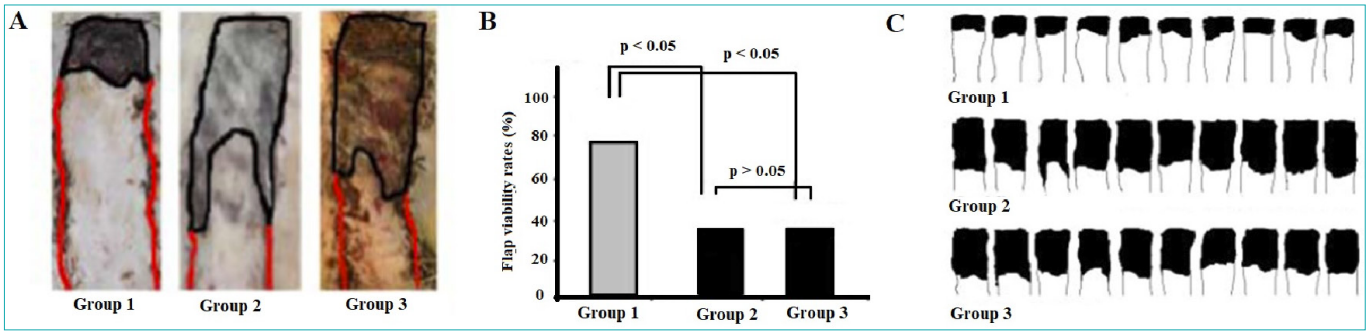

Figure 3. A) Necrosis and viable flap parts observed in the McFarlane flap distal parts of the groups (Viability rate, Group 1: 79.2±4.9% vs. Group 2: 41.0±5.9% vs. Group 3: 39.2±2.7%, p<0.001). **B)** Comparison of flap viability rates. **C)** The digital images of the necrotic and surviving areas within the groups' flaps

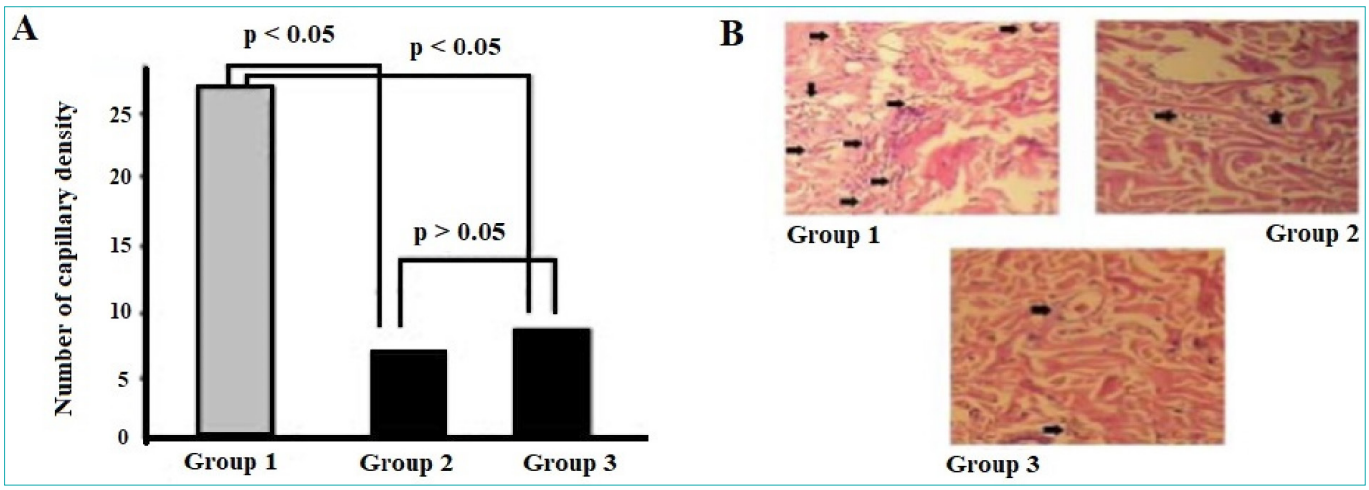

Figure 4. A) Comparison of vascular densities between groups B) The microscopic examination of the tissue samples taken from the ischemic transition zones of the flaps belonging to the groups, in terms of capillary density

with a free skin model, it was found that the SVF-treated group exhibited higher blood perfusion and flap survival rates compared to the control group. Moreover, this group not only exhibited increased angiogenesis but also improved wound healing through enhanced intercellular adhesion, cell migration, and a favorable immune response.[24] In a study involving rats exposed to freeze injury via a liquid nitrogen-cooled cryoprobe, findings demonstrated that SVF-treated rats exhibited markedly decreased acute inflammation and fibrosis on day 14, compared to the control group. Furthermore, this group demonstrated increased granulation tissue, improved re-epithelialization, and heightened neovascularization.[25] In the current study, on the 7th day post-operation, the SVF-treated group observed a higher flap viability rate and vascular density compared to other groups. Aligned with existing literature, these results demonstrate the substantial contribution of SVF to wound healing. However, the impact of SVF can differ based on the region of its extraction.

In a study conducted on female Sprague-Dawley rats, SVF were derived from fat tissues obtained from peri-ovarian, peri-renal, mesenteric, and omental regions. It was reported that the omental fat tissue, which had the least amount of fat, possessed the highest fraction of SVF cells and viable cells.[26] Regardless of the source of SVF, among its potential mechanisms for enhancing flap survival rates is the positive effect on flap circulation through direct vasodilation caused by growth factors produced by these cells, the enhancement of new blood vessel formation driven by the angiogenic action of growth factors, and the direct involvement of endothelial progenitor cells in the formation of new vessels.[23,27] An experimental study, which observed enhanced flap viability after the administration of bone marrow-derived progenitor cells, demonstrated that these injected cells differentiated into vascular endothelial cells.[23] Consistent with this study, the quantitative increase in vascular density observed in flaps treated with SVF injections in our study may have originated from new capillary formation.

The results of this study suggest that the SVF can increase flap viability, decrease the risk of necrosis, and thereby improve healing processes. The preliminary findings of this study may aid in devising novel therapeutic strategies in plastic and reconstructive surgery, and pave the way for the exploration of adipose tissue-derived cells in wider biomedical applications. To confirm and expand the findings of this study, more prospective randomized controlled trials are needed to investigate the effects of SVF obtained from different adipose tissue sources or in different animal models on flap viability.

Limitations

This study has some significant limitations. In this study, SVF was solely obtained from inguinal fat pads. Variability in sourcing SVF from various fat tissues and changes in the dosage and technique of application might result in substantial differences in outcomes. Additionally, our study's reliance on a mouse model, while advantageous for conducting controlled experiments, limits the direct application of our findings to human clinical contexts. Variations in skin physiology and wound healing processes between mice and humans might influence the relevance of our outcomes.

CONCLUSION

The use of fat tissue-derived SVF injections has been found to be advantageous in improving the survival of random pattern flaps, frequently utilized in plastic and reconstructive surgery. Fat tissue harvested from common plastic surgery procedures such as liposuction or dermolipectomy may become increasingly valuable in the future, particularly in tissue engineering applications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was performed in accordance with the Declaration of Helsinki, and was approved by the İstanbul University Experimental Medicine Research Center Ethics Committee (Date: 08.08.2001, Decision No: 0530-63-01/264).

Informed Consent

The need for informed consent was waived under the approval of the İstanbul University Experimental Medicine Research Center Ethics Committee due to the design of the study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Ankyra Medical Journal
REVIEW
DOI: 10.51271/ANKMJ-0005

Anemia in chronic kidney disease

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Cite this article: Öztürk H, Hacıömeroğlu A. Anemia in chronic kidney disease. *Ank Med J.* 2024;3(1):24-27.

Received: 05.01.2024 ◆ **Accepted**: 29.01.2024 ◆ **Published**: 31.01.2024

ABSTRACT

Anemia associated with chronic kidney disease is a common complication and a cause of increased morbidity and mortality. Hemoglobin levels should be closely monitored in all stages of chronic kidney disease. In this review, current clinical practice for anemia associated with chronic kidney disease, including pathophysiology, diagnosis, and treatment management, is reviewed.

Keywords: Chronic kidney disease, anemia, erythropoietin, darbepoetin

INTRODUCTION

Chronic kidney disease (CKD) is defined as the presence of kidney damage or a glomerular filtration rate (GFR) below 60 ml/min/1.73 m2, persisting for 3 months or longer due to any cause.[1] The disease is characterized by a progressive loss of renal function, which may necessitate renal replacement therapies such as dialysis or transplantation.

Kidney damage refers to pathologic conditions demonstrated by radiologic imaging or renal biopsy, urinary sediment pathologies, or an increased urinary albumin excretion rate. Kidney Disease: Improving Global Outcomes (KDIGO) divided CKD into 5 stages with the guidelines published in 2012.[2] Accordingly, there are 5 stages (Stage 3 is also divided into two subgroups: 3a and 3b) based on GFR, and 3 stages based on albuminuria. The CKD stages are compiled in Tables 1 and 2.[2]

Table 1. CKD classification

Category	GFR
Stage 1	>90
Stage 2	60-89
Stage 3a	45-59
Stage 3b	30-44
Stage 4	15-29
Stage 5	<15 or Hemodialysis

CKD: Chronic kidney disease, GFR: Glomerular filtration rate

Table 2. CKD classification based on albuminuria amount

Category	Albumin/creatine ratio
A1	<30 mg/g
A2	30-300 mg/g
A3	>300 mg/g

CKD: Chronic kidney disease

EPIDEMIOLOGY

Anemia is one of the most common complications of CKD. It has been found to be associated with various conditions in studies. These include decreased quality of life,[3] increased morbidity and mortality[4,5] and increased costs.[6]

Although the prevalence of CKD has increased in recent years, it is estimated that its prevalence is above 10% and affects more than 800 million people worldwide.[7] It is predicted that the prevalence of CKD will gradually increase in the coming years, especially with the increasing prevalence of underlying hypertension and diabetes mellitus.

Studies have shown that the prevalence of anemia in non-dialysis-dependent chronic kidney disease patients exceeds 60%.[8] In the same study, it was found that the prevalence of anemia increased as the CKD stage progressed, and the prevalence of chronic disease anemia was found to be over 90% in dialysis-dependent patients.[9] In addition, it has been demonstrated that the development of anemia leads to an increase in the rate of progression of CKD, and accordingly, the frequency of hospitalization, major cardiovascular events, and mortality increases.[10]

In Turkiye, the rate of chronic kidney disease in the general adult population was found to be 15.7%.[11] In the Chronic Kidney Disease Prevalence Survey of Turkiye (CREDIT) study, it was reported that CKD was more common in women (18.4%) compared to men (12.8%), the risk increased significantly with age, and the risk was higher in those living in rural areas.[11]

The frequency of kidney transplantation, which is the cheapest and best treatment option for CKD, was found to be quite low in Turkiye compared to diaysis modalities. Studies have shown that the renal transplantation rate in Turkiye is 24.68%.[12] This situation directs patients to high-cost dialysis treatments for many years.

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PATHOPHYSIOLOGY

Many mechanisms cause or predispose to anemia in chronic kidney disease. The leading cause is the progressive decrease in erythropoietin levels. In addition, inadequate iron absorption as a result of increased hepcidin levels associated with inflammation, shortened erythrocyte lifespan due to uremic toxins, weakened bone marrow response to erythropoietin, folate, and B12 deficiencies, and residual blood in the dialysis circuit during hemodialysis sessions also cause anemia. The pathophysiological mechanisms of chronic kidney disease are summarized in Figure 1.[13]

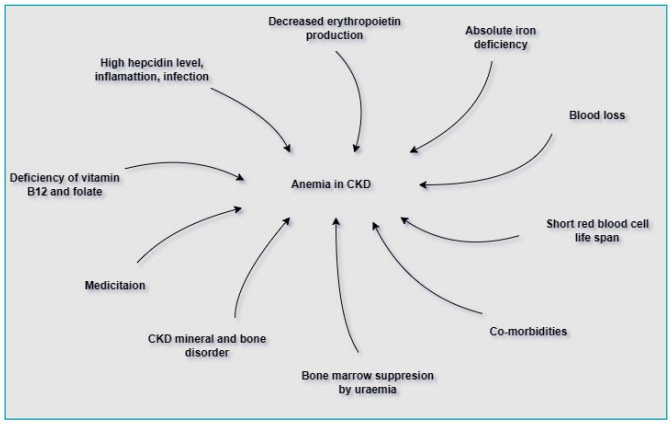

Figure 1. Pathophysiological mechanisms causing chronic kidney disease

Erythropoietin is a glycoprotein hormone, and most of it is synthesized by the peritubular cells of the kidney. In addition, it is also known to be synthesized in small amounts in the spleen, liver, bone marrow, brain, and lung.[14]

Erythropoietin has many functions in the body. Basically, it triggers differentiation into mature red blood cells and proliferation by binding to receptors on the surface of erythroid progenitor cells. In addition to this function, it is known to be effective in heart and brain protective mechanisms by reducing ischemia, regulating vascular tone by affecting nitric oxide levels, and on adipose tissue to regulate metabolic regulation.[15]

The main determinant of erythropoietin production is the decrease in oxygen levels in blood and tissue. As a result of the decrease in oxygen levels in blood and tissue, the amount of hypoxia-inducible factor (HIF) increases. This results in an increase in erythropoietin gene expression and production. Naturally, in cases of low hemoglobin, erythropoietin production increases as the oxygen level in the blood decreases. In chronic kidney disease, there is a decrease in EPO level due to inadequate function of the renal cortex, which is the main production site of EPO. This leads to a decrease in the production of erythroid serum and anemia. Anemia due to the EPO decrease in chronic kidney disease is summarized in Figure 2.

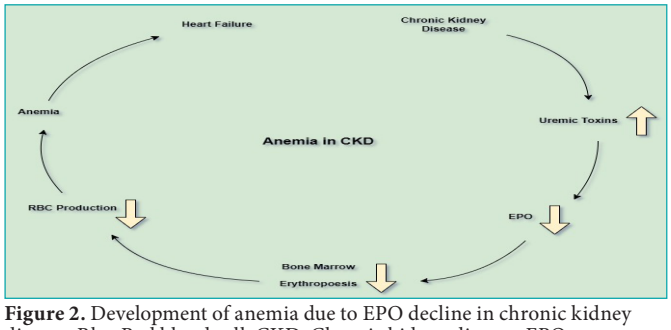

Figure 2. Development of anemia due to EPO decline in chronic kidney disease. Rbc: Red blood cell, CKD: Chronic kidney disease, EPO: Erythyropoietin

Hepcidin is a peptide hormone synthesized mostly by the liver, excreted renally, and is the main regulator of iron balance in the body. Hepcidin inhibits iron absorption through several pathways. Reduction of iron absorption from the small intestine, inhibition of iron delivery from aged erythrocytes to plasma, and inhibition of iron mobilization from liver stores are some of the mechanisms that have been identified so far. Due to its excretion from the kidney, blood levels are high in chronic kidney disease. In addition, recent studies have shown that hepcidin is an acute-phase reactant, and its levels increase in acute and chronic inflammations. Especially in chronic kidney disease, which is considered to be a chronic inflammatory process, it has been found that increased levels of hepcidin disrupt the proliferation and differentiation of erythroid series cells, and anemia develops accordingly. The increase in hepcidin and related effects are summarized in Figure 3.[16]

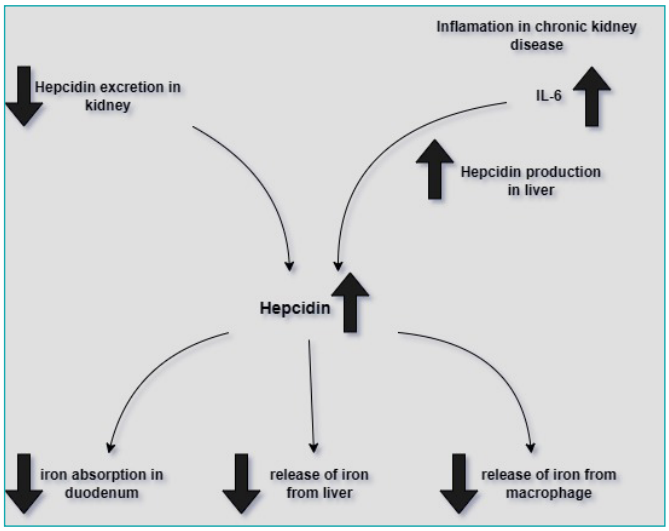

Figure 3. Increased hepcidin and related effects in chronic kidney disease

A large number of uremic toxins are present in the circulation and are continuously cleared and excreted from the blood by the renal route. In chronic kidney disease, increased levels of uremic toxins that cannot be excreted due to insufficient renal function play a key role in shortening erythrocyte life span. The reasons for this can be listed as increased erythrocyte osmotic fragility,[17] disruption of the asymmetry of erythrocyte membrane phospholipids[18] and impaired erythrocyte deformability.[19]

Another cause of anemia in chronic renal failure is blood loss. Especially in patients receiving routine hemodialysis, blood loss may occur due to both dialyzer membranes and anticoagulant use. Also, people with chronic kidney disease produce more gastric and duodenal acid because they have high uremia, which can lead to the formation of ulcers in these areas. Therefore, the incidence of gastrointestinal bleeding increases.[20]

TREATMENT AND MANAGEMENT

In addition to routine renal function monitoring, hemoglobin, transferrin saturation, and ferritin values should be measured every three months in patients with chronic kidney disease. Treatment of anemia in chronic kidney disease consists of several components. First of all, it should be aimed to improve the underlying renal dysfunction if possible. After this, it should be aimed at increasing the erythrocytic series. For this purpose,

the preferred treatment modalities for chronic kidney disease are erythropoiesis-stimulating agents and iron supplementation when necessary. Erythropoiesis-stimulating agents and recombinant erythropoietins are avoided unless the hemoglobin level falls below 10 mg/dl.[21]

In the past few years, the main treatment for chronic kidney disease has been blood transfusions. As a result of this situation, iron overload occurred in patients. In the 1980s, recombinant erythropoietin and then erythropoiesis-stimulating agents were discovered in studies conducted primarily to avoid transfusions.[22] In studies conducted over a short period of time, it was demonstrated that it increased survival and quality of life, improved cardiac functions, and decreased mortality and hospitalization.[23,24]

There are two main erythropoiesis-stimulating agents that are generally preferred in the treatment of anemia in chronic kidney disease. These are recombinant human erythropoietin and darbepoetin alfa. The initial dosing of recombinant human erythropoietin is 50-100 units/kg intravenously or subcutaneously three times a week. The standard starting dose of darbepoetin alfa is 0.45 mcg/kg intravenously or subcutaneously once a week.[25]

Knowledge of the side effects of these two agents is of great importance in patient follow-up. Predisposition to thrombotic events secondary to increased blood viscosity is considered to be the most important side effect. In addition, studies have shown an increased risk of ischemic stroke and myocardial infarction. Therefore, prophylactic antithrombotic use is recommended in some patient groups.[26,27] Benefits and risks of erythropoiesis-stimulating agents for anemia in chronic kidney disease are summarized in **Table 3**.

Table 3. Benefits and risks of erythropoiesis stimulating agents for anemia in CKD

Benefits
Increase Hb level and corrects anemia
Lessen the need for RBC transfusion
Risks
Higher rates of vascular access thrombosis, cerebrovascular events and cardiovascular events
Earlier requirement for kidney replacement theraphy
Higher rates of mortality

The peak erythrocyte level in response to both treatment regimens usually occurs between 8 and 12 weeks. In rare groups, anemia resistant to these agents may be observed, and the cause of this is thought to be the inflammatory process. Some publications have shown that high CRP levels are associated with erythropoiesis-stimulating agent resistance.[28]

Roxadustat is another preferred agent in the treatment of chronic kidney disease related anemia. Roxadustat has been in use in recent years and is also available in Turkiye. The effect is demonstrated by HIF stabilization through inhibition of prolyl hydroxylase, which activates HIF.[29] It is an oral agent, primarily metabolized in the liver.[30] There are side effects such as vomiting, peripheral edema, headache, fatigue and hypercalemia.[31] Some studies have even shown that it increases the incidence of pulmonary hypertension.[32] However, it has been found that, unlike erythropoiesis-stimulating agents, it does not significantly increase the risk of cardiovascular events.[33] Compared to erythropoiesis stimulant agents, Roxadustat has been found to normalize intestinal iron absorption, which is due to its greater suppression of hepcidin.[34] Positive effects of Roxadustat on lipid profile have also been observed. Total cholesterol, LDL cholesterol and triglyceride levels have been significantly reduced. This effect is believed to be due to HIF stabilization.[35]

Iron treatment should also be considered as an option for patients with anemia due to chronic renal failure. Especially the increase in hepcidin due to the inflammatory process and impaired iron absorption leads to the need for iron. In patients receiving hemodialysis, intravenous iron supplementation is recommended due to decreased oral iron absorption.[36]

Chronic kidney disease, anemia, is a process that requires treatment and follow-up. Clinical studies have shown that each 1 mg/dL decrease in hemoglobin level leads to a 42% increase in left ventricular dilatation.[37] Accordingly, an increase in cardiovascular mortality rates has been found.[38]

CONCLUSION

The management of anemia in CKD poses a complex challenge, as it goes beyond simply administering blood transfusions or erythropoietin to patients. Both of these products can have significant negative effects when used over a long period of time. It is important to avoid making assumptions about the cause of anemia in renal disease. There are various factors to consider, such as nutrition and chronic illness. Therefore, conducting a comprehensive evaluation is crucial in order to identify the underlying cause.

Managing patients on dialysis with anemia necessitates a comprehensive approach involving a team of healthcare professionals. This team typically includes the nephrologist, primary care provider (including nurse practitioners, physician assistants, and physicians), nursing staff, pharmacy personnel, and, in some cases, a hematologist. By working together, they can optimize patient outcomes. A healthcare professional should closely monitor vital signs and obtain complete blood counts to assess the severity of anemia. Furthermore, it is crucial for pharmacists to provide patients with thorough education regarding the significance of iron supplements. This is due to the fact that the absence of iron can lead to the development of resistance to erythropoietin in many patients.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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