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The Fourth Year of Ankyra Medical Journal

As we embark on the fourth year of the Ankyra Medical Journal (AnkMJ), it is both a privilege and an honor to reflect on our journey thus far and envision the path ahead. Since its inception, AnkMJ has remained steadfast in its commitment to advancing medical science through the publication of high-quality peer-reviewed research. This milestone is a testament to the dedication of our authors, reviewers, editorial team, and readers, who have supported us unwaveringly.

Over the past three years, AnkMJ has grown from a nascent publication to a respected platform in the medical community. Our inclusion in renowned indexing databases such as Index Copernicus, Europub, DRJI, and WorldCatSJR reflects the journal's academic rigor and the impact of our research.

The diversity of topics we have explored—ranging from groundbreaking original research to insightful reviews and compelling case reports—underscores our dedication to addressing the multifaceted challenges of modern medicine. These articles highlight the journal's broad scope and relevance across specialties.

As we step into our fourth year, our mission remains clear: to continue serving as a platform for rigorous scientific discourse and uphold the highest standards of scholarly publishing.

None of these would be possible without the tireless efforts of the contributors. To our authors, who trust us with their invaluable work; to our reviewers, whose meticulous evaluations uphold our standards; and to our readers, whose engagement and feedback inspired us to grow—thank you. We also thank our editorial board for their visionary leadership and unwavering dedication.

The fourth year of AnkMJ represents not only a continuation, but also an evolution. It is an opportunity to build on our foundation, explore uncharted territories in medical research, and reinforce our role as a catalyst for impactful discoveries.

With gratitude and anticipation,

Mehmet ÇITIRIK
Chief Editor
Ankyra Medical Journal

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Assessing the impact of non-sucrose IVIG preparations on urinary NGAL levels

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ABSTRACT

Aims: The study aimed to show whether non-sucrose-containing intravenous immunoglobulin (IVIG) administration affected urinary neutrophil gelatinase-associated lipocalin (uNGAL) levels within 24 hours and whether the uNGAL elevations preceded the development of acute kidney injury (AKI).

Methods: The study included 20 patients who received IVIG treatment in internal medicine and neurology clinics between January 2022 and September 2022 and 10 controls (2:1 ratio) with similar age, gender, and comorbidity who did not receive IVIG. The uNGAL levels were classified as elevated (>80 ng/ml) or normal (<80 ng/ml). Patients were monitored for at least 48 hours, up to a maximum of 7 days, or until discharged, to assess the development of AKI.

Results: None of the patients developed AKI during the follow-up period. Posttreatment median uNGAL levels were 7.1 ng/ml (3.35-37.45 ng/ml, p=0.37, Wilcoxon sign-rank test), similar to pretreatment levels. However, when compared categorically, only two patients (10%) had uNGAL levels higher than 80 ng/mL pretreatment, which increased to four patients (20%) posttreatment (p=0.032, Fisher's exact test).

Conclusion: In our small-scale study, although AKI did not develop after IVIG treatment, the increased percentage of patients (increases from %10% to 20) with elevated uNGAL levels suggests that AKI may develop even in formulations that do not contain sucrose as a stabilizer.

Keywords: Acute kidney injury, biomarkers, intravenous immunoglobulin, neutrophil gelatinase-associated lipocalin

INTRODUCTION

Intravenous immunoglobulin G (IVIG) has been used to treat various diseases since it was first administered in 1962.[1] In 1981, the American Food and Drug Administration (FDA) in the United States approved it for patients with immunodeficiency. Over the years, several IVIG preparations have been FDA-approved and have been a cornerstone of treatment for conditions such as multifocal motor neuropathy, chronic B-cell leukemia, immune thrombocytopenic purpura, Kawasaki syndrome, and chronic inflammatory demyelinating neuropathy.[2] As technology has advanced, chemical and enzymatic modifications have allowed for the development of stable monomeric IVIG solutions with concentrations of 4-5% suitable for clinical use.[3] The introduction of modern production techniques led to the widespread use of high-purity and well-tolerated IVIG preparations in the early 1980s.[4] While the pH of IVIG preparations produced by various companies typically falls within the range of 6-7, the optimal pH for stability is between 4 and 4.5. Maintaining a lower pH can help prevent the formation of aggregates more effectively.[5] Additional molecular stabilizers, which include sucrose, maltose, glucose, sorbitol, mannitol, glycine, and proline, are often included in these preparations to enhance stability. However, the inclusion of these stabilizers, particularly sucrose, raises concerns about potential adverse effects; it is believed that acute kidney injury (AKI) associated with IVIG administration may be linked to the lack of sucrase in the kidneys, which is particularly relevant for sucrose, one of the stabilizers utilized.[6]

Early diagnosis of AKI significantly improves the chances of effective treatment. Traditionally, serum creatinine levels and patient urine output monitoring have been used as standard markers to detect AKI. However, serum creatinine levels only begin to rise after the glomeruli's filtration capacity has been reduced by half, and these levels can be influenced by muscle damage and tubule secretion. Additionally, urine output has lower specificity for accurately identifying AKI. Therefore, there is a need for new biomarkers that can be tested in blood

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and urine to diagnose AKI better.[7] One promising biomarker is neutrophil gelatinase-associated lipocalin (NGAL), which can be detected in blood or urine (uNGAL) without any invasive procedures and provides specific responses to kidney damage.[8,9]

In this study, we aimed to demonstrate whether non-sucrose-containing IVIG administration affected uNGAL levels in patients treated with IVIG for various conditions and whether the uNGAL elevations preceded the development of AKI.

METHODS

Ethics approval was from the Maltepe University Clinical Researches Ethics Committee (Date: 15.02.2022, Decision No: 2022/900/15). All participants were informed of the study protocol and provided informed consent. All procedures were carried out by the ethical rules and the principles of the Declaration of Helsinki. The study included 20 patients who received inpatient IVIG treatment in a university hospital's Internal Medicine and Neurology clinics between January 2022 and September 2022 and 10 controls (2:1 ratio) with similar age, gender, and comorbidity distribution who did not receive IVIG. Patients hospitalized for systemic infections, with a recent history of infection or antibiotic use, patients with a current or recent infection with coronavirus (COVID-19), patients with chronic renal failure with eGFR less than 60 mL/min/1.73m^2, and patients with active malignancy were excluded from the study.

Data regarding participant age, gender, and comorbidities were obtained from patient files. Blood and urine samples were collected to measure various levels: serum sodium (mmol/L), potassium (mmol/L), calcium (mg/dl), magnesium (mg/dl), phosphorus (mg/dl), blood urea nitrogen (BUN, mg/dl), estimated glomerular filtration rate (eGFR, calculated by using chronic kidney disease epidemiology collaboration creatinine equation 2021, ml/min/1.73m^2), uric acid (mg/dl), and uNGAL (ng/ml) before and 24 hours after IVIG infusion. Additionally, urine microalbumin and creatinine levels were measured from random urine samples to calculate the urinary microalbumin-to-creatinine ratio, which was used to estimate 24-hour albumin excretion, expressed as mg/day.

The uNGAL levels were classified as elevated (>80 ng/ml) or normal (<80 ng/ml), following literature recommendations that define an optimal cut-off for AKI.[10] The kidney disease: improving global outcomes (KDIGO) criteria were employed to define AKI, characterized by either an increase in serum creatinine of ≥0.3 mg/dl within 48 hours or an increase to ≥1.5 times the baseline within seven days or a urine volume of <0.5 ml/kg/hour for six hours.[11] Patients were monitored for at least 48 hours, up to a maximum of 7 days, or until discharged, to assess the development of AKI.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 26.0 software (SPSS Inc; Chicago, USA). The conformity of continuous variables to a normal distribution was assessed using Shapiro-Wilk tests. Categorical data were presented as frequencies and percentages, while continuous variables were reported as medians and interquartile ranges. Categorical comparisons were analyzed using Pearson chi-square and Fisher's exact tests. For continuous variables, the Mann-Whitney U test and Kruskal-Wallis's test were used for comparisons. The Spearman correlation test was employed to examine relationships between continuous variables. A statistical significance level of 0.05 was adopted for the study.

RESULTS

The study group consisted of 30 participants, 20 of whom underwent IVIG administration (cases) and ten as controls. Twelve participants (40%) were female, and the median age was 66 years (IQR 53-76). Hypertension was the most prevalent comorbidity with 22 (73.3%) patients, followed by diabetes mellitus with 13 (43.3%) and chronic heart failure with 12 (40%) patients. The least prevalent comorbidity was dyslipidemia, with only 8 (26.7%) patients. Demographic and clinical data of cases and controls are presented in **Table 1**; groups were similar regarding these data.

Table 2 presents the pretreatment laboratory values of cases and controls. The control group had statistically significantly lower calcium levels than cases (p=0.04, Mann-Whitney U test), whereas cases had statistically significantly lower eGFR levels than controls (p=0.015, Mann-Whitney U test). Other laboratory results, including uNGAL levels, were similar between groups. Only one patient from the control group (10%) and two patients from cases (10%) had pretreatment uNGAL levels higher than 80 ng/ml.

None of the patients developed AKI during the follow-up period. Calcium and magnesium levels showed statistically significant changes when cases were compared for pretreatment-posttreatment changes: posttreatment median calcium levels increased to 9.05 mg/dl (8.8-9.35 mg/dl) from a median pretreatment level of 8.5 mg/dl (p=0.006, Wilcoxon sign-rank test), and median magnesium levels increased to 1.97 mg/dl (1.79-2.07 mg/dl) from a median pretreatment level of 1.88 mg/dl. Posttreatment median uNGAL levels were 7.1 ng/ml (3.35-37.45 ng/ml, p=0.37, Wilcoxon sign-rank test), which was similar to pretreatment levels. However, when compared categorically, only two patients (10%) had uNGAL levels higher than 80 ng/ml pretreatment, which increased to four patients (20%) posttreatment (p=0.032, Fisher's exact test).

Both pretreatment and posttreatment uNGAL levels did not show significant differences when compared for age, gender, and comorbidities. Pretreatment uNGAL levels showed a strong positive correlation with microalbuminuria (r=0.49, p=0.006, Spearman's correlation), which was consistent across groups (r=0.77, p=0.009 for controls, r=0.46, p=0.03 for cases, Spearman's correlation). For cases, pretreatment uNGAL levels were also correlated with pretreatment BUN levels (r=0.448, p=0.048) but not with eGFR. Posttreatment uNGAL levels did not significantly correlate with demographic, clinical, and laboratory parameters.

DISCUSSION

AKI following IVIG treatment is believed to result from the added stabilizers to prevent the dimerization and polymerization of immunoglobulins at low pH. Notably, sucrose, a common stabilizer, is associated with approximately 90% of reported AKI cases because sucrase, the enzyme responsible for breaking it down, is not produced in the kidneys. As a result, intravenous sucrose accumulates in the proximal tubule, where it cannot be metabolized. This accumulation leads to the entry of sucrose

Table 1. Demographic and clinical data of case and control groups

		Cases (n=20)	Controls (n=10)	p value
Age		68 (52-76)	62 (54-78)	0.96
Gender	Male	11 (55%)	7 (70%)	
	Female	9 (45%)	3 (30%)	0.35
Comorbidities	Diabetes mellitus	9 (45%)	4 (40%)	0.55
	Hypertension	14 (70%)	8 (80%)	0.45
	Dyslipidemia	6 (30%)	2 (20%)	0.45
	Chronic heart failure	9 (45%)	3 (30%)	0.35

Data were presented as median (IQR), count, and percentages. Data were compared using chi-square and Fisher's exact tests for categorical comparison and the Mann-Whitney U test to compare continuous data of two independent groups.

Table 2. Pretreatment laboratory data of case and control groups

	Cases (n=20)	Controls (n=10)	p value
Sodium (mmol/L)	138 (136-140)	138 (137-139)	0.77
Potassium (mmol/L)	4.13 (3.78-4.5)	4.25 (3.7-4.5)	0.98
Calcium (mg/dl)	9.45 (9.0-9.8)	8.5 (8.1-9.3)	**0.04**
Magnesium (mg/dl)	2.03 (1.88-2.22)	1.88 (1.8-1.96)	0.109
Phosphorus (mg/dl)	3.55 (3.3-4.2)	3.26 (2.86-3.4)	0.08
BUN (mg/dl)	15.4 (12.5-20.9)	16.5 (11-21)	0.55
eGFR (ml/min/1.73 m^2)	82 (70-97)	104 (95-117)	**0.015**
Uric acid (mg/dl)	5.05 (4.55-5.94)	4.75 (3.7-6.5)	0.71
Microalbuminuria (mg/d)	31.6 (15.7-56.7)	29.3 (10.1-157.5)	0.84
uNGAL(ng/ml)	8.5 (2.1-16.2)	18.35 (3.8-63.5)	0.37

Data were presented as median (IQR). Data were compared using the Mann-Whitney U test to compare continuous data of two independent groups. BUN: Blood urea nitrogen, eGFR: Estimated glomerular filtration rate, uNGAL: Neutrophil gelatinase-associated lipocalin

into tubule epithelial cells through pinocytosis, resulting in hyperosmolarity, vacuolization, narrowing of the tubular lumen, and, ultimately, AKI.[6] Herein, we aimed to demonstrate whether non-sucrose-containing IVIG administration was associated with the development of AKI and whether IVIG treatment affected uNGAL levels. In this study, none of the patients developed AKI during the follow-up, possibly due to prior hydration protocols and due to the small scale of the study. Moreover, pretreatment and posttreatment uNGAL levels did not differ significantly. However, in IVIG-treated cases, there was a significant increase in the percentage of cases with uNGAL higher than 80 ng/ml in the posttreatment period, underlying a potential suggestion that non-sucrose stabilizers may also cause renal damage.

NGAL levels serve as a reliable marker for AKI across various age groups and clinical settings, from outpatient care to critical illness.[12] Additionally, NGAL levels are useful in distinguishing between hepatorenal or cardiorenal syndrome and acute tubular necrosis, addressing a significant clinical challenge.[13,14] Apart from being a marker for AKI, the relationship between proteinuria and an increase in NGAL levels is also well-studied.[15] Several studies previously reported that in diabetic patients, NGAL levels increase even before microalbuminuria is present, which carries some potential to be used as a marker for diabetic nephropathy.[16-18] Also, there are studies reporting that NGAL is a potential biomarker for predicting kidney damage earlier that also occurs in the prediabetic stage.[19] Even though it is hypothesized that NGAL levels may have no value in predicting kidney function decline in diabetic nephropathy[20], the marker is still valuable in showing subclinical tubular damage, which other routine clinical markers can't measure. Our study has demonstrated similar results, with pretreatment uNGAL levels showing strong positive correlations with microalbuminuria. However, the lack of correlation in the posttreatment period may underline that other confounding factors have affected the levels of uNGAL, disrupting this correlation. We hypothesize that this may be due to IVIG administration, but due to the small scale of the study, we cannot conclude in this regard. This topic warrants further investigation, with larger-scale studies involving patients using IVIG for different indications and involving patients with no comorbidities that may lead to microalbuminuria, as an increase in uNGAL may also be present prior to the development of proteinuria.

Limitations

Several limitations exist due to the nature of the study. First and foremost, this study has a small sample size, and none of the patients developed AKI due to IVIG treatment. Nevertheless, an increase in the uNGAL level in some patients still underlines the need for further studies to show if non-sucrose IVIG treatment causes tubular damage to some extent. Secondly, this study does not include a subgroup analysis of IVIG indications, which may have impacted the results. Although we aimed to limit the potential confounders by the exclusion criteria, different pathologies that require IVIG treatment may have affected the risk of increased uNGAL levels.

CONCLUSION

AKI can be a significant side effect of IVIG treatment, even in formulations that do not contain sucrose as a stabilizer. In our small-scale study, we found that while none of the patients developed AKI and the median uNGAL levels were similar, however, the percentage of patients with elevated uNGAL levels did increase. This finding highlights the need for further investigation into this issue regarding tubular damage caused by non-sucrose IVIG preparations.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics approval was from the Maltepe University Clinical Researches Ethics Committee (Date: 15.02.2022, Decision No: 2022/900/15).

Informed Consent

All patients signed and free and informed consent form.

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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Original Article
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Investigation of *Staphylococcus aureus* nasal carriage rates in hemodialysis patients *Staphylococcus aureus* nasal carriage in hemodialysis patients

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ABSTRACT

Aims: This study aimed to assess the prevalence of nasal carriage of *Staphylococcus aureus (S. aureus)* in patients receiving hemodialysis and to evaluate the susceptibilities to mupirocin and fusidic acid in those with nasal carriage of *S. aureus*.

Methods: A total of 165 hemodialysis patients, 55 (33.3%) females and 109 (66.03%) males, were included in the study. Nasal swab samples obtained from the patients were inoculated on mannitol-salt agar (Beslab, Turkey) medium. The media were incubated in an oven at 37°C for 72 hours. Methicillin resistance was determined on Mueller-Hinton agar medium with cefoxitin disk (Bioanalyse, Turkey), and mupirocin and fusidic acid susceptibilities were determined by disk diffusion method with the discs of these antibiotics (Bioanalyse, Turkey).

Results: A total of 14 patients (8.48%) exhibited nasal carriage of *S. aureus*, comprising 9 patients (5.45%) with methicillin-sensitive *S. aureus* (MSSA) and 5 patients (3.03%) with methicillin-resistant *S. aureus* (MRSA). Of a total of 5 MRSA strains, 1 was resistant to mupirocin, and 1 was resistant to fusidic acid. Of a total of 9 MSSA strains, 2 were resistant to mupirocin and 2 were resistant to fusidic acid. It was determined that mupirocin and fusidic acid resistance was higher in MSSA strains.

Conclusion: In our study, the rate of *S. aureus* nasal carriage in hemodialysis patients was found to be low. In addition, the resistance rates of MSSA strains to mupirocin and fusidic acid, which are topical antibiotics that can be used in the eradication of *S. aureus* nasal carriage, were higher than the resistance rates of MRSA strains to mupirocin and fusidic acid. We think that planning the eradication of nasal carriage in dialysis patients according to mupirocin and fusidic acid susceptibility results will increase the eradication success.

Keywords: Hemodialysis patients, nasal carriage, *Staphylococcus aureus*, mupirocin, fusidic acid

INTRODUCTION

Infections in hemodialysis patients and end-stage renal failure patients are an important cause of mortality and morbidity. Hemodialysis patients are in the risk group in terms of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and colonization.[1] MRSA and coagulase-negative staphylococci are commonly identified as etiological agents of catheter-associated bacteremia in hemodialysis patients, as well as peritoneal dialysis catheter infections and peritonitis in peritoneal dialysis patients. The elevated resistance rate to mupirocin, a topical antibiotic employed in the elimination of *Staphylococcus aureus (S. aureus)* nasal carriage in these patients, constitutes a significant issue.[2] The most frequently colonized body site of *S. aureus* is the nose. It has been reported that nasal carriage of *S. aureus* plays an important role in the pathogenesis of infections due to this agent.[4-6]

Studies have reported that the rates of *S. aureus* nasal carriage in diabetic patients, hemodialysis patients, intravenous drug addicts, and patients with HIV infection are higher than the population.[4-10] The relationship between *S. aureus* nasal carriage in hemodialysis patients and infections developing due to this agent has been shown in many studies. It has been reported that the rates of bacteremia and catheter-related infections are higher in *S. aureus* nasal carriers than in non-carriers.[3,5,7,8] MRSA have an important place in staphylococcal infections. Many studies have reported the relationship between nasal MRSA carriage and MRSA infections. The main risk factors for MRSA nasal carriage are hospitalization, broad-spectrum antibiotic use, surgical intervention, residence in a nursing home, presence of hospital personnel in the family, etc.[1,3-5]

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This study aimed to ascertain the prevalence of nasal carriage of *S. aureus* in hemodialysis patients, identify the related risk factors, and evaluate susceptibilities to mupirocin and fusidic acid in patients with nasal carriage of *S. aureus*.

METHODS

A total of 165 hemodialysis patients, including 55 (33.3%) females and 109 (66.03%) males, who were dialyzed at the Private Ankara Balgat Dialysis Center, were included in the study. Nasal swab samples obtained from the patients were sown on Mannitol-salt agar (Beslab, Turkey) medium. The media were incubated in an oven at 37°C for 72 hours. Colonies that grew on Mannitol salt agar medium with yellow color reflex were evaluated as *S. aureus*, and the strains with positive catalase and coagulase tests were evaluated as *S. aureus*. MRSA1 strains was determined on Mueller Hinton agar medium with cefoxitin disk (Bioanalyse, Turkey), and mupirocin and fusidic acid susceptibilities were determined by disk diffusion method with the discs of these antibiotics (Bioanalyse, Turkey).

The mean age of the patients was 52±12.08 years. For the study, a patient consent form was obtained from hemodialysis patients, and ethics committee approval was obtained from Ankara Bilkent City Hospital Medical Research Scientific and Ethical Evaluation Board (Date: 04.12.2024, Decision No: TABED 1-24-384). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Statistical Analysis

SPSS (Statistical Package for the Social Sciences) is a software program used by researchers in various disciplines for quantitative analysis of complex data. A Chi-square test was used in the statistical analysis; p≤ 0.05 was considered statistically significant.

RESULTS

Among the 165 hemodialysis patients, nasal carriage of *S. aureus* was identified in 14 (8.48%) individuals, with 9 (5.45%) exhibiting methicillin-sensitive *Staphylococcus aureus* (MSSA) nasal carriage and 5 (3.03%) displaying methicillin-resistant *Staphylococcus aureus* (MRSA) nasal carriage.

Of a total of 5 MRSA strains, 1 was resistant to mupirocin, and 1 was resistant to fusidic acid. Of a total of 9 MSSA strains, 2 were resistant to mupirocin and 2 were resistant to fusidic acid. It was determined that mupirocin and fusidic acid resistance was higher in MSSA strains (Table 1).

Table 1. Mupirocin and fusidic acid resistance was identified in MSSA and MRSA strains

Agent	Mupirocin resistant (n)	Fusidic acid resistant (n)
MSSA (n:9)	7	7
MRSA (n:5)	1	1
Total (n:14)	8	8

MSSA: Methicillin-sensitive *Staphylococcus aureus*, MRSA: Methicillin-resistant *Staphylococcus aureus*

All patients who grew MRSA and MSSA in nasal cultures had a history of antibiotic use in the last 6 months and hospital or outpatient clinic admission in the last year as risk factors. Congestive heart failure was present in 3 patients with MRSA and 7 patients with MSSA nasal cultures. Diabetes mellitus was present in one patient with MRSA growth and in two patients with MSSA growth. Two patients who grew MSSA in nasal culture had a history of surgical intervention, and one patient had a family history of healthcare personnel. None of the patients who grew MRSA and MSSA in nasal cultures had a history of nursing home stay, hospitalization in the last 1-year, immunosuppressive treatment, or malignancy. The risk factors in patients with MRSA and MSSA growth in nasal cultures are shown in Table 2.

DISCUSSION

S. aureus nasal carriage plays a key role in the pathogenesis and epidemiology of *S. aureus* infections.[3,4,7] *S. aureus* nasal carriage rates in hemodialysis patients and patients receiving continuous outpatient peritoneal dialysis treatment have been reported to be higher than those in the general population.[4-8] *S. aureus* infections are common in hemodialysis patients due to hospitalization, immunosuppression, invasive interventions (hemodialysis catheter, subclavian catheter, etc.), frequent antibiotic use and high staphylococcal colonization on the skin and nose.[4,5]

Nasal carriage of S. aureus is one of the most important risk factors in the pathogenesis of catheter infections, bacteremia, and sepsis in hemodialysis patients.[4-13]

Compared to the general population, hemodialysis patients have been reported to be more colonized with *S. aureus*. Scheuch et al.[14] found *S. aureus* carriage in an average of 40% of hemodialysis patients in their cross-sectional study, while the carriage rate in the general population was reported as 27%.

Dialysis patients are often exposed to *S. aureus* due to their regular stay in dialysis centers, hospitals, and nursing homes. In studies, the rate of *S. aureus* carriage was reported as 51% in hemodialysis patients, 43% in patients receiving continuous outpatient peritoneal dialysis treatment, and 37% in the normal population.[3,4,14]

S. aureus is one of the most common causative agents of catheter-related bacteremia and sepsis in hemodialysis patients.[15] The eradication of *S. aureus* nasal carriage with topical antibiotics in patients undergoing hemodialysis and peritoneal dialysis has been shown to significantly reduce infection rates associated with this pathogen.[1,4,5]

In studies conducted in hemodialysis patients in Turkey, MRSA nasal carriage rates ranging from 1.8% to 40.4% have been reported.[5] Çelik et al.[5] investigated the rate of *S. aureus* nasal carriage and risk factors in 127 patients on hemodialysis. In this study, *S. aureus* nasal carriage was found in 41 (32.3%) patients, while MRSA nasal carriage was found in five (3.9%) patients. When risk factors were evaluated, a statistically significant relationship was found between *S. aureus* carriage and concomitant gastrointestinal disease and history of antibiotic use in the last year. In the present study, all of the patients with *S. aureus* nasal carriage had a history of antibiotic use within 6 months and a history of admission to a hospital or outpatient clinic within the last year as risk factors. In addition, it was noteworthy that 10 (71.4%) patients with *S. aureus* nasal carriage had congestive heart failure.

Risk factors for MRSA nasal carriage in hemodialysis patients have been reported as advanced age (≥75 years), prolonged hospitalization, history of repeated antibiotic use, and proximity to another MRSA colonized area. In the present study, the rates of *S. aureus* and MRSA nasal carriage in

Table 2. Risk factors in patients with MRSA and MSSA growth in nasal cultures

Risk factors Reproductive agent	DM (n*)	Antibiotic use in the last 6 months	History of admission to hospital or outpatient clinic in the last year	CHF	History of Surgical Intervention	Presence of health personnel in the family	Staying in a care home	Hospitalization in the last 1 year	History of immunosuppressive therapy or malignancy
MRSA (n:5)	1/5	5/5	5/5	3/5	0/5	0/5	0/5	0/5	0/5
MSAA (n:9)	2/9	9/9	9/9	7/9	2/9	1/9	0/9	0/9	0/9
Total	3/14	14/14	14/14	10/14	2/14	1/14	0/14	0/14	0/14

MRSA: Methicillin-resistant *Staphylococcus aureus,* MSSA: Methicillin-sensitive *Staphylococcus aureus,* n*: Patient number, DM: Diabetes mellitus, CHF: Congestive heart failure

hemodialysis patients were lower than the rates reported in the literature. The main risk factors for MRSA and MSSA nasal carriage in hemodialysis patients were antibiotic use in the last 6 months, history of hospital or outpatient clinic admission in the last year and congestive heart failure.

MRSA nasal carriage has been reported to be associated with poor clinical outcomes in outpatients on hemodialysis. Early identification of colonized patients, isolation, and elimination of carriage with a decolonization regimen is an appropriate approach to minimize MRSA transmission rates.[4,7,13] In studies conducted in hemodialysis patients in our country, *S. aureus* nasal carriage rates were reported by Şencan et al.[6] 67%, Kurutepe et al.[11] 33%, and Çelik et al.[5] 32.3%. The rates of MRSA nasal carriage in hemodialysis patients were reported as 3.9% by Çelik et al.[5]; 40.4% by Şencan et al.[6]; 11% by Kurutepe et al.[11]; and 1.8% by Mutlu et al.[12] Cesur et al.[9] found *S. aureus* nasal carriage in 23 (22.1%) of 104 patients on hemodialysis. Of the *S. aureus* strains isolated from the patients, 22 (95.6%) were reported as MSSA, and one (4.34%) as MRSA.

Lu et al.[7] reported *S. aureus* carriage rate as 22% and MRSA carriage rate as 2.4%, and Lederer et al.[8] reported *S. aureus* carriage rate as 53% and MRSA carriage rate as 12% in hemodialysis patients.

Limitations

The limitation of our study is that we could not determine whether S. aureus carriage was permanent or transient carriage because the patients were not followed up for a long period of time. In our study, the rate of S. aureus nasal carriage was found to be low in hemodialysis patients. Possible reasons for this may be that hemodialysis patients apply to dialysis centers on a daily basis, attention is paid to infection control measures in the dialysis center, and mupirocin pomade is applied to patients with nasal carriage.

CONCLUSION

Our study found that MSSA strains were more likely to be resistant to mupirocin and fusidic acid than MRSA strains were. Mupirocin and fusidic acid are topical antibiotics that can be used to get rid of S. aureus nasal carriage. In conclusion, we think that planning the eradication of nasal carriage in hemodialysis patients according to mupirocin and fusidic acid susceptibility results will increase the eradication success.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Ankara Bilkent City Hospital No 1 Medical Researches Scientific and Ethics Committee (Date: 04.12.2024, Decision No: TABED 1-24-384).

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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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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Stem cell therapies in ophthalmology

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ABSTRACT

Stem cells have been used for therapeutic purposes in many areas of medicine for many years. Depending on the tissues from which they are derived and their characteristics, stem cells can be classified into various groups. Some types of stem cells have the capacity to form an entire organism, while others can only differentiate into certain groups of tissues. In recent years, stem cells have also become popular in ophthalmology. Both stem cells found in ocular tissues and those derived from peripheral tissues are gaining attention for their use in ophthalmology. In ophthalmology, stem cells have a wide range of applications, from ocular surface and periocular tissue applications to retinal diseases. Some applications, such as limbal stem cell transplantation, have become common practices in clinical settings, while experimental and promising stem cell methods, such as anterior chamber stem cell transplants or subretinal supracoroidal stem cell transplants, are being investigated. Stem cells offer hope in ophthalmology for diseases that are unresponsive to traditional treatments, irreversible diseases, or dystrophic diseases that still lack approved treatments. The long-term effects of stem cell transplants in ophthalmology have not been clearly established, and the potential for tumor development due to uncontrolled proliferation has not been entirely eliminated. While there is a possibility of negative results from experimental studies and the emergence of concerning side effects, stem cells still hold promise as an alternative treatment option in ophthalmology.

Keywords: Ocular surface, ophthalmology, regeneration, retina, stem cell

INTRODUCTION

Stem cells are undifferentiated cells found in embryonic, fetal and adult tissues. They possess the properties of self-renewal, clonality and differentiation.[1] Although there are different classifications, stem cells can broadly be divided into three groups: embryonic stem cells (ESC), mesenchymal stem cells (MSC) and induced pluripotent stem cells (iPSC). While ESCs have a high capacity for self-renewal and differentiation, the ability of stem cells in adult tissues to self-renew and differentiate is limited. Therefore, ESCs can form an entire organism containing different tissue types, whereas adult tissue stem cells can only differentiate into limited cell or tissue types. ESCs originate from the blastocyst and exhibit pluripotent characteristics in terms of their differentiation capacity.[2] The high differentiation capacity of ESCs enables them to transform into various cell types in damaged ocular tissues. In the developing organism, some progenitor cells do not differentiate into terminal tissues and remain as tissue stem cells, which are called MSCs. Tissue stem cells in different tissues exhibit diverse behaviors. In tissues such as the heart, pancreas, and nervous system, tissue stem cells that can proliferate in response to tissue damage remain quiescent otherwise. However, in some tissues like bone marrow, liver, digestive system, and adipose tissue, they not only respond to tissue damage but also play a role in normal tissue turnover. In ophthalmological diseases, MSCs derived from adipose tissue and bone marrow are more commonly used. Especially, MSCs from adipose tissue are preferred because they can be easily obtained from subcutaneous fat tissue.[3] iPSCs are stem cells produced from adult somatic cells that exhibit functions similar to ESCs. Human iPSCs were first produced by Yamanaka and his colleagues.[4] The advantage of iPSCs is that they eliminate the need for a donor since they can be used autologously, and like ESCs, they have a broad differentiation capacity. However, their use is limited due to the unpredictability of complications such as tumor formation associated with genetic instability.[5]

Stem cells support tissue regeneration in target tissues and exhibit anti-inflammatory, immunomodulatory, proangiogenic and antiangiogenic, anti-apoptotic, and anti-aging effects. Stem cell therapies were first used in the 1950s and have been tested in almost every field of medicine.[6] In terms of eye diseases, stem cell treatments are being tried in degenerative diseases that result in irreversible cell damage and in tissue damage caused by mechanical, chemical, or thermal traumas, where conventional treatments have not been satisfactory. Some study results are promising. Stem cell therapies have found a wide range of applications in ophthalmology, from periocular stem cell applications to inherited retinal diseases. The small amount of stem cells required for application and the immune privilege of the eye make stem cell therapies easier

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to implement.[7] Stem cells can be applied to the eye as topical drops, through amniotic membrane, or using scaffolding tissues produced by bioengineering studies. Additionally, there are subconjunctival, intrastromal, intracameral, intravitreal, suprachoroidal, and systemic applications available. Although exciting results have been obtained in studies, widespread clinical applications of stem cells that have been approved by local authorities are still not available. Moreover, the costs of stem cell applications and the unknown long-term outcomes of treatments also limit the use of stem cell therapies. In this review we will discuss the use of stem cells in ophthalmological diseases.

OCULOPLASTY AND PERIOCULAR DISEASES

Stem cell applications around the eyes have gained popularity primarily for cosmetic and anti-aging purposes. Hyaluronic acid and collagen are widely used for cosmetic purposes. Recent studies have shown that wrinkles around the eyes decrease, and eyelids regain their former appearance after the injection of autologous adipose-derived stem cells.[8] In addition to cosmetic applications, stem cell treatments can also be applied to periocular tissues and eyelids in cases of tissue defects caused by various mechanical traumas, non-healing wounds, and burn-related injuries. In the past two decades, MSCs have been frequently tested for deep skin burns. In some centers in our country, case reports have been presented where fat tissue-derived stem cell treatments following severe facial burns led to the recovery of the eyelids in a way that allowed them to maintain normal function.[9] The main pathology in non-healing wounds is impaired tissue circulation and uncontrolled release of inflammatory agents. Stem cells, with their anti-inflammatory effects, can promote wound healing by providing immunoregulation and regulating vascularity in skin tissues.[10] In chronic wounds of the periorbital skin, stem cells can be an effective alternative in addition to traditional treatments. To optimize the effectiveness of stem cells in tissue defects, bioengineering studies have emerged. Biomaterials have been developed to serve as an extracellular matrix for stem cells.[11] The use of these biomaterials has increased the efficacy of stem cells in target tissues and improved tissue healing levels.

CORNEA AND OCULAR SURFACE DISEASES

In corneal and ocular surface diseases, the most popular stem cell applications are limbal stem cell transplantation and, although not a direct stem cell application, amniotic membrane transplantation. The amniotic membrane is separated from the placenta by blunt dissection after washing the placenta, obtained from an elective cesarean section, with various antibiotics. The epithelial surface is placed upward on nitrocellulose paper and cut to the required size. It is then stored in sterile containers containing glycerol at -80°C. The amniotic membrane graft is placed on the relevant ocular surface with the epithelial side facing upward and fixed with sutures of various sizes. The amniotic membrane, containing growth factors, accelerates tissue healing, enhances epithelial regeneration, and reduces scar formation.[12] Due to these properties, it is widely used in cases such as non-healing corneal ulcers and infections. Recently, the amniotic membrane has also been used as a carrier for stem cell therapies on the ocular surface.[13] Limbal stem cell deficiency can occur in diseases with systemic mucosal involvement, such as Stevens-Johnson Syndrome, chemical or thermal eye burns, or mechanical trauma. Limbal stem cells play a crucial role in maintaining the continuity of the corneal epithelium and its regeneration capability, and their deficiency can lead to severe vision loss.[14] In patients with unilateral eye involvement, autologous limbal stem cell transplantation can be performed from the other eye. In cases of bilateral involvement, allogeneic limbal stem cell transplantation from close family members can be performed.[15] Applications of cultured limbal stem cells have also shown successful outcomes.[16] As an alternative to limbal stem cells in ocular surface diseases, MSCs derived from adipose tissue or bone marrow are used. The most commonly used method in limbal stem cell transplantation is the simple limbal epithelial stem cell transplantation method. In this technique, a minimal amount of limbal tissue is taken from the donor eye and applied to the recipient eye's cornea, with the cornea being covered by an amniotic membrane. The covering of the cornea with the amniotic membrane facilitates the effective in vivo spread of the transplanted stem cells. The simple limbal epithelial stem cell method eliminates the need to take large amounts of tissue from the donor. The advantage of these stem cells is that they are easily obtainable, eliminating donor limitations.[17]

Additionally, iPSCs are being investigated for use in corneal diseases. iPSCs can form the three different cellular layers of the cornea: epithelium, stroma, and endothelium. These properties make stem cells a promising alternative treatment for full-thickness corneal diseases requiring transplantation and for corneal dystrophies.[18] Intrastromal MSC applications are also being studied in relatively common corneal diseases like keratoconus, and the initial results appear promising. Increased stromal collagen production has been reported after intrastromal stem cell application in patients with keratoconus.[19] In patients with dry eye disease, treatments involving the application of topical drops containing MSCs to the ocular surface and the injection of stem cells into the lacrimal gland have shown successful results.[20] Studies have also shown that in patients with bullous keratopathy, corneal clarity was restored, and there was a significant increase in corneal endothelial cells after injections of cultured human corneal endothelial cells into the anterior chamber.[21] Stem cell therapy is also being explored for the treatment of corneal opacities caused by mucopolysaccharidoses, as well as for the treatment of corneal scars and neovascularization due to various causes, with promising results.[22]

GLAUCOMA

Glaucoma is one of the leading causes of permanent vision loss worldwide. It is a progressive optic neuropathy characterized by the loss of retinal ganglion cells. The most significant risk factor for glaucoma is elevated intraocular pressure (IOP). Traditional treatments for glaucoma have focused on regulating IOP. Both topical drops and various systemic medications are widely used as antiglaucoma treatments. Additionally, various laser therapies and surgical methods for glaucoma are applied in patients with limited response to medical treatment.[23] While these widely used treatments effectively lower IOP, retinal ganglion cell damage remains irreversible and untreated. In some patient groups, cellular damage continues to progress despite all these treatments. Stem cell applications in glaucoma

patients have primarily focused on two areas: first, the retinal ganglion cell damage and neuropathy that result from all types of glaucoma; and second, the dysfunction of human trabecular meshwork cells, which plays a role in the pathophysiology of primary open-angle glaucoma. Since traditional treatments cannot reverse cell damage, alternative therapies capable of cell regeneration and slowing the progression of neuropathy have been sought. Currently, there is no accepted neuroprotective treatment for glaucoma. Various stem cell studies have shown that retinal ganglion cell neuroprotection can be achieved. It has been demonstrated that the most critical factor in retinal ganglion cell damage in glaucoma is the lack of neurotrophic factors, and that stem cell application provides neurotrophic factors at levels sufficient to reduce ganglion cell damage.[24] ESCs, iPSCs, and MSCs have each been tested in the treatment of glaucoma-related neuropathy. While human studies are limited, promising results have been obtained in experimental animal models.

In the pathophysiology of primary open-angle glaucoma, resistance to aqueous outflow in the trabecular meshwork plays a role.[25] Experimental studies have shown improvement in trabecular meshwork function following the injection of adipose-derived MSCs into the anterior chamber.[26] Similarly, the introduction of iPSC-derived trabecular meshwork cells into the anterior chamber has been found to improve trabecular meshwork function.[27] In stem cell applications for glaucoma patients, bone marrow-derived and adipose-derived MSCs are more frequently preferred due to their easy accessibility and the possibility of autologous application. These stem cell studies, which could provide an alternative for the treatment and control of glaucoma progression, are currently limited to animal experiments, and data on their long-term effects and safety remain limited.

RETINAL DISEASES

The retina is a crucial component of the visual function, as it processes the image received by the eye and transmits it to the central nervous system. Numerous systemic diseases and medications can affect retinal tissue. Among the systemic diseases that affect the retina, diabetes is the most prominent. Diabetic retinopathy (DR) is considered one of the degenerative retinal diseases, along with various other retinal disorders. Degenerative retinal diseases are characterized by irreversible cell damage in the retina, which has a multilayered structure. The leading disease in this group is age-related macular degeneration (AMD), which is the most significant cause of irreversible vision loss in individuals over 60 years of age in developed countries. AMD is classified into two types: neovascular and non-neovascular. In a specific subset of patients, intravitreal anti-vascular endothelial growth factor injections can control the disease to some extent, but both dry and wet types can ultimately result in geographic atrophy or scar tissue formation due to neovascularization. Some biologic agents recently approved by the FDA for geographic atrophy have been introduced, but treatment options remain limited once irreversible damage occurs. Retinitis pigmentosa (RP), Stargardt disease (SD), and other retinal dystrophies are also included in the group of degenerative retinal diseases, with no established treatments currently available to halt or reverse the degenerative process. Given the irreversible and progressive nature of retinal diseases and the limitations of traditional treatments, stem cell therapies have emerged as an alternative and highly researched field. Gene therapies, which also hold great potential for degenerative retinal diseases, are a subject of their own.

In DR, traditional treatments include laser photocoagulation, anti-VEGF agents, steroid implants, and vitrectomy. However, in some patients, neovascularization and progressive retinal cell damage continue despite these treatments. Stem cell therapies in DR primarily aim to limit neovascularization and restore retinal cell damage. In experimental models of DR in mice, the injection of endothelial progenitor cells derived from healthy humans showed improvements in retinal microvascular damage in both acute and chronic vascular injury.[28] Studies have also demonstrated that the application of photoreceptor cells derived from ESC can improve photoreceptor cell function in the target tissue. Additionally, adipose-derived stem cells and other MSC therapies have been investigated for their potential to restore both vascular damage and retinal cell damage in DR, with some studies yielding positive results.[29]

In AMD, stem cell therapies have focused primarily on restoring and replacing the retinal pigment epithelium (RPE). To this end, retinal stem cells obtained from donor retinas, induced pluripotent stem cells (iPSCs) that differentiate into RPE cells, and human ESCs have been used. The first transfer of RPE cells in humans was performed by Peyman and colleagues.[30] Although the initial applications resulted in significant complications, this study was a major milestone for future research. Today, various autologous and allogeneic stem cell studies continue intensively in AMD, with ESCs and iPSCs being preferred, while trials with MSC have led to relatively more complications. Moreover, in stem cell applications for AMD, subretinal application has been preferred over intravitreal application, but this method is more invasive and prone to complications.[31]

Stem cell applications also hold significant interest as a research area in hereditary retinal diseases. RP, SD, and many other hereditary retinal diseases currently lack an accepted treatment. Gene therapies and stem cell treatments are promising in this group of diseases. The general goal of stem cell treatments in hereditary retinal diseases is to prevent cell apoptosis and restore damaged cells. ESCs, iPSCs, and MSCs have been tested in various studies. Several stem cell studies, particularly for RP and SD, have been conducted and are ongoing in Turkey.[32,33] Long-term stem cell treatment in RP has been shown to provide only limited improvement. Furthermore, in addition to intravitreal and subretinal stem cell applications, supracoroidal injection has recently been described. This newly defined method is less invasive thanks to the use of micro-needles, and the injection contents exhibit a longer-lasting effect in the supracoroidal space. In subretinal application, after performing pars plana vitrectomy, varying amounts of stem cells are injected into the subretinal space around the damaged tissue. The widely used technique for supracoroidal application is the Limoli retinal restoration technique. In this technique, the globe is deviated superonazally, and a sclerotomy is performed until the choroidal color is visible in the inferotemporal region. The tissue carrying the stem cells is placed onto the choroid, and the scleral flap and the tissues above it are sutured appropriately.[34] Another research area in stem cell studies for retinal diseases involves the development of three-dimensional retinal organoids from iPSCs and their use to achieve functional capacity in the target tissue.[35]

OPTIC NEUROPATHIES

Optic neuropathies are a broad group of disorders characterized by impaired optic nerve function and optic nerve abnormalities. While they may primarily be related to the optic nerve itself, optic neuropathies can also develop secondary to infectious, inflammatory, and various systemic diseases. Glaucoma, discussed in previous sections, is one of the leading causes of optic neuropathy. In addition to systemic causes, there are also hereditary optic neuropathies. The most common hereditary forms include Leber's Hereditary Optic Neuropathy (LHON) and Autosomal Dominant Optic Atrophy (ADOA). A common feature of all these diseases is retinal ganglion cell damage. Causes of demyelinating optic neuropathy include neuromyelitis optica (NMO), multiple sclerosis (MS), and other autoimmune demyelinating diseases.[36] In an experimental study involving patients with NMO, systemic clinical improvement was observed after intravenous MSC application, along with an increase in RNFL thickness.[37] Additionally, there are studies in NMO patients where peripheral hematopoietic stem cells have been tested. LHON is a mitochondrial disease characterized by retinal ganglion cell damage due to oxidative stress. To reverse mitochondrial dysfunction in LHON, iPSCs and bone marrow-derived stem cells have been tested in humans, with reported improvements in visual acuity.[38]

Non-arteritic anterior ischemic optic neuropathy (NAION) is one of the most common acute optic neuropathies, with acute ischemia-induced optic nerve damage as the underlying pathophysiology. Various types of stem cells and different administration methods have been tested in mouse models of NAION, with positive results obtained.[39] Additionally, a clinical study involving NAION patients showed improvement in visual acuity in the majority of participants.[40] Traumatic optic neuropathy is the irreversible damage to the optic nerve caused by various types of trauma. In experimental mouse models and some human studies, stem cell applications have.[41]

STEM CELL SOURCES FOR OPHTHALMIC USE

Stem cells used in ophthalmological treatments can be obtained from ocular tissues, peripheral blood, bone marrow, adipose tissue, and embryonic tissues. Ocular tissues contain stem cells in the cornea, conjunctiva, trabecular meshwork, ciliary body, lens, retina, and choroid. Stem cells are found in the Vogt palisades of the corneal limbus. Limbal stem cells play a role in the regeneration of the corneal epithelium and are commonly used in cases of limbal stem cell deficiency.[42] The anterior stroma of the cornea also contains stem cells. The stem cells located in the corneal stroma play an important role in maintaining the organization and transparency of the cornea. The therapeutic use of these stem cells is limited to laboratory studies.[43] Conjunctival stem cells are located in the bulbar conjunctiva and can be frequently used in ocular surface disorders.[44] Iris pigment epithelial cells exhibit stem cell activity, and experimental studies on the use of these stem cells are ongoing. Stem cells have also been identified in the ciliary body and trabecular meshwork, and research on their use is in the experimental phase.[45-47] The lens capsule contains stem cells that play a role in maintaining the transparency of the lens, and their deficiency can lead to cataracts and other lens pathologies.[48] Retinal pigment epithelial (RPE) cells exhibit stem cell activity. Abnormalities in RPE cells play a role in the pathophysiology of various retinal diseases, such as retinal dystrophies, RP, and AMD. Retinal stem cell transplants are frequently used in retinal dystrophies and degenerative retinal diseases.[49]

In addition to stem cells obtained from ocular tissues in ophthalmology, other types of stem cells obtained from different tissues can also be used. Induced pluripotent keratinocytes (iPKH) are obtained from adult somatic cells and can be transformed into corneal epithelial cells, RPE cells, photoreceptor cells, and retinal ganglion cells using various transcription factors, making them useful for ophthalmological diseases.[50] Although human studies are limited, and the possibility of tumor development in the long term cannot be predicted, research continues as a promising alternative treatment. MSC derived from adipose tissue can be easily and minimally invasively obtained from peripheral adipose tissue, including fat tissue from the eyelid, during eyelid surgery.[51] These adipose tissue-derived stem cells exhibit MSC activity and can be applied periocularly, to the ocular surface, and intraocularly. Hematopoietic stem cells, bone marrow-derived stem cells, central nervous system stem cells, and ESCs are also used as sources of stem cells. Stem cells used in each ophthalmological disease represent a broad field of research, and studies on the use of stem cells in ophthalmological diseases continue to increase worldwide. Although the unpredictability of long-term effects remains the biggest concern, stem cells appear to be a promising part of future clinical practice in various ophthalmological diseases.

ETHICAL DECLARATIONS

Referee Evaluation Process

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Conflict of Interest Statement

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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

Case Report

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Enhanced diagnosis of superior branch retinal vein occlusion with collateral vessels using optical coherence tomography angiography: a case study

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ABSTRACT

A 41-year-old woman was referred to our hospital because of decreased vision in the right eye. Fundus examination revealed microaneurysms, venous compression, empty veins, and formation of collateral vessels distal to the occlusion, which were diagnosed as superior branch retinal vein occlusion (BRVO). Collateral vessels, originating from the intermediate and deep capillary plexuses, were determined using optical coherence tomography angiography (OCTA) imaging. OCTA can play an important role in BRVO diagnosis and the evaluation of microvasculature architecture. This case emphasizes the important diagnostic capabilities of OCTA in visualizing microvascular changes, such as collateral vessels, foveal avascular zone (FAZ) changes, and capillary nonperfusion.

Keywords: Branch retinal vein occlusion, collateral vessels, optical coherence tomography angiography

INTRODUCTION

BRVO is a common retinal vascular disease. The major causes of visual impairment include varying degrees of retinal hemorrhage, retinal ischemia, and macular edema. The pathophysiology of BRVO involves arteriovenous crossing-related venous compression and subsequent occlusion. Capillary nonperfusion, vascular leakage, and macular edema eventually occur. Collateral vessel formation is an adaptive response observed in response to vascular blockage; its purpose is to restore blood flow and reduce ischemia.[1] We present a case of superior BRVO, focusing on collateral vessel formation and retinal microvasculature changes, using OCTA imaging.

CASE

A 41-year-old female patient was admitted to our clinic with a history of decreased vision in her right eye for more than 6 months. She denied any systemic comorbidities except for hypertension. On examination, the best-corrected visual acuity (BCVA) was 20/200 in the right eye (OD) and 20/20 in the left eye (OS). Intraocular pressure (IOP) was 14 mmHg on the right and 15 mmHg on the left. The anterior segment examination via slit-lamp biomicroscopy was normal. Dilated fundus examination of the right eye revealed arteriovenous crossings with venous compression and microaneurysms. Additionally, an empty vessel distal to the occlusion site was observed in the superior vascular arcade, which is indicative of vascular stasis (Figure 1a). These findings were compatible with a possible diagnosis of BRVO. Further diagnostic evaluations, including optical coherence tomography (OCT) and fluorescein angiography (FA), were planned to confirm the diagnosis and assess the extent of retinal involvement. OCT revealed a cystic appearance temporal to the fovea and macular thickening, consistent with macular edema secondary to vascular occlusion. FA of the right eye showed filling defects in the superior branch retinal vein, with collateral vessel formation distal to the occlusion site (Figure 1b, 1c). Additionally, mild FAZ enlargement was noted. OCTA demonstrated the collateral vessels very well, clearly showing their origin from the deep and intermediate capillary plexuses (Figure 1d). In the deep capillary plexus, shunt vessels appeared brighter or more prominent on OCTA images. This appearance was different from that of neovascularization, which has a more irregular and diffuse appearance.

DISCUSSION

Retinal vein occlusion is an important cause of vision loss. Macular edema is the main cause of deterioration in patients with BRVO.[1] Acute phase retinal vein occlusion causes macular edema, rupture of vessel walls, and intraretinal hemorrhages. Chronic phase microvascular changes include capillary dilation, nonperfusion, microvascularization, collateral formation, and retinal vascularization.[2] Studies have shown that the size of the FAZ, retinal vessel density, and capillary perfusion are

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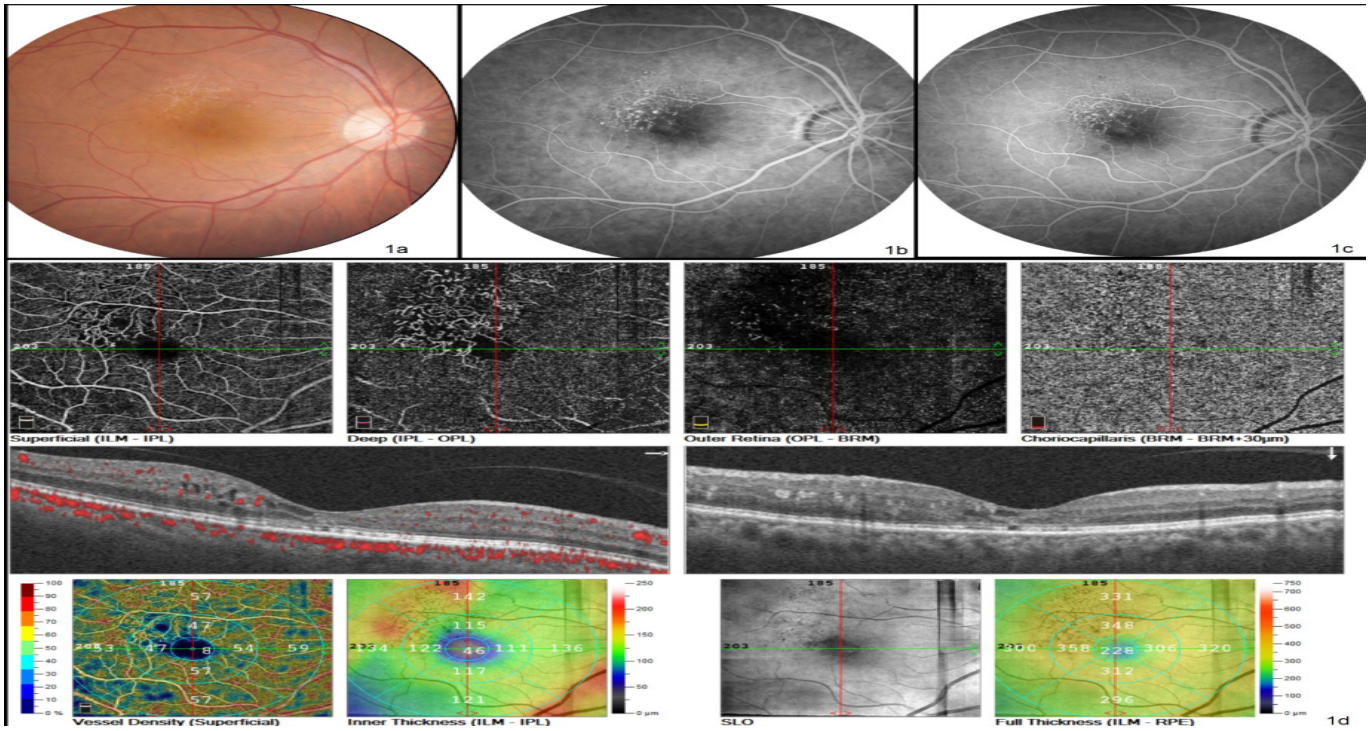

Figure 1a. Colored fundus photograph of the right eye; arteriovenous crossings with venous compression, microaneurysms, and an empty vessel distal to the superior vascular arcade. **1b-c.** Fluorescein angiography of the right eye; filling defects in the superior branch retinal vein with collateral vessel formation distal to the occlusion site. **1d.** Optical coherence tomography angiography of the right eye; the collateral vessels very well and clearly showing their origin from the deep and intermediate capillary plexuses

important determinants of visual outcomes. FAZ enlargement and decreased vascular density in the deep capillary plexus are major predictors of vision disability in BRVO.[3] FA is a gold standard for the diagnosis. However, it has certain limitations; for instance, it is an invasive procedure, carries a risk of allergic reactions to fluorescein, and provides inadequate visualization of deeper retinal layers owing to dye pooling and leakage.[1] OCTA can provide retinal and choroidal microvasculature in a non-invasive manner. In addition, collateral vessel formation can be easily detected with OCTA in contrast to FA.

This case demonstrated retinal microvasculature changes and collateral formation within specific layers, as visualized using OCTA.[2,4] In our case, the mild enlargement of the FAZ and decrease in perfusion correlated with a decrease in visual acuity. In fact, collateral vessels develop as a corrective response to bypass occluded veins, with a predilection for the deep capillary plexus. Vessel formation is associated with the extent of ischemia (non-perfused area) and the amount of congested venous blood.[4] Collateral vessels develop from preexisting capillary networks. In this manner, it reduces venous pressure and allows perfusion. They are generally located around the FAZ and temporal watershed areas.[5] However, the presence of these vessels often correlates with worse anatomical outcomes, such as persistent macular edema and greater central macular thickness (CMT). Venous collaterals appear as large, well-defined vessels that cross the intermediate and deep layers. These are compensatory and should be distinguished from retinal neovascularization, which appears more irregular and tuft-like. These collaterals form a bypass for venous blood flow to reroute around the occlusion, reducing venous congestion and alleviating ischemic damage. Their presence suggests chronic BRVO, and they generally do not require treatment unless associated with complications, such as macular edema.[2,5]

Previous studies have emphasized that collateral vessels do not leak. However, Suzuki et al.[2] demonstrated that leakage may occur in microaneurysms associated with the collateral vessels. Additionally, Suzuki et al.[2] suggested that collateral vessels may influence the recurrence and persistence of macular edema owing to the presence of collateral-associated microaneurysms. Arrigo et al.[1] suggested that eyes affected by BRVO are more likely to develop OCTA-detectable collateral vessels when macular ischemia is more severe. The treatment choice for BRVO-related macular edema is the intravitreal injection of antivascular endothelial growth factor (anti-VEGF). Leakage related to collateral-associated microaneurysms is refractory to anti-VEGF therapy. Suzuki et al.[2] stated that targeting leaky microaneurysms is an effective treatment option and can significantly reduce macular edema. Therefore, personalized diagnostic and treatment approaches are required. This case emphasizes the prognostic aspects of OCTA parameters, including vessel density, FAZ size, and the presence of collateral vessels. RVO-associated macular edema may be refractory to treatment. In such cases, OCTA may provide valuable diagnostic and prognostic information regarding the microvascular system.

CONCLUSION

In conclusion, this case demonstrates the potential contribution of OCTA in the analysis of patients with BRVO. These results have important implications for understanding disease severity and visual prognosis, including enhanced collateral vessel formation, vascular density changes, and altered FAZ size. Hence, the BRVO study should incorporate advanced imaging into standard care to improve patient outcomes and individualized treatment options.

ETHICAL DECLARATIONS

Informed Consent

The patient signed and free and informed consent form.

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

Letter to the Editor

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Comment "clinical presentation, diagnosis, complications, and treatment of obstructive sleep apnea syndrome"

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Keywords: Obstructive sleep apnea syndrome, polysomnography, neurocognitive impairments

Dear Editor,

I have read the article "clinical presentation, diagnosis, complications, and treatment of obstructive sleep apnea syndrome" by Bilgin G. with great interest. This comprehensive review provides valuable insights into the multifaceted aspects of obstructive sleep apnea syndrome (OSAS).[1] I commend the author for the depth of analysis and for addressing diagnostic challenges and therapeutic approaches.

The emphasis on polysomnography (PSG) as the gold standard for diagnosing OSAS is commendable. However, with the increasing use of home sleep apnea testing (HSAT), comparing the efficacy of PSG and HSAT could provide additional perspectives, especially for resource-limited settings. Such discussion would highlight advancements that make OSAS diagnosis more accessible globally.

While the therapeutic role of continuous positive airway pressure (CPAP) was thoroughly explored, I believe further elaboration on the long-term impact of lifestyle interventions, such as weight management and positional therapy, could enhance practical applicability for patients who struggle with CPAP compliance.

Moreover, the brief mention of neurocognitive impairments due to OSAS opens an important area of discussion. Expanding on the potential links between OSAS and long-term neurocognitive outcomes, including vascular dementia and Alzheimer's disease, could strengthen the importance of early diagnosis and management.[2]

I deeply appreciate the author's meticulous synthesis of current knowledge on OSAS and the structured presentation of findings, particularly the concise tables summarizing key symptoms and complications. This article is a valuable resource for clinicians and researchers in advancing the understanding and management of OSAS.

Thank you for considering my comments. I look forward to further discussions on this important topic.

Sincerely.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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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

Letter to the Editor

Author reply "clinical presentation, diagnosis, complications, and treatment of obstructive sleep apnea syndrome"

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Dear Editor,

I would like to thank you very much for the positive comments on the article titled clinical presentation, diagnosis, complications and treatment of obstructive sleep apnea syndrome. I would like to thank you very much for the words of appreciation for the depth of analysis, diagnostic difficulties and treatment approaches, polysomnography, and tables summarizing the main symptoms and complications.

I agree that a more detailed explanation of the long-term effects of life interventions such as weight management and positional therapy could be more practical for patients who have difficulty with CPAP compliance. I believe that researching OSAS and neurocognitive outcomes such as vascular dementia and Alzheimer's disease will strengthen early diagnosis and treatment.

I would like to thank you again for the positive contributions written on this subject.

Best regards.