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The effect of corticosteroid use in septic shock on secondary infection frequency, microorganism species, morbidity, and mortality

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Abstract

Aim: We aimed to examine the effect of corticosteroid treatment in vasopressor-refractory septic shock on secondary infections, microorganism species, survival, and length of hospital stay.

Material and methods: In this observational study, the records of 108 septic shock patients admitted to the intensive care unit (ICU) were reviewed. Patients were divided into two groups: the corticosteroid group (Group S, n=60) and the non-corticosteroid group (Group S-0, n=48). The results of three cultures [blood, endotracheal aspirate (eta), urine, wound] taken after ICU admission were recorded. The groups were compared in terms of demographic characteristics, culture growth rates and microorganisms, length of hospital stay, and survival rates.

Results: The hospital (p=0.043) and ICU stay (p=0.035) were longer in Group S. There was no significant difference between the groups in terms of survival (p>0.05). The growth rate of the first urine culture was significantly higher in Group S-0 than in Group S (p=0.018), but there was no difference in terms of microorganism species (p>0.05). There was no significant difference in growth rates and microorganism species in blood, eta and wound cultures (p>0.05), but increase in growth rates were observed in the 2nd and 3rd eta and, wound cultures compared to first culture in Group S (p<0.05).

Conclusion: There was no difference between the patients who received and did not receive corticosteroid treatment in septic shock in terms of culture growth rates, growing microorganism species and mortality; however, the frequency of growth in eta and wound cultures increased and the length of hospital stay was longer in patients who received corticosteroids.

Key words: septic shock, corticosteroid, secondary infection, mortality, morbidity

Introduction

Sepsis, a condition characterized by organ dysfunction resulting from an irregular response of the host to the infectious agent, requires immediate initiation of antibiotic therapy and administration of at least 30 mL/kg of intravenous crystalloid fluid support and colloid albumin within the first 3 hours from diagnosis [1]. However, in more severe cases, despite fluid support, septic shock may develop, which necessitates vasopressor therapy. Septic shock is defined as persistence hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) 65 mmHg or higher and a serum lactate level greater than >2 mmol/L despite adequate fluid resuscitation. Corticosteroid therapy is recommended as additional treatment in cases of vasopressor-refractory hypotension or the need for an increase in vasopressor dose in septic shock [1-3].

Glucocorticoids are steroid hormones secreted from the adrenal glands in a daily rhythm or during stress. They are both naturally produced in the body and synthetically manufactured. Cortisol is the most important glucocorticoid secreted in humans. Cortisol

is the primary corticosteroid released from the adrenal cortex. Critical illness can affect cortisol levels and function. The use of corticosteroids in septic shock is based on the possibility of developing a relative adrenal insufficiency due to impaired cortisol secretion and function, which needs to be replaced. The aim of corticosteroid therapy in septic shock is to correct the hypothalamic-pituitary-adrenal axis and to target clinical hemodynamic improvement [4]. Glucocorticoids also reduce inducible nitric oxide and prevent endogenous vasodilation, contributing to the vasopressor response produced by catecholamines. Furthermore, in septic shock, the administration of corticosteroids aims to reduce pro-inflammatory cytokines by taking advantage of their immunosuppressive and anti-inflammatory properties [5]. After binding to glucocorticoid receptors, a conformational change occurs in the receptor. Glucocorticoids inhibit transcription factors that regulate proinflammatory mediators. Their another important effects are inhibition of phospholipase A2, which is responsible for production of inflammatory mediators and suppressing genes responsible for expression of pro-inflammatory cytokines and various interleukins [6].

The recommended synthetic corticosteroid dosage in septic shock is hydrocortisone (200 mg/day) [2,3]. However, if hydrocortisone is not available, an equivalent dose of methylprednisolone can be administered. There is no definitive evidence showing that any corticosteroid drug or treatment (bolus or infusion) is more effective than the others in reducing mortality in septic shock [7].

In the literature, there are studies linking the use of corticosteroids in septic shock to the development of multisystemic adverse effects, as well as secondary infections that may arise due to immunosuppression [3,4]. Systemic corticosteroid therapy is associated with an increase risk of bacterial, viral, and fungal infections due to its dose-dependent inhibitory effects on phagocyte function. Also, intensity of therapy and several patient-specific factors such as older age, lower functional status and concomitant immunosupressive therapy influence infection risk. However, some studies have shown that the use of corticosteroids in septic shock does not affect the development of secondary infections [8,9]. Since there are different results in the literature regarding whether the use of corticosteroids in septic shock increases the incidence of secondary infections, the primary objective of our study was to determine whether corticosteroid therapy in septic shock increases the incidence of secondary infections and effects the microorganisms that grow in cultures. The secondary objective was to examine whether corticosteroid therapy influences the length of hospital stay and survival.

Material and methods

After obtaining approval from the Hospital Ethics Committee (E2-22-2188/2022), the hospital records of 150 adult patients over the age of 18 who had been hospitalized in the ICU with a diagnosis of septic shock between January 2016 and December 2017 were retrospectively reviewed. Patients who had been hospitalized for more than a week, who had no previous history of corticosteroid or other immunosuppressive treatment were included in the study. Patients who had stayed in the ICU for less than one week and those who had previously received immunosuppressive or corticosteroid therapy were excluded from the study.

Septic shock diagnoses and the recommendation of corticosteroid therapy were evaluated using the 2016 sepsis guidelines. Patients who received vasopressor therapy due to septic shock and did not achieve an average arterial pressure of 65 mmHg or systolic arterial pressure above 90 mmHg despite fluid and vasopressor therapy, were evaluated in terms of administering corticosteroid treatment (recommendation of guideline: 200 mg/day IV hydrocortisone or 40 mg/day IV methylprednisolone infusion). Corticosteroid doses were reduced when their vasopressor requirements decreased, and discontinued about total 7-10 days. Patients who included the study were divided into two groups: patients in septic shock who were given corticosteroid therapy (the corticosteroid group- Group S) and who were not given corticosteroid therapy (the non-corticosteroid group- Group S-0).

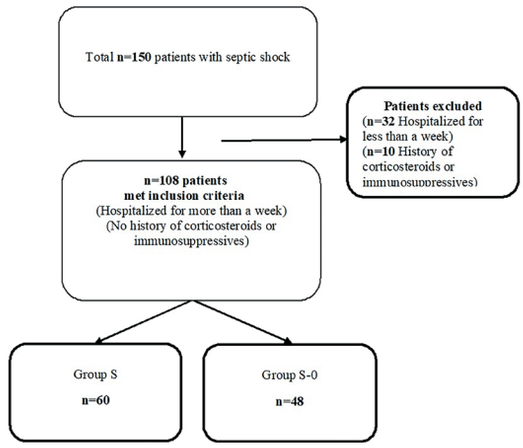
The demographic characteristics, comorbidities, length of ICU and hospital stay, and survival status (death or discharge) of the patients were retrospectively analyzed from the hospital records. The first three culture results obtained within the 28-day period following ICU admission were retrospectively recorded in chronological order. Microorganisms growing in cultures obtained from peripheral blood, blood obtained from a central venous catheter (referred to as the catheter culture), endotracheal aspirate (eta), urine, and wound (taken from decubitus ulcers or surgical incision areas of patients) were screened. Cultures taken from other body fluids (stool, pleural fluid, ascites, cerebrospinal fluid, rectal swabs) were excluded from the study as they were of limited quantity and not homogeneously distributed. The first cultures obtained from the patients were evaluated as cultures examined to determine the microorganisms causing infection, as they were taken upon admission of patients diagnosed with septic shock. The second and third cultures were taken during patients' hospitalization, upon the development of new fever, increase in acute phase reactants, and worsening clinical course. The first cultures obtained from the patients were labelled as blood-1, urine-1, catheter-1, wound-1, eta-1, the second cultures were labelled as blood-2, urine-2, catheter-2, wound-2, eta-2, and the third cultures were labelled as blood-3, urine-3, catheter-3, wound-3, eta-3. Microorganisms growing in these cultures were recorded. The patients' antimicrobial treatments were prescribed in collaboration with an infectious disease specialist, and the daily assessment of clinical and laboratory findings, as well as antibiotic susceptibility tests, was conducted. The potential side effects associated with corticosteroids, such as hypernatremia, hyperglycaemia, gastrointestinal bleeding, and cardiac events, were also recorded.

The data analysis was performed using IBM SPSS 23.0 (IBM. Corp. released 2015. IBM SPSS Statistics for windows, Version 23.0. Armonk, NY: IBM Corp.) statistical software package. Power analysis was conducted using G*Power 3.1.9.2 (Faul, F., Erdfelder, E., Buchner, A., & Lang, A.G., 2014. Germany: University of Kiel) statistical software package, and the power was determined to be 0.98, with n1=48, n2=60, α=0.05, and effect size d=0.8. Descriptive statistical methods such as frequency, percentage, mean, and standard deviation were used to evaluate the study data, as well as Pearson chi-square, Yates chi-square, and Fisher exact tests were used to compare qualitative data depending on the situation. The conformity of the data to normal distribution was evaluated by Kolmogorov-Smirnov test. Independent samples T test (independent samples T test) was used to evaluate the normally distributed quantitative data. Inter-temporal comparisons of cultures were performed by McNemar's Test. Statistically significance level of $p<0.05$ was considered.

Results

Among 150 patients, ultimately, 108 patients who met the inclusion criteria were included in the study. It was observed that the number of patients who were given steroid treatment was

Figure 1 - Flowchart of the Study



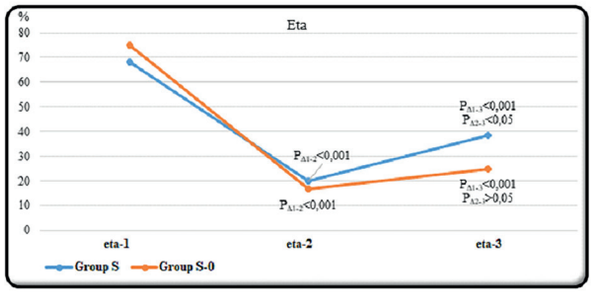
n=60 (Group S), and the number of patients who were not given was n=48 (Group S-0). The diagram of the study is presented in Figure 1. The mean age was significantly lower in Group S (68.1±18.1 years) than Group S-0 (76.3±12.5 years) (Table 1) (p=0.007). When comorbidities were examined, no significant differences were found between the groups in terms of cardiovascular disease, malignancy, and cerebrovascular disease (p>0.05) (Table 1). The length of hospital and ICU stay for patients in Group S (34.2±20.4 and 30.0±20.1 days) was found to be significantly longer than that in Group S-0 (27.5±20.2 and 23.0±13.7 days) (p=0.043, p=0.035). However, there was no significant difference between Group S (68.3%, n=41) and Group S-0 (75%, n=36) in terms of survival (p>0.05) (Table 1).

Table 1 Comparison of demographic and general characteristics of patients in groups

Variables	Groups		p value
	Group S (n=60)	Group S-0 (n=48)	
Age (year)	68.1±18.1	76.3±12.5	**0.007**
Length of ICU stay (day)	30.0±20.1	23.0±13.7	**0.035**
Length of hospital stay (day)	34.2±20.4	27.5±20.2	**0.043**
Renal Disease	13 (21.7)	7 (14.6)	0.456
Cardiovascular Disease	31 (51.7)	28 (58.3)	0.619
Malignancy	5 (8.3)	8 (16.7)	0.305
Cerebrovascular Disease	17 (28.3)	12 (25.0)	0.865
Lung Disease	20 (33.3)	5 (10.4)	**0.010**
Diabetes mellitus	5 (8.3)	13 (27.1)	**0.019**
Survival Death Discharge	41 (68.3) 19 (31.7)	36 (75.0) 12 (25.0)	0.584

Data are presented as mean ± SD and [n (%)]. p<0.05 is statistically significant. Group S: corticosteroid group, Group S-0: non-corticosteroid group

Figure 2 - Intra-group comparison of eta cultures



Data are presented as mean ± SD and [n (%)]. P<0.05 is statistically significant. Group S: corticosteroid group, Group S-0: non-corticosteroid group. $P_{\Delta1-2}$: Comparison between 1st and 2nd cultures, $P_{\Delta2-3}$: Comparison between 2nd and 3rd cultures, $P_{\Delta1-3}$: Comparison between 1st and 3rd cultures

Table 2 Comparison of eta cultures of patients in groups

Cultures		Groups		p value
		Group S (n=60)	Group S-0 (n=48)	
Eta-1	**No growth**	19 (%31,7)	12 (%25,0)	0.584
	Growth	41 (%68.3)	36 (%75)	
	A.baumannii	*11 (%18.3)*	*12 (%25)*	
	P. aeruginosa	*6 (%10)*	*8 (%16.7)*	
	Klebsiella spp.	*5 (%8.3)*	*8 (%16.7)*	
	Candida spp.	*9 (%15)*	*3 (%6.3)*	
	Other	*5 (%8.3)*	*2 (%4.2)*	
	MRSS	*2 (%3.3)*	*1 (%2.1)*	
	S. marcescens	--	*2 (%4.2)*	
	Enterococcus spp.	*1 (%1.7)*	--	
	E.coli	*1 (%1.7)*	--	
	Aspergillus	*1 (%1.7)*	--	
Eta-2	**No growth**	48 (%80,0)	40 (%83,3)	0.846
	Growth	12 (%20,0)	8 (%16,7)	
	A.baumannii	*4 (%6.7)*	*4 (%8.3)*	
	P. aeruginosa	*2 (%3.3)*	*2 (%4.2)*	
	Klebsiella spp.	*4 (%6.7)*	--	
	Candida spp.	--	*2 (%4.2)*	
	E.coli	*1 (%1.7)*	--	
	Other	*1 (%1.7)*	--	
Eta-3	**No growth**	37 (%61,7)	36 (%75,0)	0.206
	Growth	23 (%38,3)	12 (%25,0)	
	A.baumannii	*6 (%10)*	*6 (%12.5)*	
	P. aeruginosa	*6 (%10)*	*2 (%4.2)*	
	Candida spp	*5 (%8.3)*	*3 (%6.3)*	
	MRSS	*2 (%3.3)*	*1 (%2.1)*	
	Klebsiella spp.	*2 (%3.3)*	--	
	E.coli	*1 (%1.7)*	--	
	Other	*1 (%1.7)*	--	

Data are presented as mean ± SD and [n (%)]. P<0.05 is statistically significant. Group S: corticosteroid group, Group S-0: non-corticosteroid group. Eta: endotracheal aspirate. spp: species, MRSS: methicillin-resistant Staphylococcus species, E. coli: Escherichia coli, A.baumannii: Acinetobacter baumannii, P. aeruginosa: Pseudomonas aeruginosa, S. marcescens: Serratia marcescens

The microorganisms that grew in the cultures of eta-1, eta-2, and eta-3 of the patients and their distribution among the groups are presented in Table 2. There was no significant difference between the two groups in terms of culture growth rates and isolated microorganism species (p>0.05). When intra-group comparisons of eta cultures were evaluated, a significant decrease in the growth of eta-2 cultures was determined compared to eta-1 in both groups (PΔ1-2<0.001, Figure 2). However, while there was an increase in both eta-2 and eta-3 culture growth in both groups, a statistically significant increase in eta-3 culture growth compared to eta-2 was observed in Group S (PΔ2-3<0.05, Figure 2). Comparison between eta-1 and eta-3 in both groups revealed a significant increase in eta-3 culture growth compared to eta-1 (PΔ1-3<0.001, Figure 2).

There was no statistically significant difference between the two groups in terms of culture growth rates and identified microorganism species in both blood-1, blood-2, and blood-3 cultures, as well as central venous catheter cultures (catheter-1, catheter-2, and catheter-3) (p>0.05, Table III). In addition, when intra-group comparisons of blood cultures and central venous catheter cultures were evaluated, a significant decrease was observed between the 1st, 2nd and 3rd culture growths in both groups (p<0.05 - p<0.001). Although there was a decrease in the 3rd culture growth compared to the 2nd culture, it was not statistically significant (p>0.05).

Table 3 Comparison of blood and central venous catheter cultures of patients in groups

Cultures		Groups		p value
		Group S (n=60)	Group S-0 (n=48)	
Blood-1	**No growth**	32 (%53,3)	22 (%45,8)	0.561
	Growth	28 (%46.7)	26 (%54.2)	
	MRSS	*15 (%25)*	*11 (%22.9)*	
	A.baumannii	*4 (%6.7)*	*3 (%6.3)*	
	Klebsiella spp.	*3 (%5)*	*3 (%6.3)*	
	Enterococcus spp.	*3 (%5)*	*3 (%6.3)*	
	P. aeruginosa	*1 (%1.7)*	*3 (%6.3)*	
	Candida spp.	*1 (%1.7)*	*1 (%2.1)*	
	Other	*1 (%1.7)*	*1 (%2.1)*	
	E.coli	--	*1 (%2.1)*	
Blood -2	**No growth**	46 (%76,7)	37 (%77,1)	0.959
	Growth	14 (%23,3)	11 (%22,9)	
	MRSS	*7 (%11.7)*	*2 (%4.2)*	
	A.baumannii	*2 (%3.3)*	*3 (%6.3)*	
	Enterococcus spp..	*1 (%1.7)*	*4 (%8.3)*	
	P. aeruginosa	*1 (%1.7)*	*2 (%4.2)*	
	Klebsiella spp.	*2 (%3.3)*	--	
	E.coli	*1 (%1.7)*	--	
Blood -3	**No growth**	52 (%86.7)	40 (%83.3)	0.832
	Growth	8 (%13.3)	8 (%16.7)	
	MRSS	--	*5 (%10.4)*	
	Enterococcus spp.	*2 (%3.3)*	*2 (%4.2)*	
	A.baumannii	*2 (%3.3)*	--	
	Other	*2 (%3.3)*	*1 (%2.1)*	
	Klebsiella spp.	*1 (%1.7)*	--	
	Candida spp.	*1 (%1.7)*	--	
Cathater-1	**No growth**	45 (%75)	36 (%75)	1.000
	Growth	15 (%25)	12 (%25)	
	MRSS	*9 (%15)*	*3 (%6.3)*	
	A.baumannii	*3 (%5)*	*5 (%10.4)*	
	Klebsiella spp.	*2 (%3.3)*	*1 (%2.1)*	
	E.coli	*1 (%1.7)*	*1 (%2.1)*	
	Candida spp.	--	*1 (%2.1)*	
	Other	--	*1 (%2.1)*	
Cathater-2	**No growth**	56 (%93.3)	45 (%93.8)	1.000
	Growth	4 (%6.7)	3 (%6.3)	
	A.baumannii	*2 (%3.3)*	*1 (%2.1)*	
	Candida spp.	*1 (%1.7)*	*1 (%2.1)*	
	Klebsiella spp.	--	*1 (%2.1)*	
	MRSS	*1 (%1.7)*	--	
Cathater-3	**No growth**	59 (%98.3)	48 (%100)	1.000
	Growth	1 (%1.7)	--	
	P. aeruginosa	*1 (%1.7)*	--	

Data are presented as mean ± SD and [n (%)]. p<0.05 is statistically significant. Group S: corticosteroid group, Group S-0: non-corticosteroid group. Eta: endotracheal aspirate, spp: species, MRSS: methicillin-resistant Staphylococcus species, E. coli: Escherichia coli, A.baumannii: Acinetobacter baumannii, P. aeruginosa: Pseudomonas aeruginosa

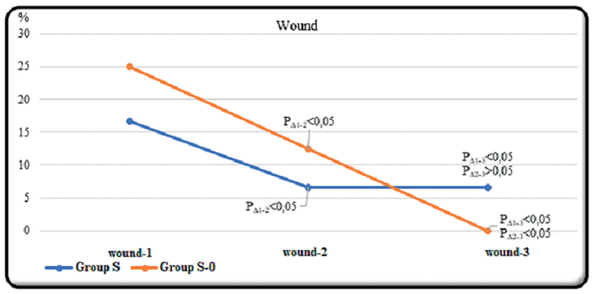
Table 4 Comparison of urine and wound cultures of patients in groups

Cultures		Groups		p value
		Group S (n=60)	Group S-0 (n=48)	
Urine-1	**No growth**	41 (%68.3)	21 (%43.8)	**0.018**
	Growth	19 (%31.7)	27 (%56.3)	
	Candida spp.	*7 (%11.7)*	*12 (%25)*	
	P. aeruginosa	*4 (%6.7)*	*5 (%10.4)*	
	E.coli	*3 (%5)*	*2 (%4.2)*	
	Klebsiella spp.	*2 (%3.3)*	*2 (%4.2)*	
	A.baumannii	*1 (%1.7)*	*2 (%4.2)*	
	Enterococcus spp.	--	*3 (%6.3)*	
	P.mirabilis	*2 (%3.3)*	--	
	Other	--	*1 (%2.1)*	
Urine-2	**No growth**	49 (%81.7)	36 (%75)	0.546
	Growth	11 (%18.3)	12 (%25)	
	Candida spp.	*6 (%10.0)*	*2 (%4.2)*	
	E.coli	*2 (%3.3)*	*4 (%8.3)*	
	A.baumannii	*2 (%3.3)*	*2 (%4.2)*	
	P. aeruginosa	--	*3 (%6.3)*	
	Klebsiella spp.	--	*1 (%2.1)*	
	Enterococcus spp.	*1 (%17)*	--	
Urine-3	**No growth**	57 (%95)	45 (%93,8)	1.000
	Growth	3 (%5)	3 (%6.3)	
	Candida spp.	*1 (%1.7)*	*1 (%2.1)*	
	P. aeruginosa	*1 (%1.7)*	--	
	Klebsiella spp.	--	*1 (%2.1)*	
	A.baumannii	*1 (%1.7)*	--	
	E.coli	--	*1 (%2.1)*	
Wound-1	**No growth**	50 (%83.3)	36 (%75)	0.408
	Growth	10 (%16.7)	12 (%25)	
	P. aeruginosa	*3 (%5)*	*4 (%8.3)*	
	A.baumannii	*3 (%5)*	*3 (%6.3)*	
	Klebsiella spp.	*2 (%3.3)*	*2 (%4.2)*	
	E.coli	*1 (%1.7)*	*1 (%2.1)*	
	Enterococcus spp.	--	*1 (%2.1)*	
	MRSS	*1 (%1.7)*	--	
	P.mirabilis	--	*1 (%2.1)*	
Wound-2	**No growth**	56 (%93.3)	42 (%87.5)	0.334
	Growth	4 (%6.7)	6 (%12.5)	
	A.baumannii	*3 (%5)*	*4 (%8.3)*	
	P. aeruginosa	--	*1 (%2.1)*	
	MRSS	--	*1 (%2.1)*	
	P.mirabilis	*1 (%1.7)*	--	
Wound-3	**No growth**	56 (%93.3)	48 (%100)	0.127
	Growth	4 (%6.7)	--	
	A.baumannii	*2 (%3,3)*	--	
	E.coli	*1 (%1,7)*	--	
	P.mirabilis	*1 (%1,7)*	--	

Data are presented as mean ± SD and [n (%)]. p<0.05 is statistically significant. Group S: corticosteroid group, Group S-0: non-corticosteroid group. Eta: endotracheal aspirate, spp: species, MRSS: methicillin-resistant Staphylococcus species, E. coli: Escherichia coli, A.baumannii: Acinetobacter baumannii, P. aeruginosa: Pseudomonas aeruginosa

The microorganisms and their distribution in patients' urine-1, urine-2, and urine-3 cultures are given in Table IV. In the first urine culture taken with the diagnosis of septic shock, the growth rate was significantly higher in Group S-0 compared to Group S ($p<0.05$). However, in patients' urine-2 and urine-3 cultures, no significant difference was observed between the groups in terms of growth rates and microorganisms that grew ($p>0.05$). When intra-group comparisons were evaluated in urine cultures, a decrease in growth was observed in urine-2 and urine-3 cultures compared to urine-1 cultures in both groups. Additionally, there was also a decrease in growth in urine-3 culture compared to urine-2 culture in both groups. The decrease in urine culture growth in urine-2 compared to urine-1, and in urine-3 compared to urine-2, was statistically significant in Group S-0 ($p<0.05$), but not in Group S. The decrease in culture growth between urine-1 and urine-3 was statistically significant in both groups (Group S-$p<0.05$, Group S-0-$p<0.001$).

Figure 3 - Intra-group comparison of wound cultures



Data are presented as mean ± SD and [n (%)]. p<0.05 is statistically significant. Group S: corticosteroid group, Grup S-0: non-corticosteroid group. PΔ1-2: Comparison between 1st and 2nd cultures, PΔ2-3: Comparison between 2nd and 3rd cultures, PΔ1-3: Comparison between 1st and 3rd cultures

The microorganisms and their distribution in patients' wound-1, wound-2, and wound-3 cultures are given in Table IV. No significant difference was observed between the groups in terms of the microorganism species and the growth rates grown in the wound cultures of the patients (p>0.05). When comparing the intra-group wound cultures (Figure 3), a statistically significant decrease in growth rate was observed in both groups in wound-2 and wound-3 cultures compared to wound-1 culture. However, the decrease in growth rate in wound-3 culture compared to wound-2 culture was only significant in Group S-0 (p<0.05).

The records of patients in both groups were reviewed, and no cases of hypernatremia, hyperglycaemia, gastrointestinal bleeding, or cardiac events were observed in any patient.

Discussion

In this study, primarily, we found that in septic shock patients who were given corticosteroids, there was a significant increase in eta culture growth and a slight increase in wound culture growth which did not reach a statistically significant level in the 3rd cultures compared to the 2nd culture. According to these findings, when corticosteroids are used in recommended doses and duration in septic shock, they slightly increase the rate of secondary infections but do not create a significant difference in terms of the species of microorganisms that grow. Secondarily, despite longer hospital and ICU stay durations, we observed no increase in hospital mortality in patients receiving corticosteroids compared to those who did not.

The use of corticosteroids in septic shock has been studied in many studies in the literature and even presented as a recommendation in sepsis guidelines. In the previous 2017 sepsis management guidelines, IV hydrocortisone treatment (200 mg/day) was recommended in case hemodynamic did not improve despite adequate fluid resuscitation and vasopressor therapy [10]. However, in the latest guidelines, hydrocortisone therapy is recommended with moderate quality of evidence (weak recommendation; moderate quality of evidence) in cases of septic shock despite adequate fluid therapy, when the dose of norepinephrine or epinephrine is ≥0.25 mcg/kg/min for at least 4 hours [2]. Corticosteroid treatment is widely used in the management of lung diseases, including obstructive pulmonary disease and interstitial lung disease [11]. In our retrospective study, we found that corticosteroid treatment was significantly less likely to be administered to elderly and diabetic patients, and significantly more likely to be administered to patients with lung disease. The reason for this could be due to the inclusion of septic shock patients in the intensive care unit between 2016-2017 in our study and the lack of clear guidelines at that time regarding when to initiate corticosteroid therapy in vasopressor-resistant septic shock. Additionally, clinicians may have been more hesitant to initiate corticosteroid treatment in elderly and diabetic patients due to concerns about potential side effects, while being more willing to do so in patients with lung disease. Our patients receiving corticosteroid therapy were younger in age and had a lower prevalence of diabetes. Despite this, we observed a higher rate of growth in their ETA cultures. We are of the opinion that the lower rates of corticosteroid treatment in patients with advanced age or diabetes might have influenced our study results.

In a study of patients with pneumonia, corticosteroid treatment was found to have no effect on mortality but was associated with prolonged hospital stay [12]. A comprehensive review on the use of corticosteroids in pneumonia showed that in a serious community-acquired pneumonia patient population, corticosteroid treatment reduced mortality, shortened treatment and hospital stays, prevented the development of shock and respiratory failure that were not present in admission to hospital however in non-severe community-acquired pneumonia, corticosteroid treatment had no effect on mortality but reduced morbidity [13]. In a study of critically ill patients with ARDS and severe sepsis treated with corticosteroids, it was found that corticosteroid treatment improved oxygenation but had no effect on mortality [14].

There are studies in the literature that demonstrate the use of corticosteroids in septic shock reduces shock duration, decreases the need for mechanical ventilation, reduces mortality, and shortens hospital and intensive care unit stays [3,5,15,16,17]. However, in a study of infants with diaphragmatic hernia who received corticosteroids for refractory shock requiring vasopressor treatment, longer hospital stay, more days on mechanical ventilation, and higher mortality rates were observed [8]. Additionally, a smaller study showed that the use of hydrocortisone in septic shock increased mortality [18]. However, in meta-analyses it was reported that the use of corticosteroids did not affect short-term mortality but provided a mild decrease in long-term mortality and shortened hospital and ICU stays [9,15]. In our study, the length of stay for those who were received corticosteroids were longer than those who were not received, but there was no significant difference in terms of hospital mortality between groups. However, in our study, we only examined patients' hospital outcomes as mortality, and did not evaluate long-term mortality. We believe that the main reason for prolonged length of stay in corticosteroid-treated patients was the slight increase in secondary infections in these patients. Additionally, although not proven with tests, we believe that corticosteroid treatment may have increased muscle weakness and prolonged the ICU and hospital discharge.

Secondary infections are known as one of the adverse effects of corticosteroid treatment [3,4,7,19]. Corticosteroid therapy may cause iatrogenic immunosuppression, which can provide a ground for opportunistic and resistant microorganisms and fungi to become infectious agents. However, in a meta-analysis that included randomized controlled trials conducted in children and adults examining the use of steroids in sepsis, it was reported that corticosteroid use probably does not cause superinfection (RR 1.06, 95% CI 0.95 to 1.19; 5356 participants; 25 studies; moderate certainty evidence) [3]. Another review on the use of steroids in pneumonia treatment has also indicated that steroid treatment did not cause superinfection [13]. In a study conducted on infants in shock who received hydrocortisone treatment, no difference was observed between patients who received steroid treatment and those who did not in terms of developing secondary bacterial sepsis [8]. A meta-analysis evaluating corticosteroid use in sepsis also showed no effect on superinfections [9]. In a study comparing hydrocortisone

and fludrocortisone treatment in septic shock to placebo, it was observed that the use of steroids did not increase the risk of superinfection [17]. In a study on sepsis patients receiving corticosteroid treatment, the risk of developing infection in the long term was found to be 5 times higher than in those not receiving corticosteroid treatment [20]. The use of corticosteroids is known to be one of the risk factors for Candida colonization [21]. In a study on malignant patients in septic shock treated with hydrocortisone, approximately 23% of the secondary infections encountered were recorded as fungal infections [19]. Moreover, in the same study, the mortality rate of patients who had secondary infections was found to be higher than those who did not [19]. Another study examining complicated urinary tract infections caused by Pseudomonas revealed that the incidence of such infections was associated with corticosteroid therapy [22]. In our study, the initial cultures obtained from the patients were taken at the time of sepsis diagnosis, therefore we did not consider the difference in the initial urine culture results between the group receiving corticosteroids and the group not receiving corticosteroids because of corticosteroid use. The number and rate of growth, species that growth in subsequent urine cultures taken during hospitalization after corticosteroid use did not differ from those in the group not receiving corticosteroids.

Bloodstream infections, often catheter-related, can also be secondary to the transfer of infection sources from other areas into the bloodstream. The most common cause of these infections are Gram-positive microorganisms [23]. Central catheters become colonized within 1-3 days after placement, and it is known that the agents in the biofilm layer are often Gram-positive and Gram-negative microorganisms, as well as Candida species [24]. In a study conducted in newborns, the most common growth observed in blood cultures was methicillin-resistant coagulase-negative staphylococci, but no association was found between the growth and steroid use [25]. In another study, coagulase-negative staphylococci and Klebsiella were the most isolated microorganisms in hospital-acquired infections, and the use of antenatal corticosteroids was found to be effective in the development of infection in these patients [26]. In a study of patients with Acinetobacter bacteraemia mortality was associated with corticosteroid therapy [27]. In a study, it has been demonstrated that the growth of Pseudomonas in the blood of patients with haematological malignancy is associated with the use of corticosteroids [28]. Although steroid use is considered a risk factor for invasive candidiasis, a study evaluating the risk factors for candidemia reported that corticosteroid therapy was not related with candidemia [29]. In our study, no significant difference was observed in the growth of microorganisms between patients who received corticosteroid treatment and those who did not, in both catheter and blood cultures. MRSS was the most cultured microorganism in blood cultures, consistent with the literature. Gram-negative microorganisms and Candida species were also found in both central venous catheter and peripheral venous blood cultures. The second and third cultures were obtained upon the development of new fever, increase in acute phase reactants, and deterioration in clinical status during hospitalization. In both corticosteroid-treated and untreated patients, a decrease in microbial growth was observed in the second and third cultures obtained from the patients.

Nosocomial pathogens isolated from the respiratory tract are mostly Gram-negative and Gram-positive microorganisms, and their growth can also be polymicrobial [13]. It is known that corticosteroid treatment is a risk factor for Aspergillus infection [30]. In our study, Gram-negative microorganisms were the most isolated from patient cultures, followed by Candida species and Gram-positive microorganisms. Aspergillus growth was detected in only one of our patients and was not associated with corticosteroid treatment as it was observed only in the first culture. Studies suggest that corticosteroid treatment may contribute to the development of resistant Gram-negative microorganisms such as Acinetobacter, Klebsiella, and Pseudomonas [19,31-33]. A study on patients with community-acquired pneumonia who received corticosteroid treatment found higher rates of nosocomial infection compared to those who did not receive corticosteroid treatment [12].

In a study on ventilator-associated pneumonia, Gram-negative microorganisms were the most isolated, and corticosteroid use was evaluated as a risk factor associated with mortality [34]. In a meta-analysis examining risk factors for resistant klebsiella growth, corticosteroid use was found to be one of the risk factors [35]. The microorganisms isolated in our study were consistent with other studies; however, the increase in growth observed in the third culture compared to the second culture in patients who received corticosteroids suggested an increased risk of secondary infection associated with corticosteroids.

Pressure ulcers are a significant source of infection in intensive care unit patients. Gram-positive and Gram-negative microorganisms are frequently isolated in soft tissue infections. The incidence of Gram-negative microorganisms has increased in surgical site infections and diabetic foot wounds of hospitalized patients [36]. In our study, wound cultures were mainly obtained from pressure ulcers, and less frequently from surgical incision sites. It was observed that pressure ulcers in patients with limited mobilization were also a source of septic shock. Moreover, in our clinically severe patients with multiple risk factors for pressure ulcer development, the microorganisms in the wounds were also predominantly Gram-negative, consistent with the literature. There was no difference in the rates of wound culture growth and types of microorganisms isolated between patients who received corticosteroids and those who did not. However, while the rate of wound culture growth decreased in patients not receiving corticosteroids, we observed that the rate of growth did not decrease and even slightly increased in the third wound cultures of corticosteroid-receiving patients, suggesting the presence of secondary infections in these patients. In our study, Acinetobacter was the most isolated microorganism in all cultures evaluated, and the other isolated microorganisms were predominantly Gram-negative bacteria. However, steroid use did not cause any differences in the types of microorganisms isolated in all cultures.

In septic shock, in addition to secondary infections, adverse effects such as hyperglycaemia gastrointestinal bleeding, and cardiac events may also be observed due to corticosteroid use [11]. It is believed that major side effects caused by corticosteroids are associated with prolonged use and high doses [2,4,9]. In our study, no major side effect related to corticosteroid use was recorded in patients receiving corticosteroids. This may be due to the low dose, infusion form, and short duration of corticosteroid administration. It has also been reported that the use of corticosteroids in septic shock does not cause any significant side effects [16,17].

Limitations of our study include its retrospective design, small sample size, heterogeneity in the distribution of patient characteristics (age, disease, etc.) and lack of examination of long-term outcomes. Only three cultures (including one baseline culture) from our patients within a 28-day period were evaluated. We believe that monitoring patients' infection symptoms and cultures for a longer period and examining post-hospital mortality could change our study results. Alongside its limitations, we think that out study is valuable in that it shows

that there may be an increase in culture growth as a result of 28-day follow-up even in patients who were given corticosteroid treatment at recommended dose and duration in septic shock. Furthermore, standardizing factors other than corticosteroids and conducting prospective studies with more homogeneous and larger patient groups may yield different results.

In conclusion, in our retrospective study of patients with septic shock who were administered low-dose corticosteroid therapy for replacement purposes and adjusted according to their vasoactive needs, we found that corticosteroids partially increased the risk of secondary infection and prolonged hospital and ICU stays but did not affect the type of microorganisms or mortality rates. Therefore, we believe that the use of corticosteroids in vasoactive treatment-resistant septic shock should be re-evaluated through randomized controlled trials with a larger number of patients, considering the potential benefits and secondary infection risks.

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