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Retrospective Assessment of the Treatment Effectiveness of β-lactam/β-lactamase Inhibitor and Carbapenem Groups Antibiotics in Upper Urinary Tract Infections Caused by Extended Spectrum β-lactamase Producing *Escherichia coli* and *Klebsiella Pneumoniae*

Genişlemiş Spektrumlu β-laktamaz Üreten *Escherichia coli* ve *Klebsiella pneumoniae* Suşlarının Etken Olduğu Üst Üriner Sistem Enfeksiyonlarında β-laktam/β-laktamaz İnhibitörü ve Karbapenem Tedavilerinin Etkinliğinin Retrospektif Değerlendirmesi

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ABSTRACT

Aim: The rate of infections caused by extended-spectrum β-lactamase (ESBL)-producing bacteria is increasing globally. The resistance problem, which has spread especially since the 21st century, has led to an increase in the use of carbapenem group antibiotics in clinical cases of upper urinary tract infection (UUTI) caused by these bacteria. In this process, the increase in the number of bacteria, including carbapenemase-producing bacteria, and the slowly developing new antibiotic processes have led experts to different antibiotic therapies. In light of this situation, current evidence regarding the effectiveness of β-lactam/β-lactamase inhibitors (BL/BLI), which are considered an effective treatment alternative for UUTI due to ESBL-producing *Enterobacterales*, is still controversial. The aim of this study is to determine the effectiveness of BL/BLI versus carbapenems in the treatment of UUTI due to ESBL-producing *Enterobacterales*.

Materials and Methods: Our study included 176 patients diagnosed with UUTI caused by ESBL-producing *Escherichia coli (E. coli)* and *Klebsiella pneumoniae (K. pneumoniae)* and treated with carbapenem or BL/BLI group antibiotics. Patients' age, gender, underlying diseases, biochemical test results, isolated microorganism and their antibiotic susceptibility, immunosuppressive therapy in the last month, accompanying bacteremia, complicating factors, having UUTI in the last year, a history of using antibiotics in the last 3 months, and a history of hospitalization admission were recorded.

Results: In patient distribution, carbapenem was used in the treatment of 99(56.2%) patients and BL/BLI treatment was used in 77(43.7%) patients. The mean age of the patients was 66.81±13.82 (years), 107 (60.8%) patients were in the ≥65 age group and 88 (50%) patients were female. It was found that 79 (45%) of the patients had malignancy and 75 (42.6%) received immunosuppressive treatment. No statistically significant difference was found in clinical response and treatment outcomes (7th, 14th and 30th day mortality) between the groups receiving specific treatment (p>0.05).

Conclusion: BL/BLI (piperacillin-tazobactam) may be an effective alternative to carbapenems in the treatment of UTI due to ESBL-producing *E. coli* or *K.pneumoniae*.

Keywords: Urinary tract infection, carbapenem, β-lactam/β-lactamase inhibitor, *E. coli*, *K. pneumoniae*

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ÖZ

Amaç: Genişletilmiş spektrumlu β-laktamaz (GSBL) üreten bakterilerin neden olduğu enfeksiyonların oranı küresel olarak giderek artmaktadır. Özellikle 21.yy itibariyle yayılan direnç sorunu, bu bakteriler ile gelişen üst üriner sistem enfeksiyonu (ÜÜSE) klinik olgularında karbapenem grubu antibiyotiklerin kullanımının artmasına neden olmaktadır. Bu süreçte karbapenemaz üreten bakterilerin de aralarında bulunduğu bakterilerin sayısının artması ve yavaş gelişen yeni antibiyotik süreçleri, uzmanları farklı antibiyoterapilere yöneltmiştir. Bu durum ışığında, GSBL üreten *Enterobakterales*'e bağlı ÜÜSE için etkili bir tedavi alternatifi olarak kabul edilen β-laktam/β-laktamaz inhibitörlerinin (BL/BLI) etkinliğine ilişkin mevcut kanıtlar halen tartışmalıdır. Bu çalışmanın amacı GSBL üreten *Enterobakterales* bağlı ÜÜSE' nin tedavisinde karbapenemlere karşı BL/BLI'nin etkinliğini belirlemektir.

Gereç ve Yöntem: Çalışmamıza GSBL üreten *Escherichia coli (E.coli)* ve *Klebsiella pneumoniae (K.pneumoniae)* bağlı gelişen ÜÜSE tanısı konulan ve tedavilerinde karbapenem yada BL/BLI grubu antibiyotik kullanılan 176 hasta dahil edildi. Hastalara ait yaş, cinsiyet, altta yatan hastalıklar, biyokimyasal test sonuçları; izole edilen mikroorganizma ve antibiyotik duyarlılığı; son bir ay içerisinde immunsupresif tedavi alımı, eşlik eden bakteriyemi, komplike edici faktörler, son bir yılda üriner sistem enfeksiyonu geçirmiş olma, son 3 ay içerisinde antibiyotik kullanma öyküsü, hastane yatış öyküsü verileri kaydedildi.

Bulgular: Hasta dağılımlarında 99 (% 56,25) hastanın tedavisinde karbapenem ve 77 (%43,75) hastada ise BL/BLI tedavisi kullanıldı. Hastaların yaş ortalaması 66,81±13,82 (yıl) olup, 107'si (%60,8) ≥65 yaş grubunda ve 88 (%50) hasta kadın idi. Hastaların 79' nun (%44,9) malignitesinin olduğu, 75 (%42,6)'nin ise immünsupresif tedavi aldığı saptandı. Özgül tedavi alan gruplar arasında klinik yanıt ve tedavi sonuçlarında (7,14. ve 30. gün mortalite) istatistiksel olarak anlamlı fark saptanmadı (p>0,05).

Sonuç: BL/BLI (piperasilin-tazobaktam), GSBL üreten *E. coli* veya *K. pneumoniae* bağlı ÜÜSE tedavisinde karbapenemlere etkili bir alternatif olabilir.

Anahtar Kelimeler: Üriner sistem enfeksiyonu, karbapenem, β-laktam/β-laktamaz inhibitörü, *E. coli*, *K. pneumoniae*

INTRODUCTION

Urinary tract infections (UTIs) are common bacterial infections in the community and hospitalized patients. It is an infection picture that develops in the urinary system organs or tissues due to microorganisms[1-3].

Most of the *Enterobacterales* family are causative agents in UTI, and *Escherichia coli* and *Klebsiella pneumoniae* are most frequently detected in urine culture[1,2,4-8]. Antibiotic resistance rates in these bacteria are increasing day by day and antibiotic resistance due to extended-spectrum β-lactamases (ESBL) is the leading mechanism. ESBL enzymes are enzymes that confer resistance to oxyimino-β-lactams such as ceftazidim (CAZ) and ceftriaxone (CRO) and aztreonam (ATM). While ESBL-producing *Escherichia coli* (ESBL-EC*)* and *Klebsiella pneumoniae* (ESBL-KP*)* strains were previously isolated only as causative agents in hospital-acquired or healthcare-associated infections, they have been identified as causative agents in community-acquired infections since the 2000s and have become a serious public health problem on a global scale[4-6,9,10].

In studies, β-lactam/β-lactamase inhibitor combination, carbapenems and/or aminoglycosides were determined as antibiotics with high *in vitro* activity in these strains[4,6,8,11]. Today, the increase in the incidence of resistant bacteria due to the increased use of this group of antibiotics is a serious problem[12,13]. Within the scope of rational antibiotic use policy, the use of carbapenems that should be used in the treatment of complicated infections and resistant pathogens should be restricted. Under these conditions, investigating the efficacy of the treatments used in ESBL-EC and ESBL-KP-associated UTI has gained importance in terms of treatment alternatives.

In this study, it was aimed to contribute to the treatment approaches by evaluating the antibiotic resistance characteristics and the effectiveness of the treatments used in patients with upper UTI (UUTI) and ESBL-EC and ESBL-KP strains isolated in urine cultures.

MATERIAL AND METHODS

In this retrospective study, patients aged 18 years and older who were followed up with a diagnosis of UUTI between January 1, 2016 and August 30, 2020 and who had ESBL-EC and ESBL-KP growth in urine cultures were evaluated. For this purpose, 562 UTI episodes with ESBL-EC and ESBL-KP growth in urine cultures sent to the Microbiology Laboratory were identified. Antibiotic susceptibility tests for identification of the strains and ESBL detection were performed by VITEK® (Biomerieux, Marcy l'Etoile, France) automated system. Minimal inhibition concentration (MIC) values for piperacillin-tazobactam were considered susceptible if ≤16/4, moderately susceptible if 32/4-64/4, and resistant if ≥128/4. Moderately susceptible patients were considered resistant. Among carbapenems, MIC values for imipenem and meropenem were considered susceptible if ≤1 and resistant if ≥4; for ertapenem, susceptible if ≤0.5 and resistant if ≥1. In addition, ESBL positivity was investigated by double-disk synergy method in accordance with EUCAST criteria. Double-disk synergy method was performed using cefotaxime (CTX), CAZ and amoxicillin-clavulanate disks. For this purpose, CAZ (10 µg), CRO (30 µg), CTX (5 µg) and ATM (30 µg) discs were placed on Mueller Hinton Agar medium with amoxicillin-clavulanic acid (20/10 µg) (AMC) in the center and CTX (5 µg) and ATM (30 µg) discs in the periphery with a distance of 25 mm between disc centers. ESBL production was judged to be present when the zone of inhibition around the

CAZ, CRO, CTX and ATM disks widened ≥5 cm towards the AMC disk after 18-24 hours of incubation of the plates at 35-37 °C and/or when there was a zone of non-growth between the two zones of inhibition in areas where bacteria grew.

A total of 176 hospitalized UUTI patients who were applied carbapenem (meropenem and ertapenem) or β-lactam/β-lactamase inhibitor (piperacillin-tazobactam) and susceptible to mentioned antibiotics and met all of the following criteria were included in the study;(1) Being at the age of 18 years or older and meeting the diagnostic criteria for UUTI (high fever, chills or a feeling of warmth and at least one of the following signs and symptoms; burning during urination, frequent urination, feeling of urinary urgency, frequent and severe need to urinate, side pain, cloudy urine appearance, ≥10 leukocytes/mL or positive Leukocyte esterase test result with evidence of pyuria in complete urinalysis) and(2) having UUTI caused by ESBL-EC or ESBL-KP strains that were started within 48 hours of the first urine culture and used carbapenem (meropenem and ertapenem) or BL/BLI (piperacillin-tazobactam) antibiotics for at least 72 hours. Ethics committee approval was obtained for the Tekirdağ Namık Kemal University Non-Interventional Clinical Research Ethics Committee (desicion no: 2021.07.01.07 date: 26.01.2021). Voluntary informed consent form was not used since no application was performed on the patients.

A separate form was filled out for each UUTI episode that was found to be eligible according to these criteria. The evaluations of the patients at the beginning of treatment, on the third day and at the end of treatment were recorded. Fever, physical examination findings and laboratory results including hemogram, renal function tests, liver function tests, albumin and C-reactive protein levels, complete urinalysis, urine culture, blood culture and antibiotic susceptibility results were used to evaluate the response to treatment. The results of the patients were classified as clinical response, bacteriologic response and no response. Clinical improvement was defined as resolution of fever, resolution of symptoms at presentation and the physician's opinion on the outcome of treatment. Bacteriologic response was defined as no growth in urine culture obtained on the 7th day of treatment. These data were compared with the data of patients diagnosed with UUTI due to ESBL-EC or ESBL-KP using statistical and analytical methods. In our study, high doses were used, which probably increased the probability of reaching the appropriate pharmacokinetic and pharmacodynamic target. Piperacillin-tazobactam (4.5 g every 6 hours), ertapenem (1 g every 24 hours) or meropenem (1 g every 8 hours) were administered. Antibiotic doses were adjusted according to the renal function of the patients[14].

Statistical Analysis

Statistical analyses were performed using the SPSS (IBM SPSS Statistics 24) package program. Frequency tables and descriptive statistics were used to interpret the findings. Parametric methods were used for measurement values suitable for normal distribution. Pearson-χ^2 and continuity correction cross-tabulations were used to analyze the relationships between two qualitative variables.

RESULTS

The mean age of the 176 UUTI patients included in the study was 66.81±13.82 (years), 88 (50.0%) were female, 34 (19.3%) had diabetes mellitus (DM), 79 (44.8%) had malignancy, 75 (42.6%) used immunosuppressive therapy, and 36 (20.4%) had urinary calculi. Hospital-acquired infection was detected in 107 (60.7%) and relapse/reinfection in 31 (17.6%) patients. Some demographic and characteristic features of the patients are given in Table 1.

E. coli was grown in the urine cultures of 121 (68.7%) of 176 patients who had UUTI attacks. In 30 (17.0%) of these patients, the same agent was also grown in the blood culture. In 55 (31.2%) attacks, K. *pneumoniae* was grown in urine culture and in 8 (4.5%) of these patients, the same agent was grown in blood culture. All strains were susceptible to piperacillin-tazobactam and carbapenems.

In the treatment of 121 (68.7%) UTIs caused by ESBL-EC, 44 (36.3%) patients were treated with ertapenem, 26 (21.4%) with meropenem and 51 (42.4%) with piperacillin-tazobactam. In the treatment of 55 UTIs caused by ESBL-KP, 13 (23.6%) patients were treated with ertapenem, 16 (29.1%) with meropenem and 26 (47.2%) with piperacillin-tazobactam. The results are described in detail in Table 2.

There was no statistically significant difference in clinical response and mortality (7-, 14- and 30-days mortality) in the treatment groups (p>0.05). The results are described in detail in Table 3.

Of the 38 patients with blood culture growth, 15 (39.4%) ended in death. Of the 15 (39.4%) patients who died, 11 (28.9%) were receiving meropenem treatment. Due to the low number of patients receiving carbapenems, subgroup analysis was not performed. There was no statistically significant difference between clinical response and mortality (7-, 14- and 30-days mortality) in patients with growth in blood cultures (p>0.05). Detailed results are given in Table 4.

Table 1. Demographic and characteristic features of patients

Variable (n=176)	n	%
Age groups [$\bar{X}$ ± S.S.→66.81±13.82 (year)]		
<65	69	39.2
≥65	107	60.8
Gender		
Female	88	50.0
Male	88	50.0
Diabetes mellitus		
Yes	34	19.3
No	142	80.7
Renal failure		
Yes	51	29.0
No	125	71.0
Malignancy		
Yes	79	44.9
No	97	55.1
Use of immunosuppressive agent		
Yes	75	42.6
No	101	57.4
Use of antibiotic in the last one month		
Yes	96	54.5
No	80	45.5
Hospitalization in the last one month		
Yes	96	54.5
No	80	45.5
History of recurring urinary tract infection		
Yes	68	38.6
No	108	61.4
Hydronephrosis		
Yes	27	15.3
No	149	84.7
Hospitalization in the intensive care unit		
Yes	36	20.5
No	140	79.5
Neutropenia		
Yes	8	4.5
No	168	95.5
Hospitalization in the last three months		
Yes	107	60.8
No	69	39.2
Source of infection		
Community-acquired	69	39.2
Hospital-acquired	107	60.8
Relapse/reinfection		
Relapse	15	8.5
Reinfection	27	15.3
None	134	76.2
Urinary system tumor		
Yes	31	17.6
No	145	82.4

Table 1. Continued		
Variable (n=176)	**n**	**%**
Urinary stone		
Yes	36	20.5
No	140	79.5
Urinary catheter		
Yes	120	68.2
No	56	31.8
Urinary catheter type		
Bladder catheter	94	78.4
Suprapubic catheter	6	5.0
İntermittent	1	0.8
Nephrostomy	19	15.8
Reason for catheter		
Obstruction	38	31.6
Neurogenic bladder	5	4.2
For follow-up	77	64.2
History of urological intervention		
Yes	64	36.4
No	112	63.6

Table 2. Distribution of antibiotic use according to factors				
Variable (n=176)	***E. coli***		***K. pneumoniae***	
	n	**%**	**n**	**%**
Ertapenem	44	36.4	13	23.7
Meropenem	26	21.5	16	29
Piperacillin/tazobactam	51	42.1	26	47.3
E.coli: Escherichia coli, K.pneumoniae: Klebsiella pneumoniae				

DISCUSSION

Increasing resistance rates at the global level lead to the use of carbapenems, which in turn leads to the emergence and increase of carbapenem-resistant strains[15-17].

In appropriate cases, BL/BLI may be a good alternative to limit antibiotic use and evaluate options. In our study, no statistically significant difference was found between clinical response and mortality (7th, 14th and 30th day mortality) when comparing carbapenem (meropenem/ertapenem) treatment with BL/BLI (piperacillin-tazobactam) treatment in the clinical picture of UTI caused by ESBL-EC and ESBL-KP. Similarly, the study by Yoon et al.[18] shows that acute pyelonephritis (APN) caused by ESBL-EC can be successfully treated with *in vitro*-active piperacillin-tazobactam. Another study by Sharara et al.[19] showed that the use of piperacillin-tazobactam in the treatment of APN caused by ESBL-producing microorganisms in the absence of bacteremia showed similar clinical results to carbapenem therapy. In fact, among the patients who were followed in this study, carbapenem resistant microorganisms were observed in cultures taken from clinical samples within 60 days after the start of treatment in 2% of patients receiving piperchailin-tazobactam and in 8% of patients receiving carbapenem. This emphasizes the potential benefits of piperacillin-tazobactam as a carbapenem protective agent in the treatment of APN caused by ESBL-producing bacteria. In a cohort study conducted by Park et al.[20] on 152 patients, they found that antibiotics outside the carbapenem (fluorokinolones, BL/BLI and TMP-SMX) were as effective as carbapenems in the treatment of APN, regardless of whether APN was accepted as complicated, as long as they were active *in vitro*[20].

These results show that BL/BLI should be accepted as a reasonable alternative to carbapenems to treat such infections under certain conditions if it is effective *in vitro*.

In our study, when the clinical efficacy of piraceilin-tazobactam against carbapeneme was evaluated in the treatment of patients with UUTI caused by ESBL-EC and ESBL-KP, which are sensitive to piperrasilin-tazobactam, the clinical efficacy of piperrasilin-tazobactam was found to be 84.4% (65/77) and microbiological eradication ratio to be 90.9% (70/77). In the study conducted by Yoon et al.[18], the clinical efficacy of

Table 3. Evaluation of clinical response and mortality for treatment groups

Treatment	Meropenem/ertapenem (n=99)		Piperacillin/tazobactam (n=77)		Statistical analysis* probability
Variable (n=176)	n	%	n	%	
Clinical response					
Yes	81	81.8	65	84.4	χ^2=0.064
No	18	18.2	12	15.6	p=0.801
Result					
Recovery	70	70.7	56	72.7	χ^2=0.016
Death	29	29.3	21	27.3	p=0.899
7th day mortality					
Yes	12	12.1	7	9.1	χ^2=0.158
No	87	87.9	70	90.9	p=0.691
14th day mortality					
Yes	27	21.2	12	15.6	χ^2=0.569
No	72	78.8	65	84.4	p=0.451
30th day mortality					
Yes	28	28.3	22	28.6	χ^2=0.002
No	71	71.7	55	71.4	p=0.966

*"Continuity correction" or "Pearson-χ^2" cross tables were used in the examination of the relationships of the two qualitative variables with each other

Table 4. Investigation of the treatment groups and parameters of patients with bacteremia

Treatment	Meropenem/ertapenem (n=27)		Piperacillin/tazobactam (n=11)		Statistical analysis* probability
Variable (n=176)	n	%	n	%	
Clinical response					
Yes	10	37.0	2	18.2	χ^2=0.561
No	17	63.0	9	81.8	p=0.454
Result					
Yes	17	63.0	8	72.7	χ^2=0.039
No	10	37.0	3	27.3	p=.843
7th day mortality					
Yes	7	25.9	3	27.3	χ^2=0.000
No	20	74.1	8	72.7	p=1.000
14th day mortality					
Yes	10	37.0	3	27.3	χ^2=0.000
No	17	63.0	8	72.7	p=1.000
30th day mortality					
Yes	11	40.7	4	36.4	χ^2=0.063
No	16	59.3	7	63.6	p=0.802

*"Continuity correction" or "Pearson-χ^2" cross tables were used in the examination of the relationships of the two qualitative variables with each other

piperacillin-tazobactam against Ertapeneme was compared in the treatment of adult patients with APN caused by ESBL-EC sensitive to piperacillin-tazobactam and encouraging results were obtained.

The clinical efficacy of piperacillin-tazobactam was 79.4% (54/68) and microbiological eradication rate was 95.6% (65/68). These results show that piperacillin-tazobactam may be an effective carbapenem protective treatment option in the treatment of UUTI caused by ESBL-EC and ESBL-KP.

There is still a discussion in the ideal antibiotic treatment of ESBL-EC and GSBL-KP blood circulation infections (BCI). Carbapenems are considered to be a priority preferable treatment, but some publications also showed good results with BL/BLI combinations and especially

with piperacillin -tazobactam. In these studies, they are supported as a legitimate option for the treatment of ESBL-*Enterobacterales* (ESBL-E) BCI especially in patients without severe sepsis or septic shock. In the INCREMENT-SOT Project, in the study comparing carbapenems and BL/BLI in the treatment of *Enterobacterales* BCI associated with UTI, significant differences in the risk of therapeutic failure (lack of treatment or clinical healing and / or death due to any reason) were not found[21]. Rodríguez-Baño et al.[22] performed a prospective cohort study in Spain between 2001 and 2007, and they compared patients treated in vitro with active BL/BLIs, carbapenem empirical treatment cohort and exact treatment cohort in the post-hoc analysis of 277 patients with ESBL-E associated BCI. As a result of the study, it was stated that when amoxicillin-clavulanic acid or piperacillin-tazobactam were used in sufficient doses and were active as *in vitro*, there were suitable options for the definitive treatment of sensitive ESBL-EC strains causing BCI, especially in the urine and bile tracks, which can help prevent excessive use of carbapenems. In addition, in the study, it was suggested that deescalation regime from carbapenems to BL/BLIs could be planned for patients whose clinical findings were subsequently stable. In this study, in the comparison of the usage of carbapenem treatment with BL/BLI that is effective in vitro for emprical or exact treatment in UTIs associated with ESBL-EC, which is sensitive to BL/BLI in the laboratory tests, increased mortality was not found to be associated with clinical and biochemical non-response. In a study conducted by Artero et al.[23], no relationship was observed between the bacterimia and the poor prognosis in a geriatric patient cohort in which UTIs were evaluated. In our study, there was no significant difference in clinical response and mortality between treatment groups in the evaluation of 38 patients with BCI associated with urinary system.

In the studies, some risk factors have been identified in the development of infections with ESBL-producing bacteria. Among the risk factors for the UTI due to multi-drug-resistant bacteria are antibiotic use in the last 1 month, hospitalization in the last three months, having UTI in the last twelve months, immunosuppression status, advanced age, male gender, medical history of cerebrovascular disease, urinary catheterization and DM[24-26]. In our study, the rate of patients having at least one of the above risk factors in terms of ESBL enzyme production, from the E. *coli* and K. *pneumoniae* strains, was 94.8% (167/176).

Study Limitations

There are some limitations of our study. First, its retrospective design made it difficult to eliminate the information and/or election bias as well as unknown factors that might affect the evaluation of treatment efficiency. Secondly, data obtained in the first assessment were mostly used to determine risk factors for death; however, the factors changing during the treatment period may have affected the results. Thirdly, piperacillin-tazobactam activity against *E. coli*, which produces different ESBL species, may significantly decrease *in vitro* in the presence of a high bacterial inoculum[27,28]. We only included ESBL-EC and ESBL-KP cases based on the phenotypic resistance profile. Fourth, automated systems were used in our study to identify bacteria and to determine resistance. Pitout et al.[29] reported that the Vitek automatic system might fail to detect piperacillin-tazobactam resistance in case of *E. coli* producing CTX-M-15 and OXA-1, and suggested the use of alternative sensitivity test methods. These situations may have limited our study and have affected the results.

CONCLUSION

According to the results of our study, it shows that piperacillin-tazobactam may be an alternative to carbapenem treatment in UUTI caused by ESBL-producing microorganisms. In addition, our existing data suggest that piperacillin-tazobactam can be an effective agent in the treatment of BCIs developing with ESBL-producing pathogens. However, these results should be interpreted cautiously due to some limitations in our study.

In order to strengthen these findings, more comprehensive randomized prospective clinical studies are required.

Ethics

Ethics Committee Approval: Ethics committee approval was obtained for the Tekirdağ Namık Kemal University Non-Interventional Clinical Research Ethics Committee (desicion no: 2021.07.01.07 date: 26.01.2021).

Informed Consent: Voluntary informed consent form was not used since no application was performed on the patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.D., N.K., İ.K., Concept: M.D., İ.E., Design: M.D., İ.E., Design: M.D., İ.E., Data Collection or Processing: E.A., N.K., Analysis or Interpretation: E.A., M.D., N.K., İ.E., Literature Search: E.A., İ.E., Writing: E.A., M.D., N.K., İ.E.

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