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Original Investigation

Evaluation of Post-operative Meningitis: Comparison of Meningitis Caused by *Acinetobacter spp.* and Other Possible Causes

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This study has been presented as a poster (PP 0194) at the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) between 21 and 24 April 2018 at Madrid, Spain.

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ABSTRACT

AIM: To analyse postoperative meningitis (POM) after craniotomy, and to compare the clinical characteristics, treatment outcomes and mortality rates of POM that were caused by *Acinetobacter spp.* or other possible causes.

MATERIAL and METHODS: In this study, POM cases in our hospital between 2008 and 2016 were retrospectively reviewed. Cases were divided into three groups; *Acinetobacter spp.* meningitis (case group), non-Acinetobacter bacterial meningitis (control group 1) and culture negative meningitis (control group 2). Demographic, clinical, laboratory features, treatment modalities and mortality rates were compared between case and control groups.

RESULTS: A total of 112 patients with POM were included in the study. Cerebrospinal fluid (CSF) culture results were negative in 50 (44.6%) patients; bacteria were isolated from CSF of 62 (55.3%) patients. *Acinetobacter spp.* was isolated from 28 (45%) patients, while bacteria other than *Acinetobacter spp.* were detected in 34 (55%) patients. No significant differences were observed between case and control groups in terms of age, gender, comorbidity and operation type. For the case group, change of treatment according to culture result was significantly different from control groups ($p<0.001$).

Mortality was 55.6% in the case group, 24.2% in control group 1 ($p=0.013$), and 24% in control group 2 ($p=0.006$). In multivariate analysis, isolation of *Acinetobacter spp.* from CSF culture [OR_{adj}5.2, 95% confidence interval (CI):1.2–22.0, $p=0.026$] and inappropriate treatment (OR_{adj}15.7, 95%CI:3.6–68.9, $p<0.001$) were determined to be independent risk factors for mortality.

CONCLUSION: Postoperative meningitis, especially caused by *Acinetobacter spp.,* and its inappropriate empirical treatment are associated with high mortality.

KEYWORDS: *Acinetobacter spp.,* Antimicrobial resistance, Empiric antibiotic treatment, Mortality, Postoperative meningitis

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INTRODUCTION

Postoperative meningitis (POM) is a serious condition, which develops in rare cases in patients who have undergone neurosurgical procedures and requires appropriate urgent intervention (16,21). POM incidence varies between 0.3%–7%, while infection rates can reach as high as 10% in the absence of antibiotic prophylaxis (2,26). The most common pathogenic agents in POM are staphylococci; however, the reported involvement of Gram (-) agents has increased recently (2). Among Gram (-) bacteria, Acinetobacteria are the most common cause of POM. Within the past three decades, infections caused by Acinetobacter have become ubiquitous (2). *Acinetobacter spp.* are among the leading causes of nosocomial infections, especially in intensive care units, and have become a significant health problem. Natural resistance to many drugs, and the ability to easily gain new resistance mechanisms, makes the treatment of Acinetobacter infections more difficult (7,8). The purpose of this unique research is to analyse postoperative meningitis rate after craniotomy, and to compare the clinical characteristics, treatment outcomes and mortality rates of postoperative meningitis that were caused by *Acinetobacter spp.* or other possible causes.

MATERIAL and METHODS

In this study, cases of postoperative meningitis, developed in our hospital between 2008 and 2016, were evaluated retrospectively. Cases with *Acinetobacter spp.* growth in the cerebrospinal fluid (CSF) were included in the case group, those with bacterial growth other than *Acinetobacter spp.*were included in Control Group 1 and those with no microbial growth in the CSF were included in Control Group 2. Postoperative meningitis was described according to guidelines by the Centers for Disease Control and Prevention (CDC) (7). Patients younger than 18 years of age were excluded.

Bacterial strains were named, and species determination were performed using VITEK 2 automated microbial identification system (BioMérieux), API 20 E (Biomérieux), API 20 Strep semi-automated system and conventional methods. Antibiotic susceptibility was determined based on Clinical and Laboratory Standard Institute criteria and European Committee on Antimicrobial Susceptibility Testing criteria, using VITEK 2 antibiotic susceptibility testing (BioMérieux), disc diffusion (Becton Dickinson) and gradient diffusion test (Becton Dickinson) methods. Empirical therapy is defined as antibiotic treatment performed in order to treat a suspicious infection prior to the definition of the pathogenic agent and its susceptibility. Proper antibiotics is defined as positive susceptibility of the identified microorganism to empirical treatment commenced invitro.

Patients who underwent craniotomy in our hospital were followed-up for three months postoperatively by the Hospital Infection Control Committee (HICC) towards active infection surveillance.

Statistical Analysis

Statistical analyses included separate comparisons between the case group and both control group 1 and 2.

Descriptive statistics and advanced analyses were performed using SPSS Statistics V23.0 and Open Epi program packages.

Data analysis included the calculation of numeric and percentage distributions, 95% confidence interval (CI) for evaluation of potential risk factors, 5% standard error and estimated odds ratio (OR). Chi-square and Fisher's exact chi-square tests were used to evaluate categorical variables; student t-test for independent samples was used to evaluate the difference between means.

Factors related to mortality in patients with postoperative meningitis were evaluated using multivariate analyses. A logistic regression model was formed for multivariate analysis of mortality risk factors for the case group and control groups. Logistic regression analyses included 95% CI, adjusted odds ratio (OR_{adj}) and Wald test.

When determining variables for inclusion in the model, those with $p<0.05$ from univariate analyses and those believed to be clinically important were included, and the decision was based on a subsequent backward stepwise method. Furthermore, variables were inspected with regards to changes in efficacy, and no changes were reported.

During this examination, two separate models were formed: the first model included the case group, control group 2 and treatment propriety; the second model included the case group, control group 1 and treatment propriety variables.

A p value <0.05 was considered statistically significant.

RESULTS

A total of 719 craniotomies were performed in our hospital between January 2015 and December 2016. According to the data reporting active surveillance performed by HICC, the postoperative meningitis rate was 3.3%.

One hundred and twelve patients with postoperative meningitis were included in the study. Bacteria were isolated from CSF of 62 (55.3%) patients. Among the patients from whom bacteria were isolated, 28 (45%) revealed *Acinetobacter spp.* growth in CSF and 34 (55%) revealed microbial growth other than *Acinetobacter spp.* CSF culture results were negative in 50 of the 112 (44.6%) patients. Microorganism growth in CSF is summarised in Table I.

No differences were observed between case and control groups regarding age, gender, comorbidity or the type of operation performed. Mean durations of preoperative hospital stay, including standard deviation (SD), were 1.9 ± 2.5 days, 4.5 ± 4.8 days ($p=0.01$) and 5.0 ± 4.8 days ($p<0.001$) for the study group, control group 1 and control group 2, respectively, revealing statistically significant differences between the case group and control groups. Postoperative symptoms and findings revealed no significant differences between groups regarding postoperative consciousness, duration until onset of first symptom or symptoms developed (headache, blurred consciousness or fever). No significant differences were observed between groups, following the diagnosis of postoperative meningitis, regarding Glasgow Coma Scale,

either (p=0.086 and p=0.128 between the case group and control group 1 and 2, respectively).

In the case group at the time of postoperative meningitis diagnosis, an extraventricular drainage catheter (EVD) was present in 14 of 28 (50%) patients, and a lumbar drainage catheter (LD) was present in three patients (10%). In control group 1, 16 of 34 patients (47%) had an EVD and 5 (15%) had an LD (p=0.8, OR 1.2, 95% CI:0.4–3.1; p=0.7 OR 0.7, 95% CI:0.2–3.2, respectively). In control group 2, 12 of 50 patients (24%) had an EVD and 5 (10%) had an LD (p=0.019, OR 3,2, 95% CI: 1.2–8.5; p=1, OR 1.1, 95% CI: 0.2–4.9, respectively). Mean duration until development of meningitis following placement of an EVD/LD (including SD) was 6.5 ± 6.1 for the case group, 4.3 ± 2.5 (p=0.4) for control group 1 and 1.2 ± 1.2 (p=0.018) for control group 2. In the case group, 6 (37.5%) EVD/LD catheters were placed at bedside and 10 (62%) were placed in the operating room; in control group 1, 3 (16%) (p=0.25) were placed at bedside, and in control group 2, 5 (27%) (p=0.54) were placed at bedside.

Mean leukocyte count at the time of meningitis diagnosis (including SD) was 17850 ± 7301 per µL for the case group, 13312 ± 5240 per µL (p=0.006) for control group 1 and 14620 ± 5847 per µL (p=0.037) for control group 2. Mean blood CRP (C-reactive protein) level (including SD) was 201 ± 137 mg/L(normal range:0–8 mg/L) for the case group, 108 ± 116 mg/L (p=0.016) for control group 1 and 137 ± 71 mg/L (p=0.003) for control group 2. Mean leukocyte cell count in CSF (including SD) was 4635 ± 11078 per µL for the case group, 645 ± 716 per µL (p=0.068) for control group 1 and 579 ± 953 per µL (p=0.064) for control group 2. Mean glucose level in CSF (including SD) was 41 ± 37 mg/mL for the case group, 51 ± 39 mg/mL (p=0.331) for control group 1 and 57 ± 30 mg/mL (p= 0.055) for control group 2. Mean protein level in CSF (including SD) was 404 ± 448 mg/mL for the case group, 228 ± 290 mg/mL (p=0.1) for control group 1 and 344 ± 864 mg/mL (p=0.749) for control group 2.

Of the 28 patients in the case group, 26 (93%) possessed *Acinetobacter spp.* in CSF, which were resistant to both imipenem and meropenem.

Empirical treatment was commenced in 89% of patients in the case group, 83% of patients in control group 1 and 100% of patients in control group 2. In the case group, 78% of patients were started on meropenem + vancomycine and 12% on meropenem + vancomycine + colistin; in control group 1 and 2,90% and 98% of patients were started on meropenem + vancomycine, respectively. Empirical treatment with meropenem+vancomycine+colistin was commenced in 3% and 2% of the patients in control group 1 and 2, respectively. Therapies for 82% of patients in the case group and 21% of patients in control group 1 (p<0.001, OR 16.3, 95% CI: 4.5–58.8) were modified based on the results of microbial culture.

Univariate analyses of mortality-related factors for all patients included in the study are presented in Table II.

Multivariate analyses of mortality data between case group and both control groups are presented in Table III.

Table I: Microorganism Growth in Postoperative Meningitis in CSF

Microorganism	n=62 (%)
Acinetobacter spp.	28 (45)
MRCoNS*	11 (18)
E.coli	3 (5)
K.pneumonia	3 (5)
Pseudomonas spp.	3 (5)
Enterococcus spp.	3 (5)
S.pneumonia	2 (3)
Serratia spp.	2 (3)
Others†	7 (11)

***: MRCoNS:** Methicillin resistant coagulase negative Staphylococcus, **†:** Haemophilus influenzae, Streptococcus oralis, Corynebacterium striatum, Burkholderia cepacia, Methicillin Sensitive Staphylococcus aureus.*

■ DISCUSSION

Diagnosis of postoperative meningitis is made based on clinical findings and examination of CSF. However, CSF cell count, glucose and/or protein level abnormalities may not be reliable parameters for indication of infection in patients with nosocomial meningitis (20). Normal CSF cell count and glucose and protein levels are not sufficient to reliably exclude infection in patients with nosocomial meningitis; however, CSF and blood samples should be collected prior to antibiotic treatment in selected patients. Negative CSF growth cannot exclude nosocomial meningitis in patients who have undergone previous antibiotic treatment. Bacterial growth was observed in CSF of 62 (55%) patients included in our study, while no growth was observed in 50 (45%); the patients with no growth were accepted as aseptic meningitis. Aseptic meningitis comprises 60%–75% of all postoperative meningitis cases. Findings in aseptic and bacterial meningitis are often similar; discrimination is made upon the outcome of CSF culture (27). According to a study by Chidambaram et al., bacterial growth was observed in the CSF in only 9.8% of POM cases, with the remaining 91% being accepted as aseptic meningitis (4). Zarrouk et al. reported that 54 of 75 cases with POM (75%) were accepted as aseptic meningitis owing to a lack of bacterial growth (27). Meningitis is a disease with high rates of mortality and morbidity, which can be fully ameliorated with appropriate treatment. Considering both clinical findings and CSF results, we believe that diagnosis should be made in favour of meningitis in cases in whichboth postoperative changes and meningitis are suspected. However, this may lead to the incidence of aseptic meningitis being over-reported.

In the present study, 28 of the 62 cases in which the growth of microorganisms was detected in CSF (45%) were confirmed to have *Acinetobacter spp.* Acinetobacter is frequently observed among nosocomial infections, including in a growing number of POM cases recently. In previous studies, both Gram (-) (3), and Gram (+) (particularly *Staphylococcus aureus*) (10,26), bacteria have been shown to predominate, varying between countries (14,22,23). However, the incidence of Gram (-) agents has increased over the past three decades. Recent

Table II: Mortality Related Factors in Patients with Postoperative Meningitis (Univariate Analysis)

Factors	Non-survivors n=35		Survivors n=75		p	OR (%95 CI)
	n	%	n	%		
Age (mean ± SD)	47.6 ± 14.4		43.2 ± 15.9		0.170	-
Gender						
Male	16	45.7	39	52.0	0.539	0.8 (0.4-1.7)
Female	19	54.3	36	48.0		
Glasgow Coma Score	9.3 ± 4.6		12.3 ± 3.9		**0.005**	-
EVD						
Done	14	40.0	26	34.7	0.588	1.3 (0.6-2.9)
Not done	21	60.0	49	65.3		
LD						
Done	5	14.3	8	10.7	0.398*	1.4 (0.4-4.6)
Not done	30	85.7	67	89.3		
Empirical treatment						
Recieved	32	91.4	68	91.9	0.599*	0.9 (0.2-4.0)
Not recieved	3	8.6	6	8.1		
Antibioticused in empirical treatment						
Meropenem+Vancomycine	27	84.4	68	93.3	0.147*	0.4 (0.1-1.5)
Meropenem+Vancomycine	3	8.8	2	2.8	0.187*	3.4 (0.5-21.3)
Treatment change according to microbial culture	15	42.9	14	18.9	**0.008**	3.2 (1.3-7.8)
Propriety of the treatment						
Unproper	20	58.8	17	24.3	**0.001**	4.5 (1.9-10.7)
Proper	14	41.2	53	75.7		
Leukocytecount	16441 ± 7140		14399 ± 5857		0.119	-
CRP (mg/L)	197.6 ± 136.2		99.4 ± 88.3		**<0.001**	-
Duration of hospital stay until the operation (days)	3.1 ± 4.5		4.5 ± 4.4		0.145	-
Duration until postop symptoms (days)	10.5 ± 7.8		8.8 ± 11.1		0.472	-
Bacterial growth in CSF						-
Acinetobacter spp.	15	42.9	12	16.0	**0.002**	3.9 (1.6-9.8)
Other bacteria	20	57.1	63	84.0		

***:** *Fisher's exact test.*

studies have reported Acinetobacter as the causative agent in as many as 30% of meningitis cases (15,19). Findings from the present study are in accordance with data from such studies.

It is well known that many sites of the human body contain flora, which act as barriers to infection. However, within several days of hospitalisation (generally after the fourth day), floral bacteria start to be replaced by resistant bacteria of endogeneous or exogeneous origin. Therefore, we sought to investigate the relationship between duration of preoperative hospitalisation and causative agents of meningitis. Long-term preoperative hospitalisation was expected to be a risk factor for Acinetobacter growth. On the contrary, duration of preoperative hospitalisation was significantly lower in the case group compared with either control group. No existing data comparisons on this topic were found in previous literature. Demirarslan et al. previously investigated antibiotic treatment, reporting significantly higher rates of antibiotic usage and

Table III: Mortality Related Factors in Case and Control Groups and all Patients (Multivariate Analysis)

Risk factors	Non-survivors (%)	Survivors (%)	OR_{adj}* (%95 CI†)	p
Mortality related risk factors in the case group and control group 1				
Acinetobacter spp. growth	65.2	32.4	5.2 (1.2-22.0)	**0.026**
Unproper treatment	58.8	24.3	15.7 (3.6-68.9)	**<0.001**
Mortality related risk factors in the case group and control group 2				
Acinetobacter spp. growth	55.6	24.0	4.2 (1.4-12.7)	**0.011**
Mortality related risk factors in all patients				
Acinetobacter spp. growth	65.2	32.4	2.7 (0.8-9.2)	0.104
Unproper treatment	58.8	24.3	6.8 (2.0-23.3)	**0.002**
CRP‡ (mg/L)	84.0	47.3	5.3 (1.4-20.8)	**0.017**

: Adjusted odds ratio; †: Confidence interval; ‡: C-reactive protein.

duration of antibiotic treatment in the group with Acinetobacter growth and previous antibiotic treatment (5).

No differences were observed regarding symptoms or clinical findings (headache, blurred consciousness or fever) upon diagnosis of POM between case and control groups. Similar findings were reported by Kurtaran et al. when comparing POM with Gram (-) and Gram (+) bacterial growth (15).

The relationship between EVD/LD and bacterial agents in meningitis is well known. Dos Santos et al. previously defined the presence of EVD/LD as a risk factor for the development of POM in both uni and multivariate analyses (6). However, in this study, no comparisons were made between types of bacteria. Kurtaran et al. observed no difference between Gram (-) and Gram (+) bacteria incidences in the presence of an EVD/LD. In the present study, presence of an EVD/LD was not detected as a risk factor for development of Acineto bacter meningitis (15).

In the present study, mean duration until development of meningitis following placement of an EVD/LD was significantly higher for the case group than that in the control group 2 (p=0.018). In a multi-centre study by Jamjoom et al., coagulase negative staphylococci and *S.aureus* growth were predominant in the CSF of patients with an EVD (13). Furthermore, it has been reported that EVDs used for longer than 10 days significantly increase the rate of infection; this is independent of the type of bacteria (6).

Proper hand and hair hygiene, provision of full body drapes, full use of protective equipment and antiseptic preparation during EVD placement would reduce the risk of infection. Previous studies have reported that EVDs should be placed in the operating room rather than the emergency unit so these conditions can be better met; equally, in case of the need for EVD placement at home, it has been recommended for each institute to create a protocol for placement (18). In our study, no differences were detected regarding Acinetobacter growth following EVD/LD placement in the operation room or bedside between the case and control groups. In a meta-analysis investigating the effect of such protocols on infection rates, consistent and significant benefits were reported in all studies, despite the poor quality of literature supporting EVD placement protocols.

In the present study, leukocyte count and CRP levels (as indicators of systemic inflammatory response in the blood) were compared between the case and control groups at the time of POM diagnosis. Blood leukocyte count and CRP levels were significantly higher in the case group than those in either control groups. No differences were detected in the leukocyte count, glucose or protein levels in CSF between case and control groups. Kurtaran et al. previously reported, when comparing Gram (-) and Gram (+) agents, that blood and CSF leukocyte count and blood CRP levels were similar between both groups, whereas CSF glucose, protein and lactate levels were significantly higher in the Gram (-) group (15).

The Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR) 2017 annual report by the World Health Organization indicated that, in Turkey, carbapenem resistance among *Acinetobacter spp.* in blood and CSF was 92%. The same report also indicated that carbapenem resistance among *Acinetobacter spp.* isolates grown in blood and CSF in all countries surveyed varied between 70% and 97%, with the exception of Switzerland (7%) (25). According to the European Antimicrobial Resistance Surveillance Networkdata, combined resistance of fluoroquinolones, aminoglycosides and carbapenems in Acinetobacteria varies between countries, ranging widely between >1% and <75% (24). In the present study, carbapenem resistance in *Acinetobacter spp.* was 93% (26/28), in keeping with the findings of CAESAR.

POM is an infectious disease, which necessitates urgent appropriate treatment. Appropriate empirical treatment should be commenced immediately on suspicion of meningitis. The combined usage of vancomycine and anti-pseudomonal β-lactam (cefepim, ceftazidime or meropenem) antibiotics is

recommended for empirical treatment of POM in the 'Healthcare-Associated Ventriculitis and Meningitis'practice guidelines published by the Infectious Diseases Society of Americain 2017 (20). Among 95 (85%) patients included in our study treated with meropenem+vancomycin, 5 (4%) were started on empirical treatment with meropenem+vancomycin+colistin. Treatments for 82% of patients in the case group and 21% of patients in control group 1 (p<0.001, OR 16,3; 95% CI: 4.5–58.8) were modified according to results of bacterial culture and antibiotic susceptibility tests. This indicates that the causative agent was *Acinetobacter spp.,* and that empirical antibiotic treatment was insufficient for POM. This is not unexpected, considering CAESAR data discussed above regarding resistance rates of these bacteria. Accounting for specific data from each institute, colistin therefore seems to be an important option for empirical treatment of POM.

Previous studies have reported POM mortality rates of between 15% and 71.4% (3,9,11,17). Metan et al., investigating Acinetobacter meningitis, reported a mortality rate of 71.4% (17). According to the literature, POM mortality rates are higher when caused by Gram (-) bacteria than Gram (+) bacteria (1, 9,15). Such high mortality rates may be explained by high global rates of antimicrobial resistance in Gram (-) bacilli (17). In instances of antibiotic resistance, treatment regimes are inappropriate, therefore poor mortality and morbidity outcomes are observed. However, in addition to improper empirical treatment, underlying neurological situations or additional comorbidities can also result in poor mortality and morbidity outcomes. In the present study, mortality was 55.6% for the case group, 24.2% for control group 1 (p=0.013), and 24% for control group 2 (p=0.006). In multivariate analysis, presence of *Acinetobacter spp.*in CSF culture (OR_{adj}5.2, 95%CI:1.2–22.0, p=0.026) and inappropriate treatment (OR_{adj}15.7, 95%CI:3.6–68.9, p<0.001) were both determined to be independent risk factors for mortality. These results strongly support data reported in the literature.

The most important limitations of this study were its retrospective nature and long duration. Therefore, we did not approve of reporting POM rates between 2008 and 2016. Instead, it was more appropriate to give HICC results of active surveillance from the past two years (2015–2016) in our hospital.

CONCLUSION

POM leads to high mortality and morbidity rates if not appropriately and urgently treated. Data from the present study support this hypothesis. Every institute should consider its own antimicrobial resistance rate when making a decision regarding empirical treatment. Finally, colistin seems to be an important option, which may be used for empirical treatment.

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