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Research article

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Comparison of serum procalcitonin and interleukin-6 levels with CRP levels in the follow-up of antimicrobial treatment of patients with pyogenic and granulomatous vertebral osteomyelitis

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Ethics Committee Approval
This study was approved by Dumlupınar University Clinical Research Ethics Committee (date: July 21, 2016, No:2016-9/20).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Infection of the intervertebral disc and adjacent vertebrae is called vertebral osteomyelitis (VO). This study aims to determine whether procalcitonin (PCT) and interleukin (IL)-6 markers are more valuable than white blood cells (WBC), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the follow-up in patients with VO who were administered antibiotherapy.
Methods: All adult patients with a diagnosis of VO were included in this prospective cohort study. The patients were divided into two groups as those with pyogenic and granulomatous VO. Serum WBC, CRP, ESH, PCT and IL-6 levels were measured at baseline, and the 2nd, 4th, 8th and 12th weeks of antibiotherapy. The changes in the laboratory parameters of the patients during follow-up were evaluated.
Results: Of the 30 patients included in the study, there were 22 and 8 patients in the PVO and GVO groups, respectively. Baseline IL-6 measurement was above the reference in all patients, CRP was elevated in 96.6%, and PCT was increased in only one patient. Although there was a paradoxical increase in PCT values in the PVO group in the 2nd week compared to the pre-treatment values, a rapid decrease was observed in the 4th and 8th weeks. In the GVO group, the gradual decrease in PCT in parallel with the treatment response was considered to predict clinical improvement. IL-6 values decreased by 43.2% and 50% compared to baseline at the 4th and 8th weeks of treatment, respectively, in the PVO group. In the GVO group, a 50% reduction was detected in the 4th week of treatment compared to baseline.
Conclusion: PCT and IL-6 biomarkers are valuable indicators in treatment follow-up. Although not statistically significant, the most stable decrease was observed in IL-6. Using IL-6 for the follow-up of the patients with VO may prevent long-term antibiotherapy.

Keywords: Vertebral osteomyelitis, Interleukin-6, Procalcitonin, C-reactive protein

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Introduction

Infection of the intervertebral disc and adjacent vertebrae is called spondylodiscitis (SPD), disc space infection or vertebral osteomyelitis (VO) [1]. VO mostly develops iatrogenically. While spontaneous pyogenic VO (PVO) is rare [2], it is the most common form of hematogenous osteomyelitis over 50 years of age. It makes up for 3-5% of all osteomyelitis cases. In a study conducted in France, the incidence of spontaneous VO was 2.4 per 100.000 [3,4]. Iatrogenic VO may develop secondary to lumbar puncture, epidural injection, spinal surgery, and penetrating trauma [1, 5]. Postoperatively, the risk of developing VO ranges from 1-8% [6].

Etiologically, it can be divided into pyogenic and granulomatous VO. Brucellosis and tuberculosis (TB) are the most common granulomatous agents. Granulomatous VO (GVO) cases can also be seen due to actinomycosis, nocardiosis, syphilis and fungi [7]. Since TB is a treatable disease, PVO is more common [1, 3].

The diagnosis of VO is challenging. The disease is typically characterized by back pain unresponsive to conservative treatment, and elevation in serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Fever may not always be seen. Magnetic resonance imaging (MRI) is often used in diagnosis. Empirical treatment is not recommended in patients without sepsis or neurologic deficit until a microbiological diagnosis is made. Microbiological and pathological examination of tissue biopsy is important in diagnosis and treatment planning [3].

Procalcitonin (PCT) is a better parameter than ESR, CRP and white blood cells (WBC) in the diagnosis of bacterial infections [8]. The serum PCT increases more rapidly than CRP [9]. The plasma level of interleukin (IL)-6 rises rapidly within 1-3 hours in bacterial infections and acute inflammation; but it decreases within a short time [10]. Thus, it has the potential to show inflammation before the onset of clinical findings [11]. In the diagnosis of infection, IL-6 has lower sensitivity and higher specificity than CRP [12].

In the evaluation of treatment response, ESR and CRP follow-up is recommended with an assessment of clinical findings. ESR and CRP values may increase despite clinical improvement in some patients. The decrease trend in these biomarkers lowers the risk of treatment failure. However, in most patients, no significant decrease is observed in these biomarkers in 4-8 weeks of follow-up due to low specificity. Therefore, whether the values are compatible with clinical findings should be assessed [3]. These parameters can be easily affected by other infectious or non-infectious conditions [10, 13], which leads to confusing results in treatment management. The clinician may resort to unnecessary antibiotic revision, prolongation of the duration of antibiotic therapy, and unnecessary surgery. To the best of our knowledge, no study evaluates IL-6 and PCT in the treatment follow-up of patients with vertebral osteomyelitis in the literature. Our study aimed to examine whether the use of procalcitonin (PCT) and Interleukin (IL) 6, which are more specific for bacterial infections compared to ESR and CRP, in the follow-up of the treatment response of VO patients is more beneficial. Although monitoring the clinical response with PCT and IL-6 is more costly than assessing CRP, the use of these biomarkers will be cost-effective if they are shown to be more beneficial in clinical follow-up, reducing unnecessary antibiotic use, shortening the treatment duration, preventing unnecessary surgery, shortening hospitalization, reducing antibiotic-related side effects and surgery-related complications.

Materials and methods

Study design and sampling

This prospective study was conducted between August 2016 and January 2018. All adult patients visiting Afyon Kocatepe University, Department of Infectious Diseases and Clinical Microbiology who were diagnosed with VO were included in the study. Serum WBC, CRP, ESR, PCT and IL-6 levels were measured at baseline, and in the 2^{nd}, 4^{th}, 8^{th}, 12^{th} and 24^{th} weeks of antibiotherapy. The patients were divided into two groups as those with PVO and GVO. Inter- and intragroup analyses were conducted in terms of laboratory parameters during treatment follow-up. For each laboratory parameter, pre-treatment values within the same group were first compared with the mean values at each follow-up week. Then, the mean values in the follow-up weeks after the beginning of treatment were compared. Finally, the mean values between the two groups were compared at the same follow-up weeks.

Diagnostic criteria for VO were defined as follows:

- Presence of clinical findings consistent with the disease (spine pain with or without fever unresponsive to conservative symptomatic treatment, presence of neurological symptoms),
- Increased CRP and ESR values,
- Presence of spondylitis, discitis or SPD demonstrated by MRI/CT in the patient.

Exclusion criteria for the study were as follows:

- Younger than 18 years of age,
-VO associated with a non-infectious inflammatory condition (such as spondyloarthropathies)
- Presence of another concomitant focus of infection
- Not attending follow-ups regularly, missing laboratory tests

Peripheral blood cultures were obtained from all patients. Brucella tube agglutination test was used for brucellosis. Purified Protein Derivative (PPD) was performed for TB. Tissue biopsy was performed in patients who had no contraindications and accepted the operation. Biopsy analyses included Gram and Ehrlich-Ziehl-Neelsen (EZN) staining, aerobic, anaerobic culture, and Mycobacteria cultures.

Diagnosis of brucellosis VO was made if *Brucella spp*. were grown in cultures, or serum brucella tube agglutination titer was ≥1/160 or increased fourfold after two weeks. TB was diagnosed in cases where acid-fast bacilli (ARB) were detected by EZN staining, or *M. tuberculosis* was grown and/or chronic granulomatous inflammation was detected in tissue biopsy. In cases where no diagnostic intervention could be performed, patients with clinical symptoms, imaging, and laboratory findings suggestive of TB, those with a history of TB and positive PPD, or patients whose peripheral smear findings were compatible with TB were considered to have TB VO. The cases

that responded to the empirical antibiotic treatment, although pyogenic bacteria were grown in cultures were considered as PVO.

Serum CRP concentrations were measured by the nephelometric method (Beckman-Coulter, USA) and serum ESR levels were determined with Vacuplus ESR-120 brand sedimentation measuring device (LEN-MED Medical Health Services, Ankara, Turkey). Serum WBC measurements were made with Mindray BC-6800 brand hemogram device (Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, China). IL-6 was measured with the DiaSource brand Human IL-6 ELISA kit (DIAsource Immunoassays S.A., Louvain-la-Neuve, Belgium). Absorbance reading was performed on a ChemWell 2910 brand ELISA reader device (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Serum PCT was measured with Cloud-Clone brand Human PCT ELISA kit (Cloud-Clone Corp. Katy, USA). Absorbance reading was performed on a ChemWell 2910 brand ELISA reader device (Awareness Technology, Inc. Martin Hwy. Palm City, USA). Threshold values for WBC, CRP, ESR, PCT and IL-6 were $4x10^3$/uL, 0.8 mg/dL, 15 mm/h, 200 pg/mL, and 3 pg/mL, respectively [14-17].

Appropriate antibiotherapy was initiated according to the results of cultures in patients without sepsis or neurological deficits. Initial treatment of PVO included intravenous (IV) administration of antibiotics. Empirical antibiotherapy were given to cover possible pyogenic agents, such as staphylococci, streptococci and gram-negative bacilli (GNB). Empirical treatment comprised glycopeptide or daptomycin effective against methicillin-resistant *Staphylococcus aureus* (MRSA) and quinolone, 3rd generation cephalosporin or carbapenem effective against GNB. Antibiotherapy was revised according to the results of microbiological sampling. Treatment was continued or revised according to the clinical and laboratory response in patients from whom no microorganisms were isolated. Patients who had a partial clinical response to the parenteral treatment were discharged with oral therapy after 2 weeks. After discharge, all patients were followed up with 2-week intervals while using antibiotherapy. At each control visit, the symptoms of the patients were questioned and serum WBC, CRP, ESR, PCT and IL-6 levels were measured.

The duration of treatment ranged between 8-24 weeks for PVO, and it was 24 weeks for patients with brucellar VO. In TB VO cases, the minimum duration of treatment was 24 weeks. Decrease in CRP and ESR values compared to baseline and complete regression of back pain were considered treatment response in patients.

Ethics statement

The study was approved by Dumlupınar University Clinical Research Ethics Committee (date: July 21, 2016, No:2016-9/20). All individuals included in the study were informed about the purpose and method of the study, and all signed the informed consent form.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 22 (Inc. Chicago, Illinois, USA) statistical package program. The conformity of the variables to the normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Number of patients and frequency tables were used for categorical variables. Descriptive statistical data for normally distributed variables were expressed as mean ± standard deviation (SD). Non-normally distributed numerical variables were presented as median (minimum-maximum). The student t test was used to compare the means between two normally distributed independent groups, while the Mann Whitney-U test was used for non-normally distributed variables. Chi-square test was used to compare categorical variables. Repeated measures ANOVA test was utilized to compare the means between dependent groups. $P<0.05$ was considered statistically significant in all analyses.

Results

Among forty patients, eight were lost to follow-up, and two patients died. Therefore, the results of 30 patients were included in the study. Twenty-two (73.3%) had PVO while 8 (26.7%) had GVO. Among GVO cases, 6 (20%) had brucellosis and 2 (6.7%) had TB.

Fifteen (50%) of the patients included in the study were male and the mean age of all patients was 56.2 (16.0) years. Twenty-eight (93.3%) had spinal pain, 18 (60%) had fever, 17 (56.7%) had neurological deficit, 2 (6.7%) had hip pain, 1 (3.3%) had palpable swelling in the lumbar region, and 1 (3.3%) had palpable swelling in the groin. The mean time between the onset of symptoms and diagnosis was 11.6 (11.7) weeks. There was no significant difference between the groups in terms of gender, mean age, frequency of pain, fever and neurological deficit symptoms, and mean time until diagnosis.

In terms of risk factors, 13 (43.3%) patients had undergone spinal surgery, 6 (20%) had diabetes mellitus, 1 (3.3%) had received immunosuppressive therapy, 1 (3.3%) had a malignancy, and 1 (3.3%) patient had chronic liver disease. All patients with VO which developed after spinal surgery were in the PVO group. The mean time between VO onset and surgery was 16.6 (16.3) weeks. Demographic and clinical characteristics of the patients are shown in Table 1.

Table 1: Demographic and clinical characteristics of VO cases

	Pyogenic VO (n=22) Value (%)	Granulomatous VO (n=8) Value (%)	*P*-value	Total VO (n=30) Value (%)
Mean age (SD)	56.8 (14.3)	54.7 (21.2)	0.762	56.2 (16.0)
Gender (female/male)	11/11	4/4	1.000	15/15
Risk factors				
-History of spinal surgery	13 (59.1)	-	0.004	13 (43.3)
- Presence of comorbidity	13 (59.1)	5 (62.5)	0.866	18 (60)
*DM	4 (18.1)	2 (25)		6 (20)
*Malignancy	1 (4.5)			1 (3.3)
*Immunosuppressive therapy	1 (4.5)	-		1 (3.3)
*Chronic liver disease	1 (4.5)	-		1 (3.3)
Time from symptom to diagnosis (mean, weeks)	11.6 (11.7)	5.8 (4.4)	0.219	10.1 (10.5)
Symptoms				
Spinal pain	20 (90.9)	8 (100)	0.377	28 (93.3)
Fever	12 (54.5)	6 (75)	0.419	18 (60)
Neurological deficit	14 (63.6)	3 (37.5)	0.242	17 (56.7)
Hip pain	-	2 (25)		2 (6.7)
Swelling in the groin	1 (4.5)	-		1 (3.3)
Swelling in the waist	1 (4.5)	-		1 (3.3)

DM: Diabetes mellitus, VO: Vertebral osteomyelitis

MRI was performed in all patients. Eight (26.6%) patients were additionally scanned with CT. There was lumbar involvement in 19 (63.3%) patients, lumbosacral involvement in

6 (20%), thoracic involvement in 4 (13.3%), and cervical vertebral involvement in 1 (3.3%). There were abscesses in 13 patients (43.3%). Paraspinal abscess was observed in 6 (20%), epidural abscess in 4 (13.3%), and psoas abscess in 3 (10%). Although statistically insignificant, the frequency of abscess was higher in the GVO group (P=0.242).

Blood cultures were obtained from all patients before the initiation of antimicrobial therapy. Tissue biopsy was obtained from 21 (70%) patients. Microorganisms were isolated in 10 (33.3%). While the same microorganism was isolated in both blood and tissue cultures in 3 patients (10%), some reproduced in the blood culture alone in 3 patients (10%), and in the tissue culture alone in 4 patients (13.3%). The microorganisms isolated in blood cultures included methicillin-resistant coagulase-negative staphylococci (MR CoNS) in 2 (6.7%), methicillin-sensitive coagulase-negative staphylococci (MS CoNS) in 1 (3.3%), methicillin-sensitive *S. aureus* (MSSA) in 1 (3.3%), *E. coli* in 1 (3.3%), and *P. aeruginosa* in 1 (3.3%). Microorganisms isolated in tissue biopsy were *M. tuberculosis* in 2 (6.7%), *P. aeruginosa* in 2 (6.7%), *Enterobacter cloaca complex* in 1 (3.3%), MSSA in 1 (3.3%), and *E. coli* in 1 (3.3%) (Table 2).

Table 2: Culture results of VO cases

Sampling status	Pyogenic VO (n=22) Value (%)	Granulomatous VO (n=8) Value (%)	Total VO (n=30) Value (%)
Patients with blood cultures	22 (100)	8 (100)	30 (100)
Patient with growth in blood culture	6 (27.2)	0	6 (20)
-MSSA	1 (4.5)	-	1 (3.3)
-MS CoNS	1 (4.5)	-	1 (3.3)
-MR CoNS	2 (9.1)	-	2 (6.7)
- *E. coli*	1 (4.5)	-	1 (3.3)
- *P. aeruginosa*	1 (4.5)	-	1 (3.3)
- Culture negative	16 (72.7)	8 (100)	24 (80)
Patients with tissue culture	17 (77.2)	4 (50)	21 (70)
Patients with growth in tissue culture	5 (22.7)	2 (25)	7 (23.3)
-MSSA	1 (4.5)	-	1 (3.3)
- *E. coli*	1 (4.5)	-	1 (3.3)
-*Enterobacter cloaca complex*	1 (4.5)	-	1 (3.3)
- *P. aeruginosa*	2 (9.1)	-	2 (6.7)
- *M. tuberculosis*	-	2 (25)	2 (6.7)
-Culture negative	12 (54.5)	2 (25)	14 (46.6)
-No review	8 (36.4)	5 (62.5)	13 (43.3)

MR CoNS: methicillin-resistant coagulase-negative staphylococci, MSSA: methicillin sensitive S. aureus, MS CoNS: methicillin sensitive coagulase negative staphylococcus, VO: vertebral osteomyelitis

Tissue biopsy samples were also examined histopathologically. Exudative inflammation was reported in 8 (26.7%), chronic granulomatous inflammation in 2 (6.7%), non-specific inflammation in 2 (6.7%), and no specific inflammation in 5 (16.7%).

WBC, CRP, ESR, PCT and IL-6 values were measured in 19 of the patients in the PVO group at baseline and at the 2nd, 4th, and 8th weeks of treatment. They were measured again at week 12 in 3 patients with longer duration of treatment, and at week 24 in 2 patients. In the GVO group, they were measured at baseline, and at the 2nd, 4th, 8th, 12th and 24th weeks of the treatment, since the duration of treatment in all patients was 24 weeks.

While baseline WBC, ESR and IL-6 levels were insignificantly higher in the PVO group than in the GVO group (p=0.197, p= P=0.851, and p=0.963, respectively), CRP and PCT levels were insignificantly higher in the GVO group (p=0.511, and p=0.083, respectively).

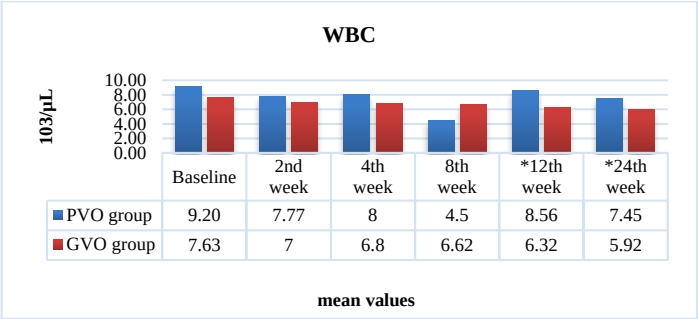
Inter- and intragroup comparisons of baseline WBC, CRP, ESR and IL-6 values and at each follow-up week were conducted. WBC values of the patients in the GVO group gradually and insignificantly decreased each week compared to baseline (P=0.347). In the PVO group, WBC levels did not decrease stably during the follow-up weeks (P=0.441) (Figure 1). CRP levels of the patients decreased at the 2nd, 4th and 8th weeks of the treatment compared to the baseline in both groups (P=0.106, P=0.053, and P=0.009, respectively, in the PVO group, and P=0.050, P=0.025, and P=0.018, respectively, in the GVO group). ESR levels decreased each week, in accordance with the clinical response in both groups compared to baseline (P=0.211, P=0.476, and P=0.025, respectively, in the PVO group, and P=0.036, P=0.012, and P=0.012, respectively, in the GVO group). The decrease between the 4th and 8th weeks of treatment in the PVO group when compared to other follow-up weeks was significant (P=0.005). While there was no difference in WBC and CRP values between the two groups in the same weeks, mean ESR values at weeks 4th and 8th were lower in the GVO group compared to the PVO group (P=0.039 and P=0.027, respectively).

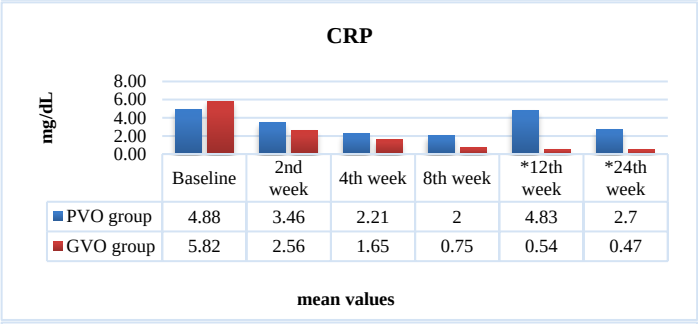
In the GVO group, PCT values decreased gradually at the 2nd, 4th, and 8th weeks of the treatment. In the PVO group, the mean PCT value increased in the 2nd week of the treatment compared to baseline and decreased in the 4th and 8th weeks. In this group, the decrease between the 2nd and 4th weeks and the 2nd and 8th weeks of the treatment was significant (P=0.001, P=0.003). IL-6 levels gradually and insignificantly decreased in the 2nd, 4th, and 8th weeks of treatment in both groups (P=0.069). The PCT values significantly differed between the GVO and PVO groups at week 4 (P=0.009).

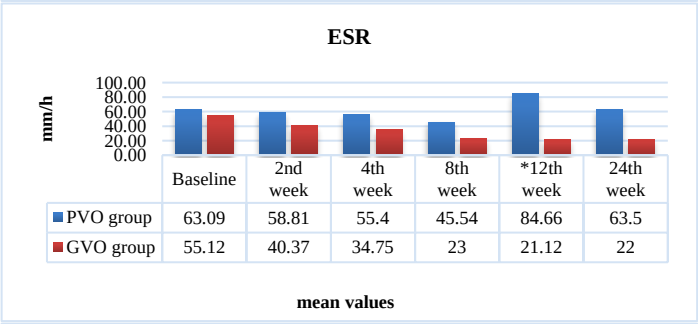
The mean total follow-up time of the patients was 13.4 (7.6) weeks. GVO cases were treated and followed for 24 weeks. Patients with PVO were given 2-4 weeks of intravenous antibiotherapy, followed by oral antibiotherapy. The total duration of antibiotherapy was 8 weeks in 19 of these patients (86.4%), 12 weeks in 1 (4.5%) patient and 24 weeks in 2 (9.1%) patients. The mean duration of intravenous antibiotherapy was 2.9 (2.2) weeks, and the total duration of antibiotherapy and follow-up time was 9.6 (4.72) weeks.

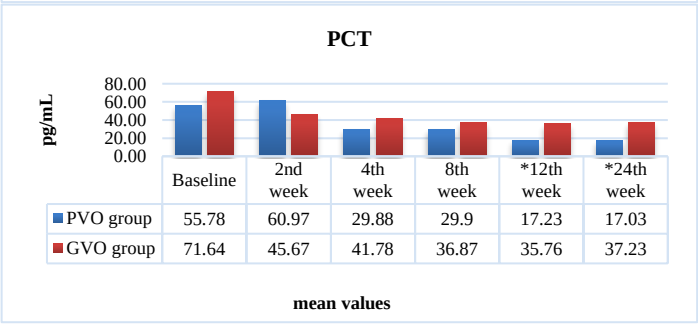
Twenty-eight patients (93.3%) were cured with medical and/or surgical treatments; 1 (3.3%) patient was considered unresponsive, and 1 (3.3%) patient had relapse.

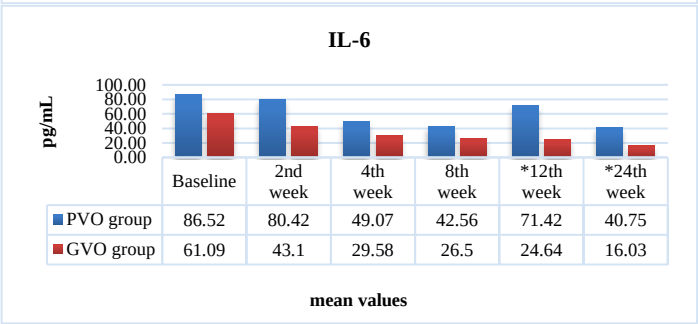
Figure 1: Comparison of baseline and follow-up laboratory parameters of PVO and GVO cases











WBC: white blood cell, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, IL: interleukin, PCT: procalcitonin, VO: vertebral osteomyelitis

P-values for mean WBC values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.197, *P*=0.159, *P*=0.241, *P*=0.044.
P-values for mean CRP values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.511, *P*=0.336, *P*=0.540, *P*=0.070.
P-values for mean ESR values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.851, *P*=0.189, *P*=0.039, *P*=0.027.
P-values for mean PCT values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.083, *P*=0.851, *P*=0.009, *P*=0.214.
P-values for mean IL-6 values at baseline, 2nd, 4th and 8th weeks, respectively: *P*=0.963, *P*=0.205, *P*=0.174, *P*=0.146.

*In the PVO group, 19 of 22 patients were treated for 8 weeks and laboratory tests were performed at 0, 2, 4, 8 and 12 weeks of treatment. The 12th week results of treatment included only 3 patients, and the 24th week results included only 2 patients. Therefore, only mean values are given for these weeks and no comparison with the GVO group was made.

Discussion

There is a surge in the incidence of VO due to the development in diagnostic modalities, increasing number of surgical interventions and the widespread use of immunosuppressive treatments. Although the mortality risk due to the disease is low, severe back pain and neurological sequelae can seriously disrupt the daily life of the patients. Multidisciplinary approach of infectious diseases and clinical microbiology specialists, neurosurgeons, radiologists and orthopedists have a great importance in the follow-up and treatment of the disease. The basis of treatment is the identification of the causative agent and antibiotic sensitivity, for which a tissue culture is required. However, usually, nor the surgeon, neither patient wants the biopsy, and the samples taken are not sent to the laboratory properly. As a result, the agent cannot be detected [3,7]. In these cases, laboratory parameters in follow-up are of great importance for patient management. In our study, we used PCT and IL-6 markers in addition to WBC, CRP and ESR, all of which are used in daily practice to evaluate the efficacy of antibiotherapy. This is the first study in the literature which evaluated PCT and IL-6 comparatively with CRP and ESR in VO treatment follow-up.

Many microorganisms can cause VO, such as pyogenic bacteria, *Brucella spp.*, TB bacillus, fungi, and parasites [3,7]. In the study of Mete et al. [18], among 100 spontaneous VO cases, 44% were caused by pyogenic bacteria, 32%, by TB bacillus and 24%, by *Brucella spp*. In another study by Kaya et al. [19], causative agents were pyogenic bacteria in 61.6% of the patients, Brucella spp. in 33.6%, and TB bacillus in 4.7%. In our study, 73.3% of the patients had PVO, 20% had brucellosis, and 6.7% had TB. The causative microorganisms were similar to those reported in the literature.

S. aureus is the most common cause of PVO. Other causative agents include GNB, other Gram-positive cocci and less often, anaerobes [7]. In the study of Chang et al. [20], *S. aureus* was the most common bacterium (72%), and GNB were found in 32.6%, *Streptococcus spp.* in 21.2%, Coagulase negative staphylococci (CoNS) in 7.2%, *Enterococcus spp.* in 5.2%, anaerobes in 4.8%, and other Gram-positive cocci, in 1.6%. The most common GNB were *E. coli*, *Klebsiella spp*. and *Salmonella spp.*. Eren Gok et al. [21] collected urine and stool cultures, as well as blood and tissue samples for microbiological sampling, and determined the agent in 42%. The most common causative agent was *S. aureus*, followed by GNBs, including *E. coli*, *Klebsiella spp.* and *Salmonella spp.*. In our study, blood and tissue cultures were used for microbiological sampling. The causative agent could be identified in 10 patients' (33.3%) blood and tissue cultures: It was MR CoNS in 2 patients (6.7%), MS CoNS in 1 patient (3.3%), MSSA in 1 patient (3.3%), *E. coli* in 1 patient (3.3%), *P. aeruginosa* in 2 patients (6.7%), and *E. cloaca complex* in 1 patient (% 3.3) and *M. tuberculosis* in 2 patients (6.7%). The distribution of the agents in our study was compatible with the literature (40% Gram positive, 40% Gram negative, 20% TB).

A 2010 review by Gouliouris et al. [7] stated that the rate of tissue biopsy for the diagnosis of VO was between 19-100%, and the rate of agent detection in biopsies varied between 43-78%. In the study of Lora-Tamayo et al. [22], culture

positivity was detected in only 19% of the patients with CT-guided tissue biopsy. In our study, 70% of the patients underwent intraoperative tissue biopsy and pathogenic microorganisms were isolated in 23%. Our results are similar to those in the literature.

The definitive diagnosis of VO is made by microbiological isolation. However, the diagnosis becomes difficult due to the low rates of tissue biopsy and isolation of agents in tissue cultures. So, the most important parameters used in diagnosis of VO are laboratory biomarkers [23]. ESR has high sensitivity and low specificity in the diagnosis of infection. The elevation of ESR is independent of the severity of the infection and the age of the patient. Most studies showed that it is elevated in more than 90% of patients with VO, and the mean value ranges between 43 to 87 mm/h. CRP is an important marker in the diagnosis of VO [3, 7]. In the literature, it is reported that both markers are 84% sensitive separately in the diagnosis of VO [24]. Their combined use yields a sensitivity of 94-100%, but specificity is low [3]. WBC count is not a sensitive marker in the diagnosis of spinal infection. Although a very slight increase is usually observed, it is within the normal range in the elderly population and immunocompromised patients. Elevated WBC levels were found in only 42.6% of PVO cases [24].

In our study, the mean baseline WBC levels were within normal limits, and those of PVO patients were higher than those of GVO patients. Leukocytosis was detected in 31.8% of the patients with PVO and in 12.5% of the patients with GVO. However, this difference was not statistically significant. The mean values were 9209.09 µL in the PVO and 7637.5/µL in the GVO groups. These results are compatible with literature data.

In the PVO group, 95.5% of the patients had elevated CRP and 100% had elevated ESR. The mean values for CRP and ESR were 4.88 mg/dl and 63.09 mm/h, respectively. In the granulomatous group, CRP and ESR elevation were detected in 100% of the patients. Mean values for CRP and ESR were 5.83 mg/dl and 55.13 mm/h, respectively. No significant difference was found between the groups. According to our data, ESR and CRP are more useful biomarkers than WBC count for diagnosing VO, regardless of the etiology.

PCT is a valuable biomarker used in the diagnosis and treatment follow-up of infections [9, 25]. There were a few studies in the literature in which PCT was used in the diagnosis and follow-up of VO. There are also studies in which the diagnostic value is investigated mostly in extremity osteomyelitis and prosthetic infections and compared with other inflammation markers [14, 17]. In the study of Maharajan et al. [14], PCT was a very sensitive and specific marker in the diagnosis of acute osteomyelitis and septic arthritis when the cut-off was 0.4 ng/ml. Jeong et al. [26] detected PCT elevation in 73% of all patients diagnosed with spinal infection, but most patients with PCT elevation had a coinfection. In a study by Maus et al. [27], two groups with PVO and disc herniation were compared. Serum CRP values were increased in all except 2 cases in the infection group, while PCT value increased in only 1 patient with infection, but not in any patient in the disc herniation group. In this study, it was concluded that PCT is not a suitable marker for the diagnosis of spinal infections. In a study by Yoon et al. [23] comparing pyogenic and TB VO cases, serum PCT levels were insignificantly higher in the PVO group. In our study, only one of our patients had PCT>200 pg/ml, which was the cut-off value. Our results may contribute to the contradictory literature data that PCT level cannot be used in the diagnosis of VO. However, it does not seem possible to reach a definite conclusion, since there was no control group in our study and the cut-off could not be determined. In this study, we did not create a control group, as our aim was not to determine the value of PCT and IL-6 biomarkers in diagnosis, but to investigate their usability in treatment follow-up.

Although there are studies on extremity osteomyelitis and prosthesis infection in the literature, we could not find any study in which IL-6 was used in the diagnosis and treatment follow-up of VO. In a study conducted in Germany in 2014, IL-6 levels in the serum and synovial fluid samples of patients with prosthesis infection and aseptic loosening were compared and IL-6 levels in both body fluids were more sensitive for diagnosis than serum WBC, ESR and CRP levels [28]. In a study of Van Asten et al. [29] on patients with diabetic foot infection, IL-6 was measured at baseline, and at the 3rd and 6th weeks, which revealed that it decreased in parallel with the treatment response in patients. It was concluded that it is a valuable parameter to use in treatment follow-up. In a study investigating the value of serum inflammation markers in chronic osteomyelitis, IL-6 was the most sensitive marker with a rate of 72.8% among WBC, CRP, ESR, PCT, IL-6 and TNF-a [30]. In a study of Bottner et al. [31] IL-6 was defined as the most sensitive laboratory parameter in patients with prosthesis after CRP with a rate of 95% when the cut-off value was 12 pg/ml. In the study of Glehr et al. [32] on prosthetic infections, when the cut-off value for IL-6 was 2.55 pg/mL, the sensitivity was 92% and the specificity was 59%. In our study, IL-6 levels were above 3 pg/ml, which was considered the cut-off value, in all 30 patients. There was no difference between patients with PVO and GVO. Although we cannot determine the cut-off value because there is no control group, the detection of elevated IL-6 levels suggests that IL-6 may be a useful biomarker in the diagnosis. Our data also seems compatible with literature.

In our study, WBC decreased by 16% in the PVO group and 13% in the GVO group compared to baseline at the 8th week of treatment, and paradoxically increased in the PVO group at 4th week. Therefore, we think that this is not a valuable parameter in VO follow-up, similar to the literature.

In this study, a decrease in CRP and ESR values was detected in all patients in parallel with the treatment response. ESR response was slower in the PVO group. In PVO patients, only a 12% decrease was detected in ESR values compared to pre-treatment values at the 4th week of treatment while in GVO patients, a 58% decrease was noted. In the PVO patient group, 60% decrease in CRP values at the 8th week of treatment compared to baseline was a significant parameter in terms of showing clinical improvement in patients.

Although a paradoxical increase was observed in the PCT values of the PVO group in the 2nd week compared to baseline, a rapid, significant decrease was observed in the 4th and 8th weeks. In the GVO patient group, the gradual decrease in PCT in parallel with the treatment response during all follow-up weeks was an indicator predicting clinical improvement. Based on our data, PCT can be used to monitor treatment follow-up in

patients with VO. However, according to the results of the study, it cannot be said whether PCT is a more useful biomarker for treatment follow-up than CRP and ESR. For more precise results, it would be appropriate to conduct a study involving more patients.

IL-6 levels were decreased in both groups in line with the treatment response. Although there was no statistically significant difference between baseline and the 2nd, 4th and 8th weeks of treatment in both groups, the decrease in IL-6 levels in parallel with the clinical response suggests that this biomarker can be used to monitor the treatment response. The fact that these decreases are more stable than CRP and ESR suggests that IL-6 may be a more useful parameter in the treatment follow-up.

Limitations

This was a single center study with a small number of patients and there was no control group.

Conclusion

Isolation of a microorganism is not always possible. In our study, the causative agent was isolated in only one third of the patients. Regardless of the etiology, the most sensitive markers in the diagnosis of VO were CRP, ESR and IL-6. PCT, detected above the threshold value in only 1 patient at baseline, was not a useful marker in the diagnosis of VO. The levels of CRP, ESR, IL-6 and PCT change in parallel with the clinical response in VO and are useful parameters for follow-up. A more stable decrease in IL-6 levels suggests that it is a more valuable biomarker that can be used in follow-up.

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