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PŮVODNÍ PRÁCE

Comparison of Clinical Features and Serum Parameters of Culture-Positive Children with Culture-Negative Children in Septic Arthritis and Acute Osteomyelitis

Porovnání klinických projevů a sérových parametrů u kultivačně pozitivních a kultivačně negativních dětí při septické artritidě a akutní osteomyelitidě

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ABSTRACT

PURPOSE OF THE STUDY

The aim of this study was to investigate the culture results of children undergoing debridement for suspected septic arthritis or acute osteomyelitis and to compare the laboratory parameters and clinical characteristics of culture-positive and culture-negative patients.

MATERIAL AND METHODS

Patients who underwent surgery in our hospital for septic arthritis and acute osteomyelitis between 2011 and 2019 were retrospectively analyzed. Seventy-two of 96 patients were included in the study. The patients had documented joint swelling, redness, pain with joint movement and weight-bearing failure. Fever was assessed preoperatively. Sedimentation rate, C-reactive protein level, white blood cell count and the leukocyte count in aspiration material as well as complications were evaluated preoperatively and 3 months postoperatively.

RESULTS

Twenty patients underwent surgery of the hip; 39 of the knee; 7 of the foot, ankle and distal tibia; 1 of the elbow; and 1 of the distal radius. Additionally, 4 patients had septic arthritis and acute osteomyelitis of the femur. The mean age of the patients was 7.8 years (1–16). The mean follow-up period was 16.2 months (3–42). Preoperative aspiration was performed in 44 of 72 patients. Thirty of 72 patients had positive cultures. No statistically significant difference in age, preoperative duration, C-reactive protein, sedimentation, white blood cell count, preoperative fever or complications was found when compared between patients with culture growth and those without reproduction ($p > 0.05$). There was a significant difference between the leukocyte count in the aspiration material ($p < 0.05$).

CONCLUSIONS

Prediagnosis of septic arthritis or acute osteomyelitis in pediatric patients is important in terms of future joint health and sepsis. According to our findings an inability to obtain bacteria does not exclude septic arthritis as a diagnosis. Empirical antibiotic therapy with a wide postoperative spectrum is important for joint health in these patients. Preoperative serum parameters cannot predict the agent needed for treatment.

Key words: septic arthritis, osteomyelitis, pediatric septic arthritis, pediatric joint infection, pediatric infection.

INTRODUCTION

Septic arthritis (SA) and acute osteomyelitis (AO) are more common in infants and young children than in other age groups. Although the literature has reported an incidence rate of 8 out of 100,000 children, the rate is actually higher, especially in low-income countries (1). Osteomyelitis is most commonly seen at three years of age, and septic arthritis is most common at two years of age (5, 21, 23). Children with suspected septic arthritis or acute osteomyelitis represent a common diagnostic challenge for emergency doctors, pediatricians and orthopedic surgeons. Acute osteoarticular infections and bone infections are not very common in pediatric age groups, but serious sequelae may result from these infections (7).

If these infections are suspected, particularly in developing countries, examinations and treatments should be initiated immediately. Various studies have reported complications (11). Complications are highly dependent on factors such as underlying co-morbidities, delayed diagnosis and treatment. In particular, in the case of a delay in treatment initiation, the risk of morbidity increases (6). If treatment is delayed for SA or AO complications such as avascular necrosis, growth arrest, related shortness or early osteoarthritis, loss of movement and systemic sepsis may occur (13).

The most commonly used serum parameters in patients with suspected septic arthritis or acute osteomyelitis are the sedimentation (SED) rate, C-reac-

tive protein (CRP) level, white blood cell (WBC) count, and leukocyte count in aspiration material (18). Glucose levels and leukocyte counts in the aspirate material after joint aspiration are also helpful. However, joint aspiration may not be applied in all pediatric patients under emergency conditions. Upon physical examination, fever, joint pain and motion limitations in the involved extremity are among the most important findings that increase clinical suspicion (22).

Transient synovitis is commonly diagnosed as septic arthritis, as clinicians have difficulty differentiating between the two. For this reason, the usefulness of laboratory parameters and physical examinations, have been widely discussed in the literature. Culture results obtained after surgical debridement or after aspiration are usually positive in 50–60% of cases according to the literature (8, 26). The presence of septic arthritis or transient synovitis in these culture-negative patients has remained unknown according to the literature. There are many reasons why cultures may be negative. Some of the reasons include the administration of antibiotherapy before surgery, the laboratory conditions, not collecting cultures from appropriate tissue and the use of inadequate materials. Is it possible to estimate the reason for negative cultures before surgery with serum parameters? The aim of our study was to investigate the culture results during debridement in children who underwent surgery due to suspected septic arthritis or acute osteomyelitis and to compare the laboratory parameters of culture-positive and culture-negative patients.

MATERIALS & METHODS

From January 2011 to January 2019, pediatric patients who underwent surgery for SA or AO in our hospital were retrospectively analyzed. Patients with metabolic diseases, patients with secondary septic arthritis or osteomyelitis due to chronic osteomyelitis, patients with sacroiliac septic arthritis or vertebra osteomyelitis, patients who were younger than 1 year of age, patients who used antibiotherapy for 3 days before surgery were excluded from the exclusion criteria patients who did not meet the Kocher criteria and patients who underwent surgery with a follow-up period of less than 3 months were excluded from the study. The diagnosis of SA or AO was based on the patient's examination and serum parameter results. Two criteria were taken into consideration when deciding whether to perform surgery. Aspiration was performed in patients who underwent debridement to obtain the leukocyte count, and in patients in whom aspiration could not be performed, we used modified Kocher criteria. We have modified the Kocher criteria (14), which are frequently used in the literature, by including the imaging systems. We used this method in the surgical indication criteria. Surgery was performed if 4 of the 5 criteria were met. These modified criteria included limitations of movement on the affected side, pain or failure, fever >37 °C, serum white blood cell (WBC) counts above 10,000 cells/mm^3, sedimentation (SED) rate >40 mm/h, and C-reactive protein (CRP) level >2.0 mg/dl, Increased synovial fluid or bone marrow edema in the involved extremity in MRI or ultrasound. With these criteria, the joint or extremity was examined by MRI or ultrasound when the age of the patients was appropriate. 28 patients who could not be aspirated. 20 of them were examined by MRI and 8 were examined by ultrasound. Seventy-two of 96 patients who underwent surgery were included in the study. 55 patients had septic arthritis and 17 patients had acute osteomyelitis. Twenty patients underwent surgery of the hip, 39 patients of the knee, 7 patients of the foot, ankle and distal tibia, 1 patient of the elbow, and 1 patient of the distal radius, and 4 patients had SA or AO of the femur. Twenty-eight of the 72 patients underwent consultation in our pediatric clinic, and a preliminary diagnosis was made. Forty-four patients were admitted to our outpatient clinic or emergency department with a preliminary diagnosis.

The patients had documented joint swelling, redness, pain with joint movement and weight-bearing failure. Preoperative fever was assessed from the patients' epicrises. The sedimentation rate, CRP level, and WBC count were measured preoperatively and postoperatively at 1 and 3 months, and the preoperative hospital stay and postoperative hospital stay were evaluated. The leukocyte count was examined in the preoperative aspirate materials. Complications observed in the controls at 1, 3, 6 and 12 months were evaluated.

According to the culture results of the patients, antibiotherapy was started by a pediatric infection specialist.

Preoperative aspiration was performed in 44 of 72 patients. Surgical cultures were positive in 30 patients and negative in 42 of 72 patients. The leukocyte count was measured in the aspirate material in 44 patients; 24 of these patients had positive cultures, and 20 of them had negative cultures.

Statistical analysis

Preoperative and postoperative serum parameters were evaluated with IBM SPSS V22 (Chicago, USA). Pre- and postoperative differences were evaluated with the Mann-Whitney U test, and $p < 0.05$ was accepted as significant. Serum parameters, fever measurements, lengths of stay and complication rates between the two groups were evaluated with independent t-tests. $p < 0.05$ was considered significant.

RESULTS

The mean age of the patients was 7.8 (1–16 years). Forty-one patients were male, and 31 were female. The mean follow-up period was 16.2 months (3–42). The mean duration from admission to surgery after the initial complaint was 9.4 days (1–35). The mean preoperative fever measurement was 37.5 °C (37–40.1). The mean preoperative CRP value in the patients was 7.38 mg/dl (2–25.6), the sedimentation rate was 62.2 mm/h (40–102), and the WBC count was 11,600 cells/mm^3 (10,300–23,600). The average leukocyte count in the

aspirate material was 50,280 cells/mm^3 (32,000–78,000). At the third month of follow-up, the mean CRP level was 1.1 (0.2–4.9) mg/dl, the sedimentation rate was 23.0 mm/h (5–44), and the WBC count was 6,500 cells/mm^3 (3,300–7,800).

There was a statistically significant difference between the preoperative and 1-month postoperative values of the sedimentation rate, CRP level and WBC count in all patients ($p < 0.05$) (Table 1).

There was no statistically significant difference between the 1-month and 3-month postoperative values of the sedimentation rate, CRP level and WBC count as assessed with the Mann-Whitney U test ($p > 0.05$) (Table 1),

In the culture-positive group, the mean age was 7.3 years (1–16), the preoperative complaint duration was 9.6 days (1–32), the postoperative hospital stay was 3.4 days (2–8), the preoperative fever measurement was 37.7 °C (37–40.1), the preoperative sedimentation rate was 63.4 mm/h (40–102), the CRP level was 7.2 mg/dl (2–25.6), the WBC count was 12,200 cells/mm^3 (10,000–16,200), and the average leukocyte count was 54,300 cells/mm^3 (38,000–78,000) in the aspirate materials.

At 3 months postoperatively, the sedimentation rate was 23.2 mm/h (5–44), the CRP level was 1.3 mg/dl (0.2–2.8), and the WBC count was 6,100 cells/mm^3. (300–9,700). Factor-specific antibiotherapy was initiated in culture-positive patients.

Among the 30 patients with positive cultures; methicillin-sensitive *Staphylococcus aureus* (MSSA) growth was found in 21 patients, *S. pyogenes* in 4 patients, *S. hominis* in 2 patients, methicillin-resistant *Staphylococcus aureus* (MRSA) in 1 patient, *E. coli* in 1 patient, and *E. cloacae* in 1 patient.

Among the culture-positive patients; ceftriaxone + clindamycin was administered in 19 patients, ceftazidime + clindamycin + teicoplanin in 9 patients, Meronem + teicoplanin in 1 patient and ceftazidime in 1 patient. These treatments were administered for 6 weeks.

In the culture-negative group, the mean age was 8.1 (1–16), the preoperative complaint duration was 9.2 days (1–35), the postoperative hospital stay was 3.8 days (2–10), the preoperative fever measurement was 37.4 °C (37–39.8), the preoperative sedimentation rate was 61.3 mm/h (46–100), the CRP level was 7.5 mg/dl (2–16.3), the WBC count was 11,200 cells/mm^3 (10,000–23,600), and the average leukocyte count was 47,400 cells/mm^3 (32,000–63,000) in the aspirate materials. At 3 months postoperatively, the sedimentation rate was 22.9 mm/h (6–44), the CRP level was 0.97 mg/dl (0.1–2.3), and the WBC count was 6,800 cells/mm^3 (4,500–11,300). 4-week antibiotherapy was started for patients who had negative culture results. Antibiotherapy was terminated according to the decrease in serum parameters in weekly controls. The treatments of ceftriaxone + clindamycin administered in 34 patients and cefotaxime + gentamicin administered in 8 patients were completed in 4 weeks.

We observed complications in 4 of 30 culture-positive patients. Two patients underwent second debridement. One of the patients who was readmitted for second debridement had 15 flexion contractures in the knee. Other patient recovered without any problem after second debridement. One patient developed avascular necrosis of the hip, and One patient developed shortness in the hip due to AO.

We observed complications in 3 of 42 culture-negative patients. Two patients underwent second debridement. After second debridement patients healed without any problems. There was no reproduction in the second debridement cultures. Movement restriction of the left hip occurred in 1 patient due to SA. After physical therapy, we observed 15 degrees of flexion restriction and 10 degrees of abduction limitation according to the opposite hip of this patient.

When the patients with complications were examined, the mean duration from admission to surgery was 10.6 days (7–24) after the onset of clinical complaints.

There was no statistically significant difference between the two groups in terms of age, preoperative complaints, postoperative hospital stay, or preoperative fever or in terms of the sedimentation rate, CRP level or WBC count between the preoperative and 3-month postoperative values. Only a statistically significant difference was found in the leukocyte count in the aspirate materials between the two groups (Table 2).

DISCUSSION

AO or SA is an inflammatory disease that causes serious damage to bones or synovial joints (9, 17). This disease is mostly caused by bacterial factors. Furthermore, AO and SA can also be clinically diagnosed together. Early diagnosis of SA or AO is very important for preventing long-term sequelae in children. Transient synovitis is the most common disease for the differential diagnosis of septic arthritis. There are many studies in

Table 1. Serum parameters of patients preoperatively, 1 month and 3 months

	Preop(72) mean ± SD	1st month (72) mean ± SD	3rd month (72) mean ± SD	p value*	p value**
CRP mg/dl	7.38 ± 4.7 (2–25.6)	1.4 ± 1.3 (0.2–3.1)	1.1 ± 1.3 (0.2–4.9)	0.000	0.552
SED mm/h	62.2 ± 21.5 (40–102)	21.2 ± 4.7 (4–35)	23 ± 3.9 (5–44)	0.000	0.692
WBC cells (.10^3)/mm^3	11.6 ± 7.83 (10.3–23.6)	6.7 ± 4.9 (3.5–7.4)	6.5 ± 4.6 (3.3–7.8)	0.000	0.791

* Mann-Whitney U test between serum parameters of preoperatif and 1st month
** Mann-Whitney U test between serum parameters of 1st month and 3rd month

Table 2. Demographics and clinical features of patients

	Total (72)	Culture-positive group (30)	Culture-negative group (42)	p value*
Age (year)	7.8 ± 5 (1–16)	7.3 ± 5.5 (1–16)	8.1 ± 4.5 (1–16)	0.072
Gender				0.88
female	31	13	18	
male	41	17	24	
Preop fever	37.5° ± 0.81 (37–40.1)	37.7° ± 0.73 (37–40.1)	37.4° ± 1.1 (37–39.8)	
Preop CRP mg/dl	7.38 ± 4.7 (2–25.6)	7.2 ± 3.7 (2–25.6).	7.5 ± 4.1 (2–16.3)	0.791
Postop CRP mg/dl	1.1 ± 1.3 (0.2–4.9)	1.3 ± 0.4 (0.2–2.8)	0.97 ± 0.2 (0.1–2.3)	0.137
Preop SED mm/h	62.2 ± 21.5 (40–102)	63.4 ± 23.7 (40–102).	61.3 ± 20.1 (46–100)	0.68
Postop SED mm/h	23 ± 3.9 (5–44)	23.2 ± 16.4 (5–44)	22.9 ± 14.1 (6–44)	0.921
Preop WBC cells (. 10^3)/mm^3	11.6 ± 7.83 (10.3–23.6)	12.2 ± 7.7 (10–16.2)	11.2 ± 8.1 (10–23.6)	0.355
Postop WBC cells (. 10^3)/mm^3	6.5 ± 4.6 (3.3–7.8)	6.1 ± 5.8 (3–9.7)	6.8 ± 4.3 (4.5–11.3)	0.586
Aspiration leukocyt amount cells (. 10^3)/mm^3	50.28 ± 8.23 (32.0–78.0)	54.30 ± 8.53 (38–78)	47.40 ± 6.72 (32–63)	0.034
Preoperative complaints duration (day)	9.4 ± 5.2 (1–35)	9.6 ± 4.9 (1–32)	9.2 ± 5.6 (1–35)	0.744
Postoperative hospital stay (day)	3.6 ± 1.55 (2–10)	3.4 ± 1.4 (2–8)	3.8 ± 1.6 (2–10)	0.259
Follow-up (month)	16.2 ± 8.6 (3–42)	17 ± 10 (3–42)	15.3 ± 7 (3–38)	0.405
Complication	7	4	3	0.259

* Independent t-test
CRP – C-reactive protein, SED – sedimantation, WBC – white blood cell

the literature that have assessed the differential diagnosis of these two diseases (12, 20, 25). Preoperative laboratory findings and physical examination results provide common values for the differential diagnosis of these two diseases. In particular, in terms of laboratory parameters, CRP levels are more significant than other parameters (3). Levine et al. showed that 87% of patients did not have septic arthritis with a CRP level <1.0 mg/dl (15). In his study, Kocher showed that 93% of the findings could be used to diagnose septic arthritis, especially for the differentiation of SA and transient synovitis, by combining physical examination results and laboratory findings (14). In our study, the selection was made using Kocher criteria in patients undergoing surgery. In this respect, we believe that we have provided a method with the lowest chance of transient synovitis in patients with negative cultures diagnosed with SA or AO.

Cultures may not be observed in patients who undergo surgery with a diagnosis of SA or OM. There are many reasons for this phenomenon. Late diagnosis of patients, antibiotherapy that starts before surgery in these patients, the materials used in the isolation of the agent, the manner in which culture tissues are removed during surgery are some of the factors that contribute to this phenomenon. In the literature, this rate varies between 40% and 60% (13, 14, 19, 22). In a prospective study by Kocher et al., culture-positive results were obtained in 24 (47%) of 41 patients with septic arthritis (14). Kinugasa et al. obtained positive cultures in 17 (56%) of the culture materials taken during irrigation in 30 patients diagnosed with septic arthritis (13). In our study, 40% of the patients had positive cultures. Does a negative culture result indicate better outcomes in these patients? Or are these patients presumed to have septic arthritis? These questions have been discussed in the literature. In our study, it was observed that physical examination and laboratory results were not different in culture-negative patients compared to culture-positive patients. According to our study, negative culture results should not be considered a reason for surgeon comfort with these patients. Many factors can cause negative cultures in these patients. Therefore, we believe that the initiation of prophylactic antibiotherapy in these patients is beneficial for joint health. In our study, we did not take blood cultures in patients. We received tissue culture or aspirate culture from the infected area during surgery. Blood culture gives 25–50% positivity in patients with septic arthritis (10). This positivity is observed in the patient's febrile period and hematogenous septic arthritis. Compared to blood culture, excision culture or aspirate culture is a more specific and easier to isolate agent.

Lyon RM et al. found positive culture results in 30% of 76 patients with SA (16). There was no significant difference between the physical examination and laboratory parameters in culture-positive patients compared with culture-negative patients. Similar results were obtained in our study; however, a higher culture repro-

duction rate was obtained. Chang WS et al. compared 145 culture-positive and 64 culture-negative patients; pain, fever, movement limitations and CRP levels were found to be different between the two groups (4), and there was no significant difference in the sedimentation rate or WBC count. In this study, patients under 15 years of age were included. In our study, the difference between clinical complaints was not evaluated. This difference is very difficult to evaluate in pediatric patients. Therefore, we did not include the difference between clinical complaints in our study. In addition, surgical criteria were not fully determined in this study. This increases the likelihood that transient synovitis patients were unintentionally involved in the study.

According to the literature, MSSA is the most common pathogen in SA and AO. In the study of Sukswai et al., of the 129 patients who underwent surgery for SA and AO, 48 had MSSA growth, and 18 had MRSA growth (24). In a study by Goergens et al., among 149 patients, MSSA growth was found in 76% of the cultures that demonstrated reproduction (8). In our study, an MSSA growth rate of 70% was observed, which is in accordance with the literature. We suggest that antibiotic therapy should be considered for the joint health of patients with negative cultures. In addition, some pathogens are more difficult to produce than normal pathogens under laboratory conditions. This may be a factor in culture-negative patients.

The leukocyte count in synovial fluid is a highly sensitive parameter for septic arthritis (12). The leukocyte count, especially one above 50,000/mm^3, is an important cut-off value for surgery in septic arthritis. In our study, aspiration was performed in 44 patients. Aspiration material provides a great help in surgeon's decision, especially in cases where there are occasional diagnoses in Kocher criteria. this value has 72% sensitivity and 92% specificity. Baran et al. Show that > 50,000 culture cells/mm^3 in 36 of 44 culture-positive patients. Although the cultures of the remaining 8 patients were positive, the leukocytes count was below 50,000 cells/mm^3 in aspiration (2). We found aspiration material on average 47,400 in patients with negative culture in our study. There was also a significant difference in leukocyte counts between the two groups with aspiration. We believe that it is important to evaluate aspirate material as a decision-making criterion for surgery. Therefore, we think that the aspiration material affects culture results more than other serum parameters. However, aspiration may not always be possible in children. It is also difficult to use this criterion in patients with suspected acute osteomyelitis.

One limitation of this study was the retrospective nature. Additionally, the patients' operations were performed by different surgeons. There was also a difference between the operation times of the patients. However, we do not believe that this had an effect on culture reproduction.

CONCLUSIONS

According to our study, absolute cultures should be obtained from all patients who undergo surgery with a diagnosis of SA or AO, and these cultures should be appropriately isolated during surgery. However, it is not always possible to produce bacteria in cultures. The inability to isolate bacteria should not indicate an absence of SA or AO in these patients. If physical examination results and serum parameters support the diagnosis, the same aggressive treatment should be applied in culture-negative patients. Considering that MSSA is the most common bacteria in these patients, we believe that the initiation of empirical antibiotherapy is appropriate for joint health in patients.

Ethics approval

Our study has been approved by the Ethics committee of The Umraniye Training and Research Hospital

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