Comparing Treatment Between Identification and Non-Identification of Micro-Organisms in Pyogenic Spondylodiscitis

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Abstract:

Objective: The aim of this study was to determine an effective treatment by antibiotic for positive culture (culture+ve) pyogenic spondylodiscitis compared to a negative culture (culture-ve) by assessment of laboratory outcomes, Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP). The secondary objective is to determine incidence of pathogen micro-organisms of pyogenic spondylodiscitis.

Material and Method: The study design was a single-center retrospective study performed by the ICD10 computer database of the Department of Orthopedic Surgery in the Prince of Songkla University for patient diagnosed pyogenic spondylodiscitis. After exclusion was done, patients were divided into 2 groups of study. The first group was tissue culture+ve while the second group was tissue culture-ve. Patient culture+ve were analyzed for bacterial pathogens along with antibiotic sensitivity. In culture-ve patients were analyzed for the types of antibiotic and its usage. Both of two groups was compared with the effectiveness of treatment with ESR and CRP beforehand, and after four-weeks of treatment.

Results: Compared with 56 culture+ve patients, the 69 culture-ve patients were no significant difference in median difference of ESR and CRP at the time before treatment and at four-weeks, after treatment.

Conclusion: Antibiotic treatment of non-identified micro-organism pyogenic spondylodiscitis can be done by using the most common incidence of micro-organism. The effectiveness of antibiotic treatment was determine by ESR and CRP beforehand, and after four-weeks of antibiotic treatment.

Keywords: CRP, ESR, negative tissue culture, positive tissue culture, pyogenic spondylodiscitis

Introduction

Pyogenic spondylodiscitis (PS) is a bacterial infection of the spine. The prevalence of PS is more frequent in males and the elderly.[1,2] Identification of micro-organisms can be obtained by many techniques such as; a percutaneous biopsy (CT-guide biopsy), a mini-open trans-pedicular biopsy or an open surgical biopsy. Despite the improvement in the techniques of biopsy's nowadays, negative culture still remains a problem. In the Carragee et al.[3] study, it was reported that positive culture from percutaneous biopsy was between 43.0-73.0%, an open biopsy at 80.0%, and a negative culture of approximately 10.0-30.0%. In the Friedman et al.[4] study, it was reported that an initial positive percutaneous biopsy culture was at 50.0% which, improved 79.0% after a repeated biopsy. Some studies report the accuracy of percutaneous biopsy to be low as; 47.5-57.0%.[5,6] The main causative microorganism include gram-positive cocci, especially *Staphylococcus aureus*, which account for 40.0-60.0% of PS patients,[2,7-10] and gram-negative bacilli which constitute 15.0-23.0% of cases.[2,9] Antibiotic treatment of PS in culture-ve patients can be observed for a prognosis of treatment outcomes with Erythrocyte Sedimentation Rate (ESR) and C-reactive protein (CRP) which, is more sensitive than a complete blood count (WBC), as stated in the Yoon et al.[12] study, a decrease in ESR and CRP in first month, after antibiotic treatment, is a good prognostic sign.

In Thailand, incidence of PS, and pathogen is still unknown, but there is a higher tendency of PS incidence. Unfortunately, a percutaneous biopsy, and an open biopsy are not available at every hospital, and not suitable for a repeat biopsy in the initial culture negative biopsy. Antibiotic treatment for culture negative of PS is widely used having been chosen by incidence, and the physicians preference. To determine incidence of pathogens in the Thai population and guide the antibiotic treatments of negative culture with, the use of ESR, CRP to predict prognostic outcomes of antibiotic administration.

The aim of this study was to determine an effective treatment by antibiotic for culture+ve PS compared to culture-ve by assessment of laboratory outcomes (ESR, CRP). The secondary objective is to determine incidence of pathogen micro-organisms of PS.

Material and Method

The study design was a single-center retrospective study performed by ICD10 computer database of the Department of Orthopaedic Surgery in the Prince of Songkla University. Discharge diagnosis code of osteomyelitis of vertebra, osteomyelitis of vertebra: multiple site in spine, osteomyelitis of vertebra: occipito-atlanto-axial region (M462,4620,4621) between 2004-2014.

Inclusion criteria

1. Diagnostic and therapeutic pyogenic spondylodiscitis patients.

2. Complete data of ESR, CRP beforehand and four-weeks after antibiotic treatment.

3. Diagnostic pyogenic spondylodiscitis by magnatic resonance imaging (MRI).

4. Percutaneous or an open tissue biopsy was performed.

Exclusion criteria

1. Non-pyogenic spondylodiscitis.

2. Post-operative pyogenic spondylodiscitis.

3. Relapse of pyogenic spondylodiscitis.

4. Prior antibiotic treatment at the time of pyogenic spondylodiscitis.

5. Non-antibiotic treatment spondylodiscitis.

6. Incomplete data of ESR, CRP and imaging (MRI).

7. Incomplete follow up of patient.

After including patient population and exclusion was completed from the exclusion criteria. Selected patient population was divided into 2 groups of study. The first group was tissue culture+ve PS, while the second group was tissue culture–ve PS. Demographic data was collected in; gender, age, duration of disease, chief complaint, site and number of vertebral body infections, epidural abscess association, tissue biopsy procedure, duration of treatment as well as, inflammatory laboratory markers (ESR, CRP) beforehand and four–weeks after antibiotic treatment. In culture+ve patients were analyzed for bacterial pathogens in addition to, antibiotic sensitivity, and culture–ve patients were analyzed for types of anti–biotic and usage. Both of two groups was compared with the effectiveness of treatment with ESR and CRP before hand, and after four–weeks of antibiotic treatment.

Statistic analysis: continuous data was described as mean and standard deviation. Range and categorical variables were described as percentages, compared to continuous data with student t–test, comparison of catego–rical variables using chi–square and Fisher's exact test. Independent variables compared with Wilcoxon Rank Sum test.

Results

Population characteristic 540 patients registered with spondylodiscitis; 303 patients were excluded, because of 194 having inadequate data to diagnosis and 109 having tuberculosis spondylodiscitis. One hundred and sixteen out of 241 diagnosed pyogenic spondylo–discitis patients had incomplete data (incomplete laboratory findings, loss of follow up, or incomplete patient data).

The remaining 125 patients were included and evaluated. Fifty–six patients had a culture+ve tissue biopsy PS with 32 percutaneous tissue biopsy techniques and 24 had an open tissue biopsy. Sixty–nine patients were negative culture tissue biopsy PS with 52 having percutaneous tissue biopsy techniques and 17 having an open tissue biopsy.

The mean onset of symptoms to begin treatment was 8.8 (±8.2 S.D.) weeks with the initial, chief compliant of pain at 77.6% (n=97), neurological compromise at 21.6% (n=27), and fever at 0.8% (n=1). The lumbosacral vertebrae were most frequency involved at 70.4% (n=88), thoracic at 16.8% (n=21), cervical at 12.8% (n=16) with 2–levels of vertebrae involvement being the most presented at 88.0% (n=110), 3–levels involvement at 9.6% (n=12), 4–levels involvement at 1.6% (n=2), and one level involve–ment being rarely involved at 0.8% (n=1). Only 32.8% (n=41) were associated with an epidural abscess.

Patients treated only with antibiotic medication was at 67.2% (n=84), open debridement with antibiotic medication was 20.8% (n=26), and open debridement and instrumentation with antibiotic medication was 12.0% (n=15). The mean, total duration of antibiotic treatment was 99.9 (±71.8 S.D.) days, initial intravenous antibiotic medication was 36.5 (±23.2 S.D.), and continuous oral antibiotic medication was 62.6 (±72.6 S.D.). The median ESR was 82 (IQR 6–140) mm/hr before antibiotic treatment, and 43 (IQR 1–140) mm/hr four–weeks after antibiotic treatment. The CRP was 2.4 (IQR 0.6–19.2) mg/dL before antibiotic treatment, and 0.6 (IQR 0.6–9.6) four–weeks after antibiotic treatment (Table 1).

Micro–organism and antibiotic

The micro–organism pathogens were identified in 56 patients (Table 2). The most frequent pathogen was *Staphylococcus species* 50.0% (n=28) which, composed of 75.0% (n=21/28) *Staphylococcus aureus* (coag. positive), 10.7% (n=3/28) *Staphylococcus epidermidis*, 7.1% (n=2/28) *Staphylococcus aureus* (coag. negative), 7.1% (n=2/28) *Staphylococcus aureus* (MRSA). The second most frequent pathogen was *Escherichia coli* 17.8% (n=10/56), 8.9% (n=5/56) *Streptococcus* species and 3.5% (n=2/56) of *Pseudomonas aeruginosa*.

Table 1 Demographic data of 125 included pyogenic spondylodiscitis patients

Demographic data	Culture positive n=54	Culture negative n=69	P–value
Gender (%)			
Female	17 (30.4)	24 (34.8)	0.739
Male	39 (69.6)	45 (65.2)	
Age (mean; S.D.)	53.1 (15.6)	57.1 (12.4)	0.116
Week from onset of symptom (mean; S.D.)	4 (4, 8)	8 (4, 12)	0.018*
Chief complaint (%)			
Pain	41 (73.2)	56 (81.2)	
Neurological compromise	15 (26.8)	12 (17.4)	0.275
Fever	0 (0.0)	1 (1.4)	
Site of lesion (%)			
Cervical	9 (16.1)	7 (10.1)	0.553
Thoracic	37 (66.1)	51 (73.9)	
Lumbosacral	10 (17.9)	11 (15.9)	
Number of vertebral involvement (%)			
1	1 (1.8)	0 (0.0)	
2	52 (92.9)	58 (84.1)	
3	3 (5.4)	9 (13.0)	0.129
4	0 (0.0)	2 (2.9)	
Epidural abscess (%)			
Positive	14 (25.0)	27 (39.1)	0.138
Negative	42 (75.0)	42 (60.9)	
Treatment (%)			
Antibiotic	32 (57.1)	52 (75.4)	
Open debridement + antibiotic	15 (26.8)	12 (17.4)	0.085
Open debridement + Instrumentation + antibiotic	9 (16.1)	5 (7.2)	
Day of antibiotic treatment (median; IQR)			
Total	84 (66.5, 118)	77 (44, 119)	0.180
Intravenous	42 (30, 42)	32 (28, 42)	0.074
Oral	42 (28, 72.2)	42 (14, 70.2)	0.278
Erythrocyte sedimentation rate (median; IQR)			
Before treatment	92.5 (61.2, 102)	79 (60, 100)	0.363
Four–week after treatment	41 (19.8, 64)	44 (25, 63)	0.823
C–reactive protein (median; IQR)			
Before treatment	4.8 (1, 9.6)	2.4 (0.6, 9.6)	0.233
Four–week after treatment	0.6 (0.6, 0.8)	0.6 (0.6, 0.6)	0.547

*statistical significance: $p < 0.05$

S.D.=standard deviation, IQR=interquartile range

Table 2 Bacteria of culture positive pyogenic spondylodiscitis

Bacteria	n=56
Staphylococcus spp.	28
Staphylococcus aureus (coag. positive)	21
Staphylococcus epidermidis	3
Staphylococcus aureus (coag. negative)	2
Staphylococcus aureus (MRSA)	2
Escherichla coli.	10
Streptococcus spp.	5
Pseudomonas aeruginosa	2
Klebsiella pneumoniae	2
Others *Salmonella, Citrobacter, Brucella*)	9

The selected antibiotic for culture–ve patients (Table 3) were 28.99% (n=20) high dose Ceftriaxone, 26.08% (n=18) standard dose Ceftriaxone, 20.29% (n=14) Cefazolin, 5.79% (n=4) standard dose Ceftriaxone plus Cloxacillin and 4.35% (n=3) Cloxacillin. The selected antibiotic for culture+ve patients was based on antibiotic sensitivity.

Table 3 The antibiotic treatment for negative culture pyogenic spondylodiscitis (n=69)

Type of antibiotic	Number (%)
Ceftriaxone 2 gm intravenous 24 hourly	20 (28.9)
Ceftriaxone 2 gm intravenous 12 hourly	18 (26.0)
Cefazolin 1 gm intravenous 6 hourly	14 (20.2)
Ceftriaxone 2 gm intravenous 24 hourly and Cloxacillin 1 gm intravenous 6 hourly	4 (5.7)
Cloxacillin 1 gm intravenous 6 hourly	3 (4.3)
Others	10 (14.4)

Two groups of patients had no difference between sex (p–value=0.739), age (p–value=0.116), onset of symptoms at the beginning of treatment time (p–value=0.018), initial chief compliant (p–value=0.275) along with the duration of antibiotic treatment (p–value=0.18).

The median of ESR had no significant difference in culture–ve patients at the time before antibiotic treatment; culture–ve group is 79 (IQR 60–100) mm/hr and culture+ve group is 92.5 (IQR 61.2–102) mm/hr; p–value=0.363, and no significant difference in median of ESR four–weeks after antibiotic treatment; culture–ve group is 44 (IQR 25–63) mm/hr. and culture+ve group is 41 (IQR 19.8–64) mm/hr; p–value=0.823, no significant difference in median difference between beforehand and four–weeks after antibiotic treatment of culture–ve group is –32.8 (±26.4 S.D.) with culture+ve group is –33.8 (±34.3 S.D.); p–value=0.857

The median of CRP had no significant difference in culture–ve group with culture+ve group at the time before antibiotic treatment; culture–ve group is 2.4 (IQR 0.6–9.6) mg/dL, and culture+ve group is 4.8 (IQR 1–9.6) mg/dL; p–value=0.233 and no significant difference in median of CRP four–weeks after antibiotic treatment; culture–ve group is0.6 (IQR 0.6–0.6) mg/dL, and culture+ve group is 0.6 (IQR 0.6–0.8) mg/dL; p–value=0.547, no significant difference in median difference between beforehand and four–weeks after antibiotic treatment of culture–ve group is –1,8 (IQR –4.2–0) with culture+ve group is –3.3 (IQR –9–0); p–value=0.241.

The median of both ESR and CRP, before and after treatment. Four–weeks, after with open debridement and antibiotic in the culture+ve group was significantly decreased.

Table 4 The antibiotic, with surgical treatment, for culture positive and culture negative pyogenic spondylodiscitis (n=41)

Treatments	Before treatment Median (IQR)	Four–weeks Median (IQR)	P–value
Open debridement + antibiotic			
Culture + (n=15)			
ESR	99.5 (82.5, 101.5)	57 (22.5, 76.5)	0.003*
CRP	9.6 (1.8, 19.2)	0.6 (0.6, 1.8)	0.005*
Open debridement + antibiotic			
Culture – (n=12)			
ESR	81 (76, 95.8)	51.5 (35, 78)	0.033
CRP	0.9 (0.6, 3)	0.6 (0.6, 1.2)	0.090
Open debridement + Instrumentation + antibiotic			
Culture + (n=9)			
ESR	82 (76, 93)	35 (23, 41)	0.019
CRP	4.8 (0.6, 9.6)	0.6 (0.6, 0.6)	0.035
Open debridement + Instrumentation + antibiotic			
Culture – (n=5)			
ESR	82 (69, 92)	64 (54, 68)	0.278
CRP	9.6 (2.4, 9.6)	0.6 (0.6, 1.2)	0.169

Wilcoxon siged rank test

*statistical significance: p<0.05

IQR=interquartile range, ESR=Erythrocyte Sedimentation Rate, CRP=C–reactive protein

Discussion

Pyogenic spondylodiscitis with serious complications caused by miss diagnosis, or inadequate treatment is severe, and may result in; spinal morphology destruction, spinal deformity, neurological impairment as well as, sepsis. Prompt diagnosis along with, correct treatment is key to a successful outcome. The significant factor associated to PS outcome is comorbidity[12] 35.6% diabetic mellitus, 15.6% chronic liver disease, 6.7% systemic infection condition, 4.4% end stage renal disease and cancer 4.4%. In this study, Incidence and comorbidity are not determined, it was however, found that incidence has risen every year (Figure 1).

The patient characteristics of PS showed no difference in each study, and correlated to this study males had higher incidence than females by about a 2:1 ratio. The mean age is 55.3. Pain is the most clinical complaint of the disease 77.6% with a mean onset of symptoms about 62.2 days, and infection site at lumbo–sacral (70.4%) is higher than thoracic (16.8%), and cervical (12.8%) with 2–levels of vertebras involved (88.0%), PS has no epidural abscess association 2:1, and a mean duration of antibiotic treatment of about 99.9 days with, 36.5 days of parenteral route with, 62.6 days of enteral route.
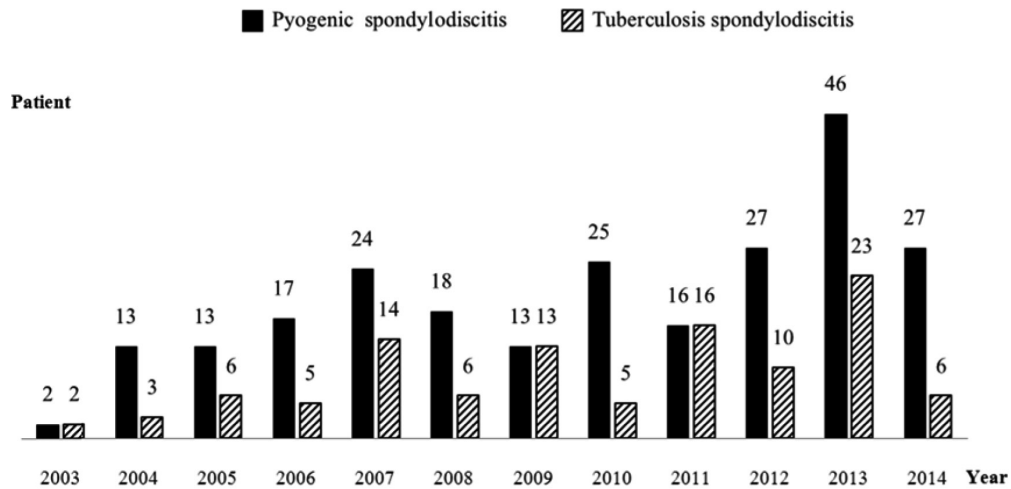
Figure 1 Incidence of pyogenic spondylodiscitis and tuberculosis spondylodiscitis

The micro–organism identification, with tissue biopsy, has an important role in the diagnosis and susceptibility of antibiotics. Friedman et al,[4] reported positive initial percutaneous biopsy culture for 50.0% of 24 cases, and improvement up to 79.0% on a repeat biopsy. Some literature suggests an open surgical biopsy rather than a negative percutaneous biopsy.[13] In this study, patients were sent for a percutaneous biopsy in 163 of the cases, and an open surgical biopsy in 78 of the cases. From 241 PS cases with positive tissue culture for 105 cases (43.0%), 59 cases for percutaneous biopsy and 46 cases for open biopsy. Negative tissue culture for 136 cases (56.4%), 104 cases for percutaneous biopsy and 32 cases for open biopsy. Unfortunately, a repetition of a percutaneous biopsy was not suitable in some conditions, and even though an open surgical biopsy still has negative tissue culture in 32 cases from 78 of open biopsy cases (41.0%). The treatment sometimes depends on incidence of micro–organism pathogens in each area.

Half of the micro–organism pathogens of PS are *S. aureus* with the second and third most common pathogens varying between each region. In the Devkota

et al.[10] study, *S. aureus* is the most common pathogen (45.2%), *E. coli* (16.6%), *K. pneumonia* (14.2%). Where as, in the Aagaard et al.,[11] study, the most common pathogen is *S. aureus* (58.0%) with the second–most common being the *Streptococcus species* (12.0%), and *E. coli* (4.0%). In this study we found that the most common pathogen is *Staphylococcus spp.* (50.0%), and the second most common being *E. coli* (17.8%), *Streptococcus spp.* (8.9%) is the third most common. There is a variable in the micro–organism pathogen in each region, but *S. aureus* is still the most common pathogen in PS.

Due to unidentified micro–organism pathogens, antibiotic treatment of PS has to use the incidence of micro–organisms to determine appropriated antibiotic treatment. In this study we identified antibiotic adminis–tration in negative tissue culture, the most common antibiotic administration being; Ceftriaxone 2 gm intra–venously once a day (28.9%), the second most common being Ceftriaxone 2 gm intravenously every 12 hrs. (26.0%) Cefazolin 1 gm intravenously every 6 hrs (20.2%) was the third most common. Because, most common micro–organisms of PS are *S. aureus* and *E. coli* from this

study, Ceftriaxone is a suitable antibiotic of choice in the treatment of PS due to its wide antimicrobial spectrum (*S. aureus*, coagulase negative *S. aureus*, *S. pneumoniae*, *Streptococcus spp.*, *E. coli*, *Enterobacteriaceae*. A high dose of Ceftriaxone (2 gm intravenous route every 12 hrs) can penetrate the blood, brain barrier, and serves as treatment for bone and joint infections.

To determine the effectiveness of antibiotic treatment of pyogenic spondylodiscitis. ESR and CRP are sensitivity inflammatory markers for infection. ESR is a sensitivity marker for infection, but has a lack of specificity. CRP is also a sensitivity marker for infection, and some authors suggest that CRP is a preferable marker for monitoring treatment response.[14]

From the Yoon et al.[12] study, reported a decrease in ESR and CRP four-weeks after antibiotic treatment is a good prognostic sign. In this study, we observed the effective of antibiotic treatment of PS from ESR and CRP, and compared the effectiveness of the treatment before and four-weeks after antibiotic treatment. Because, clinical and imaging investigation cannot represent stages of infection as well as inflammatory laboratory makers, and after spinal infection has subsided however, clinical pain or destruction signs in imaging can be persist and/or progressive from instability of spinal morphology.

In this study, we observed ESR and CRP at the time before treatment the median of ESR had no significant difference in negative (median 9 mm/hr) with positive (median 92.5 mm/hr) culture; p-value=0.363 and no significant difference four-weeks after antibiotic treatment; negative culture (median 44 mm/hr), and positive culture (median 41 mm/hr); p-value=0.823, no significant difference in the median difference between before and four-weeks after antibiotic treatment of negative culture −32.8 (±26.4 S.D.) with positive culture

−33.8 (±34.3 S.D.); p-value=0.857. The median of CRP had no significant difference in negative (median 2.4 mg/dL) with positive culture (median 4.8 mg./dL) at the time before antibiotic treatment; p-value=0.233 as well as, no significant difference four-weeks after antibiotic treatment; negative culture (median 0.6 mg/dL) and positive culture (median 0.6 mg/dL); p-value=0.547 and no significant difference in median difference between before and four-weeks after antibiotic treatment of negative culture −1,8 (IQR −4.2−0) with positive culture −3.3 (IQR −9−0); p-value=0.241

From this study, we can postulate that antibiotic treatment of non-identified micro-organism PS can be done by usage of micro-organism incidence, in meaning of *S. aureus*, *E. coli*, and *Streptococcus spp.* organism susceptibility. In addition to, the usage of inflammatory laboratory markers (ESR, CRP) to monitor treatment response.

There were several limitations in this study. The first being, we had many drop out of the population, Because of nondefinite diagnosis, and incomplete medical documentation. Secondly, in this study we determined only laboratory markers four-weeks after treatment which cannot evaluate end result outcomes over the long term. In addition to this, the antibiotic medications were too heterogeneous in positive tissue culture to compare. Lastly this study is a single-center retrospective study which represents only the southern part of Thailand.

Conclusion

Antibiotic treatment of non-identified micro-organism pyogenic spondylodiscitis can be done by using the most common incidence of micro-organism.

The effectiveness of antibiotic treatment was determine by ESR and CRP beforehand, and after four-weeks of antibiotic treatment.

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