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Conservative Treatment of Spondylodiscitis: Possible Therapeutic Solution in Case of Failure of Standard Therapy

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ABSTRACT

Introduction: Spondylodiscitis (SD) is an uncommon disease but not rare, because it represents around 3–5% of all cases of osteomyelitis. Late diagnosis and/or inadequate treatment often cause irreversible damage to cause neurological deficit. Most require only conservative treatment, sometimes a surgical approach is required. **Aim**: The purpose of this study is to propose a conservative protocol to treat spondylodiscitis when the standard conservative treatment has failed. This alternative treatment has been for a long time at the Codivilla-Putti Institute. **Methods**: We performed a prospective cohort study of 192 consecutive patients who underwent paravertebral intramuscular injections of antibiotic associated with standard treatment at our Center from January 2010 to December 2015 with SD. Of this 192 patients we selected 98 who had already undergone standard antibiotic therapy at another hospital without resolution of the disease. All patients have performed our protocol that provides a total of 3 cycles, each of 3 weeks, repeated at approximately 5 weeks apart. For each patient we evaluated Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), White Blood Cells (WBC) indexes, SF36 and VAS Score at the beginning and at the end of the treatment. **Results**: At a mean follow up of 22 months (range 60-12), clinical healing was achieved in 87 patients (88,9%) of cases with significant reduction in back pain and functional limitation. The VAS Score and the SF36 were better at the end of treatment compared to previous "GOLD STANDARD" treatments in the previous hospitalization in another hospital. In most cases there were slightly reduced in inflammatory indexes. **Conclusion**: There are no studies in the literature demonstrating the effective efficacy of local infiltrative treatment with antibiotics, associated with standard treatment protocol. We believe that our protocol in treating SD, favors an early functional recovery, and be able to offer more chance of success than the standard treatment.

Keywords : Spondylodiscitis; Pyogenic spondylodiscitis; Spinal infection; Postoperative spondylodiscitis; Vertebral osteomyelitis; Antibiotic therapy; Conservative treatment.

1. INTRODUCTION

The Spondylodiscitis (SD), also known as vertebral osteomyelitis, represent an infrequent but not rare disease, constitute about 3-5 % of all osteomyelitis with a bimodal distribution with peak incidence below 10 years and between 50-70 years of age, and mainly affect males to women (1-3). The incidence of this disease is constantly increasing, especially in patients with comorbidities such as diabetes mellitus, immunodeficiency, tumors, rheumatoid arthritis, alcoholism, hemodialysis, bacterial endocarditis, treatment with immunosuppressants and impaired nutritional status (4-5).

Staphylococcus aureus is the most frequently isolated etiologic agent in pyogenic vertebral osteomyelitis (PVO), present in 50% of patients (6), followed by gram- bacteria (E. Coli, P. aerouginosa, P. Mirablis, Enterococchi) (7-9). The treatment of this pathology is not currently standardized and is in continuous evolution (10-13).

The gold standard treatment is based, today, on conservative and/or surgical procedures (5), in cases where there is an important structural deformity (kyphosis above 15°, destruction of the vertebral body), presence of epidural abscess, neurological deterioration, chronic rachis pain, spondylodiscitis secondary to

surgical treatment or failure of conservative treatment (9, 14-15).

The cornerstone of conservative treatment consists of targeted antibiotic therapy lasting between 4 and 12 weeks associated with bed rest and the use of orthopedic busts (9, 14-15). Proper diagnosis and individual therapy can improve clinical outcomes and decrease the likelihood of failure and promote the healing. Still, the percentage of failure reported in the literature goes from 6.2 to 32% (9, 16-22) and the complete recovery from both the neurological and the analgesia point of view is very variable from 50 to 91% of cases (9, 21-25).

2. AIM

The aim of our work is to provide an alternative when the standard conservative treatment has failed, proposing a new procedure able to increase the percentage of healing and favor a return to daily life, reducing the possible complications due to the disease itself.

3. METHODS

We performed a prospective cohort study of 192 consecutive patients who underwent paravertebral intramuscular injections of antibiotic associated with oral treatment at our Center from January 2010 to December 2015 with PVO. Of this 192 patients we selected 98 according to our criteria as follows:

Inclusion criteria:

- SD pyogenic haematogenous or post-surgical (not indicated in the exclusion criteria) not responsive to standard treatment;
- Germ isolation causes infection;
- Clinic with rachialgia and functional limitation at the time of admission
- Informed consent to patient treatment and inclusion in our study;

Exclusion criteria:

- SD tubercular;
- SD post-surgical with the help of synthetic means and/or grafts;
- Structural deformity or vertebral collapse;
- Patients who have not completed the therapeutic protocol, without a minimum follow up of 24 months;
- Serious neurological deficits and/or paravertebral abscesses;
- Allergic to antibiotics;
- Concomitant infections, hepatic and/or renal failure and malignant tumors;
- Use of psychotropic drugs.

We evaluated the Indices of inflammation, white blood cells, VAS Score and SF36 at the beginning and at the end of the treatment. The study was approved by the Ethics committee of our institution and informed consent was required.

Therapeutic Protocol

It consists of daily injections of targeted antibiotic, administered by intramuscular paravertebral in correspondence of the affected vertebral segment, these are performed in synergy with the standard conservative treatment. The protocol provides a total of 3 cycles, each of 3 weeks, repeated at approximately 5 weeks apart in which the antibiotic is taken orally.

Antibiotic and Infiltration Preparation Method

A specific antibiotic is diluted with a 1 cc of mepivacaine hydrochloride at 2% and then introduced into a syringe of 5 cc. The preparation procedure is performed under conditions of complete sterility, the sterile fenestrated drape is placed, the skin is disinfected in the affected area with iodopovidone (iodine at 10%).

Position of the Patient

The patient is placed in prone decubitus, the syringe containing the diluted antibiotic is placed in the paravertebral region of the affected vertebral tract with needle inclined at an angle of 45° with respect to the horizontal plane.

Choice of the Antibiotic to be Injected by Muscle

The choice of the antibiotic is based on the interpretation of the antibiogram of the isolated germ, in collaboration with the department of infectious diseases, using the breakpoints of the EUCAST guidelines (The European Committee on Antimicrobial Susceptibility Testing), adapting the values to the sensitivity and resistance of the germs present in our Region. Taking into consideration the possibility that the patient may be allergic and/or is affected by resistant bacteria to a specific drug of first choice, we have been able to implement the protocol equally, administering drugs of second or third choice (Table 1). We have created this scheme based on the breakpoints present in the EUCAST guidelines.

Anesthetic

The use of the antibiotic intramuscularly associated with an anesthetic makes it less painful to inject some antibiotics. In our study we used Mepivacaine hydrochloride which has an average duration of action of 1,5-2 h to 5 hours, and a Emivita of 2 hours, has a molecular form very similar to that of lidocaine, compared to this lastly, it does not need to be associated with the adrenaline which has an important vasoconstrictive action at the injection site.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 24.0, SPSS, Chicago, USA). Normal distribution was determined by the Kolmogorov-Smirnov test. Categorical variables were compared using the Chi-square test or the non-parametric Mantel-Haenzel test, and continuous variables with Student's t-test for paired samples.

Data were presented as odds ratio (OR) with 95% confidence interval (CI). A value of $P < 0.05$ was considered statistically significant for all tests.

4. RESULTS

The 98 patients are so divided (51 males and 47 females) of average age 57 years (range 27-82 years), the most affected vertebral district was the lumbar side with 80 cases, followed by the dorsal and the cervical respectively with 16 and 2 cases. In 29 patients (29,59%) the cause of PVO was secondary to surgery (hemilaminoartrectomy, microdiscectomy, decompression for verte-

bral stenosis). At a mean follow up of 22 months (range 60-12), clinical healing was achieved in 87 patients (88,9%) of cases with a significant reduction in back pain and functional limitation. In the literature, it is shown that in the course of vertebral infection, the values of Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP) and White Blood Cells (WBC) are high (26, 27).

Pathogens Identified	I Choice Of Drug		II Choice Of Drug		III Choice Of Drug	
Stafilococcus	Cefazolin	1 GR	Clindamycin	600 MG	Amikacin	500 MG
Enterococcus	Penicillin G	1 GR	Daptomycin	500 MG	Ampicillin	1 GR
Pseudomonas A.	Cefepime	1 GR	Meropenem	1 GR	Ceftazidime	1 GR
Streptococcus	Penicillin G	1 GR	Ceftriaxone	1 GR	Cefazolin	1 GR
Others Antibiotics Used For MRSA/ Others Pathogens	Cefuroxime-750MG, Imipenem/Cilastatin 500+500 MG,		*Netilmicin-150MG*, Streptomycin 1 GR,		Gentamicin-80MG, *Trimethoprim/Sulfamethoxazole* 40 MG+200 *MG*.	

Table 1. Scheme of antibiotic choice, based on the interpretation of the antibiogram, using the breakpoints of the EUCAST guidelines.

In our study, the assessed data were shown to be uniform to those present in the literature with ESR values at admission which were 40,05 ±(33.72), while at the end of our treatment were ESR 14.14 ± (11.61) and were results statistically significant with a P value (P) less than 0.00 with IC to 95% (25.01 - 38.82); The CRP values at admission were 8.09 ± (33.72), while at the end of our treatment were PCR 2.75 ± (2.34) and were results statistically significant with (P) less than 0.003 with a IC to 95% (1.90 - 8.69); The WBC values at admission were WBC 6.59 ± (2.08), while at the end of our treatment were WBC 5.34 ± (1.77) and were results statistically significant with (P) less than 0.00 with a IC to 95% (1.72 – 5.23).

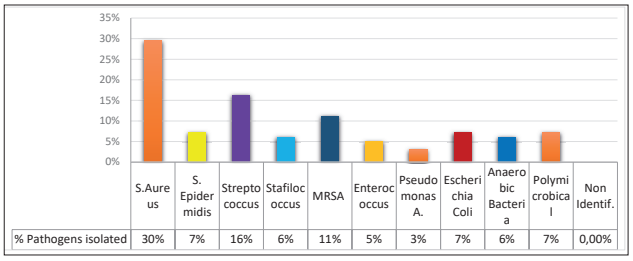

Figure 1. Graphic of pathogens isolated in percentage

The microbiology results were based on blood culture, CT guided biopsy or open biopsy. The most common offending organism was methicillin sensitive Staphylococcus aureus (MSSA) (n=29), followed by Streptococcus (n=16), Methicillin resistant Staphylococcus aureus (MRSA) (n=11), and Escherichia coli (n=7), MSSA was the most common organism found in the treatment group (Table 1, Figure 2).

For each patient were evaluated SF36, VAS Score at the entrance to the hospital, at the end of the third cycle and during follow-up. The VAS Score and the SF36 were better at the end of treatment, compared to the previous "GOLD STANDARD" treatment carried out elsewhere. The patients in our study are those patients who have not had symptomatic resolution. These had previously been treated at other centers with standard protocol without success.

We found that of these 98 selected patients, treated with our therapeutic protocol, the 88.9% (87 patients out of 98) has healed and is well. We had a 11.1% failure rate (11 patients). Over 80% of patients before starting treatment had continuous pain even in the obligatory supine position. During the first 5 days of treatment, 78% of these patients showed a significant reduction in the VAS Score and managed to assume the position sitting in bed, always with the aid of the spinal brace.

5. DISCUSSION

After careful bibliographic research, we can state that there are no studies to prove the effective efficacy of treatment with paravertebral muscle injection with antibiotic, associated with the standard therapeutic protocol. The standard conservative treatment, as understood in the literature, consists in the administration of oral and parenteral antibiotics for a duration between 6 and 12 weeks associated to the immobilization in discharge (8, 9).

In the literature is still debated the optimal duration of conservative treatment with antibiotics by endovenous (EV) and oral administrations (OS) (9, 28-36). In 2015, Rutges indicated that specific antibiotic therapy based on the antibiogram by OS and EV it must be administered for at least 6 weeks (2 weeks EV + 4 weeks OS), obtaining similar results compared to longer treatments (12 weeks) (9, 20, 34-41).

When possible, the antibiotic therapy should be targeted on a well- identified microorganism to treat the PVO. Considered the multiplicity of microorganisms, it is essential to identify the specific agent causing the disease to obtain successful therapy. If the patient is neurologically intact and has structurally stable lesions, the antibiotic therapy should be postponed until the microorganism has been identified (2, 9). Once the etiological diagnosis has been performed, the targeted antibiotic therapy requires an assessment of an infectious specialist. The medical treatment fails when the symptoms, especially pain and functional impotence persist or worsen, the levels of ESR, CRP and WBC may be normal or remain elevated, depending on the state of the infection, whether in the planktonic or quiescent phase of the microorganism, instrumental examinations can help us to demonstrate an evolution of bone damage after specific antibiotic therapy during pyogenic infections (9, 22, 35). For nonspecific SD the duration of treatment varies according to the germ that causes it and the precociousness of the diagnosis.

The favorable evolution of the treated cases leads to the disappearance of the pains, to the improvement of the general physical state, to the normalization of the inflammation indexes, to the thickening of the bone lesions, and to the more or less complete ankylosis of the involved vertebrae. From the literature, it is clear that non-tbc SD "usually" have a favorable outcome, benefiting only from traditional conservative treatment (8, 14).

In our study, all patients had undergone, previously, a standard targeted antibiotic therapy (parenteral and oral) without resolution of the disease, in 100% of cases the germ was isolated by histological examination on percutaneous tc-guided biopsy, test of culture on the sample biopsy, on intraoperative swab or hemoculture. Intramuscular injections are a convenient alternative when medications can not be taken by mouth (some pathologies alter their absorption) or there are problems with swallowing. In addition, the intramuscular pathway is a good way to inject drugs that are inactivated by the gastric juices or hepatic level. This way guarantees a bioavailability of the drug almost comparable to the intravenous one (37). Once the injection at the level of the paravertebral muscles of the affected vertebral tract has been carried out, the blood vessels supplying that particular district, distribute the drug, through the venous vertebral plexuses, to the systemic cardiovascular circulation (38); We must however remember the study of Wiley and Trueta in which it is noted that the metaphyses and the cartilaginous end plates of the vertebrae represent the most frequent site for the establishment of hematogenous infection (39); this area consists of multiple slow-flowing anastomoses which, due to their predisposition, allow the drug, via the intramuscular pathway, to remain in the site of infection at the maximum of its concentration and at the same time for a relatively longer time compared to other anatomical districts (38-40).

The efficacy of the treatment was assessed by monitoring the indices of blood inflammation and by means of serial radiological controls (X-Ray, CT and MRI) (8, 41, 42). The laboratory findings in association with radiological images constitute the pivotal points for the diagnosis of vertebral column infections. The speed of erythrocyte sedimentation (ESR) and levels of C reactive protein (CRP) are fundamental for initial assessment and to follow patient response during and after therapy (2, 26, 27). All patients completed the 3 treatment cycles with duration of each cycle of 3 week, repeated after about 5 weeks, in which the antibiotic was taken exclusively orally.

However, it is documented in the literature that the standard therapeutic protocol has a non-negligible percentage of failure ranging from 6.2 to 32% (9, 16-22), characterized by persistence of rachialgia and functional limitation; The patients in our study are those patients already treated with the standard therapeutic protocol, who did not get the cure from the disease; we found that in these 98 selected patients, treated with our therapeutic protocol, 88,9% (87 patients out of 98) recovered and were well.

Furthermore, by analyzing our statistical data, evaluated through the SPSS program, we found that, the values of inflammation (ESR, CRP and white blood cells), the Vas Score and the SF36, achieved statistically significant results to consider our therapeutic proposal as a further possibility of treatment, effective in treating the non responsive PVO to the standard conservative protocol.

6. CONCLUSION

We believe our protocol in the care of the PVO:

- It represents a valid alternative to be considered in cases where the targeted standard therapy has failed;
- Promote a functional recovery and return to normalization of inflammation indices;
- Reduce the pain symptomatology and functional impotence;
- Can offer a chance of success when standard treatment has failed.
- Further controlled randomized studies are needed in double blind with larger case to demonstrate their actual efficacy and then propose it as a possible standard treatment in the therapy of pyogenic spondylodiscitis.

- **Author's contribution:** E.M.B., D.J.O., D.F., G.R., L.M., D.L., F.T., F.C. and M.A.R. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work, E.M.B. G.R. and L.M. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they are agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
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