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A new in vivo method to investigate antibiotic penetration and concentration in spontaneous infectious spondylodiscitis

Liang Zhang [a,b,1], Wen-jie Zhang [b,1], Bo Huang [a], Lin-wei Chen [a], Qi-zhi Sun [a], Bin Ni [a,*]

[a] Department of Orthopaedics, Changzheng Hospital, The Second Military Medical University, 415 Fengyang Road, Huangpu District, Shanghai 200003, China
[b] Department of Orthopaedics, Taizhou People's Hospital, 210 Yin Chun Road, Taizhou, 225300 Jiangsu Province, China

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ABSTRACT

Spontaneous discitis is unusual and typically affects children. Hematogenous delivery of an infectious organism is the likely main cause. Common treatment method including conservative and surgical treatments, which also needs prolonged antimicrobial therapy based on an effective inhibitory concentration, can be achieved on the local disc space. Intradiscal antibiotic concentration was measured after the disc was harvested after preventive administration of antibiotics in previous studies. On the one hand the disc cannot simulate the infection situation when the inflammation leads to end plate destruction, vascular invasion and increase of permeability. On the other hand antibiotic concentrations were measured in vitro which cannot tell the actual situation in vivo. It is necessary to find a reliable evaluation method to decide whether the antibiotic can penetrate and make an effective inhibitory concentration in the local disc at the beginning of the treatment in vivo. Systemic antibiotics like nutrients enter and leave the disc by the only way of passive diffusion. The postcontrast MRI has been widely used as a noninvasive method of studying transport into the disc. The enhancement following contrast administration can be measured in T1 sagittal MR images by placing suitable cursors and evaluating the signal intensity (SI) of the region. Therefore we hypothesise that serial postcontrast MRI can be used to measure antibiotic concentration in the infected intervertebral disc in vivo. If the hypothesis is verified, we can better determine the choice of antibiotics and antibiotic treatment regime at the beginning of the treatment to improve the treatment success rate.

Introduction

Although spontaneous infectious spondylodiscitis (SIS) is relatively rare and typically affects children, it poses to spine surgeons difficulties in management and can be associated with potentially high morbidity and mortality, because the lack of specific clinical symptoms results in misdiagnosis and wrong treatment [1,2]. Exact cause of SIS is not clear yet, but most scholars tend to support that hematogenous delivery of an infectious organism is the likely method of inoculation into the disc space. Most cases have upper respiratory tract, urinary tract or other parts of infection, elevated ESR before the onset of SIS and effective anti-infection treatment, which also supports the argument for the hematogenous spread theory [2–5].

Common treatment including conservative and surgical treatments, which also needs prolonged antimicrobial therapy based on an effective inhibitory concentration, can be achieved on the local disc space. While there are many methods for detecting drug concentration in serum few methods are applicable to the avascular intervertebral disc. Complicating this situation is the fact that the disc is structurally and functionally complex, which makes it difficult to predict local drug concentration within the disc through the serum concentration [6].

Intradiscal drug concentration was measured after the disc was removed after preventive administration of antibiotics in previous studies. There are several potential limitations and pitfalls in this method [6–8]. On the one hand the disc is in normal, ageing or degenerate conditions, and cannot simulate the infection situation when the inflammation leads to end plate destruction, vascular invasion and increase of the permeability. On the other hand drug concentrations were measured under in vitro conditions which cannot tell the actual situation in vivo. So it is necessary to find a reliable evaluation method to determine drug concentrations in the infected disc in vivo.

Nutrients and cellular metabolites enter and leave by way of passive diffusion from the blood vessels reaching the vertebral endplate [9]. Systemic antibiotics must also diffuse into the disc by this route. However, diffusion remains poorly understood, primarily because of the lack of a specific method to measure disc diffusion in vivo. In recent years, postcontrast MRI has been widely

* Corresponding author. Tel.: +86 13795326380.
E-mail address: zhangliang6320@sina.com (B. Ni).
[1] These two authors contributed equally to this article.

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used as a simple and noninvasive method of studying transport into the discs in animals and humans in vivo [10–12]. One can measure enhancement following contrast administration in T1 sagittal MR images by placing suitable cursors and evaluating the signal intensity (SI) of the region [12]. The SIs obtained from the precontrast film form the baseline value for SI (SI_{base}) and the SI at a particular time period (SI_{tp}) is measured serially. The enhancement percentage (EP) for each time period for a particular region of interest (ROI) is then derived as follows: $EP_{tp} = SI_{tp} - SI_{base}/SI_{base} * 100$. The maximum SI ($SI_{max}$) is defined as the maximum value of the SI obtained over the study period [13]. The peak enhancement is attained at 5 min in the vertebral body (VB) which was consistent with the blood and at 6 h in the nucleus pulposus (NP) following injection of contrast [9,13].

Presentation of the hypothesis

Theoretically, the permeability of the vertebral endplate could be altered by the local inflammatory microenvironment that is present during an infection. The noninvasive nature of postcontrast MRI and the possibility of calculating enhancement in various ROIs of the disc over different periods of time have opened up interesting opportunities to study disc diffusion and quantify the severity of end plate damage in vivo. Contrast agents and antibiotics penetrate into the intervertebral disc by the same diffusion way. In theory the more the contrast agent permeates into the disc, the stronger the degree of enhancement percentage. Therefore we hypothesise that serial postcontrast MRI can be used to measure drug concentration in the infected intervertebral disc and in vivo.

Evaluation of the hypothesis

There are a lot of experiments which have proven the feasibility of this hypothesis in some aspects.

Rajasekaran et al. [13] summed up a scoring system to measure the extent of damage in the vertebral endplate by precontrast and series post contrast MRI studies of 730 endplates of 365 lumbar discs from 73 individuals. This suggests postcontrast MRI can be used to study the vertebral end plate destruction. Raynauld [14] found that MRI can provide reliable and quantitative data on cartilage status throughout all compartments of the knee.

To further test our hypothesis, we will perform animal experiment in two steps. In the first step, we will develop a stable animal model of bacterial discitis. In the second step, dynamic postcontrast MRI and intravenous use of certain antibiotic will be given to the infected animal model. The EP_{max} of the VB and NP will be calculated. The antibiotic concentration within the disc and the VB will be determined with the high-performance liquid chromatography technique [6]. Then we will look for the relationship between the drug concentration and the EP_{max} of VB and NP to predict the drug concentration through EP_{max}.

Consequences of the hypothesis and discussion

The drug concentration measured using series postcontrast MRI in vivo provides us with whether antibiotics can penetrate into the infected disc space and achieve the effective concentration within the disc accurately in the early stage of treatment. By this method, we can better determine the choice of antibiotics and antibiotic treatment at the beginning of the treatment to improve the treatment success rate.

Conflicts of interest statement

None.

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