Steroid-induced osteonecrosis

THE NUMBER OF LESIONS IS RELATED TO THE DOSAGE

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Severe acute respiratory syndrome (SARS) is a newly described infectious disease caused by the SARS coronavirus which attacks the immune system and pulmonary epithelium. It is treated with regular high doses of corticosteroids. Our aim was to determine the relationship between the dosage of steroids and the number and distribution of osteonecrotic lesions in patients treated with steroids during the SARS epidemic in Beijing, China in 2003.

We identified 114 patients for inclusion in the study. Of these, 43 with osteonecrosis received a significantly higher cumulative and peak methylprednisolone-equivalent dose than 71 patients with no osteonecrosis identified by MRI. We confirmed that the number of osteonecrotic lesions was directly related to the dosage of steroids and that a very high dose, a peak dose of more than 200 mg or a cumulative methylprednisolone-equivalent dose of more than 4000 mg, is a significant risk factor for multifocal osteonecrosis with both epiphyseal and diaphyseal lesions. Patients with diaphyseal osteonecrosis received a significantly higher cumulative methylprednisolone-equivalent dose than those with epiphyseal osteonecrosis. Multifocal osteonecrosis should be suspected if a patient is diagnosed with osteonecrosis in the shaft of a long bone.

Osteonecrosis can be devastating when it affects the articulating surface of the hip, knee, shoulder or ankle. It may also involve the diaphysis or metaphysis of any bone, but in these locations it seldom becomes clinically significant. When it extends to three or more separate anatomical sites, it is termed multifocal osteonecrosis and the effect on the patient is proportionately greater. In those patients in whom osteonecrosis is steroid-induced there is evidence that the number of affected sites is related to the dose of steroids which has been given. However, because metaphyseal or diaphyseal lesions are asymptomatic, these studies may have missed or underestimated some lesions. Furthermore, some conditions such as systemic lupus erythematosus, transplants treated with immunosuppressive drugs and coagulation disorders which are treated with steroids, can cause spontaneous osteonecrosis. It was therefore difficult to establish from these studies whether the severity of the osteonecrosis was related to the dose of steroids administered.

Severe acute respiratory syndrome (SARS) is a newly described infectious disease caused by the severe acute respiratory syndrome-coronavirus (SARS-CoV) which principally damages the cells of the immune system and pulmonary epithelium. Treatment with steroids is required. Our aim was to analyse the relationship between the dosage of steroids and the number and distribution of osteonecrotic lesions seen in patients treated during the SARS epidemic in Beijing, China in 2003.

Patients and Methods

SARS first emerged in southern China during the final quarter of 2002. In the early Spring of 2003 the epidemic reached Beijing and many patients received high doses of steroids. Between September 2003 and January 2004 the Beijing Municipal Government organised the follow-up of medical staff and related personnel who had contracted the disease during the treatment and transportation of infected patients. A total of 426 staff, mostly doctors and nurses, were identified as having been infected and treated between March and May 2003. The diagnosis was confirmed using established World Health Organisation diagnostic criteria. The patients in our study were generally healthy before becoming infected so we had the opportunity to study the relationship between the dosage of steroid and osteonecrosis in a population without an apparent clinical predisposition. Patients were
divided into five groups for their follow-up based on where they worked. Only the 121 patients from the same geographical zone were followed up in a designated SARS hospital which could offer MRI evaluation of any area of osteonecrosis. The study was approved by the hospital Ethics Committee and all patients provided written informed consent.

Follow-up was by questionnaire which noted clinical details (Table I) and physical examination. Demographic data were collected by nurses and clinical data by orthopaedic surgeons (N-FZ, ZRL, H-YW, Z-HL) who belonged to a specialist group for the diagnosis and treatment of post-SARS osteonecrosis and had been appointed by the Beijing Municipal Government.

Both the dosage and duration of steroid use were retrieved from the hospital records. The dosage was recorded as cumulative, peak and mean daily methylprednisolone or its equivalent. A conversion factor of 1:1.25 was used to calculate the methylprednisolone-equivalent dosage of methylprednisolone and prednisone.

MRI using a 1.5-T magnet (GE Sigma Profile/Gold USA; General Electric Medical Systems, Milwaukee, Wisconsin) was performed on both shoulders, wrists, hips, knees, ankles and on the humeral, femoral and tibial shafts. For all, coronal T1-weighted spin-echo sequence was used (590/20 repetition time msec/echo time msec, a section thickness 5 mm, intersection gap 1 mm, field of view of 350 mm, matrix 256 × 256 pixels). If the diagnosis could not be established clearly on coronal T1-weighted images, sagittal and axial T1- and T2-weighted images were obtained.

Osteonecrosis was defined by its location, either subchondral or intramedullary, in which it was demarcated by a distinct marginal rim with low signal intensity that encompassed medullary fat on the T1-weighted images. Multifocal osteonecrosis was defined as disease involving three or more separate sites.2,3 The diagnosis was established jointly by radiologists and orthopaedic surgeons. The Association Research Circulation Osseous (ARCO) system was used for staging.10

Statistical analysis. SPSS version 11.0 for Windows (SPSS Inc., Chicago, Illinois) was used for all statistical analyses. All the data were coded, checked and entered into SPSS data sets. Means and SDs were calculated to characterise continuous variables. An independent samples t-test was used for comparing means between groups. The chi-squared test or Fisher’s exact test as appropriate were applied to compare the proportions between groups. A p-value ≤ 0.05 was taken to be significant.

Logistic regression models were applied to identify significant risk factors which were predictive of osteonecrosis including age, gender, weight, body mass index, duration of therapy, peak, mean daily and cumulative methylprednisolone-equivalent doses, past disease history (including use of topical corticosteroids), past and present smoking habits and alcohol consumption.

Results

Only 114 of the original 121 patients had detailed survey results and underwent evaluation by MRI (Table I). There were 80 women and 34 men of whom 25 (21.9%) were
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Of the 114 patients, 43 (37.7%) were found to have osteonecrosis. A total of 145 ARCO stage-I osteonecrotic lesions were detected by T1-weighted coronal imaging. The distribution of the lesions is shown in Figure 1. Of the 43 affected patients, 30 (69.8%) had only one or two areas of osteonecrosis and in these, involvement of the joints was the most common presentation, 53 of the 57 sites being epiphyseal and four diaphyseal (Fig. 2). The other 13 patients (30.2%) had multifocal osteonecrosis affecting between three and seven sites. In this group there were 65 epiphyseal lesions, principally involving the hip, knees and shoulders, and 23 diaphyseal lesions (Fig. 2). Diaphyseal lesions occurred in patients with multifocal osteonecrosis more commonly than in those with uni- or bifocal osteonecrosis (Fisher’s exact two-sided test, p = 0.004).

Intravenous methylprednisolone (40 mg/day to 980 mg/day) and oral prednisone (2.5 mg/day to 20 mg/day) had been administered to all patients within a mean period of 28.2 days (6 to 72). It was initially given to those who were deteriorating and was stopped when they began to recover. The mean time interval between starting steroid therapy and follow-up was 6.5 months (5 to 8).

Logistic regression analysis showed that the peak methylprednisolone-equivalent dose was the principal risk factor for uni- or bifocal osteonecrosis (p < 0.05). No risk factor was found to be associated with multifocal osteonecrosis.
The 43 patients with osteonecrosis had received significantly higher cumulative and peak methylprednisolone-equivalent doses and had been treated for longer than the 71 without osteonecrosis (Table I). The 13 patients with multifocal osteonecrosis received a significantly higher cumulative methylprednisolone-equivalent dose than the 30 with uni- or bifocal osteonecrosis (Table II). The patients with both epiphyseal and diaphyseal lesions received a significantly higher cumulative methylprednisolone-equivalent dose than those with only epiphyseal lesions (Table III). The distribution and risk of osteonecrosis and multifocal osteonecrosis are shown in Figures 3 to 5 and in Table IV.

Patients with osteonecrosis were no more likely to smoke, have a high alcohol intake, have a combined condition (smoking and alcohol abuse), or take other medication than those without osteonecrosis (Table I). Logistic regression analysis revealed that these variables were not significant risk factors for osteonecrosis (gender, p = 0.358; age, p = 0.461; weight, p = 0.33; height, p = 0.767; BMI, p = 0.253; smoking, p = 0.772; alcohol, p = 0.204).

Discussion
SARS is a newly described infectious disease, caused by the SARS-CoV.²,⁶ It mainly targets the immune system and seems to infect a variety of cell types in different organs. Despite this, in situ hybridisation and immunohistochemical tests have detected neither viral genomic sequences nor antigens in bone marrow. Both viral isolation and reverse transcriptase polymerase chain reaction tests performed on bone marrow have been negative.³ Other studies of patients infected with SARS have reported no signs of osteonecrosis when steroids have not been used⁵,¹¹ and therefore the latter is clearly associated with osteonecrosis.¹ The incidence of osteonecrosis in SARS patients is generally believed to be related to steroid therapy.¹ We have assumed, therefore on the basis of this limited evidence, that the SARS-CoV does not itself cause osteonecrosis and that steroid administration is an independent variable for SARS-related osteonecrosis.

Our study was performed after a mean of 6.5 months (5 to 8) from the initial treatment with steroids. It confirmed that the number of osteonecrotic lesions was directly related to the dosage of steroids and that a very high dose, more than 200 mg peak dose and more than 4000 mg cumulative methylprednisolone-equivalent doses, was a significant risk factor for multifocal epiphyseal and diaphyseal osteonecrosis. The distribution of the osteonecrotic lesions in multifocal osteonecrosis has been documented previously by several authors.²,³ In our study, we found a similar pattern, with a high incidence in the femoral head,
knee and head of the humerus. None of the previous reports mentioned osteonecrosis of the shafts of long bones in patients with multifocal osteonecrosis. In the 13 patients with multifocal osteonecrosis in our series, the shafts of the long bones were frequently affected which suggests that if a patient is found to have an osteonecrotic lesion in such a location, multifocal osteonecrosis should be suspected.

It has been suggested, that total-body isotope bone scanning should be used to screen for multifocal lesions. However, several authors have remarked on its lack of sensitivity in the early stages of the disease. It is not thought to be the best method of diagnosis and neither is it a good method for screening the opposite hip in patients with osteonecrosis of the femoral head.

We found a higher incidence of osteonecrosis and multifocal osteonecrosis using T₁-weighted coronal views than has previously been reported. The causal relationship between steroids and multifocal osteonecrosis may be due to differing vascular reactivity of each part of the skeleton as well as to the action of steroids on the circulation. Recent studies in animals have shown that the influence of steroids on vasoreactivity appears to be species- and tissue-dependent. On this basis the femoral head would be the best method of diagnosis and neither is it a good method for screening the opposite hip in patients with osteonecrosis of the femoral head.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

References