Treatment of bone-marrow oedema of the talus with the prostacyclin analogue iloprost
AN MRI-CONTROLLED INVESTIGATION OF A NEW METHOD
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Bone marrow oedema syndrome of the talus is a rare cause of pain in the foot, with limited options for treatment. We reviewed six patients who had been treated with five infusions of 50 µg of iloprost given over six hours on five consecutive days. Full weight-bearing was allowed as tolerated. The foot score as described by Mazur et al was used to assess function before and at one, three and six months after treatment. The mean score improved from 58 to 93 points. Plain radiographs were graded according to the Mont score and showed grade-I lesions before and after treatment, indicating that no subchondral fracture or collapse had occurred. MRI showed complete resolution of the oedema within three months.

We conclude that the parenteral administration of iloprost may be used in the treatment of this syndrome.

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Bone marrow oedema syndrome is a well-documented condition which occurs mainly in the head of the femur, but also at other sites. Involvement of the talus is rare and often overlooked. Few cases have been reported in the literature. Various options for treatment have been described, mainly for the head of the femur and the knee. These include symptomatic non-operative management with reduction of weight-bearing, analgesic and anti-inflammatory medication and physiotherapy, and surgical treatment such as core decompression, alone or in combination with electromagnetic stimulation or bone grafting. Several authors have reported a relationship between transient bone marrow oedema and avascular necrosis, but the incidence of progression from bone marrow oedema to early avascular necrosis remains unclear. In cases of spontaneous remission, the time taken for the improvement of symptoms and changes in MRI is between six and 12 months. The success of different options for treatment, however, is dependent on the stage of the disease, with the best results obtained in marrow oedema alone with a worse prognosis for advanced bony necrosis. These methods of management should be considered as symptomatic only since an effect on the underlying vascular disturbance has not yet been described. Our aim in this prospective pilot study was to assess the efficacy of a vasoactive drug on the clinical course, as evaluated by radiography and MRI.

Patients and Methods
We studied six patients (five female, one male) with bone marrow oedema of the talus which was confirmed by MRI. Their mean age was 58.4 years (25 to 73), and the duration of symptoms was 5.4 months (1 to 12). No patient gave a history of trauma, alcohol abuse or corticosteroid medication. Routine serology was normal in three patients, one showed mild hypercholesterolaemia and one hypertriglyceridaemia. One patient played badminton regularly and was a cigarette smoker. Previous treatment had consisted of non-steroidal anti-inflammatory drugs and physiotherapy in four patients without significant effect on their symptoms, and reduction of weight-bearing in two. The foot score of Mazur, Schwartz and Simon was recorded for each patient.

Plain anteroposterior and lateral radiographs and MRI were used to confirm the diagnosis. The treatment of all patients consisted of five infusions with 50 µg of iloprost (Ilomedin; Schering AG, Germany) in 500 ml of sodium chloride solution given over six hours, on five consecutive days. The treatment was interrupted for short periods if significant side-effects occurred such as headache, nausea or flushing. These symptoms were treated with antiemetic or analgesic drugs, and the dosage reduced. Clinical examination was undertaken after one, three and six months; radiological and MRI evaluation was repeated after three months.
Results

Before treatment the mean Mazur foot score was 58 points (26 to 69). All patients had experienced severe pain during weight-bearing and after exercise, and four had some pain at rest and at night for a mean of six months (2 to 12). Plain radiographs were considered to be normal in four patients, while in two they showed slight osteoporosis (stage-I avascular necrosis of the ankle as described by Mont et al\textsuperscript{1}). MRI showed bone marrow oedema of the whole talus in four patients; the other two had focal lesions, one in the head and neck and the other in the medial aspect of the body of the talus.

During infusion, the following side-effects were seen in four patients: one severe and three mild cases of headache, and two severe and two mild cases of nausea. These resolved within 15 minutes after the end of treatment. Two patients required partial weight-bearing for one week after treatment because of severe pain on exertion.

Four patients noticed improvement within the first few days of treatment, and the other two within the first weeks. In particular, rest pain disappeared within a mean of five days (3 to 8). Pain during exercise required five weeks (3 to 6) to settle. The Mazur score improved to a mean of 91 points (81 to 100) after one month and increased to 93 points (85 to 100) after three months. At the last examination, six months after treatment, this high score had been maintained. Patients reported no restrictions in their normal daily activities. The very active young male patient was able to return to the same level of sporting activities as before the onset of symptoms.

Plain radiographs of all six patients were normal with no sign of progression, such as sclerosis or lucencies, subchondral fracture, collapse or narrowing of the joint space.

MRI showed that the bone marrow oedema had resolved completely within three months (Fig. 1) in all six patients, with normal signal intensity and no signs of progression to avascular necrosis, such as demarcation, the ’double-line sign’, or collapse.

Discussion

In 1959, Curtiss and Kincaid described a clinical syndrome characterised by pain, decreased bone density on plain radiography, followed by spontaneous regression, in the hips of women during the last trimester of pregnancy. Subsequent reports have referred to this syndrome as transient osteoporosis, transitory demineralisation and, as diagnosed by MRI, bone marrow oedema syndrome.\textsuperscript{11} The clinical course is characterised by an abrupt or gradual onset of pain, noted not only during activity but occasionally at rest and at night, which resolves spontaneously after six to 12 months. The term ‘migratory osteoporosis’ describes the fact that it may present subsequently in different joints and an incidence of bilateral involvement of 41% has been reported.\textsuperscript{12} Most series describe the condition in the hip or less often, the knee, but only a few have reported it in the foot.\textsuperscript{1,3,13-18}

Therapeutic options are limited. Some authors report good results with core decompression. This treatment has been recommended as a method of reducing the duration of symptoms rapidly and completely, with a return to normal MRI signal patterns.\textsuperscript{2-5} The theory is that pain in transient osteoporosis and avascular necrosis is caused by raised intramedullary pressure. Although this treatment has minimal morbidity and can be performed as an outpatient procedure, it requires partial weight-bearing for six weeks, sometimes followed by physiotherapy. Other authors have reported good results with a conservative regime of symptomatic treatment and avoidance of weight-bearing until the clinical and radiological findings resolve.\textsuperscript{2,3,5} Boos et al\textsuperscript{16} reported a good clinical outcome with sympathetic nerve blockade in three patients, but without improvement in the pathological MRI signal pattern. Although Laroché et al\textsuperscript{17} described reduction of pain in a small controlled study using nifedipine, and Glueck et al\textsuperscript{18} presented preliminary data on the use of stanozolol in the treatment of avascular necrosis, these methods did not apply to the treatment of the bone marrow oedema syndrome. Lakhpal et al\textsuperscript{12} reported no beneficial effect when using calcitonin, antituberculous drugs, prednisone or lumbar sympathectomy.

There is still controversy as to whether this syndrome is a distinctive self-limiting disease, a type of reflex sympathetic dystrophy,\textsuperscript{16,19} or a diffuse but reversible early phase of avascular necrosis.\textsuperscript{5,20-22}

The pathogenesis of the bone marrow oedema syndrome and avascular necrosis also remains unclear. Commonly discussed theories include thromboemboli, arteriolar obstruction, obstruction of venous outflow or injury to a vessel wall caused by vasculitis, altered lipid metabolism and decreased fibrinolysis.\textsuperscript{23-29} It was our aim to investigate the effect of a pharmacological agent with an activity spectrum on several parts of the terminal vascular bed and on the aggregation of platelets.

Since 1998 we have used iloprost given parenterally in the treatment of bone marrow oedema syndrome. This stable prostacyclin analogue is registered for the treatment of critical ischaemia secondary to peripheral atherosclerotic obliterative disease or diabetic angiopathy.\textsuperscript{30} It causes dilatation of arterioles and venules, reduction in the permeability of capillaries and inhibition of thrombocyte aggregation. As well as these improvements in the viscosity within the terminal vascular bed, it decreases oxygen radicals and leukotrienes. Its most frequent side-effects are headache, nausea and flushing. Treatment is contraindicated during pregnancy and in patients who are anticoagulated or who have gastrointestinal ulcers, cardiac failure, a recent myocardial infarction or unstable angina. In this pilot study, all patients were treated with a series of infusions of 50 μg of iloprost on five consecutive days.

With this regime, our patients showed rapid symptomatic
improvement which was maintained over six months. These results were achieved with or without a short (one week) period of protected weight-bearing. MRI was performed 12 weeks after treatment as proposed by Boos et al.\textsuperscript{16} We found a complete return to normal signal patterns. Although the clinical outcome was good, the possibility of side-effects, such as nausea, vomiting and headache, should be noted.

To date, this treatment has been given to more than 350 patients with bone marrow oedema at different sites including the femoral head, the condyles of the femur and tibia, and the hand (unpublished data). All patients with bone marrow oedema syndrome, without demarcation of avascular bone, had the same excellent results with an accelerated resolution of the condition. This treatment is relatively inexpensive and as there is no need for reduced weight-bearing it allows an early return to normal life.

This pilot study has its limitations since the number of patients was very small, due to the rarity of the condition. A multicentre, randomised study will be necessary to compare this infusion therapy with core decompression or conservative treatment.

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References


