The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost

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Bone-marrow oedema can occur both in isolation and in association with necrosis of bone, but it has not been shown whether each respond to the same methods of treatment.

We treated 16 patients with isolated oedema and 17, in which it was associated with necrosis of the proximal femur, with the prostacyclin derivative iloprost, which has been shown to be effective in the idiopathic form. The Harris hip score, the range of movement, the extent of the oedema as measured by MRI, pain on a visual analogue scale and patient satisfaction were recorded before and subsequent to treatment.

In both groups, we were able to show a significant improvement (p < 0.001) in these observations during the period of follow-up indicating that iloprost will produce clinical improvement in both circumstances.

An increase in interstitial fluid is an expression of bone-marrow oedema which, if uncorrected, can lead to necrosis with local collapse of bone. The prostacyclin derivative iloprost is a vasoactive substance which has been used in the management of vascular occlusion, vasculitis and pulmonary hypertension. Recently, it has been shown that iloprost can be used to achieve a reduction in isolated bone marrow oedema with a considerable improvement in the accompanying symptoms. However, its effect upon oedema associated with bone necrosis has not been established. We therefore investigated its efficacy in these circumstances and compared the results with those achieved in isolated lesions.

Patients and Methods

Between June 2001 and April 2003, we carried out a prospective, unselected, case-controlled observational study on 33 patients (40 hips) with bone marrow oedema. In 16 patients (group 1), the lesion was isolated and in 17 (group 2) it was associated with necrosis of the proximal femur. The criteria for inclusion in the study were the presence of an area of oedema in the femoral head demonstrable on MRI, pain in the area of the hip and a walking distance of less than 1 km. Patients with osteoarthritis, any inflammatory or neoplastic lesion and a history of trauma were excluded and the general contraindications for iloprost, as stated by the manufacturer, observed. The age and gender of the patients, the affected hip and any risk factors predisposing to oedema were recorded. There were seven women and 26 men with a mean age of 46 years (23 to 71, Table I). Risk factors identified included corticosteroid therapy, alcohol and nicotine abuse and a history of thrombosis (Table II).

The allocation of the patients to each group was made solely by the third author (CP) after determination of the Association Research Circulation Osseous (ARCO) stage on the basis of plain radiography in two planes and T1- and T2-weighted MRI. The presence of an area of oedema without necrosis was rated as ARCO stage I (group 1), while oedema accompanied by osteonecrosis was classified as ARCO stage II or stage III (group 2).

After providing the patients with detailed information and obtaining their written consent to participate in the study, iloprost (Iloomedin; Schering, Berlin, Germany) was dissolved in normal saline and given by infusion over a period of six hours in a weight-related, increasing schedule for five days (Table III). Any side-effects and adverse events were recorded.

The Harris hip score (HHS), pain on a visual analogue scale (VAS), recurrence of symptoms and the patient satisfaction score were determined by the first author (ACD), who was blinded in regard to the groups at the enrolment examination and at follow-up at four and 12 weeks. These were re-evaluated at a mean of 25 months (11 to 37) after treatment. The need for analgesics was also noted.
MRI was undertaken after 12 weeks and compared with the baseline findings. In sagittal and transverse sectional planes, the anatomical position of oedema in the proximal femur and its maximum extent were determined. Five stages were differentiated: stage 0, normal; stage 1, oedema of one-third of the femoral head; stage 2, oedema of two-thirds of the head; stage 3, oedema of the entire head; and stage 4, as in stage 3 with additional involvement of the femoral neck.

Statistical analysis. This was performed by SPSS for Windows (SPSS Inc, Chicago, Illinois). The mean, standard deviation (SD), median and the minimum and maximum readings in each group were determined at each follow-up. Significance was determined using the Wilcoxon test as a non-parametric method for the comparison of two matched samples, and the Mann-Whitney U test as a non-parametric method for the comparison of two unmatched samples. Connections between the parameters were recorded and the results measured were determined by linear regression analysis. A level of significance of 0.05 was specified for all statistical methods.

Results

No adverse effects were observed in 17 patients (43%). In 13, moderate or severe headaches occurred during the infusion. Nausea was reported by seven patients (21%), and a temporary increase in hip pain by a further seven (21%). Flushes were observed in four patients and local erythema in the area of the injection site in three. Pain in the masticatory muscles, hypotension and arrhythmia, none of which required treatment, were reported by one patient each.

There was a similar improvement in the mean HHS from 58 points (35 to 89, median 58) to 80 points (37 to 100, median 86) (p < 0.001) in both groups. This value remained constant at 80 points (40 to 100, median 82) at the second follow-up examination eight weeks later. After 25 months, the mean HHS had improved to 79.9 points (53 to 100, median 78) in both groups (p < 0.001).
Patients in group 1 showed an improvement from 57 (38 to 76, median 57) to 78 points (37 to 100, median 85) after four weeks (p < 0.001) and had achieved a mean of 81 points (40 to 100, median 86) by 12 weeks (Tables IV to VI). After 25 months a mean of 83.1 points (53 to 100, median 88) remained (p < 0.001).

Those in group 2 showed an improvement from 56 points (35 to 78, median 59) to 84 points (52 to 96, median 86) after four weeks, and to 79 points (50 to 96, median 80) after 12 weeks (Tables IV to VI). At 25 months the mean HHS score was 76.7 points (56 to 96, median 75; p < 0.001).

The range of extension, flexion and rotation improved significantly in both groups, and the level of pain decreased significantly. Both effects were reflected in an increase in patient satisfaction after treatment (Tables IV to VI). Five patients in group 1 and eight in group 2 were taking analgesics either regularly or occasionally, at the time of the second follow-up examination at 12 months. These numbers increased 25 months after treatment to eight patients in group 1 and 12 in group 2.

Comparison of the MRI before treatment (Figs 1a and 2a) and after 12 weeks, showed a significant reduction in the mean extent of oedema from stage 4 (1 to 4) to stage 1 (0 to 4) in all patients (p < 0.001) (Figs 1b and 2b). Tables V and VII give a comparison between the reduction of oedema in the two groups. At 25 months, 7 (25%) of the hips, 4 (20%) of group 1 and 3 (15%) of group 2, had no recurrence of symptoms, 23 (57.5%), 14 (70%) vs 9 (45%)
reported intermittent pain and 10 (25%), 2 (10%) vs 8 (40%) reported constant pain. Symptoms tended to recur after a mean period of eight months (1 to 24).

The reduction in pain was related to the presence of a risk factor. In patients with corticosteroid-associated oedema there was a smaller reduction in pain (16% after 12 weeks, 27% after 25 months) compared with those without risk factors (28% and 33% respectively). By contrast, the presence of thrombophilic factors was a prognostically favourable factor for early and late reduction of pain.

Discussion

Areas of bone marrow oedema in the upper end of the femur showed a significant reduction after treatment with iloprost (Figs 1 and 2). There was no difference between patients with an associated area of necrosis and those with an isolated lesion. In the former, the aim of treatment was to arrest the spread of necrosis by reducing the oedema. Previous concepts of treatment had been assessed according to the alleviation of symptoms.

An excessive accumulation of interstitial fluid leads to extension of the oedema and necrosis.\textsuperscript{19-24} Recently, there have been studies on the use of vasoactive substances, but they have not become accepted in routine clinical practice.\textsuperscript{25-33}

Iloprost is said to cause arterial and venous dilatation, to stabilise endothelial function, and curtail the activity of platelets, leukocytes and erythrocytes. The oedema-reducing effect is based on a reduction of hydrostatic pressure in the area of the venous branches of the terminal vascular bed. It influences the flow equilibrium towards absorption, and regulation of endothelial function prevents the recurrence of oedema by improving the flow characteristics of the blood.\textsuperscript{34} There have been recent studies on the use of iloprost in the treatment of bone marrow oedema in different skeletal locations.\textsuperscript{13-16}

In view of the impaired weight-bearing seen in many studies leading to clinical and radiological failure in 68% to 89% of patients,\textsuperscript{35-38} we felt that it would be improper to introduce an untreated control group in our study.

We were able to demonstrate a significant and lasting improvement in objective and subjective clinical criteria in patients with isolated lesions and also in those associated with necrosis.

Although patients with necrosis complained of more pain before treatment, the area of oedema as measured using MRI was smaller than that in patients with isolated lesions. Regardless of the baseline findings, the patients in both groups achieved comparable values for the range of movement, pain and the extent of the area of oedema. These results surpass those achieved by the use of crutches.\textsuperscript{39,40} Most of our patients (83%) reported an improvement in symptoms during the five-day period of hospitalisation, regardless of the presence of necrosis. Previously, rapid therapeutic success has only been described after trepanning or core decompression,\textsuperscript{7,8,41-51} which may be associated with specific risks; fractures have been described in as many as 15% of patients.\textsuperscript{39,43,44} In contrast to treatment with iloprost, after surgery only partial loading of the limb has been recommended. In addition, cartilage damage, infection, haemorrhage and anaesthesia-associated complications have been described.\textsuperscript{44}

The advantages of treating necrosis-associated oedema with iloprost include a short duration of treatment, a promising long-term outcome, a paucity of contraindications, and relatively mild side-effects. If this treatment fails, there is the option of surgery.

Regardless of whether bone marrow oedema is an early form of aseptic necrosis\textsuperscript{7,10,13-16,46} or an independent entity,\textsuperscript{39,45} iloprost is a conservative therapeutic option. When associated with necrosis infusion with iloprost must be seen as part of a regime of conservative treatment, with the aim of reduction of pain and early mobilisation, supplemented by additional measures if necessary.\textsuperscript{42,48,49}

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References


