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ORIGINAL PAPER

Efficiency of iloprost treatment for osseous malperfusion

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Abstract Insufficient osseous blood supply results in bone marrow oedema (BMO) and/or avascular necrosis (AVN). One treatment option to support osseous perfusion is the application of stable prostacycline analog iloprost. In this clinical study, 95 patients were treated with iloprost for BMO/AVN. One hundred eighty-six bones were affected by BMO/AVN before treatment. Average follow-up was 33.0± 17.6 months. Pain levels could be reduced (e.g. visual analogue scale, 5.0±2.2 points reduced to 1.7±2.2 points) and functional scores improved (Harris hip score, 52±21 points to 79±17 points) in the course of treatment. According to current data, healing of advanced stages of osteonecrosis is not possible. However, the results of this case series confirm previous findings that in early stages of insufficient osseous blood flow iloprost can contribute to the relief of pain and improve joint function.

Introduction

Bone marrow oedema (BMO) and avascular necrosis (AVN) represent a common and multifactorial disease where pathogenesis and cause of pain remain unclear. Frequently cited risk factors for the development of BMO and AVN include trauma, steroid therapy, hypercortisonism, alcohol abuse, smoking and several coagulopathies. Rare factors associated with malperfusion of the bone resulting in AVN are systemic infection diseases (e.g. HIV), different storage diseases (e.g. Gaucher disease), metabolic disorders (e.g. hyperuricaemia and hyperlipidaemia), sickle cell anaemia, aplastic anaemia, autoimmune disorders (e.g. systemic lupus erythematosis), shock and septic syndromes, deep sea diving, chronic inflammatory bowel diseases, local radiation and chemotherapy [1].

The current treatment strategies for BMO and AVN depend at least on the stage of the disease as classified by the Association Research Circulation Osseous (ARCO) [2–4]. Since joint preserving procedures for advanced stages of AVN are limited, early diagnosis and effective treatment are necessary [5, 6].

The vasoactive, stable prostacyclin analogue iloprost is approved for therapy of critical limb ischemia due to peripheral arteriosclerotic obliterative disease and diabetic angiopathy as well as an inhalative for patients with pulmonary arterial hypertension [7]. Other indications for iloprost application are systemic sclerosis, bone pain due to sickle crisis, Raynaud's disease and systemic lupus erythematodes [8]. The use of iloprost for the treatment of painful BMO (compartment syndrome of the bone) and AVN represents an off-label-use at present. Due to promising results of other groups [8–13] and to our own positive experience [14] we started a prospective study on the curative potential and analgesic efficiency of iloprost in 2002 as previously reported [1].

Patients and methods

In a prospective study, 131 patients with painful BMO or AVN were treated with iloprost between 2002 and 2008 in

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our institution. There were 36 cases excluded from this study population: eight patients who were treated for chemotherapy-associated AVN due to childhood cancer [15], 12 patients who underwent total joint replacement during follow-up, 11 patients who were lost to follow-up and five patients in which iloprost treatment had to be cut short due to adverse side effects, thus leaving 95 patients for evaluation.

Forty-four females and 51 males with an average age of 46.5±13.7 years (range, 15.2–80.5 years) could be evaluated before and after treatment with iloprost. Inclusion criteria for iloprost treatment were painful BMO or AVN stage greater than ARCO I. Exclusion criteria were acute and chronic infections, hypertension with systolic values >160 mmHg, ischemic heart attack or cerebral ischemia/bleeding within the past six months or surgery within the past six months, pregnancy or breastfeeding. The study protocol was approved by the local ethics committee (trial number 2355). Written, informed consent from the patients was obtained according to the latest version of the Declaration of Helsinki.

Iloprost (Ilomedin®, formally Schering AG, now BAYER Healthcare, Germany) was dissolved in 0.9 % saline solution and administered intravenously over a period of six hours per day in a weight-related schedule for a total of five days (Table 1).

Patients were admitted to hospital and monitored closely for possible adverse effects. Adverse effects were categorised as severe (hypotension, arrhythmia, bleeding, thromboembolism, acute respiratory distress syndrome, pulmonary oedema, allergic reactions with systemic clinical signs, shock) and minor (flush, erythema, headache, nausea, phlebitis).

Medical history and clinical examination were documented before iloprost treatment and after six weeks, three months, six months and at latest follow-up. The Harris hip score (HHS) served for functional evaluation in those patients with involvement of the hip joint. In addition, pain level was documented by using a visual analogue scale (VAS) ranging from 0–10 points with 0 points representing freedom of pain and 10 points representing worst imaginable pain.

Plain radiographs and MRI scans (T1-/T2-/STIR-weighted) were obtained before iloprost therapy and at three months and six months after treatment for radiographic analysis by a blinded independent radiologist (parameters including ARCO stages and extent of BME: progression, persistence, regression).

Statistical analysis was performed using SPSS 14.0 (SPSS Inc., Chicago, IL) software package. Student's *t*-test for independent statistical groups was used with $p<0.001$ indicating high statistical significance.

Table 1 Detailed iloprost infusion scheme

Body weight (kg)	Day 1 (ml/h) (0.5ng/kg/min)	Day 2 (ml/h) (0.75ng/kg/min)	Days 3–5 (ml/h) (1.0ng/kg/min)
60	2.2	3.4	4.5
70	2.6	4.0	5.3
80	3.0	4.5	6.0
90	3.4	5.1	6.8
100	3.8	5.7	7.5
110	4.1	6.2	8.3

The body weight-dependent dose was increased from day 1 to day 5. The infusion time was six hours per day

Results

One hundred eighty-six bones were affected by BME/AVN before treatment. Latest follow-up of the 95 patients was 33.0±17.6 months (range, 6–71 months). Figure 3 shows the regional distribution and ARCO stages in the 95 patients before and after treatment (Fig. 1).

Concerning aetiology, one or more risk factors per patient for the development of BME or AVN were attributable, including steroid medication (36 patients), nicotine abuse (20 patients), trauma (15 patients), alcohol abuse (eight patients), hyperlipoproteinaemia (three patients), and radiation (three patients). No statistically significant differences in terms of outcome could be determined.

Classified by ARCO stages before treatment, there were 117 ARCO I bones, 46 ARCO II bones, 17 ARCO III bones and six ARCO IV bones. There were no severe adverse effects attributable to the administration of iloprost. Iloprost treatment had to be stopped ahead of time on day one (one patient), day three (two patients) and day four (two patients) due to headaches. These patients were excluded from the study as mentioned above.

Pain levels were reduced and functional scores improved in the course of treatment as shown in Figs. 2 and 3.

Visual analogue scale (VAS) of 5.0±2.2 (range 1–10) was reduced to VAS 3.0±2.3 (range 0–10) at six weeks, to VAS 2.2±2.2 (range 1–9) at three months, to VAS 2.2±2.2 (range 1–9) at six months and to VAS 1.7±2.2 (range 0–8) at latest follow-up.

The Harris hip score improved from 52±21 (range 11–86) before treatment to 69±18 (range 19–100) after six weeks, to 74±20 (range 19–100) after three months, to 75±22 (range 19–100) after six months and to 79±17 (range 34–100) at latest follow-up.

Corresponding to the clinical findings, MRI findings during follow-up showed a significant decrease in the extent of BMO (Fig. 1). In contrast to a significant decrease

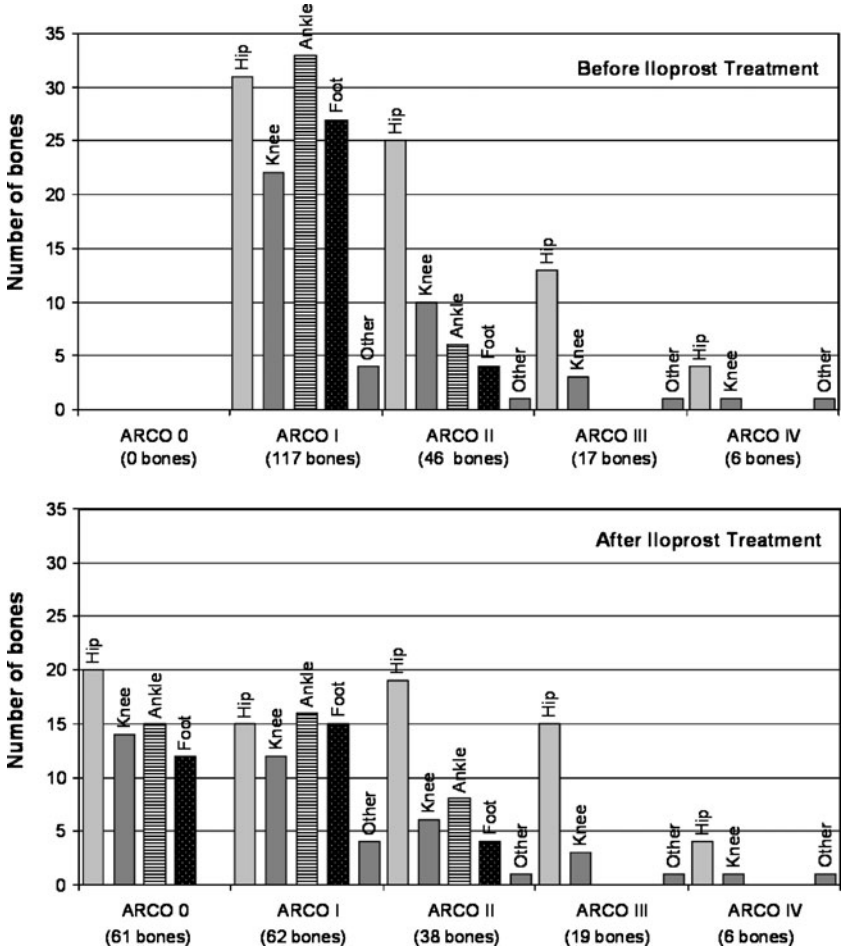

Fig. 1 Regional distribution and ARCO stages before and after iloprost therapy

in BMO and early AVN stages, advanced ANV stages (ARCO III and IV) were not affected by iloprost. Figure 4 shows two examples of a conversion of ARCO stages I and II into ARCO stages 0 and I.

In 21 cases, in addition to iloprost treatment, a core decompression was carried out five to seven days before iloprost was administered.

Discussion

Decision making on the best treatment is made difficult by the variable nature of BMO and AVN. Based on our findings during the past six years, we suggest early therapeutic intervention with iloprost in still reversible ARCO stages I or painful BMO.

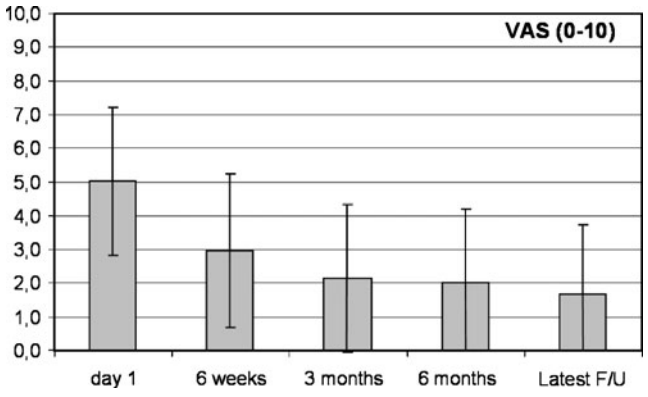

Fig. 2 Average pain level in the course of treatment according to the visual analogue scale (VAS)

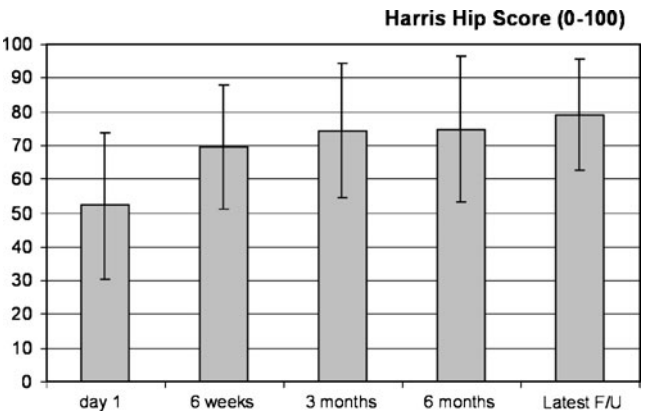

Fig. 3 Harris hip score in the course of treatment

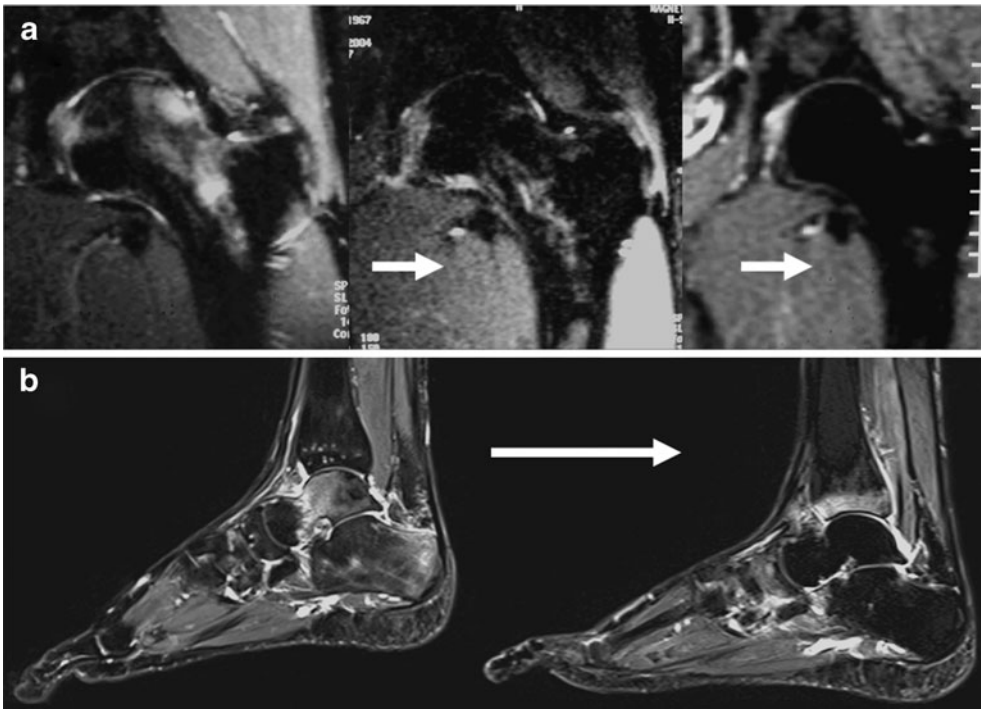

Fig. 4 Examples of regression of bone marrow oedema (BMO) in the hip and foot

Other non-surgical treatment strategies for AVN or BMO may include hyperbaric oxygen therapy [16], external electrical stimulation [17], capacitance coupling [18] or the administration of heparin or other anticoagulants [19]. The use of alendronate—a third generation bisphosphonate—seems to delay bone collapse by osteoclast inhibition [20]. However, the application of bisphosphonates includes an unclear risk of AVN of the jaws and its use is currently subject to controversial debate in the literature.

The results of our study not only show that patients in ARCO I and II AVN benefit by pain reduction and improved joint function but also document the curative potential in BMO and ARCO I stage AVN.

However, as an alternative but more invasive treatment option, core decompression in early AVN stages is meant to relieve intraosseous hypertension and venous congestion, ameliorate microcirculation and allow remodelling of the bone [21]. After core decompression, grafting with autologous bone marrow has been described with good medium-term outcome [22]. Based on the evidence that mesenchymal stem cells (MSC) are reduced in number and function in areas of AVN, several groups have implanted autologous bone marrow cells with moderate medium-term outcome [22].

Iloprost leads to vasodilatation and improves the microcirculation in affecting rheological properties of the terminal vascular bed, reducing capillary permeability, inhibiting platelet aggregation and diminishing the concentration of oxygen free radicals and leukotriens [23]. Aigner et al. successfully treated patients with BME of the forefoot and the acetabulum in 2001 and 2002 with iloprost [10, 12] and first demonstrated a clinical benefit, especially in early stages of the disease. Meanwhile, these findings were reproduced by further studies [1, 13, 24, 25].

Our data show that the pain level can be reduced and functional scores improved during follow-up after iloprost administration in a large and heterogenous cohort of patients.

It was demonstrated that there is no benefit from iloprost administration in advanced stages of osteonecrosis. However, the results of this case series confirm previous findings that in early stages of osteonecrosis iloprost can contribute to the relief of pain and improve joint function.

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Conflict of interest The authors declare that they have no conflict of interest.

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