Long-term clinical results after iloprost treatment for bone marrow edema and avascular necrosis

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Abstract

The treatments of avascular osteonecrosis (AVN) include both conservative and surgical methods which are dependent on the stage and progression of the disease. The vasoactive-prostaglandin-analogue iloprost (PGI2) has been utilized in several areas of medicine and recently has been used for the treatment of AVN. A total of 108 patients with 136 osteonecrosis of different joints, etiology and severity were treated with iloprost. The mean follow-up was 49.71 months: range 15-96 months, and outcome measurements recorded regarding subjective complaints, visual analog scale (pain), function and survival. The outcome scores used include the Harris Hip Score, Knee Society score, Foot and Ankle Survey, visual analogue scale (VAS) and a separate questionnaire. The location and etiology of AVN in our study demonstrated the typical pattern. All of the observed side effects of the therapy were minor and completely reversible. Most of patients (74.8%) showed a significant improvement of subjective complaints and decrease in VAS pain scores after the treatment with iloprost. However, 20% of the treated joints with the stadium Association for Research on Osseous Circulation (ARCO) grade 2, 71% with ARCO 3 and 100% with ARCO 4 underwent subsequent total joint replacement. The medical treatment of bone marrow edema or avascular osteonecrosis by Iloprost provides an safe and effective alternative strategy in the management of AVN presenting in the early stages (ARCO 1 or 2). For more advanced stages (ARCO 3 or 4), surgical intervention should be prioritized.

Introduction

Avascular osteonecrosis (AVN) is related to the interruption of blood supply or a disorder of the circulation to the subchondral bone, which is a particularly vulnerable location due to the capillary terminal branches. The detailed pathogenesis of AVN and the relationship between the underlying circulatory disorder is often unclear.[1] However, there are many theories on the cause of AVN and associated risk factors. The most common risk factors are cortisone therapy, alcohol and nicotine abuse, fractures and coagulopathies involving the circulatory system.[1-5] AVN can affect all joints in the body, however the highest incidence is seen in the hip, followed by the knee joint, humerus, talus and metatarsals. Bone marrow edema that is typically visible on magnetic resonance imaging is directly related to the osseous perfusion disorder and also indicates a potentially reversible initial stage of avascular osteonecrosis. However, the bone marrow edema may also occur as a transient clinical condition not associated with AVN. Thus, it is unclear if the pathogenesis of AVN arises from the bone marrow edema at the beginning of the disease or the bone marrow edema is secondary to another pathological process that is self-limited which can result in complete healing 6 to 12 months after conservative medical therapy (bone marrow edema syndrome).[6-10]

The treatment of avascular osteonecrosis is based on the clinical symptoms, stage of necrosis and the size of the affected area. To evaluate the evolution of AVN, both the Ficat and the Association for Research on Osseous Circulation (ARCO) is the mostly commonly used classification by clinicians.[11-13] Ficat introduced the original classification of AVN based on radiographic findings. However, there is greater difference in the intra and interobserver reliability associated with the Ficat system. Furthermore, it does not take into account the size and location of the necrotic area into account. Thus, ARCO developed a classification taking into account of the size and location of the lesion using both radiographs and MRI to further stage AVN. In the ARCO classification, there are four stages based on the findings of both radiographs and MRI. Surgical intervention during the advance stages of AVN including core decompression, osteotomy, and hip replacement is indicated when there are radiographic signs of osteonecrosis such as osteopenia, sclerosis, osteolytic or cystic lesions, joint space narrowing or flattening of the femoral head detectable in the conventional radiographs. Non surgical management of patients with AVN can be successful only in the early ARCO stages which is typically seen in patients that present with bone marrow edema.[10,14]

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Vasoactive prostaglandin analogue iloprost (PGI2) have been used in several areas of medicine including in the therapy of severe peripheral vascular disease, diabetic angiopathy, pulmonary hypertension and after organ transplantation.[15-19] In the recent years Iloprost has also been used in the therapy of early stage avascular osteonecrosis and bone marrow edema with promising short-term results.[20-26] In this study, we evaluated 108 patients with a total of 136 avascular osteonecrosis in different joint locations and ARCO stages that have been managed with medical Iloprost therapy during the period of 2003 to 2010. The aim of the present study was to investigate the mid to long-term results of Iloprost therapy in treatment of bone marrow edema or avascular osteonecrosis. Furthermore, the clinical and radiographic results were stratified based on the location of involvement, severity of clinical presentation and patient risk factors. Our hypothesis is that the clinical success of Iloprost is correlated to the severity of AVN that is based on the ARCO classification.

Materials and Methods

This study was approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine, University of Dusseldorf Medical School (ethics number: 2355). A total of 156 patients with painful bone marrow edema or AVN were recruited for this study and treated with Iloprost between the years of 2003

to 2010 in the orthopedic clinic of the Heinrich-Heine, University Dusseldorf. Patients excluded from this study that were no longer available (n=34), expired (n=4) or chose not to participate in the study for personal reasons (n=10). Thus a total of 108 patients (69.2% or 108 out of 156) presenting with 136 painful bone marrow edema or radiographic evidence of avascular osteonecrosis were included in our study and followed up retrospectively. These included 48 women and 60 men with a mean age of 47.7 years (11-92 years) at the time of Iloprost treatment (Table 1). All patients included in the study presented with bone marrow edema and symptomatic complaint of symptoms (pain) for more than 6 months or documented radiographic evidence of AVN including osteopenia, cystic changes, subchondral collapse, or joint space narrowing. Furthermore, their demographics and associated risk factors for AVN were recorded and analyzed. Iloprost therapy was administered in the inpatient setting with all adverse events monitored and recorded according to the provisions of the Ethics Committee. Specifically, Iloprost was dissolved in 0.9% saline and then administered intravenously over a period of 6 hours. The weight based dose was increased daily over the treatment period of five days.[24] All patients was notified of the risks and benefits of Iloprost therapy and agreed to proceed with the treatment after signing the consent form.

In 31 cases, the iloprost therapy was in combination with a surgical procedure. This included core decompression in 21 cases. In these particular cases, the Iloprost therapy was started postoperatively within the first week and carried out for 5 days postoperatively. The average follow-up was 49.7 months (15-96 months). The patient demographics including age and sex, secondary diagnoses and specific risk factors for the development of avascular osteonecrosis have also been recorded. Furthermore, the duration of the symptoms until initiation of therapy with Iloprost was documented as well as side effects of Iloprost. To document the patient satisfaction with the therapy, the patients were asked the question whether they would proceed with the Iloprost therapy for an additional cycle. For objective assessment of therapeutic success, various established clinical outcome scores were collected. Depending on the involved joint, the Harris hip score (HHS), the Knee Society score (KSS) or the Foot and Ankle Survey (FOAS) were used in our study. In addition, the range of motion of the corresponding joints was also measured with a goniometer and recorded in clinic. Pain intensity was recorded by the means of visual pain scale (VAS). This is a scale ranging from 0 to 10 with 0 representing no pain and 10 representing severe pain. The classification of AVN stages was performed according to the ARCO classification.[11-13] The initial findings were taken from the patient's medical records. All existing radiograph and MRI images of the involved joint were evaluated and used to determine the ARCO stage. All radiographs were evaluated by two fellowship trained orthopaedic surgeons and in the case of disagreement, a third fellowship trained surgeon evaluated the imaging to determine the stage. The data were collected in an Excel table (Microsoft, Redmond, WA, USA) and then examined with respect to mean values and standard deviation. Statistical analysis was performed with significance set at $P<0.05$.

Results

A total of 136 avascular osteonecrosis in 108 patients was included in our study and followed up. These were 60 (55.56%) male and 48 (44.44%) female patients. The average age was 47.69 years (11-92 years). Regarding the etiology of AVN, majority of the patients in our study (32.4%) had steroid induced AVN, 25.9% were idiopathic osteonecrosis, 18.5% of the osteonecrosis arise after a trauma, 16.7% were secondary to nicotine abuse and 7.4% were related to alcohol abuse (Figure 1). In addition, 25.9% of the patients with AVN were due to multifactorial risk factors. Majority of the AVN presented in the femoral head (52%), followed by ankle (20%) and knee (18%). In 8% of cases, the osteonecrosis was located in the foot. The duration of symptoms due to the AVN before the Iloprost therapy was on average 13.6 months, although within the periods of one month to ten years, a large scatter of data was present (standard deviation: ±20.4 months).

In terms of symptoms associated with the Iloprost treatment, overall 52% of the patients complained of side effects related to the inpatient treatment. The breakdown include 19% of patients complained of headaches, 10% of hot flushes and increased sweating, another 10% described skin and vein irritation, and 7% complained about nausea and vomiting. All side effects were reversible and disappeared completely after treatment. Severe side effects or mortality were not observed in our treatment group. The pain associated with AVN declined in the majority of patients at the time or after the cycle of Iloprost therapy. Overall, 74.8% of patients reported improvement in their symptoms and decrease in pain by the Iloprost therapy. However, 25.2% of patients reported similar symptoms or worsening of their symptoms after therapy. The question about patient satisfaction and whether they would proceed with a second cycle of Iloprost treatment demonstrated a similar trend. Here, 64% of patients reported that they would perform the therapy with Iloprost again, while 21% would not do it again. The remaining 15% of patients did not give an answer.

The evaluation of the Harris hip score for the patients who were treated for osteonecrosis of the femoral head with Iloprost showed at

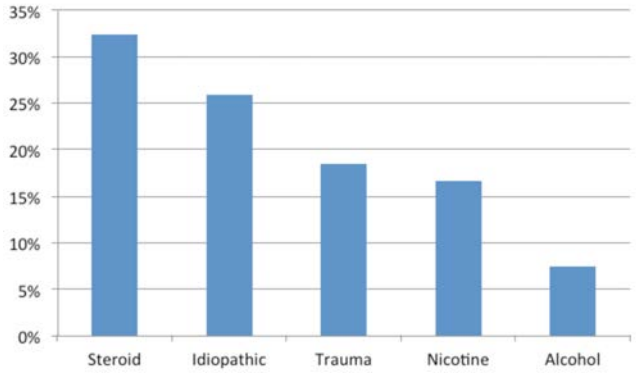

Figure 1. Etiology of avascular osteonecrosis in percent.

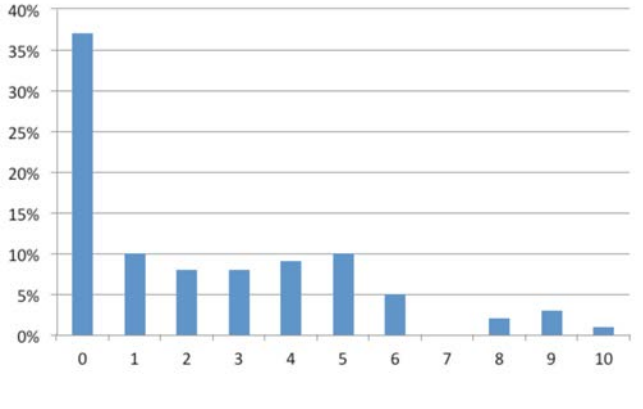

Figure 2. Visual analogue scale for pain in percent after iloprost therapy.

the last examination an average of 89±15 points (range: 47-100). For patients who were treated for AVN of the knee, the Knee Society score had a mean of 150±31 points (range 110-200). Patients who were treated for osteonecrosis of the foot or ankle were evaluated by the Foot and Ankle Survey. This resulted in a mean of 457±50 points (range: 353-500) (Table 2). Examining the VAS for pain, 80% of patients were between the values of 0 to 5 with 37% of patients stating a value of 0 or no pain (Figure 2).

Prior to the treatment with Iloprost, 69% of the involved joints demonstrated stage 1 changes according to the ARCO classification. In 18% of the joints, stage 2 was present, stage 3 was seen in 10% of patients and only 2% of patients presented with stage 4 changes according to the ARCO classification scheme. After therapy with one complete cycle of Iloprost, a restitutio ad integrum in accordance with the ARCO stages was present in 40%. Another 27% showed the stadium 1 according to the ARCO classification, in 11% the stadium 2 and in 5% the stadium 3. Additionally, at final follow-up, 16% of the joints with AVN had a total joint replacement (Table 3). In the cases that received an arthroplasty, the stage according to the ARCO classification before the Iloprost treatment was 18% (Stage 1) 23 % (Stage 2), 45% (Stage 3) and 14 % (Stage 4). In terms of the ARCO stages and the patients that had a joint replacement after Iloprost treatment, 4% of patients in Stage 1 AVN, 20% of patients in Stage 2 AVN, 71% of patients in Stage 3 AVN, and 100% of all patients that presented with Stage 4 had total joint arthroplasty, respectively (Table 4).

Discussion

Avascular necrosis of the bone can occur at various locations in the musculoskeletal system. Majority of the studies in the literature have evaluated AVN associated with the femoral head, which also accounts for the majority of patients in this study. In the United States, femoral head necrosis are responsible for between 5 to 10% of all total hip replacements.[27] According to a survey by Solacoff and Mont, 80% of the patients with femoral head necrosis were younger than 50 years of age at the time of surgery.[28] Therefore, AVN is a disease that is responsible for a significant medical and economic burden to the younger patients that develops early onset AVN. Although in some cases of AVN involving smaller lesions and early stages, spontaneous healing reaction may occur, however, in 90% of patients that presents with larger lesions or higher ARCO stage of AVN, spontaneous healing does not occur which results in further collapse of the femoral head that may ultimately necessitate surgical intervention.[29] Currently, there are more conservative treatment methods available to treat AVN but usually with limited success. In addition to modified loading of the involved extremity, various pharmacological approaches have also been explored, such as the use of lipid-lowering agents, anticoagulants and bisphosphonates.[23,30-35] There are also experiments with hyperbaric oxygen, electrical stimulation and capacitance coupling. However, a review of 21 studies with a total of 819 non-surgically treated hips with AVN showed a success rate of only 23%.[36] In many of the cases that presents with advanced stages of AVN, surgical treatment is often necessary. Surgical options include either joint preserving operation (core decompression) with or without combination of stem cell or bone substitute therapy, displacement femoral osteotomy, vascular pedicled fibular grafts or ultimately, a total joint replacement or arthrodesis.[37-39]

The primary pathogenesis of AVN involves a dysfunction in the circulatory system, thus recent studies have evaluated the conservative treatment of AVN with the prostaglandin analogue Iloprost. Iloprost leads to vasodilation and promotes microcirculation with increased blood flow. Initial studies evaluating Iloprost for the treatment of AVN demonstrated good results, particularly in patients that presents with early stages of AVN.[20-26] Aigner *et al.*[21] evaluate 6 patients with talus bone marrow edema treated with one cycle of Iloprost similar to the dosage used in our study and reported excellent outcome (Mazur foot score: 58 to 93 points) with no progression in the stage of the lesion at final follow-up. In a follow up study, Meizer *et al.*[34] analyzed 104 patients with painful bone marrow edema in different joint locations that was treated with Iloprost. With a short term follow-up of 4 months, the authors reported 73% of the patients had a decrease in their pain level and 65% of the patients had a decrease in their bone marrow edema size or complete normalization during the follow up time period. Similar to our study, this improvement in the pain score and MRI finding was seen in a heterogeneous group of patients. What is different is that in their study, majority of the patients presented with knee bone marrow edema, whereas in our study, majority of the patients presented with hip bone marrow edema or AVN. More specifi-

Table 1. Survey of patient data.

Joints with AVN	Follow-up, months	Age, years	Gender
136	49.71 (15-96)	47.7 (11-92)	male 55.56% / female 44.44%

AVN, avascular osteonecrosis.

Table 2. Clinical outcome scores after iloprost treatment.

Harris Hip score (range: 0-100)	Knee Society score (range: 0-200)	Foot and ankle survey (range: 0-500)
89±15	150±31	457±50

Table 3. ARCO stages before and after iloprost treatment.

ARCO-stage	Before therapy,%	After therapy, %
0	0	40
1	69	27
2	18	11
3	10	5
4	2	0
Arthroplasty	-	16

Table 4. Portion of replaced joints in percent.

ARCO-stadium	Replaced joints, %
1	4
2	20
3	71
4	100

cally, our study includes a heterogeneous patient population that included different locations of AVN involvement (52% hip, 20 % ankle, 18% knee), different etiologies (32.4% steroid induced, 25.9% idiopathic, 18.5% traumatic, 25.9% multifactorial) and ARCO stages (69% ARCO 1, 18 % 2 ARCO, 10% ARCO 3, 2% ARCO 4). In addition, Iloprost therapy has been combined with a surgical intervention in 31 patients (decompression core) in this study. Furthermore, in the present study with a mid to long term follow-up of patients treated with Iloprost for either painful bone marrow edema or AVN as demonstrated by the ARCO staging system. With mid to long term follow-up, over 75% of all patients expressed an improvement in the subjective pain complaints and symptoms after Iloprost therapy. Majority of the patients in this study had VAS pain of less than 5 after Iloprost treatment and 40% of the patients had no pain. Furthermore, assessment of the different functional scores (Harris Hip Score, Knee Society score, Foot and Ankle Survey) also demonstrated good to excellent results. In terms of patient satisfaction, 64% of the patients in our study were satisfied with the original Iloprost treatment and reported that they would perform a second cycle of Iloprost therapy and only 21% of patients was not satisfied.

A total of 16 % of the patients treated with Iloprost proceeded to a total joint replacement. Most of these patients had ARCO necrosis stages of 3 to 4 (59%) before treatment. In the 69% of patients with ARCO stage 1 treated with Iloprost therapy, only 4% of these patients had total joint replacement. However, in the patients with stage 4 ARCO grading and advanced AVN, 100% of the patients ended up with a total joint replacement after one cycle of Iloprost treatment with mid to long term follow-up. Long-term results of this study therefore reflect the results of other studies which look in particular on the effect of Iloprost at the ARCO stages 1 and 2. In patients with earlier stages of AVN or bone marrow edema, multiple studies have reported positive clinical and radiographic effects after Iloprost treatment with short term follow up.[20-26] The present mid to long-term study showed that the positive clinical effects of Iloprost therapy persist even with a longer term of follow up. However, in patients with advanced stages of AVN (ARCO stage 3 and 4) surgical intervention resulted in better functional outcome and symptomatic improvements. In contrast to our findings, Disch *et al*.[23] reported similar outcomes in patients with bone marrow edema versus necrosis in the proximal femur after treatment with Iloprost. In their study, both groups (edema *vs*. necrosis) had significant improvement in the range of motion, Harris Hip Scores, and MRI findings after Iloprost treatment. Furthermore, Aigner *et al*.[40] compared the results of Iloprost with core decompression in patients with bone marrow edema syndrome. The authors reported the parenteral application of Iloprost resulted in equal or better results compared to core decompression at 3 months comparing the Harris hip score and MRI findings post treatment. A risk factor to the Iloprost treatment is the minor side effects of therapy. In our study, about 50% of patients complained of minor reversible side effects that included headaches, nausea, vomiting, and increased in pain before clinical improvements, but we did not find any serious or major side effects. Similar side effects have also been reported in the literature associated with Iloprost therapy.[23]

Limitations

A major limitation of our study is a loss of 31% of patients to follow-up from the original 156 patients that received a cycle of Iloprost treatment for painful bone marrow edema or AVN from the years 2003 to 2010. A total of 108 patients (69%) were included in this study and followed up. We cannot predict the outcomes or the symptomatic relief of pain after Iloprost therapy in this patient population that was lost to follow up. A second limitation is the heterogeneity of the patient population in our study which is certainly a weakness with regard to the comparability of the results, but this is also due to the disease of AVN itself which occurs at various locations and has various presentations and etiologies. Therefore a general therapeutic approach is very difficult. However, the strength of our study is the large number of patients that were treated with Iloprost therapy and the overall longer term of follow-up. Another point is that it is not clear whether the positive effect especially in the ARCO stage 1 relates to the iloprost treatment or is it the normal progress of the bone marrow edema which is in some cases a self-limiting disease. Perhaps it is possible to get the same effect with weight bearing for example.

Conclusions

In summary, the sole use of Iloprost therapy in the early stages of AVN (ARCO Stage 1 or 2) as well as a combination with joint-preserving operational procedures (later stages of ARCO 3 or 4) represents an effective therapeutic option for the treatment of bone marrow edema and AVN involving different location in the body.

References

1. Seamon J, Keller T, Saleh J, Cui Q. The pathogenesis of nontraumatic osteonecrosis. Arthritis 2012;2012:601763.
2. Drescher W, Weigert KP, Bunger MH, et al. Femoral head blood flow reduction and hypercoagulability under 24h megadose steroid treatment in pigs. J Orthop Res 2004;22:501-8.
3. Inoue S, Horii M, Asano T, et al. Risk factors for nontraumatic osteonecrosis of the femoral head after renal transplantation. J Orthop Sci 2003;8:751-6.
4. Jones LC, Mont MA, Le TB, et al. Procoagulants and osteonecrosis. J Rheumatol 2003;30:783-91.
5. Simank HG, Brocai DR, Strauch K, Lukoschek M. Core decompression in osteonecrosis of the femoral head: risk-factor-dependent outcome evaluation using survivorship analysis. Int Orthop 1999;23:154-9.
6. Gallant GG, Fisher RL, Sziklas JJ. Transient regional osteoporosis of the ankle and foot. A report of four cases and review of the literature. Orthop Rev 1994;23:405-9.
7. Hofmann S, Engel A, Neuhold A, et al. Bone-marrow oedema syndrome and transient osteoporosis of the hip. An MRI-controlled study of treatment by core decompression. J Bone Joint Surg Br 1993;75: 210-6.
8. Kim YM, Oh HC, Kim HJ. The pattern of bone marrow oedema on MRI in osteonecrosis of the femoral head. J Bone Joint Surg Br 2000;82:837-41.
9. Plenk H Jr, Hofmann S, Eschberger J, et al. Histomorphology and bone morphometry of the bone marrow edema syndrome of the hip. Clin Orthop Relat Res 1997;334: 73-84.
10. Froberg PK, Braunstein EM, Buckwalter KA. Osteonecrosis, transient osteoporosis, and transient bone marrow edema: current concepts. Radiol Clin North Am 1996; 34:273-91.
11. Mitchell DG, Rao VM, Dalinka MK, et al. Femoral head avascular necrosis: correlation of MR imaging, radiographic staging, radionuclide imaging, and clinical findings. Radiology 1987;162:709-15.
12. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995;77:459-74.
13. Schmitt-Sody M, Kirchhoff C, Mayer W, et al. Avascular necrosis of the femoral head: inter- and intraobserver variations of Ficat and ARCO classifications. Int Orthop 2008;32:283-7.
14. Korompilias AV, Karantanas AH, Lykissas MG, Beris AE. Transient osteoporosis. J Am Acad Orthop Surg 2008;16:480-9.
15. Hsu HH, Rubin LJ. Iloprost inhalation solution for the treatment of pulmonary arterial hypertension. Expert Opin

Pharmacother 2005;6:1921-30.
16. de Donato G, Gussoni G, de Donato G, et al. The ILAILL study: iloprost as adjuvant to surgery for acute ischemia of lower limbs: a randomized, placebo-controlled, double-blind study by the italian society for vascular and endovascular surgery. Ann Surg 2006;244:185-93.
17. Bärthel E, Rauchfuss F, Hoyer H, et al. The PRAISE study: a prospective, multi-center, randomized, double blinded, placebo-controlled study for the evaluation of iloprost in the early postoperative period after liver transplantation (ISRCTN12622749). BMC Surg 2013;13:1.
18. Gohrbandt B, Sommer SP, Fischer S, et al. Iloprost to improve surfactant function in porcine pulmonary grafts stored for twenty-four hours in low-potassium dextran solution. J Thorac Cardiovasc Surg 2005;129:80-6.
19. Piaggesi A, Vallini V, Iacopi E, et al. Iloprost in the management of peripheral arterial disease in patients with diabetes mellitus. Minerva Cardioangiol 2011;59:101-8.
20. Aigner N, Meizer R, Meraner D, et al. Bone marrow edema syndrome in postpartal women: treatment with iloprost. Orthop Clin North Am 2009;40:241-7.
21. Aigner N, Petje G, Steinboeck G, et al. Treatment of bone-marrow oedema of the talus with the prostacyclin analogue iloprost. An MRI-controlled investigation of a new method. J Bone Joint Surg Br 2001;83:855-8.
22. Aigner N, Petje G, Schneider W, et al. Juvenile bone-marrow oedema of the acetabulum treated by iloprost. J Bone Joint Surg Br 2002;84:1050-2.
23. Disch AC, Matziolis G, Perka C. The management of necrosis-associated and idiopathic bone-marrow oedema of the proximal femur by intravenous iloprost. J Bone Joint Surg Br 2005;87:560-4.
24. Jäger M, Zilkens C, Bittersohl B, et al. Efficiency of iloprost treatment for osseous malperfusion. Int Orthop 2011;35:761-5.
25. Jäger M, Tillmann FP, Thornhill TS, et al. Rationale for prostaglandin I2 in bone marrow oedema: from theory to application. Arthritis Res Ther 2008;10:R120.
26. Jäger M, Zilkens C, Westhoff B, et al. Efficiency of iloprost treatment for chemotherapy-associated osteonecrosis after childhood cancer. Anticancer Res 2009;29:3433-40.
27. Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992;326:1473-9.
28. Solakoff D, Mont MA, Krackow KA. Uncemented total hip arthroplasty in patients less than 45years with avascular necrosis. Orthop Trans 1993-1994;17:1085.
29. Mont MA, Hungerford DS. Non-traumatic avascular necrosis of the femoral head. J Bone Joint Surg Am 1995;77:459-74.
30. Agarwala S, Jain D, Joshi VR, Sule A. Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study. Rheumatology (Oxford) 2005;44:352-9.
31. Agarwala S, Sule A, Pai BU, Joshi VR. Alendronate in the treatment of avascular necrosis of the hip. Rheumatology (Oxford) 2002;41:346-7.
32. Desai MM, Sonone S, Bhasme V. Efficacy of alendronate in the treatment of avascular necrosis of the hip. Rheumatology (Oxford) 2005;44:1331-2.
33. Lai KA, Shen WJ, Yang CY, et al. The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. J Bone Joint Surg Am 2005;87:2155-9.
34. Meizer R, Radda C, Stolz G, et al. MRI-controlled analysis of 104 patients with painful bone marrow edema in different joint localizations treated with the prostacyclin analogue iloprost. Wien Klin Wochenschr 2005;117:278-86.
35. Mont MA, Jones LC, Hungerford DS. Nontraumatic osteonecrosis of the femoral head: ten years later. J Bone Joint Surg Am 2006;88:1117-32.
36. Mont MA, Carbone JJ, Fairbank AC. Core decompression versus nonoperative management for osteonecrosis of the hip. Clin Orthop Relat Res 1996;324:169-78.
37. Langlais F, Fourastier J. Rotation osteotomies for osteonecrosis of the femoral head. Clin Orthop Relat Res 1997:110-23.
38. Scully SP, Aaron RK, Urbaniak JR. Survival analysis of hips treated with core decompression or vascularized fibular grafting because of avascular necrosis. J Bone Joint Surg Am 1998;80:1270-5.
39. Castro FP Jr, Barrack RL. Core decompression and conservative treatment for avascular necrosis of the femoral head: a meta-analysis. Am J Orthop (Belle Mead NJ) 2000;29:187-94.
40. Aigner N, Petje G, Schneider W, et al. Bone marrow edema syndrome of the femoral head: treatment with the prostacyclin analogue iloprost vs. core decompression: an MRI-controlled study. Wien Klin Wochenschr 2005;117:130-5.