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Treatment of Bone Marrow Edema of the Foot and Ankle With the Prostacyclin Analog Iloprost

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Abstract

Background: Bone marrow edema (BME) of the foot and ankle is challenging to treat. One approach is intravenous Iloprost treatment, which is a vasoactive prostacyclin analog. The aim of this study was to evaluate the early and intermediate outcome of intravenous Iloprost therapy on BME of the foot and ankle and to analyze the influence of its etiology and Association Research Circulation Osseous (ARCO) stage on the outcome.

Methods: This was a retrospective study with prospective follow-up. All patients treated by intravenous Iloprost for BME of the foot and ankle (ARCO I-III) at a single orthopedic reference center were included. Demographics, medical history, and MRIs were assessed prior to treatment (t0). MRIs were used to assess the BMEs' etiology (idiopathic/ischemic/metabolic, mechanical/degenerative, traumatic) and severity (ARCO). Complications as well as changes in pain, treatment, and MRI were evaluated after 3 months (t1). The following patient-rated outcome measures (PROMs) were assessed prospectively (t2): 12-Item Short Form Health Survey (SF-12), Visual Analog Scale Foot and Ankle (VAS FA), and the Foot Function Index (FFI) (also at t0). The descriptive outcomes and the influence of the etiology and ARCO on the outcome parameters were evaluated. Out of 70 eligible patients, 42 patients (60%; 47 ± 15 years; 30% female) with a mean follow-up of 28 ± 19 months were included.

Results: Twelve patients reported minor complications during Iloprost therapy. At t1, pain decreased significantly in 56%, and the amount of BME decreased in 83% of patients. Both parameters correlated moderately ($r = -0.463$, $P = .015$). The PROMs at t2 revealed moderate results. The overall FFI improved from 59 ± 21 to 30 ± 22 ($P < .001$), the overall VAS FA was 68 ± 20, the SF-12 Physical Component Summary 42 ± 12 and Mental Component Summary 50 ± 9. Subgroup analysis revealed no significant influence of the etiology or ARCO stage on any outcome measure.

Conclusion: Iloprost therapy for BME of the foot and ankle resulted in a 60% pain and 80% edema decrease after 3 months. After 2 years, patient-rated outcome measures showed residual impairment. Neither the etiology nor ARCO stage significantly influenced the outcome.

Level of Evidence: Level III, comparative study.

Keywords: Ilomedin, Iloprost, bone marrow edema, foot and ankle

Introduction

Bone marrow edema (BME) is a pathologic accumulation of fluid within a bone.[5,11] BME most often occurs at the proximal femur, but is also seen in the foot and ankle.[3-5,14,21,24,28,32] Its etiology can either be idiopathic, such as in the bone marrow edema syndrome (BMES), or occur secondary to different pathologies. According to the underlying pathology, BMEs should be subgrouped into idiopathic/ischemic/metabolic, mechanical/degenerative, or traumatic.[7,12,20] Known risk factors for BME include trauma,

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steroid therapy, hypercortisolism, alcohol abuse, smoking and various coagulopathies.[13]

BME should be radiographically classified according to ARCO (Association Research Circulation Osseous).[25] The ARCO classification was developed to stage avascular femoral head necrosis and is based on radiographs, computed tomography (CT), and magnetic resonance imaging (MRI).[22] It allows grading from a reversible bone marrow edema (ARCO I) to an irreversible local necrosis (ARCO II) with subchondral fractures (ARCO III) and secondary osteoarthritis (ARCO IV).[26]

BME might progress into avascular necrosis (AVN). Therefore, early diagnosis, identification of the underlying pathology, and treatment initiation are essential. BME with reversible causes usually presents with weight-dependent pain and resolves over 6 to 18 months.[20] Therefore, an initial conservative treatment approach should be emphasized. This includes non-weightbearing or partial-weightbearing, nonsteroidal anti-inflammatory drugs, as well as physio-, relaxation-, and massage therapy.[21]

In case of failed improvement, additional pharmacologic therapy can be considered. Bisphosphonates and Iloprost are 2 drugs frequently administered off-label to treat bone marrow edema (ARCO I-II).[13,28] Whereas bisphosphonates inhibit bone resorption, Iloprost is a vasoactive prostacyclin analog (PGI_2). In a retrospective study, Baier et al found a greater pain reduction for Iloprost within the first 3 months compared to bisphosphonates. No significant differences between the 2 groups were observed after 6 months.[5] There are conflicting data on the effect of those drugs in ARCO stages II and III.[10,13,19] Because of the proposed quicker pain relief, intravenous Iloprost has become the preferred drug treatment approach in case of failed conservative treatment in patients with BME at the authors' reference center.

The effectiveness of either drug has not sufficiently been studied for BME of the foot and ankle.[21,28] Aigner et al found promising results in 19 patients with BME of the hindfoot.[2] Röhner et al on the contrary found no significant pain relief over 3 months following Iloprost therapy in 23 patients with BME of the foot and ankle for ARCO stage I-II.[24] No study has yet investigated a possible influence of the etiology on BME drug treatment results.

In the authors' orthopedic foot and ankle reference center, intravenous Iloprost therapy is conducted over a period of 5 days in case of BME of the foot and ankle (ARCO stage I-III) and failed conservative treatment. To our knowledge, no study has assessed the value of intravenous Iloprost therapy in case of BME of the foot and ankle in ARCO stage I-III and analyzed outcome difference between the different etiologic subgroups.

The aim of this study was to evaluate the early and intermediate results of intravenous Iloprost therapy on bone marrow edema of the foot and ankle. Of special interest were the subgroup analysis on the etiologies and ARCO stages (I through III).

Methods

The study design was retrospective with a prospective follow-up at a single orthopedic reference center. The study was approved by the local ethics committee .

Patient Selection

The department's clinical database was searched for the basic documentation (Bado) "Ilomedin" and the ICD-10 code M87.XX between January 1, 2009, and June 30, 2015. The inclusion criteria were age $\geqslant$18 years, in-house intravenous Iloprost therapy without accompanying surgical intervention, initial MRI imaging available for review, and a prospective follow-up of at least 6 months. Excluded were patients with concomitant injuries, BME ARCO IV, contraindication for an Iloprost therapy, or patients unable to provide informed consent. Figure 1 illustrates the patient selection process. Of the 116 patients identified, 70 met the inclusion criteria. A prospective follow-up was available for 42 patients (60%).

Forty-two patients with a mean age of 47 ± 15 years (19-74 years), 30% female, were included in the final analysis. The left side was affected in 43%, and the mean body mass index (BMI) was 26 ± 5 (range 18-28). Duration of symptoms was 11 ± 9 months (range 4-25 months). The descriptives on the cause, localization, and initial MRI findings are presented per etiology in Table 1.

Treatment Regimen

The initial diagnostics were conducted in our out-patient clinic. Patients with symptomatic BME for at least 3 months with failed conservative treatment were offered the in-house Iloprost therapy. Conservative treatment must have been composed of partial weightbearing, nonsteroidal anti-inflammatory drugs, and complex physiotherapy.[21] Informed consent including the off-label use was obtained from every patient.

A cumulative dose of 180 µg Ilomedin (Iloprost-Trometamol 20 µg/1 mL; Bayer Vital GmbH, Leverkusen, Germany) was given over 5 days. On day one, 20 µg of Ilomedin was administered over 6-8 hours. If tolerated well, the dose was increased to 40 µg per day. All patients received physiotherapy and analgesics on demand. Weightbearing as tolerated was allowed. Patients were advised to avoid contact sports for 3 months. A follow-up visit in our outpatient clinic was scheduled 3 months following the intervention. Eligible patients were invited for a final follow-up by mail or phone.

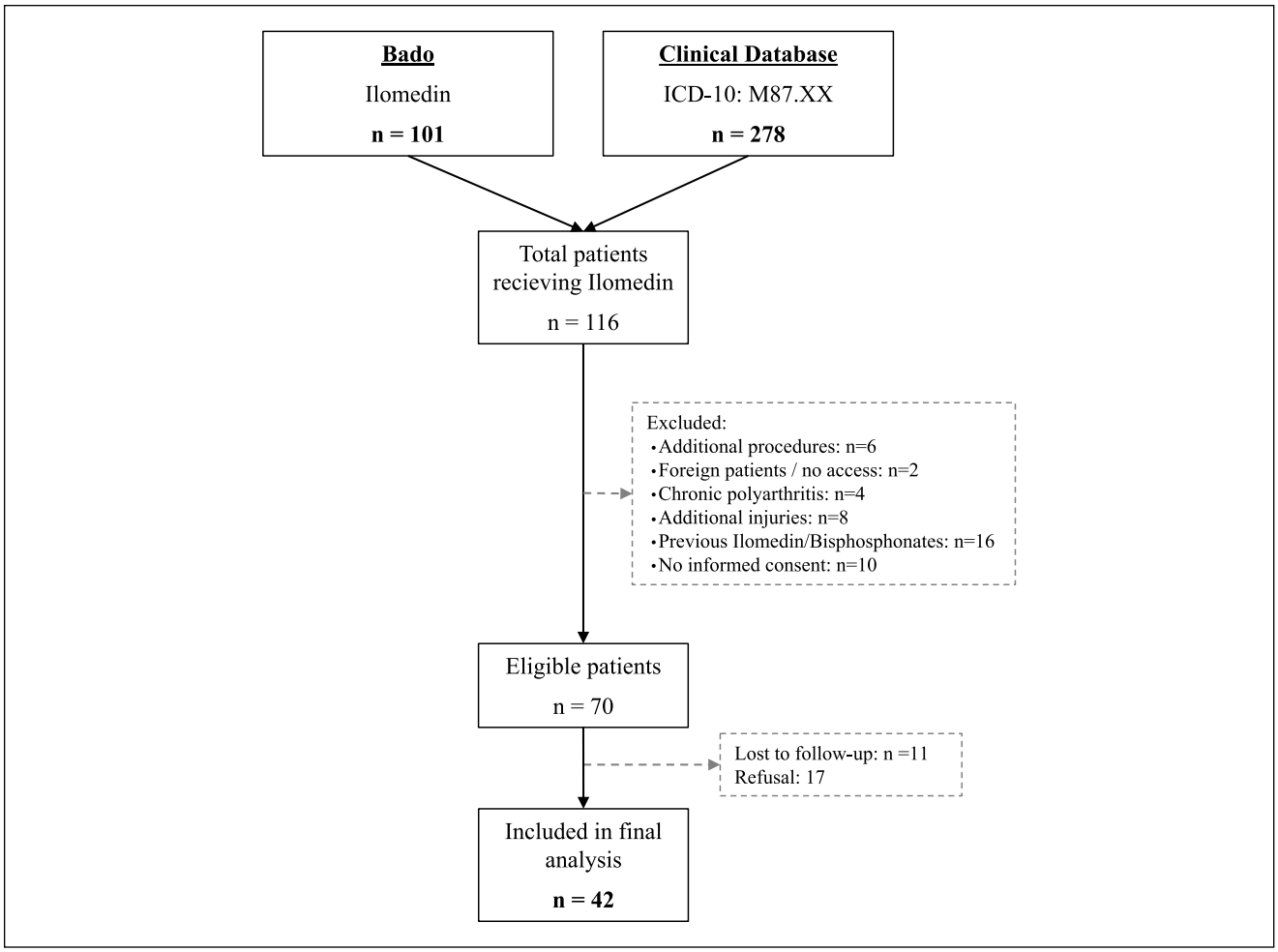

Figure 1. Flow-chart illustrating patient selection. Bado, basic documentation; n, number of patients.

Table 1. Descriptives on Etiology, Localization, and Initial MRI Findings.

Etiology	Cause	Location	ARCO	Extension
Idiopathic / ischemic / metabolic: n = 11 (26%)	Idiopathic: n = 6 Avascular osteonecrosis: n = 5 (12%)	Talus: n = 5 (12%) Metatarsal: n = 2 (5%) Navicular: n = 1 (2%) Sesamoid: n = 2 (5%) Cuneiform n = 1 (2%)	2.3 ± 0.8	Minimal: n = 0 Moderate: n = 2 (5%) Extended: n = 9 (21%)
Mechanical / Degenerative n = 16 (38%)	Osteoarthritis: n = 6 (14%) Postoperative: n = 3 (7%) Osteochondral lesion: n = 7 (17%)	Talus: n = 9 (21%) Metatarsal: n = 1 (2%) TN-joint: n = 1 (2%) TMT II joint: n = 1 (2%) Cuboid: n = 1 (2%) Tarsal bones: n = 2 (5%) Tibia: n = 1 (2%)	2.1 ± 0.7	Minimal: n = 1 (2%) Moderate: n = 7 (17%) Extended: n = 8 (19%)
Traumatic n = 15 (36%)	Posttraumatic: n = 12 (29%) Stress fracture: n = 3 (7%)	Talus: n = 4 (10%) Metatarsal: n = 3 (7%) Sesamoid: n = 3 (7%) Cuneiform: n = 1 (2%) Cuboid: n = 1 (2%) Hindfoot: n = 3 (7%)	1.3 ± 0.6	Minimal: n = 0 Moderate: n = 9 (21%) Extended: n = 6 (14%)

Abbreviation: ARCO, Association Research Circulation Osseous.

Table 2. Etiology of Bone Marrow Edema.[a]

Category	Etiology
Idiopathic / ischemic / metabolic	Avascular osteonecrosis
	Complex regional pain syndrome
	Transient osteoporosis
	Bone marrow edema syndrome
Mechanical / degenerative	Osteoarthritis
	Tumor
	Postoperative
	Osteochondrosis dissecans
Traumatic	Posttraumatic bone marrow edema
	Microfracture
	Stress fracture

[a]Adapted from Hofmann et al.[12]

Data Assessment

Retrospective data were gathered from the clinical database. Assessment included general demographics, BMI, and medical history. BME was rated on initial MRI images and classified for its etiology (Table 2), ARCO stage, location, and extent (3 items: minimal, moderate, extended). Three-month follow-up MRIs were used to measure the BME change over time (5 items: severely increased [+2] to severely improved [–2]).[12,20,26] An example is illustrated in Figure 2. MRI classification was conducted by a musculoskeletal-trained senior consultant radiologist and 2 fellowship-trained foot and ankle surgeons (U.S., H.H., S.F.B.).

Throughout the in-house stay, any complication was recorded. According to the available out-patient follow-up documentation, the change in pain 3 months after the treatment was assessed (7 item scale: severely worsened [–3] to eliminated [+3]) and any change in the treatment regimen was recorded.[20] Patient-rated outcome measures (PROMs) were assessed in a prospective follow-up, which patients were invited to. The scores used were a quality of life score (SF-12) and 2 foot and ankle–specific outcome scores, that is, the Visual Analog Scale Foot and Ankle (VAS FA), and the Foot Function Index (FFI).[9,15,23] The latter is routinely assessed in the authors' department. Therefore, it was also available prior to the treatment (t0).

Outcome Parameters

The above-outlined outcome parameters were subgrouped to 3 time points, t0 initial outpatient clinic visit, t1 3-month follow-up, and t2 final follow-up. These are recapped in Figure 3. The primary outcome parameter was the PROM FFI assessed at t0 and t2. Secondary outcome parameters were the MRI findings and pain at t1, as well as the PROM SF-12 and VAS FA at t2. In order to identify factors affecting the outcome, subgroup analysis was conducted for etiology and ARCO stages on the outcome parameters.

Statistics

A Shapiro Wilk test revealed normal distribution. Next to general descriptive statistics, independent and paired Student *t* test, analysis of variance (post hoc Bonferroni), chi-square test, and Pearson correlations were conducted. If not stated otherwise, results are given as means ± standard deviation (range). Because of the retrospective study design, a sample size estimation could not be calculated. Because of multiple testing, an alpha-level correction (Bonferroni) was conducted ($P < .01$) for the secondary outcome parameters. Statistics were computed using SPSS v. 21 (IBM Corp, Armonk, NY).

Results

In-house

On average, patients were in-house for 5 ± 0.2 days (5-6 days). Minor complications associated with the intravenous Iloprost therapy were observed in 12 patients (29%), with at least 1 of the following symptoms: headache (12 times), nausea (2 times), and hypertension (2 times).

Three-Month Follow-up (t1): Pain and MRI

At t1 follow-up (3 months, n = 34 (81%)), 56% reported considerable pain decrease (+3/+2) and 38% experienced no or minimal pain relief (+1/0). In 6%, the pain increased slightly (–1). Four patients (10%) necessitated further treatment. Two patients underwent microfracturing, 1 patient had operative debridement of the subtalar joint, and 1 patient had local injection therapy. A follow-up MRI was available for 29 (69%) patients. The BME decreased considerably (–2/–1) in 83%. No change (0) was observed in 14% of the patients. Only in 1 patient (3%) was a slight increase of the BME detected. There was a moderate correlation between pain and BME reduction ($r = -0.463$, $P = .015$).

Final Follow-up (t2): PROMs

The mean prospective follow-up (t2) was 28 ± 19 months (7-73 months) after treatment. The FFI initially (t0) was overall 59 ± 21 (7-93), for the subscale pain 52 ± 19 (7-89) and for the subscale function 65 ± 24 (7-97). At final follow-up (t2) the FFI decreased overall to 30 ± 22 (0-73) and to 21 ± 16 (0-57) / 33 ± 25 (0-74) for the subscales pain and function. In 27 patients (64%), both at t0 and t2, FFI scores were available. The paired Student *t* test showed a significant decrease for all FFI scales ($P < .001$), which remained true for the independent sample *t*-test on the whole population ($P < .001$). The overall VAS FA score at final follow-up was 68 ± 20 (21-100). Scores for the subscales pain, function, and others were 65 ± 21 (17-100), 68 ± 22 (16-100), and 71 ± 19 (29-98), respectively. The SF-12 Physical

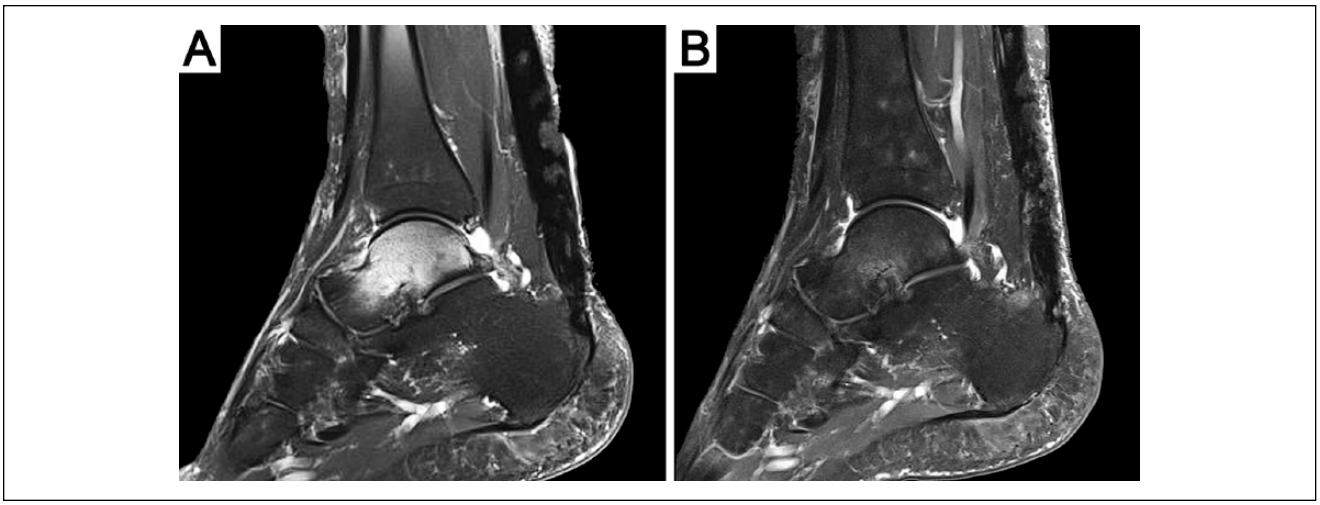

Figure 2. Illustration of a pre- (A) and postintervention MRI (B) of an idiopathic BME of the talus. Images of a 57-year-old male patient suffering an idiopathic BME. At 3 months, follow-up (t1) pain had improved considerably (+2) and the BME (ARCO 2) had decreased (–1). At final follow-up, the PROMs were as follows: FFI, 21; VAS FA, 69; SF-12 PCS, 45; SF-12 MCS, 57. (BME, bone marrow edema; MCS, Mental Component Summary; MRI, magnetic resonance imaging; PCS, Physical Component Summary; PROMs, patient-rated outcome measures; SF-12, 12-Item Short Form Health Survey.)

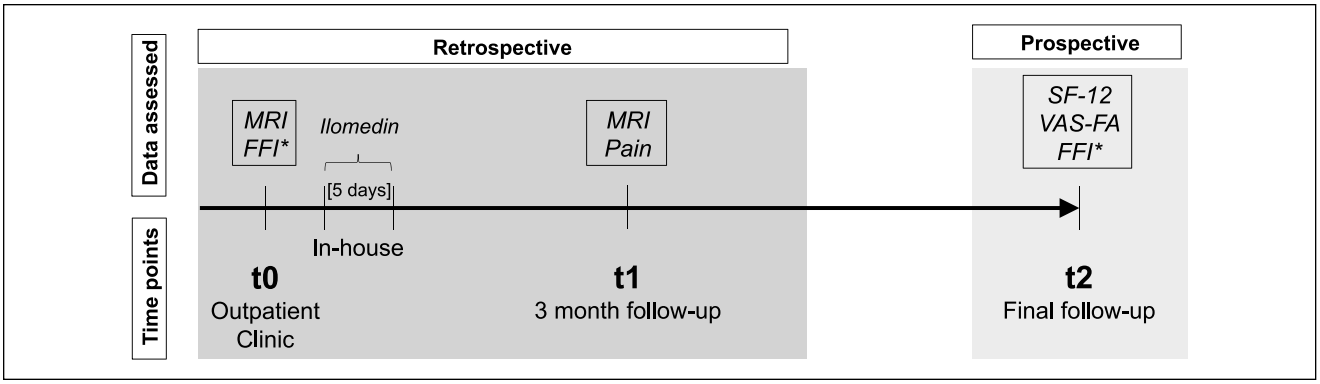

Figure 3. Timeline of data assessment.
*Primary outcome parameter.

Component Summary (PCS) was 42 ± 12 (23-59) and the Mental Component Summary (MCS) 50 ± 9 (30-64).

Subgroup Analysis

To identify factors affecting the outcome, a subgroup analysis was conducted. Etiology had no significant impact on any FFI parameter, neither at t0 nor at t2 (Figure 4). Table 3 depicts a possible effect of the etiology on any secondary outcome parameter. Only the ARCO classification showed significant differences ($P = .001$). Traumatic BME had significantly lower ARCO scores compared to idiopathic/ischemic/metabolic ($P = .002$) or mechanical/degenerative ($P = .006$) causes. Further subgroup analysis revealed that the ARCO classification had no significant influence ($P = .109$-$.774$) on any primary or secondary outcome parameter. No significant correlation (Pearson) could be found between age ($P = .169$-$.856$), BMI ($P = .346$-$.982$), or duration of symptoms ($P = .245$-$.997$) and any outcome parameter. In a final step, the population was divided into 2 groups per the reported pain decrease at t1. Group 1 (56%) were those patients with a considerable pain decrease (+3 / +2). Group 2 were patients with a pain score <+2. Table 4 depicts those 2 groups per the etiology of the BME. Overall, the chi-squared test revealed no significant differences ($P = .063$).

Discussion

The current study reported on the outcome of intravenous Iloprost therapy in 42 patients with BME of the foot and ankle of different etiologies and ARCO stages. Twelve patients (29%) had minor complications. At the 3-month (t1)

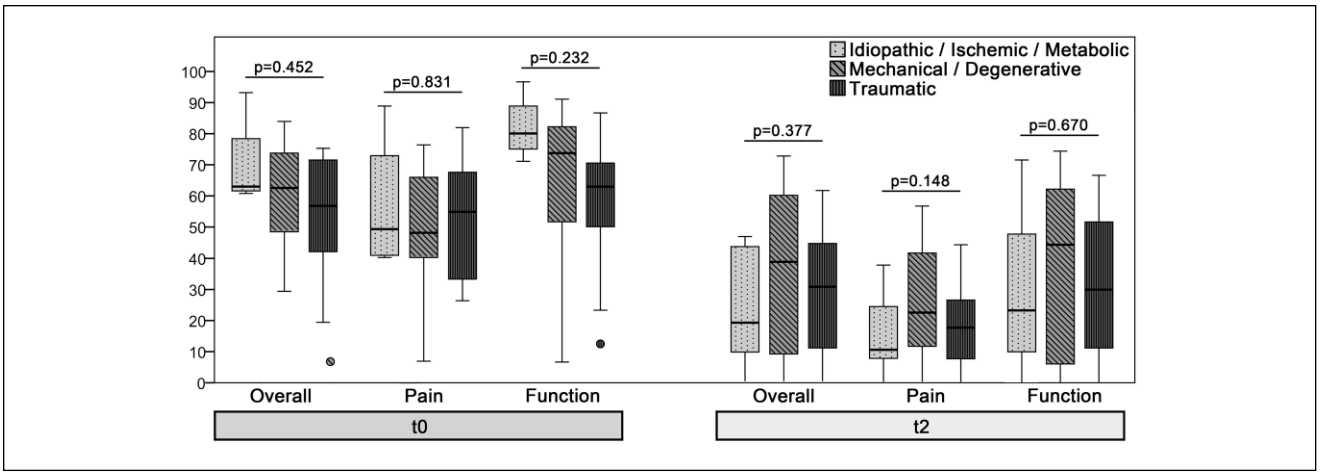

Figure 4. FFI subgroup analysis per etiology. FFI, Foot Function Index; t0, outpatient clinic; t2, final follow-up.

Table 3. Secondary Outcome Parameter per Etiology.

Etiology	ARCO Stage	Pain at t1 (3 mo)	MRI at t1 (3 mo)	VAS FA at t2		SF-12 at t2	
Idiopathic / ischemic / metabolic; n=11 (26%)	2.3 ± 0.8 *P* = .001	1.6 ± 1.0 *P* = .135	−1.0 ± 0.8 *P* = .379	Overall: 75 ± 17 Pain: 72 ± 18 Function: 75 ± 19 Other: 75 ± 16	Overall: *P* = .366 Pain: *P* = .491 Function: *P* = .281 Other: *P* = .660	PCS 44 ± 11 MCS 52 ± 11	PCS *P* = .504 MCS *P* = .561
Mechanical / degenerative: 16 (38%)	2.1 ± 0.7	0.8 ± 1.0	−1.1 ± 0.7	Overall: 63 ± 22 Pain: 61 ± 22 Function: 62 ± 25 Other: 68 ± 21		PCS 39 ± 12 MCS 48 ± 8	
Traumatic: n=15 (36%)	1.3 ± 0.6	1.6 ± 1.2	−1.5 ± 1.0	Overall: 69 ± 20 Pain: 64 ± 23 Function: 70 ± 21 Other: 72 ± 19		PCS 44 ± 12 MCS 49 ± 9	

Abbreviations: ARCO, Association Research Circulation Osseous; MCS, Mental Component Summary; MRI, magnetic resonance imaging; PCS, Physical Component Summary; VAS FA, Visual Analog Scale Foot and Ankle.

Table 4. Influence of Etiology on Pain at t1.

	Idiopathic / Ischemic / Metabolic, %	Mechanical / Degenerative, %	Traumatic
Group 1 (n=15) Pain at t1 +3/+2	20	60	20
Group 2 (n=19) Pain at t1 <+2	32	21	47

follow-up, a considerable pain decrease was observed in 56% and a BME reduction in 83% of patients (r = −0.463, *P* = .015). At final follow-up (28 ± 19 months), the PROM FFI had decreased significantly. Still, all assessed PROMs (FFI, SF-12, VAS FA) showed residual impairment. Subgroup analysis revealed no significant influence of the etiology, age, BMI, or ARCO stage on any outcome parameter.

The demographics compare well to previous studies.[2,5,13,20,24] Despite no significant alterations for the duration of in-house stay (5 ± 0.2 days (5-6 days)), a medication associated complication rate of 29% was observed. The observed minor complications are in line with previous studies. But their rate compares favorably to an average published complication rate of 50%.[2,3,5,8,20]

The primary pain-relieving effect of Iloprost on BME has been described to occur within the first 3 months.[5,13] We observed considerable pain decrease in almost 60% of patients after 3 months, which is in the range of previous studies. In one of the largest prospective studies (n=95) on BME of various locations, Jäger et al reported a decrease by 2.8 to 2.2 points (1-9) on the visual analog scale (VAS).[13] Baier et al retrospectively reported a VAS decrease by 5 to 1 points in 20 patients treated for BME of the knee or foot and ankle.[5] Meizer et al retrospectively assessed the outcome at 4 months in 104 patients with BME of various locations.[20] Using a 6-item Likert-type scale, pain decreased by 2 to 1 point. At rest, 64% reported a reduction in pain, 34% no change, and 2% an increase in pain. All these figures are in line with our reported values.

The current study showed a considerable BME decrease in more than 80% of patients on MRI. This is in line with reported high, but varying, remission rates 3 months after intravenous Iloprost.[3,4] Meizer et al retrospectively found a BME decrease of the knee, talus and navicular bone in 65% of patients.[20] In a RCT (n=21) Mayerhoefer et al showed a BME decrease in 58%.[17] A complete remission was published retrospectively by Röhner et al including only patients with ARCO stage I-II.[24] Studies on BME with ARCO stages III-IV found no change in BME after intravenous Iloprost therapy.[8,13] Still, none of these studies investigated the influence of the ARCO stage on the BME decrease.

The current study showed a moderate correlation between pain and BME reduction ($r = -0.463$, $P = .015$). Comparably moderate correlations were reported in previous studies.[30,31] For BME size and knee pain, Unay et al found a weak but significant correlation for the Stanmore Functional Rating Scale (SFRS) ($r = 0.313$, $P = .025$) but no correlation for the VAS ($r = 0.203$, $P = .153$).[31] Tonbul et al reported on idiopathic BME of the talus, showing a poor correlation to the AOFAS scores ($r = 0.313$, $P = .025$) and no correlation to the VAS ($r = 0.203$, $P = .153$).[30] These consistent findings raise the question on where the residual pain originates from. To address this question, the current study grouped BMEs per etiology and conducted a subgroup analysis. None of the chosen categories had a significant influence on any outcome parameter. Therefore, the reason for the discrepancy between BME and pain decrease remains unclear.

The primary outcome parameter overall FFI decreased significantly on average by 49% to 30 ± 22 points (0-73, $P < .001$) at final follow-up. This significant decrease was similar in all subscales. Schneider et al assessed age- and sex-related normative data for the FFI with a mean FFI overall scores of healthy individuals (40-49 years) of 17 points.[27] The herein observed overall VAS FA value of 68 ± 20 points was also below the corresponding reference values for healthy individuals (86-100) but comparable to patients with an isolated hallux valgus (45-83).[29] Consequently, the herein observed values for the foot and ankle–specific PROMS, that is, FFI and VAS FA, resemble a light to moderate impairment 28 ± 19 months after intravenous Iloprost therapy for BME of the foot and ankle.

Only 3 studies have assessed the outcome of Iloprost therapy on BME of the foot and ankle using outcome measures.[2,3,24] Aigner et al published 2 studies with 5 BME of the talus and 19 BME of the hindfoot, respectively.[2,3] They showed a significant increase of the Mazur Foot Score from 58 to 93 points and from 55 to 88 points after 3 months. Röhner et al (BME of the foot and ankle, n=23) found no significant VAS decrease but a significant increase for the Ankle Hindfoot Scale (55-70) and the Kaikkonen Scale (49-69) after 3 months.[24] Consequently, intravenous Iloprost therapy partially decreased pain but led to residual impairment.[2,24]

Keeping in mind the overall moderate PROM scores at final follow-up, efforts were made to identify possible factors that could help to identify patients predominantly benefiting from intravenous Iloprost therapy. Neither the etiology of the BME, nor the ARCO stage, correlated to any of the evaluated PROMs. Still, idiopathic/ischemic/metabolic BME resulted in nonsignificant better mean PROM values than mechanical/degenerative or traumatic BME. With regard to the limited power of the study, future studies with greater group sizes might be able to define these differences. Two studies reported similar descriptive results.[2,20] Aigner et al showed better results on the Mazur's score for ischemic (56.2-93.9) compared to osteoarthritic and stress BME (53-79.3).[2] Meizer et al found a greater pain decrease for idiopathic BME (87% at rest, 75.2% at stress) compared to degenerative BME (64% and 48%). Still both studies did not assess those changes statistically.[20] This is the first study to statistically analyze the influence of the ARCO stages on PROM.

Strengths and Limitations

Several limitations need to be discussed. First, no sample size calculation was conducted. Second, the retrospective design limits the statistical analysis but also explains the follow-up rate of 60%. Still most studies on this topic are retrospective.[3,5,8,16,20,24] and the follow-up rate achieved is comparable to studies with a similar design.[6,18,33] A further limitation could be the number of patients included. Other than few larger studies, most papers report on fewer patients.[1,3,5,8,16,17,20,24] Nevertheless, this is by far the largest cohort study on BME of the foot and ankle.[2,3,24] A final limitation is the lack of a control group. A control group, either treated by bisphosphonates or physiotherapy alone, would have allowed to assess differences at 3 months and final follow-up. Future prospective randomized trials should include a control group to assess the actual value

of drug therapy. These data will furthermore help to assess treatment costs (drug and hospital stay) to the actual treatment benefit.

Despite the above-outlined limitations, several strengths of this study are noteworthy. First, the prospective, intermediate follow-up of more than 2 years is important. Second, the radiographic evaluation was conducted by a musculoskeletal radiologist and 2 fellowship-trained foot and ankle specialists. Finally, in addition to the radiographic changes, general as well as foot- and ankle-specific PROMs were chosen to evaluate the prospective follow-up.

Conclusion

Overall, Iloprost therapy resulted in almost 60% pain decrease and in more than 80% of patients in a pronounced reduction of the BME within the first 3 months of treatment. After more than 2 years, the general as well as foot and ankle–specific PROMs showed residual impairment. Neither the etiology nor the ARCO stage of the BME had a significant influence on any outcome parameter. Consequently, treating patients with BME with intravenous Iloprost did not completely resolve their pain, independent of the BME's etiology or ARCO stage.

Declaration of Conflicting Interests

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