Aseptic osteonecrosis of the hip in the adult: current evidence on conservative treatment

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Summary

Treatment of Avascular Osteonecrosis (AVN) of the femoral head to prevent progression to an arthritic hip is a challenging subject. Many conservative treatment options have been proposed in the literature.
Weight bearing restriction as a stand-alone therapy is insufficient in preventing disease progression but it may be useful when combined with pharmacological agents or surgery.
Bisphosphonate treatment in AVN might be efficient in early stages of disease, however there are no clear recommendations on length of treatment and therapeutic dosage and, considered the limited evidence and potential side effects of treatment, it could be considered in a pre-collapse stage in selected cases. Current literature suggests that low molecular weight heparin could lower disease progression in idiopathic AVN with quality of evidence being very low. Also the evidence to support the use of statins or vasodilators in the treatment of osteonecrosis is very low and their use cannot be recommended.
Extracorporeal shock wave therapy may improve pain and function in early stages of disease with a low evidence, but there doesn't seem to be a significant change in time to the occurrence of femoral head collapse. Only one study has been conducted with pulsed electromagnetic fields therefore no recommendation can be given on clinical use of PEF in AVN. Evidence on hyperbaric oxygen therapy in the treatment of AVN is very limited and the high cost of treatment and the limited availability of structures that can provide the service poses other concerns about its feasibility.
Based on current evidence, conservative treatment may be considered in early stages of asymptomatic AVN instead of observation only.

KEY WORDS: osteonecrosis; femur head necrosis; drug therapy; physical therapy modalities.

Background

Treatment of Avascular Osteonecrosis (AVN) of the femoral head is a challenging subject, especially in early stages of disease where the goal of treatment is to reduce pain, obtain healing of the lesion and as a direct consequence prevent progression to an arthritic hip.
Conservative treatment may be considered as a treatment option in all those patients with early stages of disease (Ficat stage 1-2), but shouldn't be proposed in hips in presence of a subchondral bone fracture. There are many conservative treatment options described in the literature ranging from weight bearing restriction and pharmacological agents to biophysical therapy, but one should keep in mind that evidence from literature is very limited.

Conservative treatment

Weight bearing restriction

One of the cornerstones of conservative treatment is weight bearing restriction, but is it really efficient? Mont et al. (1), in a meta-analysis of 21 studies on conservative treatment of AVN, analyzed 819 patients with a mean follow-up of 2,8 years (range 1,6 to 10 years) and found that 78% of these patients underwent surgery and that in 74% there was a radiographic progression of the disease. Furthermore there was no difference in complete, partial or no weight bearing regimen. In another study Mont et al. (2) analyzed the natural evolution of 819 patients with asymptomatic AVN with a mean follow-up of 7 years (range 0,2 to 20 years). 59% of these patients become symptomatic (with stage of disease ranging from simple pain to head collapse). It was noted that 32% of patients with small to medium sized lesions became symptomatic as compared to 84% of patients with large sized lesions. Patients affected with sickle-cell disease had a high risk of head collapse (74%), whereas in patients with lupus the risk was quite low (17%). They concluded that disease progression depends on the site and the size of the lesion as well as on the etiology and that very small sized lesions may heal spontaneously (3). In conclusion weight bearing restriction as a stand-alone therapy is insufficient in preventing disease progression (4), but it may be considered a reasonable treatment option when combined with pharmacological agents or surgery.

Pharmacological treatment

Bisphosphonates

Bisphosphonates have proven their efficacy in treatment of osteoporosis through decreasing osteoclastic activity while improving bone mass density. Hypothetically in early stages of AVN the use of bisphosphonates could inhibit osteoclastic activity preventing subchondral bone collapse. Cardozo et al. (5) in a systematic review stated that patients affected with AVN treated with bisphosphonates had lesser pain, better

mobility and lesser occurrence of femoral head collapse. They also stated that favorable results were mostly reported by noncontrolled studies. Agarwala et al. (6) studied 395 patients treated with bisphosphonates with a mean follow up of 4 years (mean 1 to 8 years). Each patient received 10 mg of alendronate per day for 3 years. Radiographic progression to head collapse was noted in 12,6% of patients with stage Ficat 1 and 55,8% with stage Ficat 2 disease. In another observational study by Agarwala et al. (7) with 10 year follow up 53 patients (Ficat 1-2-3) received 70 mg alendronate per week for 3 years. At final follow-up 87% of patients were satisfied with treatment while the other patients underwent Total Hip Arthroplasty (THA) (71% of them being classified as Ficat 3). These results are in contrast with patients not receiving any treatment at all who develop femoral head collapse in more than 70% of cases. The Authors conclude that alendronate positively alters the natural course of AVN.

Yuan et al. (8) in a recent meta-analysis of 5 randomized controlled trials found no differences in progression to head collapse, incidence of THA and Harris Hip Score (HHS) improvement except for 1 study.

The Authors concluded that there is very limited evidence to support the use of bisphosphonates in treatment of hip necrosis and that more Randomized Controlled Trials (RCT) with larger patient groups are needed. Risks of prolonged bisphosphonate treatment such as osteonecrosis of the jaw and atypical femur fractures and potential benefits should be discussed with the patient underlining the fact that this is an off-label treatment. It seems that bisphosphonate treatment in AVN is efficient in early stages of disease, however there are no clear recommendations on length of treatment and therapeutic dosage. Considering the limited evidence and potential side effects of treatment, surgical treatment is to be preferred. In patients affected by AVN in a pre-collapse stage, a 3-years treatment with alendronate 70 mg per week should be considered in selected cases.

Anticoagulants

The use of anticoagulants has been popularized especially in patients with coagulation disorders (9). Anticoagulants seem to be effective in preventing disease progression and could conceptually reverse the pathophysiologic process in early stages of AVN. Glueck et al. (10) conducted a prospective study (level 2 evidence) on 25 patients (35 hips) affected by thrombophilia, hypofibrinolysis or both. All hips presented AVN Ficat stage 1-2. All patients received enoxaparin 6000 units per day for 3 months with a mean follow-up of 3 years (2 to 4 years). They found no disease progression in 95% (19/20 hips) of patients affected by primary osteonecrosis compared to only 20% (3 out of 15 hips) affected by osteonecrosis secondary to corticosteroid treatment. They concluded that enoxaparin is efficient in preventing disease progression in primary osteonecrosis. Chotanaphuti et al. (11) conducted a retrospective comparative study on 36 patients (49 hips) with AVN Ficat stage 1-2. The experimental study group (18 patients with 26 hips) received enoxaparin 6000 units per day for 3 months, whereas the control group (18 patients with 23 hips) received no therapy at all. Mean follow-up was 2 years. At final follow-up 43% of hips in the experimental group showed disease progression to head collapse compared to 78,3% in the control group (p=0.042). The Authors concluded that Low Molecular Weight Heparin (LWMH) could significantly lower disease progression in idiopathic AVN. Current evidence suggests that LWMH is efficient in treatment of idiopathic AVN with quality of evidence being very low. Our actual recommendation is enoxaparin 6000 units per day for 3 months (10, 12).

Statins

Fatty infiltration of the bone tissue in AVN is characteristic (13), so the use of lipid-clearing agents like statins seems to be reasonable especially in secondary AVN due to corticosteroid treatment. Pritchett et al. (14) analyzed retrospectively 285 patients that were taking both statins and corticosteroids at high dosage. Patients were checked by Magnetic Resonance Imaging (MRI) for onset of osteonecrosis. Mean follow-up was 7,5 years (range 5 to 11 years). Results showed that only 1% of patients developed osteonecrosis. This data reflects that statin therapy in AVN could be efficient when comparing their result with the incidence of osteonecrosis in a patient population on high dose corticosteroids as reported in the literature varying between 3 and 20% (15). Ajmal et al. (16) retrospectively analyzed 2881 patients that received high dose corticosteroids after renal transplantation. They selected 338 patients that took both statins and corticosteroids and confronted the incidence of AVN with 2543 patients that were taking corticosteroids alone. Mean follow-up was 7.5 years (range 3.5- 19 years). They found that 4,4% of patients taking both corticosteroids and statins developed osteonecrosis compared to 7% of the patients taking corticosteroids only. The difference wasn't significant. As there is very low evidence to support the use of statins in the treatment of osteonecrosis RCTs are definitely needed to recommend their use.

Vasodilators

Vasodilators like iloprost (a prostacycline derivate) have proven efficacy in the treatment in patients affected with vasculitis, lupus, Raynaud syndrome and painful crisis in sickle-cell disease (17-19). Prostacycline derivates induce a raise of blood flow in the terminal vessels and seem to induce bone regeneration at a cellular level. Disch et al. (20) conducted a prospective study comparing 16 patients with isolated bone marrow edema of the femoral head with 17 patients affected with AVN. Both groups were treated with iloprost for 5 days. Mean follow-up was 2 years (range 1 to 3 years). They found a significantly better HHS, range of motion, pain on visual analogic scale, patient satisfaction before/after treatment and regression of bone marrow edema in both groups ($p<0.001$). Concerning the use of vasodilators, current evidence is too low to give recommendations of any kind.

Biophysical therapy

Extracorporeal shock wave therapy

Extracorporeal Shock Wave Therapy (ESWT) causes expression of angiogenic growth factors that act as a stimulus to neovascularization (21) and could therefore be useful in the treatment of AVN. In fact, Wang et al. (22) in a randomized controlled trial on 57 hips with AVN found that EWST was more effective than core decompression with non-vascularized fibular bone graft. In another prospective study conducted on 36 hips with AVN ARCO stage 1-2-3 treated with ESWT with 2 year follow-up, Vulpiani et al. (23) found excellent results in ARCO 1-2 hips. They noted that pain, HHS and Roles-Maudsley score were significantly better in ARCO 1-2 hips when compared to ARCO 3 hips ($p<0.005$). Furthermore, 66% of ARCO III hips underwent THA at final follow-up. The Authors

concluded that ESWT slows down the disease in ARCO 1-2 hips. The current evidence suggests that ESWT improves pain and function in early stages of disease, but there doesn't seem to be a significant change in time to the occurrence of femoral head collapse and consequent THA. Evidence is very low due to small case series and short follow-up.

Pulsed electromagnetic fields

Pulsed Electromagnetic Fields (PEF) similar to ESWT seem to stimulate osteogenesis and angiogenesis (24, 25) and could therefore be useful in treatment of AVN. Massari et al. (26) conducted a retrospective study on 76 patients with AVN Ficat stage 1-2-3. All patients received PEF 8 hours per day for 5 months. Mean follow-up was 2 years (range 1 to 9 years). They found that 6% of Ficat stage 1-2 AVN and 80% of Ficat stage 3 AVN received a THA at final follow-up (level 4 evidence). Based on current evidence we cannot give any recommendation on clinical use of PEF in AVN.

Hyperbaric oxygen

Hyperbaric Oxygen Therapy (HBO) causes vasoconstriction reducing cellular edema. It also raises intracellular oxygen lowering cellular ischemia as well as intracellular pressure while raising angiogenesis and microcirculation (27). Therefore, its use in AVN could be useful. Reis et al. (28) treated 16 hips with AVN Steinberg stage 1 with HBO. All patients received 100% oxygen with 2-2,5 atm pressure for 90 minutes per day for 100 consecutive days. They found a normalization of MRI in 81% of patients. Camporesi et al. (29) conducted a double-blinded RCT on 20 hips with Ficat stage 2 disease with 7 year follow-up. Ten hips were treated with HBO while the other 10 hips were treated with hyperbaric air (30 sessions over a 6 week period). After 6 weeks the Authors changed to an observational study treating all patients of the hyperbaric air group with HBO. They found that after 20 sessions pain and mobility was significantly better in the HBO group. At final follow-up none of the patients received THA. The Authors analyzed MRI images of 9 patients that were made before treatment, at 1 year and after 7 years of HBO treatment. They found that in 7 patients the lesion had become better. Current evidence on HBO in the treatment of AVN is very limited. Others issues are the high cost of treatment, duration and frequency of treatment sessions, which poses concerns on patient compliance and last, but not least, the very limited availability of structures that can provide the service.

Discussion

Mont et al. (30) in a recent current concepts review stated that the evidence regarding all kind of conservative treatment for AVN is insufficient to make recommendations of any kind, contrary to surgical procedures like core decompression or multiple drilling of the necrotic lesion in early stages of disease. In fact there are many studies in the literature showing that in recent years the results of these procedures have significantly improved, most probably due to a more accurate patient selection specifically treating those with early stages of the disease (31-33). It has been shown that AVN, if left untreated, leads to femoral head collapse at 2 years distance (34). We also know that the risk of developing AVN on the other hip is very high within the first 2 years, mostly in those cases where the pathology that caused AVN has not been diagnosed or addressed (4, 35, 36). Current evidence is weak to support that conservative treatment alone in atraumatic AVN of the adult hip is effective in preventing disease progression (4). Nevertheless conservative treatment in early stages of AVN seems to improve pain and function (5-7, 20, 23, 29). Conservative treatment may be considered to gain time to surgery while keeping in mind that the natural course of the disease is not altered. Currently we are missing precise indications for specific conservative treatment modalities and for what stages of the disease they should be used for. There is definitely the need for RCT in order to clarify these issues. Conservative treatment may be considered in early stages of asymptomatic AVN instead of observation only. With current evidence being stronger, it seems reasonable to treat early stage AVN surgically once they become symptomatic (30).

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