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Review Article

Medical and Surgical Treatment Options for Early Osteonecrosis in Sickle Cell Disease

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Abstract

Sickle cell disease is one of the most common genetic disorders and the first molecular disease identified. Osteonecrosis defined as necrosis of bone and bone marrow. It occurs with sickle cell disease due to the polymerization of the sickle cell hemoglobin HbS, which followed by sickling and dehydration of the red blood cells. That causes slowing down of blood circulation and obstruction of the microcirculation leading to osteonecrosis. Many medical and surgical measures could be applied to reserve the joints with osteonecrosis from collapse and may be to avoid major surgical interventions. Both the hematologist and the orthopedics treating their sickle cell patients need to be aware of these available measures. The future trend also promising with the new hypo methylating drugs, new anticoagulants, autologous stem cell-based therapy, and many other new agents could be used to improve osteonecrosis and other sickle cell disease complications.This article reviews a subject poorly discussed in the literature from medical and surgical prophylactic and treatment points of view for the early detected osteonecrosis.

Keywords: Osteonecrosis; Sickle cell anemia; Sickle cell hemoglobin

Introduction

Sickle cell disease (SCD) is the most common and the first molecular disease identified. It has a high prevalence in Africa, around the Mediterranean, Middle East, United States of America, and West Indies and in Brazil [1]. In Africa, the highest prevalence is found within the sicklemic belt of Lehmann. The prevalence of SCD is variable; it is 5-20% in West Africa and reaches up to 40% in Central Africa [2]. The abnormality is due to the substitution of a glutamic acid by a valine at the sixth position on the chain of β-globin, resulting in pathologic hemoglobincalled hemoglobin S**.** This abnormality results from an autosomal recessive mutation on chromosome 11 [3]. The classic physiopathology of the SCD is based on the polymerization of hemoglobin S, followed by sickling and dehydration of the red blood cells. The slowing down of blood circulation and obstruction of the microcirculation by the deformed red blood cells is the reason of the manifestations and complications of SCD. Bone microcirculation is a common place for red blood cell sickling, which leads to thrombosis, infarct, and Osteonecrosis (OSN) [4].

This bone lesion is also referred as a vascular necrosis, ischemic necrosis or aseptic necrosis. It is defined as a necrosis of the bone and bone marrow [5]. OSN, when investigated with advanced technology, could found in as many as 76% of the people with SCD [6]. It results from temporary or permanent loss of the blood supply to the bones. Around 10,000 to 20,000 Americans typically aged between 20 and 50 years old develop OSN annually from different etiologies [7]. Vertebral bone compression and collapse induced by OSN in people with SCD have also been reported [8]. OSN in SCD found in different sites which seem it potentially affect any bone in the body as a part of the multi-organ infarcts [9]. The diagnosis and staging of OSN must be precise as the condition is complex and requires specific treatment according to the grade of bone and joint involvement [10]. There are a number of classifications or staging systems used for grading OSN joint involvement such as Steinberg classification [11] (Table 1).

The literature is poor in discussing the available methods which could be of great benefit for osteonecrosis. This review highlights the possibility of using many methods in hand beside many other methods could be an important research projects to treat osteonecrosis in hundreds of thousands of SCD patients (Table 1) [12,13] .

Medical treatment

Many non-applied medical treatment methods for OSN in its early diagnosis need to be written as a management protocols including reduced weight-bearing on the affected joints by using crutches, pain medication, exercise programs, and encouraging such patients to abstain or decrease alcohol consumption and smoking [14]. Electrical stimulation has been used in several centers to induce bone growth.In some studies,it was found to be helpful when applied before femoral head collapse [15]. The pulsed electromagnetic fields (PEMFs) used in treatment of osteonecrosis of femoral head have three fundamental mechanisms of action, local control of inflammation, repair joints activity in the areas of osteonecrosis of the femoral head and potentiation of healing process by stimulating neovascularization to induce new bone formation [16]. Extracorporeal shock wave therapy (ESWT) has been utilized in Europe for the treatment of early-stage of OSN. Wang, et al. [17] compared the results of such therapy in twenty-nine hips of thirty-two patients. With a mean of twenty-five months, 79% of the shock-wave group improved. The hyperbaric oxygen has been used in OSN with the perception that it improves oxygenation, reduces edema, and induces angiogenesis; thus causing a reduction in intra-osseous pressure and improvement in microcirculation. Apart from few case reports and review articles 16 hips in 12 patients, all with Steinberg stage I disease have been reported in the literature. Each patient was

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given hyperbaric oxygen for 100 consecutive days,which involved breathing 100% oxygen via a mask at 2-2.4 atmospheres pressure for 90 minutes. Though the follow-up period was poorly defined, it was reported that 13 of the 16 femoral heads subsequently appeared normal on MRI after this treatment [18]. However, these methods have no role in the treatment of late stages of osteonecrosis and could have limited success in preventing OSN progression even in early stage (Steinberg stage I and II) disease [19]. OSN of the femoral head may develop as a result of a physiological diversion of mesenchymal stem cells toward an adipocytic lineage [20]. So treatment with lovastatina cholesterol lowering agent was tried to prevent this diversion of normal osteoblastic cellular differentiation [21]. Also, OSN treated with the use of anabolic steroid stanozolol (6 mg/day) has been reported. All patients showed a decrease of symptoms at one year following treatment. Among 17 patients with early-stage osteonecrosis of the femoral head, all had clinical and radiographic improvements at one year after treatment with anabolic steroid stanozolol [22]. Using enoxaparin (60 mg/day for twelve weeks) to treat patients who had thrombophilic or hypofibrinolytic disorders and early stages of osteonecrosis of the femoral head, at two years, thirty-one (89%) of thirty-five hips had not required surgery in early OSN stages [23]. Bisphosphonates and denosumab regularly used for treatment of osteoporosis and other pathologic conditions of bone, have been found to be promising for clinically treatment of OSN to postpone surgical interventions [24]. Randomized studies have shown that alendronate delays or prevents progression of femoral head collapse in Steinberg stage I and II disease, and may ultimately reduce the need for joint arthroplasty, although longer term follow-up was needed.Alendronate resulted in improved hip function and decreased dependency on non-steroidal anti-inflammatory drugs over a period of 2.5 years. In addition, there was decreased of femoral head edema on MRI, suggesting bone remodeling and slower progression of osteonecrosis [19]. Bisphosphonates are important inhibitors of osteoclastic bone resorption *in vivo* and are used in OSN due to malignancy, Paget's disease of bone and osteolytic bone disease [25]. The inhibition of osteoclast activity by the use of Bisphosphonates could lead to an increase in bone mass and strength in these sites [26], but on a controversy the Bisphosphonates for unknown etiology could cause jaw necrosis in a rare prevalence of 0.07 to 0.1 in long-term use [27]. Treating the underlying coagulation disorders may arrest or delay the progression of the OSN if started in the early stages of the lesion before the collapse [23]. Eight clinical reports of the use of alendronate in OSN highlightits potential benefit for patients with osteonecrosis of the femoral head [28,29].

Surgical treatment

Core decompression prophylactic surgery is commonly used in pre-collapse OSN prior to Steinberg stage III, in which necrotic cancellous bone in the femoral head is drilled and removed from the lateral femoral cortical entry point [30]. This can be stabilized with structural allograft or with autograft by harvesting cancellous bone from the greater trochanter and proximal femur. The cancellous bone graft contains osteoprogenitor cells that aidin healing. However, augmentation of the core decompression can be achieved with the addition of bone morphogenic proteins, electromagnetic stimulation, or demineralized bone matrix [31,32]. Although core decompression for Steinberg stage I disease was successful as a definitive procedure in > 80% of patients. In Steinberg stage II and III, the osteonecrosis treated with decompression required further surgical reconstructive intervention in 37% and 71% of patients, respectively [33,34]. Multiple drilling of the femoral head osteonecrosis lesion can be an alternative procedure [35]. Another biologic option that has met with some success is the harvesting and *in vitro* culture of autologous mesenchymal stem cells and re-implantation in the core decompression site [36,37]. Studies of the long-term success of using bone morphogenic proteins and autologous mesenchymal stem cells are still under evaluation [38].

Table 1: Steinberg's classification of a vascular necrosis [13].

	Steinberg Classification
Stage 0	Normal or non diagnostic radiographs, bone scan, and/or MRI
Stage I	Normal radiographs; abnormal bone scan/ MRI:
	A. Mild, <15% of head affected
	B. Moderate, 15% to 30% of head affected
	C. Severe, >30% of head affected
Stage II	Abnormal radiograph; abnormal bone scan/MRI:
	A. Mild, <15% of head affected
	B. Moderate, 15% to 30% of head affected
	C. Severe, >30% of head affected
Stage III	Subchondral collapse, crescent sign, without flattening:
	A. Mild, <15% of head affected
	B. Moderate, 15% to 30% of head affected
	C. Severe, >30% of head affected
Stage IV	Flattening of femoral head:
	A. Mild, <15% of head affected
	B. Moderate, 15% to 30% of head affected
	C. Severe, >30% of head affected
Stage V	Joint space narrowing and/or acetabular changes:
	A. Mild
	B. Moderate
	C. Severe
Stage VI	Advanced degenerative changes, secondary osteoarthritis

Transtrochanteric rotational osteotomy is a controversial procedure with reported inconsistent results [39]. Several other studies have advocated various osteotomy as an effective head preservation surgery in which the lateral intact area of the femoral head can be placed into the acetabular weight bearing portion, thus preventing progression of collapse [40-44]. Vascularized bone grafting procedures with powerful support are used as a head-preserving method. Quadratus femoris muscle pedicle bone grafting; has yielded satisfactory results for the long-term clinical extensive lesion [45]. Total hip arthroplasty is commonly utilized as a definitive treatment for high-grade osteonecrosis with articular collapse [46].

The future trend of OSN treatment in SCD

The future trend in treatment SCD OSN is very promissing. The Studies by Massari and Santori concluded that capacitive electromagnetic stimulation with pulsed electromagnetic fields in combination with core decompression and autologous bone grafting

had a positive short-term effect on catabolic inflammatory response in the joint cartilage and bone [47,48]. Weak electromagnetic fields can have a positive influence on angiogenesis and osteogenesis [49]. The new drugs in medical research for SCD could have effective results on OSN prevention and treatment such as the hypomethylating agents (5-azacytidine and decitabine) which increase Hb F [50,51]. Aes -103 (5-HMF) that increase Hb-oxygen affinity and subsequently decrease RBC fragility in SCD [52], it also works as a direct-acting hemoglobin modifier that prevent sickling of red blood cells, increase hemoglobin's affinity for oxygen, inhibits polymerization of HbS, and restores normal RBC function in preclinical SCD models [53]. Low molecular weight heparin tinzaparin (Innohep) showed efficacy in SCD vaso-occlusive painful crises [54]. An initial trial of Sulfated non-anticoagulant heparin Sevuparin (Dilaforette) has been shown to inhibit adhesion of sickle red blood cells to endothelium with no effect on coagulation [55], it removes antithrombin binding domain through chemical depolymerization [56]. Platelets inhibitors: Prasugrel inhibit platelet aggregation by blocking adenosine diphosphate (ADP)-dependent activation. Platelets inactivation reduces the SCD pain and the vascular thrombosis [57,58]. The ongoing research trials for the autologous stem cell-based therapy for osteonecrosis of the femoral head in SCD resulted in significant pain relief and halted progressive improvement of early stages of OSN [59]. Most recently core decompression and autologous bone marrow concentrate installation commenced for the treatment of femoral head osteonecrosis [60].

Conclusion

Osteonecrosisis acommon complication of sickle cell disease. Usually, it ends up in many patients with hip and shoulder replacement. Preventing of bone osteonecrosis progression and collapse could be possible according to some research studies in the literature. Organizing the medical treatment of osteonecrosis under clear guidelines and protocols could delay or minimize the need for surgical intervention or arthroplasty for the affected joints before the collapse. The future promising research work on sickle cell bone could help in controlling the sickle cell osteonecrosis pain and other devastating complications.

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