TITLE: Stem Cell Injections with or without Core Decompression for Pediatric Patients with Legg-Calvé-Perthes Disease: Clinical and Cost-Effectiveness and Guidelines

DATE: 01 October 2015

RESEARCH QUESTIONS

1. What is the clinical effectiveness of stem cell injections with or without core decompression in pediatric patients with Legg-Calvé-Perthes Disease?

2. What is the cost-effectiveness of stem cell injections with or without core decompression in pediatric patients with Legg-Calvé-Perthes Disease?

3. What are the evidence-based guidelines associated with the treatment of pediatric patients with Legg-Calvé-Perthes Disease?

KEY FINDINGS

One evidence-based guideline was identified regarding the treatment of pediatric patients with Legg-Calvé-Perthes Disease.

METHODS

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2010 and September 18, 2015. Internet links were provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

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SELECTION CRITERIA

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

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<th>Table 1: Selection Criteria</th>
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<td><strong>Study Designs</strong></td>
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RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

One evidence-based guideline was identified regarding the treatment of pediatric patients with Legg-Calvé-Perthes Disease. No relevant health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, or economic evaluations were identified.

Additional references of potential interest are provided in the appendix.

OVERALL SUMMARY OF FINDINGS

Guidelines for the conservative management of Legg-Calvé-Perthes Disease from the Cincinnati Children’s Hospital Medical Center recommend that patients who are classified as candidates for conservative treatment should undergo supervised physical therapy. If the patient’s condition deteriorates while undergoing physical therapy, they should then be referred back to an orthopedic surgeon for additional examination and assessment.
REFERENCES SUMMARIZED

Health Technology Assessments
No literature identified.

Systematic Reviews and Meta-analyses
No literature identified.

Randomized Controlled Trials
No literature identified.

Non-Randomized Studies
No literature identified.

Economic Evaluations
No literature identified.

Guidelines and Recommendations

1. Evidence-based care guideline for conservative management of Legg-Calve-Perthes disease in children aged 3 to 12 years. Cincinnati (OH): Cincinnati Children's Hospital Medical Center; 2010 Oct. 16

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APPENDIX – FURTHER INFORMATION:

Meta-Analyses – Stem Cell Treatment Not Specified in Abstract


BACKGROUND: Legg-Calve-Perthes disease (LCPD) is an idiopathic avascular necrosis of the femoral head primarily affecting children of ages 4 to 12 years. There is no clear consensus on nonoperative or operative treatment protocols for pediatric patients presenting with LCPD. This study uses meta-analysis and a binary logistic regression model to analyze the radiographic outcomes of these treatment modalities in pediatric patients. METHODS: Clinical studies describing patients undergoing either nonoperative or operative treatment of LCPD published from 1960 through 2010 were searched electronically and manually. Eligible studies consisted of (1) a minimum of 10 patients; (2) listed age at the time of diagnosis or treatment; (3) performed an initial severity assessment using the Herring or Catterall classification; (4) detailed the type of intervention; and (5) reassessment of radiographic outcome after a minimum of 1 year after treatment using the Mose or Stulberg classification. RESULTS: Twenty-three studies, 1232 patients, and 1266 hips met the inclusion criteria. Among patients younger than 6 years, operative and nonoperative treatments are equally as likely to result in a successful radiographic outcome [odds ratio (OR)=1.071; P=0.828; 95% confidence interval (CI), 0.737-3.293]. In patients older than 6 years, operative treatment is nearly twice as likely to result in a successful radiographic outcome (OR=1.754; P<0.0001; 95% CI, 1.299-2.370). For age at treatment less than 6 years, a patient treated with a pelvic rather than femoral procedure was approximately 5 times as likely to have a good radiographic outcome (chi=4.488; P=0.034; unadjusted OR=5.20; 95% CI, 1.021-26.471). Among patients ages 6 or older, pelvic procedures were equally as likely as femoral procedures to yield a successful radiographic outcome (chi=1.845; P=0.174; unadjusted OR=1.329; 95% CI, 0.881-2.004). Sex had no significant influence on radiographic outcome (OR=1.248; P=0.486; 95% CI, 0.670-2.325). CONCLUSIONS: This meta-analysis suggests that operative treatment is more likely to yield a spherical congruent femoral head than nonoperative methods among patients 6 years or older. Among patients younger than 6 years, operative and nonoperative methods have the same likelihood to yield a good outcome. Patients who were 6 years or older were treated operatively, and had the same likelihood of a good radiographic outcome regardless of treatment with femoral or pelvic procedures. Among patients younger than 6 years, pelvic procedures were more likely to result in a good radiographic outcome than femoral procedures. LEVEL OF EVIDENCE: Level IV meta-analysis.

Review Articles


INTRODUCTION: Hip osteonecrosis is a pathological condition resulting from cellular
impairment due to reduction in osteoblast activity and local mesenchymal stem cell populations. Cell-based therapies might aid in overcoming these deficiencies by providing stem cells and other progenitor cells to potentially improve the local cellular environment in the affected hip. METHODS: A PubMed search, using the search terms “hip osteonecrosis” and “mesenchymal stem cells”, was conducted in December 2013. A total of 15 publications were identified and reviewed for clinical outcomes. FINDINGS: Clinical studies of patients with osteonecrosis treated with mesenchymal stem cells showed beneficial effects. No unexpected adverse events were identified in these studies. Core decompression was the usual method for autologous bone marrow cell implantation into the femoral head. However, other methods have been used such as arterial or venous delivery. A rationale for the use of cytotherapy, as well as the different descriptions of the techniques of implantation MSCs (autologous vs. allogenic, concentration vs. expansion), is provided in the context of treating hip osteonecrosis. Current problems and future challenges with cytotherapy and associated techniques are discussed. This article is part of a Special Issue entitled “Stem Cells and Bones”.


Bone is one of the most transplanted tissues. While most bone defects heal spontaneously, critical size defects caused by major trauma/malignant tumor and osteonecrosis of femoral head in young adults pose a great challenge in treatment. While the golden standard in treating bone defects is autologous bone grafting, available bone for grafting is quite limited in an individual. To solve the dilemma, stem cell therapy has been tried as a new modality of treatment in lesions not amenable to autologous bone grafting. While successful results were reported from individual studies, the stem cell therapy is still not an established treatment modality for bone regeneration and needs further assessment. Our focus herein is to introduce stem cell sources that have been investigated so far and review the current status of stem cell reutilization for bone regeneration as well as suggesting future perspectives.


The general ease of availability and strong fundamental science of autologous mesenchymal stem cells has prompted increasing application of such biologic therapies to address inherent orthopedic challenges of limited vascularity and ability to self-repair. This article provides a concise review of emerging mesenchymal stem cell applications for bone-related pathologies including cartilage, avascular necrosis, and fractures.


Osteonecrosis of the femoral head (ONFH) is a type of common and refractory disease in
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the orthopedic clinic that is primarily caused by a partial obstruction of the blood supply to the femoral head, resulting in a series of pathological processes. Mesenchymal stem cells (MSCs) comprise a mixture of various stem cells in myeloid tissue with multipotential differentiation capacity. They can differentiate into bone cells under specific conditions and can be used to treat ONFH through cell transplantation. This review summarizes research on MSCs in the field of ONFH in recent years, reveals the inner characteristics of MSCs, describes their potential to treat osteonecrosis disease, and analyzes the existing challenges of using MSCs in clinical applications.


Avascular necrosis (AVN) of the femoral head is a progressive disease that predominantly affects younger patients. Although the exact pathophysiology of AVN has yet to be elucidated, the disease is characterized by a vascular insult to the blood supply of the femoral head, which can lead to collapse of the femoral head and subsequent degenerative changes. If AVN is diagnosed in the early stages of the disease, it may be possible to attempt surgical procedures which preserve the hip joint, including decompression of the femoral head augmented with concentrated bone marrow. The use of autologous stem cells has shown promise in halting the progression of AVN of the femoral head, and subsequently preventing young patients from undergoing total hip arthroplasty. The purpose of this study was to review the current use of stem cells for the treatment of AVN of the femoral head.


Mesenchymal stem cells (MSCs), the non-hematopoietic progenitor cells, are multi-potent stem cells from a variety of tissues with the capability of self-renewal, proliferation, differentiation into multi-lineage cell types, as well as anti-inflammatory and immunomodulatory. These properties make MSCs an ideal source of cell therapy in bone and joint diseases. This review describes the advances of animal study and preliminary clinical application in the past few years, related to MSC-based cell therapy in the common bone and joint diseases, including osteoarthritis, rheumatoid arthritis, osteoporosis, osteonecrosis of the femoral head and osteogenesis imperfecta. It highlights the promising prospect of MSC in clinical application of bone and joint diseases.


Cellular therapy has gained an increasing popularity in recent years. Mesenchymal stem cells (MSCs) have the potential to differentiate into bone, cartilage, or fat tissue. In recent studies, these cells have also shown healing capability by improving angiogenesis and preventing fibrosis, which could have a role in tissue repair and tissue regeneration. Preclinical and clinical orthopedic studies conducted in the adult population support the use of MSCs for bone-healing problems, early stages of osteonecrosis, and local bone...
defects. Only a few published studies support the use of MSCs in pediatric osteoarticular disorders, probably due to the unknown long-term results of cellular therapy. The purpose of this review is to explain the mechanism by which MSCs could exhibit a therapeutic role in pediatric osteoarticular disorders.


It is of paramount importance to distinguish hips that may or may not be suitable for containment in the transitional stage (fragmentation to early reossification stage), because long-term clinical and radiological outcomes may be influenced by the choice of treatment. This article summarizes the definition of hinge abduction, pathoanatomy of hinge segment, assessment of hinge abduction, determination of reducible and irreducible hinge abduction, and treatment strategies for containable and uncontrollable hips in the transitional stage.


Legg-Calve-Perthes disease is an idiopathic hip disorder that produces ischemic necrosis of the growing femoral head. Permanent femoral head deformity is the most significant sequela. Experimental studies indicate that the pathologic repair process, which is marked by an imbalance of bone resorption and formation, contributes to the pathogenesis of femoral head deformity. Important prognostic factors include degree of deformity, age at disease onset, extent of head involvement, head-at-risk signs, and lateral pillar collapse. Treatment should be guided by age at disease onset, current best evidence, and prognostic factors. Patients aged <6 years at onset are best managed nonsurgically, whereas older patients may benefit from surgical treatment. Good surgical results have been reported in 40% to 60% of older patients (>8 years), indicating the need to develop more effective treatments based on the pathobiology of the disease.

Additional References


Perthes disease refers to self-limiting idiopathic avascular necrosis of capital femoral epiphysis in a child. There is no consensus for the optimum treatment of Perthes disease even 100 years after the first description. The prime aim of the treatment is to maintain the sphericity of the femoral head and the congruency of the femur-acetabulum relationship to prevent secondary degenerative arthritis. Early diagnosis and management can help the collapse of femoral head, progressive femoral head deformity, and impingement.