systematic review on Role of Intra-Articular injection of hyaluronic acid in treatment of knee Osteoarthritis

Submitted for partial fulfillment of Master Degree in Orthopedic Surgery

By

Mahmoud Said Mohamed Ibrahim Abo elseoud

M.B.B.Ch.

Supervised by

Prof. Dr.Tarek Mohamed khalil

Professor of orthopedic surgery

Faculty of Medicine

Ain Shams University

Dr. Hisham Mohamed kamal

Lecturer of Orthopedic Surgery

Faculty of Medicine

Ain Shams University

2017

Acknowledgement

Thanks God for all the blessings all through my life,including this work the people I encountred through it,the experience and knowledge I gained by passing through it.

I would nevre be able to express my gratitude to my family for their encouragement and support all through my life .

I would like to express my deeply felt gratitude ***Prof. Dr.Tarek Mohamed Khalil*** Professor of orthopedic surgery, Faculty of Medicine, Ain Shams University, for his kind and gentle guidance beside the valuable time he spent.

I would like to express my appreciation to ***Dr. Hisham Mohamed kamal*** Lecturer of Orthopedic Surgery Faculty of Medicine, Ain Shams University, for ideas and valuable discussions throughout the process of writing the essay.

I would like seize this opportiunity to thank all my ***professors in the Egyptian Armed forces for learning,*** exercising and how to love orthopedics.

To my ***father***, my ***mother***, my ***brother*** and my ***sister*** for their encouragement, love, support and for always being when I need them.

I would like to thank all ***my friends***, ***collegues***, ***professors*** and co-workers who helped me in my way and in my work.

Contents

List of abbreviations

ACL	anterior cruciate ligament
ACR	American college of rheumatology
b-FGF	Beta-fibroblast growth factor
BMI	body mass index
CD44	cell surface glycoprotein
COX-1	Cyclooxygenase 1
DVS	divinyl sulfone
ECM	Extracellular matrix
FDA	Food and Drug Administration
GAG	Glycosaminoglycan
GHAP	glial hyaluronate-binding protein
GI	Gastrointestinal
GMHA	Greene Metropolitan Housing Authority
HA	Hyaluronic acid
HAS1	hyaluronan synthase 1
hESC	human embryonic stem cell
ICAM-1	Intercellular Adhesion Molecule 1
IGF-1	Insulin-like growth factor
IL-1ra	Interleukin 1 receptor antagonist
IPN	Interpenetrating network
JSN	joint space narrowing
K-L	Kellgren and Lawrence
LCL	lateral collateral ligament
MCL	medial collateral ligament
MMPs	matrix metalloproteinases
MSC	mesenchymal stem cells
NSAID	Non-steroidal anti inflammatory drug
OA	Osteoarthritis
OTC	Over-the-counter
PCL	posterior cruciate ligament
PEG	Poly ethylene glycol
RHAMM	receptor for HA-mediated motility
ROM	Range of motion
ROS	Reactive oxygen species
SAIRS	Severe acute inflammatory reaction
TGFß	Transforming growth factor ß
TIMPs	tissue inhibitors of MMPs
TLR	Toll-like receptors
TNF	Tumor necrosis factor
VAS	visual analogue scale

List of Tables

List of Figures

Abstract

Osteoarthritis affects about 10% of the population over 55 years of age. Of those, one-quarter are severely disabled. About 13% of women and 10% of men aged 60 years and older have symptomatic knee osteoarthritis.

Although osteoarthritis has been classified as a non-inflammatory arthritis, increasing evidence has shown that inflammation occurs as cytokines and metalloproteinases are released into the joint. These agents are involved in the excessive matrix degradation that characterizes cartilage degeneration in osteoarthritis.

Methodology: Systematic review will be done on Role of Intra-Articular injection of hyaluronic acid in treatment of knee Osteoarthritis.

Pubmed search will be done on the following titles: Role of Intra-Articular injection of hyaluronic acid in treatment of knee osteoarthritis.

Keywords: hyaluronic acid**,** knee osteoarthritis**,** Intra-Articular injection**.**

Conclusion: HA is useful on long run, meanwhile effect of cortisone is limited to short time. Also, the minimal adverse effect profile for HA including allergic reaction, redness, hotness, tenderness compared to cortisone adverse effect.

Introduction

Osteoarthritis affects about 10% of the population over 55 years of age. Of those, one-quarter are severely disabled. About 13% of women and 10% of men aged 60 years and older have symptomatic knee osteoarthritis[(1)].

Several factors including cytokines, leptin, and mechanical forces are pathogenic factors of knee osteoarthritis[(2)].

Although osteoarthritis has been classified as a non-inflammatory arthritis, increasing evidence has shown that inflammation occurs as cytokines and metalloproteinases are released into the joint. These agents are involved in the excessive matrix degradation that characterizes cartilage degeneration in osteoarthritis[(3)].

Hyaluronic acid, a glycosaminoglycan, is widely used for the treatment of osteoarthritis of the knee. A survey of 2 general practices in the United Kingdom showed that about 15% of patients with osteoarthritis received intra-articular treatment4[(4)] .

Treatment with intra articular hyaluronic acid product appears to offer significant advantage over aspiration and placebo injection for up to 6 months. it also may have an advantage over intra-articular glucocorticoids[(5)]

The unique viscoelastic nature of hyaluronic acid along with its biocompatibility and non-immunogenicity has led to its use in

several clinical applications, including the supplementation of joint fluid in arthritis.[6]

Hyaluronic acid possesses several protective physio-chemical functions that may provide some chondroprotective effects, this may explain its longer-term effects on articular cartilage[7].

Hyaluronic acid can reduce nerve impulses and nerve sensitivity associated with pain. It enhances proteoglycan synthesis and reduces the production and activity of pro-inflammatory mediators and matrix metalloproteinases, which alters the behavior of immune cells[8].

Hyaluronic acid also regulates leukocyte and macrophage migration and aggregation and the regulation of fibroblast proliferation[9].

Aim of the work

Systematic review study on the result of Intra-Articular injection of hyaluronic acid as aline of treatment of knee osteoarthritis.

This review will show different literature, research and statistical analysis of result concerned with Intra-Articular injection of hyaluronic acid as aline of treatment of knee osteoarthritis.

Basic science of articular cartilage of the knee joint

The knee is composed by tendons and ligaments that are essentially constituted by connective tissues. The former connect muscle to bones and the latter connect bone to bone. Whether the tendons as ligaments are made of strands of elastic proteins. Ligaments prevent bones from moving too far and tendons help in the movement of muscles. The patella is inside a tendon, the patellar tendon which annexes the quadriceps muscles on the front of thigh and cover the patella[(10)].

Moreover, knee joint include the tibiofemoral joint, a condyloid joint between the condyles of the femur and tibia, and patellofemoral joint, that it is between the posterior surface of the patella and the patellar surface of the femur. The upper tibiofibular joint often communicates with the femorotibial joint[(11)].

The articular capsule: that lining a synovial joint is constituted by fibrous capsule (thick outer layer) and synovial membrane (inner layer). The joint capsule is vital to the function of synovial joints. It protects the joint space, allowing stability by restricted movements, promoting active stability through nerve endings and may form articular surface for the joint, lined with synovium and forms a sleeve around the articulation bones to which it is attached[(12)].

The synovial membrane: of the knee-joint is the largest in the body. This membrane start at the upper edge of the patella, on the

lower part of the front of the femur that communicates with a bursa interposed between the tendon and the front of the femur.

The synovial membrane is a specialized mesenchymal tissue covering the spaces of diarthrodial joints, bursae, and tendon. This membrane has two layers, the inner layer, constituted by macrophages or synoviocytes, and outer layer, composed of two to three layers of synoviocytes over connective tissue with fibroblasts, secreting collagen, and other extracellular matrix proteins[13]. The outer layer has few macrophages and lymphocytes, blood vessels with contain nutrients to the synovial membrane and the adjacent avascular cartilage and fat cells.

The synovial membrane is surrounding the cavity of joints, taking the space with synovial fluid. It has an important role in nutrition of the articular cartilage. The synovial fluid lubricates the ends of the bones making possible them to move often. The inefficiency to keep the level of metabolism starts destructive process[14].

The synovial fluid: secreted by the synovial membrane, composed of hyaluronic acid (synthesized by the synovial membrane) and lubricin (also named as Proteoglycan 4). is responsible of the joint:

(1) lubrication (which reduces friction and avoids shock between the surfaces of cartilage)

(2) nourishment (supplying oxygen and nutrients).

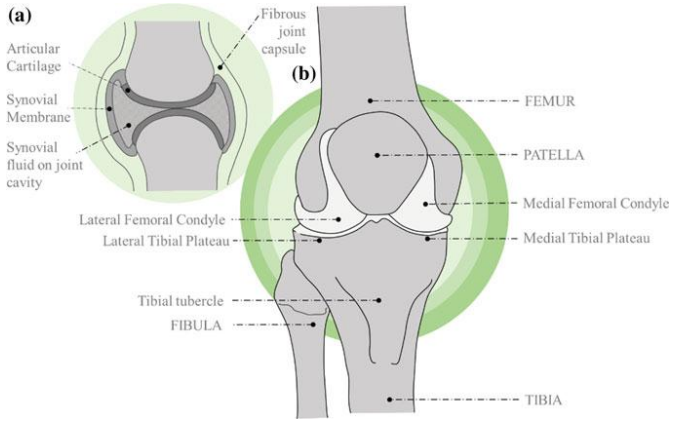

Figure (1): Structure of synovial joint (a) and the anatomy of the knee (b)[15]

Structure And Composition Of Articular Cartilage

Articular cartilage is hyaline cartilage and is 2 to 4 mm thick. Unlike most tissues, articular cartilage does not have blood vessels, nerves, or lymphatics. It is composed of a dense extracellular matrix (ECM) with a sparse distribution of highly specialized cells called chondrocytes. The ECM is principally composed of water, collagen, and proteoglycans, with other noncollagenous proteins and glycoproteins present in lesser amounts Together, these components help to retain water within the ECM, which is critical to maintain its unique mechanical properties[16].

Along with collagen fiber ultrastructure and ECM, chondrocytes contribute to the various zones of articular cartilage the superficial zone, the middle zone, the deep zone, and the calcified zone (Figure 2). Within each zone, 3 regions can be identified the pericellular region, the territorial region, and the interterritorial region[17].

Zones

1.The thin superficial (tangential) zone protects deeper layers from shear stresses and makes up approximately 10% to 20% of articular cartilage thickness. The collagen fibers of this zone (primarily, type II and IX collagen) are packed tightly and aligned parallel to the articular surface (Figure 2). The superficial layer contains a relatively high number of flattened chondrocytes, and the integrity of this layer is imperative in the protection and maintenance of deeper layers. This zone is in contact with synovial fluid and is responsible for most of the tensile properties of cartilage, which enable it to resist the sheer, tensile, and compressive forces imposed by articulation[(18)].

2. The middle (transitional) zone, which provides an anatomic and functional bridge between the superficial and deep zones. The middle zone represents 40% to 60% of the total cartilage volume, and it contains proteoglycans and thicker collagen fibrils. In this layer, the collagen is organized obliquely, and the chondrocytes are spherical and at low density. Functionally, the middle zone is the first line of resistance to compressive forces.

3.The deep zone is responsible for providing the greatest resistance to compressive forces, given that collagen fibrils are arranged perpendicular to the articular surface. The deep zone

contains the largest diameter collagen fibrils in a radial disposition, the highest proteoglycan content, and the lowest water concentration. The chondrocytes are typically arranged in columnar orientation, parallel to the collagen fibers and perpendicular to the joint line. The deep zone represents approximately 30% of articular cartilage volume[19].

The tide mark distinguishes the deep zone from the calcified cartilage. The deep zone is responsible for providing the greatest amount of resistance to compressive forces, given the high proteoglycan content. Of note, the collagen fibrils are arranged perpendicular to the articular cartilage. The calcified layer plays an integral role in securing the cartilage to bone, by anchoring the collagen fibrils of the deep zone to subchondral bone. In this zone, the cell population is scarce and chondrocytes are hypertrophic.[19]

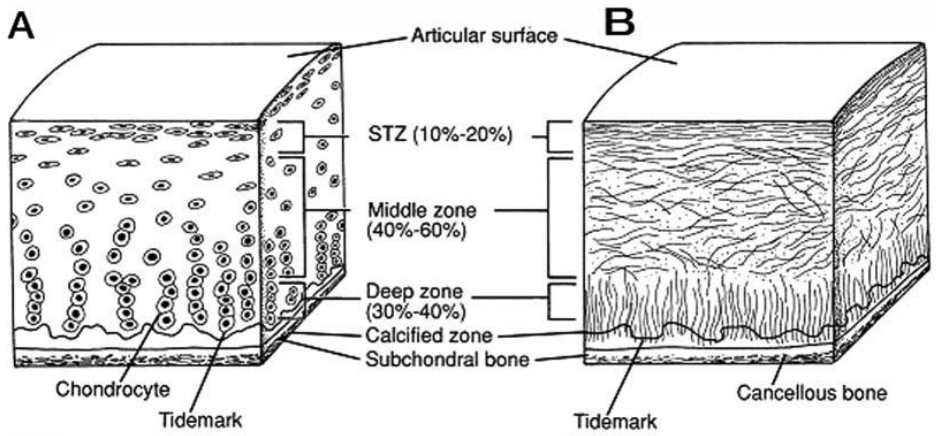

Figure (2): Schematic, cross-sectional diagram of healthy articular cartilage: A, cellular organization in the zones of articular cartilage; B, collagen fiber architecture[20].