

Comparison Between Low and High Molecular Weight Hyaluronan In The Treatment Of Osteoarthritis Knee Joint

THESIS

Submitted for partial fulfillment of the requirement of master degree in rheumatology and rehabilitation

By

Osama Eid Ahmed Ahmed
M.B.B.Ch

Supervisors

Prof. Dr. Eman mahmoud El Serougy
Professor of Rheumatology and Rehabilitation
Faculty of Medicine , Cairo University

General. Prof. Dr. Mohamed Reda Awad
Professor Of Rheumatology and Rehabilitation
Agouza Armed Forces Rheumatology and Rehabilitation Center

Dr. Dalia Mohamed El Zorkany
Assistant Professor Of Rheumatology And Rehabilitation
Faculty of Medicine , Cairo University

Faculty of Medicine,Cairo University

2010

Acknowledgements

First and foremost , thank to ALAAH for giving me the strength and persistence to overcome every obstacle I faced to carry out this work .

It is with deep appreciation and gratitude that I acknowledge the great help of *prof . DR. Eman El Serougy* professor rheumatology and rehabilitation faculty of medicine cairo university for her kind assistance, continous support and supervision which were essential for completion of this work .

I would like to express my thanks to

General. prof. DR. Mohamed Reda Awad Prof of Rheumatology and Rehabilitation and General Manager of Agouza Armed Forces Rheumatology and Rehabilitation Center for his help and continuous guidance throughout this work .

I wish to express my deep appreciation to

DR. Dalia El-Zorkany Assistant Professor of Rheumatology and Rehabilitation Faculty of Medicine Cairo University for her kind help and encouragement throughout this work

Lastly I would like to thank all patients participating in this study , without them nothing could be done.

Osama Eid Ahmed

Abstract

Intra-articular treatment with HA and hylans has recently become more widely accepted in the armamentarium of therapies for OA pain. Intra-articular HA treatment for osteoarthritis of the knee was approved by the US Food and Drug Administration in 1997.

This study is the 1st study in Egypt that analyzes the comparison between intra-articular injection of LMW and HMW hyaluronan in the treatment of osteoarthritis knee which was assessed using WOMAC index and visual analogue scale.

Key words:

Comparison between HMW and LMW hyaluronan in treatment of OA of the knee.

Table of Contents

	Page
Introduction	١
Aim of the Work	٣
Functional Anatomy of Knee Joint	٤
Synovial Tissue	١٤
Osteoarthritis of the Knee	١٩
Biochemistry of Hyaluronan	٣٤
Hyaluronan and Hylans	٣٨
Intra-articular Injection of Hyaluronic Acid in the Treatment of Osteoarthritis	٥٢
Material and Methods	٥٧
Results	٧٤
Discussion	٨٨
Summary and Conclusions	٩٩
References	١٠٤
Arabic summary	١

List of Tables

Table	Page
Table 1: Definition and characteristics of hyaluronan (hyaluronic acid) and hylans	٣٩
Table 2: Effects of hyaluronan (hyaluronic acid) and hylans on the extracellular matrix.	٤٤
Table 3: Effects of hyaluronan (hyaluronic acid) and hylans on inflammatory mediators.	٤٦
Table 4: Effects of hyaluronan (hyaluronic acid) and hylans on immune cells.	٤٩
Table 5: Molecular weights of hyaluronic acid (HA) products.	٥٤
Table 6: Kellgren-Lawrence Radiographic Grading Scale of Osteoarthritis of the Tibiofemoral Joint.	٦٨
Table 7: WOMAC scoring	٧٢
Table 8: General features of our patient.	٧٤
Table 9: Clinical features of our patients.	٧٤
Table 10: Comparison between both groups regarding general features.	٧٥
Table 11: Comparison between both groups regarding clinical history.	٧٦
Table 12: Comparison of WOMAC Index before injection.	٧٧
Table 13: Comparison of WOMAC index after 1st injection.	٧٨
Table 14: Comparison of pain items after 2nd injection.	٧٩
Table 15: Comparison of WOMAC index After 3rd injection.	٨١
Table 16: Comparison of WOMAC index after follow up.	٨٢
Table 17: Comparison between both groups regarding Score during study.	٨٤
Table 18: Comparison between both groups regarding VAS during study.	٨٥
Table 19: Comparison between both groups according to side effect of injected knees.	٨٦

List of Figures

Figure 1: The Weber brothers created cross-sectional images of the femoral condyles by cutting cadaveric specimens, coating them with ink, and pressing them to paper.	9
Figure 2: a) The trochlea is offset to the lateral side of the distal femur and its lowest point, the sulcus, is lateral to the midplane. b) The orientation of the sulcus (sulcus axis) lies between the mechanical and anatomical axes of the femur.	10
Figure 3: The patella sits lateral on the distal femur, consistent with the location of the sulcus of the trochlea.	12
Figure 4: Several factors contribute to the breakdown and synthesis of cartilage.	21
Figure 5: The extracellular matrix of cartilage is composed of proteoglycans attached to a backbone of hyaluronic acid that is intertwined among collagen fibrils.	21
Figure 6: Pharmacologic agents for osteoarthritic knee pain.	26
Figure 7: Chemical structures of (A) hyaluronan, and (B) unsulfated chondroitin and chondroitin sulfates	36
Figure 8: Visual analogue score scale.	58
Figure 9: One method for injecting a knee joint.	69
Figure 10: Alternative method for injecting a knee joint.	69

List Of Abbreviations

IT	iliotibial band
MCL	medial collateral ligament
LCL	lateral collateral ligament
ACL	anterior cruciate ligament
PCL	posteror cruciate ligament
HA	hyaluronic acid
NSAID	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
BMP	bone morphogenetic protein
BFGF	basic fibroblastic growth factor
IGF	insulin like growth factor
IL	interleukin
MMP	matrix metalloproteinase
PG	proteoglycan
TGF	transforming growth factor
TNF	tumor necrosis factor
WOMAC	western Ontario and McMaster universities OA Index
VAS	Visual Analogue Scale

PGE2	prostagladin E2
TIMP	tissue inhibitor of metalloproteinases
OMT	osteopathic manipulative treatment
OTC	over the counter
COX	cyclooxygenase
GI	gastro-intestinal
FDA	food and drug association
GAG	Glycosaminoglycan
NMR	nuclear magnetic resonance
MD	molecular dynamic
MW	molecular weight
NO	nitric oxide
PS	post-surgery
RA	rheumatoid arthritis
PMN	polymorphonuclear
IA	intra-articular

Introduction

Osteoarthritis, the most common form of arthritis, is a chronic disease characterized by the slow degradation of cartilage, pain, and increasing disability. The disease can have an impact on several aspects of a patient's life, including functional and social activities, relationships, socioeconomic status, body image, and emotional well-being (*carr., 1999*).

Intra-articular treatment with HA and hylans have recently become more widely accepted in the armamentarium of therapies for OA pain, HA is responsible for the viscoelastic properties of synovial fluid. This fluid contains a lower concentration and molecular weight (MW) of HA in osteoarthretic joints than in healthy ones (*Balaz, 1982*).

Thus the goal of intra-articular therapy with HA is to help replacement of synovial fluid that has lost its viscoelastic properties. The efficacy and tolerability of intra-articular HA for the treatment of pain associated with OA of the knee have been demonstrated in several clinical trials (*Adams, et al., 1995*).

Three (hylane G-F 20) to five (sodium hyaluronate) injections can provide relief of knee pain from OA for up to 6 months (*Altman., et al.,1998*).

Intraarticular hylan or HA is also generally well tolerated, with a low incidence of local adverse events (from 0% to 13% of patients) which was similar to that found with placebo (*wobig,et al .,1999*).

Aim of the Work

This study aimed to analyze the comparison between intra-articular injection of low molecular weight and high molecular weight hyaluronan in the management of osteoarthritis knee, this difference is going to be assessed using Western Ontario and McMaster Universities osteoarthritis index (WOMAC) (*Cocharne et al., 1991*) and visual analogue scale VAS (*Kjken et al., 1995*).

Functional Anatomy of Knee

Joint

The knee is a compound condylar joint with three articulations: the patellofemoral, the lateral and medial tibiofemoral condyles with their fibrocartilagenous menisci (*Press et al., 1996*).

I. Soft-tissue Sleeve:

Protection and nutritional support of the knee are provided by skin, fat, capsule, and synovium. Located in these soft tissues is a network of vessels (arteries, veins, lymphatics) and nerves. In general terms, the vessels and nerves pass from the hip to the ankle along the posterior aspect of the limb and send branches both medial and lateral around the knee to meet near the anterior midline (*Bellemans et al., 2005*).

Muscle-tendon units lie in the soft-tissue sleeve and are a significant component of the functional anatomy of the knee. The quadriceps (rectus femoris, vastus lateralis, vastus intermedius, vastus medialis) and articularis genu lie anterior to the femur. They arise from the pelvis (rectus femoris), the proximal femur (vastus lateralis, vastus intermedius, vastus medialis), and distal femur (articularis

genu), and attach by way of a conjoined tendon to the tibia to form the extensor mechanism of the knee. Invested in the conjoined tendon is the body's largest sesamoid bone, the patella. Retinaculum and synovium attaching to the patella and its tendon pass around the medial and lateral aspects of the knee to the distal femur and proximal tibia (**Bellemans et al., 2005**).

The muscle-tendon units lying posterior to the femur are referred to collectively as the hamstrings. The lateral hamstring (biceps femoris) and the medial hamstrings (sartorius, gracilis, semitendinosus, semimembranosus) arise from the pelvis and attach to the fibular head and medial aspect of the tibia, respectively. These muscles function collectively in knee flexion. They also function in rotating the knee, with the lateral hamstrings rotating the tibia external relative to the femur and the medial hamstrings rotating the tibia internal relative to the femur (**Eckhoff, 2005**).

Also implicated in knee construction are the gastrocnemius muscles, the popliteal muscle, and the iliotibial band. The gastrocnemius originate just proximal and posterior to the femoral condyles and insert through the Achilles tendon on the calcaneus. The popliteal muscle arises from the posterior lateral femur and attaches to the posterior lateral tibia. The iliotibial (IT) band arises from

the lateral pelvis and attaches to the anterolateral tibia at Gerde's tubercle (**Eckhoff, 2005**).

Ligaments joining the femur and tibia are four in number, two cruciates and two collaterals. The medial collateral ligament (MCL) can be separated into two components, superficial and deep. The deep MCL originates from the area of the medial femoral epicondyle and inserts on the mid body of the medial meniscus and the proximal medial tibial plateau, forming a confluence with the coronary ligament attaching the meniscus to the tibia. The superficial MCL has an origin similar to that of the deep MCL but lacks any attachment to the meniscus and inserts more distally along the medial tibia. The MCL slopes from posterior proximally to anterior distally. The lateral collateral ligament originates from the area of the lateral epicondyle and inserts on the fibular head. It slopes opposite the MCL, passing from anterior proximally to posterior distally. The origins of the collaterals (MCL and LCL) lie on a line joining the femoral epicondyles, also known as the epicondylar line (**Bellemans et al., 2005**).

There are two cruciate ligaments. The anterior cruciate ligament (ACL) originates from the lateral wall of the femoral intercondylar notch and inserts on the mid tibia between the articular surfaces, passing from posterior proximally to anterior distally. Passing in the opposite

direction, from anterior proximally to posterior distally, is the posterior cruciate ligament (PCL), which arises from the medial wall of femoral intercondylar notch and inserts over an area approximately 2 cm in vertical length on the posterior aspect of the tibia. The origin of the cruciates (ACL and PCL) is not on the same line as the origins of the collaterals, i.e., the epicondylar line. The cruciate origins lie on a line passing through the center of the condyles, a line equidistant from points on the posterior articular surface of the condyles, but it is important to recognize for the purpose of balancing the soft tissues and restoring the kinematics of a knee that the origins of the cruciates and collaterals are not on the same line (*Eckhoff, 2005*).

II. Bony Architecture (Bone Morphology):

The distal femur has a unique three-dimensional shape marked by asymmetry. The two rounded asymmetrical prominences that articulate with the tibia, referred to as condyles, are separated by a space referred to as the intercondylar notch. The condyles are joined proximally by the femoral trochlear groove, the site of articulation between the patella and the femur. The trochlear groove is characterized as a trough with its
