Lasers and Intralesional Steroids in the Treatment of Keloids and Hypertrophic Scars

Thesis

submitted to

National Institute of Laser Enhanced Sciences(NILES), Cairo University
for Fulfillment of the PhD Degree of Laser Applications in Dermatology
Department of Medical Applications of Laser

By

Tarek Kamal Shokry El-Gendy

(M.B.B.Ch, M.Sc.)

Supervisors

Prof.Dr.

Mohamed H. Al-Batanouny

Prof. of General & Vascular Surgery
Faculty of medicine – Cairo University

Prof.Dr.

Hesham A. Shokeir

Prof. of Dermatology
National Institute of Laser Enhanced Sciences (NILES)
Cairo University

Prof.Dr.

Mona M. Soliman

Prof. of Dermatology
National Institute of Laser Enhanced Sciences (NILES)
Cairo University

National Institute of Laser Enhanced Sciences (NILES)
Cairo University
2008

بسم الله الرحمن الرحيم

وَاللَّهُ أَخْرَجَكُمْ مِنْ بُطُونِ أُمَّهَاتِكُمْ

لا تَعْلَمُونَ شَيْئاً وَجَعَلَ لَكُمُ السَّمْعَ

وَالأَبْصَارَ وَالأَفْئِدَةَ لَعَلَّكُمْ تَشْكُرُونَ.

صدق الله العظيم

(النحل:٧٨)

This work is dedicated to the memory of the great lady whom I owe too much (my late mother).

Acknowledgment

Firstly and above all, thanks and praise should be to ALLAH.

I would like to express my appreciation and gratitude to ***Prof. Dr. Mohamed H. Al-Batanouny ,*** Prof. of General and Vascular Surgery, Kasr Al-Aini, Cairo University, for his valuable suggestions and continuous encouragement during his supervision of this work.

I am also grateful to ***Prof. Dr. Hesham Ali Shokeir,*** Professor of Dermatology, National Institute of Laser Enhanced Sciences (NILES), Cairo University, for his close supervision and generous support. His knowledge, experience and remarks had added much to this work.

I am also honoured to express my deep thanks to ***Prof. Dr. Mona M. Soliman,*** Professor of Dermatology, National Institute of Laser Enhanced Sciences (NILES), Cairo University, who helped me and gave me much of her valuable experience and sincere directions to complete this work.

I am also grateful to ***Dr. Abeer Attia***, lecturer of Dermatology, National Institute of Laser Enhanced Sciences (NILES), Cairo University, who helped me in doing laser therapies to all patients in this work.

I am particularly grateful to ***Dr. Larissa S. Ananieva***, PhD Biology, consultant of Electron Microscopy at the Armed Forces Laboratories of Electron Microscopy for her assistance in finding the important ultrastructural changes in the research samples, choosing and photographing images, and interpreting of the found data.

Lastly, my thanks to the personnel at Ain-Shams University Specialized Hospital (ASUSH) - Electron Microscope Laboratory especially ***Prof. Dr. Elham I. Seif***, Prof. of Pathology and the head of EM Lab. for their help in preparation of the research samples.

Dr. Tarek Kamal Shokry

Contents

List of Abbreviations

α – SMA	α – Smooth muscle actin
BFGF	Basic fibroblast growth factor
CO_2 laser	Carbon dioxide laser
CTGF	Connective tissue growth factor
CW	Continuous wave
ECM	Extracellular matrix
EGF	Epidermal growth factor (Epithelial GF)
FGF-IL-8	Fibroblast growth factor interleukin - 8
FPDL	Flashlamp – pumped pulsed dye laser
5-FU	5 – Fluorouracil
HLA	Human leukocytic antigen
H & E	Haematoxylin and Eosin stain
ICM	Intracellular matrix
IFγ	Immunofluorescence gamma
IFN – α	Interferon – α
IFN – β	Interferon – β
IFN –γ	Interferon – γ
IGF – 1	Insulin – like growth factor – 1
ILI	Intralesional injection
PDGF	Platelet – derived growth factor
PWS	Port wine stain
SEM	Scanning electron microscopy
SPT	Selective photothermolysis
TAC	Triamcinolone acetonide
TB stain	Toluidine blue stain
TEM	Transition electron microscopy
TGF – α	Transforming growth factor – α
TGF – β	Transforming growth factor – β

Introduction and Aim of The Wrok

Introduction

Keloids and hypertrophic scars could be seen frequently in some people who have increased tendency to their formation and usually cause psychological upset and cosmetic disfigurement to them (***Hunter, et al; 1995***).

Keloids are erythematous, raised, and firm benign fibrous tumours with smooth shiny surface. They are more common in blacks and a familial predilection may be present. Although they may follow injury, a history of trauma is not obtained in all cases (***Hunter, et al; 1995***).

Hypertrophic scars are initially red, raised, firm and often pruritic. With time, they flatten and become white in colour. They differ from keloids in that they flatten spontaneously after one or several years, but keloids persist and may even extend beyond the site of the original injury (***Hunter, et al; 1995***).

Keloids could also be differentiated microscopically from hypertrophic scars by the presence of large esoinophilic collagen bundles and more abundant mucin (***Hunter, et al; 1995***).

The therapeutic management of hypertrophic scars and keloids includes occlusive dressings, compression therapy, excision, intralesional corticosteroid injections, cryosurgery, radiation therapy, interferon therapy, silicon patch, intralesional injections of 5- fluorouracil (5-FU) and laser therapy (***Berman & Flores; 1998***).

The carbon dioxide (CO_2), Neodimium: Yetterium Aluminium Garnet (Nd: YAG), and Argon lasers have been used as tools for the treatment of proliferative scarring (***Berman & Flores; 1998***).

The 585-nm flashlamp – pumped pulsed dye laser (FPDL) can significantly improve the clinical appearance of erythematous or hypertrophic facial acne scars (***Alster & McMeekin; 1996***). Also, early pulsed dye laser treatments can change fundamentally the physiology of wound healing through the reduction of scar microcirculation and prevention of excessive scar formation if it is applied in the first few weeks (***McCraw, et al; 1999***). However, the combination of CO_2 and FPDL laser systems are superior to CO_2 laser vaporization alone for management of non-erythematous hypertrophic scars (***Alster, et al; 1998***).

Aim of the Work

Is to evaluate the clinical outcome of keloids and hypertrophic scars treated with two types of lasers, either carbon dioxide (CO_2) laser or flashlamp-pumped pulsed dye laser (FPDL); intralesional injection (ILI) of steroids; or both combined together as regards safety, effectiveness and complications.

Review of Literature

Review of literature

Anatomy and Physiology of the Skin

The skin is the largest organ system of the body. It provides many functions: temperature regulation, immunological surveillance, sensory reception and serves as a barrier between a person and the environment. The skin consists of the epidermis, dermis and the subcutaneous tissue ***(Biesman BS; 1999).***

The thickness of the epidermis is 0.04 – 1.5 mm as compared with the total thickness of the skin which is 1.5 – 4.0 mm. The epidermis is a stratified squamous epithelium, largely made up of continuously replicating keratinocytes. The epidermis rests on the basement membrane (a structure that provides support and acts as a semipermeable interface between the epidermis and dermis) ***(Holbrook & Wolff; 1993).***

The dermis is the connective tissue layer of the skin. It lies immediately below the epidermis and contains the skin appendages: hair follicles, sebaceous glands, eccrine glands, apocrine glands, smooth muscle fibres, blood vessels, lymph channels and nerve bundles. It also contains collagen and elastin in a ground substance milieu (***Biesman BS; 1999).***

Collagen and elastin account for the most of the fibrous connective tissue of the dermis. Non-fibrous components of the connective tissue include the glycosaminoglycans and glycoproteins. Collagen makes up about three quarters of the dry weight of the skin and provides both tensile strength and elasticity to the dermis. It is made of fibrous proteins organized into bundles. Elastic fibres form a network in the dermis and provide elasticity to the skin. They account for about 1-2% of the dry weight of the dermal proteins (***Wolff, et al; 1993***).

The dermis has two components : the papillary dermis and the reticular dermis. The papillary dermis is immediately below the epidermis and the basement membrane zone, and is roughly, the same thickness as the epidermis. The reticular dermis is below that, making up the bulk of the dermis (***Holbrook & Wolff ; 1993***)

The subcutis (lies immediately below the reticular dermis) provides insulation for the body, acts as a cushion for trauma, allows for the mobility of skin over the underlying structures and provides the contour for cosmosis (***Biesman BS; 1999***).

Wound Healing

Physiology of wound healing

Wound healing is a complex group of biochemical and cellular events designed to achieve restoration of the tissue integrity. "Partial thickness wounds" heal rapidly by simple re-epithelialization while "full thickness wounds" which extend to the dermis heal by primary or secondary intention. Healing by "primary intention" occurs when the wound edges are pulled together by sutures or an adhesive to bring them into apposition (***Akasaka, et al; 2001***).

Delayed primary intention occurs if the wound is infected. Closure should be delayed until it has been cleared by the natural defense mechanism together with appropriate antibacterial treatment. This delayed closure reduces morbidity but does not affect or delay the development of wound strength (***Beldon P; 2000***).

Healing by "secondary intention" occurs if there is a major skin loss. The wound is allowed to heal from its base by the formation of granulation tissue. In this process, there is deposition of a new collagen but contraction of the wound is also important in repairing the defect. These simple methods of wound management can produce excellent cosmetic results especially on concave surfaces (***Beldon B; 2000***).

Phases of wound healing

Classically, there are three phases for normal wound healing: inflammatory, fibroblastic and the maturation phases (***Peled, et al; 2000***) and (***Prathiba, et al; 2001***).

In the first "inflammatory phase", wounding is immediately followed by classic inflammatory reaction. Capillaries dilate and pour fluid out into the wound and the fibrin clots to seal the wound. Biochemical substances that cause vasodilation and pain are released. Inflammatory cells are moved into the wound area. During this phase, the epithelium grows across the sealed wound (***Prathiba, et al; 2001***).

In the second "fibroblastic phase", the main strength of the wound is generated. Fibroblasts move into the fibrin clot and begin synthesizing large amount of new collagen in a structural framework. During this phase, the strength of the wound is rapidly increased (***Peled, et al; 2000***).

In the third "maturation phase", the nodularity of the fibroblastic phase gradually softens and flattens, and the redness becomes light in colour. Biochemically, there is ongoing simultaneous collagen synthesis and degradation. There is a continuing slow increase in the wound strength up to one year after the injury (***Peled, et al; 2000***) and (***Prathiba, et al; 2001***).

Events in the process of wound healing

Platelet degranulation results in the release and activation of the potent cytokines including transforming growth factor-β (TGF-β), epidermal growth factor (EGF), insulin-like growth factor-l (IGF-l) and platelet-derived growth factor (PDGF). These growth factors function in the recruitment and activation of the neutrophils, epithelial cells, endothelial cells, macrophages, mast cells and fibroblasts. A prolonged inflammatory phase results in increase in the activity of the cytokines. An increased risk of scar formation has been correlated with these exaggerated cytokines activation (***Ishihara, et al; 2000***) and (***Shang, et al; 2001***).

Granulation tissue formation and scar maturation require a balance between matrix degradation and collagen biosynthesis for optimal wound healing (***Niessen, et al; 2001***). Matrix degradation is coordinated through the action of collagenases, proteoglycogenases and other proteases. Antifibrotic factors including interferon–α (IFN-α), interferon-β (IFN-β) and interferon-γ (IFN-γ) are also released. These interferons decrease the development of fibroblasts and inhibit their synthesis of collagen and fibronectin (***Niessen, et al; 2001***) and (***Shang, et al; 2001***).

Epidemiological factors of keloids

Keloids occur in individuals with familial predisposition, enlarge, and extend beyond the margins of the original wounds. Keloids may develop even after the most minor skin wounds, such as insect bites or acne lesions. The time lag between injury and keloid formation is variable though the majority tends to form within the first year after healing of the skin wound. Furthermore, keloids rarely regress with time (***Tredget, et al; 1997***) and (***Hom DB; 2001***).

Although keloids occur in all age groups, patients with the highest incidence of their development are between the ages of 10 and 30 years old. They are rarely found in newly borns and elderly people (***Appleton, et al; 1996***).

The exact prevalence of keloids is unknown. Male to female ratio is approximately 1:1. Studies that report higher female incidence reflect greater cosmetic concern and are more frequent with ear lobe piercing (***Venugobal, et al; 1999***).

Cosman, et al; (1996) in a review of three large series based on clinical impression found an incidence ratio between 4-5% and 16% in