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Topical Beta Blockers as a Treatment for Superficial Cutaneous Infantile Haemangiomas

Thesis

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بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ
لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا ۖ
إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

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Emad El Deghedy

List of Contents

List of Tables

List of Figures

List of Abbreviations

ARS	Adrenergic Receptors
AVF	Arterio Venons Fistula
AVM	Arteriovenous Malformation
BFGF	Basic Fibroblast Growth factor
BMI	Body Mass Index
CAVM	Capillary Arteriol Venous Malformation
CBECFCS	Card Blood Endothelial Colony-forming Cells
CCM	Cerebral Cavernous Malformation
CLAVM	Capillary Lymphatic Anteriovenous Malformation
CLM	Capillary Lymphatic Malformation
CLVAVM	Capillary Lymphatic Venous at the end Venous Malformation
CLVM	Capillary Lymphatic Venous Malformation
CM	Capillary Malformation
CMAVM	Capillary Marformation Anteriovenous Malformation
CMTC	Cutis Marmorata Telangiectatica Congenita
CVAVM	Capillary Venous Arteria Venous Malformation
CVM	Capillary Venons Malformation
DCMO	Diffuse Capillary Malfermatran With Overgrowth
e NOS	Endothelial Nitric Oxide Synthase
EGF	Epidermal Growth Factor
FAVA	Fibro Adipose Vascular Anomaly
GFS	Gel Forming Solution
GLA	Generalized Lymphatic Anomaly
GLUT I	Glucose Transporter I
GVM	Glomuvenous Malformation
HDMECS	Human Dermal Microvascular Endothelial Cells
Hem	Hemangioma Pericytes
Hem EC	Hemangioma Derived Endothelial Cells
Hemsc	Hemangioma Derived Stem Cells
HHT	Hereditary Hemorrhagia Telangictaftia
HIF	Hypoxia Inducible Factor
HPA	hypothalamic Pituitary Adrenal
HSPGs	Heparan Sulfate Proteoglycans
HUVECS	Human Umbilical Vein Endothelial Cells
IFN-B	Interferon ß
IGF	Insulin Resembling Growth Factor
IH	Infantile Hemangioma
IHC	Immunohistochemistry

ISSVA	International Society for the Study of Vascular Anomalies
KHE	Kaposiform Hemangio Endothelioma
KLA	Kaposiform Lymphangiomatosis
KMP	Kasabach-Merritt Phenomenon
LM	lymphatic Malformation
LVM	Lymphatic Venous Malformation
MCAP	Megalencephaly-Capillary Malformation Polymicrogyria
MLT/CAT	Multifocal lympheingioendotheliomatosis with thrombocytopenia /Cutaneovisceral angiomatosis with thrombocytopenia
MRI	Magnetic Resonance Imaging
mTOR	Mammalian Target of Rapamycin
NFAT	Nuclear Factor of Activated T Cells
NF-KB	Nuclear Factor KB
NG	Neural Glial
NICD	Notch Intracellular Domain
NICH	Non Involuting Congenital Hemangioma
NRPS	Neuropilins
PDGFR	Platelet Derived Growth Factor Receptor
PDL	Pulsed Dye Laser
PGS	Pyogenic Granulomas
PI	Phosphoinositide
PICH	Partially Involuting Congenital Hemangioma
PILA	Papillary Intra-lymphatic Angio-endothelioma
PL	Phospholipase
PLGF	placental Growth Factor
RICH	Rapidly Involuting Congenital Hemangioma
RNA	Ribonucleic Acid
smMHC	Smooth Muscle Myosin Heavy Chain
TEM	Tumor Endothelial Marker
VAS	Visual Analogue Scale
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptors
VM	Venous Malformation
VMCM	Venous Malformation Cutaneomucosal
αSMA	Alpha Smooth Muscle Actin

Introduction

INTRODUCTION

Haemangiomas are the most common tumors of infancy. The true incidence of infantile haemangiomas is unknown. Although they are classically said to occur in up to 10 percent of Caucasian infants, 4 to 5 percent is probably a better estimate. Infantile haemangiomas are generally noticed within the first few days to months of life ***(Kilcline and Frieden, 2008)***.

Although most haemangiomas occur sporadically, familial transmission in an autosomal dominant fashion has been reported. In one series of 136 patients/families, 34 percent had a family history of infantile haemangiomas, most often in first-degree relatives ***(Castrén and Salminen, 2016)***.

Known risk factors include low birth weight, Caucasian ethnicity, female gender, advanced maternal age, and a variety of prenatal complications including placenta previa and pre-eclampsia ***(Haggstrom et al., 2007)***.

The exact pathogenesis of Infantile Haemangioma is incompletely understood, though markers not expressed in normal dermal or subcutaneous tissues are frequently detected in IH. In particular, vascular endothelial growth factor (VEGF), glucose transporter-1 (GLUT-1), and placenta-associated vascular antigens (i.e., FcγRII, merosin, and Lewis Y antigen) are highly expressed in the endothelial cells of IH throughout both the rapid growth phase and the involution phase.Interestingly, the only other vascular tissue known to share a similar expression profile is from placental chorionic villi. Some current experimental evidence proposes that IH may derive from clonal proliferations of endothelial cells through the de novo formation of primitive blood vessels from angioblasts ***(Barnés et al., 2005)***.

Increased numbers of mast cells and levels of tissue metalloproteinase (an inhibitor of new blood vessel formation), upregulation of interferon-induced genes, and decreased quantities of fibroblast growth factor (FGF) have been identified as potential molecular mediators of IH involution ***(Ritter et al., 2006)***.

Infantile haemangiomas are common, particularly in female, white children of low birth weight, with approximately 6% affected. They are often present at birth, although may not be noticed until a few weeks later when the lesion begins its proliferative phase. The lesions grow rapidly in the first few months of life before stabilizing and finally involuting. There are no reliable indicators to predict the degree and rate of involution ***(Skrobal and Haderer, 2014)***.

The mainstay of therapy for IH is active nonintervention (i.e., watchful waiting) as most lesions are uncomplicated and will involute spontaneously without significant sequel ***(Metry and Hebert, 2000)***.

First reported on the use of topical treatment for Infantile Haemangioma using a non-selective beta-blockers solution and the curative effect was obvious ***(Guo et al., 2010)***.

Timolol maleate used topically is effective and safe for treating superficial haemangiomas. We began to treat then with timolol maleate applied topically in October 2012 ***(Ye et al., 2012)***.

Aim Of The Work

AIM OF THE WORK

The aim this study was to evaluate the role of topical beta-blocker solution (Timolol maleate 0.5%ml gel forming solution) in the treatment of superficial cutaneous infantile hemangiomas.

Review Of Literature