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ROLE OF ANGIOTENSIN CONVERTING ENZYME INHIBITORS IN TRABECULAR MESHWOKR REMODELING IN OCULAR HYPERTENSIVE RAT

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Dissertation submitted in partial fulfillment of the requirements
For the degree of
MBBS with Advance Medical Science

October 2013

ACKNOWLEDGEMENT

In the name of Allah the Most Merciful and the Most Gracious

Alhamdulilah, all praises to Allah for the strengths and His blessing in completing this report. Foremost, I would like to express my sincere gratitude to my supervisor, Dr Anna Krasilnikova, for her supervision and continuous support throughout this one year of Advanced Medical Science Program. My sincere appreciation also goes to my co-supervisor, Assoc. Prof. Dr.Renu Agarwal and Prof. Dr. Nafeeza for their support and knowledge regarding this topic. Not forgotten, Dr. Norhafiza Ismail and Dr. AlimahNasir, master students those also help to guide me through this programme.

I would like to express my gratitude to the Dean, Faculty of Medicine Universiti Teknologi MARA, Prof. Dato' Dr. Khalid Yusoff and Deputy Dean, Prof. Dr. Mohd Hamim Rajikin for giving me the opportunity to embark myself in MBBS with Advance Medical Science program. Not forgotten, Coordinator, of this AMS programme, Prof. Dr. Mohammed Nasimul Islam for his contribution and the university for providing the Fund of Excellence 600-RMI/DANA 5/3/RIF (607/2012).

My acknowledgement also goes to Laboratory Animal Care Unit (LACU), Institute of Molecular Medicine and Biotechnology (IMMB), Centre for Pathology Diagnostic & Research Laboratory (CPDRL) of UiTM for support and help towards my research. Special thanks to Dr.NorSalmahBakar and Prof. KananKutty for contributing their knowledge and help in completing my research topic. I also wish to thank all the technicians and office staffs for their co-operations.

Last but not least, I would like to thank my beloved parents, and others family members, friends and lab mates, Siti Nur Laili Mohamed, Sarah Diyana Saad, Aliza Hani Mansor, Izza Liyana Azizan and lastly to my best friends Fatin Kamilah Zakaria for their love and encouragement. To those who indirectly contributed in this research, your kindness means a lot to me. Thank you very much.

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ABSTRACT

Glaucoma is the major cause of an irreversible blindness worldwide and it is commonly associated with an elevation of intraocular pressure. ACE inhibitors have been shown to have ocular hypotensive effect in animals and human subjects. The aim of the study was to evaluate the ocular hypotensive effect and the effect on attenuation of trabecular meshwork remodelling by topical application of ACE inhibitor, enalaprilat dehydrate in chronic steroid-induced ocular hypertensive rat model.

Ocular hypertension was developed in normotensive *Sprague Dawley* rats (100-120g) of either sex by topical instillation of dexamethasone 0.1%, 2 times daily for 36 days. The rats that developed more than 25% rise in IOP were considered ocular hypertensive. Study 1: Ocular hypertensive rats were randomly divided in 2 groups (n=7) and unilaterally treated with single drop (10μL) of either 1.00% enalaprilat dehydrate (n=7) or 0.005% latanoprost in test eyes (TE). The contralateral eyes served as control (CE). IOP measurements were done by applanation tonometry (TonoLab) at 0 hour (baseline), hourly for the first 12 hours post-instillation and subsequently 4 hourly till the 24 hours. Study 2: Ocular hypertensive rats were divided in 3 groups (n=6) and were treated bilaterally with enalaprilat dehydrate 1% (group 1), latanaprost 0.005% (group 2), HPMC 1% (group 3) respectively for 21 days. Ocular normotensive rats (n=6) were amounted to control group (group 4) and were also treated with HPMC 1% for 21 days. IOP estimations were done at baseline (0 day of treatment) and subsequently 2 times a week. On day 21, aqueous humor was collected and MMP-2 and MMP-9 activity estimation was done. Eye balls were enucleated and subjected for H&E staining to assess the morphology of trabecular meshwork. Statistical analysis in both study 1 and 2 was done.

Enalaprilat dehydrate single drop treatment shown to reduce the IOP significantly ($p<0.01$) in ocular hypertensive rats for 11 hours post-instillation with the peak IOP reduction of 25.88% compare

CHAPTER 1: INTRODUCTION

Glaucoma is a progressive optic neuropathy which results in retinal ganglion cells (RGC) death. Glaucoma is recorded as the second cause of blindness worldwide after cataract (Vaajanen & Vapaatalo, 2011) and it is the first cause of irreversible blindness (Agarwal, Gupta, Agarwal, Saxena, & Agrawal, 2009). It is estimated to be 79.6 million people with open angle and closure angle glaucoma by 2020 (Quigley & Broman, 2006)

Glaucoma is believed to be multi-factorial disease with established genetic and biological risk factor (Goel, Picciani, Lee, & Bhattacharya, 2010). Elevation in intraocular pressure is known as one of the major risk factors for glaucoma (Fan & Wiggs, 2010). Intraocular pressure is regulated to its normal average by the balance of aqueous humour secretion form ciliary epithelium and aqueous humour outflow through trabecular and uveoscleral pathways (Goel et al., 2010). Over production or impaired in aqueous outflow both lead to elevated IOP and ocular hypertension, which is involved in the mechanism of trabecular meshwork remodelling(Liao, Bai, & Zhang, 1994). Trabecular meshwork remodelling itself also increases the aqueous outflow pathway resistance, and closes pathological circle (Gonzalez, Epstein, & Borrás, 2000)

Elevated IOP is the only single modifiable risk factor of glaucoma (Crooke, Colligris, & Pintor, 2012), making it the primary goal in the glaucoma treatment. However, most of currently available ocular hypotensive drugs provide inadequate control of IOP and are associated with several adverse effects. Therefore, the investigation of newer ocular hypotensive agents with adequate efficacy and safety profile is essential.

Angiotensin-converting enzyme (ACE) inhibitors are one of the potential new ocular hypotensive options that have become an attention in the treatment of glaucoma as it has shown ocular hypotensive effects. Several studies have evaluated the ocular hypotensive effect of ACE inhibitors in