INDAPAMIDE IN HYPERTENSIVE DIALYSIS PATIENTS

THESIS

SUBMITTED IN PARTIAL FULFILMENT

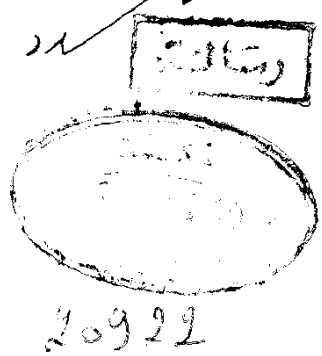
FOR THE MASTER DEGREE OF

MEDICINE

By

Mounir El-Sayed Abd Allah Shahin

M.B., B.Ch.



SUPERVISORS

Prof. Dr. Badawy L. Mahmoud

Prof of Medicine

AIN SHAMS UNIVERSITY

Dr. Adel Mohammed Afify

Lec of Medicine

AIN SHAMS UNIVERSITY

FACULTY OF MEDICINE

AIN SHAMS UNIVERSITY

1986

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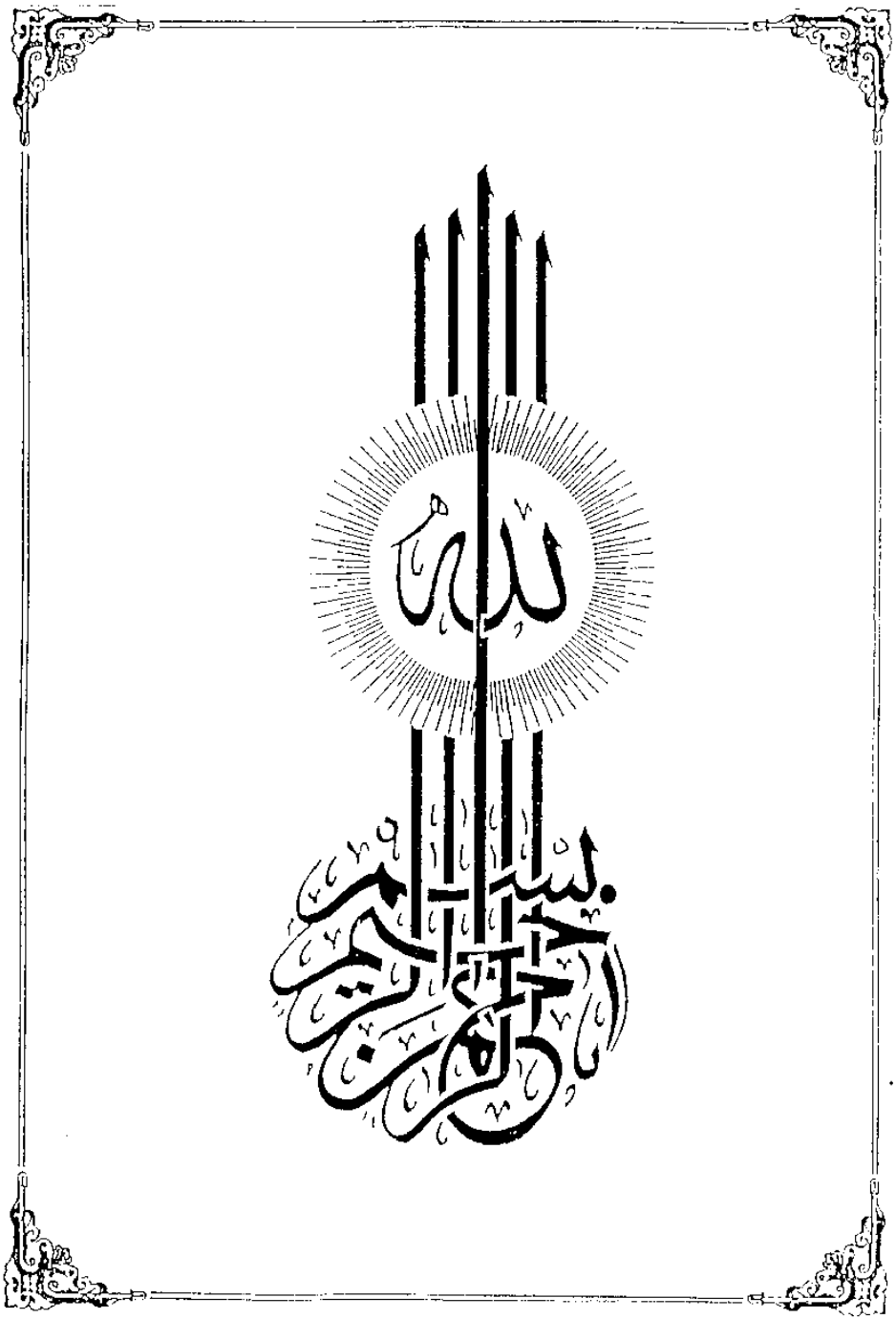

C O N T E N T S

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ABBREVIATIONS

B.P.	Blood pressure
bpm	Beat per minute
BW	Body weight
ECG	Electro-cardiography
HDL	High density lipoprotein
HR	Heart rate
LDL	Low density lipoprotein
MABP	Mean arterial blood pressure
MEq/L	Milli equivalent per litre
No.	Number
PCV	Packed cell volume
PGA	Prostaglandin A
PGE	Prostaglandin E
PGF	Prostaglandin F
SD	Standard deviation
Sig	Significant

INTRODUCTION

AND

AIM OF WORK

INTRODUCTION

Hypertension in end-stage chronic renal failure and especially in uraemics on regular dialysis treatment is often observed.

For patients treated with maintenance dialysis, blood pressure monitoring and modification acquire paramount position as hypertension is a significant predisposing factor to accelerated atherosclerosis and to high incidence of cardio-vascular and cerebro-vascular diseases in dialysis patients **(Merrill, 1974).**

In the majority of cases, hypertension is due to increased body water, while in several cases it is due to increased peripheral resistance because of the hyperactivity of the renin-angiotensin system, therefore in many cases, hypertension is well managed by dialysis especially by ultrafiltration while this is not sufficient in others **(Robert et al., 1983).**

Indapamide, a new potent anti-hypertensive drug was shown to be effective and safe in treating hypertensive patients undergoing long-term maintenance hemodialysis. **(Acchiardo et al., 1983).**

AIM OF THE WORK:

The aim of the work is to study the efficacy of indapamide therapy on dialysis resistant hypertension and to report its various side effects.

Also this work aimed at giving a short review about the pathogenesis of hypertension in chronic renal failure and the pharmacological actions of the drug.

REVIEW OF LITERATURE

HYPERTENSION IN CHRONIC DIALYSIS PATIENTS

Approximately 80% of patients with progressive renal failure approaching dialysis have hypertension as arbitrarily defined by a diastolic pressure greater than 90 mmHg or a systolic pressure over than 150 mmHg **(Lazarus et al., 1974).**

The percentage of dialysis patients considered to have dialysis-resistant hypertension requiring anti-hypertension medications varies considerably depending on the approach of specific dialysis unit or the individual physician.

Robert and Rubin in (1983) reported that, dialysis alone controls blood pressure in about 65% of the total dialysis population, 25-30% require at least one anti-hypertensive medication in addition to regular dialysis, about 5% have severe hypertension resistant to drug therapy and may require surgical bilateral nephrectomy for adequate blood pressure control.

PATHOGENESIS OF HYPERTENSION IN CHRONIC DIALYSIS PATIENTS

Of the many factors that contribute to the hypertension seen in uremia, three are of paramount significance **(See Table I).**

Table I: Factors in blood pressure regulation

I	Salt and water
II	Renin - angiotensin
III	Neurogenic factors

Firstly the major pathogenetic factor for hypertension in all dialysis surveys is increased body water **(Kim et al., 1980).**

Secondly if volume is corrected and hypertension persists, an absolute or relative hyperreninemia, originating from the diseased kidney may be responsible **(Huysmans et al., 1980).**

Thirdly a significant factor that causes or accentuates hypertension in uremia is the nervous system central and autonomic. **(TaJiri et al.,1979).**

With the proper use of dialysis and medication these three principal determinants for blood pressure control in uremia can be modified.

I. **Fluid volume:**

Excessive fluid volume usually connotes increased salt and water volumes, although the two components can vary independently **(Blumberg et al.,1967).**

The use of dialysis solution containing bicarbonate as the predominant buffer anion reportedly allows blood pressure stabilization during ultrafiltration and concomitant dialysis **(Graefe et al., 1978).**

While salt (i.e sodium) can be independently removed during dialysis by lowering the sodium content of the dialysis fluid below 130m mol/l, cramps usually ensue and commercially available dialysis is fluid with a sodium content of 130m mol/l or more is used at most centers. A special form of volume dependent

hypertension is seen in the anephric patient. Although both sympathetic tone and a remnant of the renin-angiotensin system may influence blood pressure in anephric patients the predominant factor remains fluid volume **(Badder et al., 1979).**

II. Renin-angiotensin:

While hypertension is controlled in most dialysis patients by salt and water manipulation, a significant number remain hypertensive despite adequate dialysis and ultrafiltration **(Weidmann et al., 1971).** These patients may have abnormal renin levels and thus pathologically active angiotensin levels. Whether this elevation of renin is absolute or relative in regard to salt and water content is difficult to document. Release of renin from the Juxtaglomerular apparatus is governed by at least three mechanisms. These are neurogenic, including circulatory catecholamines and direct sympathetic innervation **(Reid et al., 1972),** intra-renal baroreceptor impulses **(Thurau et al., 1967)** and, finally sodium responsive intra-renal chemoreceptors **(Freeman et al., 1974).**

In patients with end-stage kidney disease treated with hemodialysis, a relative dilutional hyponatremia, resulting from excess water intake or dialysis related excess sodium removal, delivers hyponatremic blood to the kidneys and stimulates renin release. Even though the overall arterial pressure may be normal or even elevated, renal blood flow through diseased blood vessels of end-stage kidneys may be low and may be a further stimulus to renin release.

An abnormal sympathetic tone, also may cause renin release. Evidence for delayed destruction of renin and angiotensin in uremia is lacking **(Robert et al., 1983).**

III. **Neurogenic factor:**

Hypertension that is enhanced by, or derived from, neurogenic sources is usually responsive to appropriate medication, with the exception of the hypertension associated with pheochromocytoma. Both central and autonomic nervous systems are involved, but there is more acceptance of the role of the autonomic, especially the sympathetic system. Not only are the catecholamines direct pressors themselves,

but they also stimulate the renin system and in turn their production and release is stimulated by angiotensin **(Peach, 1971).**

Uremic sympathetic neuropathy is another possible cause of abnormal blood pressure response **(Lilley et al., 1976).**

Although one observer has demonstrated that altered tone alone cannot be responsible **(Nies et al., 1979).**

IV. Other causes:

Another cause of hypertension in dialysis patients may be abnormal prostaglandin production from the diseased kidney. Prostaglandins have wide spread and varied effects including alterations of blood pressure **(Anderson et al., 1976).**

Certain prostaglandins (PGA, PGE, PGF) are known to be synthesized by renal tissue **(Lee et al., 1965).** Specific prostaglandins have been implicated in modifying blood pressure by various mechanisms including a direct effect on blood vessel tone, modification of renal response to ischemia and activation