



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

بسم الله الرحمن الرحيم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم



شبكة المعلومات الجامعية التوثيق الإلكتروني والميكروفيلم



HANAA ALY



شبكة المعلومات الجامعية
التوثيق الإلكتروني والميكروفيلم

جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات



يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HANAA ALY



HIGH FLUX VERSUS HEMODIAFILTRATION IN REMOVAL OF INDOXYL SULPHATE

Thesis

Submitted for partial fulfillment of MD degree in internal Medicine

Presented by

Amira Mohamed Mahmoud Abd El Ghani

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

Supervised by

Prof. Dr. Iman Ibrahim Sarhan

Professor of Internal Medicine and Nephrology

Faculty of Medicine, Ain Shams University

Dr. Mohamed Saeed Hassan

Lecturer of Internal Medicine & Nephrology

Faculty of Medicine, Ain Shams University

Dr. Mohamed Sary Gharib

Lecturer of Internal Medicine & Nephrology

Faculty of Medicine, Ain Shams University

Dr. Marwa Shaban Abd el samea

Lecturer of Internal Medicine & Nephrology

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2020



الاستشفاء الدموي الترشحي مقابل الاستشفاء الدموي باستخدام فلاتر عاليه التدفق في ازاله سم اندوكسيل الكبريتات

رسالة

توطئة للحصول علي درجة الدكتوراة في أمراض الباطنة العامة

مقدمة من

الطبيب/ اميره محمد محمود عبد الغني

بكالوريوس الطب و الجراحة- ماجستير أمراض الباطنة

تحت إشراف

أد/ ايمان ابراهيم سرحان

استاذ امراض الباطنه العامه و الكلي

كلية الطب- جامعة عين شمس

د/ محمد سعيد حسن

مدرس امراض الباطنه العامه و الكلي

كلية الطب- جامعة عين شمس

د/ محمد ساري غريب

مدرس امراض الباطنه العامه و الكلي

كلية الطب- جامعة عين شمس

د/ مروه شعبان عبد السميع

مدرس امراض الباطنه العامه و الكلي

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

لَسْبَحَانَكَ لَا عِلْمَ لَنَا
إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢



Acknowledgement

*First of all, all gratitude is due to **God** almighty for blessing this work, until it has reached its end, as a part of his generous help, Throughout my life.*

*Really I can hardly find the words to express my gratitude to **Prof Dr Iman Ibrahim Sarhan**, Professor of Internal Medicine, faculty of medicine, Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she has done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

*I owe much to **Dr. Mohamed Saeed Hassan**, Lecturer of Internal Medicine faculty of medicine, Ain Shams University, for his continues help, valuable suggestions and patience throughout the whole work,*

*I owe much to **Dr. Mohamed Sary Gharib**, Lecturer of internal Medicine faculty of medicine, Ain Shams University, for his continues help, valuable suggestions and patience throughout the whole work,*

*I owe much to **Dr. Marwa Shaban Abd el samea**, Lecturer of internal Medicine faculty of medicine, Ain Shams University, for her continues help, valuable suggestions and patience throughout the whole work,*

*Last but not least, I dedicate this work to my **family** and **friends** whom without their sincere emotional support, pushing me forward this work would not have ever been completed..*

CONTENTS

Subjects	Page
• List of Abbreviations	I
• List of Table	III
• List of Figures.....	IV
• Introduction	1
• Aim of the work	4
• Review of literature.....	
Chapter (1): Gut toxins in ESRD	5
Chapter (2): Management of gut toxins in ESRD ..	21
Chapter (3): HDF	33
• Patients and methods	51
• Results	55
• Discussion.....	67
• Summary	74
• Conclusions	76
• Recommendations	77
• References	78
• Arabic summery	92

LIST OF ABBREVIATIONS

AhR	:Aryl hydrocarbon receptor.
CC-HDF	:Convective-controlled double high-flux hemodiafiltration.
CKD	:Chronic kidney disease
CRP	:C-reactive protein.
CVD	:Cardiovascular disease
ELISA	:Enzyme linked immunosorbent ssay
EPC	:Endothelial progenitor cell.
ESKD	:End-stage kidney disease.
ESRD	:End Stage Renal Disease
FGF-23	:Fibroblast growth factor-23.
GFR	:Glomerular filtration rate
GI tract	:Gastrointestinal tract.
HD	:Hemodialysis
HDF	:Hemodiafiltration
HF	:High flux.
hs-CRP	:High sensitivity C-reactive protein.
IAA	:Indole acetic acid
ICAM-1	:Intercellular Adhesion Molecule-1.
IL	:Interleukin
IS RR	:Indoxyl sulfate reduction ratio.
IS	:Indoxyl sulfate
LF	:Low flux.
LPS	:Lipopolysaccharide
MAPKs	:Mitogen-activated protein kinases.
MCP-1	:Monocyte chemoattractant protein-1.

List of Abbreviations

MMW	:Middle molecular weight.
mRNA	:Messenger Ribonucleic acid.
MW	:Molecular weight
NADPH	:Nicotinamide adenine dinucleotide phosphate.
NF	:Nuclear factor
NF-κB	:Nuclear factor- κ B.
NO	:Nitric oxide
OATs	:Organic anion transporters.
PAA	:Phenylacetic acid
PAI-1	:Plasminogen activator inhibitor-1.
PBTs	:Protein-bound toxins
PBUTs	:Protein bound uremic toxins.
PCS	:P-cresyl sulfate
PD	:Peritoneal dialysis.
PTH	:Parathyroid hormone.
RAS	:Renin–angiotensin system
ROS	:Reactive oxygen species
SCFA	:Short chain fatty acid.
SF	:Super flux.
TGF	:Transforming Growth Factor
TGF-β1	:Transforming growth factor- β 1.
TMAO	:Trimethylamine n-oxide
TMP	:Transmembrane pressure.
TNF-α	:Tumor necrosis factor α .
VSMC	:Vascular smooth muscle cell.
WSCs	:Water-soluble compounds.
β2M	: β 2-microglobulin.

LIST OF TABLE

Tab. No:	Subjects	Page
Table 1:	Effects of different uraemic toxins at the cellular and tissue level	19
Table 2:	Demographic and clinical data of all study groups.....	55
Table 3:	Etiology of ESRD in all study groups.....	57
Table 4:	Predialysis and postdialysis blood pressure in all groups.....	58
Table 5:	Laboratory data of all groups	59
Table 6:	Comparison between groups as regard CRP level	60
Table 7:	Comparison between groups as regard indoxyl sulfate level	61
Table 8:	Comparison between groups as indoxyl sulphate reduction ratio	62
Table 9:	Correlation between indoxyl sulphate pre dialysis level and demographic, clinical data and lab results in all patients (n=60)	63
Table 10:	Correlation between indoxyl sulphate pre dialysis level and demographic and clinical data and lab results in each group	64
Table 11:	Correlation between indoxyl sulphate level post dialysis and demographic and clinical data and lab results in all patients.....	65
Table 12:	Correlation between indoxyl sulphate post dialysis level and demographic and clinical data and lab results in each group	66

LIST OF FIGURES

Fig. No:	Subjects	Page
Figure 1:	Fermentation of the amino acids tyrosine and tryptophan by intestinal microbiota generates p-cresol and indole.	7
Figure 2:	Molecular mechanisms of tissue damage induced by indoxyl sulfate.....	13
Figure 3:	Role of indoxyl sulfate in the pathogenesis of various forms of cardiovascular disease in chronic kidney disease. EPC indicates endothelial progenitor cell; VSMC, vascular smooth muscle cell.	16
Figure 4:	Possible mechanisms of action of uremic toxins from gut microbiota that may modify bone metabolism in chronic kidney disease (CKD) patients.	18
Figure 5:	Potential treatment modalities targeting protein-bound uremic toxins in cardiorenal syndrome. CKD, chronic kidney disease; ESRD, end-stage renal disease; IS, indoxyl sulfate; pCS, p-cresyl sulfate.	21
Figure 6:	Metabolism of indoxyl sulfate and effect of AST-120.....	29
Figure 7:	Post-dilution online HDF.....	46
Figure 8:	Pre-dilution online HDF.....	46
Figure 9:	Patient characteristics regarding etiology of renal failure	57
Figure 10:	Description of lab results regarding urea reduction ratio.	60
Figure 11:	Description of lab results as regard indoxyl sulfate	61
Figure 12:	Indoxyl sulphate reduction ratio in each group.....	62

ABSTRACT

- **BACKGROUND:** protein-bound compounds such as the p-cresol conjugates p-cresyl sulphate (p-CS) and Indoxyl sulphate (IS) have attracted most interest in recent years due to their poor clearance by conventional dialysis and their potential toxicity. **Aim of the study:** To compare removal of indoxyl sulphate toxin during single session between low flux, high flux hemodialysis and hemodiafiltration. **METHODS:** Cross sectional study was concluded upon 60 randomly selected ESRD patients on regular hemodialysis from nephrology Department in Ain Shams University Hospitals. Serum indoxyl sulphate was measured (pre dialysis and post dialysis) using low flux, high flux hemodialysis and hemodiafiltration. **Results:** 60 test subjects were randomly selected had mean age 43.95 (± 11.91 years) in low flux HD group, 48.35 (± 13.25 years) in high flux HD group and 45.10 (± 18.56 years) in HDF group, were males 66.67 % (n=40) and females 33.33% (n=20). The mean indoxyl sulphate reduction ratio using low flux filter was 13.5% (± 9.52), using high flux 19.7% (± 14.31) and in hemodiafiltration 24.2% (± 10.73). There was a statistically significant difference between low flux HD group and HDF group as regard indoxyl sulphate reduction ratio (P value 0.015). There was no statistically significant difference between high flux HD group and HDF group as regard indoxyl sulphate reduction ratio.

Conclusion: Removal of indoxyl sulphate by hemodiafiltration is higher than hemodialysis using low flux membrane and there is no difference between hemodiafiltration and high flux hemodialysis.

Keywords: p-cresyl sulphate (p-CS), Indoxyl sulphate (IS), End Stage Renal Disease (ESRD), Chronic kidney disease (CKD), Hemodiafiltration (HDF), Hemodialysis (HD), peritoneal dialysis (PD)

INTRODUCTION

Indoxyl sulfate, a uremic toxin, is accumulated in the serum of chronic kidney disease (CKD) patients. A part of the dietary protein-derived tryptophan is metabolized into indole by tryptophanase in intestinal bacteria. Indole is absorbed into the blood from the intestine, and is metabolized to indoxyl sulfate in the liver. Indoxyl sulfate is normally excreted into urine. In CKD, however, an inadequate renal clearance of indoxyl sulfate leads to its elevated serum levels (*Niwa, 2010*)

The imbalance in gut microbiota associated with alterations in colonic epithelium contributes to the accumulation of gut-derived uraemic toxins. Toxic gases, indoxyl sulphate (IS), p-cresyl sulphate (p-CS), amines, ammonia and trimethylamine n-oxide (TMAO) as well as precursors for lipopolysaccharides (LPS) may be absorbed into the bloodstream and be responsible for systemic inflammation (*Mafra & Fouque, 2015*).

Indoxyl sulfate stimulates progression of both tubulointerstitial fibrosis and glomerular sclerosis by increasing the expression of transforming growth factor- β 1, a tissue inhibitor of metalloproteinase-1 and pro α 1 (I) collagen, leading to a further loss of nephrons (*Niwa, 2010*)

Indoxyl sulphate accumulates in the blood of patients with ESRD. Moreover, Indoxyl sulphate cannot be efficiently removed by conventional hemodialysis because of its high binding affinity for albumin. The role of Indoxyl sulphate as a uremic toxin was first revealed by its accelerating effects on the progression of CKD. Recently, it has been reported that Indoxyl sulphate may also act as a vascular toxin. In endothelial cells, Indoxyl sulphate has been shown to induce oxidative stress by modifying the balance between pro- and antioxidant mechanisms stimulate the release of endothelial microparticles and blunt endothelial healing ability. Furthermore, Indoxyl sulphate directly stimulates vascular smooth muscular cell proliferation in a concentration dependent manner (*Barreto et al., 2009*).

Retained Indoxyl sulphate in renal failure is also associated with several detrimental effects on other organs such as altered thyroid function, endothelial dysfunction, vascular smooth muscle cell proliferation and an increased risk of atherosclerosis (*Lekawanvijit et al., 2010*)

It was found that serum IS levels are significantly higher in the presence of coronary artery disease and correlate with the severity of the disease and coronary atherosclerosis scores, which suggest that increased serum IS may be involved in the pathogenesis of coronary atherosclerosis (*Hsu et al., 2014*)