Role of Nitric Oxide in intradialytic hypotension in HCV positive hemodialysis patients

Thesis

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Mohammed Adel Mansour

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List of Abbreviations

Abb.	Full term

AASLD.....*American Association for the Study of Liver Diseases*

ACEi .....*Angiotensin-converting enzyme inhibitors*

ADMA .....*Asymmetric dimethylarginine*

ALT .....*Alanine aminotransferase*

AUC .....*Area under the curve*

CAD .....*Coronary Artery Disease*

CDC .....*Center for Disease Control and Prevention*

cGMP .....*Cyclic GMP*

CHF .....*Congestive heart failure*

CKD .....*Chronic Kidney Disease*

DAAs .....*Direct-acting antivirals*

DDAH .....*Dimethylarginine dimethylamino-hydrolase*

EBPG .....*European Best Practice Guideline*

ESRD .....*End-Stage Renal Disease*

ET1 .....*Endothelin 1*

GFR .....*Glomerular filtration rate*

GTP .....*Guanosine triphosphate*

HCV .....*Hepatitis C virus*

HD .....*Hemodialysis*

hHGF .....*Human hepatocellular growth factor*

IDH .....*Intradialytic hypotension*

IFN γ .....*Interferon gamma*

List of Abbreviations (Cont...)

Abb.	Full term
IL-1b	*Interleukin-1b*
IMCD	*Inner medullary collecting duct*
IRS	*Insulin receptor substrate proteins*
ITT	*Intention to treat*
KDOQI	*Kidney Disease Outcomes Quality Initiative*
LV	*Left ventricular*
LVH	*Left ventricular hypertrophy*
MAP	*Mean arterial pressure*
mITT	*Modified Intention to treat*
MOH	*Ministry of Health*
NIVMs	*Non-invasive blood volume monitors*
nNOS	*Neuronal NOS*
NO	*Nitric oxide*
NOS	*NO synthase*
NS5A	*Nonstructural protein 5A*
QoL	*Quality of life*
RASs	*Resistance associated substitutions*
RBV	*Relative blood volume*
SBP	*Systolic blood pressure*
SDMA	*Symmetric dimethylarginine*
TGF	*Tubuloglomerular feedback*
USRDS	*United States Renal Data System*
WHO	*World Health Organization*

INTRODUCTION

Intradialytic hypotension (IDH) is considered one of the most frequent complications of haemodialysis treatment and is associated with increased cardiovascular morbidity and mortality ***(Sands et al., 2014).***

Symptomatic IDH occurs in approximately 20%–30% of all hemodialysis sessions ***(Stefánsson et al., 2014).***

The European Best Practice Guideline (EBPG) on haemodynamic instability defines IDH as a decrease in systolic blood pressure (SBP) ≥20 mmHg or a decrease in mean arterial pressure (MAP) by ≥10 mmHg associated with a clinical event and the need for a nursing intervention ***(Kooman et al., 2007).***

Dialysis techniques have improved and there is more awareness of strategies to prevent IDH, e.g. by lowering the dialysate temperature and monitoring relative blood volume changes. At the same time, the average age of dialysis patients as well as the proportion of patients with significant co-morbidities such as diabetes mellitus and heart failure has increased. It follows that the current prevalence of IDH is unknown, may be changed ***(Kuipers et al., 2016).***

It was previously thought that fluid removal during dialysis and accompanying haemodynamic consequences such as hypovolaemia, or decrease in circulating filling pressure and cardiac output were important factors contributing to IDH.

However, inappropriately low peripheral arterial resistance contributes to intradialytic decrease in blood pressure ***(Chang et al., 2014).***

It is evident that the prevalence of dialysis hypotension is influenced by the dialysis settings. Shorter treatment times, higher ultrafiltration rates and relatively high dialysate temperatures are all risk factors for dialysis hypotension ***(Kuipers et al., 2016).***

It is suggested that nitric oxide (NO), a potent endogenous vasodilator, caused intradialytic blood pressure reduction. NO production increases significantly during HD, resulting in significant and rapid vasodilatation and hypotension. Formed via NO synthase (NOS), NO undergoes a short half-life and rapidly metabolizes to nitrate and nitrite – markers of NO production – and increase in concentration in patients with intradialytic hypotension ***(Chang et al., 2014).***

Nitric oxide synthase (NOS) uses L-arginine as a substrate to synthesize nitric oxide ***(Aslam et al., 2006).*** There are three kinds of NOS: endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). In most cases during haemodialysis, eNOS and iNOS regulate haemodynamic changes ***(Chang et al., 2014).***

However, given that it takes 6 h to induce RNA synthesis and protein formation, iNOS most likely will not lead to

intradialytic hypotension within a 4 hour dialysis session. Therefore; eNOS is most likely to regulate blood pressure during haemodialysis ***(Tota et al., 2010).***

Beside this, NO has Role in different physiologic processes in kidney low levels linked to progression of renal disease (iNOS), ischemic nephropathy; increased production (nNOS) in macula densa attenuates transforming growth factor and maintains GFR in the face of increasing distal salt delivery ***(Sarkar et al., 2004).***

One of the major limitations of HD in chronic liver disease patients is the occurrence of intradialytic hypotension, which limits the amount of ultrafiltration and results in sustained or worsening ascites. Patients with cirrhosis and ascites have decreased peripheral vascular resistance due to a variety of reasons, including high circulating levels of nitric oxide ***(Kunal et al., 2008).***

AIM OF THE WORK

To evaluate the role of Nitric oxide in intradialytic hypotension in HCV positive hemodialysis patients.

Chapter 1
INTRADIALYTIC HYPOTENSION

Introduction

The increasing global epidemic of Chronic Kidney Disease (CKD) and resultant End-Stage Renal Disease (ESRD) continues to be a serious challenge for many developing countries. ESRD negatively impacts the quality of life (QoL) of patients by acting negatively on their social, financial and psychological wellness. The disease can also damage the body image and general QoL of patients in addition to physical, functional, metabolic, social and mental conditions. Patients with ESRD who receive maintenance dialysis therapy have a significantly higher mortality rate compared to the healthy population about 20% per year, primarily due to cardiovascular disease ***(Zazzeroni et al., 2017).***

IDH is considered one of the most frequent complications of haemodialysis treatment and is associated with increased cardiovascular morbidity and mortality ***(Sands et al., 2014).***

There is no generally accepted definition of intradialytic hypotension. Kidney Disease Outcomes Quality Initiative (KDOQI) and EBPG define intradialytic hypotension as the presence of a diminishing in SBP ≥20 mmHg or a diminishing in MAP ≥10 mmHg, providing the decrease in blood pressure is

associated with clinical events and need for nursing interventions that include: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety. It impairs the patient's well-being, can induce cardiac arrhythmias, predisposes to coronary and/or cerebral ischemic events. In addition, IDH precludes the delivery of an adequate dose of dialysis, as hypotension episodes lead to the compartment effect and result in suboptimal Kt/V_{urea} ***(Kooman et al., 2007).***

Epidemiology and Risk Factors

Symptomatic hypotension during (or instantly following) hemodialysis complicates 5 to 30 percent of all dialysis sessions. In one study that included 44,801 dialysis sessions in 1137 patients, 75 percent of patients had at least one episode of intradialytic hypotension. In a few patients, more than 50 percent of sessions are convoluted by intradialytic hypotension ***(Sands et al., 2014).***

Patients with intradialytic hypotension have serious medical conditions requiring quick consideration. These conditions incorporate systemic disease, arrhythmias, pericardial tamponade, valvular disorders, myocardial infarction, hemolysis, hemorrhage, air embolism, and a reaction to the dialyzer membrane ***(Reilly, 2014).***