Loop Diuretics in Acute Heart Failure; Decongestive Relief Against Renal Side Effects

Essay

Submitted for Partial Fulfillment of Master Degree
in General Intensive Care

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2017

Abstract

Background: In patients with acute heart failure (AHF), the risk of death or rehospitalization within 60 days from admission ranges from 30 to 60 %.

The symptoms that drive hospital admission are linked to congestion, and loop diuretics are the most common initial therapeutic approach (used in 90 % of cases).

In most patients, the increased diuresis is accompanied by a decrease in LV ventricular filling pressures and improvement of symptoms by reducing pulmonary capillary wedge pressure and intra-alveolar edema.

Aims: The aim of this essay is to figure out the role of loop diuretics in the management of systemic and peripheral congestion due to acute heart failure and discussing impaired renal function that occurs as an adverse effect.

Conclusion: Current goals in the acute treatment of heart failure are focused on pulmonary and systemic decongestion with loop diuretics as the cornerstone of therapy. Despite rapid relief of symptoms in patients with acute decompensated heart failure, after intravenous use of loop diuretics, the use of these agents has been consistently associated with adverse events, including hypokalemia, hypotension, and increased mortality.

The impaired renal function often associated with this treatment is not extensively explored and could deserve more specific studies. Several questions remain to be answered about the best diuretic modality administration, global clinical impact during acute and post-discharge period, and the role of renal function deterioration during treatment.

Keywords: Loop Diuretics, Acute Heart Failure, Decongestive Relief Against Renal

سورة البقرة الآية: ٣٢

First of all, thanks to Allah whose magnificent help was the main factor in completing this work.

No words can express my deep sincere feelings Towards Prof. Dr. Ahmed Ali Fawaz, Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine-Ain Shams University for his continuous encouragement, guidance and support he gave me throughout the whole work. It has been a great honor for me to work under his generous supervision.

I would like to express my deepest appreciation, respect and thanks to Ass. Prof. Dr. Wael Reda Hussein, Assistant Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine-Ain Shams University, for his continuous guide in all aspects of life beside his great science, knowledge and information.

I would like to express my deepest appreciation, respect and thanks to Dr. Ahmed Abdel Daiem Abdel Hak, Lecturer of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine-Ain Shams University, for his continuous guide in all aspects of life beside his great science, knowledge and information.

Last but not least, sincere gratitude to *My Family* for their continuous encouragement and spiritual support.

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List of Abbreviations

Abbre.	Full term
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
ADHF	Acute decompensated heart failure
AHF	Acute heart failure
AKI	Acute kidney injury
AMI	Acute myocardial infarction
Ang II	Angiotensin II
AVP	Arginine vasopressin
BNP	B-type natriuretic peptide
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CART	Classification and regression tree
CCU	Cardiac care unit
cGMP	Cyclic guanosine mono-phosphate
CHF	Congestive heart failure
CKD	Chronic kidney disease
CRS	Cardiorenal syndrome
Cr	Creatinine
CysC	Cystatin C
ECG	Electrocardiogram
ED	Emergency departement
eGFR	Estimated glomerular filtration rate
FiO_2	Fraction of inspired oxygen
GFR	Glomerular filtration rate
HF	Heart failure
HFCRN	Heart failure clinical research network

Abbre.	Full term

ICU : Intensive care unit
KIM-1 : Kidney injury molecule-1
LV : Left ventricle
LVEF : Left ventricle ejection fraction
MR-proANP: Midregional pro-atrial natriuretic peptide
NGAL : Neutrophil gelatinase–associated lipocalin
NP : Natriuretic peptide
NT-proBNP: N-terminal pro-B type natriuretic peptide
NTG : Nitroglycerin
NSTEMI : Non ST segment elevated myocardial infarction
NYHA : New york heart association
PCWP : Pulmonary capillary wedge pressure
RA : Right atrium
RAAS : Renin angiotensin aldosterone system
RV : Right ventricle
SBP : Systolic blood pressure
SNS : Systemic nervous system
STEMI : ST segment elevated myocardial infarction
TGF : Tubuloglomerular feedback
WRF : Worsening renal function

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Introduction

In patients with acute heart failure (AHF), the risk of death or rehospitalization within 60 days from admission ranges from 30 to 60 % ***(McMurray et al., 2012).***

The symptoms that drive hospital admission are linked to congestion, and loop diuretics are the most common initial therapeutic approach (used in 90 % of cases) ***(Nohria et al., 2003).***

These agents promptly improve symptoms and have been shown to reduce dyspnea scores and peripheral edema ***(Gheorghiade et al., 2009).***

It has been difficult to demonstrate a uniform benefit with respect to any individual therapeutic intervention in patients with acute heart failure ***(Valente et al., 2014).***This is probably due to a wide range of pathophysiologies that result in a common phenotypic appearance of pulmonary congestion and peripheral edema ***(Hasselblad et al., 2007).***

Although pulmonary and systemic congestion may be the most overt findings, these may be the "tip of the iceberg" reflecting significant congestion of multiple organs, including the kidneys ***(Parrinello et al., 2015)*** .

The administration of intravenous loop diuretics to patients with heart failure (HF) and congestion results typically in a prompt diuretic effect. In most patients, the increased diuresis is accompanied by a decrease in LV ventricular filling pressures and improvement of symptoms by reducing pulmonary capillary wedge pressure and intra-alveolar edema ***(Brater et al., 1994)***.

However, loop diuretics have been associated with increased rates of mortality and readmission in a graded fashion with cumulative dose and with continuous infusions ***(Valente et al., 2014).***

Loop diuretic administration, particularly higher doses and continuous infusions, is associated with higher rates of acute kidney injury (AKI). Loop diuretics markedly increase activation of the renin-angiotensin and sympathetic nervous systems. Indirect effects of loop diuretics include reductions of renal blood flow and enhanced proximal tubule sodium reabsorption in between loop diuretic doses. The previous functional and parenchymal kidney modifications could potentially result in sudden creatinine increase and epidermal growth factor receptor reduction, amplifying the acute kidney injury independently from primary kidney disease ***(Metra et al., 2008).***

Aim of the Essay

The aim of this essay is to figure out the role of loop diuretics in the management of systemic and peripheral congestion due to acute heart failure and discussing impaired renal function that occurs as an adverse effect.

Acute Heart Failure and Mechanism of Action of Loop Diuretics

Physiological considerations:

- **Ventricular Function:**

►**Systolic Function.** The heart provides the force needed to deliver the blood throughout the cardiovascular system to supply nutrients and to remove metabolic waste products. Because of the anatomic complexity of the right ventricle (RV), the description of systolic function is usually limited to the left ventricle (LV). Systolic performance of the heart is dependent on loading conditions and contractility. Preload and afterload are two interdependent factors extrinsic to the heart that affect cardiac performance ***(Aslanger et al., 2016).***

►**Diastolic Function.** Diastole is ventricular relaxation, and it occurs in four distinct phases: (1) isovolumic relaxation; (2) the rapid filling phase (i.e., the LV chamber filling at variable left ventricular pressure); (3) slow filling, or diastasis; and (4) final filling during atrial systole. The greatest amount of ventricular filling occurs in the second phase, whereas the third phase adds only approximately 5%

of total diastolic volume and the final phase provides 15% of ventricular volume from atrial systole.

Many different factors influence diastolic function: magnitude of systolic volume, passive chamber stiffness, elastic recoil of the ventricle, diastolic interaction between the two ventricular chambers, atrial properties, and catecholamines. Whereas systolic dysfunction is a reduced ability of the heart to eject, diastolic dysfunction is a decreased ability of the heart to fill. Abnormal diastolic function is now being recognized as the predominant cause of the pathophysiologic condition of congestive heart failure ***(Brutsaert et al., 2006).***

►**Preload and Afterload.** *Preload* is defined as the ventricular load at the end of diastole, before contraction has started. In clinical practice, surrogate representatives of left ventricular volume such as pulmonary wedge pressure or central venous pressure are used to estimate preload. With the presence of transesophageal echocardiography, a more direct measure of ventricular volume is available.

Afterload is defined as systolic load on the LV after the beginning of contraction. Aortic compliance is an additional determinant of afterload. Aortic compliance is the ability of the aorta to give way to systolic forces from

the ventricle. Changes in the aortic wall (dilation or stiffness) can change aortic compliance and thus afterload ***(Keith, 2016).***

Acute heart failure:

Definition:

Heart failure (HF) is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/ or elevated intracardiac pressures at rest or during stress. Acute heart failure (AHF) can be defined as rapid onset or worsening of symptoms and/or signs of HF ***(Ponikowski et al., 2016).***

Classifications of acute heart failure:

AHF can present itself as acute de novo (new onset of acute heart failure in a patient without previously known cardiac dysfunction) or acute decompensation of chronic heart failure. Large number of overlapping classifications of AHF based on different criteria have been proposed ***(Ponikowski et al., 2015).***