

# بسم الله الرحمن الرحيم



HOSSAM MAGHRABY



# شبكة المعلومات الجامعية التوثيق الالكتروني والميكروفيلم



HOSSAM MAGHRABY



# جامعة عين شمس

## التوثيق الإلكتروني والميكروفيلم

### قسم

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



## يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار



HOSSAM MAGHRABY



# **Safety and Efficacy of Ivabradine as A Rate Control For the Heart in Sepsis**

*Thesis*

*Submitted for Partial Fulfillment of Master  
Degree in Intensive Care*

*By*

**Ahmed Mohammed Ibrahim Borham**

*MB.B.Ch, Mansoura University* □

*Under Supervision of*

**Prof. Dr. Sherif Samir Wahba**

*Professor of Anesthesia, Intensive Care and Pain Management*

*Faculty of Medicine, Ain Shams University* □

**Dr. Osama Ramzy Youssef**

*Assistant Professor of Anesthesia, Intensive Care and Pain Management*

*Faculty of Medicine, Ain Shams University*

**Dr. Marwa Mamdouh Mohamed**

*Lecturer of Anaesthesia, Intensive Care and Pain Management*

*Faculty of Medicine Ain Shams University* □

*Faculty of Medicine  
Ain Shams University*

*2021*



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قَالَ

سَبِّحْ اِنَّكَ لَا تَعْلَمُ لَنَا  
اِلَّا مَا عَلَّمْتَنَا اِنَّكَ اَنْتَ  
الْعَلِيمُ الْعَظِيمُ

صدق الله العظيم

سورة البقرة الآية: ٣٢

# Acknowledgment

*First and foremost, I feel always indebted to **ALLAH**, the Most Kind and Most Merciful.*

*I'd like to express my respectful thanks and profound gratitude to **Prof. Dr. Sherif Samir Wahba**, Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

*I am also delighted to express my deepest gratitude and thanks to **Dr. Osama Ramzy Youssef**, Assistant Professor of Anesthesia, Intensive Care and Pain Management, Faculty of Medicine, Ain Shams University, for his kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

*I am deeply thankful to **Dr. Marwa Mamdouh Mohamed**, Lecturer of Anaesthesia, Intensive Care and Pain Management, Faculty of Medicine Ain Shams University, for her great help, active participation and guidance.*

*Ahmed Borham* □

# *List of Contents*

Title	Page No.
List of Abbreviations	iii
List of Tables	iv
List of Figures	vi
Introduction	1
Aim of the Study	5
Review of Literature	
Sepsis and Septic Shock	6
Ivabradine	54
Patients and Methods	73
Results	78
Discussion	113
Study Limitations	118
Summary & Conclusion	120
Recommendations	119
References	124
Arabic Summary .....	—

# *List of Abbreviations* □

Abb.	Full term
ACCCM .....	American College of Critical Care Medicine
ACCP .....	American College of Chest Physicians
ACEP .....	American College of Emergency Physicians
ADH .....	Antidiuretic hormone
ALI .....	Acute lung injury
ALP .....	Alkaline phosphatase
ALT .....	Alanine aminotransferase
aPTT .....	Activated partial thromboplastin time
ARDS .....	Acute respiratory distress syndrome
AST .....	Aspartate aminotransferase
BB .....	Beta-blocker
BUN .....	Blood urea nitrogen
CBC .....	Complete blood count
CIRCI .....	Corticosteroid insufficiency
CNS .....	Central nervous system
CPAP .....	Continuous positive airway pressure
CRRT .....	Continuous RRT
CSF .....	Cerebrospinal fluid
CT .....	Computed tomography
CVP .....	Central venous pressure
CYP3A4 .....	Cytochrome P450 3A4
DIC .....	Disseminated intravascular coagulation
DNA .....	Deoxyribonucleic acid
ECG .....	Electrocardiography
ED .....	Emergency department
EGDT .....	Early goal- directed therapy
ERCP .....	Endoscopic retrograde cholangiopancreatography
ESICM .....	European Society of Intensive Care Med
FFP .....	Fresh frozen plasma



## *List of Abbreviations Cont...*



Abb.	Full term
FIO 2.....	Fraction of inspired oxygen
GI.....	Gastrointestinal
H2RAs .....	Histamine- 2 receptor antagonists
HPA .....	Hypothalamic-pituitary-adrenal
HR.....	Heart rate
ICU .....	Intensive care unit
IE .....	Infective endocarditis
IHD .....	Ischemic Heart Disease
INR .....	International Normalized Ratio
IRB.....	Institutional review board
IV .....	Intravenous
LMWH.....	Low- molecular-weight heparin
LVEF .....	Left ventricular ejection fraction
MAP .....	Mean arterial pressure
MODS.....	Multiple organ dysfunction syndrome
MOFS .....	Multiple organ failure syndrome
MRI.....	Magnetic Resonance Imaging
PaO2.....	Arterial oxygen tension
PBW.....	Predicted body weight
PEEP .....	Positive end-expiratory pressure
PPIs .....	Proton pump inhibitors
PT .....	Prothrombin time
RBC .....	Red blood cell
RNA .....	Ribonucleic acid
RR.....	Respiratory rate
SA .....	Sinoatrial
SCCM .....	Society of Critical Care Medicine
SICU .....	Surgical ICU
SIRS.....	Systemic inflammatory response syndrome

□

## *List of Abbreviations Cont...*

Abb.	Full term
SOFA .....	Sepsis Related Organ Failure Assessment
UFH .....	Unfractionated heparin
UTI .....	Urinary tract infection
VTE.....	Venous thromboembolism
WBC .....	White blood cell

□

□

□

# *List of Tables* □

Table No.	Title	Page No.
<b>Table (1):</b>	Age and gender distribution of whole study. ■■■■■	79 □
<b>Table (2):</b>	Comparison between group A & group B regarding gender and age. ■■■■■	80 □
<b>Table (3):</b>	Source of infection among all the studied patients. ■■■■■	82 □
<b>Table (4):</b>	Comparison between Group A & Group B regarding source of sepsis. ■■■■■	84 □
<b>Table (5):</b>	Co-morbidities in whole study population. ■■■■■	86 □
<b>Table (6):</b>	Comparison between group A & group B regarding risk factors. ■■■■■	87 □
<b>Table (7):</b>	Comparison between Group A & Group B regarding laboratory data at day of admission. ■■■■■	89 □
<b>Table (8):</b>	Comparison between group A & group B regarding clinical data at day of admission. ■■■■■	90 □
<b>Table (9):</b>	Comparison between group A & group B regarding MABP. ■■■■■	92 □
<b>Table (10):</b>	Heart rate of whole study population. ■■■■■	93 □
<b>Table (11):</b>	Comparison between group A & group B regarding heart rate. ■■■■■	94 □
<b>Table (12):</b>	Comparison between group A & group B regarding heart rate after treatment. ■■■■■	96 □
<b>Table (13):</b>	Mechanical ventilation of whole study population. ■■■■■	97 □
<b>Table (14):</b>	Weaning from mechanical ventilation of whole study population. ■■■■■	99 □
<b>Table (15):</b>	Comparison between group A & group B regarding mechanical ventilation (MV) and duration of MV. ■■■■■	100 □

Table No.	Title	Page No.
<b>Table (16):</b>	Comparison between group A & group B regarding weaning from mechanical ventilation.	03
<b>Table (17):</b>	Comparison between Group A & Group B regarding SOFA score.	04
<b>Table (18):</b>	APACHE II score.	05
<b>Table (19):</b>	Comparison between group A & group B regarding APACHE II score and mortality rate.	05
<b>Table (20):</b>	Outcome on the whole study population.	07
<b>Table (21):</b>	Comparison between group A & group B regarding mortality.	09
<b>Table (22):</b>	Average length of ICU stay.	12
<b>Table (23):</b>	Length of ICU stay (comparison between the two groups).	12



# *List of Figures* □

Fig. No.	Title	Page No.
<b>Figure (1):</b>	Surviving Sepsis Guidelines Criteria for Organ Dysfunction .....	11
<b>Figure (2):</b>	Sequential [Sepsis-Related] Organ Failure Assessment Score.....	17
<b>Figure (3):</b>	Pathogenesis of sepsis and multiorgan failure .....	23
<b>Figure (4):</b>	Pathophysiology of sepsis .....	24
<b>Figure (5):</b>	Mediators of sepsis.....	25
<b>Figure (6):</b>	Mechanism of action of Ivabradine .....	63
<b>Figure (7):</b>	Change in time to limiting angina (exercise tolerance test) criteria with Ivabradine at trough of drug activity.....	69
<b>Figure (8):</b>	Effect of Ivabradine on primary end point.....	71
<b>Figure (9):</b>	Gender. ....	79
<b>Figure (10):</b>	Age distribution in the two studied groups. ....	81
<b>Figure (11):</b>	Gender distribution in the two studied groups.....	81
<b>Figure (12):</b>	Source of infection in the whole study population. ....	83
<b>Figure (13):</b>	Source of infection in the two studied groups. ....	85
<b>Figure (14):</b>	Co-morbidities in whole study population.....	86
<b>Figure (15):</b>	Risk factors in the two studied groups.....	88
<b>Figure (16):</b>	SBP & DBP & MAP in the two studied groups. ....	91
<b>Figure (17):</b>	Comparison between group A and group B regarding MABP. ....	92

9

Fig. No.	Title	Page No.
<b>Figure (33):</b>	Rate of hospital mortality and 28 day mortality in the two studied groups.	10
<b>Figure (34):</b>	Expected mortality in the two studied groups.	11

