

Procalcitonin versus C- reactive protein as early markers for postoperative sepsis after major abdominal surgery

*Thesis submitted for Partial Fulfilment of M.D.
Degree in Anesthesiology*

By

Islam Mohamed Amin Diab

M.B., B.Ch, M.Sc., Anesthesiology
Faculty of Medicine, Ain Shams University

Supervised by

Prof. Dr. Sohair Abbas M. Sadek

*Professor of Anesthesia and Intensive Care
Faculty of Medicine, Ain Shams University*

Prof. Dr. Adel Mikhael Fahmy

*Professor of Anesthesia and Intensive Care
Faculty of Medicine, Ain Shams University*

Dr. Sahar Mohamed Talaat

*Assistant Professor of Anesthesia and Intensive Care
Faculty of Medicine, Ain Shams University*

**Faculty of Medicine
Ain Shams University
2015**



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وقل زدني علماً

صدق الله العظيم

سورة طه آية (114)





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. Sohair Abbas M. Sadek**, Professor of Anesthesia and Intensive Care, faculty of medicine, Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she her done in the meticulous revision of the whole work. It is a great honor to work under his guidance and supervision.*

*I would like also to express my sincere appreciation and gratitude to **Prof. Dr. Adel Mikhael Fahmy**, Professor of Anesthesia and Intensive Care, faculty of medicine, Ain Shams University, for his continuous directions and support throughout the whole work.*

*Really I can hardly find the words to express my gratitude to **Dr. Sahar Mohamed Talaat**, Assistant Professor of Anesthesia and Intensive Care, Faculty of Medicine, Ain Shams University for her continuous directions and meticulous revision throughout the whole work. I really appreciate their patience and support.*

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



Islam Mohamed Amin Diab

Contents

List of Abbreviations	i
List of Tables	vi
List of Figures	vii
Introduction and Aim of the Work	1
Review of Literature	3
* Sepsis	3
* Postoperative sepsis	42
* CRP	48
* Procalcitonin	57
Patients and Methods	67
Results	76
Discussion	95
Summary	115
Conclusion	118
References	119
Arabic Summary	--

List of Abbreviations

ASA	:	American Society of Anesthesiologists
ACCP	:	American College of Chest Physicians
AD	:	Alzheimer's disease
ADH	:	Anti Diuretic Hormone
ALI	:	Acute Lung Injury
ARDS	:	Acute respiratory distress syndrome
ATS	:	American Thoracic Society
BBB	:	Blood-brain barrier
CAP	:	Community-acquired pneumonia
CBC	:	Complete blood count
CDC	:	Center for Disease Control and Prevention
CI	:	Cardiac Index
CINC	:	Cytokine induced neutrophil chemoattractant
CNS	:	Central Nervous System
CPAP	:	continuous positive airway pressure
CRP	:	C-reactive protein
CS	:	Complement S
CT	:	Computerized Tomography

List of Abbreviations (Cont.)

DIC	:	Disseminated intravascular coagulation
ECG	:	Electrocardiogram
ED	:	Emergency Department
EGDT	:	Early goal-directed therapy
ESICM	:	European Society of Intensive Care Medicine
ESR	:	Erythrocyte Sedimentation Rate
FDA	:	Food and Drug Administration
FIO ₂	:	Fraction of Inspired oxygen
FUO	:	Fever of Unknown Origin
HLA	:	Human Leukocytic Antigen
HPV	:	Hypoxic pulmonary vasoconstriction
HR	:	Heart Rate
Hs-CRP	:	Highly Sensitive CRP
IBD	:	Inflammatory bowel disease
ICU	:	Intensive care unit
IFN	:	Interferon
IL	:	Interleukin
INR	:	International Normalized Ratio
IV	:	Intravenous
KDa	:	Kilo Dalton

List of Abbreviations (Cont.)

LBP	:	Lipopolysaccharide binding protein
LDL	:	Low Density Lipoprotein
MAP	:	Mean Arterial Blood Pressure
MHC	:	Major histocompatibility complex
MODS	:	Multiple organ dysfunction syndrome
MOF	:	Multiple Organ Failure
NICE-		
SUGAR	:	Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation
NIGMS	:	National Institute of General Medical Sciences
NK	:	Natural killer
NO	:	Nitric Oxide
N-ProCT	:	N- Procalcitonin
NPV	:	Negative predictive value
OSA	:	Obstructive Sleep Apnea
PaCO ₂	:	Partial Pressure of Carbondioxide
PAF	:	Platelet Activating Factor
PaO ₂	:	Partial Pressure of Oxygen

List of Abbreviations (Cont.)

PCT	:	Procalcitonin
PG	:	Prostaglandin
PH	:	Power of Hydrogen
PICs	:	Postoperative Infectious Complications
PIRO	:	Predisposition, Insult infection, Response, Organ dysfunction
PMN	:	Polymorph Nuclear cells
POD	:	Post operative day
PTT	:	Partial Thromboplastin Time
RR	:	Respiratory Rate
SBP	:	Systolic Blood Pressure
SCCM	:	Society of Critical Care Medicine
SD	:	Standard Deviation
SIRS	:	Systemic inflammatory response
SIS	:	Surgical Infection Society
SPO ₂	:	Oxygen Saturation
SVR	:	Systemic Vascular Resistance
TNF- α	:	Tumor Necrosis Factor alpha
VO ₂	:	Oxygen Uptake
WBCs	:	White Blood Cells

List of tables

<i>Table</i>	<i>Title</i>	<i>Page</i>
1	Definition of bacteremia, SIRS, sepsis, severe sepsis and septic shock	7
2	Diagnostic criteria for sepsis in adults	10
3	Demographic data	76
4	Perioperative Bone Score changes in Both Study Groups	79
5	Perioperative (MAP) changes in both study groups	80
6	Mean Perioperative HR Changes in Both Study Groups	81
7	Mean Perioperative Respiratory Rate Changes in Both Study Groups	83
8	Mean Perioperative Temperature Changes in Both Study Groups	84
9	Mean Perioperative Urine Output Changes in Both Study Groups	86
10	Mean Perioperative pH Changes in Both Study Groups	88
11	Mean Perioperative PaCO ₂ Changes in Both Study Group	89
12	Mean Perioperative PaO ₂ Changes in Both Study Groups	90
13	Perioperative Serum Bicarbonates Changes in Both Study Groups	91
14	Mean perioperative leukocytic count changes in both study groups	92
15	Mean Perioperative CRP blood levels in both study groups	93
16	Mean perioperative PCT blood levels in both study groups	94

List of Figures

<i>Fig.</i>	<i>Title</i>	<i>Page</i>
1	The relationship between infection, systemic inflammatory response syndrome (SIRS) and sepsis syndromes	8
2	The Host Response in Severe Sepsis	19
3	Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria	28
4	Crystal structure of C-reactive protein complexed with phosphocholine from Thompson et al., 1999 The calcium ions are yellow, and phosphocholine is green	49
5	Structure of procalcitonin	60
6	Age	77
7	Sex	77
8	Weight	78
9	Duration	78
10	Mean Perioperative MAP Changes in Both Study Groups	80
11	Mean Perioperative Heart Rate Changes in Both Study Groups	82
12	Mean Perioperative Respiratory Rate Changes in Both Study Groups	83
13	Mean Perioperative Temperature Changes in Both Study Groups	85
14	Mean Perioperative Urine output Changes in Both Study Groups	87
15	Mean Perioperative pH Changes in Both Study Groups	88
16	Mean Perioperative PaCO ₂ Changes in Both Study Group	89

17	Mean Perioperative PaO ₂ Changes in Both Study Groups	90
18	Perioperative serum Bicarbonates Changes in Both Study Groups	91
19	Mean perioperative leukocytic count changes in both study groups	92
20	Mean perioperative CRP blood levels in both study groups	93
21	Mean perioperative PCT blood levels in both study groups	94

Introduction

The first mention of the word sepsis in a medical context was more than 2700 years ago in the poems of Homer. The word derives from the Greek word *Sepein*, meaning “to rot.” (*Huan et al., 2010*).

The early identification of patients who developed infectious complications is crucial for timely and adequate treatment. Severe sepsis is still a major cause of postoperative morbidity and mortality after major surgery, with an incidence ranging between 9 to 12% and high mortality (42% to 80%) (*Nakamura et al., 2008*).

Infectious complications occur frequently after major abdominal surgery and have a major influence on patient outcome and hospital costs (*Gans et al., 2015*).

Septic complications after major abdominal surgery consist mainly of surgical site infections (up to 40%), pulmonary infections (10%) and urinary infections (5%) (*Rovera et al., 2007*).

Anastomotic leakage and intraabdominal abscess are the most feared complications and are frequently diagnosed late in the postoperative period since the initial clinical manifestations are very subtle. About 30% of patients admitted to the ICU with intraabdominal infection died, with mortality rates even higher when peritonitis arises as a complication of a previous operative procedure (*Evans, et al., 2001*).

The early identification of patients at risk for post-operative infection would be of clinical importance, since clinical signs are usually insensitive and do not allow an early diagnosis. Several biochemical tests are used to identify persistent inflammatory activity in postoperative patients, including CRP, PCT and interleukins (*Silvestre et al., 2014*).

Aim of the Work

The aim of the work is to evaluate the efficacy of procalcitonin (PCT), C- reactive protein (CRP) and leukocytic count as early markers of subsequent postoperative sepsis in patients undergoing major abdominal surgeries and evaluate the best detector for postoperative sepsis and septic shock.

Sepsis

Definitions

Sepsis is a potentially fatal disease, it coexists with an infection, and often with other diseases, all of which produce their own signs and symptoms. The challenge is to pick out the signs of sepsis from among the other abnormalities plaguing the patient. To make sepsis easier to identify, there has been an effort to standardize its definition despite its wide range of presentations. The current clinical definitions of sepsis and its related terms (*Dellinger et al., 2008; Nguyen and Smith 2007; Levy and Dunne 2003*) are shown in table (1).

Sepsis is an unchecked whole-body response to an infection, regardless of whether the infection is local, extensive, or blood-borne. This response produces two or more of the signs of SIRS, defined below. The septic reaction threatens to damage distant organs and to destabilize the circulatory system. Sepsis can lead to organ failure, shock, and death.

Systemic inflammatory response syndrome (SIRS) is an inflammatory reaction that produces at least two of the following four signs:

Abnormal body temperature: hypothermia, <96.8°F/36°C; or fever, >100.4°F/38.3°C, tachycardia (>90 beats/min), tachypnea (>20 breaths/min or a rate sufficient to produce PaCO₂ <32 mm Hg), and abnormal white blood cell count (>12,000/mm³, <4000/mm³, or >10% immature forms) (*Dellinger et al., 2008*).

SIRS due to abnormal white blood cell count can be triggered by an infection, but it can also arise from non-infectious sources such as trauma, hemorrhage, burns, surgery, adrenal insufficiency, pulmonary embolism, dissecting or ruptured aortic aneurysm, myocardial infarction, occult hemorrhage, cardiac tamponade, post-cardiopulmonary bypass syndrome, autoimmune disorders, pancreatitis, vasculitis, anaphylaxis, or drug overdose. SIRS can lead to organ failure, shock, and death (*Neviere, 2013a,b*).

Severe sepsis, or “sepsis syndrome,” is present when the patient has progressed to a stage in which organs or