NEW STRATEGIES IN CNS , KIDNEY AND LUNG PROTECTION IN POLYTRAUMATIZED ICU PATIENTS

ESSAY

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By
Tarek Ibrahim Mohammed Elgaria
M.B.B.CH
Tanta University

Under supervision of

Professor Doctor / Galal Abo Elseoud Saleh
Professor of Anesthesiology and Intensive Care
Faculty of Medicine, Ain Shams University

Doctor / Adel Mohamed Alansary
Assistant Professor of Anesthesiology and Intensive Care
Faculty of Medicine, Ain Shams University

Doctor / Mohammed Yousef Khashaba
Lecturer of Anesthesiology and Intensive Care
Faculty of Medicine, Ain Shams University

Ain Shams University
Faculty of Medicine
٢٠١٢

الاستراتيجيات الحديثة لحماية الجهاز العصبي المركزي والكلى والرئتين لمرضى الإصابات المتعددة بالرعاية المركزة

رسالة توطئة للحصول على درجة الماجستير في الرعاية المركزة
مقدمه من,,,

الطبيب/طارق إبراهيم محمد الجارية

تحت إشراف

الأستاذ الدكتور/جلال أبو السعود صالح
أستاذ التخدير والرعاية المركزة
كلية الطب- جامعة عين شمس

الدكتور/عادل محمد الأنصاري
أستاذ مساعد التخدير والرعاية المركزة
كلية الطب- جامعة عين شمس

الدكتور/ محمد يوسف خشبة
مدرس التخدير والرعاية المركزة
كلية الطب- جامعة عين شمس

جامعة عين شمس
كلية الطب
٢٠١٢

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ABBREVATIONS

AA	Arachidonic Acid
ADP	Adenosine diphosphate
AE	Arterial Embolization
AKI	Acute Kidney Injury
AM	Adrenomoduline hormone
AMBP	Adrenomoduline Binding Protein
APAF	Apoptosis Activating Factor
ARDS	Acute Respiratory Distress Syndrome
ARF	Acute Real Failure
BUN	Blood Urea Nitrogen
CAT	Catalase enzyme
CBF	Cerebral Blood Flow
C_{cr}^{24}	Creatinine clearance
CDI	Central Diabetes Insipidus
CGRP	Calcitonine Gene Related Peptide
CNS	Central Nervous System
CSA	Cyclosporine A
DHA	Docosahexaenoic Acid

DRS	Disability Rating Scale

Continue abbreviations:

DVT	Deep Vein Thrombosis
ECMO	Extra Corporeal Membrane Oxygenation
EPA	Eicosapentaenoic Acid
EPO	Erythropoietin Hormone
ET	Early Tracheostomy
ETC	Electron Transport Chain
FITC	Flurocin IsoThiocyanate
GCS	Glasgow Coma Scale
GFAP	Glial Fibrillary Acidic Protein
GPx	Glutathione Peroxidase
GSSG	Oxidized glutathione
GSH	Reduced Glutathione
HBO	Hyperbaric Oxygen
Iba ١	Ionized Calcium Binding Adaptor ١
ICP	Intracranial Pressure
IHI	Intracranial Haemorhagic Injury
IL	Interleukin
I/R	Ischemic Reperfusion

LDH	Lactate Dehydrogenase

Continue abbreviations:

LOS	Length Of Stay
LNA	Linolenic Acid
LT	Late Tracheostomy
MPTP	Mitochondrial Permeability Transition Pore
MV	Mechanical Ventilation
NGAL	Neutrophil Gelatinase associated Lipocalin
NOM	Nonoperative Management
NOS	Nitric Oxide Synthase
NO	Nitric oxide
OFR	Oxygen Free Radicals
PKA	Protein Kinase A
PKC	Protein Kinase C
PRBCs	Packed Red Blood Cells
PROG	Progesterone hormone
PUFAs	Polyunsaturated Fatty Acids

ROS	Reactive Oxygen Species
RRT	Renal Replacement Therapy

Continue abbreviations:

SCI	Spinal Cord Injury
SCr	Serum Creatinine
SOD	Superoxide Dismutase
SR	Sarcoplasmic reticulum
TBI	Traumatic Brain Injury
TNF	Tissue Necrosing Factor
VAP	Ventilator Associated Pneumonia
VTE	Venous Thromboprophylaxis

CHAPTER (1)

INTRODUCTION

Chapter (1)

INTRODUCTION

Trauma is a major global contributor to premature death and disability. The burden of injuries is especially notable in low and middle-income countries and is expected to rise during the coming decades .Harm from major trauma may be minimized through early access to pre-hospital and in-hospital trauma care.(**Rehn et al.,2011)**

Pathophysiology of trauma is multifactorial that includes hypoxemia and reperfusion injury, leading to multiple organ dysfunction and failure.**(Wen-Hong et al .,2008)**

Traumatic brain injury (TBI) is an insult to the brain from the application of external physical force that leads to temporary or permanent structural and functional impairment of the brain. TBI is a leading cause of injury-related death and disability . Around 1.7 million people sustain a TBI in the U.S. annually and 53,000 of them die from TBI-related injuries . In TBI survivors, neuropsychiatric abnormalities, such as cognitive deficits, emotional and behavioral problems are common and

contribute substantially to post-TBI disabilities**.(Hu et al.,2012)**

It has been recently reported that the use of some medications and maneuvers may have a positive effect on the outcome of CNS trauma patients such as early tracheostomy for mechanically ventilated trauma patients ***(Ganuza et al.,2011)***,the use of cyclosporine A ***.(Mazzeo et al ,2009)*** as well as the use of adrenomoduline hormone. ***.(Shah et al .,2010)***

Trauma admissions to ICU are frequently complicated by early Acute Kidney Injury (AKI). Although the development of AKI is associated with an increased length of stay (LOS) it does not appear to influence patient mortality. **(Gomes et al .,2010)**

The evaluation and management of renal trauma have undergone significant changes during the past decade. The liberal use of computed tomographic evaluation in blunt and penetrating trauma has improved the diagnosis and grading of the severity of kidney injuries. More than 90% of blunt trauma renal injuries can safely be managed nonoperatively**.(Starnes et al.,2010)**.

CHPTER (2)

ISCHEMIA REPERFUSION INJURY CASCADE

Chapter (2)

Ischemia / Reperfusion Injury cascade.

Pathophysiology of trauma is multifactorial that includes ischemia and reperfusion (I/R) injury, leading to multiple organ dysfunction and failure. ***(Wen-Hong et al .,2008).***

Several mechanisms have been proposed to cause reperfusion injury including formation of oxygen free radicals (OFR), calcium overload, neutrophils-mediated tissues injury, progressive decline in microvascular flow to the reperfused tissues, or depletion of the high-energy phosphate store. Among these factors, overproduction of OFR during the first few minutes of reperfusion is considered as a key event***.(Huang et el.,2011).***

Excessive OFR causes cell DNA breakage, degeneration, and lipid peroxidation, ultimately leading to cell death. The key antioxidant enzymes, including superoxide dismutase (SOD)**,** catalase (CAT) and glutathione peroxidase (GPx), provide a defense system against oxidative stress by removing the OFR, thus protecting cells from oxidative damage***.(Huang et el.,2011).***

The traumatically induced influx of calcium is recognized to be a causative factor in triggering early cell death and axonal damage. Elevated intracellular calcium has been linked to an opening of the mitochondrial permeability transition pore (mPTP), allowing calcium to flood the mitochondrion and causing mitochondrial swelling, the generation of oxygen free radicals, and the ultimate failure of mitochondrial function. ***(Mazzeo et al.,2009)***

Such mitochondrial dysfunction plays a significant role in TBI-induced early neuropathological events, causing the loss of ATP and increased production of reactive oxygen .These effects, in turn, lead to cell death by either necrotic or apoptotic routes, since pro-apoptotic factors such as caspase C are also released from mitochondria**.** ***(Mazzeo et al.,2009)***

Mitochondria are involved in a myriad of complex signaling cascades regulating cell death vs. survival. Importantly, mitochondrial dysfunction and the resulting oxidative and nitrosative stress are central in the pathogenesis of numerous human maladies including cardiovascular diseases, neurodegenerative diseases, diabetes, and retinal diseases, many of which are related**. (*Camara et al ., 2011)***

Myocardial ischemic reperfusion injury cascade is the most well studied form of ischemic reperfusion injury so it will be discussed as an example.

While the etiology of postischemic myocardial dysfunction after cardiac surgery is multifactorial, three basic types of injury occur during heart surgery: ***myocardial stunning, apoptosis, and myocardial infarction***. Myocardial stunning is an injury that may last for only a few hours or persist for several days despite the restoration of normal blood flow. Cells that have been reversibly injured ***(stunned)*** exhibit no sign of ultrastructural damage. Apoptosis is "suicidal" programmed cell death, characterized by retention of an intact cell membrane, cell shrinkage, chromatin condensation, and phagocytosis without inflammation***. (Gill et al., 2002).***

There is increasing evidence that apoptotic death of cardiomyocytes caused by ischemia-reperfusion contributes significantly to the development of infarction as well as the loss of cells surrounding the infarct area. A large fraction of dying cells may exhibit features of both apoptosis and necrosis, i.e., both nuclear condensation and plasma membrane damage. Ultimately, however, after more prolonged ischemia, the heart begins to sustain irreversible injury in the form of infarction, necrosis. Early reperfusion is an absolute prerequisite for the survival of ischemic myocardium. However, reperfusion has been referred as the “double-edged sword” because reperfusion itself may lead to accelerated and additional myocardial injury beyond that generated by ischemia, which results in a spectrum of reperfusion-