Role of Renin-Angiotensin System and Enalaprilat an Angiotensin-Converting Enzyme (ACE) Inhibitor in Emergence Hypertension in Craniotomy Operations

Thesis
Submitted in Partial Fulfillment for the Degree of M.D.
in Anesthesia

By
Osama Mohamed Hosny Abdel Rahman
M.B., B.Ch. M.Sc.,
Faculty of Medicine, Cairo University

UNDER SUPERVISION OF

Prof. Dr. Omar Wagih Abbas
Professor of Anesthesiology
Faculty of Medicine, Cairo University

Prof. Dr. Azza Mohamed El Khawaga
Professor of Chemical Pathology
Faculty of Medicine, Cairo University

Ass. Prof. Dr. Naser Ahmed Fadel
Assistant Professor of Anesthesiology
Faculty of Medicine, Cairo University

Principle supervisor: *Prof. Omar Wagih Abbas*

Faculty of Medicine
Cairo University
2006

Abstract

Hypertension developing in patients after craniotomy operations can be difficult to control and may lead to morbidity. The renin-angiotensin system mediates at least part of this hypertension. Enalaprilat, the only intravenous angiotensin-converting enzyme inhibitor, is used to treat hypertension in these patients. However, its control over postoperative hypertension during the early postoperative period is not enough alone but would be achieved best by combining its use with the use of other faster acting drugs of short duration.

Key words: (postoperative hypertension, enalaprilat, craniotomy. plasma renin activity)

AKNOWLEDGEMENT

It is my pleasure to express my deepest gratitude, full respect, and sincere appreciation to ***Professor Dr. Omar Wagih Abbas,*** Professor of Anaesthesia, Cairo University, for his overwhelming kindness, fatherly support, limitless encouragement, and valuable supervision.

I am also honored to extend my sincere gratitude and true appreciation and respect to ***Professor Dr.Azza Mohamed El Khawaga,*** Professor of Chemical Pathology, Cairo University. It was through her kind encouragement, sincere advice, constant support, valuable guidance and constructive observations and remarks that this work came to see light.

I am also proud to express my full gratitude, unlimited thanks, sincere appreciation and respect to ***Dr. Naser Ahmed Fadel*** Assistant Professor of Anaesthesia, Cairo University. I feel deeply indebted for his constant guidance, valuable instructions, mastery teaching, precious observations, patient supervision, and time he gave freely for this work to be completed.

Wards will never be enough to express my true gratitude and sincere thanks for my professors, colleagues, and residents in Anaesthesia Department at Kasr El Ainy Hospital.

List of Abbreviations

ICH	Intracranial Hemorrhage
HR	Heart Rate
CBFV	Cerebral Blood Flow Velocity
HTN	Hypertension
BP	Blood Pressure
MAP	Mean Arterial Pressure
APH	Acute Postoperative Hypertension
SVR	Systemic Vascular Resistance
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
GMP	Guanosine Mono Phosphate
SNP	Sodium Nitro Prusside
SD	Standard Deviation
FDA	Food and Drug Administration
IV	Intravenous
ACE	Angiotensin Converting Enzyme
ACEI	Angiotensin Converting Enzyme Inhibitor
KDa	Kilo Dalton
PRA	Plasma Renin activity
ACTH	Adreno-Cortico-Trophic Hormone
SFO	Subfornical Organ
OVLT	Organum vasculosum of the Laminae Terminalis
AT	Angiotensin
AMP	Adenosine Mono Phosphate
JG	Juxta Glomerular
ECF	Extra Cellular Fluid

NO	Nitric Oxide
CST	Contraction Stress Test
NST	Non-Stress Test
BPP	Bio-Physical Profiling
MRHDD	Maximum Recommended Human Daily Dose
ANA	Anti-Nuclear Antibody
ASA	American Association of Anesthesiologists
KPa	kilo-Pascal
CVP	Central Venous Pressure
ANOVA	Analysis of Variance
PACU	Post-Anesthesia Care Unit
EDTA	Ethylenediaminetetraacetic Acid
RAAS	Renin-Angiotensin Aldosterone System
PICU	Postoperative Intensive Care Unit
ICT	Intracranial Tension
ANP	Anti-natriuretic peptide

List of Tables

List of figures

CONTENTS

Introduction

Emergence from anesthesia for intracranial surgery may be accompanied by coughing, ventilatory insufficiency and hypertension. Anesthesiologists and surgeons share a concern that this may cause intracranial complications such as bleeding and brain edema. [(1)] Early intracranial hypertension after elective craniotomy occurs in nearly 20% of patients. Intracranial hemorrhage (ICH) accounts for a substantial portion of this incidence [(2)]. ICH can be a devastating complication of surgery, occurring in 0.9%–3.5% of cranial surgery cases [(3)].

Recovery from general anesthesia and extubation is a period of intense physiological stress for patients. Oxygen consumption, catecholamine blood concentration, blood pressure, and heart rate (HR) increase after intracranial surgery. [(4)] Cerebral hyperemia was also demonstrated at extubation by a concomitant increase in cerebral blood flow velocity (CBFV) and jugular venous bulb saturation in oxygen. There was a 60 % - 80 % increase in CBFV in the middle cerebral artery from preinduction value on extubation that persisted at a lower level for 1 h. this observation occurred after anesthesia with propofol or isoflurane[(5).]

The perioperative course of patients undergoing intracranial procedures is frequently complicated by the occurrence of systemic hypertension (HTN). Intraoperatively acute hypertensive episodes may occur during brain manipulation. [(6)] But more often are produced by

events such as epinephrine-containing local anesthetic administration, head-pin application, periosteal dissection, and emergence. HTN may be associated with a number of adverse pathophysiologic consequences. When cerebral autoregulation is disturbed or its limits are exceeded, blood flow passively increases with blood pressure (BP). [7]

This in turn can increase intracranial pressure or cause breakdown of blood brain barrier with resultant transudation of intravascular fluid. Bleeding and signs of encephalopathy may ensue. After intracranial surgery, acute HTN may also increase morbidity and mortality by exacerbating cerebral edema, raising intracranial pressure, or disrupting the delicate postoperative haemostatic state. [8] Intracranial hemorrhage (ICH) can be a serious and sometimes fatal complication when it occurs during or after intracranial surgery. Perioperative HTN and coagulopathy are factors that predispose to intracranial bleeding. [9]

The frequency of postoperative HTN has been reported to be 6 % after general surgery and 35-50 % after cardiac surgery. An incidence of 57 % for postcraniotomy HTN. This figure is relatively low compared with previous reports noting incidences from 54- 91% [10]

In one study, more than 90 % of the patients developed emergence and early postoperative hypertension, defined as blood pressure exceeding the preoperative blood pressure by more than 20 % or as constant elevation of systolic arterial blood pressure over 160

mmHg or diastolic arterial blood pressure over 95 mmHg. [11]

Prolonged or severe hypertension may determinately affect prognosis, especially in patients with severe baseline illness or in those undergoing cardiac and craniotomy surgery such severe hypertension tends to occur more in patients with poor preoperative blood pressure control, autonomic disorders, or in those with history of acute alcohol or cocaine use. The pathophysiology of emergence and early postoperative hypertension is characterized by hyperresponsiveness to the trauma of surgery and is characterized by high levels stress hormones, an activated rennin-angiotensin-aldosterone system, and altered baroreceptor function in some types of surgery.[12] Anesthesia itself as well as surgical stress affects the plasma level of many vasoactive substances. [13]

These postoperative changes cause a rapid rise in peripheral vascular resistance and blood pressure in the immediate postoperative period. Emergence and early postoperative hypertension is unique in several ways. Because these patients cannot take oral medications, parenteral or topical antihypertensive drug need to be administered.

Several studies on noncranial surgery have revealed changes in the plasma level of some vasoactive substances (adrenaline, nor adrenaline, renin, aldosterone and cortisol), the most significant increase is in the early postoperative period and consequently, it has been assumed that the

stress of recovery is at least as great as that of surgery. However the number of studies in dealing with the level of these substances in cranial surgery is still very few. (14)

It is known that cerebral blood pressure autoregulation may be abolished regionally or globally after brain injury, leading to an increase in the cerebral blood flow when mean arterial pressure (MAP) increases. It is also known that luxury perfusion as illustrated by the low arteriovenous oxygen content difference occurs after craniotomy. This in turn may lead to hyperemia and vasogenic brain edema. *(15)*

It is now possible to control blood pressure quite well during emergence from craniotomy without affecting CBF.(16) Much less certain is whether blood pressure control can avert or even reduce the risk of intracranial bleeding after craniotomy, the occurrence of which substantially increases length of hospital stay, mortality, and, by implication, the cost of care (17)

Aim of the work:

In this study we evaluate the role of the renin angiotensin aldosterone system measured (RAAS) by the plasma renin activity (PRA) on postoperative hypertension after craniotomy operations and we are assessing the effect of the new drug Enalaprilat the only intravenous ACE inhibitor over postcraniotomy hypertension.

Acute postoperative hypertension (APH)

Acute postoperative hypertension is a common occurrence after surgery that has important implications for care provided on the postanesthesia unit, the intensive care unit, and the surgical floor. APH has been defined as a significant elevation in arterial blood pressure (BP) during the immediate postoperative period that may lead to serious neurologic, cardiovascular, or surgical-site complications and therefore requires intervention and management. [18] Despite the widespread and long-standing recognition of APH, there is no agreement in the literature on a more precise, quantitative definition. APH has an early onset, being observed within 2 hours after surgery in most cases, and is typically of short duration, with most patients requiring treatment for 6 hours or less. Occasionally, APH may persist for 24–48 hours. [19]

Postoperative complications of APH may include hemorrhagic stroke, cerebral ischemia, encephalopathy, myocardial ischemia, myocardial infarction, cardiac arrhythmia, congestive heart failure with pulmonary edema, failure of vascular anastomoses, and bleeding at the surgical site. For some complications, it is unclear whether the BP elevation precedes the development of the complication or is a sequel of the complication. [20]

Although APH may occur following any major surgery, it is most commonly associated with cardiothoracic, vascular, head and neck, and

neurosurgical procedures. The reported frequency of APH is quite variable and depends on the quantitative definition of APH being used. In one study of 94 patients undergoing radical neck dissection, the frequency of APH increased from 9.6% to 25.5% as less stringent criteria for the definition of APH were used. [21]

Other factors that may affect the frequency of APH include the surgical technique, the method of anesthesia, patient characteristics, and the pain management strategy. [22] Table 1 lists surgical procedures commonly associated with APH and the reported frequencies of APH. Most of the data come from studies conducted 20–30 years ago; advances in anesthesia, surgical methods, intraoperative fluid management, and pain control have probably reduced rates of APH, although there is little direct evidence to support this. [23]

Table (1): Frequency of Acute Postoperative Hypertension (APH) by Surgical Procedure:

Procedure	Frequency of APH (%)
Carotid endarterectomy	9–64
Cardiac surgery	22–54
Abdominal aortic surgery	33–75
Radical neck dissection	10-20
Intracranial neurosurgery	57–91
Elective general surgery	3–9
Elective surgery (noncardiac)	20
Release of flexion contractures	46

Pathophysiology:

The pathophysiologic mechanism underlying APH is uncertain and may vary with the surgical procedure and other factors; however, the final common pathway leading to hypertension appears to be activation of the sympathetic nervous system, as evidenced by elevated plasma catecholamine concentrations in patients with APH. At the time of development of postoperative hypertension, plasma catecholamine concentrations are significantly greater than in normotensive postoperative patients. Activation of the rennin-angiotensin–aldosterone system may also contribute to APH [(24)]; however, plasma renin, angiotensin II, and aldosterone activity are not significantly different between hypertensive and normotensive patients in all studies, suggesting that the predominant mechanism in APH is sympathetic activation. Wallach et al. [(14)] reported significant correlations between mean arterial pressure (MAP) and both plasma epinephrine ($r = 0.59$, $p < 0.01$) and norepinephrine ($r = 0.58$, $p < 0.01$) concentrations after coronary artery bypass grafting.

The primary hemodynamic alteration observed in APH is an increase in afterload (systemic vascular resistance [SVR], systolic blood pressure [SBP], and diastolic blood pressure [DBP]), with or without tachycardia; there is no difference in cardiac index, left ventricular stroke volume, or left atrial pressure compared with normotensive patients.