CORRELATION BETWEEN SERUM CALCIUM AND MAGNESIUM LEVELS AND SEVERITY OF ISCHEMIC CEREBRO-VASCULAR STROKE

CLINICAL AND LABORATORY STUDY

Thesis

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By

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عن مناقشة رسالة الماجيستير الخاصة بالطبيبة/ مني مصطفي عبد الخالق الشربيني توطئة للحصول علي درجة الماجيستير في الامراض العصبية.

اجتمعت لجنة المناقشة و الحكم علي الرسالة المقدمة من الطبيبة/ مني مصطفي عبد الخالق الشربيني توطئة للحصول علي درجة الماجيستير في الامراض العصبية و المشكلة بقرار من مجلس الكلية و المعتمد من السيد الاستاذ الدكتور / نائب رئيس الجامعة للدراسات العليا.

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ADP	Adenosine pyrophosphoric acid
AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ASIC	Acid-sensing ion channels
ATP	Adenosine triphosphate
ATP-ase	Adenosine triphosphatase
BBB	Blood brain barrier
BDNF	Brain-derived neuro-trophic factor
BI	Barthel Index
CKD	Chronic kidney disease
CSF	Cerebrospinal fluid
CLA	Conjugated linoleic acid
cIMT	Carotid intimal thickening
DNA	Deoxyribonucleic Acids
DCT	Distal convoluted tubules
ECF	Extracellular fluid
ER	Endoplasmic reticulum
GSH	Glutathione
GFR	Glomerular filtration rate
H_2O_2	Hydrogen peroxide
HDLs	High-density lipoproteins
HMG-CoA reductase	3-hydroxy-3-methylglutaryl-CoA reductase
I-Ca	Ionized calcium
IgE	Immunoglobin E
IGF-I	Insulin-like growth factor I
IL-1β	Interlukin- 1β
IP	Isoprostanes
IL-6	Interlukin-6
iNOS	Inducible Nitric Oxide Synthase
IEIC	Inward excitotoxic injury current calciupermeable channels
InsP3Rs	Inositol-1,4,5-trisphosphate receptors
IP3	Inositol-trisphosphate
LDLs	Low-density lipoproteins
LCAT	Lecithin: cholesterol acyltransferase

Mg^{2+}	Magnesium
MMPs	Metallo proteinases
$MgCl_2$	Magnesium chloride
NMDA	N-methyl-D-aspartate
Na^+	Sodium ion
NIHSS	National Institutes of Health Stroke Scale
NO	Nitric oxide
NCX	Sodium-calcium exchanger
$O_2^{\cdot -}$	Superoxide anions
OH	Hydroxyl radicals
$ONOO^-$	Peroxy-nitrite
PTH	Parathyroid hormone
PUFA	Poly unsaturated fatty acids
PPAR	Peroxisome proliferators activated receptor
PCMA	plasma membrane Ca(2+)-ATPase
PWV	Pulse wave velocity
PAI-1	Plasminogen activator inhibitor type 1
RNA	Ribonucleic acid
ROS	Radical Oxygen Species
RyRs	Ryanodine receptors
RDS	Rankain disability scale
SOD	superoxide dismutase
SOCE	Store-operated intracellular calcium entry
SERCA	Sarco(Endo)plasmic reticulum calcium
tPA	Tissue plasminogen activator
TALH	Thick ascending limb of the loop of Henle
TAL	Thick ascending limb
TNF-α	Tumour necrosis factor
TRP	Transient receptor potential channels
TCA	Tricarboxylic acid
T-Ca	Total calcium
VDCCs	Voltage-dependent calcium channel
WHO	World Health Organization
1, 25 $(OH)_2D$	**1**,25-Dihydroxyvitamin D

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ABSTRACT

Background: Calcium (Ca2_) and magnesium (Mg2_) influence the molecular pathways of ischemic neuronal death Intracellular Ca accumulation leads neuronal damage by triggering the cycle of cytotoxic events**.** Magnesium is an important co-factor, it inhibits the release of excitatory neurotransmitters at the presynaptic level and blocks voltage-gated calcium channels

Purpose of study: To investigate Magnesium, Total calcium and Ionized calcium levels in serum in the early stage of ischemic stroke. To evaluate the relationship between their serum levels and severity of neurological deficit on admission and short-term prognosis.

Subject and Methods: This study was conducted on 50 Egyptian ischemic stroke patients compared to 25 healthy control subjects. Patients were subjected to clinical evaluation (history& examination). Severity of stroke was assessed by NIHSS, Barthel Index, Oxbury scale. MRI brain was done to all patients.

Results: There was a statistical correlation between serum magnesium level and NIHSS and Oxbury scale on admission but not on follow up after 1 month. A significant correlation is found with changes in scores. Total and ionized calcium serum levels are not statistically correlated with severity of stroke.

Conclusion: A significant reduction of Mg, total and ionized calcium levels were found among ischemic stroke patients. The decrease of the Mg serum level during the acute phase of stroke seems to correspond with worse neurological status. The decrease of the total and ionized calcium serum levels during the acute phase of stroke is associated with worse outcome although this result is not significant.

Keywords:

Ischemic stroke, serum calcium levels, serum magnesium levels, clinical severity).

INTRODUCTION

INTRODUCTION

Stroke is a sudden and devastating illness. WHO defined stroke as 'rapidly developed clinical signs of focal disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than vascular origin **(Huang** *et al.,* **2010).**

There are approximately 152,000 strokes in the UK every year **(Townsend** *et al.,* **2012).** That is more than one every five minutes. There are approximately 1.1 million stroke survivors living in the UK. The costs of stroke are estimated to be between £3.7 billion and £8 billion. These estimated costs include direct health care costs, productivity loses due to mortality and morbidity, and informal care costs **(Stroke Association – January 2013).**

Cerebral Ischemia (stroke) is one of the foremost causes of high morbidity and mortality for both developed and developing countries. Cerebral ischemia impairs the normal neurological functions, which are triggered by a complex series of biochemical and molecular mechanism **(Aggarwal** *et al.,* **2010)**.

In developing country, the stroke patients usually arrive to hospital after 6 hours and then, thrombolytic therapy would not be used and if patients arrive sooner, these drugs are expensive and inaccessible. But neuroprotective agents such as magnesium are accessible, cheaper and more beneficial **avoiding a** potentially dangerous side effect associated with tissue plasminogen activator (tPA) use which is cerebral hemorrhage **(Mousavi** *et al.,* **2004).**

Metal ions are used in biology in many ways and are integrated parts of numerous enzymes and proteins. They function as cofactors in cellular and genetic signaling and, therefore, have important roles in biochemistry ranging from essential to toxic. Perturbed homeostasis of metal ions in stroke has been well recognized for several decades. In cellular and biochemical responses following stroke, metal ion imbalance in neurons is in the center of these cellular events, which is immediate results of stroke and, in turn, leads to the over activation of several deleterious enzymes and signaling process that impairs neuronal function or lead to cell death **(Huang** *et al.,* **2010).**

The most studies and well-characterized metal ion in stroke-associated ionic imbalance is calcium (Ca). The fluctuations of elements homeostasis can be the reason of numerous diseases. Magnesium ions as the essential constituents of ATP -Mg^{2+} complex play the key role in the metabolism of brain tissue **(Kurzepa** *et al.,* **2009).**

The only currently approved medical stroke therapy, tissue plasminogen activator (tPA), is a thrombolytic that targets the thrombus within the blood vessel. Neuro-protective agents, another approach to stroke treatment, have generated as much interest as thrombolytic therapies.

Greater understanding of the pathophysiology of neuronal damage in ischemic stroke has generated interest in neuro-protection as a management strategy. Neuro-protection is an increasingly recognized management strategy in ischemic stroke that promises to assist clinicians in reducing stroke mortality rates and improving the quality of life of survivors **(Onwuekwe & Adikaibe, 2012).**

Neuro-protection aims to rescue ischemic tissue and improve functional outcome by intervention on the ischemic cascade; and to reduce the intrinsic vulnerability of brain tissue to ischemia. Cellular neuro-protective approaches have focused mainly on blocking excitotoxicity, that is, neuron death triggered by the excitatory transmitter glutamate, and mediated by cytotoxic levels of calcium influx **(O'Collins** *et al.*, **2006).**

The ideal neuroprotective agent for stroke would be inexpensive, readily available, easy to administer and has no significant adverse side effects **(Saver & Starkman, 2011).**

Magnesium may act as a neuro-protective agent in brain ischemia via several mechanisms. It acts as an endogenous calcium channel antagonist. It inhibits the release of excitatory neurotransmitters such as glutamate. Magnesium antagonizes the NMDA receptor and has a direct vascular smooth muscle relaxant effect. The use of hyperacute magnesium therapy to provide neuro-protection is still under investigation **(Jaworski & Brambrink, 2011).**

The questionable relationship between serum calcium, magnesium levels and severity of ischemic cerebrovascular stroke deserves to be objectively studied. As establishing a role for these minerals in stroke may help in improving the sequlae of the medical condition through using them as prognosticators of ischemic stroke.