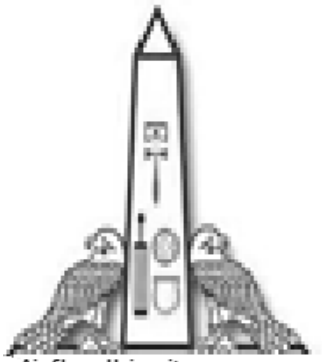

New trends in prevention and management of cerebral vasospasm after subarachnoid hemorrhage.

An Essay

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Contents

List of Abbreviations

1-NA :1-nitro - arginine

3D-CTA : Three dimensional computed tomography Angiography

Ach : Acetyl choline

ADH : Antidiuretic hormone

AEDs : Anti epileptic drugs

APACHE-II : Acute physiology and chronic health evaluation

aSAH : Aneurysmal subarachnoid hemorrhage

AVM : Artriovenous malformation

BBB : Blood brain barrier

BH4 : Tetra hydrobiopterin

BKca : large conduetance Kca

(Ca^{2+}) 4CAM: Ca^{2+} - calmodulin complex

CA : Cerebral autoregualtion

cAMP : Adenosine 3',5' – cyclic monophosphate

Cav : Voltage – operated calcium channels

CBF : cerebral blood flow

CCE : Capacitative calcium entry

CPP : Cerebral perfusion pressure

cGMP : Cyclic guanine monophsphate

COX : Cytochrome oxidase

COX-1 : Cyclooxygenase -1

CSD : Cortical spreading depression

CSF : Cerebro spinal fluid

CSWS : Cerebral salt – wasting syndrome

CT : Computerized tomography

CTA : Computed tomography angiography

Cx : Conncexin

CyP4A : cytochrome P450 4A
DAG : Diacylglycerol
DCI : Delayed cerebral ischemia
DIND : Delayed ischemic neurological deficit
DSA : Digital subtraction angiography
DVT : Deep venous thrombosis
DWI : Diffusion weighted imaging
EC : Endothelial cell
EDHF : Endothelium-derived hyperpolarizing factor
EET : Epoxyeicosatrienoic acid
ENaC : Epithelial sodium cation channel
eNOS : Endothelial NOS
EPO : Erythropoitin
ET-1R : Endothelin -1 receptor
ET-A : Endothelin receptor –A
ET-B : Endothelin receptor –B
FD : Forced dilation
FLAIR : Fluid-attenuated inversion recovery
GPCR : G-protein – coupled receptor
ICP : Intra cranial pressure
ICU : Intensive care unit
IEL : Internal elastic lamina
IKca : Intermediate - conductance calcium – activated potassium channels
iNOS : inducible NOS
IP3 : Inositol triphosphate
IP3R : Inositol triphosphate receptor
Kca : Calcium – activated potassium channels
MAP : Mean arterial blood pressure
MEGJ : Myoendothelial gap junction

MEJ : Myoendothelial junction
MgSO4 : Magnesium sulfate
MLC : Myosin light – chain
MLC20 : Myosin light - chain regulatory domino (20 kDa)
MLCK : Myosin light - chain kinase
MLCP : myosin light-chain phosphatase
MR : Myogenic reactivity
MRA : Magnetic resonance angiography
MRI : Magnetic resonance imaging
MT : Myogenic tone
nNOS : Neuronal NOS
NO : Nitric oxide
NOS : No synthase
NPRIs : Nicardipine prolonged – release implants
$Pbto_2$: Partial pressure of brain tissue oxygen
PGD_2 : Prostaglandin D_2
PGE_2 : Prostaglandin E_2
$PGF_2\alpha$: Prostaglandin $F_2\alpha$
PGH_2 : Prostaglandin H_2
PGI2 : Prostaglandin I2 (prostacyclin)
PKC : Protein kinase C
PLC : Phospholipase **C**
Po_2 : Partial pressure of oxygen
PRBCs : Packed red blood cells
RBCs : Red blood cells
RyR : Ryanodine receptor
SAH : Subarachnoid Hemorrhage
sER : Smooth endoplasmic reticulum
Ser 1177 : Serine - 1177
sGC : Soluble guanyl cyclase

SIADH	: Syndrome of in appropriate anti diuretic hormone secretion
SIRS	: Systemic inflammatory response syndrome
SK1	: Sphingosine kinase -1
SKca	: Small - conductance calcium - activated potassium channels
SMC	: Smooth muscle cell
SSS	: superior sagittal sinus
TCD	: Trans cranial Doppler
TF	: Tissue factor
Thr 495	: Thereonine - 495
Tripple-H	: Hemodilution, hypertension, hypervolemia
TRP	: Transient receptor potential
TXA_2	: Thromboxane A_2
VDCC	: Voltage dependent calcium channels
VSM	: Vascular smooth muscle

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AIM of THE ESSAY

The aim of this essay is to discuss clinical picture, recent trends and updated guidelines for prevention and management of cerebral vasospasm after subarachnoid hemorrhage.

INTRODUCTION

Subarachnoid hemorrhage (SAH) is a type of hemorrhagic stroke caused by bleeding in the subarachnoid space around the brain. The incidence of SAH in the UK is approximately 8 per 100,000 populations (**Linn et al., 1998**).Approximately 85% of non-traumatic SAH is a result of rupture of an intracranial aneurysm (IA), although it is not clear whether this percentage is the same over different age and sex categories. Subarachnoid hemorrhage may also be caused by head trauma, vascular malformations, hypertension or coagulation disorders, but aneurysms (aSAH) are the most common cause, accounting for approximately 85% of cases(**VanGijn et al.,2007**).Case-fatality of non-traumatic SAH was high: around 26% within one month and this increased with age. Severe cases may have died before undergoing imaging; in that case an aneurysm could not be proven. Less severe cases will probably have survived the 30 day period (**Risselada et al., 2011**).Headache is the most common complaint of patients who present with aneurysmal subarachnoid hemorrhage (SAH).physical exam findings may vary widely with one study demonstrating most patients with SAH arriving to the emergency center with a GCS of 15 (55%)(**Adkins Kristin 2012**).Complications such as neurogenic pulmonary edema or neurogenic stunned myocardium kill 25% of the treated patients (**Solenski et al., 1995**).Vasospasm is one of the main causes for prolonged neurologic deficit in patients who reach either neurosurgical or endovascular treatment for the aneurysm. 7% die of vasospasm and another 7% develop severe neurologic deficit (**Kassell et al., 1985**).Computed tomography (CT) of the cranium provides 98% sensitivity to detect SAH within 12 hours of hemorrhage. It is recommended that CT angiography scans (CTA) be routinely performed in order to also rule out the presence of an intracranial aneurysm in the same diagnostic procedure. Magnetic resonance imaging (MRI) reveals subarachnoid blood even after several days in gradient echo sequences (94%–100% sensitivity) and fluid attenuated inversion recovery sequences

(81–87% sensitivity)(**Schatlo et al., 2014**).Mechanical endovascular interventions such as balloon angioplasty or stenting are options for vasospasm of the great vessels; however, the distally located smaller vessels cannot be reached by the neuroradiologist and therefore need to be treated with pharmacologic agents(**Brisman et al., 2006**).Currently, the strongest evidence supports use of prophylactic oral nimodipine and initiation of triple-H therapy for patients in cerebral vasospasm. Other agents presented in this report include magnesium, statins, endothelin receptor antagonists, nitric oxide promoters, free radical scavengers, thromboxane inhibitors, thrombolysis, anti-inflammatory agents and neuroprotectants (**Adamczyk et al., 2012**).

Anatomical Considerations of Cerebral Circulation:

Vascular anatomy of the cortex:

Cortical vessels can be divided into short, inter-mediate and long vessels, depending on their cortical penetration depth. Duvernoy et al., (1981), have extended this classification to six groups. Group 1 vessels feed/drain cortical layers I and II, whereas group 2 vessels reach layer III. The most numerous vessels are the group 3 vessels that feed/drain cortical layer IV, as well as the lower layer III and layer V. Group 4 vessels reach layer VI and white matter. Group 5 arteries and veins vascularize the cortex as well as the adjacent white matter. Group 6 vessels are restricted to arteries that run through the cortex without branching to vascularize exclusively the white matter ***(Hirsch et al., 2012)***.

An interesting aspect is the ratio between descending cortical arteries and ascending cortical veins. Many authors have previously estimated this (AV) ratio to be 1.6 in favor of arteries ***(Weber et al., 2008)***.

The Arteries:

The brain is one of the most highly perfused organs in the body. It is therefore not surprising that the arterial blood supply to the human brain consists of two pairs of large arteries, the right and left *internal carotid* and the right and left *vertebral arteries*. The internal carotid arteries principally supply the cerebrum, whereas the two vertebral arteries join distally to form

the *basilar artery*. Branches of the vertebral and basilar arteries supply blood for the cerebellum and brain stem. Proximally, the basilar artery joins the two internal carotid arteries and other communicating arteries to form a complete anastomotic ring at the base of the brain known as the *circle of Willis*,which gives rise to three pairs of main arteries, the *anterior*, *middle* and *posterior cerebral arteries* which divide into progressively smaller arteries and arterioles that run along the surface until they penetrate the brain tissue to supply blood to the corresponding regions of the cerebral cortex***(Cipolla et al., 2009)***.

Cerebral Vascular Architecture:

The pial vessels are intracranial vessels on the surface of the brain within the pia–arachnoid (also known as the leptomeninges) or glia limitans (the outmost layer of the cortex comprised of astrocytic end-feet). Pial vessels are surrounded by cerebrospinal fluid (CSF) and give rise to smaller arteries that eventually penetrate into the brain tissue (Fig. 1) ***(Cipolla et al., 2009)***.