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Severity of Stroke: A Determinant of Quality of Life

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ABSTRACT

Stroke remains global health care problem and one of the leading causes of death and adult disability. It affects 17 million people per year globally and about 70% of all the stroke patients live with residual symptoms. HRQOL is a well recognize outcome after stroke. The aim of this review of the literature was to examine the current state of knowledge regarding the literature on extent of cerebral damage, mechanism and its impact on quality of life after stroke. Many factors have been shown to influence Health-Related Quality of Life (HRQOL) of stroke survivors. African Journal Online, PsychINFO, PubMed and Web of Science databases were searched using pertinent keywords. Search themes 'Stroke', 'Quality of life' and 'Cerebral Damage. Studies identified in this review were summarized. All studies identified in this reviewed showed decline in health related quality of life of stroke survivors to be proportionally related to the extent of cerebral damage as indicated by stroke severity.

INTRODUCTION

Stroke is the world's second-leading cause of mortality and a major cause of disability. The worldwide incidence of stroke was around 17 million persons per year as at 2010, with 33 million people living in stroke adjusted life. In addition, about 70% of all stroke survivors have residual symptoms. Stroke is a rapid development of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or more, or which leads to death with no apparent cause other than vascular origin. Health is a total state of physical, mental, and social well-being and not merely the absence of disease or infirmity. This statement underlines the recent shift in focusing toward Quality of Life (QoL) in health issues [1]. The term QoL defines how an individual perceive his status in life within the context of his culture and value systems in relation to their goals, expectations, standards and concerns. Closely related to QoL but more focused towards health is the term health-related quality of life (HRQOL), which indicates functioning and well-being of an individual in terms of physical, mental and social context of life impacted by disease, injury, treatment and policy. Stroke decreases or impairs health-related quality of life (HRQOL) of its survivors and many factors have been shown to determine and influence the HRQOL of stroke patients. Prominent among these factors is the extent of stroke severity which determines degree of neurologic impairment after stroke. Currently, focus is being shifted to finding effective strategies for rehabilitation and ensuring good quality of life (QoL) for the stroke

patients rather than to finding cure and prevention. The extent of cerebral damage indicates the severity of stroke which can be assessed clinically either subjectively by degree of neurologic impairment or objectively by neuroimaging using Magnetic Resonance Imaging (MRI) or computed tumourgraphy (CT) scan. There is increasing evidence that stroke severity is potential predictor of HRQOL outcome in stroke patients. This review discussed an overview of the literature on mechanism of cerebral damage after stroke, as well as current research findings on extent of cerebral damage impact on quality of life after stroke.

LITERATURE REVIEW

We searched the African Journal Online, PsychINFO, PubMed and Web of Science databases by using pertinent keywords. Search themes 'Stroke', 'Quality of life' and 'Cerebral Damage' were combined using the Boolean operator 'OR' and then combined using the Boolean 'AND' all types of studies were considered.

Mechanism of cerebral damage after stroke

Brain stroke results from either vessel occlusion (ischemic stroke) or cerebral blood-related neurotoxicity (haemorrhagic stroke). Thus, the mechanism of cerebral damage after stroke is relative to whether the type of stroke is ischaemic or haemorrhagic. Ischaemic stroke consists of five distinct pathophysiologic mechanism each of which has distinct time frame; these includes immediate (within minutes) peri-infarct depolarization and excitotoxicity, hours later by inflammation and oxidative stress, days later by apoptosis [2]. In addition to ischaemia related cascade of events of excitotoxicity, inflammation, oxidative stress and apoptosis, haemorrhagic stroke is associated with two additional unique pathophysiologic phases. The primary; acute phase which is the physical effect of haematoma (mass effect) from the mass accumulated blood, and the secondary; subacute phase termed as cytotoxicity from secondary metabolites of blood components.

Peri-infarct depolarization

Within seconds of abrupt ischaemic insult, neuronal cells in the centre of ischemic region termed as ischaemic prenumbra undergoes anoxic depolarization due to loss of ATP-dependent ionic pump homeostasis, and they never depolarize. This necrotic core of ischaemic prenumbra is surrounded by a region of less severely affected tissue termed as ischaemic penumbra, which remained functionally silent by reduced blood flow but is metabolically active and therefore can repolarise as a result of further energy consumption. This repetitive depolarization and repolarisation of of ischaemic penumbra is called peri-infarct depolarization and the critical period of time during which this volume of infarcted brain tissue is prone to ischaemic damage is referred to as window of opportunity since the neurological deficits created by ischemia can partly or completely be reversed by reperfusing the ischemic yet viable neuronal cells within a critical time period of several hours. Failure in the functioning of ATP dependent sodium potassium pump in the ischaemic prenumbra that results in massive uncontrolled anoxic depolarization results in opening of voltage-sensitive calcium channels, mitochondrial dysfunction, an abnormally extracellular buildup of excitatory amino acids, and long term risen in intracellular calcium, thus triggering a series of secondary biochemical changes that will subsequently cause neuronal demise of prenumbral cells. Neuronal cells of the ischaemic penumbra may undergo apoptosis only after several hours or days, and, therefore are potentially recoverable for some time after the onset of cerebral ischaemia.

Excitotoxicity

There is also excessive release of glutamate neurotransmitter and other related excitatory amino acids such as aspartate in response to cerebral ischaemia, and glutamate hyperexcitation of glutamate N-methyl-D-aspatate (NMDA) receptor, which is arguably the most calcium-permeable ionotropic glutamate receptor; results in massive influx of calcium ion (Ca++) into hypoxic neuron. Calcium ion triggers series of cascading events that ultimately lead to neuronal demise through proteolytic enzymes activation, pathogenic genes activation, lipid peroxidation and free radical generation. For this; glutamate and other excitatory amino acids are collectively called excitotoxins, and their associated neuronal damage, excitotoxicity.

Calcium activates key number of destructive intracellular proteolytic enzymes such as proteases, kinases, lipases, and endonuclease that not only allows release of cytokines and other mediators that are lethal to cellular integrity but also orchestrated triggering of intrinsic apoptotic pathway of neuronal death. Specifically, calcium activation of enzyme phospholipases result in hydrolysis of membrane bound glycerophospholipids to free fatty acids, thus facilitating free radical peroxidation of other membrane bound lipids. Calcium activation of enzyme proteases

results in lysis of structural proteins, so also activation of enzyme nitric oxide synthase that initiates free radical mechanism.

Inflammation

Prior excitotoxicity activates glial cells, majorly microglia and other residential glial cells such as astrocytes which when these glial cells becomes activated reacts by secreting cytokines, chemokines (chomotaxic cytokines), and matrix metallopeoteases (MMPs). Activation of microglia cells constitutes the first key inflammatory response in acute stroke, and in such condition microglia response becomes inappropriately more reactive and exaggerated to produce plethora of inflammatory mediators that triggers apoptosis and exaggerate neuronal damage. Microglia when activated transformed into phagocytes that release numerous substances many of which are cytotoxic and/or cytoprotective [3]. While cyto-protective substances include neuro-trophic molecules such as brain-derived neurotrophic factor (BDNF), insulin-like growth factor I (IGF-I), several other growth factors, and anti-inflammatory factors, cytotoxic substances include pro-inflammatory cytokines such as tumour necrosis alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and other potentially cytotoxic molecules. Pro-inflammatory TNF-α being one of the most key important early initiators of neuro-inflammation interacts with two receptors TNFR1 and TNFR2 to induce extrinsic apoptotic cellular death pathway via Fas associated death domain (FADD) through TNFR1 and inflammation via nuclear factor kappa-light- chain enhancer of activated B cells (NFκB) through TNFR2 cognate receptor. NFκB is a major regulatory transcription factor with a central role in inducing genes involved in inflammation.

Blood-brain barrier (BBB) which confers brain with protection against systemic toxins is disrupted by enzyme matrix metalloproteinases (MMPs) with two major metalloproteinase; MMP-2 (gelatinase A) and MMP-9 (gelatinase B) being implicated in cerebral ischaemia. MMP-2 that is normally expressed at low levels becomes increased during cerebral ischaemia to cleaves and activates MMP-9, which degrades components of the basement membrane in the vascular wall leading to blood-brain barrier disruption and increased BBB permeability, thus allowing further infiltration of inflammatory mediators and other potential toxins.

DISCUSSION

Oxidative stress

Oxidative stress denotes the imbalance between enhanced generation of oxidants (free radicals) and low tissue content of antioxidants. Long term cerebral hypoperfusion produces abnormal levels of oxidants, majorly Reactive Oxygen Species (ROS) and/or Reactive Nitrogen Species (RNS) through various injury mechanisms, such as mitochondrial inhibition, calcium ions overload, reperfusion injury, and inflammation. Under normal cellular conditions, mitochondrial respiratory chain generate NADP as by-product of ATP generation by oxidative phosphorylation, this NADP through NADPH oxidase activity generate superoxide (O_2) which is further converted to hydrogen peroxide (H_2O_2) either simultaneously or through enzymatic catalysis of Superoxide Dismutase (SOD) by combining with hydrogen ion (H^+). This H_2O_2 when leaves the mitochondria into the cytosol can form the hydroxyl radicals (-OH) radical either in the presence of transition metal ions (Fenton reaction) or in the presence of superoxide radical [4]. During cerebral ischaemia, there is mitochondrial inhibition of oxidative phosphorylation due to the lack of sufficient oxygen, and the oxygen depleted cell switch to glycolytic pathway of ATP production that results in lactate acid and hydrogen ion (H^+) build-up in the mitochondria and the subsequent reversal of the H^+ uniporter on the mitochondrial membrane result in excess cytosolic H^+ accumulation and acidosis. Acidosis is directly related with oxidative stress by providing excessive H^+ for the successive progression in the generation of H_2O_2 and the final ·OH through aforementioned reactions, with this effect more pronounced in neurons due to inherently low anti-oxidant defense. In addition, the potent protein and lipid oxidant peroxynitrite (OONO_) of RNS is favourably formed in the oxygen depleted cell by the reaction of nitric oxide (NO) and superoxide (O_2), thereby also contributing to oxidative stress.

Calcium overloads, as a result of glutamate mediated NMDA receptor excitotoxicity, contributes in neuronal oxidative stress at cytosolic and mitochondrial level. At cytosolic level, excessive calcium ion activation of key intracellular enzymes such as neuronal nitric oxide synthase (nNOS) *via* $Ca2^+$ binds calmodulin, nNOS catalyses intracellular reaction that lead to the formation of nitric oxide (NO) free radical from L-arginine. At the mitochondrial level, excessive calcium ion influx into mitochondrial matrix leads to the inner mitochondrial accumulation of significant amount of $Ca2^+$ *via* Mitochondrial Calcium Uniporter (MCU) which propagates disruption of normal bio-energetic, mitochondrial ROS, and membrane permeability.

Apoptosis

Apoptosis denotes physiologic mechanism of cell death which occurs under various physiological and pathological conditions initiated and triggered by either extrinsic or intrinsic pathways. In the nervous system, the claim that ischemic insults cause neurons to undergo necrosis is strengthened by the involvement of excitotoxicity in ischaemic neuronal death; growing evidence support that cerebral ischemia may additionally induce programmed apoptotic neuronal death in a fashion where apoptosis becomes dysregulated. While the neurons within the core infarct die by immediate necrosis due to insufficient ATP. Penumbra die by ATP requiring process of apoptosis, supporting the established evidence that cellular demise from cerebral ischaemic damage occurs through the dual pathways of necrosis and apoptosis.

Multiple pre-existing pathophysiologic mechanisms that can induce apoptosis after cerebral ischaemia includes oxidative stress, glutamate excitotoxicity, calcium influx and pro-inflammatory cytokines. There are two distinct pathways that can initiate the caspase-dependent apoptosis: The intrinsic (or mitochondrial) pathway and the extrinsic (or death receptor) pathway, and these two pathways converge on the same terminal, or execution pathway in which caspase leads to the degradation of cellular components and consequently cell death.

Mass Effect

The injury mechanism of ischemic and haemorrhagic stroke shares similar damaging processes, such as ecitotoxicity, inflammation, oxidative stress, and apoptosis. However, unlike ischaemic stroke, haemorrhagic stroke mechanism of damage begins with additional process of mass effect from the mass accumulated blood, and cytotoxicity from the secondary metabolites of blood components. The initial bleed from the cerebral haemorrhage causes immediate physical disruption of brain cellular architecture and increase in local pressure which can compress brain regions, potentially infarcting blood flow and leading to brain herniation. The subsequent expansion of haematoma causes mass effect of haematoma growth leading to further rise in intracranial pressure, brain herniation, and impacted blood flow that is associated with neurologic deterioration and worsened clinical outcomes. Depending upon the dynamic of haematoma expansion (growth), this primary damage as a result of mechanically associated mass effect occurs within minutes to hours from the onset of bleeding.

Cytoxicity

Secondary injury after cerebral haemorrhage termed as cytotoxicity occurs by a series of events initiated by the primary injury mechanism (mass effect), by the tissue response to the haematoma (such as inflammation) and from the multiple blood components released from haematoma. The extravasated blood components released from haematoma being implicated to cumulatively imposed cellular toxicity includes; the most commonly which are erythrocytes and plasma proteins, and the Damage-Associated Molecular Patterns (DAMPs) which are nucleic acids, extracellular matrix components, proteins, lipid mediators, Adenosine Triphosphate (ATP) and uric acid released from necrotic tissues [5]. At the early stage of cytoxicity, the extravasated blood plasma components such as coagulation factors complement components, and immunoglobulins are known to be the main contributing factor of cytotoxicity cellular damage. Subsequently, erythrocytes lysis leads to release of its major intracellular component Haemoglobin (Hb), which when metabolise *via* haemoglobin metabolic pathway release degradation products; heme and iron (Fe). Both Hb and its degradation products are potent cytotoxic chemicals capable of causing cellular demise of neuronal brain cells through mechanism of free radical generation that substantially increase oxidative stress and consequent DNA damage.

Studies on the extent of cerebral damage and its impact on quality of life

Various studies that indicate the extent of cerebral damage and impact on quality of life after stroke are represented (Table 1).

Table 1. Extent of cerebral damage impact on quality of life after stroke.

Outcome Measure Used to Assess Extent of Cerebral Damage	Findings
Questionnaire that contains stroke levity scale classified stroke severity as mild, moderate, and severe.	Stroke severity was a very important determinant of HRQOL among recruited stroke survivors, as it predominantly affected all major domains of HRQOL. Mild stroke is associated with better improvement of HRQOL.
National Institutes of Health Stroke Scale	NIHSS score that predict stroke severity was found to be

(NIHSS) assessment tool that provides a quantitative measure of stroke-related neurological deficit.	robust factor in determining strength and overall HRQOL of patients with stroke, especially the physical domains of HRQOL.
National Institutes of Health Stroke Scale (NIHSS) as measure of impairment score.	Higher NIHSS score among post-stroke survivals was found to be independent predictor of impaired QoL.
The stroke levity scale (SLS) that assess stroke severity.	Stroke levity has significant impact on HRQOL in stroke survivors.
Stroke severity was measured using National Institute of Health Stroke Scale (NIHSS), stroke levity scale (SLS) and modified Rankin scale.	All physical domains of HRQOL were significantly correlated to all measures of stroke severity. Thus, stroke severity was found to have significant impact on the physical sphere of HRQOL.
The National Institute of Health Stroke Scale (NIHSS) was administered at ictus to assess stroke severity.	Stroke severity along with other co-morbidity was found to be a significant determinant of poor QoL and death among stroke survivors.
Stroke severity was indicated by level of consciousness at stroke onset, and was assessed using Glasgow Coma Scale (GCS).	Severely impaired QoL patterns were found to be related to stroke severity.
Stroke severity assessment tool assessed using National Institute of Health Stroke Scale (NIHSS).	The initial NIHSS score was found to be an independent factor that predicts HRQOL at two years post-stroke in both deceased and surviving post stroke patients.
Severity of stroke measured using National Institute of Health Stroke Scale (NIHSS).	Stroke severity has significant impacts on the physical and mental domains of HRQOL.
National Institute of Health Stroke Scale (NIHSS) at baseline was used to assess severity.	Scores of NIHSS at baseline was independent predictor of poor HRQOL at day 90 for recruited subjects with either a transient ischaemic attack (TIA) or minor stroke largely attributed to recurrence of stroke.
Baseline National Institutes of Health Stroke Scale (NIHSS) score was used as measure of stroke severity.	Higher baseline NIHSS scores was found to be an independent predictor of poor HRQOL.
Stroke severity was assessed using baseline Scandinavian Stroke Scale (SSS) as prognostic factor.	Very low health-related quality of life is related to poor baseline Scandinavian Stroke Scale score.
Initial National Institutes of Health Stroke Scale (NIHSS) was used to determine baseline severity of stroke.	Overall QoL assessed using Stroke Specific Quality of Life Scale (SS-QoL) was found to be not influenced by stroke severity in ischemic stroke patients undergoing intra-arterial therapy.
Severity indicated by the presence of an aneurysm, worse clinical condition at admission, and more blood on the computed tumourgraphy (CT) scan.	Three domains out of five dimensions EQ-5D quality of life measure, namely mobility, self-care, and usual activities were found to worse in patients with more severe subarachnoid hemorrhage (SAH) stroke.
Glasgow Coma Scale (GCS) was used as clinical marker for severity.	There was significant variation in survival and HRQOL among stroke patients that is independent to stroke severity.
National Institutes of Health Stroke Scale (NIHSS) score on admission was used to determine baseline severity of stroke.	A high NIHSS score on admission (indicating more severe stroke) was found to a significant independent predictor of impaired quality of life (QoL) among stroke survivors.
Stroke severity evaluated using NIHSS score from neurologic examination.	Quality of life index declined more among stroke patients and was found to be associated stroke severity.

CONCLUSION

All the identified studies have shown that stroke survivors experienced a decline in quality of life (QoL) domains (physical, functional, psychological, and social health) as a result of stroke. Accordingly, the QoL in these studies were evaluated by means of either structured interviews or written questionnaires. Moreover, with the exception of all the reviewed studies have identified decline in health related quality of life of stroke survivors to be proportionally related to the extent of cerebral damage indicated by stroke severity. The negative findings in the aforementioned three studies could be attributed to the specific therapy received by the subjects involved as pointed. Only one study used objective outcome measure (MRI) to assess extent of the cerebral damage.

RECOMMENDATION

There is need for more studies investigating this phenomenon using objective outcome measures.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

SIA and RYA: Electronic search of literature, draft of manuscript; MM and SIA Data extraction and Articles screening, Mechanism of cerebral damage after stroke. All the authors read and approved the final version of the manuscript.

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