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by Robert Sinurat

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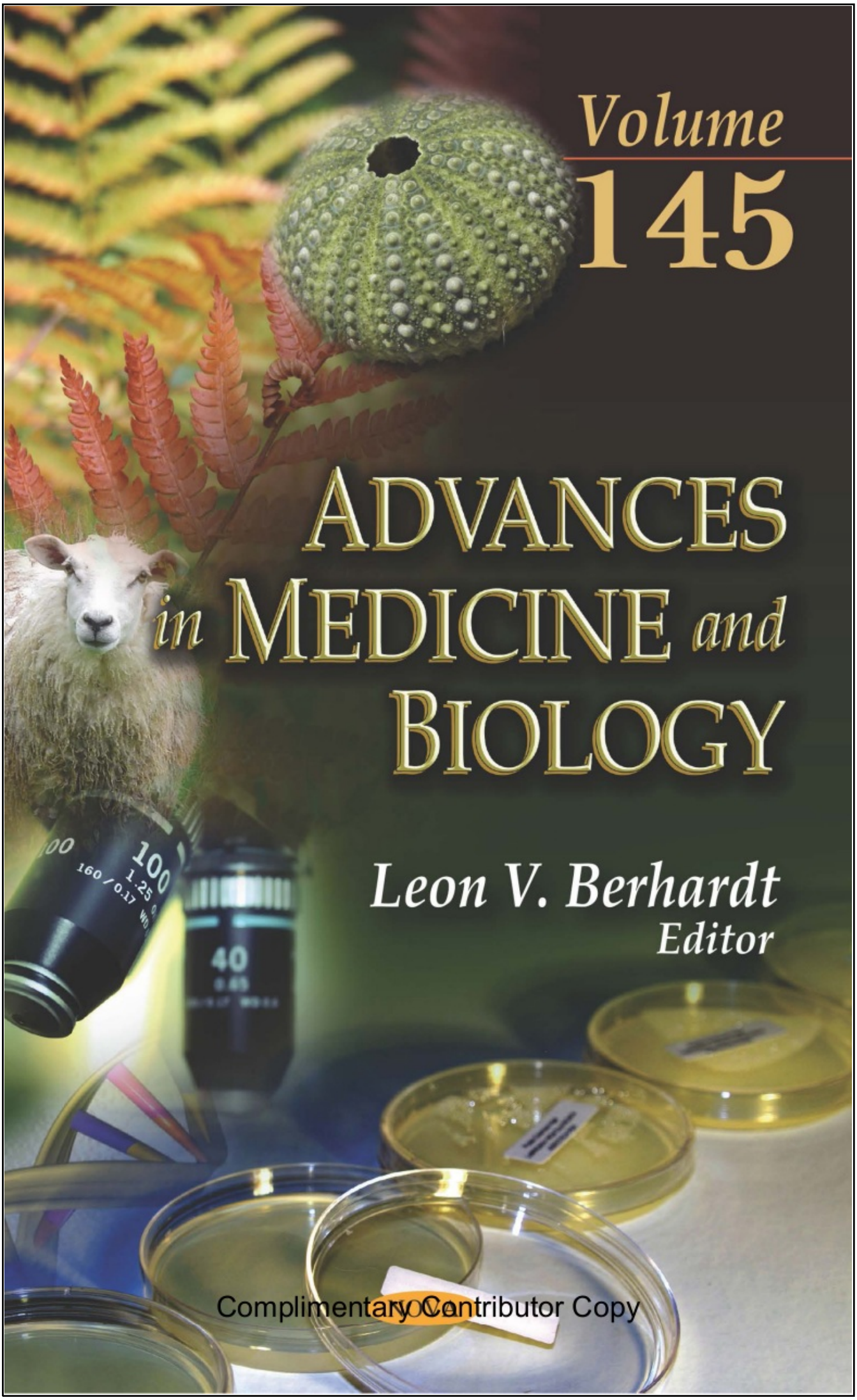
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Chapter 5

ANTI INFLAMATORY MECHANISMS AND EFFECT OF CELECOXIB FOR ENDONEURAL STEM CELLS SURVIVAL IN SPONTANEUS INTRACEREBRAL HEMORRHAGE

Robert Sinurat*
Surgery Department, Universitas Kristen Indonesia,
Jakarta, Indonesia

ABSTRACT

Spontaneous intracerebral hemorrhage (SICH) is part of a hemorrhage stroke type with high morbidity and mortality. Neuron cells die in SICH due to primary injury caused by compression and damage directly by blood clots, and secondary injury by the neuroinflamation process. When the neuroinflamation process was very excessive, normal or dying neuron cells can die too. Besides the dying cells process, there was also migration of

* Cooresponding Author's Email: robertsinurat@yahoo.com.

endoneural stem cells from their niches in the hippocampus and subventricle zones to the lesion area which was triggered by differentiation quantity of stromal derived factor-1 (SDF-1) between niches and the lesion area. Only small amounts of these neural stem cells can be differentiated to adult neuron cells, while the others could not survive due to the impact of neuroinflammation. Celecoxib as selective cox 2 inhibitor can decrease the neuroinflammation itself by preventing the production of prostaglandin E2 (PGE2) from arachidonic acid, and decreased fas ligand (FasL) expression which is important for activation of caspase 8 and 3 as extrinsic pathway apoptosis. In this article, the author showed algorithm of cell dead mechanism in SICH and how the impact of intraperitoneal celecoxib treatment can increase the survival of neural stem cells.

Keywords: neuroinflammation, apoptosis, cox, survival

INTRODUCTION

Stroke is a neurologic disease resulting from brain vessels occlusion (ischemic stroke) or ruptures (hemorrhage stroke). Hemorrhage stroke is divided into intracerebral and subarachnoid hemorrhage. Intracerebral hemorrhagic is due to ruptures of small penetrating arteries, secondary to hypertensive changes or other vascular abnormalities. The highest risk factor was hypertension. Spontaneous intracerebral hemorrage (SICH) incidence was not changed in the last 30 years and was the highest in Asia. The incidence rate per 100, 000 person-years was 51,8 in Asia, 24,2 in whites, 22,9 in blacks, and 19,6 in Hispanic [1, 2].

SICH fatality rates were 25 - 30% in developed countries and 30-48% in the non developed countries [3]. In one month, a case fatality rate of SICH is approximately 40%, and increased about 54% at 1 year. Only 12% to 39% of patients can have long-term functional independence [2].

Every effort must be carried out to decrease those fatality rates and increasing outcomes of SICH patients. The author reviewed pathophysiology of SICH and proposes a new algorithm of cell dead mechanism in SICH and the impact of intraperitoneal celecoxib treatment to increase the populations of neural stem cells in the lesion zone.

DIAGNOSIS AND UPDATE MANAGEMENT OF SICH

All patients with severe headache suddenly, vomiting and decreased level of consciousness progressively must be first managed as SICH patients. After stroke attacks, patients can get worse for a few hours with a decrease of Glasgow Coma Scale (GCS) because of hypoxia or haematoma expansion. To prevent hypoxia, stabilisation of the airway with breathing and circulation (ABCs) management is essential for preventing secondary brain injury. Endotracheal tube insertion is crucial for airway protection of patients with GCS 8 or lower, and another patient with significant respiratory distress. When ABCs management is completed, a computerized tommograhphy (CT) scan is performed to show intracerebral haematoma location and extension, volume, mass effect and hydrocephalus [4, 5]. A peripheral blood test was needed to rule out deficiency of coagulation factors and should accept replacement treatment immediately [6]. Indications of surgery for hematoma evacuation were dependent on haematoma volume, location and mass effect of haematoma. American Heart and Stroke Association had guidelines up to date in 2015 for the management of SICH including surgery indications and management of hypertension. The guidelines recommended that patients with systolic blood pressure (SBP) between 150mm Hg and 200mmHg were safely decreased to 140mm Hg. It was effective for improving functional outcome [6, 7]. The blood pressure of patients with SBP >220mm Hg should be reduced with continuous antihypertensive drug intravenous infusion and frequent monitoring. Any clinical deterioration in association with aggressive reduction of blood pressure should be reviewed for the blood pressure target. Nicardipine titration is one of the intravenous calcium channel blocker's choice for blood pressure reduction, and oral antihypertensive agents can be initiated as soon as possible. Angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB), calcium channel blocker (CCB) and a thiazide-like diuretic at maximal are recommended for resistant hypertension [6, 8].

Craniotomy for clot removal was indicated for fossa posterior haematoma with > 3cm in diameter, especially when brain stem compression

or hydrocephalus exists. Procedures were approved for supratentorial haematoma while any evidence of deterioration due to haematoma volume or edema expansion, and minimal invasive surgery plus recombinant tissue-type plasminogen activator for ICH evacuation trial II (MISTIE II) suggested a better outcome. The MISTIE III trial is on progress [6, 9]. Severe intraventricular extensions of hemorrhage with or without hydrocephalus needed placement of external ventricular drainage [4, 10]. Mannitol 0,5 – 1 gram intra vein bolus was indicated for elevated intracranial pressure with mass effect and herniation [4].

PROGNOSTICS FACTORS

Many factors are involved in the outcome of SICH. Some poor porgnostic factors were low grade of GCS, haematoma volume > $30Cm^3$, hemorrhage intraventricular extension, and old age > 80 years old [11]. Fever and high vital signs also increased mortality and morbidity in SICH patients [12, 13].

NEUROINFLAMMATION AND NEURON CELL DEATH

When brain vessels were ruptured, the hematoma compressed the neurons and glia immediately, and micro vascular ischemic was involved. Then glutamate was released. Calcium influx into cells and mitochondria failed. Sodium was accumulated and cell became edema and necrotic. It was primary injury mechanisms for spontaneous intracerebral haematoma. The primary injury is always followed by secondary injury as a neuroin-flammation response to blood products as hemoglobin, thrombin, ferrous, haemin, ferrous, and halotransferin. Microglia was activated by those to produce reactive oxygen species (ROS), matrix metalloproitenase (MMP), Cyclooxygenase 2 (Cox2), Prostaglandin (PG), heme oksigenase-1 (HO-1),

complement factor, tumor necrotizing factor-α (TNFα), and interleukin 1β (IL-1β) [7, 14].

ROS, TNFα, and IL-1β will increase Aquaporin 4 (AQ4) expression and blood brain barrier (BBB) damage. BBB permeability was increased. Vasogenic edema showed up, and macrophage recruitment like polymorphonuclear (PMN), especially neutrophil, was engaged to destruct the brain [7, 14, 15]. Meanwhile, caspase enzyme will be activated by complement C3a, C5a, TNF-α, and Interleukin 1β to induce apoptosis process of neuron and glia [7, 16]. Heme as eritrosit derivative from hematoma was degraded into bilirubin and bilirubin oxidation products (BOXes).

They also activate microglia and astrocytes to release cytokine which contributes to neuron and glial detrimental effects [17].

Cyclooxygenase (Cox) enzyme was involved in neuroinflammation, especially cox-2. Cyclooxygenase 1 (Cox-1) and cyclooxygenase 2 (Cox-2) can changes arachidonic acid and become prostaglandin PGG2 and PGH2 before they have changed into one of these five prostanoids. The prostanoids were prostacycline (PG12), thromboxan (TxA2), prostaglandin D2 (PGD2), prostaglandin F2 (PGF2), or prostaglandin E2. Prostaglandin E2 became involved in the initiation and propagation of neuroinflammation. PGE-2 was produced by prostaglandin E synthases (PGES).

There were 3 types of PGES that change PGH2 into PGE2, microsomal PGES-1 (mPGES-1), microsomal PGES-2 (mPGES-2) and cytosolic PGES (cPGES). Cytosolic PGES were involved in Cox1 pathway, and mPGES-1 in Cox-2 pathway, while microsomal mPGES-2 related to golgi membrane were released into plasma. Four types of PGE2 receptors consisting of EP1, EP2, EP3, dan EP4. EP1 activation increased intra cell calcium 2+ level, while EP3 decreased cyclic adenosine monophosphate (cAMP) [18, 19]. Cox-2 will induce Fas Ligand (FasL) expression, which is important for activation of caspase 8 and 3 as an extrinsic pathway apoptosis [20]. Cox-2 also overactivates N methyl D- aspartate (NMDA) receptors causing excessive influx of Ca^{2+} and leads to excitotoxicity [21].

CELECOXIB AS COX-2 INHIBITOR FOR NEUROPROTECTION

Celecoxib is a selective cox-2 non steroidal anti-inflamatory drug (NSAID). Many authors reported impact of celecoxib for protection of neuron and glia. Combination of celecoxib and memantine were reported to decrease hematoma volume, brain edema and induce neurology recovery [22]. Celecoxib can inhibit cox2 and become a neuroprotector by decreasing synthesis of prostanoids, free radicals and protected neuron from excitoxicity from NMDA receptors in ischemic stroke [21, 23]. One researched treatment by injected celecoxib and sodium chloride intraperitoneally to intracerebral rats model resulted in a decreasing of brain edema and perihematoma cell death [24]. Efficacy of administration of celecoxib 400mg twice a day can reduce the perihematomal edema in the acute stage of SICH patients [25].

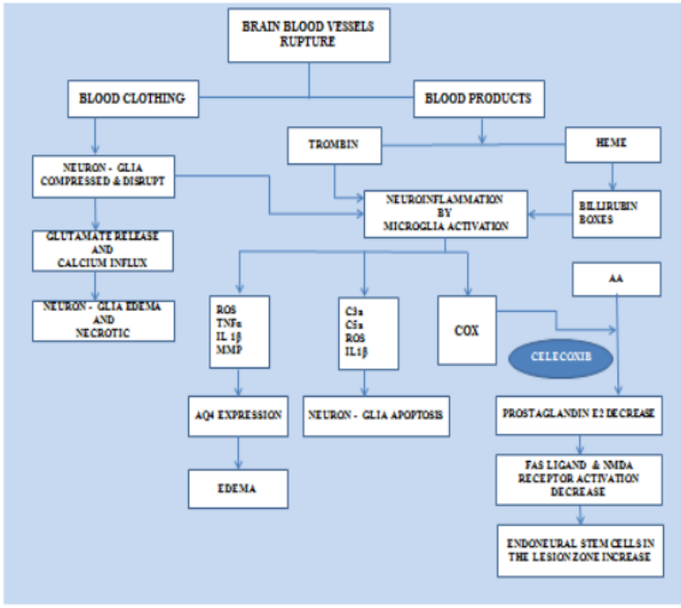

Figure 1. Cell death mechanisms of SICH, and cox inhibition by celecoxib to increase neural stem cells in the lesion zone.

Besides neuroinflammation processes, endoneural stem cells were migrated from the niche (hippocampus and subventricles zone) into the lesion zone around the haematoma as neurogenesis [26]. But most of them (80%) died because of inflammation [27]. The author had treated SICH rat models with celecoxib injection intraperitoneally 20mg/kg body weight. The results conclude that the population of endoneural stem cells in the lesion zone was higher compared to controls. When celecoxib reduced the cox-2 activation, FasL expression and NMDA receptor activation were reduced. Thus excessive neuroinflammation was inhibited, and more neural stem cells can survive [28].

NEW ALGORITHM OF SPONTANEOUS INTRACEREBRAL HAEMATOMA

With all of the previous knowledge and many author's and researcher's results, the author proposes an algorithm of the cell death mechanism in SICH and impact of intraperitoneal celecoxib treatment to increase the survival of neural stem cells in the lesion zone (Figure 1).

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BIOGRAPHICAL SKETCH

Robert Sinurat

Affiliation: Surgery Department Universitas Kristen Indonesia, Jakarta, Indonesia.

Education: Neurosurgeon, PhD

Business Address: Jalan Mayjen Sutoyo, Cawang, Jakarta Timur, Indonesia, 13650.

Research and Professional Experience: PhD program

Publications from the Last 3 Years:

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