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Review Article

The Role of Nimodipine as a Neurorestorative Drug in Preventing Cerebral Vasospasm Related to Subarachnoid Aneurysmal Hemorrhage

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ABSTRACT

Cerebral vasospasm (CV) is dreaded complications of aneurysmal subarachnoid hemorrhage (aSAH). The figure reached 70% of patients with aSAH. This CV occurs between the 3rd days to the 21st aSAH. 30% of patients with CV will have cerebral ischemia, an emergency condition that can increase mortality and morbidity. Research articles obtained from PubMed databases are used based on the suitability and relevance of the purpose of this article. We searched all journals that related to the keywords about nimodipine in the CV. The investigation result reported that CV is a life-threatening condition but can be prevented by the administration of nimodipine. Nimodipine is mainly used for the management of aSAH and has a neurorestorative effect. Its role in vasodilatation can repair damaged neurons. In this review, we will discuss nimodipine use in aSAH management in terms of their mechanism of action and safety as a neurorestorative drug.

Key words: Cerebral ischemia, cerebral vasospasm, neurorestorative, nimodipine.

1. INTRODUCTION

Cerebral vasospasm (CV) is constriction of the large vessel arteries in the cerebral [1, 2]. A CV is one of the dreaded complications of aneurysmal subarachnoid hemorrhage (aSAH) [3, 24]. The depiction of occurring constriction in the post-aSAH cerebral artery can be seen from the angiographic examination. A CV often occurs within 3-5 days after the rupture of aneurysms, with vasoconstriction peak occurring between 5 to 14 days, and spontaneously changes after 21 days of post-aSAH [4.13]. CV involves

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various cascades that affect blood vessels and neurons, such as increased intracellular calcium, presence of vasoactive components, and injury on blood vessel walls [1,4, 26].

The reported incidents of aSAH in the United States is between 10 and 15 people per 100,000 populations. The lowest incidence was in China (2 cases per 100,000) and South & Central America (4 cases per 100,000), while the highest incidence was reported in Finland and Japan (19-23 cases per 100,000) [5]. The incidents of aSAH are counted for less than 5% of stroke total incidents. Despite having a low incidence, the aSAH output has terrible impacts. Its mortality reached 45%, while its morbidity to patients survived from the aSAH was still significant [6].

The prevalence rate of patients with aSAH reaches 70%, and as many as 30% of patients with CV will suffer from cerebral ischemia [1, 25]. Cerebral ischemia is included in emergency conditions since it increases post- aSAH mortality and morbidity. This morbidity might be depression (45%), apathy (42%), rejection reactions (21%), catastrophic reactions (17%), sleep disturbances (37-45%), anxiety (54%) and decreased memory function (60 %) [7].

The recommended management of therapy for aSAH patients based on the Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage AHA/ASA 2012 and the European Stroke Organization Guidelines for the Management of Intracranial Aneurysms and Subarachnoid Hemorrhage 2013 in addressing and preventing the complications of vasospasm includes nimodipine, crystalloid fluid, arterial hypertension based therapy, neurovascular intervention, hydrocortisone and fludrocortisone [13,16,19]. Nimodipine is primarily used in aSAH management through its vasodilation mechanism and is thought to have neuroprotective effects [8, 9]. Its neuroprotective effect has been shown in several clinical trials and animal experiments [17,31-34]. This article describes nimodipine therapy based on its acting mechanism and its safety as a neurorestorative drug. Nimodipine is used as a preventive approach of vasospasm based on increasing intracellular calcium and its effect on repairing damaged neurons. This review article is expected to contribute to science, particularly regarding the management of vasospasm prevention.

2. DISCUSSION

This article obtained from PubMed databases is used based on the suitability and relevance of the purpose of this article. We searched all journals that related to the keywords about nimodipine in the CV. The investigation result reported that CV is a life-threatening condition but can be prevented by the administration of nimodipine. The cause of vasospasm is complicated and still hard to understand. Some of the involving factors in vasospasm occurrence include endothelial dysfunction, loss of autoregulation, and hypovolemic function, which causing decreased cerebral blood flow [2]. Subarachnoid hemorrhage (SH) might be caused by rupture of aneurysms, arteriovenous malformations, perimesencephalic and idiopathic, cerebral hemodynamic disorders, vascular disease, head trauma, infection, chemicals (drug abuse), cerebral neoplasia, and cerebral surgery [10]. The rupture of cerebral aneurysms is the most significant cause of SH [11, 27, 28]. Vasospasm involves various cascades affecting blood vessels and neurons, such as increased intracellular calcium and the presence of vasoactive components and injury to blood vessel walls. Activation of the cascade by factors released into the subarachnoid space will induce arterial vasoconstriction, endothelial damage, and smooth muscle cell contraction. Other spasmogenic substances in the form of lysis of blood clots in the subarachnoid space will spur changes in the blood vessel response and the onset of inflammatory and immunologic reactions that occur in blood vessel walls, which further lead to cerebral ischemia [1, 4, 35].

Calcium is known to play a significant role in the occurrence of vasospasm, in addition to other elements such as inflammatory mediators, blood rheology, or microcirculation disorders. Products produced by red blood cells (bilirubin) and endothelial (endothelin- 1, free radicals) are considered as mediators of vasospasm triggers [2]. In the acute phase, 3 to 5 days post- aSAH, oxy-hemoglobin, which is a red blood cell product, can inhibit nitric oxide (physiological vasodilator) and stimulates leucocytes to produce endothelin-1 (physiologic vasoconstrictor) so that it can cause potent vasoconstriction. In addition, the impact of oxyhemoglobin in subarachnoid space leads to local and a systemic inflammatory reaction followed by platelet activation and coagulation and leads to decreased activity of the potassium canal, which makes membrane depolarization and vasoconstriction [2, 4, 8].

The next process is the release of species of reactive oxygen and Fe that cause damage to the walls of blood vessels. Production of post- aSAH vasoactive components includes serotonin, norepinephrine, and angiotensin II which is also a potent vasoconstrictor post- aSAH, the calcium that enters smooth muscle cells and neurons rapidly through N-Methyl-D-Aspartate (NMDA) receptors and in general activation of voltage-gated L-type calcium channels, followed by increased glutamate further activates NMDA receptors again. Glutamate and activation of NMDA receptors will lead to an increase in intracellular calcium concentration the bond between calcium and calmodulin, so will activate myosin light chain kinase (MLCK). This leads to myosin phosphorylation and interactions between myosin-actin, resulting in smooth muscle cell contraction and constriction of blood vessels [4, 23].

Based on the pathophysiology, the role of increased intracellular calcium underlying the occurrence of vasospasm, so that can be used nimodipine as inhibition of intracellular calcium entry and further used as prevention of vasospasm in patients with aSAH. Nimodipine is the 1,4-dihydropyridine L type voltage-gated calcium channel. It

binds to the α1 subunit of the L-type calcium channel and is rapidly and widely distributed in cerebral tissue. It is lipophilic, quickly penetrates the blood-brain barrier and achieves comparatively high concentrations in cerebrospinal fluid. Nimodipine has a dilatation effect of the blood vessels of the brain that can improve cerebral blood flow [12, 29, 30].

Nimodipine is a class I medication, Level of Evidence A for all patients with aSAH [13]. Nimodipine is approved for indications of subarachnoid hemorrhage in the states of Europe and America [11]. Nimodipine has a neurorestorative function, which is able to save the damaged neuron cells due to cerebral ischemia caused by CV. It is able to improve neurologic functional outcomes when administered as prophylaxis when the initial patient is admitted to the hospital [4, 22]. The role of nimodipine is based on the effects of vasodilatation and neuroprotective mechanisms on the brain in general that increase fibrinolytic activity and inhibit the occurrence of ischemic spread in the cortex. The exact mechanism is not known for preventing and limiting the expansion of ischemic areas. The neuroprotective effect of the nimodipine is thought to be by excessive calcium reduction in cellular post-ischemic neurons that may end up in cell death [4, 8, 14].

Prevention of cerebral ischemia due to vasospasm with nimodipine can be started with a dose of 1-2 mg / h intravenously in the first 6 hours and increased 1.5 mg / h in the next 6 hours (maximum dose 2 mg / h) or orally 60 mg (maximum dose 360 mg/day) every 6 hours on day 3 for 21 days [16]. FDA issued a warning regarding the side-effects of nimodipine injection that can lead to death, cardiac arrest, rapid drop in blood pressure, and other cardiovascular complications [15]. The practical implication is that the regimen in the dominant nimodipine trial study (60 mg orally every 4 hours for three weeks) is currently considered a standard treatment in aSAH patients. If the patient is unable to swallow, the nimodipine tablet may be smoothed before use or by intravenous administration of nimodipine recommended by the manufacturer and more expensive, but there is no evidence to support its use [4, 16]. Intravenous nimodipine is not recommended superior to oral because of the hypotensive side effects that can occur, especially in hypovolemic patients (systolic blood pressure 130-150 mmHg [4].

A study review or Cochrane Review, including 16 studies with 3361 patients with subarachnoid hemorrhage, found relative risk (RR) 0.81 (95% CI 0.72-0.92) for mortality or dependence on patients treated with calcium antagonists, the number of patients needed to get the drug or Number needed to treat (NNT) is 19 (95% CI; 1-51). These data suggest that calcium antagonists decrease the risk of poor neurologic outcomes and secondary ischemia post aSAH [17].

An experimental study in animals with SAH reporting that in the range of days 4 to 21 post ictus, there was a significant decrease in high voltage-activated gated calcium channel and an increase in low voltage-activated gated calcium channel [40]. Overall, there are ten types of voltage-gated calcium channels, but only four types can be related to L-type calcium voltage channels. The specificity of nimodipine on L-type Ca^{2+} channels reduces during treatment, leading to additionally therapeutic effects on other types of voltage-gated Ca2+ channels, like R-type VGCCs [36-39].

A meta-analysis study by Liu, 2011 related to the use of nimodipine versus placebo in patients with aSAH reported that administration of nimodipine significantly improved clinical outcome and reduced the occurrence of symptomatic CV, delayed neurological function deficits and cerebral infarction, but did not reduce the rate of recurrent hemorrhage incidents [20, 21].

In aSAH, blood pressure should be monitored and controlled to prevent the risk of recurrent post-A SAH ischemic stroke. In patients with acute hemorrhagic strokes, a blood pressure target of TDS 140-160 mmHg is used to prevent recurrent bleeding. While the TDS target 160-180 mmHg is used to prevent the occurrence of vasospasm risk [18]. In therapeutic doses, nimodipine does not affect peripheral vascular dilation, and systemic arterial pressure, so minimal hypotensive effects can occur [12].

3. CONCLUSION

A CV is one of the aSAH complications that may end up in a cerebral ischemic condition, is included in emergency conditions as it may increase post- aSAH mortality and morbidity. A CV is a scary thing but can be prevented by giving nimodipine. Nimodipine is a neurorestorative drug characterized by both its use in aSAH in preventing and repairing neurons and showing good outcomes and reducing the occurrence of ischemic neurologic deficits. The choice of oral nimodipine route is preferred over intravenous by considering its safety. Intravenous administration of nimodipine is more expensive and potentially causes potential side effects of hypotension. Based on a review of literature studies and supporting research related to the use of nimodipine in the CV. It can be concluded that nimodipine could be used in CV as a neurorestorative drug

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