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TIME SUBMITTED	04-NOV-2020 07:08AM (UTC+0700)	WORD COUNT	3811
SUBMISSION ID	1435430376	CHARACTER COUNT	21150

Annals of Medicine and Surgery 60 (2020) 36–40

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Experimental Research

Role of MLC901 in increasing neurogenesis in rats with traumatic brain injury

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ARTICLE INFO

Keywords:
MLC 901
Neurogenesis
IHC Markers
Synaptophysin
Traumatic brain injury

ABSTRACT

Background: Traumatic brain injury is dangerous life threatening condition. This study examines the role of MLC901 in increasing neurogenesis. The aim of this study was to demonstrate the role of MLC901 in increasing nerve cell (neurogenesis) in rat with traumatic brain injury using the synaptophysin marker.

Methods: The synaptophysin levels were measured as a marker for neuron cell (neurogenesis) of brain nerve cells in Sprague-Dawley rats aged 10–12 weeks, weighing 200–300 g. All rats (n = 10) were performed as traumatic brain injury using The Modified Marmourou Model, then they were divided into 2 group, one group was given MLC901 (n = 5) and the other group was not given MLC901 (n = 5). The synaptophysin levels in both groups were assessed after 6 weeks and also carried out an examination of immnuhistochemical from the brain tissue of both groups.

Results: There was an increase in the number of neuron cells as evidenced by synaptophysin ihc staining in the rats given MLC 901 (Neuroaid II) compared to those without MLC 901. Synaptophysin levels were lower in the control group than in the MLC 901 group (81.6, SD: 13.52 vs 118.4, SD: 12.198, p = 0.062).

Conclusion: These research suggest that MLC901 can increase neurogenesis in traumatic brain injury and also appeared as synaptophysin antibody that binding to cytoplasm of neuronal cells in the rat brain.

1. Introduction

Traumatic brain injury is a major cause of death and disability in modern society, today this condition most often faced by neurosurgeons related to advances in science and technology especially in industry and transportation in large cities that were not accompanied by good road construction [1–3]. In the past two years, researcher has experience the use of neuroid drugs in patients with traumatic brain injury and it has a significant results. Many pathological processes contributes to traumatic brain injury are targeted by neuroaids [4,5].

MLC 901 (Neuroaid II) is a traditional chinese medicine that facilitate the restoration of neuron circuits by its antioxidant properties, initiating cell proliferation, and stimulation of axonal and dendritic neuron circuits after traumatic brain injury. In rat models, neuroaids have been shown to prevent cell death and stimulate new neurogenesis. Rats that given neuroaids after ischemic injury showed increased in survival, improved neurological recovery, improved cognitive function and decreased neurodegeneration [5,6].

Neurogenesis or cell proliferation is the initial process of neuron formation, then the neuron migrates and survives until it becomes mature and integrates as a new neuron [7]. The neurogenesis process starts from cell proliferation to migration and differentiates into neuronal cells in the hippocampus, it is estimated to take approximately 4 weeks [8].

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https://doi.org/10.1016/j.amsu.2020.10.013
Received 14 September 2020; Received in revised form 7 October 2020; Accepted 8 October 2020
Available online 19 October 2020

Synaptophysin is an integral membrane protein located in the synaptic vesicles and part of the neuroendocrine secretory granule membrane that is recognized by monoclonal antibodies. Synaptophysin is a broad-spectrum neuroendocrine marker, formed when vesicles fuse with the presynaptic membrane. It is a specialized and sensitive marker at the synaptic terminal of nerve cells [9,10]. This research is hypothesized that the administration of neuroaid can increase neuronal cell or neurogenesis in traumatic brain injury.

2. Methods and materials

This study examined the administration of MLC 901 to number of neuronal cell (neurogenesis) after traumatic brain injury in serum and brain tissue, then compared the responses between two groups; groups that were given neuroaid and groups that were not given MLC 901.

2.1. Animals

This study was approved by the ethics commission of The Faculty of Medicine, Hasanuddin University, with license number: 771/UN 4.6.4.5.31/PP36/2020. The surgical procedure was carried out aseptically. Ten Sprague-Dawley rats, (aged 10–12 weeks, weight 280–300 g) obtain standard food (Comfeed AD-2) and water until research occurs. Rats were divided into two groups: (1) brain injury with MLC 901 administration, (2) brain injury without MLC 901 administration.

2.2. Treatment of brain injury and tissue retrieval

Ten Sprague Dawley rats with brain injury were randomly divided into two groups: (1) with MLC 901 administration, and (2) without MLC 901 administration (placebo). Anesthetics are performed with diluted ketamine (dose 3–10 mg/kgBW). The brain surgery is done by a corona incision along center line of the head and then making a burr hole in which a hole is drilled or scraped into the rats skull, until the dura mater is exposed. The trauma was performed as The Modified Marmarou Model [11,12], using 20 g of load then dropped from 20 cm of height, through a tube [13,14]. The part of dura mater that has been exposed is placed below the tube, so that the load falls on precisely at dura mater and it is confirmed that the trauma has caused brain damage. One rat was subjected to pathology examination (the result was bleeding from the brain tissue), while the other rats were treated according to the standard craniotomy procedure. The wound was sutured and antibiotic ointment was applied. All surgical procedures are carried out aseptically with the principle of sterility. After the procedure, all rats were treated at room temperature in standard cages for recovery.

At 6 weeks after treatment, the rats were euthanized using 400 mg of phenobarbital via parenteral (injection) [15,16], then the brain tissue extraction performed by carniectomy. The brain tissue was immediately frozen at −80 °C until further processed through immuno-histochemical examination using synaptophysin markers.

2.3. Administration of MLC 901

At 30 min after brain injury, MLC 901 was administered per sonde at a dose of 68.4 mg/day until termination at sixth week.

2.4. Sampling and testing

Brain tissue samples were taken 6 weeks after MLC 901 administration. The brain tissue was using paraffin and hematoxylin eosin (HE) staining method and was tested immunohistochemically using synaptophysin markers.

2.5. Statistical analysis

Data are presented as mean ± SD. All data were processed and analyzed using Excel 2013 and SPSS version 23 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Number of Neuron Cell, with Synaptophysin markers staining levels were analyzed by using the T Independent Test. P value less than 0.05 was considered statistically significant.

3. Result

3.1. Subject characteristics

This study examines the role of MLC 901 in increasing neurogenesis. By using a brain injury model in rats (Sprague Dawley), this study aims to explain the benefits of MLC 901 in increasing number of neuronal cell (neurogenesis) after traumatic brain injury. Characteristics of subjects, such as body weight, are listed in Table 1.

3.2. Synaptophysin levels

In the table above, it was found that synaptophysin levels were higher in MLC901 administration (118.4) than without MLC 901 administration (81.6), and also there was a significant difference ($p = 0.002$). These findings can also be illustrated clearly in the boxplot chart below.

3.3. Histopathological image

The histopathological image of rat brain tissue on immunohistochemical examination with synaptophysin antibody stains can be seen in Fig. 2 and Fig. 3 below.

4. Discussion

The traumatic brain injury is an injury to brain tissue, not due to a degenerative or congenital process but because of an external impact that can result in a decrease or change in the state of consciousness. Brain injury is the leading cause of death from accidents under the age of 40. Each year around 10 million people worldwide are hospitalized for brain injuries [17,18].

Traumatic brain injury is a complex condition involving primary and secondary brain injury. Combined therapy could be a better treatment strategy, using formulations that contain more than one active ingredient. Traditional Chinese Medicine (TCM) has been recommended for centuries to treat a wide variety of medical conditions. Traditional Chinese Medicine which consists of several extracts of herbal medicine has received attention from the medical world. MLC 901 (Neuroaid II) have emerged as a promising treatment to support neurological recovery. Several clinical trials and reports have established its safety profile [19]. Research by Tsai et al., 2014, found that MLC 601 (Neuroaid I) had a positive effect on reducing brain contusion in rat with traumatic brain injury. Contusions due to traumatic brain injury are associated with neurological motor deficits, brain apoptosis, and activated microglia [20].

The experimental animals used were Rattus Norvegicus strain, Sprague Dawley rats, with an average body weight of 290.07 (±10.48) grams; there is no significant difference in the body weight of the subjects. Any differences in the expression of dependent variable are

Table 1
Weight data of sprague dawley rats.

	Rat Weight (g)	P-value
Mean	290.7	0.155
SD	±10.48	

The Levene's test of homogeneity in Sprague Dawley rat with brain injury obtained p value > 0.05, and it can be concluded that the weight of each rat is not significantly different.

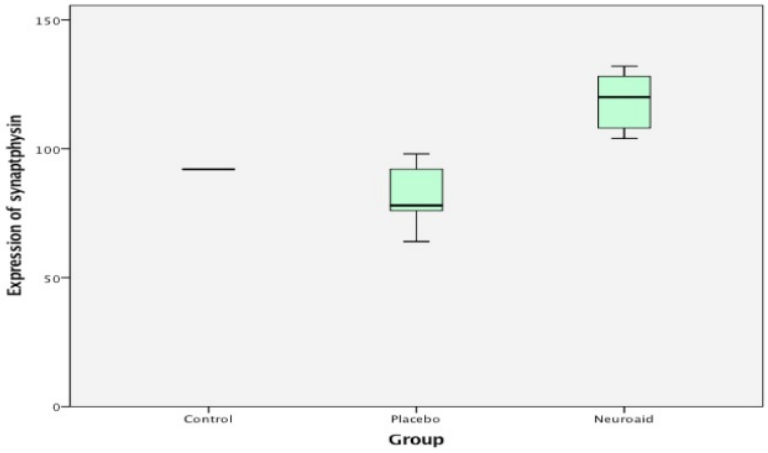

Fig. 1. Synaptophysin levels in rats with MLC 901 and without MLC 901.

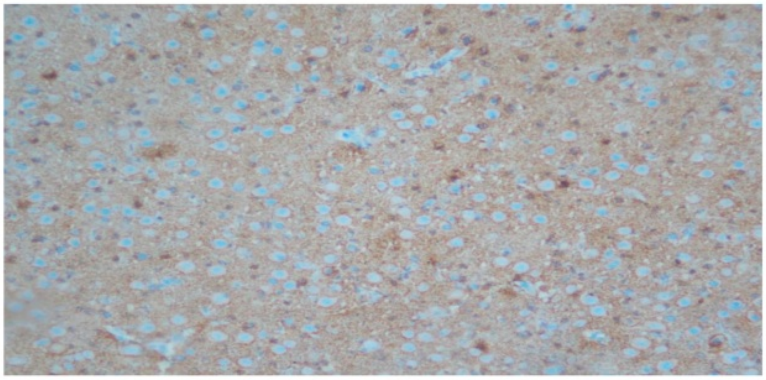

Fig. 2. Normal immunohistochemical features of Sprague Dawley rat brain tissue. This figure shows pieces of brain parenchyma tissue, that consist of neuron cells and granule cells. 100× magnification.

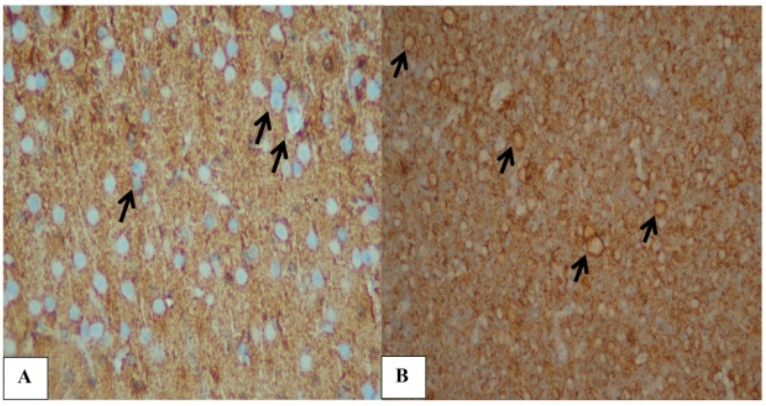

Fig. 3. Image of synaptophysin antibodies in rat brain tissue. A). Without MLC901. Synaptophysin antibody is not smeared on the cytoplasm of neuron cell (arrow sign). There is no antibody binding between synaptophsyin and cytoplasm of neuron cell, so that the cytoplasm remains blue. 400× magnification. B). MLC 901 (Neuroaid II) administration. Immunohistochemical stain with synaptophysin antibodies. Synaptophysin antibody smeared on the cytoplasm of neuron cell (arrow sign). There is an antibody bond between synaptophsyin and cytoplasm of neuron cell, so that the color of the cytoplasm turns brown. 400× magnification. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

expected to be the result of neuroaid treatment in traumatic brain injury.

The aim of this study was to determine the effect of MLC 901 (neuroaid II) in increasing number neuronal cell (neurogenesis) in rat brain tissue that had traumatic brain injury using immuno-histochemical examination with neuronal cell markers (synaptophysin markers). Synaptophysin is a component of presynaptic vesicle membrane and as a

marker of nerve cell in surgical neuropathology and most commonly used neuronal cell markers. Synaptophysin is a sensitive marker of neuron differentiation and neuroendocrine which can also be found in nerve cell tumors such as medulloblastoma and primitive Neuro-Ectodermal Tumors (PNET) [21,22]. Synaptophysin play an important role in maintaining the fusion of vesicles on the presynaptic neuronal activity by provide the complement of the synaptobrevin-II molecule in vesicles presynaptic. The absence of synaptophysin results in a progressive reduction of exocytosis presynaptic vesicle component [23,24]. In vivo research by Tarsa (2009), conclude that the synthesis of synaptophysin secretion is regulated by neuron growth factors which then act as a development regulator for trigeminal ganglion cells. Neuron growth factor and synaptophysin together facilitate the transportation of synaptic vesicles from the cell body to the presynaptic terminal for the development of trigeminal ganglion cells [25].

MLC 901 derived from traditional chinese medicine, MLC 901 shown to have neuroprotective and neurorestorative properties in preclinical models of stroke, global cerebral ischemia and traumatic brain injury. Neuroaid contains 9 herbal components namely Radix astragali, Radix salvia miltiorrhizae, Radix paeoniae rubra, Rhizoma chuanxiong, Radix angelicae sinesis, Carthamus tinctorius, Prunus persica, Radix polygalae, and Rhizoma acori tatarinowii [6].

MLC 901 have neuroprotective and neurorestorative effects that lead to improved recovery of cognitive function in rats with traumatic brain injury. This is a great base to explore the effect of neuroid therapy to improve recovery of patients with traumatic brain injury [26].

In Table 2, there was an increase in the expression of synaptophysin levels in MLC 901 group. These results indicate that the administration of MLC 901 in trauamtic brain injury gives a good response to increasing neurogenesis process. Previous Study from Quintard, H. et al., 2014 showed positive MLC901 effects were associated with an upregulation of vascular endothelial growth factor (VEGF) as well as an increase of endogenous hippocampal neurogenesis and gliogenesis around the lesion. MLC901 reduced cognitive deficits induced by TBI. Rats subjected to TBI displayed a suppression of temporal order memory, which was restored by MLC901. This work provides evidence that MLC901 has neuroprotective and neurorestorative actions, which lead to an improvement in the recovery of cognitive functions in a model of traumatic brain injury. Previous Clinical studies conducted on 32 patients with moderate brain injury, showed the result of study were significant clinical outcome in MLC 601 (Neuroaids I) group compared to control group and no side effects were found [26,27].

Immunistochemical examination of rat brain tissue is shown in Fig. 3. There is a bond of synaptophysin antibody in the cytoplasm of nerve cell in the group that given MLC 901 (neuroaid II) compared with the group that was not given MLC 901. These results indicate that the effect of MLC 901 can increase the neurogenesis process of nerve cells. MLC 901 treatment stimulates gliogenesis and neurogenesis, which can be helpful in inducing dynamic brain remodeling and leading a better neurological recovery in the first weeks after traumatic brain injury. The positive effect of MLC 901 on neuronal plasticity (as characterized by increased neurogenesis, neurite growth, axonal growth, dendritic arborization and/or synaptogenesis) has been observed in focal and global ischemia and correlates with functional recovery [5,26]. The limitation of this study is that the research was carried out on experimental animals so that it needs to be continued in the future with clinical research involving neurogenesis biomarkers.

5. Conclusion

From the results and descriptions above, it can be concluded that the administration of MLC 901 (neuroaid II) can increase number of neuronal cell (neurogenesis) in a rat model with brain injury.

Table 2
The effect of MLC901 administration on number of neuronal cells with synaptophysin marker levels in rats with traumatic brain injury can be seen in Table 2.

MLC 901	Synaptophysin		P- Value
	Mean	SD	
–	81.6	13.52	0.002
+	118.4	12,198	

Note: SD = standard deviation, *independent T-test* with a significant p value < 0.05.

Ethical approval

All procedure for Animal experiment has been approved by Ethics Commission Faculty of Medicine, Hasanuddin University, Number: 137/UN4.6.4.5.31/PP36/2020.

Sources of funding

No funding or sponsorship.

Author contribution

RHA, BAM, AAI, MH and ASB wrote the manuscript and participated in the study design. RHA, BAM, AAI, MH, NAA, ASB, RAN and RZ drafted and revised the manuscript. RHA, AAI, BAM, MH, ASB and RAN performed head trauma treatment and surgery. RHA, NAA, and RZ performed bioinformatics analyses and revised the manuscript. All authors read and approved the final manuscript.

Registration of research studies

1. Name of the registry:
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3. Hyperlink to your specific registration (must be publicly accessible and will be checked): None

Guarantor

Rohadi Muhammad Rosyidi.

Declaration of competing interest

The authors declare that they have no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2020.10.013.

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