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Research Article

Executive Function and Nitric Oxide in Mild-Moderate Traumatic Brain Injury

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Abstract: Incidence of Traumatic Brain Injury (TBI) mostly in mild – moderate TBI, increasing the brain disorders due to primary insults and secondary insults by the multiple pathomechanisms. Brain damaging process manifested in brain function disorders primarily the cognitive function, included the executive function disorders. Executive function is a wide description about processes involving in cognitive areas and behavioral control. The aim of this study is to compare the executive function in mild-moderate TBI to the normal population. This is a comparative study design conducted in Kandou General Hospital, Manado, North Sulawesi in September – November 2014 involving of 19 cases and 37 control subjects. The executive function examinations that significanly associated to NO levels in mild-moderate TBI are MoCA, TMT-A and TMT-B ($p < 0.05$). The results provides evidence for a prevention againts the risk for neurobehavior disorders in mild-moderate TBI.
Keywords: Mild-moderate TBI - Executive function - NO

INTRODUCTION

Traumatic brain injury (TBI) leading to temporary and permanent changes of the brain, resulting the brain disorders. Even the mild TBI with the good outcomes might be reveal the long term neurobehavior deficit [1].

According to Riskesdas data (2007) there are 18.9% of traffic accident victims with head injuries [2]. Studi at Tebing Tinggi shown that patients with head injuries due to traffic accidents with the highest proportion in the age group 16-24 years (39.5%), male (67.5%), mild head injury (74.6%), the average treatment time 3.97 days, outpatient home care (51.8%), and own costs (52.6%) [3].

TBI defined by Perdossi (Indonesia Neurology Asscociation) as injury to the head and brain, both direct impact by the primary or indirect impact by the secondary insults [4].

TBI classification helps the early management in emergency room by clinical symptoms and signs. The clinical classification is using the Glasgow Coma Scale (GCS), loss of consciousness (LOC) and post traumatic amnesia (PTA) are :Mild TBI:GCS 13 - 15, LOC < 30 minutes, PTA < 1 day; Mild TBI:GCS 9 - 12, LOC 30 minutes – 24 hours, PTA 1-7 days and Severe TBI: GCS 3 – 8, LOC > 24 jam, dan PTA > 7 days [1, 5-7].

First step of TBI characterized by direct damage to the brain and the cerebral blood flow (CBF) adjustment disorder [1, 8, 9], so with the metabolism. There looks ischaemic-like appearance due to lactic acid accumulation, anaerob glicolysis, cells membran permeability increased and the consecutive edema formation [11-13].

The second step is terminal membran depolarization along with the excessive excitatoric neurotransmitter release (eq. glutamate dan aspartate) [10].

Factors which roled in the TBI damaging process are Cerebral blood flow (CBF) ie. Hipoperfusion and hyperperfusion; Cerebrovascular autoregulation and reactivity CO and. Cerebral vasospasm, and also Cerebral metabolism dysfunction, Cerebral Oxigenation Excitotoxicity and Oxidative stress, Edema, Inflamation and Necrosis and apoptotic [8, 10].

Mechanisms that underlying for behavioral changes in the first day-weeks after brain injury are

various and range from changes in CBF up to apoptosis and neuropathology [11].

Exitotoxicity resulting in cell death by both of apoptotic and necrotic ways. Primary insults as the secondary insults are related to the massive release of excitatoric amino acid neurotransmitter release especially glutamate.This action will resulting an excessive stimulation of glutamate receptors, hydrogen peroxidase, nitrite oxide and peroxinitrite, as a response to the brain injury and metabotrophic, to end as the influx of Ca, Na, K.

Nitric oxide (NO) playing an important role in development of the secondary insults of TBI [10, 11]. Since NO is a strong vasodilator and regulates cerebrovasculear tone and perfusion [9].

The brain is an organ that active metabolically, consum high oxygen and product the large amount ROS. These ROS are kept in optimal limit by an elaborate network of endogenous antioxidants, if the work failure, the neuron falled to the oxidative stress. Oxidative stress correlated to oxygen reactive species (ROS – RNS) formation, that is a free radical oxygen related to superoxide, depend on early stimuli intensity and the cells population characterization ROS are neurotoxic, and the execissive ROS associated with decreased performance in cognitive function. But actually in normal range ROS is involved in functional change necessary for synaptic plasticity and hence for normal cognitive function [12].

Cognitive function is an element of the behavior as well as the emotion and the executive function. 13 The executive function consist of those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior [13].

The neurobehavior disorders due to TBI is important, since the behavior and personality problems and the takes time in recovering, that will be make problem in the family or even failure in neurorestoration – rehabilitation and lost of occupation.

MATERIALS AND METHODS

This is a comparative case-control study designed at Kandou General Hospital Manado, North Sulawesi in September – November 2014. The samples number 60 persons, including 17 females and 39 males aged 15 – 48 years. The subjects divided in two groups consists of 20 mild-moderate TBI patients as a case group and 40 normal people the control group.

Case inclusion criterias were mild-moderate TBI, 15 – 60 years, willing to be a research participant exclusion criterias were opened TBI, hipertension, diabetres mellitus, using vasodilator drugs, history dementia. After underwent the anamnesis, physical examination and laboratory procedures; a subject from case group and three subjects of control group unwilling to undergo NO blood sampling.

RESULTS

Table 1 shown the demographic characteristics was predominance of males both case (72.2%) and control group (68.4%). The average age was 30.74 ± 11.87 years in case group and 29.11 ± 6.20 years in control group. Mostly in the age group of 25 – 34 years (young adult). 44.6% of the subjects are well educated.

Table 1: Demographic Characteristics

Variable	n	%
Sex		
- Females	17	30.4
- Males	39	69.6
Age (yrs old)		
- 15-24	18	32.1
- 25-34	22	39.4
- 35-44	11	19.6
- 45-54	5	8.9
- 55-60	0	0.0
Education		
- Elementary School	1	1.8
- Junior High School	6	10.7
- Senior High School	24	42.9
- Colleges	25	44.6

Table 2 summarized the values of MMSE, MoCA-Ina, TMT-A and TMTB in each group. MMSE was varies in the same range in both group and still in the normal range, but the MoCA-Ina of the case did not reach the maximum value and the averages in case group is below normal range. The averages In TMT-A and TMT-B in the normal range.

Table 3 shown that the minimum NO consentration of the subjects was 0.70 µL (average 3.12 ± 2.85 µL) in the case group and 2.1µL (average 6.91 ± 4.04 µL), both of this values below the normal range (2.5 – 35 µL); the maximum was 13.0µL and 18.8 µL.

Table 4 shown that each component of the executive function significantly different in each group.

Table 5 shown the relationship between components of executive function and NO levels analyzed by Spearman correlation test. The results revealed that there was a significant positive correlation between MMSE and NO levels (r = 0.324, p = 0.007) and there waa significant positive correlation between MoCA-Ina and No levels (r = 0.311, p = 0.01).

Furthermore, there was a significant negative correlation between TMT-A and NO levels (r = - 0.429, p = 0.006) and there was a significant negative correlation between TMT-B (r = - 0.333, p = 0.001).

Tabel 2: Components of Executive Functions

Variable		Descriptitive Analysis		
	n	Min	Max	Average ± SD
MMSE				
Case	19	22	30	27.69 ± 2.19
Control	37	23	30	29.65 ± 1.09
MoCA-Ina				
Case	19	19	28	23.84 ± 3.13
Control	37	16	30	28.81 ± 2.33
TMT-A				
Case	19	0.32	3.20	1.07 ± 0.64
Control	37	0.18	0.45	0.32 ± 0.05
TMT-B				
Case	19	1.14	5.00	2.55 ± 0.93
Control	37	0.33	3.00	0.75 ± 0.63

Table 1: NO levels

Variabel	Min	Max	Mean	Med	SD
[NO]					
Case	0.70	13.0	3.12	2.10	2.85
Control	2.10	18.8	6.91	6.10	4.04

Table 4: Executive function component between group

Variable	Bivariate		
	Mean	SD	p value
MMSE			
- Case	27.69	2.19	0.001*
- Control	29.65	1.09	
MoCA-Ina			
- Case	23.84	3.13	0.001**
- Control	28.81	2.33	
TMT-A			
- Case	1.07	0.64	0.001**
- Control	0.32	0.05	
TMT-B			
- Case	2.55	0.93	0.001**
- Control	0.75	0.64	

* Mann-Whitney ** Unpaired T-test

Table 2: Relationship between Executive Function and NO

Variable	Correlation with NO	
	Bivariate	
	Corelation Coefficient (r)	p Value
MMSE	0.324	0.007*
MoCA	0.311	0.01*
TMT-A	-0.429	0.006*
TMT-B	-0.333	0.001*

*Spearman correlation test

DISCUSSION

The average of TBI patients have a normal values of MMSE, does not means without executive disfunctions. The normal value of MMSE is still has 10% false positive interpretation value. MMSE has already use world wide, yet it is not explored the entire brain, especially the prefrontal lobe, where as the executive function sited. MMSE is good for screening of global cognitive function, yet not the executive function [14].

The average of MoCA-Ina below the normal values, MoCA in this study used the Indonesian version (MoCA-Ina) is also use for screening the cognitive function and can be used for executive function examination, since it explored the frontal lobe function. Shown that average of the TBI patients got the executive dysfunctions.

Although the TMT-A and TMT-B still in the normal Values but it was far from the average values of normal people.

The average NO levels in TBI patients in this study was in the normal limit 3,12 µL (N : 2,5 – 35 µL), there were 65% among the TBI patients has NO below the normal values. This is indicating that there was a damaging brain process, especially in area or cells involved in cognitive function. Executive disorders can affect cognitive functionning directly in compromised strategies to approaching, planning or carrying out cognitive tasks, or in defective monitoring of the performance [15]. In this study the excecutive function domain as examined by the executive function tools. MoCA-Ina to visuosptial, naming, memory, atenttion, language, astract thinking and orientation, where as TMT-A and TMT-B to measure of visual searching, visual squencing, perceptuomotor speed, and the ability to make alternating conceptual shifts efficiently [15, 16]. The area that concerned with the planning and execution of complex motor actions is the prefrontal cortex [13], as well as the directing and maiantaining attention, problem solving, adjusting behavior to social norms, working memory, deliberate decisions and morality [17]. This study reveals the significant correlation between executive function and the NO level in the mild – moderate TBI mostly by TMT-B ($p < 0.001$) Demery JA *et al*. found the similar result that the executive dysfunction is common following M/S TBI [18] and Schiehser DM *et al*. found the cognitive complaints are associated with objective executive function in mild – moderate TBI [19].

NO has been studied extensively and shown to be a critical signaling molecule, both for synaptic transmission as well as for synaptic plasticity. Several study proved the direct involvement of NO in formation of both spatial and associate memories in multiple species. NO attenuated the long term potentiation and the memory formation [12].

Ischemia in TBI causes neuronal dysfunction and cell death, although the precise timing and mechanisms not certainly known yet. Ischemia is characterized by the a transient block in blood flow that leads to decreased glucose and oxygen perfusion to the brain, resulting in energy failure, neuronal dysfunction and death due to cognitive function impairments; mostly if the focal point of iscemia is the learning and memory areas. The core are is severely injured surrounded by the penumbra where the neuron are impaired, but sufficiently active to maintain the membrane potentials.

Several studies on the oxidative damage in TBI, demonstrating an immediate post-injury increase in free radical oxygen upto 1 hours post injury. The average time is about 5 minutes – 24 hours [20]. Under pathologic conditions, there was reduction NO produced by NO_3 resulting in hypoperfusion of the area of injury [20].

In this study the NO level nearly below the lower level, this is might accordance to the studi that show the NO levels in TBI could be deminished. because of the brain tissue too damage to produced the NO.

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