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THERAPEUTIC MILD HYPOTHERMIA TOWARDS BLOOD LACTATE LEVELS AND GLASGOW COMA SCORE IN SEVERE TRAUMATIC BRAIN INJURY

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Background: Raised body temperature is a common occurrence after severe traumatic brain injury (TBI). TBI is accompanied by regional alterations of brain metabolism, reduction in metabolic rates and possible energy crisis. This metabolic disturbance reflected by increase and accumulation of the brain lactate levels. The study aimed to evaluate the effect of therapeutic mild hypotermia (TMH) on lactate levels and GCS (Glasgow Coma Score) of severe TBI. **Methods:** Fourthy patients with TBI were randomly divided into normothermia (n=20) and mild hypothermia (n=20) group. Body temperature of hypothermia group was maintained at 35°C for 72 hours. Blood lactate level and GCS were determined before and after hypothermia therapy (on 3th and 7th day). **Results:** The mean lactate {5.370 vs 4.025 mmol/L, p<0.001 (on 3th day); 5.070 vs 2.775 mmol/L, p<0.001(on 7th day)}. TMH group was lower than in the normothermia group after TMH. The mean GCS was higher in TMH group than in the normothermia group {8.45 vs 7.80, p < 0.002 (on 3th day); 9.85 vs 8.25, p<0.005 (on 7th day)}. **Conclusion:** There was a significant correlation between blood lactate level and GCS according to TMH. Mild hypothermia therapy improves neurologic outcomes in patients with severe TBI, and reduction in blood lactate level may be partially responsible for the improved outcomes.

Keywords: severe; brain; metabolism; reduction; improved.

INTRODUCTION

Traumatic brain injury due to trauma (TBI) was a major cause of morbidity and mortality in both developed and developing countries. Statistically estimated that each year 2% of the world population suffered TBI. Causes of TBI most are due to motor vehicle accidents (50%), due to falls (21%), due to sports (10%), the remainder due to other events.[1]

TBI caused pathological changes in both the system vascularization and cerebral metabolism, where there is a close relationship between the two systems.[2] Based on the impact to the head, injury or mechanisms are classified into two phases, namely the primary injury (primary insult) and secondary injury (secondary insult). The primary injury was a direct result of trauma that causes primary damage or mechanical damage. While the secondary injury is a pathological process that began at the time of injury with a delayed clinical presentation.[3]

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The management ofTBI, particularly severe TBI is an attempt to prevent the process becomes secondary to primary brain injury, secondary brain injury because there will be more extensive damage due intracellular biochemical processes, such as cerebral edema, ischemia and apoptosis. Ischemia process became the main line on the secondary brain injury involves damage to the blood brain barrier.[4]

An effort in the management of secondary TBI is giving neuroprotectors that are medical or non-medical. As is well known how difficult determining neuroprotector best choice for these patients. Because the pathophysiology of severe TBI is heterogeneous, complex and has a cell and molecular biochemical pathways are wide so it is not possible a neuroprotector agent could inhibition to all lines. For that chosen neuroprotector are capable of inhibition of many pathways are treating mild hypothermia in patients with severe TBI.[5]

The use of therapeutic mild hypothermia (TMH) as a therapeutic strategy in the treatment of neurological emergencies recorded since early 1940, when Temple Fay did hypothermia treatment in 124 patients with TBI. Since the 1970-1990 early research on TMH occurs rapidly growing though still pros and cons.[6] Definition of TMH is a temperature below normal body temperature (37^0C). In terms of mechanism, hypothermia can be

divided into two, i.e. accidental hypothermia that occurs in part of a systemic disorder of the body and the hypothermia induced hypothermia treatment. Classification based on degrees of temperature on hypothermia treatment selected hypothermia treatment at a temperature of 34-36^{0}C because at this temperature is considered safe and easy technically. When the temperature is below 30^{0}C, there will be the risk of heart failure, blood clots and infection.[7]

It is said that the mechanism of hypothermia as a neuroprotective behavior is reducing the need for brain cell metabolism by 5-6% on each drop in temperature of 1^{0}C.[7] Recent study suggest that TMH can affect the release of neurotransmitters in patients with posttraumatic,[10] and prevent the opening of the blood brain barrier.[12] Another mechanism is to reduce free radicals, brain edema, improve the release of ions, reducing the release of amino acids, reduce the accumulation of lactic brain, prevent hyperglycemia, inhibit the excessive influx of calcium into the neuron cells and to prevent excessive accumulation of intracellular calcium.Lactate has long been regarded as one of the markers that are sensitive to changes in intracerebral metabolism, although the pathophysiology of the increase in lactate itself is not yet fully understood. The study said that ischemia after brain injury is responsible for rising levels of lactate intracerebral, but other study said that the occurrence of ischemia in the aftermath of brain injury is not to the level of ischemia in the majority of patients with head injury.[8,9]

The first step of neuroprotective effects of TMH associated with a decrease in metabolism, inhibiting the release of amino acids and free radicals, reduce the formation of lactate, and lower the cyto-skeletal structure damage.[10]

Based on the above, this study aims to examine the correlationTMH with improved output in patients with severe TBI with the benchmark score of the Glasgow Coma Scale and blood lactate levels.

MATERIALS AND METHODS

This research applied an analytic experimental design to analyze the effect of TMH on blood lactate levels and GCS in patients with severe TBI in the Emergency Surgical, Prof. Dr. R. D. Kandou Hospital, Manado-Indonesia. The study started from January until June 2015. A total of 40 patients met inclusion criteria and were divided into 2 groups, with and without TMH. Patients are given TMH by means of cooling surface method. TMH consists of three phases: induction phase (performed 6 hours post-injury), the maintenance phase for 24 hours (34-36^{0}C) and the warming phase (0.05^{0}C until 0.1^{0}C per hour) within 72 hours. Assessment of blood lactate levels and GCS were on days 0, 3 and 7. Assessment of blood lactate levels checked by using a portable lactate analyzer (Accutrend® Plus).

All data were analyzed using SPSS software V.22.0. When p<0.05 indicates a statistically significant difference. Since, data were not distributed normally Mann-Whitney test was applied to determine the different.

RESULTS

Sample characteristics

During the period January to June 2015, a total of 40 patients who met the inclusion criteria (Table 1).

Table 1
Sample distribution (N=40)

Parameter	n	%
Sexes		
Male	31	22.5
Female	9	77.5
Age (y)		
14 – 23	17	42.5
24 – 33	6	15.0
34 – 43	7	17.5
44 – 53	4	10.0
54 – 63	6	15.0

Blood lactate levels

In this study, blood lactate levels in each group of patients were examined 3 times, i.e. day 0 (at time of entry), day 3, day 7 (Table 2).

Table 2
TMH and Lactate Blood Level

TMH	Lactate Levels (nmol/L)		
	Day-0	Day-3	Day-7
Without			
Minimum	4.60	4.40	4.00
Maximum	7.10	6.80	6.60
Median	5.55	5.50	5.10
Mean	5.58	5.37	5.07
With			
Minimum	4.00	2.90	2.00
Maximum	7.20	5.20	3.90
Median	5.85	4.05	2.65
Mean	5.59	4.03	2.78

Tabel 3
The test results of GCS change

GCS	THR	Median	p*
Day-0	With	8.00	0.225
	Without	7.00	
Day-3	With	9.00	0.002
	Without	8.00	
Day-7	With	10.00	0.001
	Without	8.00	

GCS = Glasgow Coma Scale
THR = Therapeutic Mild Hypothermia
*Mann-Whitney Test
Significant at p<0.05

Table 4
Results of test changes in blood lactate levels

Lactate	THR	Median	*p**
Day-0	With	5.85	0.480
	Without	5.55	
Day-3	With	4.05	0.001
	Without	5.50	
Day-7	With	2.65	0.001
	Without	5.10	

THR = Therapeutic Mild Hypothermia
*Mann-Whitney Test
Significant at $p < 0.05$

DISCUSSION

In this study, we obtained that the distribution of patients with severe TBI between the sexes as a result of traffic accidents occurs more frequently in males than females (77.5%:22.5%). While the distribution according to age, most people with severe TBI are between the ages of 14-23 years were as much as 42.5%. Both of these are highly correlated to traffic accidents become the most common cause of severe traumatic brain injury and experienced by men of reproductive age. Riyadina, et al studied patients with severe TBI is most common in men than women of 6.27:1, this is a form of social reflection of a country's culture because women worked as housewives and rarely work outside the home. As well as reports of Cipto Hospital,Jakarta in 1992 where TBI occured mostly under the age of 44 years and is still productive age.[11]

Dependent T-test and Mann-Whitney test indicates there is no difference in lactate levels early in both groups (p = 0.480), no difference was very significant levels of lactate day 3 in both group (p<0.001), and there are very significant differences in the levels of lactate day 7 in both groups (p<0.001).

GCS is a strong predictive factor in determining prognosis, a low GCS at the beginning of injuries associated with a poor prognosis. Jennet, et al reported that 82% of sufferers with a GCS score of 11 or more, within 24 hours after the injury has a good outcome or moderate disabled and only 12% died or received severe disability. Outcome progressively decreases when the initial GCS decreased. Among the sufferers with initial GCS of 3 or 4 in the first 24 hours after injury only 7% who got good outcome or moderate disability. Among the sufferers with a GCS of 3 at the time of entering treatment, 87% will be die.[12]

Zhao et al in a study of 81 patients with severe traumatic brain injury were divided into two groups in China in 2011, claimed that severe TBI patients performed TMH associated with improved patient outcomes compared with untreated mild hypothermia. Roman Gal et al study that included 30 patients with TBI who were divided into two groups also claimed that TMH can be used to improve outcomes and recovery of consciousness in patients with severe TBI .[13]

This is consistent with the literature that TMH in patients with severe TBI is one of the efforts in the treatment of secondary brain injury outcomes which relate to recovery of consciousness and severe TBI patients. Pathophysiology of severe TBI is heterogeneous, complex and has a cell and molecular biochemical pathways are wide so it is not possible a neuroprotector agent can inhibition to all lines. TMH is a potent neuroprotector are capable of inhibition on many cascade.[14]

After statistical test research the correlation of TMH with blood lactate levels with unpaired t test and Mann-Whitney test, there is no difference in lactate levels early in both groups (p=0.480), no difference was very significant levels of lactate day 3 in both group (p<0.001), and there are very significant differences in the levels of lactate day 7 in both groups (p<0.001).

The results showed that the lactate will be increased in patients with traumatic brain injury due to one trauma. As a rule, that found in every trauma is the metabolic changes. One effect is the occurrence of hyperglycemia and increased production of lactate which lasted a few moments. Hyperglycemia indicates mobilization of glycogen reserves to meet energy needs, while high lactate production that reflects the depletion of energy supply to the permintaan.[15]

Guyette et al reported a study in 1168 patients hospitalized for trauma. The results showed that lactate is associated with mortality (odds ratio [OR], 1:23; p<0.0001), surgery (OR, 1:13; p<0.001), and multiple organ dysfunction syndrome (MODS) (OR and 1.14; p<0.0001). When the threshold of lactate passed 2 mmol / L is used to predict the shock, respiratory distress or impairment of consciousness, which increases the sensitivity mortality from 88% to 99%, surgery of 64% to 86%, and multiple organ dysfunction syndrome (MODS) of 94% to 99% .[16]

Laode et al. conducted a prospective observational study in 60 patients with severe TBI. The result is no significant relationship between blood lactate levels with severity of brain injury due to trauma associated with GCS . The lower the GCS , the higher the blood lactate levels and vice-versa. Therefore, the initial examination of blood lactate levels can be used in predicting the outcome in patients with TBI.[17]

Lactate level study was corresponding with the literature said that the main mechanism of TMH is to reduce the level of cellular metabolism. TMH also decreases the average of oxygen and glucose metabolism, lowers high energy phosphate associated with a reduction in CO2 and lactate production. Transport of oxygen to the brain tissue increased with temperature changes, referring to the

change in the oxygen dissociation curve, and the affinity of oxygen to hemoglobin. This study was in line with Soukup, et al who did research on 84 patients and divided into two groups. Patients without TMH indicates reduced levels of glucose and lower lactate (p<0.0001) compared to patients with TMH. Eventually proven that TMH associated with reduced levels of glucose and lactate were significantly (p<0.0001). Changes in lactate levels greater (65%) compared to glucose (49%) after TMH.[18]

CONCLUSION

Based on the results of this study, it can be concluded that there is a significant correlation between TMHwith the GCS insevere TBI patients. There is significant correlation between TMH with blood lactate levels insevere TBI patients.

CONFLICT OF INTEREST

All authors declare no conflict of interest to disclose.

ETHIC LEGAL PERMISSION

Reg.No.055/EC-UPKT/VI/2015 (Integrated Health Research Unit, Prof. Dr Kandou Hospital, Manado-Indonesia).

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