Supplementation of Turmeric Extract Does Not Improve Neurological Function Following Repetitive Mild Traumatic Brain Injury in the Rat

Andre Marolop Pangihutan Siahaan[1] and Iskandar Japardi[1]
[1]*Department of Neurosurgery, Faculty of Medicine, Universitas Sumatera Utara, Jl. Dr. Mansyur No. 5, Medan, Indonesia*

Keywords: Repetitive Traumatic Brain Injuries, Curcumin, Psychomotor Assessment.

Abstract: Turmeric has been in use since ancient times as a condiment and due to its medicinal properties. Curcumin, the yellow coloring principle in turmeric, is a polyphenolic and a major active constituent. Besides the anti-inflammatory, thrombolytic, and anti-carcinogenic, curcumin was also reported to have therapeutic potential in Alzheimer's disease by inhibiting the amyloid-β-protein aggregation. Inflammation and early degeneration are two of main processes believed happened after repetitive mild traumatic brain injury. The effect of curcumin was evaluated in weight drop model of repetitive mild traumatic brain injury. Male Sprague dawley rats (n=10) were given multiple brain injury (40 gr mass drop from 1 m heights, 3 times daily on day 0,1,3, and 7). Curcumin (500 mg/kg) were given orally. On the last day of injury, psychomotor assessment (beam walk assessment and exit circle test) were performed. Control injured rats had a significant neurological deficit ($p<0.01$). No significant different found control and treatment group. The study does not demonstrate the efficacy of curcumin in rat with repetitive mild traumatic brain injury model.

1 INTRODUCTION

Traumatic brain injury (TBI) results from impact to the head. The severity of this injury is varied, from mild (brief and little change in consciousness or mental status) to severe (prolonged loss of consciousness and coma to fatal). Either mild of severe TBI can result in short and long-term disability. On a global scale, TBI is a serious health concern and is the leading cause of mortality and disability among individuals in young-age population. TBI is one of the most common neurological diagnoses in the US and the CDC has estimated that 1.7 million people sustain TBI annually (Rutland-Brown, 2006).

Repetitive mild TBI (rmTBI) is the form of TBI that has gained public awareness, as well as within military, scientific, and medical communities. TBI accounts for around 28% of all combat casualties in Iraq and Afghanistan (Okie, 2005). Persistent accounts of rmTBI suffered by athletes have also directed much attention. It is estimated that 1.8-3.8 million sports-related TBIs occur every year (Halstead & Walter, 2010). About 60% of retired professional football players sustained at least 1 concussion during their careers and approximately 25% experienced repeated injury (Guskiewicz, 2005).

Repetitive mild TBIs generally produce a constellation of symptoms (e.g. headache, dizziness, confusion) collectively known as post-concussive syndrome (Halstead and Walter, 2010). Reports of more serious consequences of rmTBI such as chronic traumatic encephalopathy and increased co-morbidity of neurodegenerative disorders (Omalu, 2010), (Guskiewicz, 2007). This situation becomes even more complex by the fact that rmTBI is extremely difficult to detect. For the most part, routine imaging approaches (CT and MRI) contribute little to the evaluation and management of mild concussion (Boven, 2009). The more advanced and specialized approaches such as diffusion tensor imaging are showing promise (Donald, 2011).

Histologically, there is protein aggregation happened after rmTBI. The primary proteinopathy is tau protein, in form of neurofribrillary tangle (NFT). The most common secondary proteinopathies are TDP-43 and amyloid-β-protein aggregation (McKee, 2013).

Turmeric (Curcuma longa) is a traditional medicinal plant that also is commonly used as spice in South as well as Southeast Asia. Curcumin, the active ingredient of this plat, had been isolated since long time ago and is considered as a potent antiinflammation. In animal model, curcumin will be bounded to beta structure in amyloid, so that reduces

Siahaan, A. and Japardi, I.
Supplementation of Turmeric Extract Does Not Improve Neurological Function Following Repetitive Mild Traumatic Brain Injury in the Rat.
DOI: 10.5220/0010075504860490
In *Proceedings of the International Conference of Science, Technology, Engineering, Environmental and Ramification Researches (ICOSTEERR 2018) - Research in Industry 4.0*, pages 486-490
ISBN: 978-989-758-449-7

the plaque formation. Curcumin also will decrease the aggregation process and stimulate the clearance. Curcumin was also reported decreased the accumulation of soluble NFT and inhibit kinases that are involved in tau formation. Moreover, also in animal model, curcumin supplementation was proved to be effective in Alzheimer's disease (Darvesh, 2012).

Until now, there is no proved effective therapy for rmTBI. Curcumin, that was proved to be effective in neurodegenerative disease, might potential to be therapeutic agent in rmTBI. The aim of this study was to prove the role of curcumin in neurological function after rmTBI.

2 MATERIAL AND METHODS

2.1 Animal Model and Experimental Groups

Male Sprague dawley rats (n=30) weighing 350 to 400 gr were housed in polycarbonate cages maintained at 50 ± 10% humidity with a 12-hour light and dark cycle. Rats were fed with standard laboratory chow and water ad libitum. The experimental protocol was approved by an Institutional Review Committee of Universitas Sumatera Utara, Medan, Indonesia. The animals were also acclimatized to the laboratory condition prior to experimentation for two weeks.

The rats were randomly allocated into three groups (n=10) as following; a control (sham-operated) group, a trauma group, and turmeric extract (TE) groups. The rats in controlled group were placed only in stereotactic apparatus, with neither trauma nor drug treatment. The control group underwent trauma protocol and the TE group underwent trauma protocol and turmeric extract treatment

2.2 Drug Treatment

Turmeric extract (Sido Muncul, Semarang, Indonesia) was given in 500 mg/kgBW dose, suspended in 2 cc of double-distilled water. All rats were weighed before the extract was given. The extract was given orally via oral gavage every day for consecutively eight days, at least two hours before trauma protocol.

2.3 Weight Drop Brain Injury Model

Rats were placed under a stereotaxic frame. This protocol was done without any anaesthesia. A 40-gram weight was dropped from a height of 1 m unto 5 mm diameter pipe resting on the vertex. To prevent skull fracture, a round metal with 3 cm diameter was placed on the rats' vertex. The trauma was given three times daily, every 4 hours on day 0,1,3, and 7. Every rat in control and TE groups underwent 12 traumas in this research.

2.4 Outcome Assessment

2.4.1 Mortality and Body Weight

Death of the rats following trauma protocol were noted. Every rat was weighed on day-0 before the protocol started and on day -7, i.e on the last trauma protocol.

2.4.2 Beam Walk Assessment

Rat was placed on a 1.5 m length plywood with 10 cm width. For baseline data, we recorded the time needed to cross the plywood and the maximal walking distant before did the protocol. We also recorded maximal time before rats fell down and marked whether there was sign of disequilibrium. We repeated the assessment

2.5 Statistical Analysis

The total time needed were reported in mean and standard deviation. When comparisons were made between groups, significance in between-group variability was analysed using the one-way Anova test with Tukey as post hoc test. Differences were considered significant at the $P < 0.05$.

3 RESULT

3.1 Mortality and Weight

There was no mortality in all groups. The rats still survived, moved actively, and had good appetite after three days protocol. We did not find significant weight changes between day 0 and day 7 either in negative sham control, trauma, or TE group ($p>0.05$; table 1.

Table 1. Weight Change (gr)

Group	Before traumas	After traumas	p
Negative sham	377.22 ± 29.72	378.44 ± 29.66	0,910
Trauma	351.78 ± 29.89	349.33 ± 38.90	0,482
TE	367.89 ± 36.70	357.89 ± 39.89	0,950

One way Annova, significant if $p<0.05$

Table 2. Time needed to walk along the stick

Group	*n*	x ± *SD (*s)	p
Negative sham	10	9,7 ± 1,95	0,342
Trauma	5	12,20 ± 3,89	
TE	5	8,80 ± 1,30	

One way Annova, significant if $p<0.05$

3.2 Disorder of Equilibrium

Repetitive TBI generated disorder of equilibrium. On the negative sham control group, none of the rat showed any sign of disequilibrium. On the trauma group, 90% of the showed sign of disequilibrium one day after trauma. On the TE group, 60% of the rats showed the same sig, whether 30% among them showed psychomotor depression, and only 10% showed no sign of disequilibrium.

3.3 Walking Length and Fell Down

On negative sham control group, all of the animals could walk for 1.5-metre long. Conversely, only 50% of the animals in the trauma group that could walk for 1.5-metre long. 40% of them could not walk for 1.5 metre and 10% of them did not move at all. On the TE group, 50% of animals could walk for 1.5-metre length. 20% of the could not walk till the edge and 30% did not move at all.

The same finding could be seen regarding fell down. None of the negative sham control group fell down while walking on the plywood. Conversely, 40% animals on the control group fell down while walking on the stick and 50% animals on the treatment group fell down while walking.

Regarding the time needed to walk along the stick, there was no significant different in all three groups (table 2).

4 DISCUSSION

Repetitive mild traumatic brain injury is one of major concerns in neurology right now. Many people are prone to suffer this condition, such as athlete and military personnel. In animal study, it is said that the cellular as well as molecular balance will be back to normal state in around 7-10 days (Giza and Hovda, 2014). This fact makes hypothesis arising, that brain will be in prone-to-injury condition if the second impact happened in this time period.

We used the modified weight drop model in this study with modification from Marmarou procedure. We showed zero mortality rate, compared to report by Marmarou (64%) or by Kane (10%) (Marmarou, 1994), (Kane, 2012). Our finding was consistent with the next study. They also reported the same mortality rate (Xu, 2016). The other unique feature in our model is no need of anesthesia. All the trauma procedures were performed without anesthesia, even this method could produce a non-uniform injury site. Even so, this situation fitted contact injury happened during sport.

We also did not find changes in body weight in all groups following trauma. In many reports of animal model of traumatic brain injury, there are significant body weight decrease that probably happened due to injury affecting feeding behavior and injury to the anterior hypothalamus (Wei, 2012), (Samini, 2013), (Moon, 2009).

We found significant different regarding motoric and equilibrium. Rats in traumatic brain injury and turmeric extract group could not maintain the stability in the plywood. After trauma, only half of groups in

either trauma or TE group that could maintain the stability. A study reported that motoric disfunction was one of common manifestation in Chronic traumatic encephalopathy, a sequel of repetitive mild traumatic brain injury (Montenigro, 2015).

Turmeric extract is a well-known potent antioxidant and antiinflammation. On animal study, many reports showed the effectivity in degenerative disease, but it was failed in human clinical study (Darvesh, 2012), (Tang, 2017). In our study, we did not find significant different regarding outcome in trauma and turmeric extract group. One of the main problems of crude turmeric extract is the low bioavailability. If the challenge of the low bioavailability is overcome, curcumin as medication in repetitive mild traumatic brain injury may still be in horizon.

The main limitation of this study is the outcome that only limited to clinical. For the next research, it is advised to do biochemistry analysis to determine the cellular status and cell expression. Besides, a long follow up period is advisable to make sure the long-term outcome in this condition.

In conclusion, we found no significant improvement after curcumin supplementation in repetitive mild traumatic brain injuries.

ACKNOWLEDGEMENTS

This research was fully funded by Research Committee of Universitas Sumatera Utara in TALENTA Grant 2017.

REFERENCES

Darvesh, A.S., Carroll, R.T., Bishayee, A., Novotny, N.A., Geldenhuys, W.J., Van der Schyf, C.J. (2012). Curcumin and neurodegenerative diseases: a perspective. *Expert Opin Invest Drugs*, 21(8), 1123–1140.

Giza, C.C., Hovda, D.A. (2014). The New Neurometabolic Cascade of Concussion. *Neurosurgery*, 75, S24–S33.

Guskiewicz, K.M., Marshall, S.W., Bailes, J., McCrea, M., Harding Jr, H.P., Matthews, A., Mihalik, J.R., Cantu, R.C. (2007). Recurrent concussion and risk of depression in retired professional football players. *Med Sci Sports Exerc*, 39, 903–9.

Guskiewicz, K.M., Marshall, S.W., Bailes, J., McCrea, M., Cantu, R.C., Randolph, C., Jordan, B.D. (2005). Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*, 57, 719–26.

Halstead, M.E., Walter, K.D. (2010). Sport-related concussion in children and adolescents. *Pediatrics*, 126, 597–615.

Kane, M.J., Angoa-Pérez, M., Briggs, D.I., Viano, D.C., Kreipke, C.W., Kuhn, D.M. (2012). A mouse model of human repetitive mild traumatic brain injury. *J Neurosci Methods* 203(1), 41–49.

Mac Donald, C.L., Johnson, A.M., Cooper, D., Nelson, E.C., Werner, N.J., Shimony, J.S., Snyder, A.Z., Raichle, M.E., Witherow, J.R., Fang, R., Flaherty, S.F., Brody, D.L. (2011). Detection of blast-related traumatic brain injury in US military personnel. *N Engl J Med*, 364, 2091–100.

Marmarou, A., Foda, M.A., van den Brink, W., Campbell, J., Kita, H., Demetriadou, K. (1994). A new model of diffuse brain injury in rats. Part I. Pathophysiology and biomechanics. *J Neurosurg,* 80, 291–300

McKee, A.C., Stein, T.D., Nowinski, C.J., Stern, R.A., Daneshvar, D.H., Alvarez, V.E., et al. (2013). The spectrum of disease in chronic traumatic encephalopathy. *Brain*, 136(1), 43–64.

Montenigro, P.H., Bernick, C., Cantu, R.C. (2015). Clinical Features of Repetitive Traumatic Brain Injury and Chronic Traumatic Encephalopathy. *Brain Pathol*, 25(3), 304–317.

Moon, R.J., Wilson, P., Kirkham, F.J., Davies, J.H. (2009). Growth monitoring following traumatic brain injury. *Arch Dis Child*, 94, 699–701.

Okie, S. Traumatic brain injury in the war zone. (2005). *N Engl J Med*, 352, 2043–7.

Omalu, B.I., Hamilton, R.L., Kamboh, M.I., DeKosky, S.T., Bailes, J. (2010). Chronic traumatic encephalopathy (CTE) in a National Football League Player: case report and emerging medicolegal practice questions. *J Forensic Nurs*, 6, 40–6.

Rutland-Brown, W., Langlois, J.A., Thomas, K.E., Xi, Y.L. (2006). Incidence of traumatic brain injury in the United States. *J Head Trauma Rehabil*, 21, 544–8.

Samini, F., Samarghandian, S., Borji, A., Mohammadi, G., Bakaian, M. (2013). Curcumin pretreatment attenuates brain lesion size and improves neurological function following traumatic brain injury in the rat. *Pharmacology, Biochemistry and Behavior,* 110(C), 238–244.

Tang, M., Taghibiglou, C. (2017). The Mechanisms of Action of Curcumin in Alzheimer's Disease. *J Alzheimers Dis*, 58(4), 1003-1016.

Van Boven, R.W., Harrington, G.S., Hackney, D.B., Ebel, A., Gauger, G., Bremner, J.D., D'Esposito, M., Detre, J.A., Haacke, E.M., Jack Jr, C.R., Jagust, W.J., Le Bihan, D., Mathis, C.A., Mueller, S., Mukherjee, P., Schuff, N., Chen, A., Weiner, M.W. (2009). Advances in neuroimaging of traumatic brain injury and posttraumatic stress disorder. *J Rehabil Res Dev*, 46, 717–57.

Wei, J., Pan, X., Pei, Z., Wang, W., Qiu, W., Shi, Z., et al. (2012). The beta-lactam antibiotic, ceftriaxone,

provides neuroprotective potential via anti-excitotoxicity and anti-inflammation response in a rat model of traumatic brain injury. *J Trauma Acute Care Surg*, 73, 654–60.

Xu, L., Nguyen, J.V., Lehar, M., Menon, A., Rha, E., Arena, J., et al. (2016). Repetitive mild traumatic brain injury with impact acceleration in the mouse: Multifocal axonopathy, neuroinflammation, and neurodegeneration in the visual system. *Experimental Neurology*, 275(Part 3), 436–449.