The Effect of sCOX2 inhibitor on S100B Protein Level, Cognitive Dysfunction and Glasgow Outcome Scale (GOS) in Moderate Traumatic Brain Injury Patient

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Abstract

S100B protein is a marker to predict outcome and corresponding prognosis in neurotrauma. Glasgow Outcome Scale (GOS) score is the most frequently used for clinical outcome scoring in traumatic brain injury (TBI) patients and cognitive dysfunction as a part of parameter outcome. The aim of this study is to determine the role of sCOX-2 inhibitors as inflammatory process inhibitor in patients with TBI through the measurement of S100B protein level, cognitive dysfunction and GOS. A double blind randomized controlled study involving patients with moderate TBI who underwent surgery in Dr. Hasan Sadikin General Hospital Bandung Indonesia. After obtaining approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital number 364//UNDC2.1.1/KEPKFN/2013, samples were divided randomly into 5 groups consisting of 6 patients: control group, COX2-group I (with a single dose of 40 mg sCOX-2 inhibitor), COX2-group II (with two separate doses of 40 mg sCOX-2 inhibitor), COX2-group III (with three separate doses of 40 mg sCOX-2 inhibitor), and COX2-group IV (with four separate doses of 40 mg sCOX-2 inhibitor four times). Blood test for S100 protein done in preoperative period and 6 hours after the last sCOX2 inhibitor given. The measure of cognitive dysfunction using MMSE score in the preoperative period, postoperative day 1, 2 until 7. The measure of GOS score in 1, 1,5 and 2 month post operatively. Data were then analyzed using Paired t-test, Chi Square and One-Way Anova statistical tests with a p-value of <0.05 considered as statistically significant. There was a change in S100B that occurred in five groups which were stated to have a significant decrease. The GOS score reached 5, achieved within 1 month postoperatively in the COX2-III and COX2-IV groups significantly, which means the effect of giving COX-2 inhibitors on the GOS score is significant. While the control group achieved GOS5 after 2 months postoperatively. In all groups including control, there was a significant improvement in MMSE, only in the COX2-IV group there was the fastest increase in MMSE value ($P<0.001$). sCOX-2 inhibitor can improving the cognitive dysfunction and GOS score in patients with moderate TBI but the mechanism not clear as anti-inflammatory effect on decreasing S100B protein level.

Keywords: GOS, moderate traumatic brain injury, MMSE, selective COX-2 inhibitor, S100B protein.

Traumatic brain injury (TBI) elicits an inflammatory response in the central nervous system (CNS) that involves both central and peripheral immune response.[1] TBI cause many reactions, one of the most prominent is neuroinflammation. However, administration of antiinflammatory drugs shortly after injury was not effective.[1,2]

Cyclooxygenase (COX2) inhibitors are drugs that work by inhibiting COX2 activity. COX2 expression is increase for prolong periods in brain region specifically associated with functional deficits after neurotrauma. COX2 has been associated with worse outcomes after brain injury, as well as early onset dementia. Reducing COX2 levels is expected to improve outcomes.[3,4,5]

S100B protein has been proposed as a putative biochemical marker in determining the extent of brain injury and corresponding prognosis in neurotrauma. Initial S100B levels have a limited prognostic value in neurotrauma with cerebrospinal fluid (CSF) concentration being highly sensitive to smallest influences like external ventricular drainage (EVD) placement. However, high initial S100B level of >0.7ug/dL (700 ng/dL) in serum are associated with 100% mortality, which might help to guide therapy strategies in severe neurotrauma.[6]

S100B performs a dual function that at low concentration is beneficial and at higher concentration, the effects are harmful. Rapidly increasing extracellular levels of S100B have shown to result in cell death and neuronal dysfunction because of an inflammatory response that activates astrocytes, microglia along with extracellular elevation in calcium level and nitric oxide level. Some authors claim that through the disrupted blood brain barrier (BBB), S100B is released into the serum. The concentration of S100B in the CSF could be up to 100 times higher than in serum. [7]

Abnormal S100 serum concentration and symptom or sign of cognitive impairment were not significant associated in patient with mild traumatic brain injury and a Glasgow Coma Scale of 14 or 15.[8]

S100B is a calcium-binding protein released into the blood from astroglial cells due to brain injury. Some authors have described a correlation between S100B serum concentration and severity of brain damage. S100B concentration in serum were significantly in patient who were dead a month after the accident compared to survivor. The best cut-offs for S100B serum were 0.461 ug/L. Determination of S100B levels in serum act as a sensitive and effective biomarker for the early prediction of mortality after severe TBI. Due to specificity of its cellular expression, S100B protein is useful biological marker of acute neurological disorder, such as ischemic or hemorrhagic stroke and traumatic brain injury.[9]

S100B can be used as a versatile screening, monitoring, and prediction tool in the management of TBI patients.[10] There was a significant positive association between S100B protein concentration and mortality.[11]

Since the S100 protein can predict the outcome, the higher the S100 protein content the higher the mortality. Outcome can be assessed by determining the improvement of cognitive dysfunction and the value of GOS or GOSE. So if with COX2 inhibitors S100 protein levels can be lowered, it will increase GOS and improve cognitive dysfunction.[11]

Evaluate of Glasgow Outcome (GOS) score as a prognostic indicator in patient with TBI.[12]. The GOS is used to objectively assess and categorized patient recovering from brain injury and divided them into group, which allow a standardized description of recovery. The assessment is divided into 5 categories which give a prediction of a long term course of rehabilitation and recovery.[13]

Cognitive dysfunction measure by mini mental state examination (MMSE) and divided into 3 categories. No cognitive dysfunction if the value of MMSE is 24-30, mild cognitive dysfunction if 18-23 and severe cognitive dysfunction if the value of MMSE is 0-17.[14,15]

The aim of this study was to explore the relation between the level of protein S100B and cognitive dysfunction as measured by the MMSE and total outcome as measured by the Glasgow Outcome Scale. Want to prove that if TBI is an inflammatory disease, it will improve with the administration of COX2 inhibitors with signs of decreased S100 protein, improvement of GCS and improvement of cognitive dysfunction.

Research Methods

A double-blind experimental Randomized Controlled Trial (RCT) study was performed on 30 subjects consisting of patients with head injuries undergoing neurosurgery in Dr. Hasan Sadikin General Hospital Bandung-Indonesia

from December 2013 until December 2015. who met the inclusion and exclusion criteria.

Inclusion criteria:

1. Men and women aged 13-60 years.
2. Traumatic brain injury with GCS 9-12 and without other injuries.
3. All patients who underwent surgery (epidural hematoma, subdural hematoma, intracranial hemorrhage).
4. Incidence of traumatic brain injury less than 24 hours.
5. American Society of Anesthesiologist (ASA) physical status II.

Exclusion criteria:

1. Had taken non steroidal antiinflammatory drugs (NSAIDs) during the period of 30 days.
2. Unstable blood pressure (systolic blood pressure <90 mmHg).
3. Pregnant and menstruating.

Drop out criteria:

1. Died before the 3rd postoperative day.
2. Surgical time of more than 4 hours.

Analysis of all data with general characteristics was performed using One-Way Anova while the gender variable was analyzed using Chi Square. Results were considered as significant if $p < 0.05$ and highly significant if $p < 0.01$.

The type of analysis used for decrease of S100B protein was decided based on the data distribution; if all data were normally distributed, Paired t-test (Paired t test) was used with the One-Way Anova as the comparison test for more than two independent groups. However, if one group was not normal, Wilcoxon's test was used for two paired group comparison and Kruskal Wallis was used for comparison of more than two independent groups.

The study was started after approval of the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital number 364//UNDC2.1.1/KEPKFN/2013. After informed consent from the family member, patients with moderate TBI (GCS 9-12) and without injury elsewhere were positioned head-up 30^0, had their blood pressure, core temperature, blood sugar, SpO_2, and GCS measured non-invasively. Blood was sampled baseline S100B protein measurement.

Samples were divided into 5 groups, 4 COX2 treatment groups and control. The treatment groups (COX-2) were COX2-I, COX2-II, COX2-III, and COX2-IV, each consisting of 6 patients who received 40 mg intravenous COX-2 inhibitor once, twice, 3 times, and four times, respectively. The interval from the first dose was 12 hours. The control group received 0.9% NaCl in the same time with COX-2 inhibitor.

Intravenous induction was performed with propofol 2 mg/kg, vecuronium bromide 0.8 mg/kg, fentanyl 2 μg/kg, lidocaine 1.5 mg/kg, and 1.5 MAC isoflurane with oxygen 6 L/min followed by non-kinking endotracheal intubation. Maintenance of anesthesia was conducted using isoflurane 1 MAC, oxygen 3 L/min, air 2 L/min, continuous propofol 0.5-1 mg/kg/hour, and continuous vecuronium 0.1 mg/kg/hour. An additional intravenous line with a No. 18 intravenous catheter and a urinary catheter was done. Patient's breathing was controlled during surgery and 0.5 g/kg mannitol was given intravenously. The second group received 500 mg intravenous metamizole analgesics postoperatively.

Depending on the group, the treatment group was granted another dose of COX-2 inhibitor 12 hours, 12 and 24 hours after the first, and 12, 24 and 36 hours after the administration of pre-induction COX-2, while the control group was given 2 cc of 0.9% NaCl. In Group I, II, III, and IV, blood sample was drawn 6 hours after the administration of the final COX-2 dose for S-100 protein examination. The GOS score was conducted during the preoperative and 1 month, 1.5 months, and 2 months postoperative days. Mini Mental State Examination (MMSE) assessment was conducted during the preoperative and first until seventh postoperative days.

Result and Discussion

General characteristics

The general characteristics include the age, weight, range of events, systolic blood pressure, diastolic blood pressure, blood glucose, GCS, oxygen saturation, temperature and operating time variables, which were tested using the One-Way Anova test. Meanwhile, the gender variable was tested using the Chi Square test. Results were considered significant if $p < 0.05$ and highly significant if $p < 0.01$.

The results of the statistical tests on the general characteristic data of the five groups

presented a value of p> 0.05, meaning that there was no significant difference between the five groups and that the groups were relatively homogeneous to be compared. The statistical test results are presented in table 1.

Table 1. General Characteristics

General Characteristics	Group					p-value
	Control	COX2-I	COX2-II	COX2-III	COX2-IV	
	n=6	n=6	n=6	n=6	n=6	
Age (year)	36.17 (16.68)	31.67 (13.62)	24.67 (12.61)	28.33 (16.21)	26.83 (9.37)	0.650
Sex Man	5	5	5	6	5	0.886
	(83.30%)	(83.30%)	(83.30%)	(100%)	(83.30%)	
Woman	1	1	1	0	1	
	(16.70%)	(16.70%)	(16.70%)	(0%)	(16.70%)	
Body Weight (kg)	65.00 (10.49)	62.17 (8.50)	58.67 (7.12)	61.67 (9.31)	64.17 (11.14)	0.798
Incidence range (h)	9.00	11.00	12.00	10.17	8.00	0.389
	(2.61)	(2.53)	(5.18)	(4.71)	(3.52)	
SBP (mmHg)	118.67 (12.24)	137.33 (32.63)	117.17 (30.33)	120.67 (22.99)	122.67 (16.48)	0.617
DBP (mmHg)	75.17 (6.15)	72.5 (10.62)	63.33 (20.1)	72.83 (11.43)	78.50 (5.79)	0.287
Blood glucosa (mg%)	181.33 (40.27)	142.5 (8.62)	139.67 (33.1)	138.33 (28.39)	160.5 (26.4)	0.079
GCS	11.00 (1.26)	11.17 (1.17)	10.50 (0.84)	10.50 (1.22)	11.50 (1.38)	0.535
Core temp (°C)	35.62 (0.84)	35.98 (1.01)	36.30 (0.53)	36.35 (0.67)	36.53 (0.79)	0.308
SpO_2 (%)	100	100	100	99.67 (0.82)	99.83	0.537
	0	0	0	(0.82)	(0.41)	
LOS (hour)	2.61	2.58	2.56	2.63	2.57	0.998
	(0.45)	(0.49)	(0.35)	(0.43)	(0.34)	

Note: p-value was obtained from One Way Anova test. Except for gender variable which used Chi Square. Significant difference was reached if p <0.05 and a highly significant difference was reached if p< 0.01. COX2-I: COX-2 inhibitor was given once; COX2-II: COX-2 inhibitor was given twice; COX2-III: COX-2 inhibitor was given three times COX2-IV: COX-2 inhibitor was given 4 times; Control: NaCl 0.9%, SBD= Systolic blood pressure, DBP= Diastolic blood pressure, GCS= Glasgow coma scale. LOS=length of surgery.

S100B protein Level

The results of the pre- and post-operative levels of S100B protein for each group are presented in table 2.

In the following section, a comparison of the pre- and postoperative S100B protein values between the five groups studied is presented. Also seen the comparison of the value of S100B protein in the five study groups, both preoperative and postoperative. This type of analysis uses a paired

t-test to compare pre and postoperative, as well as the One Way Anova comparison test to test the comparison of S100B protein in five groups.

Table 2. Comparative test S-100B protein

Group		Comparative Test of S-100B protein (ng/mL)		Mean Changes (Δ)	p-value
		Pre Op	Post Op		
		Mean (SD)	Mean (SD)		
COX2-I	Mean (SD)	32.29 (14.72)	9.96 (4.22)	-22.33	**0.015***
	Median (Range)	29.57 (10.29 – 54.17)	10.92 (4.55 – 15.09)		
COX2-II	Mean (SD)	13.37 (6.65)	3.65 (2.42)	-9.73	**0.028***
	Median (Range)	13.38 (2.92 – 21.13)	3.02 (1.96 – 8.46)		
COX2-III	Mean (SD)	12.33 (6.49)	3.59 (0.38)	-8.74	**0.020***
	Median (Range)	13.86 (3.21 - 20)	3.67 (2.92 – 4.05)		
COX2-IV	Mean (SD)	20.18 (5.3)	4.32 (2.09)	-15.87	**0.001****
	Median (Range)	20.36 (11.83 – 28.34)	3.53 (2.13 – 7.38)		
Control	Mean (SD)	39.48 (21.57)	27.7 (17.01)	-11.78	**0.042***
	Median (Range)	51.25 (5.71 – 56.88)	31.02 (5.33 – 45.42)		
p-value		**0.003***	**0.001***	**0.132**	

Note: p value is obtained from the result of the analysis: a) Paired Samples t Test, b) One Way Anova. *) significant difference if $p < 0.05$, and **) very significant difference if $p < 0.01$

The cut-off of S100B level of >0.7ug/dL (>7 ng/mL) in serum are associated with 100% mortality, which might help to guide therapy strategies in severe neurotrauma.6 In the COX2-IV group from 20.18 ng/ml it felt very significant to 4.32 ng/mL (p=0.001).

Comparative analysis of the S100B protein values in the five preoperative groups resulted in a p-value of $0.003 < 0.01$ which indicated significant differences in S100 protein were found in the five preoperative study groups. Similarly, a comparative analysis of the S100B protein values in the five postoperative groups resulted in a p-value of $0.000 < 0.01$ which indicated a very significant difference in S100 protein in the five postoperative study groups. This means that both preoperative and postoperative administration of different treatments resulted in significant differences in S100 protein levels, including when compared to the control group. However, if we compare the value of the difference in changes from preoperative to postoperative, the difference is not significant ($p = 0.132 > 0.05$) which indicates that the difference in changes from preoperative to postoperative in the five treatments (including control) is the same no group produced significantly higher results than the other groups.

Based on Table 2, it can be seen that after surgery there was a significant decrease in S100B protein in all treatment groups including the control group, where the resulting p-value was less than 0.05. The highest decrease in S100B protein occurred in the control group (29.27 ng/mL), then the second highest was in the COX2-I group (22.33 g/mL) and the third highest was in the COX2-IV group (15.87 ng/mL). By using one Way Anova analysis, obtained a p-value of 0.035

which exceeds 0.05. These results indicate that the changes in S100B protein that occurred in the five groups experienced a significant decrease.

Glasgow Outcome Score (GOS)

Table 3. GOS 5 Post-Operative

GOS 5 Post Operative	Group					p-value
	COX2-I	COX2-II	COX2-III	COX2-IV	Control	
	n = 6	n = 6	n = 6	n = 6	n = 6	
1 month	2/6	4/6	6/6	6/6	0/6	
1.5 months	4/6	2/6	0/6	0/6	4/6	**0.003**
2 months	0/6	0/6	0/6	0/6	2/6	

Note: p-value was obtained from Chi Square. *) Significant difference if p <0.05, and **) highly significant difference if p <0.01. COX2-I: COX-2 inhibitor was given once; COX2-II: COX-2 inhibitor was given twice; COX2-III: COX-2 inhibitor was given three times, COX2-IV: COX-2 inhibitor was given 4 times; Control: NaCl 0.9%.

The GOS score reached 5, achieved within 1 month postoperatively in the COX2-III and COX2-IV groups significantly which means the effect of giving COX-2 inhibitors on GOS scores is significant. While the control group achieved GOS5 after 2 months postoperatively.

Based on the table 3 above, it is known that patients who achieved the GOS 5 scale within 1 month were dominated by patients with COX2-III and COX2-IV treatment with 6 people each (6/6), then the COX2-II group of 4 people. (4/6) and 2 people in the COX2-I group (2/6), all from the treatment group and none from the control group. Patients who achieved the GOS 5 scale within 1.5 months were dominated by patients with COX2-I treatment and the control group with 4 people each (4/6), then the COX2-II group with 2 people (2/6). Meanwhile, patients who achieved the GOS 5 scale within 2 months were only found in the control group, namely 2 people (2/6). Based on the Chi Square test, a p-value of 0.003 < 0.01 was obtained. This shows that the duration of achieving postoperative GOS 5 has a very significant relationship with the study group. The faster time to reach GOS 5 was produced by the COX2-III and COX2-IV treatment, then the COX2-II group and finally the COX2-I group, while the longer time to reach GOS 5 was produced by the control group. Thus, it can be concluded that the treatment group, especially COX2-III and COX2-IV, was shown to provide a faster time to reach GOS 5 or be discharged from the hospital compared to the control group.

Based on the table above, it is known that the fastest time to reach the GOS 5 scale was produced by patients in the COX2-III and COX2-IV groups with 1 month each, while the COX2-II group was 1.17 months and the COX2-I group was 1.33 months. The longest time was produced by the control group with an average of 1.67 months.

From the table above, it is known that significant differences in the length of time to reach GOS were found between the control group with COX2-IV, control with COX2-III, and control with COX2-II. Meanwhile, the COX2-I group and the control group were still classified as the same or not significantly different.

MMSE Score

Table 4. Comparative test MMSE Score

Group	**Median MMSE Score**								**p-value** [a)]
	P0	**POD1**	**POD2**	**POD3**	**POD4**	**POD5**	**POD6**	**POD7**	
COX2-I	11.0	14.0	21.0	21.0	24.0	27.0	27.0	27.0	**< 0.001****
COX2-II	15.0	19.0	22.5	22.5	27.0	28.5	28.5	30.0	**< 0.001****

COX2-III	10.5	14.0	18.5	22.5	25.5	26.5	30.0	30.0	< **0.001****
COX2-IV	18.0	21.5	24.0	24.0	27.0	30.0	30.0	30.0	< **0.001****
Control	15.0	19.0	22.5	22.5	27.0	28.5	28.5	30.0	< **0.001****
p-value [b)]	0.187	0.324	0.376	0.659	0.614	0.585	0.855	0.125	

Note: p value obtained from the result of the analysis using: a) Friedman test (comparison of more than two groups in pairs), b) Kruskal Wallis test (comparison of more than two independent groups). *) significant difference if $p < 0.05$, and **) very significant difference if $p < 0.01$. P0: preoperative, POD: postoperative day. MMSE value 0-17 severe cognitive dysfunction, 18-23 mild cognitive dysfunction, 24-30 no cognitive dysfunction.

In all groups including controls, there was a significant improvement in MMSE, only in the COX2-IV group the fastest increase in MMSE values occurred at 2 postoperative days ($p<0.001$).

Based on Table 4 above, it can be seen that in all treatment groups including the control group, there was a consistent increase in the median MMSE Score, where the COX2-III treatment resulted in the highest increase in MMSE scores among the other groups (from 10.5 in P0 to 30 in POD7). The comparison of the MMSE scores in the five groups at each time of observation was not significantly different ($p > 0.05$), but the increase in the median MMSE score from P0 to POD7 showed a very significant increase in all treatment groups including the control group ($p < 0.01$).

Table 5. Correlation analysis of S100B changes with changes in MMSE

	Correlation of changes in S100B with changes in MMSE (P0 - POD7)		
	r	Interpretation	p-value
COX2-I	-0,646	Strong enough	0,023*
COX2-II	-0,773	strong	0,003**
COX2-III	-0,870	strong	0,000**
COX2-IV	-0,608	Strong enough	0,036*
Control	-0,330	weak	0,294

Note: r is the correlation coefficient Pearson, correlation is significant if p-value < 0,05, very significant if < 0,01, P0 = preoperative, POD = postoperative day

Based on the table above, it is known that the correlation between changes in S100B and changes in MMSE (P0 - POD7) is stated to be quite strong for the COX2-I and COX2-IV groups, and is stated to be strong for the COX2-II and COX2-III groups, and all are significant ($p < 0.05$) was even very significant for the COX2-II and COX2-III groups. The nature of the correlation is negative, meaning that the decrease in S-100 protein was followed by an increase in the MMSE score. Weak and not significant correlation occurred in the control group.

DISCUSSION

S-100 protein Level

S100B is a calcium-binding protein released into the blood from astroglial cells due to brain injury. Some author have described a correlation between S100B serum concentration and severity of brain damage. S100B serum concentration were significantly higher in patient who were dead a month after the accident compared to survivor. [9]

S100B level of >0.7ug/dL (>7 ng/mL) in serum are associated with 100% mortality, which might help to guide therapy strategies in severe

neurotrauma.8 The best cut-offs for S100B serum is 0.461 ug/L with a sensitivity of 90% and a specificity of 88.4%. The determination of S100B level in serum act as a sensitive and an effective biomarker for the early prediction of mortality after severe TBI. [9]

The characteristics of S100B protein are S-100B can be safely integrated into existing clinical guideline, patients with low S100B level after mild TBI can safely be discharge without a CT scan, not affected by alcohol intoxication in mTBI patients, higher in elderly patient with mTBI, and the implementation of S100B into clinical guidelines was cost saving.[16]

Abnormal S100 serum concentration and symptom or sign of cognitive impairment were not significant associated in patients with mild traumatic brain injury and a Glasgow Coma Scale score of 14 or 15. [8]

Elevated cerebrospinal fluid S100B level after severe brain injury may reflect ongoing structural damage and cell death. Numerous studies have demonstrated increased S100B level, significantly above control level, after severe TBI in both CSF and serum.[17, 18]

Most of these studies have focused on serum measurement and have found the strongest positive predictive correlation with mortality.[18]

Measurement of plasma S100B on admission of patient with minor head injury is a promising screening tool that may be of help to support the clinician's decision not to perform CT imaging in certain cases of low-risk head injury.[19]

Serum S100B protein reflects injury severity and improve prediction of long term outcome after mild and moderate TBI traumatic patients.20 In the COX2-IV group, it decreased from 20.18 ng/ml to 4.32 ng/ml ($p=0.001$). In the COX 2-II to COX2-IV groups there was a decrease in S100 protein below 7 ng/mL which based on previous studies would improve outcome. The decrease in S-100B protein level was significant in the COX2-II and COX2-III groups and very significant in the COX2-IV group. Decreased levels of S100B protein can predict an improvement in outcome as indicated by the acceleration of reaching GOS 5 and improvement in cognitive dysfunction as measured by the MMSE. The administration of COX2 inhibitor, an analgesic drug that has anti-inflammatory effect, due to its anti-inflammatory effect, will reduce cerebral edema, reduce intracranial pressure, reduce cerebral ischemia and improve outcomes as indicated by accelerated improvement of cognitive function back to normal values and accelerated achievement of GOS 5.

GOS Score

Glasgow Outcome Scale (GOS) is a scoring system that is most commonly used to assess the level of outcome in patients after a traumatic head injury. This test is simple and correlates with outcome. Various factors may cause secondary injuries that can worsen or lower the GOS score.

Circumstances such as hypotension, hypertension, hypoxemia, hypercarbia, anemia, increased body temperature, and increased severity of cerebral inflammation can cause secondary injuries that decrease the GOS score.1 Due to the fact that the blood pressure, body temperature, hypoxemia, hypercarbia, and blood sugar in this study were controlled to prevent secondary injuries, it can be concluded that the GOS improvement is due to the effect of the anti-inflammatory drug, namely COX-2 inhibitor.[11,20]

Inflammation of the brain as a result of traumatic brain injury may cause cerebral edema and increased intracranial pressure. Increased intracranial pressure can lower the GOS score; therefore, preventing increased pressure in brain edema is one way to maintain GOS.[2]

Significant improvements of GOS scores was seen in the groups that received COX-2 inhibitor.

MMSE Score: Cognitive dysfunction

The contribution of brain COX2 in cognitive function has recently become a topic of intense investigation. Many studies have demonstrated the benefit of COX2-selective inhibitors in improving memory function after brain injuries. Interestingly, non-selective cyclooxygenase inhibitor treatments resulted in sustained deficits in spatial learning in the Morris Watermaze. In hippocampal slice preparations, oxygen-glucose deprivation causes a rapid and persistent tissue depolarization within 5 min. These challenges also induce rapid increases in COX2. Other findings in hippocampal slices showed selective inhibition of COX-2 (but not COX-1) decreased excitatory responses.[3]

Abnormal S-100 serum concentration and symptom or sign of cognitive impairment were not significant associated in patients with mild traumatic brain injury and a Glasgow Coma Scale

score of 14 or 15. [8]

In our research, administration of COX2 inhibitors accelerated recovery of cognitive function after TBI. The score of cognitive dysfunction are 24-30 (no cognitive dysfunction), 18-23 (mild cognitive dysfunction) and 0-17 (severe cognitive dysfunction). The treatment groups (COX-2) were COX2-I, COX2-II, COX2-III, and COX2-IV, each consisting of 6 patients who received 40 mg intravenous COX-2 inhibitor once, twice, 3 times, and four times, respectively. In all groups including controls, there was a significant improvement in MMSE, only in the COX2-IV group the fastest increase in MMSE values occurred at 2 postoperative days ($P<0.001$).

CONCLUSION

As conclusion, GOS score of 5 within 1 month was achieved by giving COX-2 inhibitors 3 times and 4 times. Recovery of cognitive dysfunction to normal levels was obtained by giving COX-2 inhibitors 4 times. A decrease in S100 protein to a safe value was obtained by giving COX2 inhibitor 2, 3 and 4 times.

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