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Effect of Selective COX-2 Inhibitor on IL-1 β and Glasgow Coma Scale (GCS) Score in Moderate Traumatic Brain Injury Patients

Dewi Yulianti Bisri[1], Zafrulah Arifin[2], Ike Sri Redjeki[1] and Tatang Bisri[1*]

[1]*Department of Anesthesiology and Intensive Care, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia*

[2]*Department of Neurosurgery, Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia*

[*]**Corresponding author:** Tatang Bisri, Department of Anesthesiology and Intensive Care, Faculty of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, Bandung, Indonesia, E-mail: tatang.bisri@yahoo.co.id

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Abstract

Glasglow Coma Scale (GCS) is the most frequently used clinical scoring for traumatic brain injury patients. The lower the GCS score is, the higher the morbidity and mortality. Neuroinflammation is one of the mechanisms of secondary brain injury. Selective cyclooxygenase (sCOX-2) inhibitors are drugs commonly used in postoperative pain which also possesses an anti-inflammatory effect. The aim of this study is to determine the role of sCOX-2 inhibitors as inflammatory process inhibitor in patients with head injury through the measurement of IL-1β and GCS score.

This is a double blind randomized controlled study involving patients with moderate head injuries who underwent surgery in Dr. Hasan Sadikin General Hospital Bandung Indonesia from December 2013 to December 2015. After obtaining approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran/Dr. Hasan Sadikin General Hospital, samples were divided randomly into 5 groups consisting of 6 patients: control group, COX2-group I (with a single dose of sCOX-2 inhibitor), COX2-group II (with two separate doses of sCOX-2 inhibitor), COX2-group III (with three separate doses of sCOX-2 inhibitor), and COX2-group IV (with four separate doses of sCOX-2 inhibitor four times). All patients received a standard therapy as recommended by the Traumatic Brain Foundation in 2007 as well as having their GCS, blood pressure, pulse rate, respiratory rate, oxygen saturation, temperature and blood sugar monitored pre- and post-operatively. Data were then analyzed using Paired Sample T-test and One-Way Anova statistical tests with a p-value of <0.05 considered as statistically significant.

Results showed that there was a very significant improvement in GCS score in COX2-group II, III, IV with p values of 0.003, 0.002, and 0.001, respectively. No significant difference was found in IL-1β between COX2-1, COX2-II, COX2-III and control group ($p<0.05$), but IL-1β increased significantly in group COX2-IV ($p=0.043$).

It is concluded that sCOX-2 inhibitor has a brain protective effect by improving the GCS score in patients with moderate head injury.

Keywords: GCS; Moderate traumatic brain injury; Neuroinflammation; Selective COX-2 inhibitor; IL-1β

Introduction

In 2010, the Centers for Diseases Control and Prevention (CDC) estimated that traumatic brain injuries (TBIs) accounted for approximately 2.5 million emergency department visits, hospitalizations, and deaths in the United States, either as an isolated injury or in combination with other injuries. Of these, approximately 87% were treated in and released from emergency departments, another 11% were hospitalized and discharged, and approximately 2% died [1]. In United Kingdom, around 1.4 million TBI patients per year were seen. TBI is the leading cause of death among adults younger than 45 years of age and children (1-15 years old). Although many patients may return to work after a mild TBI, around 50% of survivors have moderate or severe disabilities as assessed by the Glasgow Outcome Scale (GOS) or the disability outcome scale; this represents a significant morbidity [2].

In a head trauma, the primary injury results from the biomechanical effect of forces applied to the skull and brain at the time of insult and are manifested within miliseconds. Currently, there is no treatment for the primary injury. Secondary injury begins within minutes, hours, or days after the impact and represents complicating processes initiated by the primary injury [2-4].

Post-traumatic brain damage is determined by a combination of head injuries, consisting of primary and secondary head injuries. Unlike the primary head injury, the secondary head injury evolves over time; hence, it may happen during the perioperative period following the primary head injury. The typical secondary head injury involves a complex cascade of molecular and biochemical changes that leads to neuro-inflammation, brain edema, and slowly leads to the death of brain cells [2-4]. Some reports in the period of 1977 to 2002 mentioned that morbidity and mortality are still high with treatment focuses on the management of intracranial pressure and cerebral perfusion pressure (CPP). However, attempts to deliver drugs that will protect the brain are also necessary. Several pharmacological studies aiming to determine the brain protector nature of some drugs are still ongoing

with no single drug available has been proven to prevent secondary injury as a therapeutic strategy against head injuries [2-4].

Secondary head injury is an event consisting of a combination of ischemia, inflammatory and cytotoxic processes. Shortly after a traumatic brain injury, glutamate, pro-inflammatory cytokines interleukin-1α (IL-1α), interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and free radicals are released. The concentration of IL-1β is higher than the concentration of IL-1α. This can lead to brain edema which ends with brain death. The inflammatory process is caused by the release of inflammatory mediators such as quinine, cyclooxygenase products, and the cytokines IL-1α, IL-1β, IL-6, and TNF-α. This inflammatory state leads to brain edema, brain barrier damage, and increased amount of leucocytes [5-9].

Previously, it was understood that a secondary head injury triggers the release of pro-inflammatory cytokines, prostaglandins, chemokines, glutamate, free radicals, and cell death by apoptosis. Head injury is said to be an inflammatory disease; therefore, it is logical to perform a therapy that comprises anti-inflammatory agent administration. Corticosteroids and non-steroidal anti-inflammatory drugs (NSAID) COX-1 inhibitors and COX-2 inhibitors have been introduced as an analgesic anti-inflammatory and are used for the management of postoperative pain. In 2004, a study was conducted on the effect of corticosteroid after significant head injuries (CRASH) by delivering high doses methylprednisolon to 20 thousand people with head injury [10]. The study was stopped and considered a failure because it increases the mortality rate by 50% on day 14, leading to a guideline of head injury management without corticosteroids for patients with head injury [10].

The death of brain cells after a head injury may be caused by the release of glutamate and pro-inflammatory cytokines. Excessive expression of COX-2 would worsen the outcome; so, the inhibition of COX-2 may slow down cell deaths and neuro-inflammation which could make the use of NSAIDs strong anti-inflammatory effect that COX-2 inhibitors as anti-inflammatory agent in head injuries beneficial [11].

The incidence of head injuries with poor clinical outcome is still high. Therapies, which are based on guidelines that focus on managing increased intracranial pressure and cerebral perfusion pressure, do not produce satisfactory results, leading to the need of management at the cellular level. A head injury is an inflammatory disease and the severity of inflammation will affect the decline of the clinical outcomes assessed through GCS. Cyclooxygenase-2 (COX-2) inhibitor is an anti-inflammatory drug and is a promising drug for the treatment of head injuries. Therefore, understanding the mechanism of COX-2 inhibitor therapy at the cellular level through pro-inflammatory cytokine interleukin-1β (IL-1β) level and GCS score is necessary.

Materials and 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 who met the inclusion and exclusion criteria.

Inclusion criteria:

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

Exclusion criteria:

1. Had taken 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. Operating time of more than 4 h.

Data Analysis

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 IL-1β 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.

Procedure

The study was started after approval of the Health Research Ethics Committee of the Faculty of Medicine, University of Padjadjaran/Dr. Hasan Sadikin General Hospital. After informed consent from the family member, patients with moderate head injury (GCS 9-12) and without injury elsewhere were positioned head up 300, had their blood pressure, core temperature, blood sugar, SpO_2, and GCS measured non-invasively. Blood was sampled baseline IL-1β 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 IV COX-2 inhibitor once, twice, 3 times, and four times, respectively. The interval from the first dose was 12 h. The control group received 0.9% NaCl the induction of anesthesia.

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/h, and continuous vecuronium 0.1 mg/kg/h. An additional intravenous line with a No. 18 intravenous catheter and a urinary catheter was done. Patient's breathing was controlled during surgery. 0.5 g/kg Mannitol was given intravenously. The second group received 500 mg IV metamizole analgesics postoperatively.

Depending on the group, the treatment group was granted another dose of COX-2 inhibitor 12 h, 12 and 24 h after the first, and 12 h, 24 h and 36 h 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 interleukin-1β (IL-1β) Examination. The GCS score assessment was conducted during the preoperative and first, second, and third postoperative days.

Results

General characteristics

The general characteristics include the age, weight, range of events, systolic blood pressure, diastolic blood pressure, blood sugar, 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 below.

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 (83.30%)	5 (83.30%)	5 (83.30%)	6 (100%)	5 (83.30%)	0.886
Woman	1 (16.70%)	1 (16.70%)	1 (16.70%)	0 (0%)	1 (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 (2.61)	11.00 (2.53)	12.00 (5.18)	10.17 (4.71)	8.00 (3.52)	0.389
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 (h)	2.61	2.58	2.56	2.63	2.57	0.998
	(0.45)	(0.49)	(0.35)	(0.43)	(0.34)	

Table 1: General characteristics. 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.

Interleukin-1β (IL-1β) Level

The results of the pre- and post-operative levels of interleukin-1β (IL-1β) for each group are presented in Table 2.

Group		Interleukin-1β Level		P value
		Pre-Operative	Post-Operative	
		Mean (SD)	Mean (SD)	
Control	Mean (SD)	1.345 (0.863)	0.84 (0.142)	0,249
	Median (Range)	1.33 (0.38-2.74)	0.86 (0.65-0.99)	
COX2-I	Mean (SD)	0.71 (0.714)	0.571 (0.238)	0,753
	Median (Range)	0.47 (0.19-2.08)	0.53 (0.25-0.93)	
COX2-II	Mean (SD)	1.017 (0.676)	0.713 (0.426)	0,449
	Median (Range)	0.96 (0.33-2.1)	0.63 (0.25-1.25)	
COX2-III	Mean (SD)	1.075 (0.669)	0.698 (0.334)	0,184
	Median (Range)	1.2 (0.14-1.82)	0.7 (0.19-1.19)	
COX2-IV	Mean (SD)	0.417 (0.1)	0.983 (1.094)	0,043*
	Median (Range)	0.4 (0.27-0.56)	0.59 (0.4-3.2)	
P Value		0,221	0.623	

Table 2: Pre- and Post-Operative Interleukin-1β (IL-1β) Level. p-value was obtained from analysis: a) Wilcoxon Test, b) Paired Samples Test, c) Kruskal Wallis Test. *) Significant difference if $p<0.05$, dan **) 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 reduction of interleukin-1β levels in group COX2-I, II, III, and control was visible but not significant, which was indicated by a p value of >0.05. In the COX2-IV group, the increase in IL-1β level was significant ($p=0.043$).

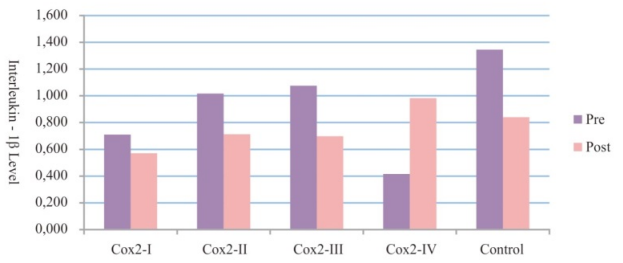

Figure 1: Glutamate Level Changes (Pre-Post) in all groups.

In Figure 1, there is a significant difference in the COX2-IV group, showing that the administration of COX2-IV in patients with head injuries increased the levels of IL-1 significantly (p=0.043). The provision of COX-2 inhibitors reduces IL-1 level in patients with moderate head injury, although not significantly. The control group presented no difference in IL-1 level.

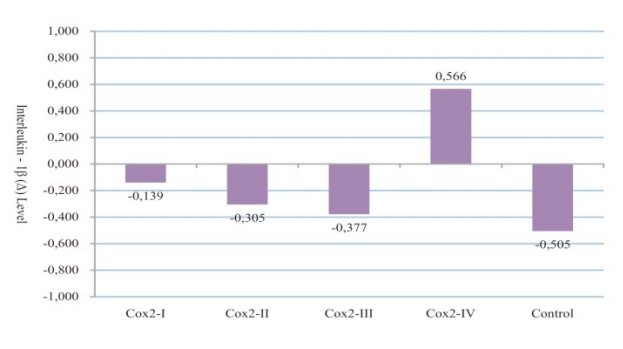

Figure 2: Comparison of Interleukin-1β changes (Pre-Post) in all groups.

GCS score

Examination of the GCS score was used to determine the clinical degree of head injury based on the parameters: eye opening, verbal response, and motor response. The GCS scores range from 3 to 15 with 15 as the best value and 3 as the worst value. In this study, the GCS score was used as a predictive for the outcome of patients with head injury.

GCS	Group					P Value
	Control	COX2-I	COX2-II	COX2-III	COX2-IV	
	n=6	n=6	n=6	n=6	n=6	
Pre-Post	11 (10-13)	11 (10-13)	10 (10-12)	10 (9-12)	12 (10-13)	0.514
Operative (day)						
I	11 (10-13)	12 (10-13)	12 (11-13)	14 (11-15)	15 (13-15)	0.003**
II	12 (10-13)	13 (12-14)	14 (13-14)	15 (12-15)	15 (14-15)	0.001**
III	12 (11-13)	15 (13-15)	15 (14-15)	15 (14-15)	15 (14-15)	0.002**
P Value	0,622	0,001**	0,001**	0,003**	0,001**	

Table 3: GCS score in postoperative Day 1 to Day 3. The p-value in the last column was obtained from Kruskal Wallis test, while the p-value in the last line was obtained from Friedman Test, *difference is significant if $p<0.05$ and **highly significant if $p<0.01$.

Table 3 presents the results from all groups that shows no significant difference in terms of the preoperative period (p=0.514), whereas the groups given a COX-2 inhibitor had significantly improved GCS scores with p=0.001, 0.001, 0.003, and 0.001, respectively. No significant increase of GCS score was found in the control group (p=0.622). The statistical tests used were Kruskal Wallis test and Friedman test.

Discussion

Central inflammation following TBI includes the proliferation of activated astrocytes and microglia proximal to the injury site that may exacerbate tissue damages after injury. Cytokines affect inflammatory cell proliferation and infiltration. Pro-inflammatory cytokines such as interleukin-1β and interleukin-6 initiate inflammation after TBI and anti-inflammatory interleukin-10 reduces this activity.

Interleukin-1 induces COX2 in endothelial, inflammatory, and lining cells of the brain. COX-2 may promote inflammatory cell proliferation and infiltration into the central nerve system (CNS) after injury. Thus, prolonged COX-2 activity may contribute to brain infiltration by macrophages and leukocytes, which is implicated in the secondary processes that produce edema, cavity, and scar formation at delayed times post injury [11].

One study showed that COX-2 inhibition reduces COX-2 expression in the cortex and hippocampus 72 h after TBI. This treatment also reduces interleukin IL-1β, a proinflammatory cytokine, in the injured brain at the cut of 12 h time point. IL-1β is proteolytically activated by caspase-1; thus, it is not surprising that its biphasic appearance closely follows that of AC3. Intracerebral microinjection of IL-1β in rat increases inflammatory cells, neuronal death, and vasogenic edema. Histochemical analysis also indicates a reduction in vascular endothelial adhesion molecule expression, similar to that described in cardiac vascular endothelial cells [11].

Cellular adhesion molecules (I-CAM, V-CAM, E-selectin) facilitate the adherence of peripheral inflammatory cells to the cerebrovascular endothelium, which is the first step in extravasation into the brain. Infiltration and proliferation of peripheral blood cells, e.g neutrophils and macrophages, exacerbate brain injury. In a pig model of ischemic brain injury, leukocyte depletion lowers mortality, improves behavioral recovery and neuropathology scores at day 7 postinjury. In addition, vasogenic edema was resulted from changes in the blood-brain barrier, emanating from the interaction of astrocytic end-feet and the cerebral vascular endothelium. If astrocyte and endothelial cell metabolism is stabilized by P-450 eicosanoids, their ability to withstand the injury and retain an intact blood brain barrier may be preserved [11].

Activation and/or inhibition of NF-κB transcription factor are likely the candidate mechanism for COX-2 inhibitor-mediated

neuroprotection. Activated NF-κB increases transcription of COX-2 in neural tissue. Its inhibitor, I-κB, can be inactivated via phosphorylation or by direct oxidation by free radicals. By reducing prostaglandin and ROS production, COX-2 inhibition may reduce NF-κB activation thus affecting its own transcription and that of other apoptosis-related genes. In addition, other eicosanoid activities might involve stabilization of NF-κB or its inhibitor, I-κB. Hence, increased brain eicosanoid production and COX-2 deficiency reduce peripheral inflammatory infiltration, glial proliferation, and scar formation [11].

GCS score

Glasgow Coma Scale (GCS) is a scoring system that is most commonly used to assess the level of awareness in patients after a traumatic head injury. This test is simple and correlates with outcome. Significant improvements of GCS scores were seen in the groups that received COX-2 inhibitor. Various factors may cause secondary injuries that can worsen or lower the GCS 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 GCS score [3]. 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 GCS improvement is due to the effect of the anti-inflammatory drug, namely COX-2 inhibitor [3,11].

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 GCS score; therefore, preventing increased pressure in brain edema is one way to maintain GCS [11].

Interleukin-1β (IL-1β) Level

In humans who suffer a head injury as an inflammatory response, micro circular endothelial cells secrete IL-1β and TNF-α that will stimulate the release of neurotoxic agents such as arachidonic acid and metabolites [5,6,12,13].

Activation of the parasympathetic nervous system produces cholinergic activation of nerve fibers of the vagus nerve and issued efferent acetylcholine at synapses. Along with this, the inflammatory activation of the vagus nerve fibers or "inflammatory reflex" occurs. This is a fast mechanism of the inflammatory response in the brain mainly of nerve fiber cholinergic. Acetylcholine secretes pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-8) but not the anti-inflammatory cytokine IL-10. Cytokines are important factors in the liaison and modulation of the immune system in the neuroendocrine system. Cytokine system can affect the brain through several mechanisms, including active transport through the blood brain barrier [6,14].

In head injuries, the inflammatory response affects the injured brain tissue. Inflammatory stress responses triggered include complement activation and up-regulation of cell-cell endotel associated with neutrophil accumulation and cytokine formation. The role of pro-inflammatory mediators in the formation of secondary lesions has been examined, including their role as serial mediators as well as the role of cytokines. Of all cytokines, the focus is primarily on IL-1β, TNF-a, IL-6 and IL-8 [5,12,15].

Immediately after injury, astrocytes and microglia release IL-1β and TNF-α, causing additional release of cytokines and mediators manufactured in the peripheral immune system. Clinical studies also show a high level of TNF-α in head injury [5,12,15].

Head injuries are considered as an inflammatory disease, in which an increase in pro-inflammatory cytokines, IL-1, IL-6 and TNF-α, will stimulate the release of neurotoxic agents such as arachidonic acid and its metabolites [5,6,12,13]. Cyclooxygenase (COX)-2 inhibitor given to the treatment groups is a drug that has anti-inflammatory effects; however, with or without COX-2 inhibitors, IL-1 decreases.

Cyclooxygenase (COX) -2 inhibitor as a drug that has anti-inflammatory effect does not work directly to reduce the level of IL-1β; it works indirectly by inhibiting arachidonic acid metabolism into prostaglandins leading to reduced amount of IL-1β produced [16-19].

In normal circumstances, IL-1β presents in the human brain; however, the level is very low. During a head injury IL-1β increases. The levels of some cytokines (IL-1β, IL-5, IL-15, IL-1 and IL-3) cannot be detected in healthy subjects due to their very low levels (under the lower limit of detection (LLOD)). In the control group in this study, the IL-1β cytokine was performed after a head injury. In this condition the levelIL-1β can be measured, reflecting the increased level of IL-1β. After COX-2 inhibitor was administered, the IL-1β level decreased in groups COX2-I, COX2-II, and COX2-III compared to the preoperative level.

In a head injury a penumbra region will be formed. The ability to recover the penumbra region depends on the speed of treatment. The IL-1β level will be reduced 24-48 h after the head injury. When given COX-2 inhibitors, the levels of IL-1β will be reduced to below normal; hence, the IL-1β in the penumbra region will be excluded as, physiologically, a normal IL-1β level protects the brain [20].

Conclusion

It can be concluded from this study that COX-2 inhibitor given intravenously has a protective effect on the brain of patients with head injuries which is reflected from improved GCS score. Faster improvement in GCS can be gained through a more frequent administration of COX-2 inhibitors. Provision of COX-2 inhibitors in various doses does not provide a real effect in reducing the level of IL-1β.

Conflict of Interest

The previous publication are similar in methodology, the difference is in the variable effect. In this research, we aimed to investigate variable effects of interleukin-1b and GCS score. We want to know clinical effect of selective COX-2 inhibitor to block citokin proinflammatory IL-1b and if we can block the inflammation processes by s-COX2 inhibitor will improving GCS score.

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