

Serum Interleukin-6 Level after Cyclooxygenase-2 Inhibitor Treatment in Moderate Traumatic Brain Injury

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Abstract

The most clinical scoring of traumatic brain injury patient is Glasgow Coma Scale (GCS) score. Lower GCS score higher IL-6 level and higher morbidity and mortality. Neuroinflammation is one mechanism of secondary brain injury. Selective cyclooxygenase (sCOX-2) inhibitors are drugs commonly used in treatment of postoperative pain but also possess an anti-inflammatory effect. The aim of this study is to determine the role of sCOX-2 inhibitors as inhibitors of inflammatory processes in patients with head injury measured by IL-6.

This is a double blind randomized controlled study involving patients with moderate head injuries who underwent surgery in Dr. Hasan Sadikin Hospital Bandung Indonesia since December 2013 until December 2015. After obtaining approval of research ethics committees from School of Medicine Universitas Padjadjaran/Dr. Hasan Sadikin Hospital, samples were divided randomly into 5 groups: control group, COX2-group I (given sCOX-2 inhibitor ones), COX2-group II (given sCOX-2 inhibitor twice), COX2-group III (given sCOX-2 inhibitor thrice), and COX2-group IV (given sCOX-2 inhibitor four times), each group containing 6 patients. All patients received standard therapy as recommended by Traumatic Brain Foundation in 2007 as well as monitoring of GCS, blood pressure, pulse rate, respiratory rate, oxygen saturation, temperature and blood sugar in pre and postoperative stages. The data was analyzed using statistical tests Paired Samples T-test and One Way Anova, p-value <0.05 as statistical significant.

Result shows that data pretest IL-6, data posttest and IL-6 changes of both groups is not significance ($p > 0.05$). In treatment group (Cox-2 I, Cox-2 II, Cox-2 III dan Cox-2 IV) overall are decrease of IL-6=10%, which is $p = 0.083 < 0.10$, if $p = 0.05$ that is not significance ($p > 0.05$).

The study is concluded that sCOX-2 inhibitor has a brain protective effect by lowering IL-6 level in patients with moderate head injury.

Keywords: Moderate traumatic brain injury; Neuroinflammation; Selective COX-2 inhibitor; IL-6

Introduction

Pathophysiology of brain injury is functionally divided into 4 categories, namely: (1) primary brain injury that occurs upon impact of injury, (2) secondary injury, that involves high lactate level, free oxygen radical, interleukin, glutamate and free intracellular Ca as a response to primary injury, (3) inflammation response with further neurodegeneration involving free radicals and toxic neurochemicals, and (4) regeneration with unclear explanation [1,2].

Head injury will stimulate neural cells to synthesize and release inflammatory cytokines such as peptides from interleukin (IL) group and TNF- α . Patients with moderate head injury have increased levels of IL-1, IL-6, and TNF- α in their circulation and cerebrospinal fluid [3-6].

After head injury in mice, microglia is responsible for IL-1 and IL-6 production. Astroglial have demonstrated the relationship between upregulation with inflammatory cytokines such as IL-1 α , IL-1 β , and

TNF- α in post-traumatic murine. In humans with head injury, as part of inflammatory response, microcellular endothelial cells release IL-1 β and TNF- α that will eventually stimulate the release of neurotoxic agents such as arachidonic acid and their metabolites [3-6].

Inflammatory response is a modulation of a direct two way relationship between brain tissue and immune system. The relationship between brain tissue and immune system is divided into 2 broad mechanisms, (1) a hormonal response, especially involving hypothalamus-pituitary-adrenal, identical to hypothalamus-pituitary-gonad (HPG); hypothalamus-pituitary-thyroid (HPT); hypothalamus-growth hormone axis, (2) autonomic nervous system, including release of noradrenaline and acetylcholine from sympathetic and parasympathic nervous system, immune system also involves cytokine release [3].

Parasympathic nervous system activation results in cholinergic activation of the efferent vagus nerve fibers and release acetylcholine on the synapse. There is also inflammatory activation of vagus nerve fibers called inflammatory reflex. This is a rapid inflammatory brain response from cholinergic nerve fibers. Acetylcholine releases pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6 and IL-8) but not anti-inflammatory cytokine IL-10. Cytokine play an important role as a

communicator and modulator between immune and neuroendocrine system. Cytokine system may modulate brain tissue through various mechanisms, including active transport in the blood brain barrier [1,3].

In head injury, inflammatory response affects injured brain tissue. Inflammatory stress response is part of the complement activation and upregulation of endothelial cells that are linked with neutrophil accumulation and cytokine production. The role of proinflammatory mediator in formation of secondary lesions has been investigated, including serial mediators such as cytokine. Among the cytokines, IL-1 β , TNF- α , IL-6 and IL-8 are especially important [4,5,7].

IL-6 has both pro- and anti-inflammatory properties. High level of IL-6 in the plasma and cerebrospinal fluid are found in post-traumatic brain injury patients. IL-6 may also promote vasopressin secretion and plays a role in the pathogenesis of syndrome of inappropriate antidiuretic hormone (SIADH) after traumatic brain injury [4,5,7].

COX-2 inhibitors are potent neuroprotectors both *in vitro* and *in vivo*. Inhibition of COX-2 protected neurons in mixed cultures against NMDA excitotoxicity. Significantly, COX-2 specific inhibition blocked neuronal cell death, whereas COX-1 specific inhibition did not [8].

The aim of this study is to examine whether the administration of COX-2 inhibitor will reduce IL-6 as inflammatory marker and if so, whether COX-2 inhibitor has a brain protection effect in patients with traumatic brain injury.

Subject and Method

This is an experimental double blind randomized controlled trial involving patients with moderate head injury admitted to Dr. Hasan Sadikin Hospital who will undergo neurosurgery and fulfilled inclusion and exclusion criteria.

Inclusion criteria:

- 1. Male and female between 13-60 years old.
- 2. Moderate head injury with GCS 9-12 with no other injuries.
- 3. All patients undergoing surgery (epidural hematoma, subdural hematoma, intracranial haemorrhage).
- 4. Injury <24 h.
- 5. ASA II.

Exclusion criteria:

- 1. NSAID usage within 30 days.
- 2. Unstable blood pressure (systolic blood pressure <90 mmHg).
- 3. Pregnancy and menstruation.

Drop-out criteria:

- 1. Patient died before 3 days postoperative.
- 2. Surgery >4 h.

Sample size is determined based on formula sample of five groups using Kastenbaum curve with confidence level of 95% and power test of 80% and $d/s=0.5$ therefore each group contains of 6 subjects. Total number of subjects is 30 patients with 10% drop out yielding 33 patients. Statistical analyses for characteristic data using One Way ANOVA, with gender variable as the exception using Chi-Square,

significant statistical difference if $p<0.05$ and very significant statistical difference if $p<0.01$.

Method

Study is conducted after obtaining ethical clearance from Ethical Committee of Medical Faculty of Universitas Padjadjaran/Hasan Sadikin Hospital Bandung Indonesia. After obtaining informed consent, patients with moderate head injury (GCS 9-12) without other injuries were positioned 300 head up along with examination of non-invasive blood pressure, core temperature, blood glucose and SpO₂.

Sample was divided into 5 groups, treatment group COX2 and control. The treatment groups (COX2) was divided into 4 subgroups, COX2-I, COX2-II, COX2-III, and COX2-IV each consisting of 6 patients, each of whom receives 40mg of intravenous COX-2 inhibitor similar dose for analgesia in adult patient. Group COX2-I: receives 1 dose of COX-2 inhibitor; group COX2-II: receives 2 doses of COX-2 inhibitor; group COX2-III: receives 3 doses of COX-2 inhibitor; group COX2-IV: receives 4 doses of COX-2 inhibitor with 12 h interval. Control group receives 0.9% NaCl prior to anaesthetic induction.

Intravenous induction was performed using 2 mg/kgBW propofol, 0.8 mg/kgBW vecuronium bromide, 2 μ g/kgBW fentanyl, 1.5 mg/kgBW lidocaine and 1.5 MAC isoflurane with 6 L/minute oxygen. Subjects were intubated using non-kinking endotracheal tube. Maintenance of anaesthesia using 1 MAC isoflurane, 3 L/minute oxygen, 2L/minute air, continuous 0.5-1 mg/kgBW/h of propofol, and continuous 0.1 mg/kgBW/h of vecuronium. Each patient receives additional 18 G intravenous and urinary catheter placement. Ventilation was controlled throughout the surgery. Each patient receives 0.5 mg/kgBW intravenous mannitol and 500 mg metamizole as postoperative analgesia.

Depends on the subgroup, patients in COX2-II group receives another dose of COX-2 inhibitor after 12 h, 24 h for COX2-III group and 36 h for COX2-IV group after initial dose of COX-2 inhibitor prior to induction, and patients in control group receive 2cc of 0.9% NaCl. Blood samples were obtained from patients in subgroup I, II, III and IV 6 h after the last COX-2 inhibitor dose to examine the level of IL-6. In the control group, blood sampel take in the similar time with treatment group. The usual recommended dose of COX-2 inhibitor parexocib is 40 mg intravenously every 12 h (twice per day). The measuring IL-6 serum using ELISA.

Result and Discussion

General characteristics of study subjects

General characteristics including age, body weight, onset of injury, systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose level (BGL), GCS, oxygen saturation, core temperature and duration of surgery were analyzed using One Way ANOVA, whereas gender was analyzed using Chi-Square test. Significant statistical difference if $p<0.05$ and very statistical significant if $p<0.01$.

Analysis on characteristic data shows no statistical difference with $p>0.05$ among the five groups therefore eligible for comparison. The result of statistical analysis of general characteristic is displayed on Table 1 below. Comparison of IL-6 in all groups can be seen in Tables 2 and 3 below.

General Characteristic	Groups					p value
	Control	COX2-I	COX2-II	COX2-III	COX2-IV	
	n=6	n=6	n=6	n=6	n=6	
Age (years)	36.17 (16.68)	31.67 (13.62)	24.67 (12.61)	28.33 (16.21)	26.83 (9.37)	0.650
Gender	5 (83.30%)	5 (83.30%)	5 (83.30%)	6 (100%)	5 (83.30%)	0.886
M	1 (16.70%)	1 (16.70%)	1 (16.70%)	0 (0%)	1 (16.70%)	
F						
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
Onset of injury (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
BGL (mg%)	181.33 (40.27)	142.5 (8.62)	139.67 (33.1)	138.33 (28.9)	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 temperature (°C)	35.62 (0.84)	35.98 (1.01)	36.30 (0.53)	36.35 (0.67)	36.53 (0.79)	0.308
Oxygen saturation (%)	100 0	100 0	100 0	99.67 (0.82) (0.82)	99.83 (0.41)	0.537
Duration of surgery (h)	2.61 (0.45)	2.58 (0.49)	2.56 (0.35)	2.63 (0.43)	2.57 (0.34)	0.998

p-value was obtained using One Way Anova, with exception for gender variable using Chi Square test, significant statistical difference if p<0.05 and very significant statistical difference if p<0.01, COX2-I: 1 dose of COX-2 inhibitor administration; COX2-II: 2 doses of COX-2 inhibitor administration; COX2-III: 3 doses of COX-2 inhibitor administration; COX2-IV: 4 doses of COX-2 inhibitor administration; control: 0.9% NaCl administration, SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BGL: Blood Glucose Level; GCS: Glasgow Coma Scale.

Table 1: General Characteristics of Study Subjects (mean-SD).

Variable	Group					All sample N=30	p value ^{a)}
	COX2-I	COX2-II	COX2-III	COX2-IV	Control		
	n=6	n=6	n=6	n=6	n=6		
IL-6							
IL-6 Pre-operative	119.28 (178.16)	54.25 (79.24)	56.09 (51.92)	31.89 (26.16)	100.39 (106.51)	72.36 (100.86)	0.572
IL-6 Post-operative	48.35 (49.97)	40.21 (27.9)	19.3 (9.4)	25.63 (13.01)	36.39 (40.5)	33.97 (31.67)	0.55

	ΔIL-6 (Pre-Post)	70.93	14.03	36.8	6.26	64	38.4	0.72
		(143.64)	(81.97)	(56.53)	(27.2)	(129.21)	(94.68)	
p-value (pre-post) ^{b)}		0.281	0.692	0.172	0.597	0.297	0.034	

p-value was obtained using: a) One Way Anova, b) paired t-test, significant statistical difference if p<0.05 and very significant statistical difference if p<0.01.

Table 2: Comparison of IL (6 level in all groups (mean (SD)).

Variable	Group		p value ^{a)}
	COX2 I-IV	Control	
	(n=24)	(n=6)	
IL-6			
IL-6 Pre	65.38 (100.52)	100.39 (106.51)	0.457
IL-6 Post	33.37 (30.10)	36.39 (40.5)	0.839
Δ IL-6 (Pre (Post)	32.00 (86.37)	64 (129.21)	0.469
p-value (pre (post) ^{b)}		0.083	0.279

p-value was obtained using: a) independent (t-test, b) paired t-test, significant statistical difference if p<0.05 and very significant statistical difference if p<0.01.

Table 3: Comparison of IL-6 between treatment (COX-2) and Control Group.

Based on the table above, there is no significant difference in either pre (operative IL-6, post (operative IL-6 or change in IL-6 between the two groups (p>0.05). In treatment group (COX2 (I, COX2 (II, COX2 (III, and COX2 (IV) there is an overall 10% reduction of IL-6 level, where p 0.083<0.10, however, using=0.05, the value is not significant (p>0.05).

Table 1 and Figure 1 show a reduction of IL-6 from preoperative to post (operative in all groups, both treatment and control. However, the reduction in IL-6 level in each group is not significant, shown by p value>0.05 using paired t-test.

Comparison of preoperative IL-6 among all groups using One Way ANOVA showed that the difference is not statistically significant with p>0.05. Similarly, comparison of postoperative IL-6 among all groups using One Way ANOVA showed no difference with p>0.05.

Table 2 and Figure 2 above show significant reduction in IL-6 (p<0.05) from 72.38 pg/mL to 33.97 pg/mL. We can conclude that there is a reduction in average level of IL-6 in all treatment group (n=30) from preoperative to postoperative, however, if assess individually for each group, where number of sample is 6, the difference is not statistically significant (p>0.05).

This may be explained by reduction of IL-6 level only occurs in a few number of samples, whereas a few other samples experience an increase in IL-6 level.

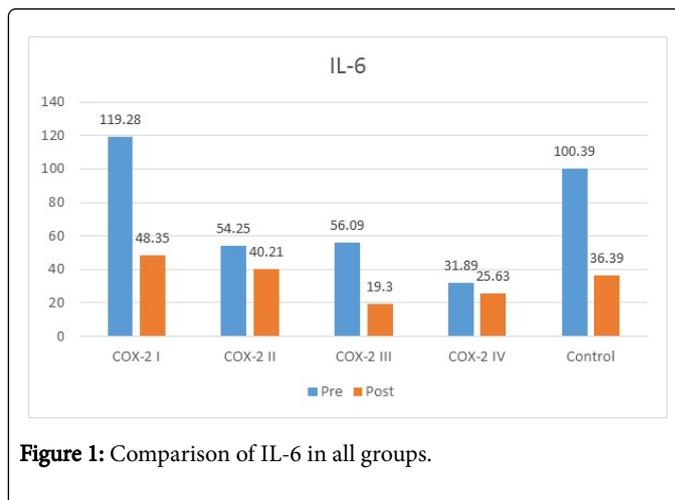


Figure 1: Comparison of IL-6 in all groups.

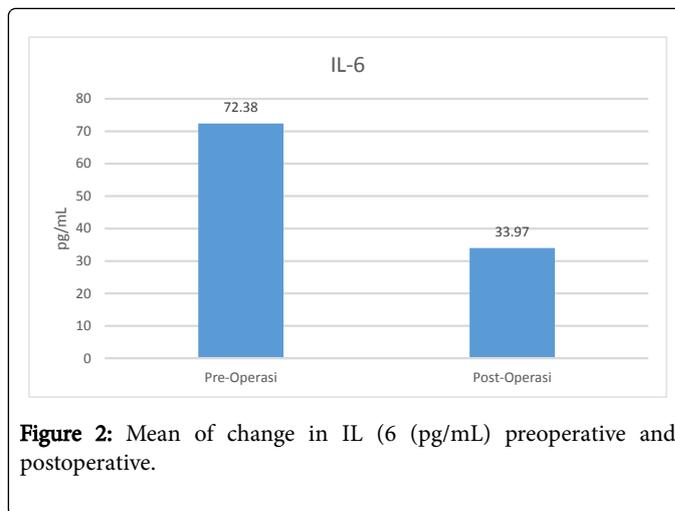


Figure 2: Mean of change in IL (6 (pg/mL) preoperative and postoperative.

Discussion

Cyclooxygenase (COX) is an enzyme that catalyzes prostaglandin synthesis from arachidonic acid. Prostaglandin mediates many processes in the body including secretion of gastric protective layer, maintenance of renal function, and platelet aggregation. Nonsteroidal anti-inflammatory drugs (NSAID) block the mechanism of COX therefore reduce the formation of prostaglandin, resulting in both positive (analgesia, anti-inflammation) and negative (gastric ulceration, reduction in renal function, bleeding) outcomes. The activity of COX is linked with 2 isoenzymes, namely COX-1 and COX-2. COX-1 is found mainly in gastric mucosa, renal parenchyme and platelet. COX-1 has minimal effect on pro (inflammatory hormonal response. This enzyme is essential in homeostasis such as

platelet aggregation, maintenance of gastrointestinal mucosal integrity and renal function. On the contrary, COX-2 causes and is expressed in injured tissues (renal and brain) and mediates inflammation, fever, pain and carcinogenesis. COX-2 does not have a protective role. COX-2 expression may facilitate a few oncogenic processes, such as tumor invasion, angiogenesis, haematemesis. Regulation of COX-2 occurs in spinal cord in response to surgical stimulation which may play an important role in central sensitization. In response to inflammation, COX-2 expression increases by 10-20 times [9-12].

Nonsteroidal antiinflammatory drugs (NSAID) suppress prostaglandin and thromboxane, which play an important role in gastric homeostasis (PGE₂ and PGI₂), renal (PGE₂) and platelets (thromboxane A₂ and PGI₂), the primary mechanism where NSAID cause some negative effects. Additionally, inhibition of prostaglandin synthesis by NSAID has been considered to contribute to bronchospasm and inhibition for new bone formation [13].

Nonsteroidal antiinflammatory drugs (NSAID) is drug with analgesia, anti (inflammatory and anti (pyretic effects. These drugs are categorized as conventional none (specific inhibitor in two forms, COX (ibuprofen, naproxen, aspirin, acetaminofen, ketorolac) and selective COX-2 inhibitor (celecoxib, rofecoxib, valdecoxib, parecoxib). All NSAID and COX-2 inhibitors have ceiling effects and increasing their dosage will only increase the risks of toxicity. Inhibition of COX-1 is responsible for many adverse effects caused by conventional NSAID [9-13].

Non-steroidal anti-inflammatory drugs (NSAID) work peripherally (without involvement of central nervous system) and the analgesia effect is secondary to anti (inflammatory effect, caused by inhibition of prostaglandin. Inhibition of prostaglandin is also responsible for the main adverse effects namely platelet dysfunction and gastritis. NSAID are commonly used as a single agent for mild and moderate postoperative pain. NSAID have an opioid sparing effect if used in conjunction with opioid. Considering the advantages and disadvantages, they are only used to 1-2 days. NSAID are contraindicated in patients with bleeding disorder, receiving anti (coagulants, history of peptide ulcer disease and gastritis, and renal dysfunction [9-13].

Nonsteroidal anti-inflammatory drugs (NSAID) are drug with analgesia, anti (inflammatory and anti (pyretic effects. NSAID have both central and peripheral effects. Anti (pyretic is achieved centrally through hypothalamus whereas analgesia is peripherally. Latest studies showed that there is an also possible central analgesia effect through inhibition of descending pain pathway. Most dominant theory is that NSAID works peripherally through inhibition of prostaglandin synthesis therefore reducing inflammation and pain. Prostaglandin synthesis is prevented by inhibition of COX-2. Cyclooxygenase-2 (COX-2) converts arachidonic acid from cellular damage into prostaglandin D, E and F, prostacylin and thromboxane. Damaged cells and activation of phospholipase release arachidonic acid, which will be converted into prostanoid and leukotriene by COX-2 and lipoxygenase, resulting in production of reactive free radicals [13].

The role of COX (2 and its inhibition in the brain must be evaluated in a broader context than metabolism of arachidonic acid. Perturbation or brain insult will activate phospholipase, releasing arachidonic acid from membrane reserve. Cyclooxygenase-2 (COX-2) catalyses the conversion of arachidonic acid and molecular oxygen into vasoactive prostaglandin, a process which produces free radicals [9-14].

Cyclooxygenase-2 (COX-2) overexpression illustrates marker and effector from damage cells after brain injury, and in normal and pathological aging processes in the brain. Cyclooxygenase-2 (COX-2) inhibitor may have a neuroprotective effect by reducing prostanoid and free radical production, or by substituting metabolic pathway of arachidonic acid. Arachidonic shunting hypothesis states that neuroprotective effect of COX-2 inhibitor may be mediated by the increase of production of eicosinoids. Under the condition where activation of COX-2 is inhibited, accumulation of arachidonic acid or conversion into eicosanoids through lipoxygenase and cytochrome P (450-CYP) epoxygenase. A number of P450 eicosanoid have been shown to have a beneficial effect on brain tissue and/or peripherally. We suspect that shunting of arachidonic acid may play an important role in functional recovery after brain injury that alters prostanoid per se. Therefore, inhibition of COX-2 and arachidonic acid shunting has a therapeutic implication outside the suppression of prostaglandin synthesis and formation of free radicals [9-14].

The severity of neural injury appears to correlate to the degree and duration of COX-2 overexpression, mild injury yield shorter elevation (≤ 24 h) of COX-2 mRNA and prostaglandin production, while moderate to severe injuries yield extended elevation (≥ 3 days) in brain cells. This may due to a vicious cycle, in which secondary injury cascades promulgate COX-2 expressions. Increase COX-2 expression has been observed with head trauma, cerebral ischemia, spreading depression, and seizure. Overexpression of brain COX-2 may reflect its role in chronic inflammation and neural cell death. Early on after moderate brain injury, neuron show increase COX-2 level that may persist for 1-3 days [8].

Several COX-2 specific inhibitors have been employed to treat brain injury. Their efficacy, when administered at various dose and time before or after neurological insult has not been entirely consistent, perhaps because of widely different partition coefficients across the blood-brain barrier [8]. However, the overwhelming preponderance of evidence clearly shows that protracted brain COX-2 activity mediates a toxic response that worsen functional and neuroanatomical deficits after brain and spinal cord injury. Thus, COX-2 inhibitors that benefit in the injured brain likely produce their effect primarily by reducing COX-2 activity rather than by suppressing free radical-mediated brain damage or other specific mechanism [8].

In this study, administration of COX-2 inhibitor blocks the production of COX-2 which reduces overexpression of COX-2, therefore reducing neural cell damage, shown by a reduction in IL-6 level.

Conclusion

The study concludes that COX-2 inhibitor has a brain protective effect by lowering IL-6 level in patients with moderate head injury.

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