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Effect of folinic acid on serum homocysteine, TNFα, IL-10, and HMGB1 gene expression in head injury model

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ABSTRACT

Background: Head injury or traumatic brain injury is the leading cause of mortality and morbidity. Many modalities of neuroprotection had been developed in brain injury but there was no much information regarding folinic acid's effect on neuroinflammation associated with homocysteine, TNFα, IL-10, and HMGB1.
Objective: This study aimed to investigate whether folinic acid has improving effect on head injury model.
Method: This study was done in the rat's head injury model using modified Marmarou weight drop model. Fifteen rats were randomized and grouped into 3 groups: Group A: Folinic acid (+), head injury (−); Group B: Folinic acid (−), head injury (+); Group C: Folinic acid (+), head injury (+). Folinic acid was administered intraperitoneally with a dose of 60 mg/m^2. Blood samples were taken immediately after head injury (H0), 12 h (H12), and 24 h (H24) after head injury from the lateral vein of tail. Serum level of homocysteine, TNFα, and IL-10 were measured using ELISA, and HMGB1 gene expression was measured with Real-Time RT-PCR.
Results: This study found serum level of homocysteine, TNFα, IL-10 and HMGB1 gene expression were markedly increased at all time points after head injury. Significantly lower level of serum homocysteine, TNFα, IL-10 and HMGB1 gene expression were found after 24 h treatment with folinic acid in group C compared to those in group B.
Conclusion: Folinic acid may have anti-inflammatory properties in traumatic brain injury by inhibition of serum level of homocysteine, TNFα, IL-10 and HMGB1 gene expression.

1. Introduction

Head injury or traumatic brain injury is the leading cause of mortality and morbidity. The highest incidence of head injury by region was in South East Asia and West Pacific region [1]. Generally, head injury incidence is increasing, predominantly in developing countries [2]. Cases of head injury frequently affect the productive population; thus, disability and death will impact the economy of a family and country.

After the onset of head injury, inflammatory responses will occur like in other normal tissues in the body. Primary and secondary insults will activate the release of proinflammatory mediators (cytokines, chemokines, prostaglandin, free radicals, complement, cell adhesion molecules (Intracellular Adhesion Molecule (ICAM1) and Vascular Cell Adhesion Molecule (VCAM1)). Inflammatory mediators will cause recruitment and infiltration of neutrophils, macrophages, lymphocytes and upregulation of proinflammatory enzymes (Tumor Necrosis Factor (TNF) and interleukins (IL)). Further damage will cause the release of neurotoxic mediator directly or nitric oxide (NO) and cytokines indirectly. The release of vasoconstrictors (prostaglandin and leukotriene) and damage of microvascular structures caused by the adhesion of leucocyte and

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thrombocyte, blood-brain-barrier damage, and tissue edema will cause a decrease in tissue perfusion, thus increasing the severity of secondary brain injury [3–5]. Neuroinflammation in head injury is like a symphony and balance between proinflammatory and anti-inflammation responses [6,7]. This study evaluated homocysteine, TNFα, IL-10, and HMGB1 as a biological markers of inflammation in traumatic brain injury.

Homocysteine is a natural amino acid (2-amino-4-sulfanylbutanoic acid). This protein is non proteinogenic, has sulphur bond, and a by-product of methionine metabolism. Methionine is known as the single source of homocysteine. In oxidative stress environment, homocysteine will go *trans*-sulphuration into glutathione. In brain injury, there is a condition of nitrogen imbalance, indirectly causing a decrease of methionine level, thus increasing homocysteine. This condition is related with the degree of injury [8]. In inflammatory process, homocysteine is one of risk factors for developing vascular, cardiovascular, and cerebrovascular diseases [9]. In head injury cases, plasma homocysteine level is an independent risk factor for a significantly worse outcome [10].

TNFα is a cytokine produced by macrophages and monocytes stimulated by lymphocytes B and T and mast cells. This cytokine has major function of cell proliferation and cell death. TNFα works through its receptor, TNF receptor (TNFR), a TNFR1-associated death domain protein (TRADD). The interaction of TNFα with its receptor will increase activation of Nuclear Factor kappa B (NFkB) and Mitogen Activated Protein Kinases (MAPKs), thus causing inflammation, tissue degeneration, cell proliferation, cell survival, and immune response regulation [11].

The main known anti-inflammatory agent in inflammation process is IL-10, which has a property to influence immunomodulation function and has an important part in resolution phase. IL-10 has been described as cytokine synthesis inhibitory factor. IL-10 has the ability to decrease the expression of cytokine receptors and inhibition of its activation. By decreasing T-cell activity, monocyte, and macrophage [12], IL-10 cause inhibition of proinflammatory cytokine, antigen presentation, and cell proliferation [13]. IL-10 also participates in inflammation, IL-10 paradox, by increasing differentiation, proliferation, cell survival and B-cell antibody production. IL-10 may also increase the proliferation of mast cells and thymocytes [14]. In the animal model with head injury experiment, the expression of IL-10 in brain tissue was found to be increased immediately after injury, and its protein was found to increase after 2–24 h [15].

HMGB1 is a non-histone nuclear protein which can directly interact with DNA and has an important role in cell's live or death after injury or stress [16]. First described in 1999, this protein was described to has an extracellular role in inflammation [17]. This protein has two domains which can interact with DNA, called Box-A and Box-B. Furthermore, HMGB1 has three cysteine residues (C23, C45, C106). Structural differences from the residues are called isoform redox, which will give different effect of HMGB1. HMGB1 will increase autophagy and chemotaxis through CXCL12, CXCR4, and RAGE in all-thiol structure. In disulfide bond of C23–C45 will cause extracellular proinflammation and cytokine induction through extracellular RAGE or TLR4. In all-oxidized form, HMGB1 will cause apoptosis cascade [6,16]. Intracellularly, HMGB1 has a role as a transcription factor, enhancer, sliding nucleosome, DNA repair, V(D)J recombination, and telomere homeostasis. In the cytoplasm, HMGB1 functions as autophagy process and viral sensing. Extracellularly, HMGB1 has a role as Damage Associated Molecular Pattern (DAMPs) [18]. In brain injury model, using LPS as the insult has increased plasma HMGB1 about thirty times compared to control in 45 min [19,20] to 1 h after injury, which then stabilize in 2–6 h after injury [21] and peaked in 16 h [22]. HMGB1 has a role in blood-brain-barrier compromise and brain inflammation, also indirectly has a role in secondary brain damage [23,24].

Folinic acid (FA) is a derivative of folic acid and its metabolism would influence homocysteine concentration. FA has been used in combination with 5-fluoro-uracil (a chemotherapy agent) since 1982 for treatment of colorectal cancer, and also has been used in conjunction with methotrexate as a salvage treatment. FA and folic acid could decrease homocysteine concentration and there were no difference in effect between both [25]. The effects of FA on serum levels of homocysteine, TNFα, IL-10 and HMGB1 gene expression and the association amongst them are not well described; thus it is reasonable to see their interaction in the current study.

2. Material and method

This study examined the effect of intraperitoneal (i.p.) injection of FA on serum level of homocysteine, TNFα, IL10, and HMGB1 gene expression in weight-drop head injury model. The model was categorized into three groups: A, B, and C. Group A with FA (+) and head injury (−), group B with FA (−) and head injury (+), and group C with FA (+) and head injury (+). There were no control group (FA (−) head injury (−)), baseline data could be extracted from group A before treated with FA. This study was done at Molecular Biology and Immunology Laboratory, Hasanuddin University, Indonesia in August and October 2020. This study was approved by the Faculty of Medicine Ethics committee, Hasanuddin University (Reference Number: 649/UN4.6.5.31/PP36/2020). Fifteen healthy male Sprague-Dawley rats, aged more than 2 months-old, weighing 150–250g, were randomly and equally divided into group A,B, and C. Water and diet provided *ad libitum* (Comfeed AD-2) with 12 h day and night cycle. The rats were acclimatized and treated under the Ethical principles of animal use and care. Confounders were not controlled.

2.1. Surgical procedure

Rats were weighted and anesthetised with i.m. ketamine at 2–10 mg/kg. In antiseptic and aseptic procedure using povidone iodine, linear incision was done with no. 15 blade on midline 1,5 cm posterior from coronal suture, periosteum subsequently elevated. One burr hole with a diameter of 0,5-1 cm was made to expose the dura mater. This head injury experiment was done in accordance with the modified Marmarou model [26,27]. The exposed dura mater area was placed on a platform attached with a tube. A mass of 20 g was dropped from 20 cm height, with the tube as a tract, enabling the impact was directly on the exposed area. A thread was attached to the end of the mass, easily pulled to avoid secondary impact after recoil. After head injury, wound was sutured with 3–0 silk and antibiotic ointment was applied. Rats in group A, the group without head injury, no mass was dropped. All rats were observed in a recovery room before returned to their designated group cages.

2.2. Folinic acid administration

Folinic acid obtained as calcium folinate (PT. Kalbe Farma, Jakarta, Indonesia), diluted with normal saline solution into 10 mg/ml concentration, administered as i.p. injection, 1 h after head injury at a dose of 60 mg/m^2 [28]. Rat's body surface area was calculated from weight using Meeh formula (total body surface area = kW$^{2/3}$, with k as a constant of 9,83 [29].

2.3. Sample collection and examination

0.3 ml of blood sample were collected from lateral tail vein using 0.5 ml syringe immediately (H0), 12 h (H12), and 24 h (H24) after head injury. Serum was collected for ELISA examination. There were no samples excluded from the study.

Serum homocysteine, TNFα and IL-10 levels were measured using ELISA for homocysteine (Cusabio, USA), TNFα and IL-10 (Life Span Bioscience, Inc. of Seattle, North America) according to the manufacturer's instructions.

Blood samples were divided into two, one part for quantitative RT-PCR of HMGB1 gene expression was mixed with L6 buffer solution

and processed into nucleic acid extract, the other part were centrifuged to extract the serum. All samples were stored at −80 °C before RT-PCR and ELISA examinations.

HMGB1 gene expression was measured with β-actin as the house-keeping gene (Oligo, Macrogen, catalog number: OG280920). Primers are: β-actin forward: 5′-CCATTGAACACGGCATTG-3'; β-actin reverse: 5′-GAAGGAAGGCTGGAAGAG-3'; HMGB1 forward: 5′-TGATTAAT-GAATGAGTTCGGGC-3'; HMGB1 reverse: 5′-TGCTCAGGAAACTT-GACTGTTT-3'. RT-PCR was performed using PCR-Bio-Rad BR004129USA machine. A mixture of 22.5 μl PCR Mastermix and SYBR green QRT was prepared. DNA extract of 2.5 μl was added to 22.5 μl mixture of PCR mix. First stage amplification was performed at 94 °C for 2s and continued up to 40 cycles 60s at 94 °C, and 45s at 57 °C. Expression of mRNA were calculated according to previous study [30–32].

2.4. Statistical analysis

Data were expressed as means ± SD. All data was processed and analysed using the One-way ANOVA statistical test and continued with Tukey's post-hoc analysis. Statistical significant values were determined at $p < 0.05$.

3. Results

The average weight of the rats in group A was 194.8 g, group B was 192.6 g, and group C was 193.8 g. There were no significant differences between the three experimental groups ($p > 0.05$).

3.1. Serum homocysteine level

From the statistical analysis, data was in normal distribution. The mean serum homocysteine level of the group A at H0 was 61.74 ± 30.25 nmol/ml, H12 was 104.57 ± 25.52 nmol/ml, and H24 was 132.80 ± 27.75 nmol/ml. Mean serum homocysteine level of the group B at H0 was 302.81 ± 55.08 nmol/ml, H12 was 435,72 ± 39.83 nmol/ml, and H24 was 476.64 ± 37.64 nmol/ml. The mean serum homocysteine level of the group C at H0 was 258.82 ± 42.74 nmol/ml, H12 was 412.93 ± 54.37 nmol/ml, and H24 (median) was 340.11 ± 49.26 nmol/ml (not in normal distribution and there was an outlier with a value of 254.43 nmol/ml). The serum homocysteine levels can be seen in Fig. 1.

The serum homocysteine level data was in a normal variance. A one-way ANOVA and post-hoc Tukey analysis found statistical differences between group A and B, group A and C, but no statistical differences between B and C at H0. There were statistical differences between group A, B, and C at H12 ($p < 0.05$) and H24 ($p < 0.05$). The mean serum homocysteine level of the group C was lower than that of the group B at H12 and H24.

3.2. Serum TNFα level

Serum TNFα level data was in normal distribution. The mean serum TNFα level of the group A at H0 was 9,506.70 ± 2050.12 pg/ml, H12 was 10,739.61 ± 1,718.25 pg/ml, and H24 12,238.44 ± 1,815,91 pg/ml. Mean serum TNFα level of the group B at H0 was 1,8705.15 ± 2,361.90 pg/ml, H12 was 23,648.86 ± 1,331.25 pg/ml, and H24 2,561.95 ± 1,942.17 pg/ml. Mean serum TNFα of group C at H0 was 17,387.39 ± 2,599.41 pg/ml, H12 23,834.77 ± 780.80 pg/ml, and H24 19,377.61 ± 2,067.01 pg/ml. Serum TNFα levels of the groups in the time points can be seen in Fig. 2.

Serum TNFα level data was in a normal variance. One-way ANOVA and post-hoc Tukey analysis revealed statistical differences between the group A and B and the group A and C ($p < 0.05$), but there were no statistical differences between the group B and C at H0 and H12. There were statistical differences between the group A, B and C at H24 ($p < 0.05$). The mean value at H24 showed serum TNFα level in the group C was lower than that of in the group B.

3.3. Serum IL-10 level

From the statistical analysis, serum IL-10 level data was in normal a distribution. The mean serum IL-10 level of group A at H0 was 6,812.56 ± 1,962.95 pg/ml, H12 7,900.42 ± 2,222.07 pg/ml, and H24 8,922.75 ± 2,454.94 pg/ml. The mean serum IL-10 level of group B at H0 was 15,594.08 ± 2,025.94 pg/ml, H12 23,484.35 ± 1,869.49 pg/ml, and H24 23,611.53 ± 2,220.13 pg/ml. The mean serum IL-10 level of group C at H0 14,786.32 ± 1,802.98 pg/ml, H12 21,462.55 ± 2,330.68 pg/ml, and H24 17,343.74 ± 2,064.17 pg/ml. Serum IL-10 levels of the groups in the time points are shown in Fig. 3.

Serum IL-10 level data was in a normal variance. One-way ANOVA and post-hoc Tukey analysis showed statistical differences of serum IL-10 level between the group A and B and the group A and C ($p < 0.05$),

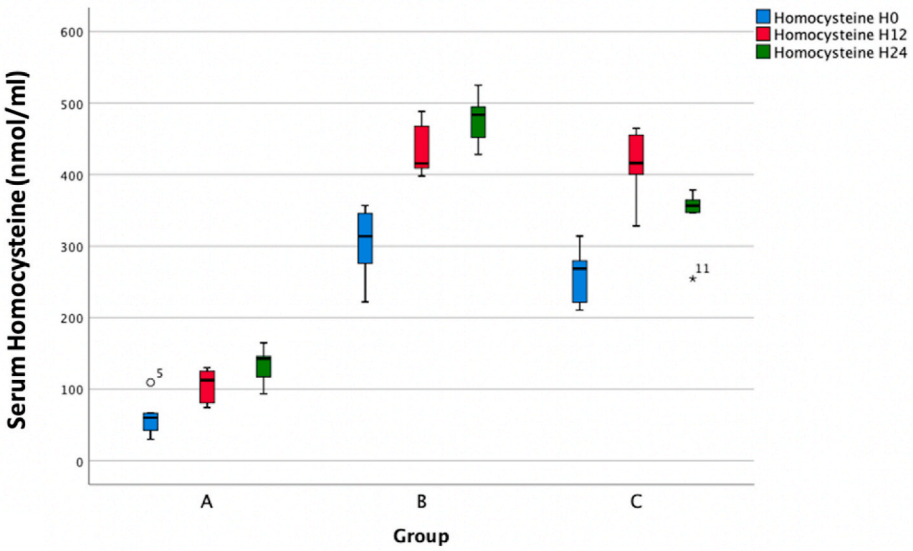

Fig. 1. Box-plot of serum homocysteine (nmol/ml). There were significant differences between group B and C. The values of H12 and H24 on group C were lower than group B. (H0: immediately after injury, H12: sample taken 12 h after injury, H24: sample taken 24 h after injury).

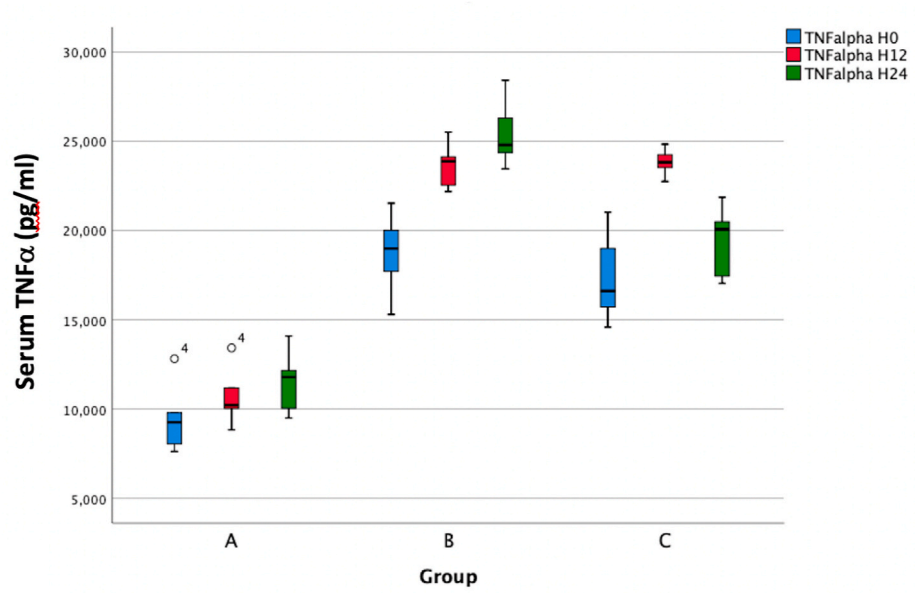

Fig. 2. Box-plot of serum TNFα (pg/ml). There were significant difference between group B and C. The values of H24 on group C were lower than group B. (H0: immediately after injury, H12: sample taken 12 h after injury, H24: sample taken 24 h after injury).

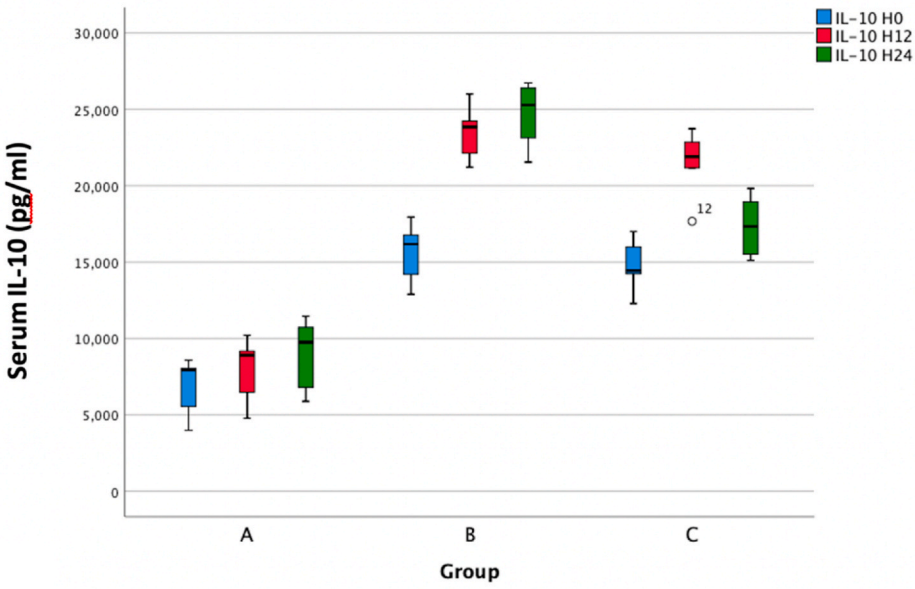

Fig. 3. Box-plot of serum IL-10 (pg/ml). There were significant difference between group B and C. The values of H24 on group C were lower than group B. (H0: immediately after injury, H12: sample taken 12 h after injury, H24: sample taken 24 h after injury).

but there were no statistical differences of serum IL-10 level between the group B and C ($p > 0.05$) at H0 and H12. There were statistical differences of serum IL-10 level in group A, B and C at H24 ($p < 0.05$). The mean value of serum IL-10 level of the group C at H24 was lower than that of in the group B.

3.4. *HMGB1 gene expression*

HMGB1 gene expression data was in normal distribution. The mean HMGB1 gene expression of the group A at H0 was 6.64 ± 1.13 fold change, H12 was 7.22 ± 1.11 fold change, and H24 was 7.58 ± 1.09 fold change. The mean HMGB1 gene expression of the group B at H0 was 11.15 ± 1.26 fold change, H12 14.58 ± 1.18 fold change, and H24 15.22 ± 0,99 fold change. The mean HMGB1 gene expression of the C at H0 was 10.49 ± 0.82 fold change, H12 14.05 ± 0.51 fold change, and H24 11.81 ± 0.63 fold change. HMGB1 gene expression in fold change can be seen in Fig. 4.

HMGB1 gene expression data was in a normal variance. One-way ANOVA and post-hoc Tukey analysis revealed statistical differences between the group A and B ($p < 0.01$), group A and C ($p < 0.05$), but there were no statistical differences between the group B and C ($p > 0.05$) at H0 and H12 samples. HMGB1 gene expression amongst groups at H24 showed statistical differences ($p < 0.05$). The mean value of HMGB1 gene expression in group C at H24 was significantly lower than that in group B.

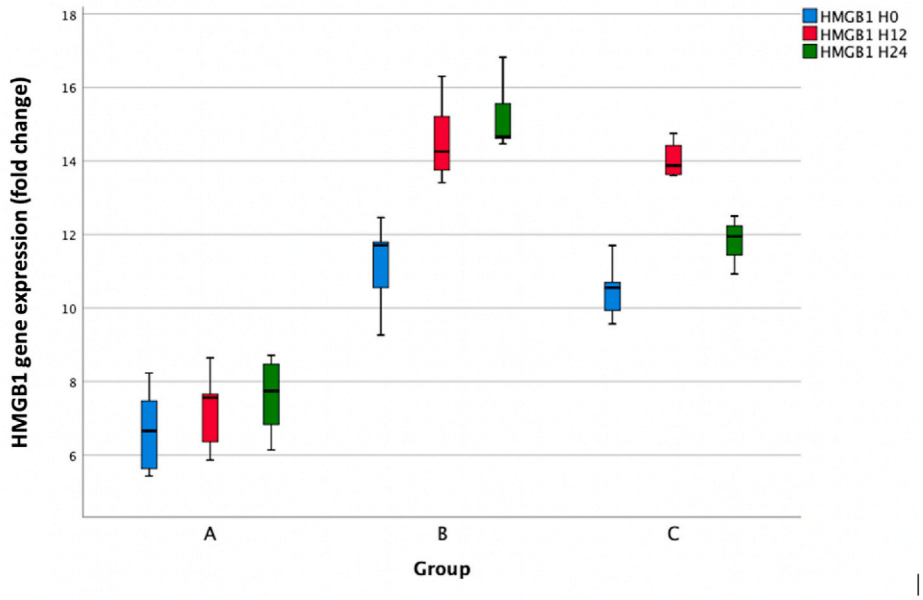

Fig. 4. Box-plot of HMGB1 expression (in fold change). There were significant difference between group B and C. The values of H24 on group C were lower than group B. (H0: immediately after injury, H12: sample taken 12 h after injury, H24: sample taken 24 h after injury).

4. Discussion

This study assessed the effect and relationship between FA administration with serum homocysteine, TNFα, IL-10, and HMGB1 gene expression in head injury model. The head injury model has been thoroughly described as one modality to study the neuroinflammation process. It has been also known that homocysteine, TNFα, IL-10 and HMGB1 are inflammation markers and their level will be found to be increased in circulating blood in the event of injury or infection.

In group A with FA (+) and head injury (−), we observed a slightly increased levels of homocysteine, TNFα, IL-10 and HMGB1 expression. This finding was in accordance with theory that inflammatory markers would be increased in injury. The incision procedure and craniotomy were a sufficient insult that could upregulate inflammatory responses.

In group B with FA (−) and head injury (+), in comparison with group A, head injury caused a major insult and corresponded to a markedly higher of inflammatory markers concentration compared to those in the group A.

In group C with FA (+) and head injury (+), all markers showed significant decrease at H24 compared to the control group B without FA. It can be concluded that administration of FA affected this reduction phenomenon. Interestingly, the same conclusion could not be seen in group A, the FA administration might not be effective in minor injuries. From the results, it could also be seen that at H0, group B and group C had the same baseline level which were higher compared with group A that did not have head injury.

Based on previous studies, HMGB1 is considered as an inflammation marker associated with coagulopathy, cerebral edema (through activation of aquaporin 4) [33], complement activation, and systemic inflammatory responses [20]. Severe injury with tissue hypoperfusion is needed for HMGB1 to be released [19] thus this statement is in line with the result of this study (small increase of markers in group A and significant increase in group B).

Inflammation causes cellular proliferation which could cause vitamin deficiency and this condition is related with hyperhomocysteinemia. Inflammation also causes nitric oxide synthesis which will bind with vitamin B12 and inhibit methionine synthase thus increasing homocysteine level. Hyperhomocysteinemia condition will cause oxidative stress which induces acute and chronic inflammation through regulation of NFkB, which is known as an agent of genetic transcription regulator of the inflammatory agents and cellular proliferation [34]. Homocysteine – methionine cycle is related with folic acid cycle, hence folic acid cycle could indirectly influence inflammatory process by its relation with homocysteine metabolism. Intervention to folic acid cycle could be done using oral intake of folic acid or folinic acid injection, as stated by a study conducted by Soleimani et al. [25] that there were no difference in effect between both agents in homocysteine reduction. From the results of this study, it could be seen that after head injury, homocysteine levels were increased up to 24 h after injury (group B) and folinic acid administration could decrease its level (group C).

The function of TNFα and IL-10 in inflammation have been thoroughly described in modern literature. In inflammation, macrophages and monocytes will secrete TNFα then causing potentiation of the immune system. When TNFα binds with its receptors, TNFR, it will cause complexes that upregulates NFkB and induces inflammatory responses further. IL-10 is known anti-inflammatory agent which has important role in resolution phase of inflammation by inhibiting pro-inflammatory agents, reducing expression and activity of cytokine receptors, reducing the activity of T cells, monocytes, and macrophages [12]. After binding with its receptors, IL-10 will inhibit translocation of NFkB into nucleus and inhibition of TLR, gene transcription, expression of class II MHC, and suppression of IL-2 and CD28. TNFα and IL-10 levels could be seen increasing in the first 24 h after injury, this findings is in accord with acute phase of inflammation.

For further studies, it would be beneficial to find any differences between local and systemic inflammatory responses and the effect of treatment of folinic acid in brain injury. The effect of folinic acid on HMGB1 in local inflammatory responses could be assessed by quantifying its expression in brain tissue or measuring protein level in tissue or CSF, and also measuring TLR or RAGE receptors in brain tissue. In systemic inflammatory responses, more data are needed to evaluate the concentration of inflammatory markers in acute, chronic, and resolution phase.

Several limitations of the study had been identified. There was no dedicated sham group, FA (−) and head injury (−), so we have limited data to extrapolate and extract conclusions. FA (−) and head injury (−) could be seen only in data in the group A at H0. The experiment was conducted solely on systemic markers (using serum and blood), hence local neuroinflammatory responses could not be evaluated. Lastly,

observation time was only in 24 h. Longer and multi-point data collection will be valuable to be evaluated in the future study to give more understanding of the inflammatory process. Furthermore, clinical function of the rats were not assessed because it was not the scope of this study. Additional handling for clinical assessment bore risks of stressors (physical and psychological) that might interfere results.

The results obtained support the conclusion that head injury model used in this study could be used to study inflammatory response after head injury. Secondly, there were decreased levels of inflammatory markers in 24 h after injury with FA treatment. Thus, FA has anti-inflammatory properties with mechanisms via suppression of homocysteine level as previously reported [25]. Whether FA decreased TNFα, IL-10 and HMGB1 levels via its effect on homocysteine or other direct or indirect mechanisms has yet to be determined in the future study.

Provenance and peer review

Not commissioned, externally peer reviewed.

Ethical approval

Ethical approval has been approved by the ethics commission of Faculty of Medicine, Hasanuddin University reference no. 649/UN4.6.5.31/PP36/2020.

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Author contribution

Thomas Tommy (TT), Andi A. Islam (AAI), Mochammad Hatta (MH) initiated and designed the study.

TT, Agussalim Bukhari (AB), MH, AAI drafted and wrote the manuscript.

Nasrullah (NS), Willy Adhimarta (WA) and Aminuddin (AM) contributed in the data processing, Andi Alfian (AAZ) performed the statistical analysis. All authors have read and approved the final manuscript.

Consent

Not applicable to the study.

Trial registry number

This study was not involving human participants. Registration was not applicable.

Guarantor

Thomas Tommy.
Mochammad Hatta.

Declaration of competing interest

There are no potential conflict of interest to be disclosed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102273.

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