

Original Research Article

Effect of levocetirizine hydrochloride on chronic urticaria and serum levels of total IgE and inflammatory factors

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Abstract

Purpose: To investigate the curative effect of levocetirizine hydrochloride tablets on chronic urticaria as well as its mediating effect on serum levels of total IgE and inflammatory factors.

Methods: Ninety-two (92) patients with chronic urticaria, were randomly divided into control group (CG) and study group (SG). Patients in CG were treated with oral administration of desloratadine citrate tablets while SG patients received oral levocetirizine hydrochloride tablets. A comparative analysis was conducted between the two patient cohorts encompassing clinical therapeutic outcomes, symptom scoring, T lymphoid subset cell levels, serum total IgE concentrations, serum inflammatory factor levels, as well as adverse reactions.

Results: Total treatment effectiveness was higher in SG (97.83 %) than in CG (82.61 %; $p < 0.05$). After treatment, wheal duration, size and number as well as pruritus scores were markedly lower in SG than in CG, albeit non-significantly ($p > 0.05$). The levels of CD3+ CD4+, and CD4+/CD8+ ratio in SG after treatment were significantly higher than those in CG ($p < 0.05$). Furthermore, the serum IgE, IL-4 and IL-13 levels were significantly lower in SG than in CG, while the IFN- γ level was significantly higher ($p < 0.05$).

Conclusion: Levocetirizine hydrochloride tablets produce a significant clinical curative effect on chronic urticaria relative to desloratadine citrate tablets. It reduces the levels of inflammatory factors and mitigates immune dysfunction in patients by increasing the serum level of total IgE. Therefore, it is a potential candidate for further clinical investigations on a larger and more diverse population.

Keywords: Levocetirizine hydrochloride tablets, Chronic urticaria, Curative effect, Serum total IgE, Inflammatory factors, Regulatory effect

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INTRODUCTION

Urticaria is one of the most common diseases in clinical dermatology and studies have shown that it is caused by a combination of several factors. The clinical manifestations of urticaria are dense

wheals of different numbers and sizes, accompanied by severe itching or angioedema [1]. Chronic urticaria is one of the clinical types of urticaria that is characterized by frequent and recurrent episodes. It occurs in all age groups, although the risk is higher in the female

population aged 40 - 50 years [2]. The occurrence of chronic urticaria is closely related to pathogen infection, environmental factors, drug stimulation, poor diet and vitamin D deficiency [3].

Anti-histamines are currently the first choice for the clinical treatment of urticaria. Desloratadine citrate, one of the common anti-histamines used in clinical practice, specifically interacts with peripheral H1 receptors [4,5]. Due to its high selectivity, desloratadine citrate is often used clinically to treat allergic rhinitis and allergic skin diseases. Levocetirizine hydrochloride, a second-generation antihistamine, is the left-handed R-enantiomer of cetirizine hydrochloride. It retains the main pharmacodynamic characteristics of cetirizine and is a highly effective and selective peripheral H1 receptor antagonist [6]. It also has been demonstrated to possess better anti-histamine and anti-inflammatory effects, and it is more effective than previous antihistamine drugs, including cetirizine [7].

In the present study, the effects of levocetirizine hydrochloride dispersible tablets and desloratadine citrate on chronic urticaria patients were compared.

METHODS

Patients

A total of ninety-two (92) patients with chronic urticaria, who were admitted to Changzhou No.4 People's Hospital, China from October 2021 to October 2022, were selected as the research subjects. Basic data such as gender, age, course of disease and educational level of the patients were collated. The random number table method was used to divide the patients into control group (CG) and study group (SG), with 46 subjects in each group. This protocol of this clinical study has been approved by the Ethics Committee of Changzhou No. 4 People's Hospital, China (approval no. C204425831). All procedures were carried out in accordance with the guidelines of Declaration of Helsinki [8]. All patients and their families were informed about the purpose of the study and they signed relevant consent forms.

Inclusion criteria

The included patients were those who were diagnosed with chronic urticaria through relevant clinical tests; patients who were ≥ 18 years old, and those whose medical records were complete. In addition, patients who had had urticaria for more than 6 weeks, and those who did not receive antihistamine, anticholinergic,

glucocorticoid and other drugs 14 days before the study, were included.

Exclusion criteria

The study excluded patients falling within the following categories: Individuals with significant organ dysfunction, those with allergies or related contraindication reactions to the drugs, methods and devices used in this research; patients with acute urticaria or malignant tumors and those whose condition was complicated with severe malnutrition and anemia. In addition, patients in special physiological periods as well as those who were unable to cooperate with the researchers due to mental or cognitive problems, were excluded from the study.

Treatments

On admission to the hospital, the patients were given calamine lotion to rub on their skin. The topical treatment was done continuously for 1 month and the patients were instructed to avoid spicy and irritating foods while concentrating on light diets.

Patients in CG were treated with desloratadine citrate tablets (Yangzijiang Pharmaceutical Group Guangzhou Hairui Pharmaceutical Co. Ltd., Zhunzi, approval no. H20090138). The treatment was given via the oral route at a dose of 8.8 mg once daily. In SG, patients received levocetirizine hydrochloride tablets (Chongqing Huabang Pharmaceutical Co. Ltd., approval no. H20040249), which were given by oral administration at a dose of 5 mg once a day.

Evaluation of parameters/indices

Treatment efficacy classification

Treatment effectiveness was classified into four categories viz: "Cured", "Markedly Effective", "Effective", and "Ineffective". A patient was considered "cured" if their clinical symptoms completely disappeared for a minimum duration of one week. Treatment outcome was adjudged "markedly effective" if the patient's rash was cured, but wheals and itching occasionally occurred. If the patient's clinical symptoms were basically reduced, but the rash, wheal, pruritus and other symptoms occurred frequently, the treatment was "effective". However, if the patient's clinical symptoms were not significantly reduced, or if the symptoms were worsened, the treatment was "ineffective".

Symptom scores

The urticaria symptom score scale was used to determine patient-related symptom scores before and after treatment. The scores ranged from 0 to 3, with scores of 0, 1, 2 and 3 points indicating asymptomatic, mild, moderate and severe, respectively.

Levels of T lymphoid subset cells

Prior to and following treatment, fasting venous blood (5 mL) was collected from each patient in the morning and serum was subsequently separated by routine methods. Levels of CD3+ and CD4+ cells, as well as the CD4+/CD8+ ratio, were determined using CytoFLEX flow cytometry.

Serum total IgE and inflammatory factor levels

Prior to treatment initiation and post-treatment, 5 mL of fasting venous blood was drawn from patients in the morning. Serum levels of immunoglobulin E (IgE), interleukin-4 (IL-4), interleukin-13 (IL-13) and interferon- γ (IFN- γ) were quantified using ELISA kits following the manufacturer's instructions.

Adverse reactions

The adverse reactions monitored were dry mouth, drowsiness, dizziness, headache, fatigue and gastrointestinal reactions.

Statistical analysis

GraphPad Prism 8 was employed for graphical visualization, while SPSS 25.0 was utilized for data analysis. Measurement data is expressed as mean \pm standard deviation (SD) and was compared using the t-test. Count data is presented as numbers and percentages, n (%), and comparisons were conducted using the χ^2

test. A significance level of $p < 0.05$ was indicative of statistically significant differences.

RESULTS

Baseline data

As shown in Table 1, the baseline data of the two groups of patients were comparable ($p > 0.05$).

Treatment effectiveness

Table 2 shows that total treatment effectiveness was significantly higher in SG (97.83 %) than in CG (82.61 %; $p > 0.05$).

Symptom score levels

As depicted in Figure 1, the duration, size, number and pruritus scores of wheals were similar in both groups before treatment. However, SG exhibited significantly reduced wheal duration, wheal size, wheal number and pruritus scores post-treatment compared to CG ($p > 0.05$).

Cell levels of T lymphoid subsets

As shown in Figure 2, the levels of CD3+ CD4+ and CD4+/CD8+ ratio in SG after treatment were significantly higher than those in CG ($p < 0.05$).

Serum levels of total IgE and inflammatory factors

As shown in Figure 3, before treatment, the serum levels of IgE, IL-4, IL-13 and IFN- γ in CG were 221.84 ± 36.84 , 85.04 ± 9.53 , 78.96 ± 9.65 and 9.58 ± 1.86 , respectively. In SG, they were 221.68 ± 36.79 , 84.98 ± 9.46 , 78.72 ± 9.38 and 9.65 ± 1.72 , respectively. The serum levels of IgE, IL-4, IL-13 and IFN- γ did not show a significant difference between the two groups.

Table 1: Comparison of baseline between the groups

Variable	CG	SG	t/ χ^2	P-value
Gender			0.044	0.834
Male	21	20		
Female	25	26		
Age range (years)	22-59	21-60		
Mean age (years)	38.68 ± 5.84	38.75 ± 5.79	-0.058	0.954
Course of disease	6 weeks-7 years	6 weeks-8 years		
Mean duration of disease (years)	3.11 ± 1.16	3.19 ± 1.21	-0.324	0.747
Educational level			0.183	0.669
High school and below	19	17		
College and above	27	29		

Table 2: Comparison of clinical treatment effectiveness

Variable	CG	SG	χ^2	P-value
Cured	12	18		
Markedly effective	15	21		
Effective	11	6		
Ineffective	8	1		
Total effectiveness (%)	38 (82.61%)	45 (97.83%)	6.035	0.014

Table 3: Comparison of adverse reactions between the 2 groups

Adverse reaction	CG	SG	χ^2	P-value
Dry mouth	1	1		
Drowsiness	1	0		
Dizziness Headache	0	1		
Weakness	2	2		
Gastrointestinal reaction	1	2		
Total incidence (%)	5 (10.87%)	6 (13.04%)	0.103	0.748

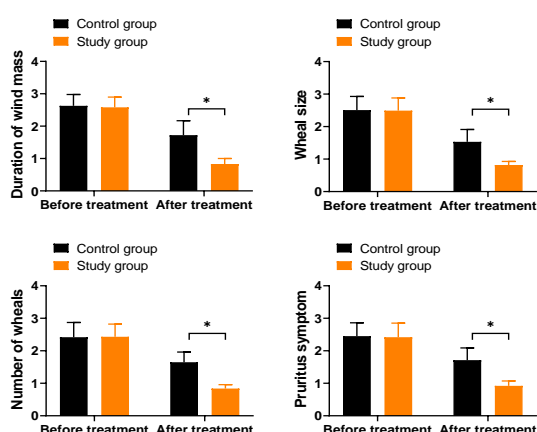


Figure 1: Comparison of symptom scores between the groups. * $P < 0.05$ vs. CG

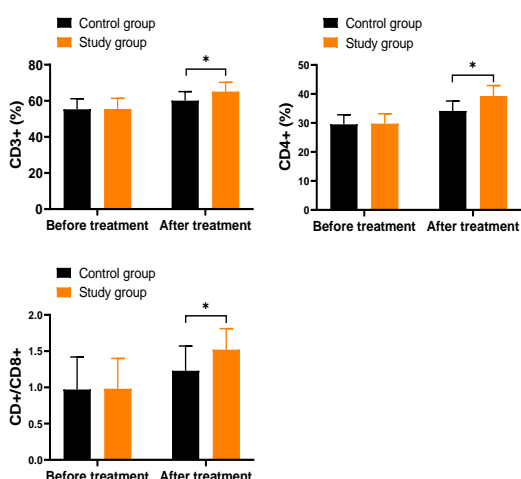


Figure 2: Comparison of levels of T lymphoid subset cells. * $P < 0.05$ vs. CG

After treatment, however, the serum levels of IgE, IL-4, IL-13, and IFN- γ in CG were 105.26 ± 20.54 , 53.58 ± 6.02 , 41.86 ± 7.25 and 22.48 ± 3.56 , respectively. In SG, they were 76.18 ± 18.85 , 46.32 ± 7.25 , 34.12 ± 6.33 and $34.19 \pm$

4.38 , respectively. The serum levels of IgE, IL-4 and IL-13 were significantly lower in SG than in CG, while the IFN- γ level was significantly higher ($p < 0.05$).

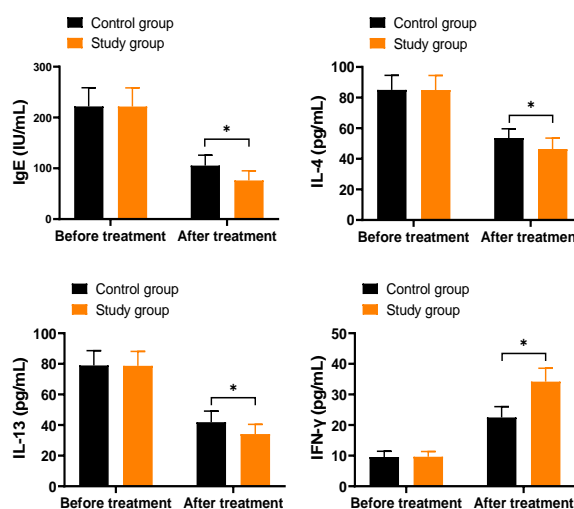


Figure 3: Serum levels of total IgE level and inflammatory factors. * $P < 0.05$ vs. CG

Adverse reactions

The incidence of adverse reactions in CG was 10.87 % while that of SG was 13.04 %. There was no significant differences in the occurrence of adverse reactions between the two groups ($p > 0.05$; Table 3).

DISCUSSION

Chronic urticaria is a common clinical allergic disease caused mostly by the action of the inflammatory factor histamine on the H receptor [1,9]. It causes severe itching and tingling in the skin of the patient. Although these situations are not life-threatening, their impact on the daily life

the patient cannot be ignored. The etiology and pathogenesis of chronic urticaria have not been fully elucidated. However, studies suggest that the disease is related to type I allergy mediated by IgE receptors [10,11]. Since it is difficult to ascertain the cause of chronic urticaria, the treatment of this disease is relatively problematic. The treatment cycle is relatively long due to frequent attacks and high recurrence rate of the disease. At present, the clinical treatment of chronic urticaria is still based on the "symptomatic" principle, that is, the use of anti-histamine drugs to block H receptors in patients, thereby alleviating and controlling the symptoms of the disease [12].

Desloratadine citrate is one of the commonly used drugs for the treatment of chronic urticaria. A third-generation antihistamine, it is a widely-used, rapid-onset and selective inhibitor of peripheral H receptors [5,13]. The drug is the left-handed R-enantiomer of cetirizine hydrochloride, and it retains the pharmacodynamic characteristics of cetirizine hydrochloride [6]. At the same time, it acts as a highly selective peripheral H₁ receptor. The anti-histamine effects of some antagonists have been reported in some clinical studies [14,15]. Another study showed that levocetirizine not only exerted potent anti-histamine effect, but it also inhibited the release of various inflammatory mediators related to allergies [16]. These features make it more effective than conventional anti-histamines in the treatment of urticaria. In a randomized, double-blind study involving healthy male volunteers, 5 mg levocetirizine hydrochloride tablets produced stronger inhibitory effect on histamine-induced wheal and flushing, when compared with a single oral administration of 10 mg mizolastine, ebastine or loratadine, and the onset time was significantly shorter [17]. This finding is consistent with the results of the present study which suggest that, compared with loratadine, levocetirizine hydrochloride tablets are more effective in the treatment of chronic urticaria. This may be related to the anti-inflammatory effect and higher bioavailability of cetirizine hydrochloride. Previous clinical studies revealed that the onset of chronic urticaria was closely related to humoral immunity mediated by IgE [18,19].

Another study showed that suppression of cellular immune function is common in patients with chronic urticaria [20]. The results of this study indicate that cellular immunity is also involved in the occurrence and development of chronic urticaria. In addition, another related study reported an imbalance in T helper cell subsets (Th1/Th2) in patients with chronic

urticaria, with Th2 response as the main response, and an imbalance between Th1 and Th2 cells resulting in chronic urticaria [21]. The Th1 and Th2 cells in humans always maintain a relationship of mutual regulation and mutual restriction. When the two are in a state of dynamic balance, they stabilize immune function. The Th2 cells secrete IL-4 and IL-13 which indirectly regulate the synthesis of total IgE in the serum of patients, with IgE enhancing the infiltration of inflammatory cells, thereby further aggravating the inflammatory response [22]. In contrast, IFN- γ is secreted by Th1 cells. It is the main cytokine for the transformation of CD4+ cells into Th1 cells. It is also involved in a two-way regulation of the immune system, and further inhibits the differentiation of Th2 cells to IgE, thereby inhibiting the occurrence of type I allergy in patients [23,24].

The study's findings revealed that post-treatment, SG exhibited significantly reduced levels of CD3+ and CD4+ cells, as well as a lower CD4+/CD8+ ratio compared to CG. Additionally, the serum concentrations of IgE, IL-4, IL-13, and IFN- γ in SG were significantly elevated in comparison to CG. These results indicate that compared with desloratadine citrate treatment, levocetirizine hydrochloride reduced levels of inflammatory factors and mitigated immune dysfunction in the patients by increasing serum level of total IgE. A comparison of drug safety between the two groups of patients showed no significant differences in the incidence of adverse reactions, suggesting that levocetirizine hydrochloride improved the effect of treatment on patients and reduced the immune dysfunction and inflammatory response without risk of adverse reactions.

Limitations of this study

The study is constrained by its small sample size of only 92 patients, which may limit the statistical power and generalizability of the findings. Additionally, the inclusion of patients from a specific hospital and region might introduce biases related to geographical and demographic factors, restricting the applicability of the results to a broader population.

CONCLUSION

Levocetirizine hydrochloride tablets produces significant clinical efficacy in the treatment of chronic urticaria relative to desloratadine citrate tablets. The use of this drug enhances the curative effect on chronic urticaria patients and reduces the degree of immune dysfunction in patients. It improves serum total IgE and reduces

inflammatory factor levels of patients and is safe. However, clinical trials on a larger and more diverse population are recommended.

DECLARATIONS

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None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lijuan Hua has the greatest contributed most to this work; Junjun Che and Wen Yuan contributed equally to the study.

Ethical Approval

This study was approved by the Ethics Committee of Changzhou No. 4 People's Hospital, China (approval no. C204425831).

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Use of Artificial Intelligence/Large Language Models

None provided.

Use of Research Reporting Tools

None provided.

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REFERENCES

1. Antia C, Baquerizo K, Korman A, Bernstein JA, Alikhan A. Urticaria: A comprehensive review: Epidemiology, diagnosis, and work-up. *J Am Acad Dermatol* 2018; 79(4): 599-614.
2. Saini SS, Kaplan AP. Chronic spontaneous urticaria: The devil's itch. *J Allergy Clin Immunol Pract* 2018; 6(4): 1097-1106.
3. He L, Yi W, Huang X, Long H, Lu Q. Chronic urticaria: Advances in understanding of the disease and clinical management. *Clin Rev Allergy Immunol* 2021; 61(3): 424-448.
4. Wedi B. Emerging treatments for chronic urticaria. *Expert Opin Investig Drugs* 2022; 31(3): 281-290.
5. AlMasoud N, Bakheit AH, Alshammari MFM, Abdel-Aziz HA, AlRabiah H. Loratadine. *Profiles Drug Subst Excip Relat Methodol* 2022; 47: 55-90.
6. Levocetirizine, in drugs and lactation database (LactMed). 2006, National Institute of Child Health and Human Development: Bethesda (MD).
7. Mirankó M, Tóth J, Fodor-Kardos A, Móricz K, Szenes-Nagy AB, Gácsi A, Spaits T, Gyenis J, Feczko T. Topical formulation of nano spray-dried levocetirizine dihydrochloride against allergic edema. *Pharmaceutics* 2022; 14(12): 2577. doi: 10.3390/pharmaceutics14122577
8. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA* 2013; 310(20): 2191-2194.
9. Hon KL, Leung AKC, Ng WGG, Loo SK. Chronic urticaria: An overview of treatment and recent patents. *Recent Pat Inflamm Allergy Drug Discov* 2019; 13(1): 27-37.
10. Johal KJ, Saini SS. Current and emerging treatments for chronic spontaneous urticaria. *Ann Allergy Asthma Immunol* 2020; 125(4): 380-387.
11. Giménez-Arnau AM, DeMontojoye L, Asero R, Cugno M, Kulthanan K, Yanase Y, Hide M, Kaplan AP. The pathogenesis of chronic spontaneous urticaria: The role of infiltrating cells. *J Allergy Clin Immunol Pract* 2021; 9(6): 2195-2208.
12. Iriarte Sotés P, Armisén M, Usero-Bárcena T, Rodríguez Fernández A, Otero Rivas MM, Gonzalez MT, Mejjide Calderón A, Veleiro B. Efficacy and safety of up-dosing antihistamines in chronic spontaneous urticaria: A systematic review of the literature. *J Investig Allergol Clin Immunol* 2021; 31(4): 282-291.
13. Van den Eynde C, Held K, Ciprietti M, De Clercq K, Kerselaers S, Marchand A, Chaltin P, Voets T, Vriens J. Loratadine, an antihistaminic drug, suppresses the

- proliferation of endometrial stromal cells by inhibition of TRPV2. *Eur J Pharmacol* 2022; 928: 175086.
14. Phinyo P, Koompawichit P, Nochaiwong S, Tovanabutra N, Chiewchanvit S, Chuamanochan M. Comparative efficacy and acceptability of licensed dose second-generation antihistamines in chronic spontaneous urticaria: A network meta-analysis. *J Allergy Clin Immunol Pract* 2021; 9(2): 956-970.e57.
 15. Cataldi, M, Maurer M, Taglialatela M, Church MK. Cardiac safety of second-generation H(1)-antihistamines when updosed in chronic spontaneous urticaria. *Clin Exp Allergy* 2019; 49(12): 1615-1623.
 16. Ino H, Shiramoto M, Eto T, Haranaka M, Irie S, Terao T, Ogura H, Wakamatsu A, Hoyano K, Nakano A. Levocetirizine oral disintegrating tablet: A randomized open-label crossover bioequivalence study in healthy Japanese volunteers. *Clin Pharmacol Drug Dev* 2020; 9(7): 805-812.
 17. Sarkar TK, Sil A, Pal S, Ghosh C, Das NK. Effectiveness and safety of levocetirizine 10 mg versus a combination of levocetirizine 5 mg and montelukast 10 mg in chronic urticaria resistant to levocetirizine 5 mg: A double-blind, randomized, controlled trial. *Indian J Dermatol Venereol Leprol* 2017; 83(5): 561-568.
 18. Asero R, Cugno M. Biomarkers of chronic spontaneous urticaria and their clinical implications. *Expert Rev Clin Immunol* 2021; 17(3): 247-254.
 19. Votto M, Achilli G, De Filippo M, Licari A, Marseglia A, Moiraghi A, Di Sabatino A, Marseglia GL. Pediatric chronic spontaneous urticaria: A brief clinician's guide. *Expert Rev Clin Immunol* 2022; 18(9): 889-899.
 20. Hori H, Fukuchi T, Sugawara, H. Chronic urticaria with inflammation. *Eur J Intern Med* 2021; 83: 84-85.
 21. Nochaiwong S, Chuamanochan M, Ruengorn C, Awiphan R, Tovanabutra N, Chiewchanvit. Evaluation of pharmacologic treatments for h1 antihistamine-refractory chronic spontaneous urticaria: A systematic review and network meta-analysis. *JAMA Dermatol* 2021; 157(11): 1316-1327.
 22. Yu Q, Lin W, Zhang J, Peng L, Kong Q, Zhong R, Lan Y, Xiao M, Chen M. The association of Th17/Treg cells expression in peripheral blood and chronic spontaneous urticaria: A protocol of systematic review and meta-analysis. *Medicine (Baltimore)* 2020; 99(36): e22014.
 23. Grieco T, Porzia A, Paolino G, Chello C, Sernicola A, Faina V, Carnicelli G, Moliterni E, Mainiero F. IFN- γ /IL-6 and related cytokines in chronic spontaneous urticaria: Evaluation of their pathogenetic role and changes during omalizumab therapy. *Int J Dermatol* 2020; 59(5): 590-594.
 24. Du F, Zhang D. Effect of naloxone hydrochloride on δ -EP, CD4+, CD8+, IL-2, MMP-9 and S100-B levels in peripheral blood after traumatic brain injury in rats. *Trop J Pharm Res* 2019; 18(4):735-740 doi: 10.4314/tjpr.v18i4.8