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NEUROPROTECTIVE EFFECT OF TELMISARTAN IN BRAIN ISCHEMIC REPERFUSION INJURY IN MALE RATS

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Abstract
Background: cerebral ischemia is one of the most common causes of morbidity and mortality over the world. Limitation of blood supply to the brain tissue by thrombi result in ischemic stroke which disrupt cellular homeostasis due to diminished oxygen and nutrient supply to the brain.
However, the restoration of blood flow to the area affected by ischemia can cause more worsening to the ischemic tissue due to a group of inflammatory and apoptotic event that result with ischemia – reperfusion injury and cause neuronal cell death and neurological dysfunction.
Aims: To study the neuroprotective effects of Telmisartan in focal cerebral ischemia reperfusion injury in rats,
Material and methods: forty male *Wister albino* rats were divided randomly into four groups as flow:
Group (1) Healthy group: the rats were subjected to the same surgical procedure as other groups but the common carotid artery was not occluded
Group (2) Control group :(ischemic-reperfused) this group will be subjected to the same surgical procedure with the unilateral common carotid artery occluded for 30 minutes.
Group (3) Telmisartan pre ischemia group: the rats orally administered (3mg/kg) for 7 days before carotid artery occlusion**.**
Group (4): Telmisartan post ischemia group: the rats orally administered (3mg/kg) for 7 days after carotid artery occlusion**.**
Results: in comparison with healthy group, the control group show significant increase in inflammatory mediator (IL-1β, IL-6, IL-8, TNF-α). Telmisartan pre and post ischemia was significantly reducing the cerebral level of (IL-1β, IL-6, IL-8, TNF-α) in comparsion with control group.
Also, the histopathological analysis revealed that each of Telmisartan pre and post ischemia reduce the severity of brain injury and damage in comparison to the control group.
Conclusions: the results of the present study showed that the use of Telmisartan in pre and post ischemia confer neuroprotection in focal cerebral ischemia reperfusion injury due to their anti-inflammatory anti-apoptotic effect.
Key word: brain ischemia, Telmisartan, neuroprotection, ischemia reperfusion injury.

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INTRODUCTION

There are two types of stroke these are ischemic and hemorrhagic, Sudden obstruction of blood flow, caused by thrombi or emboli, results in ischemic events in approximately 85% of stroke cases (Mozaffarian *et al.* 2016).
Ischemic stroke is usually caused by a short or permanent obstruction of local cerebral blood flow, which in turn triggers various pathophysiological changes (Wang *et al.* 2018).
Global cerebral ischemia result from cardiac arrest and shock is a problem of exacerbating clinical significance (Green *et al.* 1992), while focal cerebral ischemia occurs when a blood clot has occluded a cerebral vessel. Focal brain ischemia reduces blood flow to a specific brain region, increasing the risk of cell death to that particular area. It can be either caused by thrombosis or embolism (Li *et al.* 2019).
An animal model for focal cerebral ischemia is induced by disruption of blood flow to the brain for 30 min by blocking one common carotid artery and then allow for reperfusion for a one hour (Sun *et al.* 2003).
Cerebral injury is tissue damage that is aggravated by the restoration of blood supply to brain tissue that has suffered from ischemia for a certain period. Post-ischemic inflammation represents a critical component in the evolution of brain injury (Koh 2012).
The process of inflammation begins within hours after an

ischemic event occurs but can last from days up to weeks after the ischemia, Pro-inflammatory cytokines including tumor necrosis factor (TNF-_), interleukin-1_(IL-1_), and interleukin-6 (IL-6) can be released within the systemic circulation and locally within the central nervous system (CNS) parenchyma (Disdier *et al.* 2018).

MATERIAL AND METHODS

A total of 40 adult *Wister albino rat* weighing (200-300g) were purchased from the college of veterinary medicine – Tikrit university they were housed in the animal house at Tikrit University, and the temperature of the animal house was maintained at about 25 C, the humidity was maintained at a range of (60-65%) with alternating 12 hour light -12 hour dark cycles.

Until the beginning of the experiment, rats could freely access water and diet. after two weeks of adaptation, the rats were distributed randomly into 4 groups as follows:

Group (1) Healthy group: the rats were subjected to the same surgical procedure as other groups but the common carotid artery was not occluded

Group (2) Control group :(ischemic-reperfused) this group will be subjected to the same surgical procedure with the unilateral common carotid artery occluded for 30 minutes.

Group (3) Telmisartan pre ischemia group: the rats orally administered (3mg/kg) for 7 days before carotid artery occlusion**.**

Group (4): Telmisartan post ischemia group: the rats orally administered (3mg/kg) for 7 days after carotid artery occlusion**.**

Preparation of Drugs

Telmisartan powder was purchased from hyperkem, the dose was freshly prepared by dissolving it in Distilled water in a dose of 3 mg/kg **(Haraguchi *et al.* 2010)** and was given orally for 7 days before ischemia and in another group for 7 days after 1 hour of induction of ischemia.

Induction of Focal Cerebral Ischemia

Focal cerebral ischemia was produced by middle cerebral artery occlusion (MCAO) for 30 min followed by 1 hr reperfusion (Thiyagarajan and Sharma 2004), animals temperature was preserved about 37 c by the light bulb, and each rat was anesthetized by intraperitoneal injection of ketamine at a dose of 100mg/kg and xylazine at a dose of 10mg/kg (Gu *et al.* 2012).

After the rat anesthetized was placed on the back and fixed in the supine position and a small incision was performed in the middle of the neck by fine surgical tools, the carotid arteries which found under the trachea was isolated from the vagal nerve and occluded by mini vascular clamps to induce ischemia, after 30 minutes of occlusion the clamps were removed and reperfusion was allowed for 1 hour.

Preparation of Samples

The rat was decapitated after one hour of reperfusion and the brains were isolated and washed in ice-cold phosphate buffer solution, they were kept on ice and weighed then sectioned into 2 coronal slices, one slice was kept in 10 % formalin for histopathological analysis, The other slice was mixed in 1:10 (w/v) ratio with ice-cold 0.1 M PBS (Ph 7.4), then homogenized by an ultrasonic liquid processor, the homogenates were centrifuged at 15000 RPM for 30 minutes at 4 c^{o} and the supernatant was withdrawn and stored at -80 c^{o} for measurement of the biological marker by ELISA technique (Bolanle *et al.* 2012).

2.6.1 Tissue Sampling for Histopathology

The slice that fixed underwent tissue processing to be embedded in paraffin wax and were longitudinally cut into 5-micrometer sections for all specimens, the sections then stained with H&E stain for histopathological examination **(Chandrashekhar *et al.* 2010a).**

2.6.2 Histopathological Analysis and Scoring of Cerebral Injury

The histopathological analysis was done by the senior pathologist (who is blinded to the study design),The scoring system for the pathological changes in ischemia-reperfusion injury will be as follows (Pokela 2003):

0(normal)= no morphological signs of damage

1(slight)= edema or eosinophilic or dark neurons (pyknotic) or dark/ shrunk cerebellar Purkinje cells

2(moderate)=at least two small hemorrhages

3(sever)= clearly infarctive foci (local necrosis)

3. RESULTS OF THE STUDY :

3.1.1 Effect of telmisartan on Cerebral Cytokine IL-1β level

Both of Telmisartan pre and post-ischemia groups showed significantly ($p<0.05$) lower in IL-1β cerebral concentration than control.

The change in IL-1β cerebral concentration are summarized in table (1) and figure (1)

Table (1): cerebral concentration of IL-1β in different study groups (no. of animals = 10 animal in each group)

Group	IL-1β conc. In pg/ml	
	Mean ± SEM	Std
Healthy	39.32±0.82	2.61
Control	44.47±1.1	3.64
Telmisartan pre ischemia	40.61±1.1	3.37
Telmisartan pre ischemia	40.21±1.2	3.35

3.1.2 Effect on Cerebral Cytokine IL-6 level

The cerebral concentration of IL-6 was significantly ($p< 0.01$) elevated in the control group at the end of the study in comparison with the healthy group.

Both telmisartan pre and post-ischemia groups showed significantly ($p<0.05$) lower cerebral IL-6 concentration in comparison with control.

The change in IL-6 cerebral concentration are summarized in table (2) and figure (2)

3.1.3 Effect on Cerebral Cytokine IL-8 level

The cerebral concentration of IL-8 was significantly ($p<0.01$) elevated in the control group at the end of the study in comparison with the healthy group.

Both telmisartan pre and post-ischemia groups showed significantly ($p<0.01$) lower cerebral IL-8 concentration in comparison with control.

The change in IL-8 cerebral concentration are summarized in

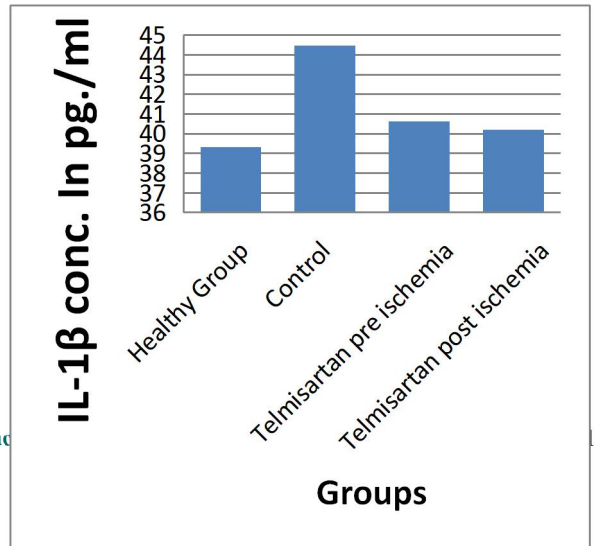


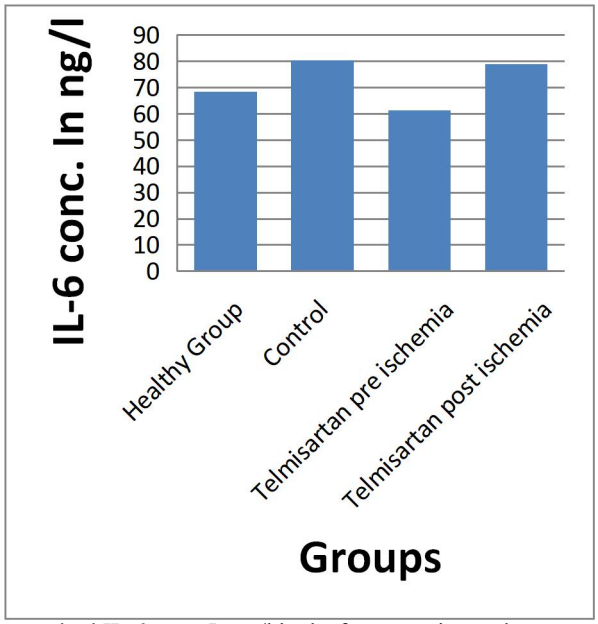
table (3) and figure (3)

Figure (1) bar chart showing the difference in the mean of cerebral IL-1β conc. In pg/ml in the four experimental groups at the end of the study (no. of animal = 10 animal in each group)

Table (2): cerebral concentration of IL-6 level in different study groups (no. of animals = 10 animal in each group)

Group	IL-6 conc. In pg/ml	
	Mean ± SEM	Std
Healthy	68.26±0.67	2.13
Control	80.30±1.9	6.10
Telmisartan pre ischemia	61.3±4.2	13.1
Telmisartan pre ischemia	78.80±1.0	3.28

Figure (2) bar chart showing the difference in the mean of



cerebral IL-6 conc. In ng/l in the four experimental groups at the end of the study (no. of animal = 10 animal in each group)

Table (3): cerebral concentration of IL-8 level in different study groups (no. of animals = 10 animal in each group)

Group	IL-8 conc. In pg/ml	
	Mean ± SEM	Std
Healthy	136.9±5.4	18.1
Control	169.4±4.8	15.0
Telmisartan pre ischemia	146.2±6.4	20.2
Telmisartan pre ischemia	145.1±6.4	20.3

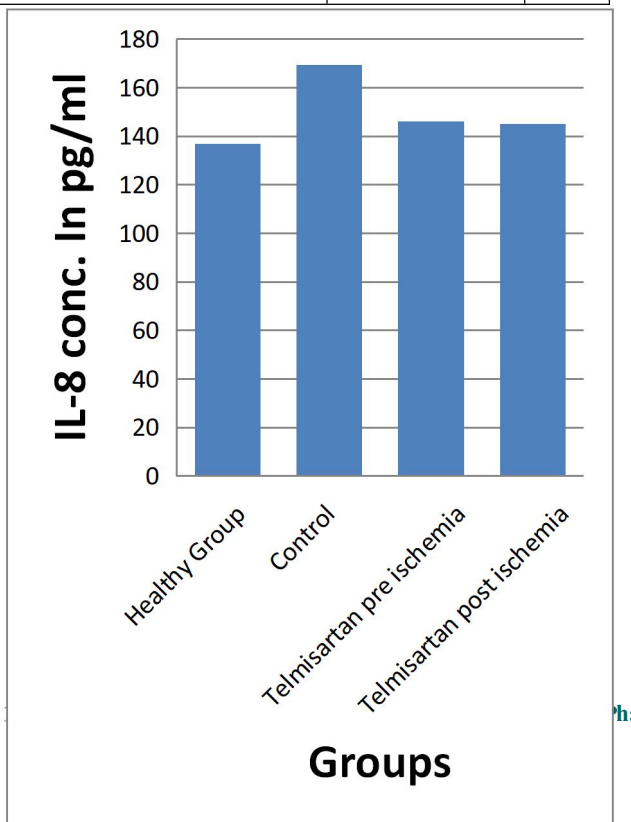


Figure (3) bar chart showing the difference in the mean of cerebral IL-8 conc. In pg/ml in the four experimental groups at the end of the study (no. of animal = 10 animal in each group)

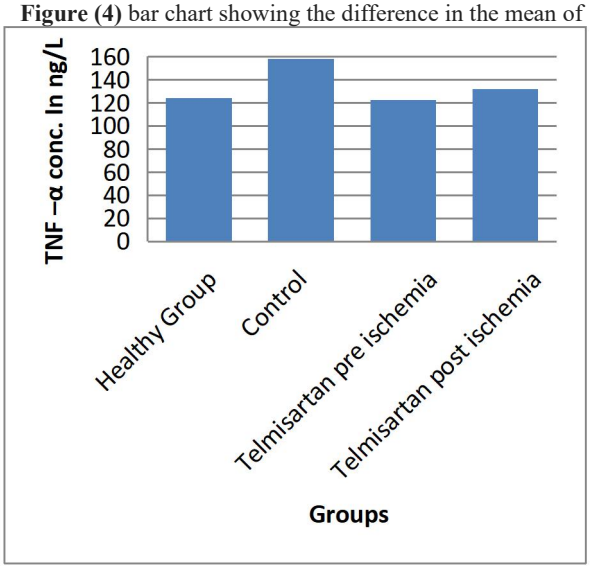
3.1.4 Effect on Cerebral Tumor Necrosis Factor (TNF-α) level

The cerebral concentration of Tumor Necrosis Factor (TNF-α) was significantly ($p<0.01$) elevated in the control group at the end of the study in comparison with the healthy group. Both telmisartan pre and post-ischemia groups showed significantly ($p<0.01$) lower cerebral Tumor Necrosis Factor (TNF-α) concentration in comparison with control The change in TNF-α cerebral concentration is summarized in table (4) and figure (4).

Table (4): cerebral concentration of TNF-α level in different study groups (no. of animals = 10 animal in each group)

Group	TNF-α conc. In pg/ml	
	Mean ± SEM	Std
Healthy	123.8±1.7	5.48
Control	157.8±3.7	11.8
Telmisartan pre ischemia	122.5±4.0	12.8
Telmisartan pre ischemia	131.8±3.7	11.7

Figure (4) bar chart showing the difference in the mean of



cerebral TNF –α conc. In ng/L in the four experimental group at the end of the study (no. of animal = 10 animal in each group)

3.2.2 control group

The histopathological score of (30 %) of rats in this group showed moderate brain injury while (70%) of them showed severe brain injury as shown in table (5) and figure (5), (8) (9) , In figure (8) we notice the zone of multiform and plexiform pyramidal cells were seen with the presence of

hyperplasia of glial cell and white blood cell among it. , The figure (9) showing the surface of the brain cortex devoid of the membrane of meninges, the glial cell hyperplasia was present in many zones of the brain cortex, and deeply, these cells were present in a great group surrounded by a cavity for the whole these cells.

3.2.4 Telmisartan pre ischemia group

The histopathological score of (80%) of rats in this group showed mild brain injury, while (20 %) of them showed a moderate change in brain tissue as shown in table (5) and figure (5), (10),(11) ,In figure (10) The cerebellum medulla was containing myelinated nerve fibers with many vacuoles and glial cells and this area appeared on foamy appearance. In figure (11) hyperplasia of glial cell (gliosis) was demonstrated in a certain place of brain cortex and cavitation around a certain number of these was detected.

3.2.4 Telmisartan post ischemia group

The histopathological score of (70%) of rats in this group showed mild brain injury, while (30 %) of them showed a moderate change in brain tissue as shown in table (5) and figure (5), (12), (13). , In figure (12) the deepest layer of the brain cortex was containing glial cell and larger pyramidal cell which are surrounded by a zone of vacuolations and this zone was surrounding the coarse of a cerebral blood vessel. In figure (13) the glial cells were hypertrophied and hyperplasia of these cells was present at a deeper layer of the brain cortex with fine blood congestion of micro blood vessels.

Table (5): Histopathological Score in different study groups

Histo Score Cases / GROUPS	No. Of animal	No change 0	Mild change 1	Moderate change 2	Sever change 3	Total
Healthy	10	10	0	0	0	10
Control	10	0.0	0	3	7	10
Telmisartan pre ischemia	10	0.0	8	2	0	10
Telmisartan post ischemia	10	0.0	7	3	0	10
Total	40	10	15	8	7	40
	**Chi-Square = 102.693 P-Value = 0.00002					

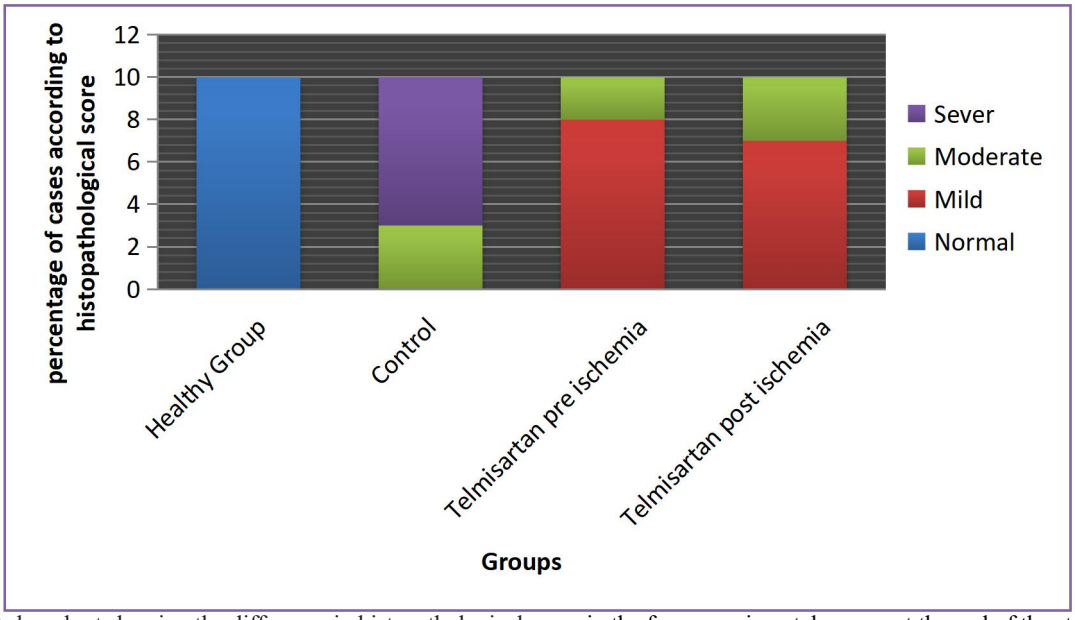


Figure (5): bar chart showing the difference in histopathological score in the four experimental groups at the end of the study (no. of animal = 10 animal in each group)

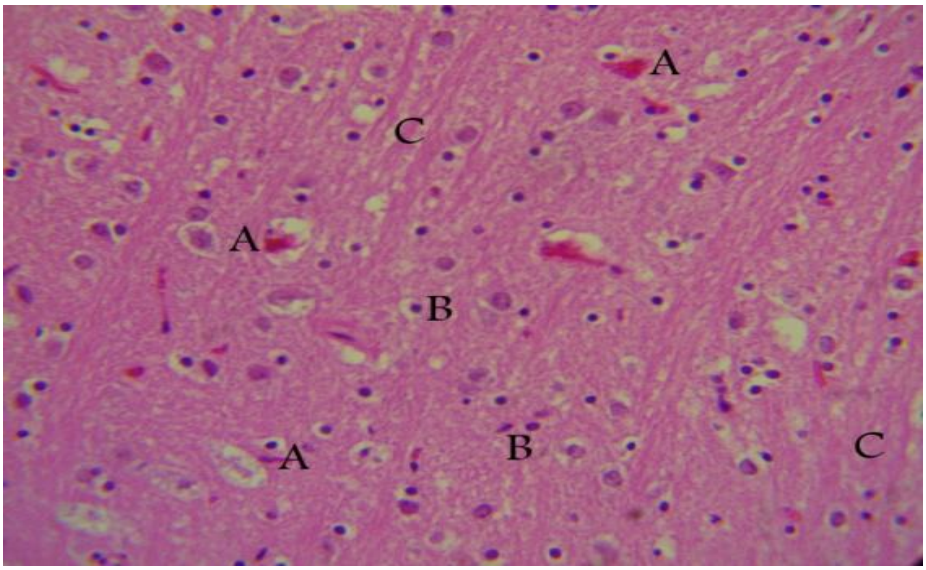


Figure (6) photograph of rat brain cortex section for healthy group score (0), Nerve cell (A), Glial cell (B), Myelinated nerve fiber (C), the section stained by H&E (X40).

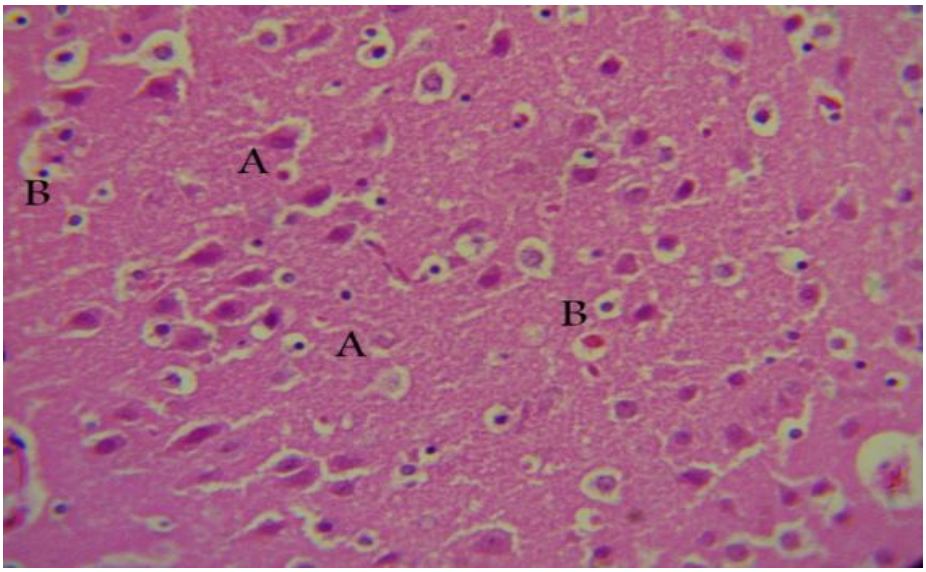


Figure (7) photograph of rat deep layer of brain cortex section for healthy group score (0), Multiform pyramidal nerve cell (A), Glial cell (B), the section stained by H&E (X40).

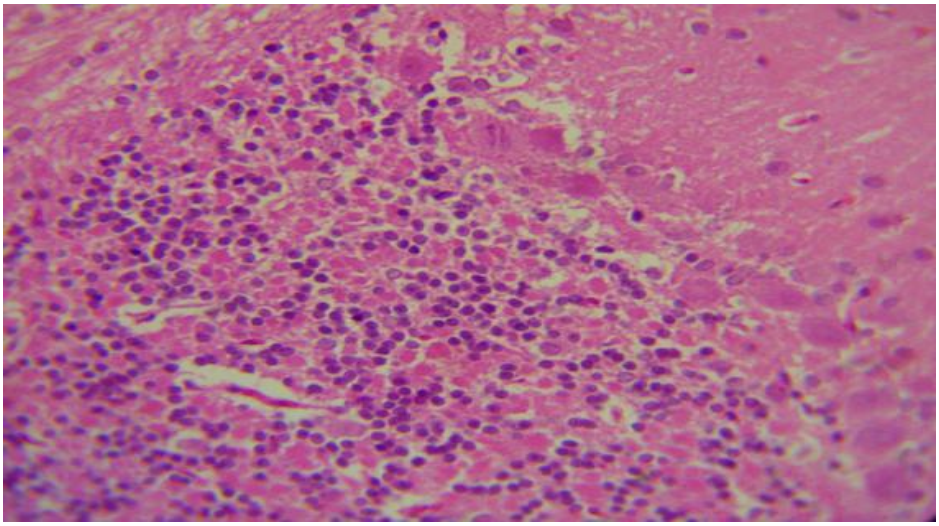


Figure (8) photograph of rat deep layer of brain cortex zone for control group score (3), showing plexiform pyramidal nerve cell with oligodendrocyte of great number with WBC, the section stained by H&E (X40).

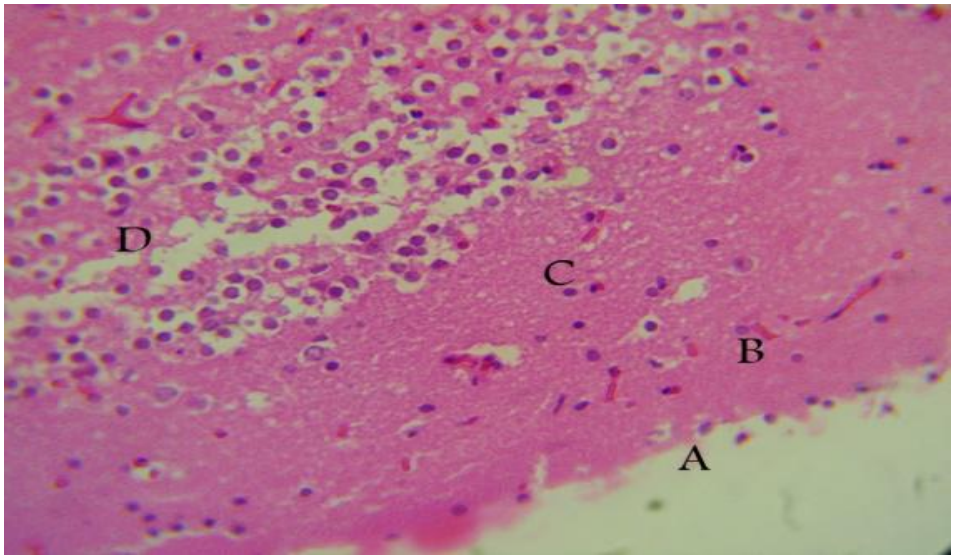


Figure (9) photograph of rat brain section for control group score (2), loss of pial membrane of meninges (A), molecular layer (B), granular layer (C), hypertrophy of glial cell, and hyperplasia (D) the section stained by H&E (X40).

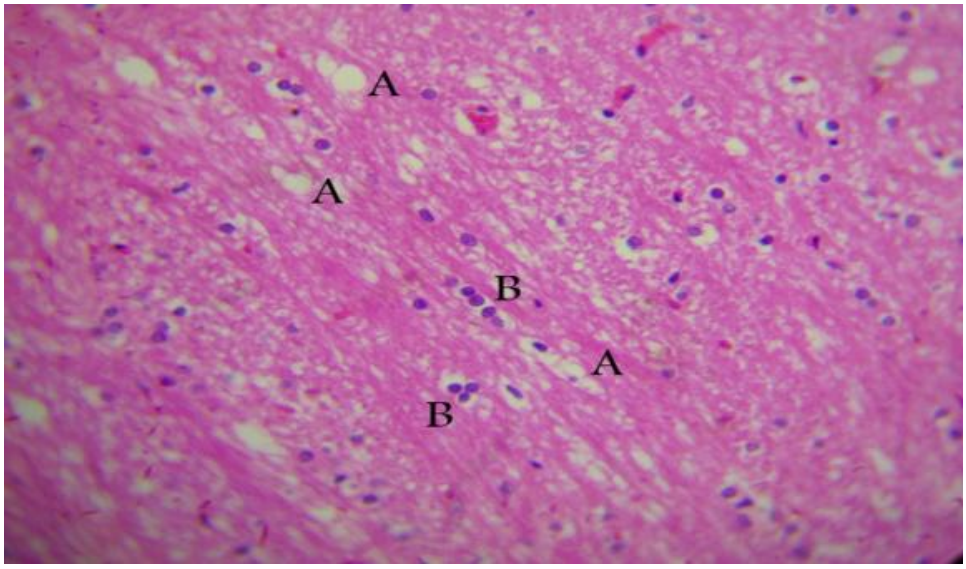


Figure (10) photograph of rat brain cerebellum section for Telmisartan pre ischemia group score (1), the foamy appearance of myelinated nerve fibers of cerebellum medulla (A), glial cells surrounded by vacuole (B), the section stained by H&E (X40).

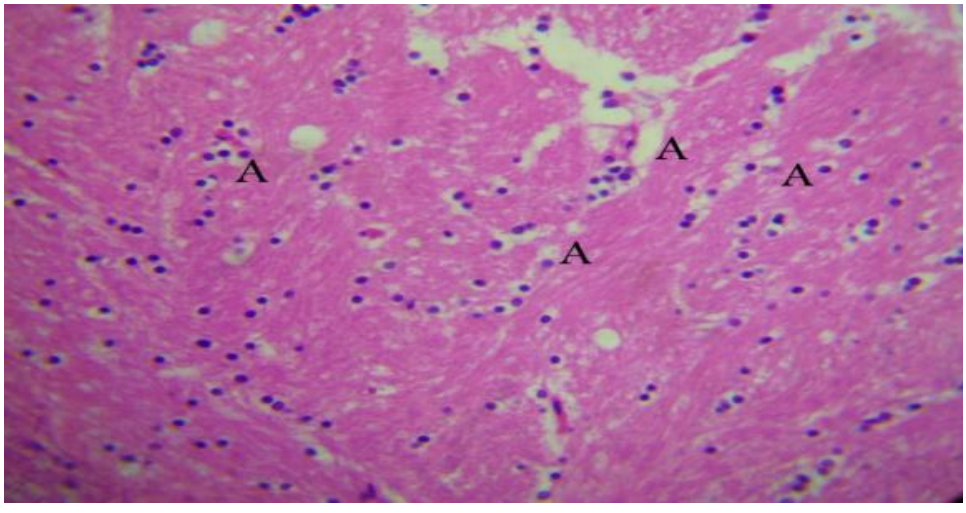


Figure (11) photograph of rat brain section for Telmisartan pre ischemia group score (2), Hyperplasia of the glial cell of brain cortex surrounded by vacuole (A), the section stained by H&E (X40).

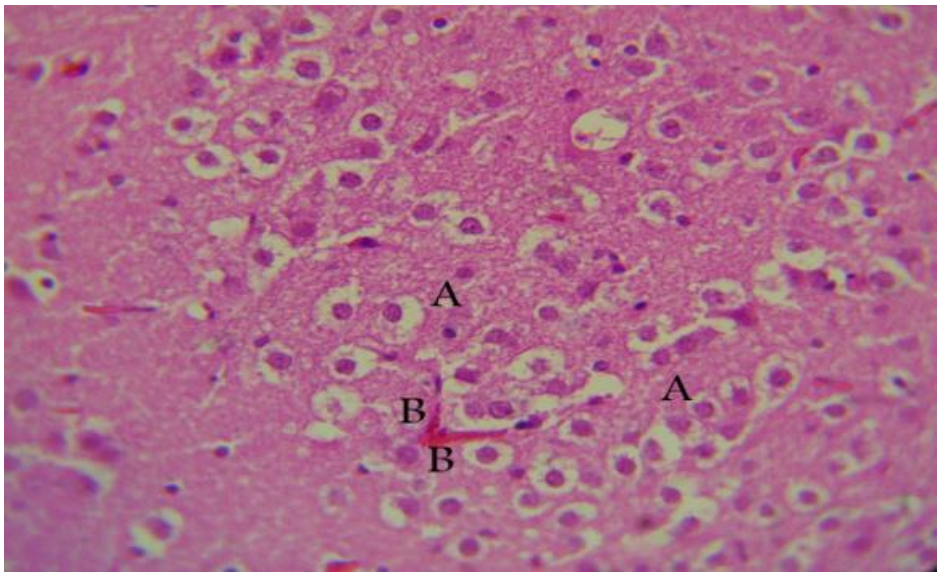


Figure (12) photograph of rat deep layer of brain cortex section for Telmisartan post-ischemia group score (1), the white zone around pyramidal cells (A), glial cell (B), blood congestion (C) the section stained by H&E (X40).

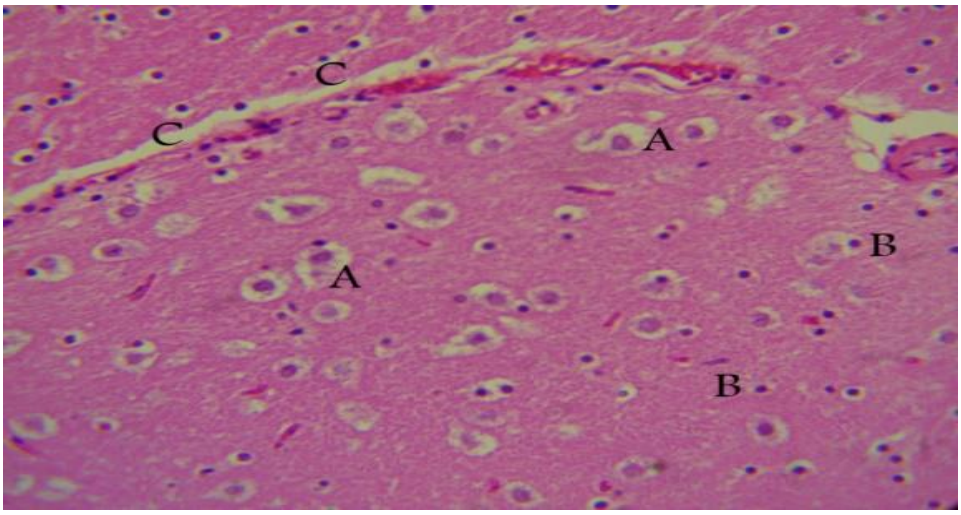


Figure (13) photograph of rat brain cortex section for Telmisartan post-ischemia group score (2), hypertrophic and hyperplasia of the glial cell (A), fine blood congestion of micro blood vessel (B), the section stained by H&E (X40)

DISCUSSION

4.11 Effect of telmisartan pre and post-ischemia on the inflammatory mediator (IL-1β and IL-6)

In this study, we found that the use of telmisartan at a dose of (3 mg/kg/day) orally for 7 days pre and post-induction of focal ischemia significantly decrease the cerebral level of the inflammatory mediator IL-1β and IL-6 in comparison to the control group. The finding of this study comes in line with the study done by (Pang *et al.* 2012) that shows telmisartan directly reduce IL-1β-induced neuronal inflammatory response by inhibition of the c-Jun N-terminal kinase (JNK) and c-Jun activation pathway and oxidative stress, this results support the theory that AT_1 receptor blockers are directly neuroprotective, and should be used for the treatment of brain inflammatory conditions. Another study has shown that telmisartan reduces the pro-inflammatory cytokine (IL-1β, IL-6, TNF-α), lipid peroxide, and nitric oxide levels, while anti-inflammatory cytokine IL-10 level was found to be simultaneously increased (Justin *et al.* 2014).

Recent research suggests that rats exposed to 30-min cerebral ischemia followed by 24-h reperfusion, telmisartan, and xanthenone in the higher doses restored nitric oxide end products, malondialdehyde, TNF-α, IL-6, caspase-3, glial fibrillary acidic protein, ACE and back to normal levels and significantly increased Glutathione, IL-10, and ACE2 compared to I/R control values (Abdel-Fattah *et al.* 2018). This study showed that telmisartan when used at a dose of (3mg/kg) orally greatly reduce inflammation and protect the neurovascular unit by reducing the inflammatory mediator like (*N*-acetyl glucosamine oligomer [NAGO], collagen IV, and glial fibrillary acidic protein [GFAP]) and neuroinflammation (matrix metalloproteinase-9 [MMP-9] (Kono *et al.* 2015).

4.12 Effect of telmisartan pre and post-ischemia on the inflammatory mediator (IL-8 and TNF-α)

In this study, we found that the use of telmisartan at dose of (3 mg/kg/day) orally for 7 days pre and post-induction of focal ischemia significantly decrease the cerebral level of the inflammatory mediator IL-8 and TNF-α in comparison to the

control group.

In a study done by (Fouad *et al.* 2010), It was concluded that telmisartan, by its anti-inflammatory, antioxidant, and antiapoptotic effects, can be regarded a powerful drug to protect against acute ischemia/reperfusion injury by inhibition of tumor necrosis factor-α, nitric oxide, caspase-3 activity. In an animal model for Alzheimer's disease, telmisartan decrease the hippocampal amyloid-beta protein, tumor necrosis factor-alpha, and nuclear factor kappa-B, phosphorylated tau protein (Khalifa *et al.* 2020). In Alzheimer's disease animal models, where neuroinflammation occurs, increased levels of cortical AT_1Rs (angiotensin 1 receptor) have been shown, the Intranasal administration of telmisartan (1 mg/kg/day) for up to two months significantly decreased lipopolysaccharide (LPS) -induced NO, inducible NO synthase, TNF-α and IL1-β synthesis (Torika *et al.* 2016).

4.13 Effect of telmisartan pre and post-ischemia on brain histopathology

In this study, the histopathological examination showed that the use of telmisartan pre and post-induction of focal cerebral ischemia at a dose of 3mg/kg for 7 days significantly reduce brain tissue injury as compared to the control group, and the histopathological score of telmisartan pre and post-ischemia groups respectively showed 80% and 70% of theme nearly normal brain tissue with mild injury and 20% and 30% have a moderate injury while control shows 70% severe injury and 30% moderate brain damage. This comes in line with the study that showed the histopathological examination of the hippocampus, cerebral cortex, and cerebellum sections were done using special Congo red stains, Telmisartan improved cognition, reduce brain beta-amyloid deposition and brain-derived neurotropic factor depletion, decreased TNF-α, nitric oxide brain levels, and parallel to confirmatory histopathological evidence with inhibition of neuroinflammation and oxido-nitrosative stress (Khallaf *et al.* 2017). Another study also suggests that the histopathological, stereological, functional, and molecular data suggest that telmisartan improves nerve regeneration in peripheral nerve injuries by inhibiting inflammatory cytokine IL-1β and apoptotic caspase-3 (Yuksel *et al.* 2015).

5.1 CONCLUSIONS

From the finding of our study we can conclude the following :

1. Emphasizing the role of inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α) in the pathogenesis of cerebral I/RI.
2. Telmisartan decrease the cerebral level of the inflammatory mediators (IL-1β, IL-6, IL-8, and TNF-α) which might suggest the mechanism for prevention and treatment of ischemic stroke.
3. Telmisartan may improve the histopathological damage that occurs in the ischemia/reperfusion injury.

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