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EFFECT OF *MOMORDICA CHARANTIA* (KOROLA) IN GLOBAL CEREBRAL ISCHEMIA-INDUCED NEURONAL DAMAGE IN RAT BRAIN

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ARTICLE INFO | **ABSTRACT** | **ORIGINAL RESEARCH ARTICLE**

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Key Words: Stroke, *Momordica charantia* (Korola), Therapeutic effects, Global cerebral ischemia

Background: Stroke is primarily a cardiovascular disease with a neurological outcome. Prophylactic neuroprotection might be a useful treatment approach with better outcome than current options. *Momordica charantia* (Korola) fruit juice has been shown different therapeutic effects including neuroprotection.

Objective: The objective of the study was performed to evaluate neuroprotective effect of *Momordica charantia* fruit juice in global cerebral ischemia induced neuronal damage in rats.

Methodology: Global cerebral ischemia was produced surgically by ligating bilateral and unilateral common carotid artery. Fresh raw juice of *Momordica charantia* (2-2.5 ml/rat/day) was given to experimental group starting one month before and continued up to two weeks after surgery. Forty wester Kyoto rats were recruited for experiment and divided into two groups. Neuroprotective role was measured with the Histopathological assessment of decapitated rat brain in terms of unaffected neuronal cell density and necrotic foci per high power field (HPF). The data analysis was done by unpaired t- test with the software SPSS version 17.0.

Results: Among 40 rats, 24 rats were alive until completion of experiment. The rats under experimental group who got *Momordica charantia* fruit juice had significantly more neuronal cell density (p=0.001) and less necrotic foci (p=0.001) compared with control

group.
Conclusion: In this study, we found that *Momordica charantia* fruit juice has neuroprotective activity in global cerebral ischemia induced neuronal damage in rat brains. Since herbal drugs have been accepted widely in the recent years because of its' relative higher therapeutic window, less serious side effects, and economical, *Momordica charantia* fruit juice might be the alternative of other synthetic neuroprotective agents in global cerebral ischemia-induced neuronal damage. However, in vivo study is warranted to establish this relation.

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INTRODUCTION

This case-controll study was designed with the aim to establish the neuroprotective role of *Momordica charantia* (korola) beverage on rat following iatrogenic global cerebral ischemia induced neuronal injury as experimental model study. Stroke is primarily an upset with a neurological outcome. Stroke is a major reason behind death and disability worldwide. The incidence of stroke resulting burden on the society. No pharmacological treatment is effective aside from recombinant tissue proteinase that's employed in about 4% of patients presenting with ischaemia.[1] Variety of medicine are often used for the treatment of stroke like thrombolytics (rt-PA), Calcium channel blocker, Neuroprotectant, Combination drug, but none has desired efficacy.[1] One approach in treatment is that the idea of combined therapy. Combinations of thrombolytics and a neuroprotecting agent or a mixture of two neuroprotecting agents are effective in experimental stroke.[2] Another approach towards treatment of stroke is prophylactic. it's been seen that in animal models of stroke, with many drugs, pretreatment yields better outcome than post onset treatment. For the drugs to be effective, further suggestions from the clinical trials have shown that the very early treatment after stroke is also necessary. Therefore, in a very sub group of patients that are at a considerable risk for stroke. Patients with a light episode of stroke or transient ischemic attacks, prophylactic neuroprotection might offer a useful approach and a stronger outcome than is expected normally. Should be efficacious, safe, orally available and affordable, the agent to be used prophylactically.[3] For the treatment of assorted ailments, herbal drugs are described in ancient systems of drugs. These are now-a-days revalued by extensive research on different plant species and their therapeutic principles. For prophylactic treatment in stroke, since they need a comparatively higher therapeutic window, lesser side effects, and are economical and herbal drugs have gained plenty of acceptance within recent years and may be potential candidates. variety of traditional Chinese medicines are tried both in animal models of stroke and human patients and are found to be effective. Indian traditional medicines, though tried and located useful in various neurological disorders, haven't been studied in stroke models.[4] However, there's no comprehensive review associated with herbal products within the prophylaxis and treatment of stroke. With an identifiable, substantial risk for stroke, certain invasive procedures are associated. Such trials include arterial blood vessel bypass graft, valve replacement, cardiac transplant, carotid endarterectomy, aneurysmectomy, resection of arteriovenous malformations, and endovascular therapy. Patients undergoing these procedures have an outlined risk period, and short-term neuroprotection, initiated Before the procedure with a neuroprotective agent that doesn't interfere with the procedure, is attractive. This approach requires that safe, efficacious, orally available, and comparatively inexpensive neuroprotective

drugs must be developed.[5] However, there's scarcity of knowledge describing the neuroprotective effects of *Momordica charantia* on rat or the other animal in our country.

OBJECTIVE

General Objective:

To evaluate the neuroprotective role of *Momordica charantia (Korola)* fruit juice on rat in global cerebral ischemia induced neuronal injury.

Specific Objective:

To demonstrate pathological changes in global cerebral ischemia induced neuronal injury in rats.

METHODS AND MATERIALS

This was an experimental study. conducted during January 2014 to November 2014 at Department of Cardiac Surgery, BSMMU and department of Pathology, BSMMU, Dhaka, Bangladesh. Number of animal was 40, but we created two groups for this study, group 1 was control group and group 2 was experimental group. We recruited 20 rats for this group. Ten (10) rats for unilateral and ten (10) rats for bilateral common carotid artery ligation. This group had only surgical intervention but did not get *Momordica charantia* fruit juice. We recruited 20 rats for this group. Ten (10) rats for unilateral and ten (10) rat for bilateral common carotid artery ligation. This group had both surgical intervention and got *Momordica charantia* fruit juice starting one month before surgery and continued for 15th post-operative days. We recruited a non-interventional rat that was sacrificed by decapitation and brain was sent for histopathology. Histological findings of this rat brain worked as our working standard.

Inclusion criteria:

Wister kyota (20 rats) / Long evans rats (20 rats) and had following: Weight 200 to 400 gm Apparently healthy rat based on motor function.

Study procedure

Animal: The study conducted on randomly selected Wister Kyoto (20 rats) and Long Evans (20 rats) rats and collected from animal house of BSMMU. Weight of each rat was recorded. The animals were housed in cages and kept in room temperature in University animal house. They had unlimited access to food pellets and water and fasted for 18-24 hours before surgery except water.

Ethical Clearance:

The study protocol was approved by Institutional Review Board (IRB) of BSMMU and principles of animal handling guideline was followed throughout.

Momordica charontia:

Fruits of *Momordica charantia* was collected from local market of Dhaka city. After thorough washing, juice of whole fruits was made by a juicer. Freshly prepared raw juice was introduced in the stomach of experimental rats with nasogastric tube (5Fr) with a dose of 8ml/kg/day for 45 days. *Momordica charantia* juice 8 ml/kg/ day is corresponds to 520 mg/kg/day dry powder if freeze dried. 100 ml fresh juice contains 6.5 gm dry powder if freeze dryed.[6]

Surgery and experimental procedure:

Each rat had identification number (ID). Shaving of surgical area (neck) was done on the day before surgery. We used Sodium pentobarbital (50 mg/kg body wt.) intraperitoneally as anesthesia.[7] Global cerebral ischemia was produced surgically by ligating common carotid artery. Rat was placed in supine position. Incision was made along anterior border of sternocleidomastoid muscle, retracting the sternocleidomastoid muscle, carotid sheath was identified and was incised longitudinally. Common Carotid artery was identified in the carotid sheath by its pulsatile nature. Vagus nerve, Internal Jugular vein was separated and maintained properly. Common carotid artery was separated and ligated with 2-0 silk [7] Wound closed in layers. Skin closed with 2-0 silk and povidone iodine

ointment was applied in the wound. Each rat was kept in separate case during postoperative period. Dextrose aqua and saline water was introduced (2-3 ml) by nasogastric tube during post-operative period. After reversal of anesthesia, normal food was given to each rat. Freshly prepared raw juice of Momordica Charontia was given to experimental group (dose 520 mg/kg body weight) starting one month before and continued up to 15th post-operative day of common carotid artery occlusion.[9] On 15th post-operative day, (60 minutes after last dose of Momordica Charontia) rats was sacrificed maintaining animal handling protocol by decapitation and scalp tissue was removed. For safe and intact removal of brain, all suture lines were separated and individual bones were removed gently. Then total brain was removed and brain size was measured. Intact brain kept in plastic container containing 10% formalin for 2 to 3 days for fixation and sample sent for histopathological study.[8]

RESULTS

We recruited 40 rats for this experiment. Among them 24 rats (60%) was alive up to end of experiment. Sixteen (16) rats died in perioperative period (40%). Two (2) rats died on preoperative period of which one was under and fourteen (14) rats died of post-operative period. From Group I, total eight (8) rat was died ((40%) and rest twelve (12) rats was alive (60%).Among 8 died rats, one (1) rat died preoperatively that was planned for bilateral common carotid artery ligation and four (4) rats died in post-operative period after bilateral common carotid artery ligation. Rest three (3) rats died after unilateral common carotid artery ligation. From group II, total eight (8) rats was died (40%) and rest twelve (12) rats was alive (60%) up to end of experiment. One (1) rat died on preoperative period that was planned for bilateral common carotid artery ligation and six (6) rats died in post-operative period after bilateral common carotid artery ligation. Rest one (1) rats died after unilateral common carotid artery ligation. Among bilateral common carotid artery ligated rats, eight (8) rats was alive (40%) and 12 rats died preoperatively (60%). Among unilateral common carotid artery occluded rats only four (4) rats died (20%) at perioperative period and remaining 16 rats (80%) were alive.

Comparison of weight of rats in between two groups:

We observed that weight of the rats in group II ranging from 240 to 280 grams and its mean ± SD was 259.5 ± 11.7 grams. In group I, weight of the rats was ranging from 240 to 300 grams and its mean ±SD was 269.5±16.8 gram but this weight differences between group I and group II was statistically non-significant.

Table 1: Comparison of weight of rats in between two groups:

Variable	Group		p value
	Group II (Experimental group) (n=12) Mean ±SD (Min - Max)	Group I (Control group) (n=12) Mean ±SD (Min - Max)	
Weight (gm)	259.5 ± 11.7 240.0 - 280.0	269.5 ±16.8 240.0 - 300.0	0.106

Photograph of non-interventional rat brain slide:

During experiment, we decapitated one non interventional rats and histopathology was done. This was our working standard. From histopathology report we observed that neuronal cell density was 512 per high power field without any necrotic focus

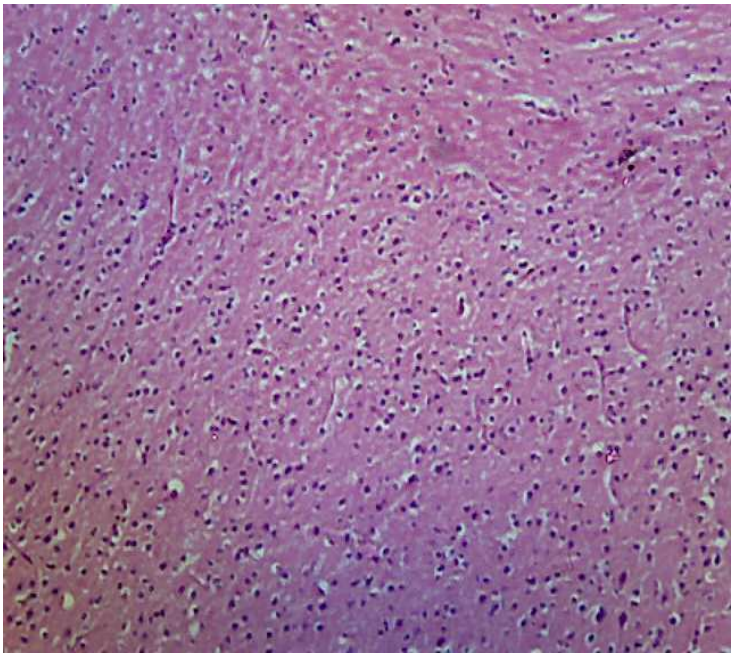

Figure I: photograph of non-interventional rat brain slide

Note: Coronal section was taken from front parietal region of rat brain and the slide was stained with H&E. Magnification 10X

Comparison of brain size between two groups:

It was observed that the brain size of experimental rats was ranging from 2.62 to 6.80 cm³ and its Mean ±SD was 4.24±1.43 cm³. Brain size of control rats was ranging from 1.56 to 5.30 cm³ and its mean ±SD was 3.40±1.07 cm^3 The brain size in experimental rats was comparatively larger than that of control rats but this differences was statistically non-significant which is shown in table II.

Table 2: Comparison of brain size between two groups:

Variable	Group		p-value
	Group II (Experimental) (n=12) Mean ±SD (Min - Max)	Group I (Control) (n=12) Mean ±SD (Min - Max)	
Brain size (cm3)	4.24±1.43 2.62 - 6.80	3.40 ±1.07 1.56 - 5.30	0.135ns

Comparison of neuronal necrotic foci per high power field between two groups:

In this study, we observed that number of neuronal necrotic foci per high power field in group II was ranging from 2.00 to 6.00 and its mean ±SD was 4.16±1.19 per high power field**.** In group I**,** number of neuronal necrotic foci per high power field was ranging from 7.00 to 12.00 and its mean ±SD was 9.80±1.64 per high power field. The number of neuronal

necrotic foci per high power field in control rats was comparatively larger than that of experimental rats. This differences was statistically significant which is shown in table 3.

Table 3: Comparison of neuronal necrotic foci per high power field between two groups (N=24)

Variable	Group		p value
	Group II (Experimental group) (n=12) Mean ±SD (Min - Max)	Group I (Control group) (n=12) Mean ±SD (Min - Max)	
Necrosis/HPF	4.16±1.19 2.00 - 6.00	9.80±1.64 7.00 - 12.00	0.001s

Photograph of unilateral common carotid artery ligated control rat brain slide

In this study, This photograph shows scattered necrotic foci with reduced cellularity. The histopathology report of this photograph revealed neuronal cell density was 81 per high power field and a number of necrotic foci was 12 per high power field.

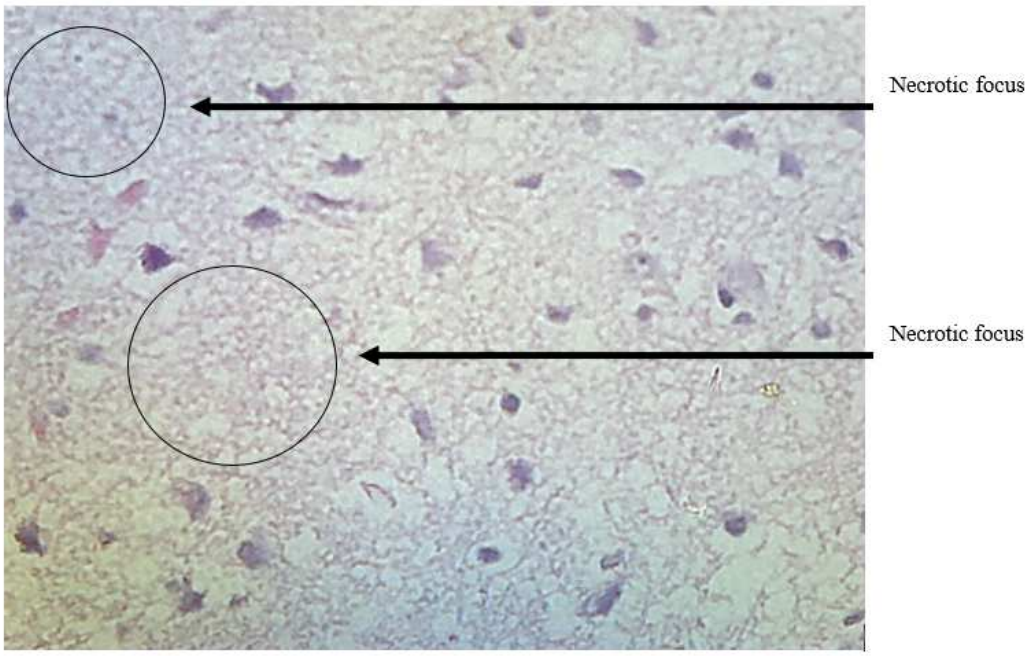

Figure II: Photograph of unilateral common carotid artery ligated control rat brain slide
Note: Coronal section was taken from front parietal region of rat brain and slide was stained with H&E. Magnification 40

Comparison of number of neuronal cell density per high power field between two groups:

From this study, we observed that, in experimental rat's number of neuronal cell was ranging from 155.0 to 250.0 per high power field and its mean ±SD was 191.16±31.90 per high power field**.** In control rats, number of neuronal cell was ranging from 60.0 to 120.0 per high power field and its

mean ±SD was 97.91±16.58 per high power field. The number of neuronal cell per high power field in experimental rats was comparatively more than that of control rats. This differences were statistically significant which is shown in table 4.

Table 4: Comparison of neuronal cell density per high power field between two groups:

Variable	Group		p value
	Group II (Experimental rat) (n=12) Mean ±SD (Min - Max)	Group I (Control rat) (n=12) Mean ±SD (Min - Max)	
Number of neuronal cell density/HPF	191.16±31.90 155.0 - 250.0	97.91±16.58 60.0 -120.0	0.001[s]

Photograph of bilateral common carotid artery ligated experimental rat brain slide: In the present study, we observed few scattered necrotic foci with reduced cellularity in bilateral common carotid artery ligated experimental rat brain slide. Histopathology of this section revealed number of neuronal cell was 151 per high power field and number of necrotic foci was 6 per high power field.

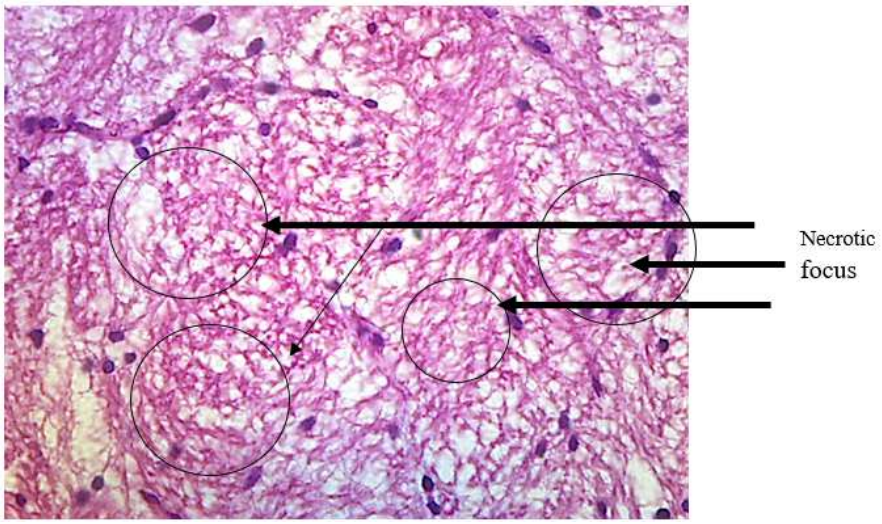

Figure III: Photograph of bilateral common carotid artery ligated experimental rat brain slide
Note: Coronal section was taken from front parietal region of rat brain and slide was stained with H&E. Magnification 40X

Comparison of number of neuronal necrotic foci per high power field between unilateral common carotid artery ligated rats:

We observed that number of neuronal necrotic foci per high power field was ranging from 2.00 to 6.00 and number of mean ±SD was 4.22±1.09 per high power field in experimental rats (group II). Number of neuronal necrotic foci per high power field was ranging from 8.00 to 12.00 and its mean ±SD was 9.85±1.67 per high power field in control rats. The number of neuronal necrotic

foci per high power field in control rats was comparatively more than that of experimental rats. This differences were statistically significant which is shown in table 5.

Table 5: Comparison of number of neuronal necrotic foci per high power field between unilateral common carotid artery ligated rats:

Variable	Group		p value
	Group II (experimental rats) (n=9) Mean ±SD (Min - Max)	Group I (Control rats) (n=7) Mean ±SD (Min - Max)	
Number of necrotic foci /HPF	9.85±1.67 8.00 -12.00	4.22±1.09 2.00 - 6.00	0.001[s]

Photograph of unilateral common carotid artery ligated experimental rat brain slide:

In unilateral common carotid artery ligated experimental rat slides, we observed multiple scattered necrotic foci with reduced cellularity. Histopathology of this slide showed that number of neuronal cell was 160 per high power field and number of neuronal necrotic foci was 4 per high power field.

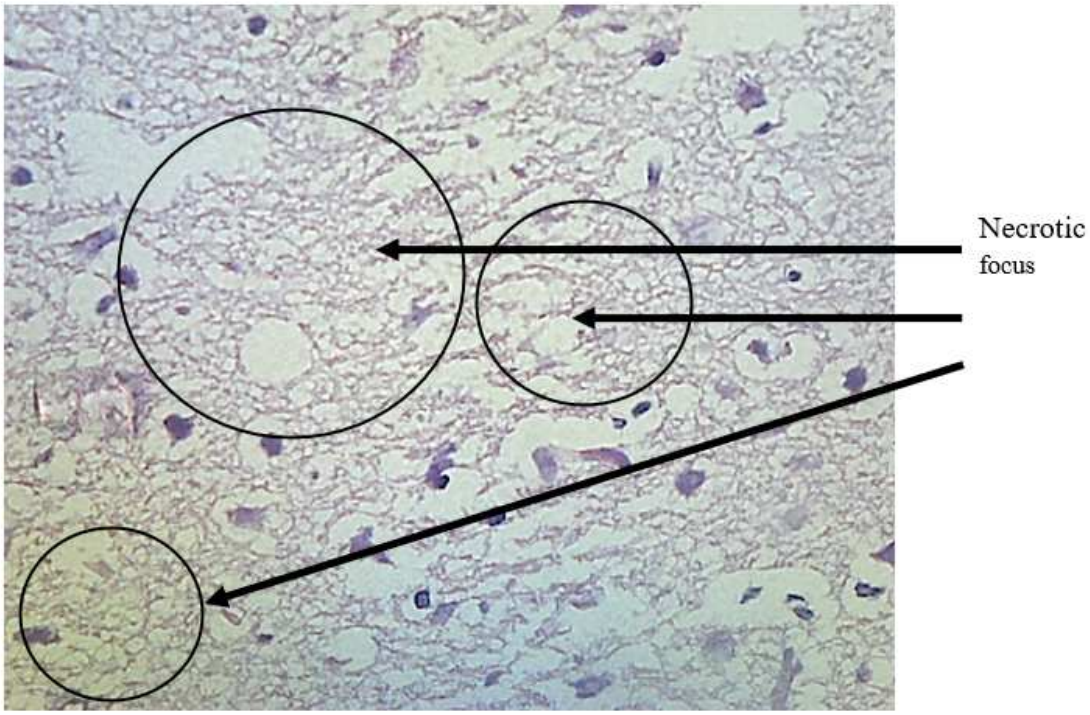

Figure IV: photograph of unilateral common carotid artery ligated experimental rat brain slide. Magnification 40X

Note: Coronal section was taken from front parietal region of rat brain and slide was stained with H&E. Magnification 40X

Comparison of neuronal cell density per high power field between unilateral common carotid artery ligated groups:

From this study, we observed that, number of neuronal cell per high power field was ranging from 155.0 to 218.0 and its mean ±SD was 187.55±26.95 per high power field in experimental rats. The neuronal cell density per high power field was ranging from 60.0 to 110.0 and its mean ±SD was 91.57±18.25 per high power field in control rats. The neuronal cell density per high power field in experimental rats were comparatively more than that of control rats. This differences were statistically significant that is shown in table 6

.

Table 6 Comparison of neuronal cell density per high power field between unilateral common carotid artery ligated groups:

Variable	Group		p value
	Group II (Experimental) (n=9) Mean ±SD (Min - Max)	Group I (Control) (n=7) Mean ±SD (Min - Max)	
Neuronal cell density/HPF	187.55±26.95 155.0 - 218.0	91.57±18.25 60.0 - 110.0	0.001[s]

Comparison of number of neuronal necrotic foci per high power field between bilateral common carotid artery ligated rats:

We observed that number of neuronal necrotic foci per high power field was ranging from 3.00 to 6.00 and number of mean ±SD was 4.00±1.73 per high power field in experimental rats (group II). Number of neuronal necrotic foci per high power field was ranging from 8.00 to 12.00 and its mean ±SD was 9.80±1.78 per high power field in control rats. The number of neuronal necrotic foci per high power field in control rats was comparatively more than that of experimental rats. This differences were statistically significant which is shown in table 7.

Table 7: Comparison of neuronal necrosis per high power field between bilateral common carotid artery ligated groups:

Variable	Group		p value
	Group II (Experimental) (n=3) Mean ±SD (Min - Max)	Group I (Control) (n=5) Mean ±SD (Min - Max)	
Number of neuronal necrotic foci /HPF	9.80±1.78 8.00 - 12.00	4.00±1.73 3.00 -6.00	0.004[s]

Photograph of bilateral common carotid artery ligated control rat brain slide

In this study, we observed multiple scattered neuronal necrotic foci with reduced cellularity in the histological slide of bilateral common carotid artery ligated control rats.

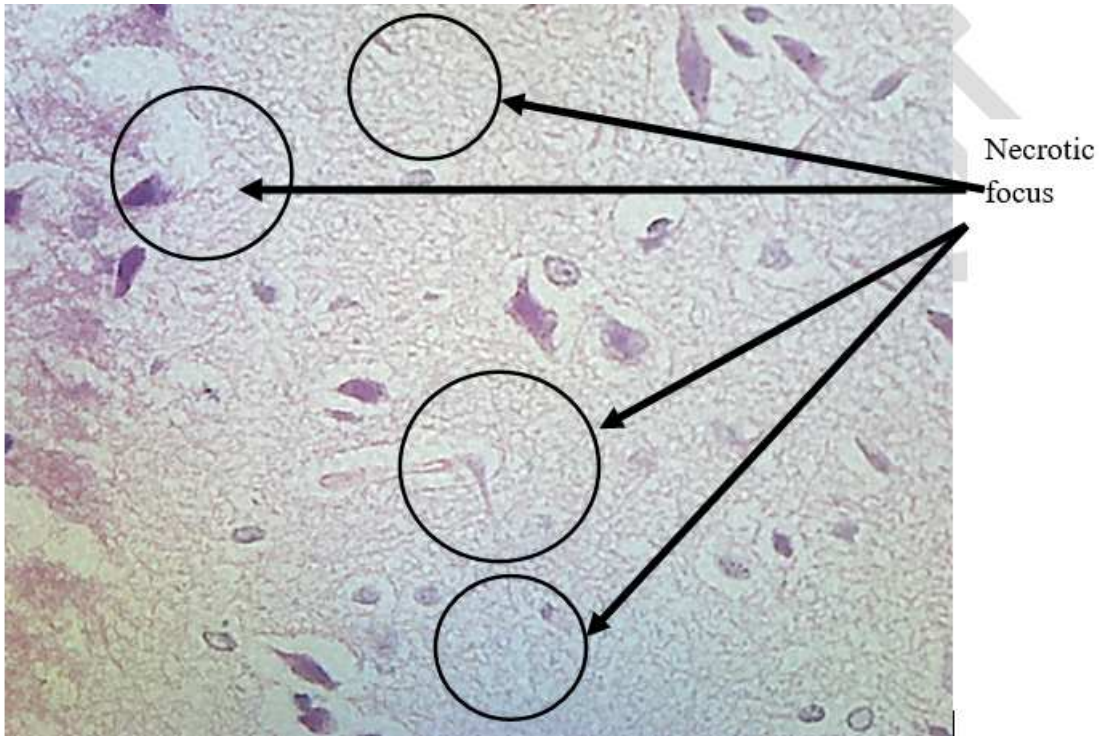

Figure V: Photograph of bilateral common carotid artery ligated control rat brain slide. Amplification 40X

Histopathology report of this slide revealed neuronal cell density 96 per high power field and number of necrotic foci was 11 per high power field.

Comparison of neuronal cell density per high power field between bilateral common carotid artery ligated rats:

We observed that number of neuronal cell per high power field was ranging from 151.00 to 250.00 and number of mean ±SD was 202.00±49.56 per high power field in experimental rats (group II). Number of neuronal cell per high power field was ranging from 96.00 to 120.00 and its mean ±SD was 106.80±90.33 per high power field in control rats (group I). The neuronal cell density per high power field in experimental rats was comparatively more than that of control rats. This differences were statistically significant which is shown in table 8.

Table 8: Comparison of neuronal cell density per high power field between bilateral common carotid artery ligated rats:

Variable	Group		p value
	Group II (Experimental) (n=3) Mean ±SD (Min - Max)	Group I (Control) (n=5) Mean ±SD (Min - Max)	
Neuronal cell density/HPF	202.00±49.56 151.0 - 250.0	106.8±9.33 96.0 - 120.0	0.005[s]

Correlation of necrosis per high power field with neuronal cell density per high power field.

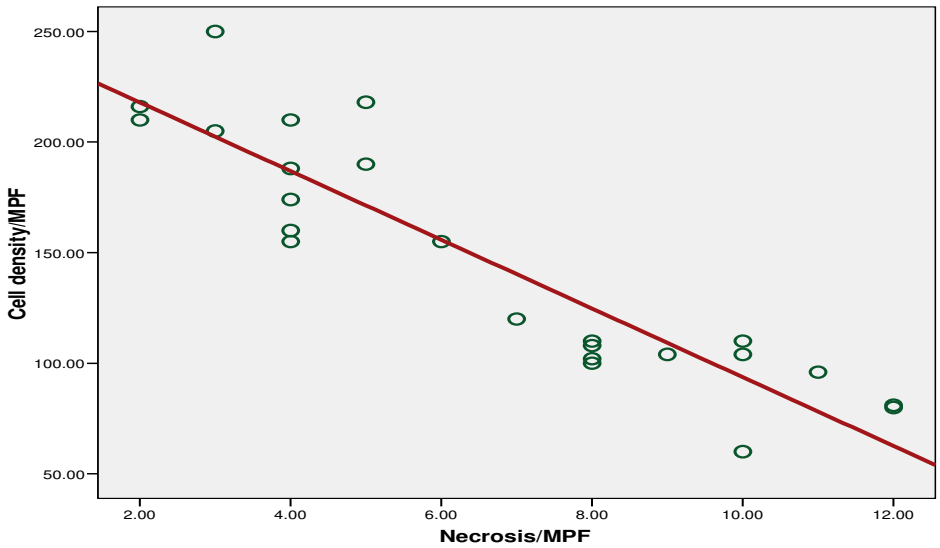

Figure VI: Correlation of necrosis/ HPF with neuronal cell density/HPF. (r = -0.885; p = 0.001)
Figure 1 shows that Necrosis per high power field (HPF) is negatively correlated with cell density/HPF.

DISCUSSION

The present study was carried out to see the effect of *Momordica charantia* fruit juice on global cerebral ischemia induced neuronal damage in rat brain. It was observed that occlusion of common carotid artery either unilateral or bilateral evidenced by a decrease in neuronal cell density and increased necrotic foci in front parietal region of rat brain. The mean weight difference between experimental and control rats was not statistically significant (p= 0.106). While, the difference in mean brain size of rats between the groups was not statistically significant (p= 0.135). This indicates similarity of groups and thus grouping was not biased. *Momordica charontia* has shown many therapeutic properties.[9] Among all study rats there was significantly less necrotic foci per high power field (HPF) in the brain of experimental rats than that of control rats (p= 0.001). But the neuronal cell density/HPF was found significantly higher in experimental rats than that of control rats (p= 0.001). This opposite trends in both histological results indicated the neuroprotective effects of *Momordica charantia* fruit juice which is supported by the study conducted in India to reveal the neuroprotective effects of *Momordica charantia* fruit juice in global cerebral ischemia and reperfusion induced neuronal damage in diabetic mice.[6] Although Indian study used biochemical and physical findings as the marker of neuroprotective effect. They used diabetic mice in their study but we used normal healthy rats. Indian investigators used biochemical and physical findings as parameter but in our study we used histopathology of rat brain as parameter. Similar result was observed in Ezypt where investigators used mixed procedure including histopathology of necrotic cells and neuronal cell density to see the neuroprotective effects of resveratrol in diabetic cerebral ischemic-reperfused rats.[10] When we examined the histology of unilateral common carotid artery ligated rats, the number of necrotic neuronal foci per high power field was also significantly less in experimental rats than in control rats (p = 0.001). Similarly, the neuronal cell density per high power field among unilateral common carotid artery ligated in experimental rats was reported to be significantly much higher than that of control rats (p= 0.001).

These two findings further strengthen our previous statement that *Momordica charantia* fruit juice exhibited the neuroprotective effects in rat brain.[6] Even among the bilateral common carotid artery ligated rats the histological findings showed that the necrotic foci per high power field in experimental rats was significantly lower than in control group ($p<0.004$), and the neuronal cell density/HPF among bilateral common carotid artery ligated experimental rats showed significantly higher than that of control rats ($p= 0.005$). These results also strengthen our hypothesis that *Momordica charantia* has neuroprotective role in global cerebral ischemia. All the histological findings showed the neuroprotective effects of *Momordica charontia* fruit juice on experimental rats which might be concluded with the idea that *Momordica charontia* fruit juice can be used as an effective neuroprotective agent in global cerebral ischemia. Although, there have been several studies on herbal products that reported effectiveness of herbal drugs in animals,[6] however our current ever first study in Bangladesh, on effects of *Momordica charontia* fruit juice as neuroprotector revealed good therapeutic effect in rats. Our present study would be more valuable, reliable and credible if we can use mixed procedure like physical findings, biochemical markers, immunohistopathology and Apoptosis as parameter. However, we expect *Momordica charontia* juice to be shown neuroprotective effects in human which would be confirmed by clinical trial in future.

LIMITATION

We faced some limitations throughout the study period as follows: In bilateral common carotid artery occlusion (BCCAO) group, perioperative death was high (60%). So, out of 20 rats only 8 rats completed the experiments. In animal house, there was no veterinary doctor and only one-man power that hampered proper animal care. For this experiment, we had to depend on animal house and manpower of department of Pharmacology that frequently hampered our working schedule and working hours.

RECOMMENDATION

A large scale experimental study is needed to prove the effectiveness of *Momordica charontia* fruit juice as neuroprotective agent. We used raw fruit juice of *Momordica charantia*, but we do not know which component is responsible for its neuroprotective role. So analytical study is essential for this purpose.

CONCLUSION

Momordica charontia fruit juice might be the alternative treatment option as neuroprotective agents in global cerebral ischemia induced neuronal damage. We expect Momordical charantia fruit juice will be new hope for stroke patient in near future.

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