International Surgery Journal
Khan OS et al. Int Surg J. 2022 Feb;9(2):280-286
http://www.ijsurgery.com
pISSN 2349-3305 | eISSN 2349-2902

DOI: https://dx.doi.org/10.18203/2349-2902.isj20220313

Original Research Article

Role of valproic acid and allopurinol in neuroprotection after cardiac surgery on Bangladeshi patients

Omar Sadeque Khan[1]*, Rezwanul Hoque[1], Mostafizur Rahman[1], Nasif Imtiaz[2]

[1]Department of Cardiac Surgery, [2]Department of Cardiac Anaesthesia, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh

Received: 04 January 2022
Revised: 19 January 2022
Accepted: 20 January 2022

***Correspondence:**
Dr. Omar Sadeque Khan,
E-mail: omar_m32@hotmail.com

ABSTRACT

Background: Neurological complications are very much common after cardiac surgery in postoperative setting in Bangladesh. However, we are dealing these complications in our day-to-day practice and it costs money, longer hospital stays and admissions to rehabilitation facilities. The aim of the study was to evaluate the effectiveness of sodium valproic acid and allopurinol in preventing neurological injury following cardiac surgery with cardiopulmonary bypass.
Methods: This cross-sectional study was conducted by the department of cardiac surgery, Bangabandhu Sheikh Mujib medical university (BSMMU), Dhaka, Bangladesh from January 2019 to June 2021. Total 70 patients were included and divided into two groups (36 patients with sodium valproic acid and allopurinol in group A and 34 patients without sodium valproic acid and allopurinol in group B). 10 patients were dropped out. As these two drugs were FDA approved was used per-orally for 5 perioperative days (2 days prior surgery, 1 day in operation day, 2 days postoperatively). Collected data were entered, checked and edited (to remove the outliers) with the help of the statistical package for social sciences (SPSS) software, version 26 and analyzed.
Results: The intervention group (group A) had maximum survival rate (no mortality) less ICU stay, less hospital stay, early intubation, no neurological injury ($p<0.05$). On the contrary group B (no intervention) had 6 mortalities, several mild to moderate neurological injury, more ICU and hospital stay and morbidity.
Conclusions: Sodium valproic acid and allopurinol gives neuroprotection in on-pump cardiac surgical patients. So, these two medicines can be prescribed prophylactically on individual basis.

Keywords: Per-oral perioperative, Sodium valproic acid, Allopurinol, On-pump cardiac

INTRODUCTION

Cardiac surgical procedures such as coronary artery bypass grafting (CABG), valve replacement, intra-cardiac repair and congenital surgery as well as many others lifesaving procedures performed on thousands of Bangladeshi patients every year. These procedures were performed by using cardiopulmonary bypass. However, despite all necessary precautions many patients who undergo on pump cardiac surgery suffer neurological injury as a result. In addition to the morbidity and mortality caused by neurological injury, these complications are associated with increases in hospital length of stays, costs and admissions to rehabilitation facilities. By far, the most feared neurological complication of cardiac surgery is stroke, with an incidence of between 1% and 6%.[1,2] However, subtle decreases in neurocognition and impairments in level of consciousness occur frequently in the early postoperative period and can be equally distressing for patients and their families. Impaired consciousness can lead to additional neurological sequelae including

encephalopathy, delirium and depression.[3] It is believed that atherosclerotic emboli from the aorta, hypoperfusion in watershed brain territories and free radical injury are the principal causes of stroke following cardiac surgery. The pathogenesis of cognitive impairment is likely multifactorial and generally depends on whether the impairment occurs early or late after cardiac surgery. Early deficits are likely related to micro-emboli, hypotension, free radical injury, general anesthesia and inflammatory state initiated by cardiopulmonary bypass (CPB) while late deficits are likely related to increasing age, preoperative neurocognitive conditions and vascular disease common for this group of patients.[3] Cerebrovascular accident (CVA) is a common postoperative complication after open heart surgery with incidence approaching 7.7% to 40% and significantly increases morbidity and mortality risks. Brain injury that occurs after hypothermic circulatory arrest (HCA), a commonly utilized technique in arch replacement in cardiac surgery, which unfortunately also can result in deleterious neurological complications. Postmortem histology after HCA (hypothermic circulatory arrest) shows a pattern of selective neuronal death. The neurons most affected are those in the basal ganglia, cerebellum and hippocampus. These affected brain regions are protected against injury by glutamate receptor antagonists suggesting that excitotoxicity is the mechanism of cell death in this model.[2] Glutamate, the most abundant free amino acid in the central nervous system (CNS), serves as a neurotransmitter that mediates signaling in excitatory pathways. Excessive accumulation of glutamate contributes to neuronal ischemic injury by over activating neuronal receptors. Precipitating cascade of intracellular events that leads to neuronal death, a phenomenon termed glutamate excitotoxicity by Olney in 1978.[4] NO (nitric oxide) and its derivatives can damage cells via a variety of mechanisms. First, NO interacts with superoxide (02-) to form peroxynitrite (ONOO-), which can oxidize nitrate tyrosine residues. NO and its derivatives can further activate ADP ribose polymerase, which depletes NAD and leads to cell death. Additional studies have shown that NO can damage DNA directly.[5-7]

Neurological complications after cardiac surgery are a national and international health concern and the development of preventative strategies can have benefits, not only for those patients with neurologic complications from cardiac surgery, but potentially for those patients suffering brain injury from stroke, traumatic brain injury and anoxic brain injury. CNS complications of CPB are generally attributed to the following factors: cerebral embolization-macro and microembolization of gaseous and particulate matter; hypoperfusion-secondary to emboli, hypotension, low-flow sates or shunting; and/or inflammatory response-cytokines release and activation of the kallikrein-kinin and complement systems; free radical injury (Robert 2011). The brain is such a complex organ, even small injuries may produce symptomatic, functional losses that would not be detectable or important in other organs. Regional hypoperfusion, edema, micro-emboli, circulating cytotoxins, free radicles or subtle changes in blood glucose, insulin or calcium may result in changes in cognitive function, ranging from subtle to profound.[8] A small 2 mm infarct may cause a disruption of behavioral patterns, physiologic and physical function changes can pass unnoticed be accepted and dismissed, profoundly compromise the patient's quality of life. The most obvious neurologic abnormalities are paresis, loss of vital brain functions such as speech, vision, comprehension or coma. But transitory episodes of delirium and confusion are often dismissed as due to anesthesia or medications.[8] Sodium valproic acid acts as histone deacetylase (HDAC) enzyme inhibitor which allow the transcription of proteins that protect against oxidative stress and Allopurinol is xanthine oxidase inhibitor which inhibits production of oxygen free radicles and scavenges oxygen free radicles.[8]

This study was performed to evaluate protective role of sodium valproic acid and allopurinol in patients who underwent surgery using cardiopulmonary bypass.

Objective

The aim of this study was to find out neuroprotective role sodium valproic acid and allopurinol to prevent neurological injury following on-pump cardiac surgery.

METHODS

This cross-sectional study was conducted by the department of cardiac surgery, BSMMU, Dhaka, Bangladesh from January 2019 to June 2021. Total 70 patients were included and divided into two groups (36 patients with Sodium valproic acid and allopurinol in group A and 34 patients without sodium valproic acid and allopurinol in group B). As these two drugs were FDA approved was used per-orally for 5 perioperative days (2 days prior surgery, 1 day in operation day, 2 days postoperatively). Dose of sodium valproic acid was 10 mg/kg/day and allopurinol 5 mg/kg/day. Sodium valproic acid reduced neurological injury by the means of reducing reporter excitation in the neurons and allopurinol was a free radical scavenger which reduced free radical induced injury to neurons. Postoperatively the outcome was noted using GCS (Glasgow coma scale), S. CK-BB (serum creatine kinase brain) level, neurocognitive function/MoCA test, ICU stay, hospital stay.

Inclusion criteria were all patients undergoing cardiac surgery using cardiopulmonary bypass, aged between 10 to 70 years and patients with normal neurological function.

Exclusion criteria were patient with previous history of cerebrovascular disease, patient with neurological deficit, patient with autism, Parkinsonism. congenital neurological disease and patient having carotid artery stenosis.

Collected data were entered, checked and edited (to remove the outliers) with the help of the SPSS software, version 26 and analyzed.

RESULTS

After dropping out of 10 patients the total sample size was 60. Dropout was due to death following cardiac surgery, frank stroke and refusal to continue to participate in the study. Between the study population mean age in group A was 36.7±18.285 years and in group B was 32.40±15.18 years. The difference age between two groups was not statistically significant (p>0.05). There was no statistical difference of gender between the two study groups (p>0.05). The mean BMI in group A was 24.13±2.49 kg/m² and that in group B was 24.62±3.71 kg/m^2. The findings were statistically not significant (p>0.05). Table 2 shows that there were no statistically significant differences in findings between two groups in terms of serum CK-BB level, GCS, cognitive function test/MoCA test (Montreal cognitive assessment test) and left ventricular ejection fraction (LVEF%) (p>0.05). Table 3 shows that there were no statistically significant differences in findings between two groups in terms of total bypass time, cross clamp time and activated clotting time, total duration of surgery time (p>0.05). The mean among 6 surgical group was 3.23±1.88 and range was 5. There was no statistically significance among these group and within the group where p>0.05). Postoperative data was collected from group A and group B in the terms of GCS, cognitive function test/MoCA test (Montreal cognitive assessment test), postoperative CK-BB, neurological injury (convulsion and paresis). ICU stay, hospital stay, survival week, mortality. All the variables were very highly statistically significant between group A and group B, which shows group A or intervention group had achieved highest benefit through the medication and p<0.05. Postoperative data was collected from group A and group B in the terms of GCS, cognitive function test/MoCA test (Montreal cognitive assessment test), postoperative serum CK-BB, neurological injury (convulsion and paresis). ICU stay, hospital stay, survival week, mortality. All the variables are very highly statistically significant between group A and group B, which showed group A or intervention group had achieved highest benefit through the medication and p<0.05. Postoperative outcome was also evaluated using Pearson correlation. Data were analyzed in the terms of postoperative S. CK-BB level, GCS, MoCA test. Survival week, neurological injury. ICU stay, hospital stay and grouping (group A and group B). All the correlation data were statistically very significant (p<0.05). The r value of correlation was not 0 meant that there was proportional or inverse correlation within the variables.

Table 1: Comparison of demographic and anthropometric variables.

Variables	Group A (n=30)	Group B (n=30)	P value
Age (in years)			
Mean±SD	36.7±18.285	32.40 ±15.18	0.271
Range	(52 to 53)		
Sex			
Male, N (%)	18 (60.0)	18 (60.0)	0.604
Female, N (%)	12 (40)	12 (40)	
BMI (kg/m^2)			
Mean±sd	20.20±1.29	20.17±1.34	0.943

Table 2: Comparison of preoperative biochemical and other variable evaluation.

Variables	Group A (n=30)	Group B (n=30)	P value
S. CK-BB (ng/ml)	2.36±0.92	2.32±40.89	0.09
GCS (15/15)	15±0	15±0	1.0
Cognitive function (MOCA test, 30/30)	30±0.09	30±0	1.0
LVEF (%)	52.96±6.19	51.60±7.34	0.08

Table 3: Comparison of peroperative variables.

Variables	Group A (n=30)	Group B (n=30)	P value
Total bypass time	110.16±63.54	137.83±79.20	0.124
Cross clamp time	61.60±43.84	83.10±59.63	0.084
ACT (sec)	485.1±26.86	489.1±26.86	0.934
Duration of surgery (hours)	4.38±0.57	4.53±0.66	0.347

Table 4: Comparison of operation types.

Surgery	Frequency	Percent	Group A	Group B	P value
MVR	13	21.7	6	7	
ASD closure	17	28.3	9	8	
DVR	5	8.3	2	3	
TOF correction	5	8.3	3	2	0.688
VSD closure	8	13.3	5	3	
AVR	12	20.0	5	7	
Total	60	100	30	30	

Table 5: Comparisons of postoperative outcome.

Variables	Group A (mean±SD)	Group B (mean±SD)	P value
GCS	15.0±0	12.93±3.65	0.003
MOCA test	30.0±0	24.47±11.16	0.009
Postop S. CK-BB	5.43±2.60	84.93±149.77	0.00001
Neurological injury (convulsion and paresis)	1.0±0	1.27±0.45	0.00001
ICU stay (days)	3.56±0.57	7.93±1.95	0.00001
Hospital stays (days)	11.10±1.02	17.93±1.94	0.00001
Survival week	5.96±0.18	4.50±1.65	0.00001
Mortality	1.00±0	1.17±0.38	0.019

Table 6: Pearson correlation among different postoperative outcome.

Pearson correlation		Post-operative serum CK-BB Level	GCS	MoCA test	Survival test	Neurological injury	ICU stay	Hospi-tal stay	Grouping
Postoperative serum CK-BB level	Pearson correlation	1	-0.959	-0.963	-0.676	0.772	0.646	0.566	0.357
	Significance (2-tailed)		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.005
	total	60	60	60	60	60	60	60	60
GCS	Pearson correlation	-0.959	1	0.967	0.752	-0.729	-0.655	-0.579	-0.377
	Significance (2-tailed)	0.0001		0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	total	60	60	60	60	60	60	60	60
MoCA test	Pearson correlation	-0.963	0.967	1	0.754	-0.761	-0.652	-0.563	-0.336
	Significance (2-tailed)	0.0001	0.0001		0.0001	0.0001	0.0001	0.0001	0.0001
	total	60	60	60	60	60	60	60	60
Survival test	Pearson correlation	-0.676	0.752	0.754	1	-0.603	-0.695	-0.657	-0.535
	Significance (2-tailed)	0.0001	0.0001	0.0001		0.0001	0.0001	0.0001	0.0001
	total	60	60	60	60	60	60	60	60
Neurological injury	Pearson correlation	0.772	-0.729	-0.761	-0.603	1	0.623	0.561	0.392
	Significance (2-tailed)	0.0001	0.0001	0.0001	0.0001		0.0001	0.0001	0.0001
	total	60	60	60	60	60	60	60	60
ICU stay	Pearson	0.646	-0.655	-0.652	-0.695	-0.623	1	0.981	0.840

Continued.

Pearson correlation		Post-operative serum CK-BB Level	GCS	MoCA test	Survival test	Neurological injury	ICU stay	Hospital stay	Grouping
	correlation								
	Significance (2-tailed)	0.0001	0.0001	0.0001	0.0001	0.0001		0.0001	0.0001
	total	60	60	60	60	60	60	60	60
Hospital stay	Pearson correlation	0.566	-0.578	-0.563	-0.657	0.561	0.981	1	0.913
	Significance (2-tailed)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001		0.0001
	total	60	60	60	60	60	60	60	60
Grouping (group A and group B)	Pearson correlation	0.357	-0.377	-0.336	-0.535	0.392	0.840	0.913	1
	Significance (2-tailed)	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	
	total	60	60	60	60	60	60	60	60

Table 7: Review of mortality and survival data.

Surgery	Group A	Mortality	Group B	Mortality	Survival group A	Survival group B	P value
MVR	6	0	7	1	100%	80%	0.0001
ASD closure	9	0	8	1			
DVR	2	0	3	1			
TOF correction	3	0	2	2			
VSD closure	5	0	3	0			
AVR	5	0	7	1			
Total	30	0	30	6		20% mortality	

DISCUSSION

The patients were divided into two groups (group A and group B; 30 patients in each) based on sodium valproic acid and allopurinol intake and who did not take any medicine. Roach et al described most feared neurological complication of cardiac surgery was stroke, with an incidence of between 1% and 6%.[1,2] Robert stated that a 2 infarct can cause disruption of behavioral patterns, physiological and physical function changes.[8] Patients were selected randomly and divided into two group. Group A (intervention group who took per-oral sodium valproic acid 10 mg/kg/day and allopurinol 5 mg/kg/days) and group B was not taking any of this medication.

The demographic variables of the participating patients were recorded and analyzed. The mean age for group A was 36.7±18.285 years and in group B was 32.40±15.18 years. The difference in age between two groups was not statistically significant (p>0.05). The age range of the patients of this study was from 10 years to 70 years. Baumgartner stated that there was no statistical significance of age on his study on neuroprotection during cardiac surgery which was very similar with our study.[3] In group A, the population were male 18 (60%) and 12 (40%) were female. In group B, male was 18 (60%) and female 12 (40%) respectively. Male patients were predominant in both the groups. The distribution of gender between the groups were not statistically significant (p=0.60). Robert et al also found insignificant relationship between neurological injury and gender 90 males and 65 females (p=0.92).[9] A study done by Redmond et al in 1996 included patients undergoing on-pump cardiac surgery and showed that sex distribution had no significant influence (p=0.389) on neurological injury.[2] When average BMI was compared between the two groups, the mean BMI in group A was 24.13±2.49kg/m² and that in group B was 24.62±3.71 kg/m². The findings were statistically not significant (p=0.943). This finding correlated to this study of Robert et al where they found BMI distribution among the groups was not significant (p=0.65).[9] Demographic data are listed in Table 1.

Comparison of preoperative variables were also done in between two groups in terms of serum CK-BB level, GCS, cognitive function test/MoCA test and LVEF% (p>0.05). Comparison of serum creatine kinase BB done where mean of group A was 2.36±0.92 and mean in group B was 2.32±0.89 and Chi square and independent t

test p value was (p=0.09). Comparison of GCS done where mean of group A was 15±0 and mean in group B was 15±0 and Chi square and independent t test p value was (p=1.0). Comparison of cognitive function/MoCA test done where mean of group A was 30±0.09 and mean in group B was 30±0 and Chi square and independent t test p value was (p=1.0).

Among the preoperative echocardiographic parameter ejection fraction (EF) were considered for comparison between group A and group B. The difference of EF in between the two groups was not statistically significant (p=0.08) which was consistent with the findings of Pickel et al.[10] Group A had a mean EF of 52.96±6.19% and that of group B was 51.60±.34%. Per operative data also collected in two groups in terms of total bypass time, cross clamp time and activated clotting time, total duration of surgery time (p>0.05) which was not statistically significant. Comparison of total cardiopulmonary bypass time done where mean of group A was 110.16±63.54 minute and mean in group B was 137.83±79.20 minute and Chi squared and independent t test p value was (p=0.12). Comparison of cross clamp time done where mean of group A was 61.60±43.84 minute and mean in group B were 83.10±59.63 minute and Chi squared and independent t test p value was (p=0.08). Our study was consistent with Pickel et al and Pramod et al.[10,11]

The difference in ACT after heparinization and ACT after heparin neutralization between the two groups was statistically not significant (p>0.05). Mean ACT after heparinization was 485.9±26.86 seconds in group A and 489.1±26.86 seconds in group B (p=0.142). The average ACT after heparin neutralization in both groups were 123.27±9.17 seconds and 129.47±8.24 seconds (p=0.332). Comparison of total surgery time done where mean of group A was 4.38±0.57 minute and mean of group B was 4.53±0.66 hours and Chi square and independent t test was (p=0.34). This was also consistent with the study done by Pramod et al.[11]

Postoperative variable analysis done terms of GCS, cognitive function test/MoCA test, postoperative serum CK-BB, neurological injury/convulsion paresis, ICU stay, hospital stay, survival week, mortality. All the variables were very highly statistically significant between group A and group B which showed group A or intervention group had achieved highest benefit through the medication and p<0.05. Comparison of postoperative GCS on 1st, 3rd and 5th postoperative day done respectively where mean of group was 15.0±0 and mean in group was 12.93±3.65 and Chi square and independent t test value was (p=0.003) which was statistically very significant. These findings were consistent with the findings of Richmond et al.[12]

Comparison of postoperative mortality noted where mean of group A was 1.0±0 and mean in group B was 1.17±0.38 days and Chi square and independent t test p value was (p=0.019) which was statistically very significant. The Pearson co-efficient correlation test for postoperative serum CK-BB and GCS showed a significant inverse relationship, which was statistically very significant (r=0.95, p=0.0001). The Pearson co-efficient correlation test for postoperative serum CK-BB and MoCA test showed a significant inverse relationship, which was statistically very significant (r=-0.96, p=0.0001). The Pearson co-efficient correlation test for postoperative serum CK-BB and survival showed a significant inverse relationship, which was statistically very significant (r=-0.67, p=0.0001). The Pearson co-efficient correlation test for postoperative serum CK-BB and neurological injury showed a significant proportional relationship which was statistically very significant (r=0.77, p=0.0001). The Pearson co-efficient correlation test for postoperative serum CK-BB and ICU stay showed a significant proportional relationship, which was statistically very significant (r=0.65, p=0.0001). Rodríguez et al and Ren et al also showed that allopurinol and sodium valproic acid can prevent neurologic injury and helps in lowering serum CK-BB.[13,14]

The Pearson co-efficient correlation test for postoperative serum creatine kinase BB and hospital stay showed a significant proportional relationship, which was statistically very significant (r=0.56, p=0.0001). The Pearson co-efficient correlation test for postoperative neurological injury and no intervention (group B) showed a significant proportional relationship, which was statistically very significant (r=0.39, p=0.002) and Pearson co-efficient correlation test for postoperative neurological injury and intervention (group A) showed a significant inverse relationship, which was statistically very significant (r=-0.69, p=0.0001) These findings were also consistent with the study done by Sotaniemi in 1980.[15] Overall mortality and survival data showed 20% rise of risk of neurological injury after cardiac surgery in Bangladeshi population in group B which differed from Pickel et al and Ren et al (Table 7).[4,10] Finally, inference was allopurinol and sodium valproic acid intake caused less the chance of neurological injury.

Limitations

The present study was conducted in a very short period due to time constraints and funding limitations. The small sample size was also a limitation of the present study.

CONCLUSION

Sodium valproic acid and allopurinol gives neuroprotection in on-pump cardiac surgical patients. So, these two medicines can be prescribed prophylactically on individual assessment basis.

Recommendations

Long term follow up needed for better understanding the role of Valproic acid and Allopurinol in neuroprotection after complicated cardiac surgery.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Roach GW, Kanchuger M, Mangano CM. Adverse cerebral outcomes after coronary bypass surgery. Multicenter study of perioperative ischemia research group and the ischemia research and education foundation investigators. N E Med J. 1996;335(25):1857-63.
2. Redmond JM, Gillinov AM, Zehr KJ. Glutamate excitotoxicity: a mechanism of neurologic injury associated with hypothermic circulatory arrest. J Thorac Cardiovascul Surg. 1994;107(1):776-86.
3. Baumgartner WA. Neurocognitive changes after coronary bypss surgery. J Am Heart Assoc. 2007;116(16):1879-81.
4. Olney J. Neurotoxicity of excitatory amino acids as a tool in neurobiology. J Neurosci. 1978;65(1):95.
5. Endres M, Wang ZQ, Namura S, Wacher C, Moskowitz MA. Ischemic brain injury is mediated by the activation of poly (ADP-ribose) polymerase. J Cereb Blood Flow Metabol. 1997;17(11):1143-51.
6. Mandir AS, Poitras MF, Berliner AR. NMDA but not non-NMDA excitotoxicity is mediated by Poly (ADP-ribose) polymerase. J Neurosci. 2000;20(21):8005-11.
7. Pieper AA, Blackshaw S, Clements EE. Poly (ADP ribosylation) basally activated by DNA strand breaks reflects glutamate-nitric oxide neurotransmission. Intens Care Ann Update. 2000;97(16):1845-50.
8. Robert SB. Brain protection in cardiac surgery. 1st ed. London: Springer; 2011.
9. Robert RC, Susan AM, James EG, Deborah GH, Norwood J, William G, et al. Allopurinol neurocardiac protection trial in infants undergoing heart surgery using deep hypothermic circulatory arrest. Am Acad Pediatr J. 2000;108(1):61-70.
10. Pickel Z, Williams AM, Alam B, Cindy H. Histone deacetylase inhibitors: a novel strategy for neuroprotection and cardioprotection following ischemia/reperfusion injury. J Am Heart Assoc. 2020;9(11):234-9.
11. Pramod KD, Sara AO, Zhang M, Raymond JG, Pati S, Jing Z, et al. Valproate administered after traumatic brain injury provides neuroprotection and improves cognitive function in rats. Pub Lib Sci One. 2010;5(6):53-60.
12. Redmond JM, Greene PS, Goldsborough MA. Neurologic injury in cardiac surgical patients with a history of stroke. Ann Thorac Surg. 1996;61(1):42-7.
13. Rodríguez FJ, Fernández DC, Lopez MA, Lopez RM, Balada CR, Alcantara HS, et al. Neuroprotection with hypothermia and allopurinol in an animal model of hypoxic-ischemic injury: is it a gender question? Pub Lib Sci One. 2017;25(6):131-9.
14. Ren M, Leng Y, Jeong M, Leeds PR, Chuang DM. Valproic acid reduces brain damage induced by transient focal cerebral ischemia in rats: potential roles of histone deacetylase inhibition and heat shock protein induction. J Neurochem. 2004;89(3):1358-67.
15. Sotaniemi KA. Brain damage and neurological outcome after open-heart surgery. J Neurol Neurosurg Psychiat. 1980;43(2):127-35.

Cite this article as: Khan OS, Hoque R, Rahman M, Imtiaz N. Role of valproic acid and allopurinol in neuroprotection after cardiac surgery on Bangladeshi patients. Int Surg J 2022;9:280-6.