DOI: https://doi.org/10.3329/bjns.v10i1.49161

Original Article

Glucocorticoid In Cytotoxicity Followed by Delayed Edema

Ali MA[1], Islam MA[2], Chowdhury RU[2], Salek MAA[2], Mukherjee SK[3], Khan RK[3], Chowdhury AUM[3], Manik AH[3], Faisal MH[4], Ashrafee P[4]

Conflict of interest: There is no conflict of interest relevant to this paper to disclose.

Funding Agency: was not funded by any institute or any group.

Contribution of Authors: Principal Investigator and Manuscript preparation-
Data collection-
Scalp block with anaesthesia-
Editorial formatting-

Received: 15.08.19
Accepted: 07.11.19

Abstract

Background: *Cytotoxicity is the toxicity to cell. Any type of brain oedema producing raised intracranial pressure (ICP) which may be a fatal pathological state. Corticosteroid is contraindicated in cytotoxic brain oedema but in vasogenic oedema, it is beneficial. Cytotoxic oedema in its consequences induces vasogenic oedema where the corticosteroid may helpful.*

Objectives: *To determine the effects of corticosteroid on tertiary vasogenic brain oedema from cytotoxic edema.*

Methods: *Total of 328 patients was diagnosed as brain oedema and they had been first time reported & all were admitted in Combined Military Hospital (CMH) Dhaka, between Jan 2017 to Jun 2019. Out of 328 patients, brain oedema due to spontaneous ICHs was 219 (66.77%) and traumatic ICHs were 109(33.33%). Diagnosis was based upon history, clinical examination and non-contrast Computed Tomography (CT) scan of brain.*

Results: *Total 328 admitted patients in CMH Dhaka from Jan 2017-Jun 2019 were included in our study who full-fill the criteria. Males were 231 (70.43%); females were 97(29.57%) and were aged between 1 to 95 year. Intracranial haemorrhage rate among age group less than 55 years old being 76 (34.70%) and 55 years or above 143 (65.30%) of total 219 patients. Traumatic ICHs were 109 and 1 to 44 years age is most vulnerable, 69(63.30%) and 45 years and above 40 (36.70%) patients. Corticosteroid was used after vasogenic brain oedema formation following cytotoxic oedema which was diagnosed mainly radiologically. Cytotoxic oedema induced by 24 hours and vasogenic oedema in two to four days of brain insult. Vasogenic oedema developed in 24 -48 hours, 65 (19.82%) patients and 117 (35.67 %) by 48-72 hours and above 72 hours rest 146 (44.51%) patients after brain insult. After vasogenic oedema formation, out of 164 patients that is 50% patients were treated with corticosteroid and GOS was assessed- GOS 4,5 -103(62.80%), GOS 3-34 (20.73%), GOS 2- 23(14.02%) and GOS 1-4(2.44%) whereas without corticosteroid treatment of rest vasogenic oedema 164 (50%) , GOS was- GOS 4,5 -85(51.83%), GOS 3-43 (26.22%), GOS 2- 27(16.46%) and GOS 1-9(5.49%) at 30 days of incidence. There is more than two times mortality without corticosteroid therapy than with steroid therapy.*

Conclusion: *Cytotoxic brain oedema is contraindicated for steroid but we observed that corticosteroid gives better GOS in vasogenic oedema which develops after cytotoxic brain oedema. Outcome in cytotoxic oedema followed by vasogenic oedema is beneficial for corticosteroid.*

Keyword: *Intracranial pressure (ICP), Combined Military Hospital (CMH), Intracerebral hemorrhage(ICH).*

Bang. J Neurosurgery 2020; 10(1): 45-51

1. Lt Col (Dr) Md Amir Ali, Neurosurgeon, CMH Dhaka.
2. Col (Dr) Aminul Islam, Head of dept. Neurosurgery, CMH Dhaka.
3. Col (Dr) R U Chowdhury, Consultant Neurosurgeon, CMH Dhaka.
4. Lt Col (Dr) Al-Amin Salek, Neurosurgeon, CMH Dhaka.
5. Dr. Sudipta Kumer Mukherjee, Assistant Prof. Paediatric Neurorosurgery, National Institute of Neurosciences and Hospital, Dhaka, Bangladesh.
6. Dr. Rafiul Karim Khan, Assistant Professor, Dept. of Surgery, SSMCH, Dhaka.
7. Lt Col (Dr) Ahmed Mursalin Chowdhury, Neurosurgeon, CMH Dhaka.
8. Lt Col (Dr) Abdul Hye Manik, Neurosurgeon, CMH Dhaka.
9. Maj (Dr) Md Hasnain Faisal, Neurosurgeon, CMH Dhaka.
10. Dr Pariza Ashrafee, Senior medical officer, Ha-meem group, Dhaka.

Address of Correspondence: Lt Col Md Amir Ali, Neurosurgeon, Neurosurgery Center, CMH, Dhaka, mob-01742516625, Email- lt.col.amirali@gmail.com

Introduction

Brain oedema is a potentially fatal pathological state in which brain volume increases due to abnormal accumulation of fluid within the cerebral parenchyma1.

This brain oedema is observed in a range of medical conditions, including stroke, traumatic brain injury (TBI), brain tumors or metastases, meningitis, brain abscess, water intoxication, liver failure, altitude sickness, malignant hypertension, hypoglycemia and metabolic encephalopathies2.

Oedema is a pathological process that may aggravate injury by either causing cellular dysfunction when fluid accumulates intracellular, or by increasing the distance and consumption of time through which oxygen, nutrients and wastes have to diffuse if it is extracellular.

This space limitation can set in motion a vicious cycle where elevated ICP compresses both capillary perfusion and venous drainage, which if unchecked causes further edema, cerebral ischemia, brain herniation and a lethal compression of brainstem cardiorespiratory centers. The abnormal accumulation of fluid results of an increase brain volume and elevation of intracranial pressure (ICP) because of an enclosed rigid skull.

The severity of brain edema is correlated to the increased ICP. It causes an irreversible impairment of neurological function, and worst permanent vegetative state to death. Although the serious pathogenesis of brain edema, medical strategies are very limited. Vasogenic oedema treated with corticosteroid but cytotoxic edema treatment is still nonspecific.

Pathogenesis

Brain edema is classified mainly into vasogenic, cytotoxic, osmotic and interstitial.

Vasogenic oedema-usually seen in brain tumour due to release of TNF alpha and is resulting in extravasation of fluid, protein and accumulation of fluid into the cerebral parenchyma caused by disruption of the blood-brain barrier (BBB). The extravasated fluid evokes an increase of brain volume as well as ICP. Brain insult produce reversible and irreversible disruption of BBB induces vasogenic oedema. Following brain injury, temporal ischemic reperfusion causes excitotoxicity and oxidative stress through mitochondrial dysfunction. This mechanism may directly damage BBB-constituting cells, resulting in irreversible BBB disruption3.

Vasogenic oedema following BBB disruption are commonly observed in cerebral trauma,hemorrhage and the secondary phase of ischemia and are usually reversible BBB disruption4,5. Thus recovery is possible for these types of injury.

Cytotoxic oedema is due to intracellular accumulation of fluid and Na+ resulting in cell swelling by decreased ATP. Head injury & cerebral ischemia are the main aetiological factors for ATP depletion. The depleted ATP induces a failure of intra-extracellular Na+ transport system and results in excessive intracellular Na+ accumulation. The increase of intracellular Na+ leads to an abnormal entry of extracellular fluid into cell produce cell swelling (Figure 1).

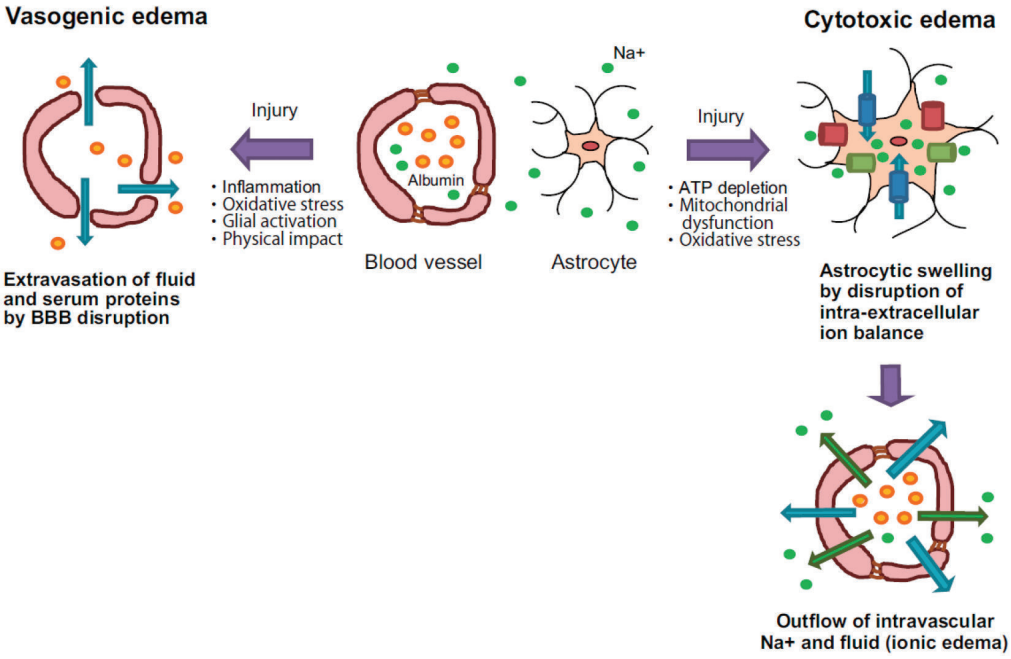

Fig.-1: *Pathogenesis of cytotoxic & vasogenic oedema*

After cellular edema formation, the outflow of Na+ from vascular compartment is accelerated to improve depleted extracellular Na+ and fluid. From intravascular Na+ outflow induces an extravasation of fluid without causing BBB disruption, and produce extracellular fluid accumulation known as ionic oedema[6].

In osmotic oedema, it is due to less osmolality in extracellular space of CNS tissue rather than intracellular CNS component-like SIADH or excessive intake water. In liver failure, several products such as ammonia accumulate in various tissues including the brain. In CNS tissue, these products are taken into astrocytes and causes oxidative stress and mitochondrial dysfunction. These lead to astrocytic dysfunction and swelling7. Interstitial oedema is due to more CSF accumulation in brain parenchyma due to obstruction of CSF pathway and water intoxication.

High altitude oedema is due to both cytotoxic due to ischemia and vasogenic due to release of VEGF.

Traumatic brain injury (TBI) induces focal cerebral damage by physical impact in that area, and subsequently, secondary injury is evoked and induces diffuse cerebral damage in the peri- core area. The secondary injury persistently causes disruption of BBB, brain edema and neuronal degeneration in diffuse cerebral area[8]. And treating the secondary injury is essential to reduce TBI damage.

After initial ICH, continued bleeding is observed and hematoma expansion is induced. In the area surrounding hematoma, secondary injury happened by neuronal and glial dysfunction that causes glutamate release, membrane depolarization and mitochondrial dysfunction. This mitochondrial dysfunction leads to cellular swelling9. In addition, activated glial cell release cytokines that induce BBB breakdown, resulting in extravasation of blood components (e.g., thrombin and hemoglobin) and inflammatory response. So, both vasogenic and cytotoxic edema are observed after hemorrhage10. Cytotoxic oedema is observed in the early phase of injury, *i.e.*, within one day, whereas vasogenic oedema is evoked usually after two to four days[11].

Brain endothelial cells constitute tight junctions through extracellular adhesion proteins and form BBB with astrocytes and pericytes.

After brain insult astrocyte, neuron and endothelial cell release various inflammatory markers such as tumor necrosis factor (TNF), interleukins (IL) 6 and I beta.

Cytotoxity followed by dead cell consequently necrosis, release tumor necrosis factor α (TNFα) ,(inducible Nitric oxides) iNOS , High-mobility group box1 *(*HMGB-1*)* protein and interleukin 1,6,8 induces inflammation & disruption BBB, and TNFα, interleukin 8 also produce vasodilatation12 (Figure-2).

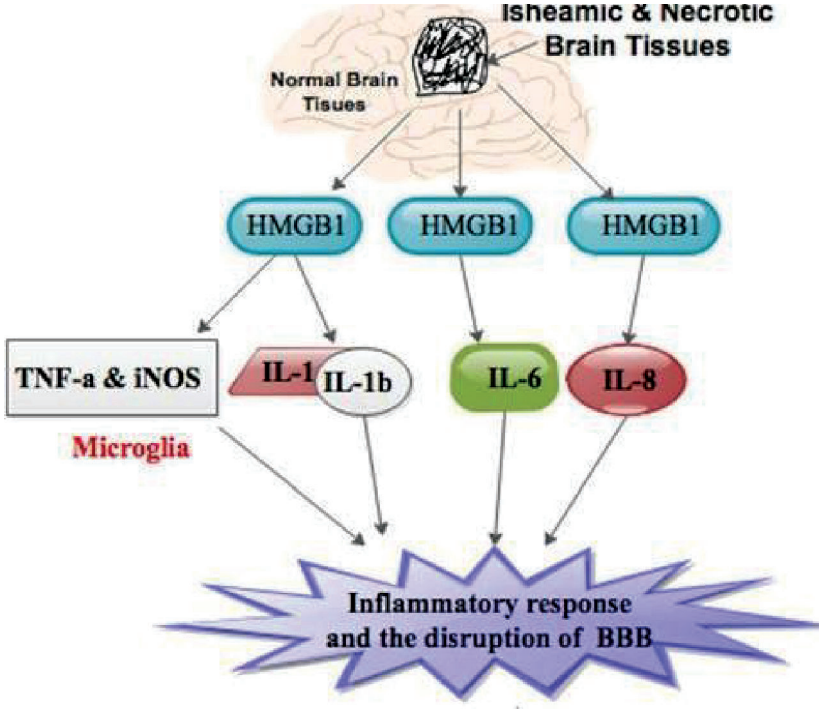

Fig-2: *Pathogenesis of cytoxicity followed by vasogenic oedema*

In additional molecular pathway, distortion of BBB is due to release of metalloproteinase (MMP) after head injury. The MMPs are end peptidases cause the destruction of zona occludens of tight junction of BBB after brain injury. MMP-2, -3, -9 are increased after TBI. The MMP-2,-9 cause degradation of ZO-1, claudin-5, and occludin of BBB leading to increased permeability of BBB13. Usually up-regulation of MMP-2 after 72 hours of injury- related to disruption of the BBB14. As cerebral oedema is a multi-pathway phenomenon, the aim of treatment should be in a phased manner. As the cerebral edema increases ICP and decreases the CPP, priority should be control of ICP by reducing the progression of cerebral oedema.

Dexamethasone reduces permeability of blood-brain barrier (BBB). Dexamethasone reduces cerebral edema by decreasing the permeability of the cerebral vasculature for macromolecules. Na, K-ATPase in capillary plays an important role in BBB sodium transport and the rate of sodium transport from blood to brain appears to determine the rate of oedema15.

Dexamethasone (DEX) is the most common synthetic glucocorticoid and leads to activation of glucocorticoid receptor (GR). The beneficial effects of DEX for cerebral edema have been shown clinically in various brain insults. Inflammatory responses by cytokines and chemokines induce BBB breakdown and development of brain edema16. The DEX may exert anti-edema action through attenuation of inflammatory response. DEX increases the levels of angiopoietin-

1, which stabilizes the BBB structure and reduces the level of VEGF in astrocytes and pericytes through GR activation17. Dexamethasone has been shown to decrease the transmonolayer paracellular permeability through increases of tight junction-regulating proteins such as ZO-1 and occludin in cultured brain endothelial cells. These findings imply that DEX not only reduce inflammatory responses but also stabilizes BBB, leading to reduction of vasogenic brain edema18.

In this background to come into conclusion we tried to see the effects of corticosteroid on tertiary vasogenic brain oedema from cytotoxic edema in CMH Dhaka, Bangladesh.

Materials and methods:

This study is a prospective study. All patients with brain insult with cerebral oedema who were admitted in the Neurosurgery Centre, CMH, Dhaka, during the period from Jan 2017 to Jun 2019 were enrolled for the study.

Total of 328 cases in either sex & age variables from 1 year to 95 years were randomly selected and divided into two groups depending on cerebral oedema specially due to spontaneous ICH and ICH in head trauma in Bangladesh.

All patients were analyzed and evaluated by their hospital; clinical and radiological data of computerized patient record from hospital record, picture archive and communication system. Patients with cerebral oedema specially due to spontaneous ICH and ICH in head trauma with any volume. All of them were computed tomography scan sorted and included in this study. Patients of age 1 year to 95 years but irrespective of gender, co-morbidities such as DM, HTN, MI; on anticoagulant, coagulopathy etc. were included in this study.

Evaluation of brain oedema was done at least by 1st, 2nd, 3rd, 4th and 5th day(until significant vasogenic oedema developed) of brain insult and was compared with / without dexamethasone treatment from remarkable vasogenic oedema development following cytotoxic oedema.

Cerebral oedema in cytoxicity and followed by vasogenic oedema by Non-Contrast CT scan of head showing in figure 3, 4 respectively.

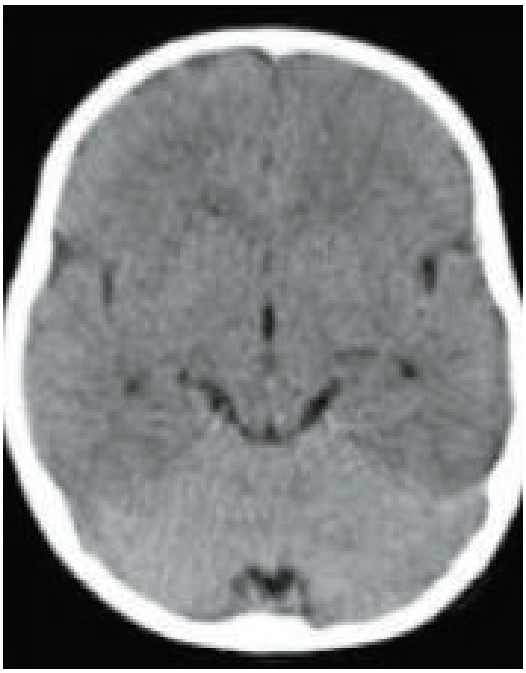

Fig.-3: *Cytotoxic oedema in both gray-white mater*

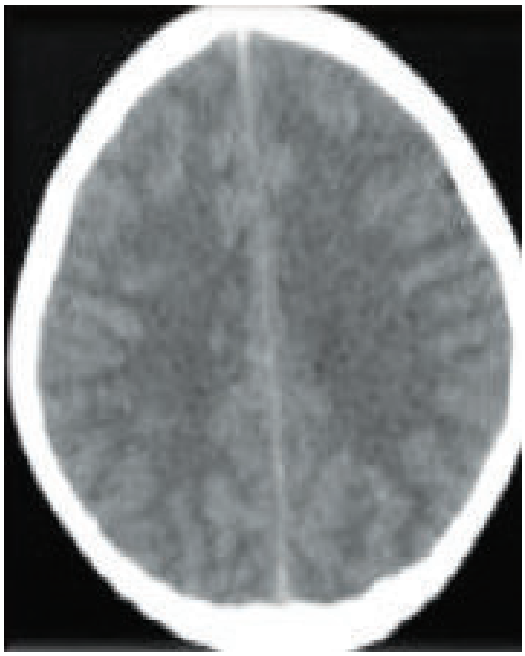

Fig.-4: *Vasogenic Oedema- mainly in white mater*

Results:

Total 328 patients of cerebral oedema were admitted in CMH Dhaka from Jan 2017-Jun 2019. All of patients were evaluated by details history, clinical examination & relevant investigation.

Regarding gender, males were 231 (70.43%); females were 97(29.57%) & males were predominant (Figure-5).

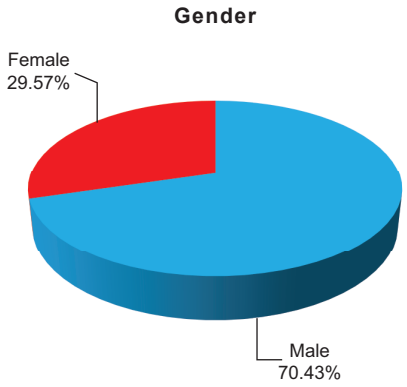

Fig.-5

Spontaneous intracranial haemorrhage rate among age group less than 55 years old being 76 (34.70%) and 55 years or above 143 (65.30%) of total 219 patients and old age group having higher incidence. Traumatic ICHs were 109 and 1 to 44 years age is most vulnerable that is 69(63.30%) and 45 years and above are 40 (36.70%) patients and child and young age group is predominant.

Cytotoxic oedema induced by 24 hours and vasogenic oedema in two to four days of brain insult. Vasogenic oedema developed by 24 -48 hours, 65 (19.82%) patients and 117 (35.67 %) by 48-72 hours and above 72 hours rest 146 (44.51%) patients after cerebral insult. (Figure-6).

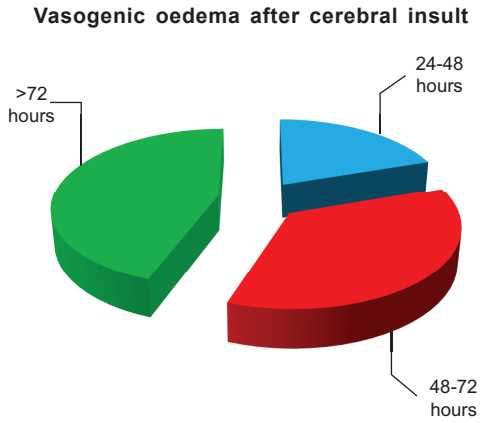

Fig.-6

After definite vasogenic oedema formation, out of 164 patients that is 50% patients were treated with corticosteroid and GOS was assessed- GOS 4, 5 - 103(62.80%), GOS 3-34 (20.73%), GOS2-23(14.02%) and GOS 1-4(2.44%) ; whereas without corticosteroid treatment of rest vasogenic oedema 164 (50%), GOS was- GOS 4, 5 - 85(51.83%), GOS 3-43 (26.22%), GOS

2- 27(16.46%) and GOS 1-9(5.49%) at 30 days of incidence (Figure-7).

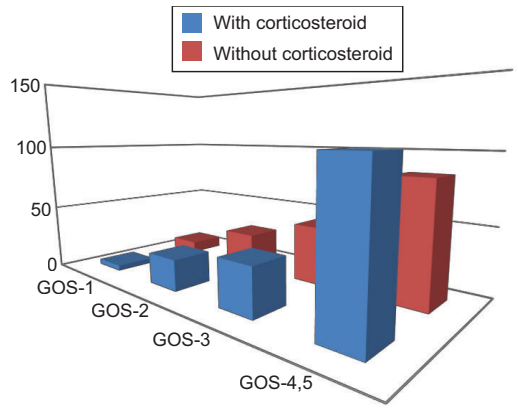

Fig.-7

There is more than two times mortality without corticosteroid therapy than with steroid therapy.

Discussion:

Regarding corticosteroid in brain oedema we have shown in vasogenic oedema following cytotoxicity have significant effects of steroid to reduce oedema, some studies showed a variation in effects of brain oedema cases; data from these studies are in consistent and conflicting.

During a 72-hour period of study, large doses of dexamethasone did not favorably affect severity of neither brain edema nor survival[19].

Single dose of either dexamethasone or progesterone significantly reduced the intact barrier edema seen; however, dexamethasone was more potent than progesterone[20].

Dexamethasone may act as free radical scavenger that improve cellular viability and reduce edema as other free radical scavenger. Steroid may reduce ischemic brain damage by improving blood flow to the tissue[21], which is similar to our study.

Corticosteroid is less effective in cytotoxic edema, and is not recommended in treatment of edema secondary to stroke or haemorrhage. In fact, systemic complications of steroids can worsen the patient's condition like chronic kidney disease, osteoporosis, osteopenia, hypertension and hypercholesterolemia[22].

Corticosteroids lower intracranial pressure primarily in vasogenic edema because of their beneficial effect on the blood vessel[23].

GR activation by DEX not only reduces inflammatory responses but also stabilizes BBB, leading to reduction of vasogenic brain edema[18].

Pathophysiologically ischaemic and traumatic brain edema is initially cytotoxic because of disturbances in cell membrane, later vasogenic edema sets in due to disruption of BBB[23].

There is no obvious reliable international study when we will use steroid in cytotoxicity followed by vasogenic oedema and its outcome.

We found that vasogenic oedema formation after 24 hours of brain insult & we used corticosteroid after significant vasogenic oedema developed following cytotoxicity that is , out of 328 patients 50% ;164 in number, were treated with corticosteroid and GOS was assessed- GOS 4,5 -103(62.80%), GOS 3-34 (20.73%), GOS 2- 23(14.02%) and GOS 1-4(2.44%) ; whereas without corticosteroid treatment of rest vasogenic oedema 164 (50%) , GOS was- GOS 4,5 -85(51.83%), GOS 3-43 (26.22%), GOS 2-27(16.46%) and GOS 1-9(5.49%) which also correlates with the study of Thrane et al.2014 who showed cytotoxic edema is observed in the early phase of injury, *i.e.*, within one day, whereas vasogenic edema is evoked usually after two to four days11.Though there are lot many side effects like HTN, DM, osteoporosis, hypercholestremia, acne, baldness but side effects of steroids very much depend on the dose and how long they are taken. If dose is low and short time use, risk of serious side effect is quite small.

The limitation of our study is, it was done in single center, CMH Dhaka but as our patients both serving, retired soilders and parents of our military members live in different parts of the country and reported to our CMH Dhaka , it can reflects some overall scenario of at least Bangladesh.

Conclusion:

Cytotoxic brain oedema is contraindicated for steroid but we observed that corticosteroid gives better GOS in vasogenic oedema which develops after cytotoxic brain oedema. Outcome including mortality and morbidity in cytotoxic oedema followed by vasogenic oedema is reduced by corticosteroid therapy.

References:

1. Nag S, Manias J L, Stewart D J. Pathology and new players in the pathogenesis of brain edema. Acta Neuropathol. 2009; 118:197–217.
2. Marmarou A.The pathophysiology of brain edema and elevated intracranial pressure. Cleve Clin J Med. 2004 Jan; 71 (1): S6-S8.
3. Paschen W.Glutamate excitotoxicity in transient global cerebral ischemia. Acta Neurobiol Exp (Wars). 1996; 56(1):313-22.
4. Unterberg A W, Stover J, Kress B, Kiening K L. Edema and brain trauma. Neuroscience 2004; 4:1021–30.
5. Simard J M, Kent T A., Chen M, Tarasov K V, Gerzanich V. Brain oedema in focal ischaemia: Molecular pathophysiology and theoretical implications. Lancet Neurol. 2007; 6:258–68.
6. Kahle K T, Simard J M, Staley K J, Nahed BV, Jones P S, Sun D. Molecular mechanisms of ischemic cerebral edema: Role of electroneutral ion transport. Physiology (Bethesda) 2009; 24: 257–65.

7. Rabinstein A A. Treatment of brain edema in acute liver failure. Curr. Treat. Opt. Neurol. 2010; 2:129–41.

8. Donkin J J, Vink R. Mechanisms of cerebral edema in traumatic brain injury: therapeutic developments.Curr Opin Neurol. 2010 Jun; 23(3):293-99.

9. Qureshi A I, Mendelow A D, Hanley D F. Intracerebral haemorrhage. Lancet 2009;373:1632–44.

10. Yang G Y, Betz A L, Chenevert T L, Brunberg J A, Hoff J T. Experimental intracerebral hemorrhage: Relationship between brain edema, blood flow, and blood- brain barrier permeability in rats. J. Neurosurg. 1994; 1:93–102.

11. Thrane A S, Rangroo Thrane V, Nedergaard M Trends . Drowning stars: reassessing the role of astrocytes in brain edema. Neurosci. 2014 Nov; 37(11):620-28.

12. Nagata S Hanayama , Kohki Kawane M. Autoimmunity and the Clearance of Dead Cells. Cell 2010 Mar 5; 140(5):619-30.13. Iffland P H, Grant G A, Janigro D. Mechanisms of Cerebral Edema Leading to Early Seizures After Traumatic Brain Injury. New York: Springer Series in Translational Stroke Research; 2013.

14. Roberts D J, Jenne C N, Léger C, Kramer A H, Gallagher C N, Todd S, et al. A prospective evaluation of the temporal matrix metalloproteinase response after severe traumatic brain injury in humans. J Neurotrauma 2013;30: 1717-26.

15. Reid A C, Teasdale G M, McCulloch J. The effects of dexamethasone administration and withdrawal on water permi ability across the blood-brain barrier. Ann Neurol.1983;13:28-31.

16. Stamatovic S M, Dimitrijevic O B, Keep R F, Andjelkovic A V. Inflammation and brain edema: New insights into the role of chemokines and their receptors. Acta Neurochir. Suppl. 2006;96:444–50.

17. Kim H, Lee J M, Park J S, Jo S A, Kim Y O, Kim C W, Jo I. Dexamethasone coordinately regulates angiopoietin-1 and VEGF: A mechanism of glucocorticoid- induced stabilization of blood-brain barrier. Biochem. Biophys. Res. Commun. 2008;1:243–48.

18. Romero I A, Radewicz K , Jubin E, Michel C C, Greenwood J, Couraud P O, Adamson P. Changes in cytoskeletal and tight junctional proteins correlate with decreased permeability induced by dexamethasone in cultured rat brain endothelial cells. Neurosci. Lett. 2003;2: 112–16.

19. Barry A Siegel, Rebecca K Studer. Steroid Therapy of Brain Edema Ineffectiveness in Experimental Cerebral Microembolism.Arch Neurol. 1972; 27(3):209-212.

20. A. Lorris Betz and Hans C. Coester. Effect of Steroids on Edema and Sodium Uptake of the Brain during Focal Ischemia in Rats. Ahajournals.org. Stroke 1990 Aug: 21(8).

21. Suzuki J, Imaizumi S, Kayama T, Yushimoto T. Chemiluminescence in hypoxic brain —The second report: Cerebral pro- tective effect of mannitol, vitamin E and glucocorticoid. Stroke 1985;16:695-700.

22. Rosenberg G A. Neurology in clinical practice. 3rd ed .Boston:Butterworth Heinmann ;2000:1545–59.

23. S K Jha.Cerebral Edema and its Management. Med J Armed Forces India. 2003 Oct; 59(4): 326–31.