ScientificScholar®
Knowledge is power
Publisher of Scientific Journals

www.surgicalneurologyint.com

Surgical Neurology International

Editor-in-Chief: Nancy E. Epstein, MD, Clinical Professor of Neurological Surgery, School of Medicine, State U. of NY at Stony Brook.

SNI: Trauma

Editor
Iype Cherian, MD
Bharatpur College of Medical Sciences, Chitwan, Nepal

SNI
Open Access

Original Article

Steroids for delayed cerebral edema after traumatic brain injury

G. Lakshmi Prasad

Department of Neurosurgery, Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India.

E-mail: *G. Lakshmi Prasad - lakshmi.prasad@manipal.edu

***Corresponding author:**
G. Lakshmi Prasad,
Department of Neurosurgery,
Kasturba Medical College,
Manipal, Manipal Academy of
Higher Education, Manipal,
Karnataka, India.

lakshmi.prasad@manipal.edu

Received : 23 October 2020
Accepted : 15 January 2021
Published : 10 February 2021

DOI
10.25259/SNI_756_2020

Quick Response Code:

ABSTRACT

Background: Brain edema is a common phenomenon after traumatic brain injury (TBI) resulting in increased intracranial pressure and subsequent neurological deterioration. Experimental studies have proven that brain edema is biphasic (cytotoxic followed by vasogenic). Till date, all studies, including the corticosteroid randomization after significant head injury (HI) trial, have used high-dose steroids in the acute period during which the edema is essentially cytotoxic in nature. No clinical data exist pertaining to delayed cerebral edema (vasogenic) and steroids.

Methods: Patients who had received steroids for delayed cerebral edema after TBI were retrospectively analyzed over a 2-year period. Steroid dose, timing of steroid prescription, time to improvement of symptoms, and complications were noted.

Results: There were six males and three females. Mean age was 41.1 years. There were no severe HI cases. All subjects had cerebral contusions on imaging. Dexamethasone was the preferred steroid starting with 12 mg/day and tapered in 5–7 days. The mean interval to steroid administration after trauma was 7 days. The mean duration of steroid prescription was 6.3 days. All patients had complete symptomatic improvement. The mean time to symptom resolution was 3.8 days. No patients experienced any complications pertinent to steroid usage.

Conclusion: This is the first study to document efficacy of steroids for delayed cerebral edema after TBI, at least in mild/moderate head injuries. The timing of steroid usage and dose of steroids is key aspects that might determine its efficacy in TBI which was the drawbacks of the previous studies. Future prospective trials with the above factors in consideration may confirm/refute above findings.

Keywords: Brain edema, Corticosteroids, Delayed cerebral edema, Steroids, Traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is one of the most common causes of morbidity and mortality.[13] Brain edema is a very common finding noted after TBI that may result in increased intracranial pressure (ICP), leading to subsequent neurological deterioration.[10,14] It is a well-known fact that cerebral inflammation plays an important role in the pathogenesis of secondary brain injury after TBI.[2,10] Various inflammatory mediators are known to be released after TBI that may accentuate the cerebral edema.[10,16,17] Hence, theoretically, anti-inflammatory agents should help in reduction of the cerebral edema and improve functional outcomes. Since steroids reduce tissue edema, there existed a controversy regarding its usage in patients with TBI. However, the 2004

corticosteroid randomization after significant head injury (CRASH) multi-centric trial which used steroids in the acute period concluded that steroids do more harm than good and are not recommended in head injury (HI).[15] Till date, no clinical data exists pertaining to the delayed cerebral edema, in which the edema will be vasogenic in nature and steroid usage. The present study presents an analysis of functional outcomes of nine consecutive cases of delayed cerebral edema who were managed with steroids.

MATERIALS AND METHODS

Patients who received steroids for delayed cerebral edema after TBI were retrospectively analyzed over a 2-year period. Hospital records were utilized for retrieval of data. Variables analyzed included age, gender, mode of injury, nature of symptoms (headache, vomiting, focal neurological deficits, and neurological deterioration), admission Glasgow coma scale (GCS) score, pupillary reactivity, computed tomography (CT) findings (contusion, subdural hematoma [SDH], diffuse axonal injury, cerebral edema, status of basal cisterns, midline shift [MLS] etc.), time to clinical deterioration after trauma (either a drop in GCS score or worsening of symptoms), dosage of steroids, duration of steroid treatment, time to clinical and radiological improvement, and Glasgow Outcome Scale score at discharge at follow-up and follow-up duration.

Steroids were prescribed only in those cases where the cerebral edema persisted and patient showed worsening/non-improvement of symptoms despite administration of standard cerebral decongestants such as mannitol/hypertonic saline. Dexamethasone was used in all subjects and was administered parenterally for 24–48 h that was later converted to oral tapering doses for a total duration of 5–7 days.

RESULTS

Of the nine cases, there were six males and three females. The mean age of the cohort was 41.1 years (SD = ±6.62). Six subjects sustained TBI as a result of road traffic accidents (RTA). Based on GCS scores, there were eight mild and one moderate head injuries (mainly because of low verbal output). The median admission GCS score was 15. The mean GCS score was 13.4 (SD = ±2.60). No patients had focal neurological deficits or pupillary abnormalities on admission.

On radiology, all subjects had parenchymal contusions (five unifrontal, three bifrontal, and one temporal), two subjects had additional thin acute SDH and one subject had additional posterior fossa extradural hematoma. Basal cisterns were partially effaced in seven cases. MLS was noted in four cases and the mean MLS among them was 4.7 mm (SD = ±1.25). CT scan done at the time of clinical worsening showed increased edema in all cases with additional blooming of contusion in one case.

The patient of moderate HI had a drop in GCS score by two points, while other cases developed worsening of headache/new-onset disabling headache. The mean time to steroid administration after the trauma was 7 days (SD = ±1.58). The mean duration of steroid prescription was 6.3 days (SD = ±0.86). All patients had symptomatic improvement and the mean time to symptom resolution was 3.8 days (SD = ±0.78). Repeat CT after steroids was performed in eight cases. There was no change in cerebral edema in two cases, while reduction of cerebral edema was seen in six cases. The median GCS score at discharge was 15. None of the subjects suffered any complications attributable to the steroid usage. The mean follow-up duration was 5.6 months (SD = ±0.93).

Representative case description

Case 5: A 47-year female presented to our emergency services after an alleged RTA 1 day prior. She complained of mild-to-moderate left-sided headache, not associated with vomiting. On examination, she was conscious, alert with coherent speech, and bilaterally reactive pupils. CT scan showed small left temporal contusion with minimal mass effect [Figure 1a]. Three days later, she developed moderate-to-severe disabling headache and giddiness. Her GCS score was 15/15 with no pupillary abnormalities or focal deficits. A repeat CT scan showed blossoming of the contusion with increase in the perilesional edema and mild effacement of basal cisterns. A MLS of 3 mm was seen [Figure 1b]. She was prescribed mannitol for 3 days but had no improvement in her headache. Later, she was started on parenteral dexamethasone with a starting dose of 4 mg thrice a day and then tapered for a total duration of 7 days. She noticed significant improvement in her headache within 48 h and headache was completely resolved in 5 days. A repeat CT scan done 5 days after steroid administration showed reduction of cerebral edema [Figure 1c]. She did not develop any adverse effects of steroid prescription.

[Table 1] summarizes the clinicoradiological details of the nine cases.

DISCUSSION

Although termed to be highly simplistic, brain edema is said to be of two major types – vasogenic and cytotoxic. Other subtypes include osmotic and interstitial edema.[9-11] An increased blood brain barrier (BBB) permeability with extracellular water accumulation is seen in vasogenic type, whereas the cytotoxic edema results from intracellular water accumulation due to substrate and energy failure and subsequent cell death. Cytotoxic edema affects both gray and white matter and is found in infarct and stroke,

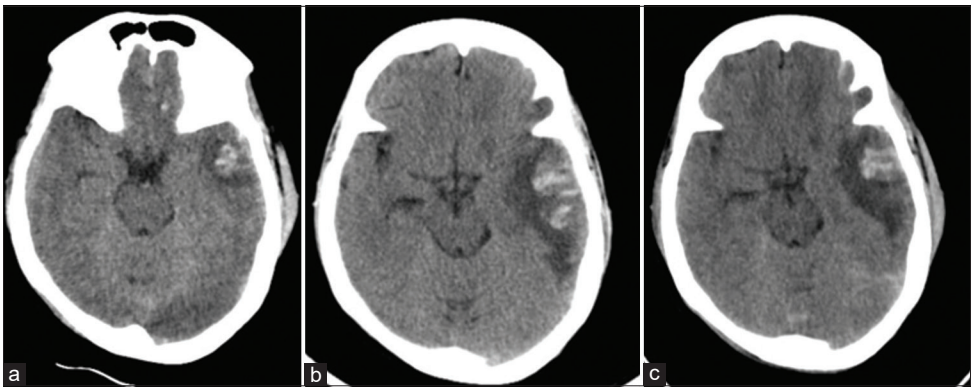

Figure 1: (a) Non-contrast computed tomography (CT) showing small left temporal contusion. (b) CT performed after the onset of disabling headache showing blooming of contusion and increase in the perilesional edema with partial effacement of basal cisterns. (c) CT done 5 days after steroid administration showing resolution of cerebral edema.

while vasogenic type involves predominantly the white matter and is seen in neoplasms and inflammatory conditions.[10,11] Various mediators such as glutamate, nitric oxide, arachidonic acid and its metabolites, free oxygen radicals, histamine, kinins, and MMP-9 are known to be released after TBI. These inflammatory mediators contribute to the development of/accentuation of brain edema.[10,11,16,17] In particular, kinins (bradykinins) and tachykinins (substance P) seem to play an important role in modulating BBB permeability after trauma.[16] Based on animal models of TBI, few authors have also noted increased levels of NF-kappa B, pro-inflammatory cytokines, and intercellular adhesion molecule-1.[2,5] Nimmo *et al.* concluded that neurogenic inflammation may play an integral role in the development of edema following TBI and neuropeptides may serve as a novel target for development of pharmacological strategies.[12] Thus, the authors suggested that attenuating BBB permeability may show a promising approach in treating brain edema.[16] In animal TBI experiments, studies have noted attenuation of the inflammatory responses with substance P antagonists, recombinant human erythropoietin (rhEPO), and others. Gabrielian and associates observed that administration of a substance P antagonist profoundly reduced the BBB permeability and edema formation with improvement in functional outcomes. The authors concluded that substance P antagonists could offer a novel therapeutic approach in the treatment of TBI.[6] In an animal model of TBI by Chen *et al.*, rhEPO reduced brain edema, BBB permeability, and apoptotic cells with the authors concluding that inflammatory responses after TBI might be inhibited by rhEPO.[2]

It has been proven in experimental studies that brain edema is actually biphasic in nature, with an initial cytotoxic component and a subsequent vasogenic one. This is because increases in cranial water content can only be derived from the vasculature.[5,7] Further, it has also been concluded that a breach in BBB and subsequent increased permeability is a key event occurring after TBI, resulting in increased brain water content. Glucocorticoids are among the most potent anti-inflammatory agents. The mechanism of action of steroids appears to be related to the inhibition of gene expression of pro-inflammatory molecules.[3] Vasogenic edema is classically seen in infections and tumors, and steroids are the mainstay of medical treatment in such conditions. Steroids stabilize the cell membranes and reduce the cellular permeability, in turn reducing brain edema and the resultant ICP.[10] Since, multiple mediators are released after trauma that can alter the membrane permeability, theoretically, steroids should be able to counteract the vasogenic/inflammatory edema occurring after TBI and reduce the ICP. Recently, Hue *et al.* concluded that dexamethasone potentiates *in vitro* blood-brain barrier recovery after primary blast injury.[8]

The role of steroids in clinical studies of TBI has been conceptualized from spinal cord injury trials, most notably the NASCIS, wherein the investigators found difference in outcomes with high-dose methylprednisolone, if given within 8 h of the spinal injury.[1] Till date, in all the studies relating to steroids and TBI, steroids (either dexamethasone or methylprednisolone) were prescribed during the acute period (mostly given within 6–8 h) of trauma, during which the edema is in fact cytotoxic in nature. Furthermore, the prescribed doses have been very high. A randomized trial by Dearden and associates evaluated the role of steroids in TBI. Severe HI subjects were randomized to either steroid or placebo groups (68 and 62, respectively) and steroids were administered within 8 h of the trauma. High-dose dexamethasone was used as a 50 mg IV bolus on admission followed by 100 mg daily on day 1, 2, and 3, tapered to 50 mg on D4 and finally 25 mg on day 5 as a continuous IV infusion. The authors found no beneficial effect of steroids. On the contrary, they observed a poorer outcome in patients

Table 1: Summarizing the clinicoradiological details of the cohort.

Case number	Age/ sex	GCS score	MOI	Initial CT findings	Clinical findings at deterioration	CT findings at deterioration	Steroids administration-day of injury	Steroid duration (d)	Time to complete symptom improvement (d)	Repeat CT findings	FU duration (m)
1	53/M	13	RTA	L frontal contusion, thin SDH	Drop in GCS score by 2 points	Edema	10	7	4	Edema reduced	7
2	42/M	15	Fall	PF EDH, B/L basifrontal contusions	Severe headache	Edema	8	6	3	Edema same	5.5
3	40/M	13	Fall	B/L basifrontal contusions	Severe headache	Edema	7	7	4	Edema same	6.5
4	35/F	15	RTA	B/L basifrontal contusions	Severe headache	Edema	5	6	3	Edema reduced	6
5	47/F	11	RTA	L temporal contusion, thin SDH	Severe headache, giddiness	Edema, blooming of contusion	7	7	5	Edema reduced	5
6	45/M	15	RTA	R frontal contusion	Severe headache	Edema	7	5	4	NP	6.5
7	32/M	15	RTA	R Frontal contusion	New onset headache	Edema, resolving contusion	8	5	3	Edema reduced	4
8	35/M	15	RTA	L frontal contusion	Severe headache	Edema	6	7	5	Edema reduced	5
9	41/F	15	RTA	L frontal contusion	Severe headache	Edema	5	7	4	Edema reduced	5.5

No patient had pupillary abnormalities or focal deficits. None experienced steroid-induced adverse effects. GCS: Glasgow coma scale, MOI: Mode of injury, CT: Computed tomography, d: Days; M: Male, RTA: Road traffic accident, FU: Follow-up, m: Months, L: Left, SDH: Subdural hematoma, MLS: Midline shift, PF EDH: Posterior fossa extradural hematoma, B/L: Bilateral, NP: Not performed, F: Female, R: Right.

with elevated ICP who had received steroids. However, there was no increase in pulmonary or gastrointestinal complications noted in the steroid group.[4] The landmark multicentric double-blinded CRASH included 10008 adult patients (≥16 years) with HI with a GCS ≤14 (5007 steroid group and 5001 control group) and randomized to either a 48-h steroid infusion or placebo treatment, within 8 h of the injury. The protocol followed was along the lines of the previous spinal cord injury trials. The study results showed that there was no reduction in mortality with corticosteroids, but on the other hand, there was a small increase in deaths, leading to a conclusion that steroids should not be used routinely in TBI.[15] However, an important point to note is that all patients in the CRASH trial were severe HI cases and steroids were given in the acute period, during which the edema is actually cytotoxic in nature and steroids are bound to fail during that period. In the present study, low-dose steroids were used in the delayed edema period (when the edema is of the vasogenic type) and only for mild (n = 8) and moderate HI (n = 1) categories of subjects. Steroids were not prescribed for severe HI cases. The present study provides some clinical evidence to the well-known fact that delayed brain edema after TBI is vasogenic in nature and steroids may be beneficial in such cases, at least in mild/moderate head injuries. Given the host of inflammatory mediators that are released after TBI and the potent anti-inflammatory properties of steroids that have been documented through various animal and clinical research, the role of steroids in TBI cannot be completely negated in TBI. However, the timing of the steroid administration remains paramount. Steroids may not be beneficial for acute conditions and the author is of a strong opinion that steroids may have a potential role for delayed brain edema as seen in our patients. However, it is to be noted that radiological improvement may lag behind clinical improvement as was observed in two of these cases (cases 2 and 3). However, all of them had complete symptomatic relief within 5 days. With the positive results of this retrospective study, a prospective study is being planned involving multiple centers within the country. The timing of steroid usage and dose of steroids is important key aspects that might determine its efficacy in TBI. New study designs are needed and future prospective randomized trials with these factors taken into consideration might confirm/refute the above findings.

Merits of the study

First clinical study to document the effectiveness of steroids for delayed cerebral edema after TBI that may be of potential benefit to patients, in whom standard decongestants have not benefitted. Furthermore, decompressive surgeries for such delayed brain edema may potentially be avoided. This may form a basis for future multicentric clinical trials.

Drawbacks

The study being retrospective in nature and the limited number of cases are the main drawbacks of the study.

CONCLUSION

This is the first study to document the efficacy of steroids for delayed cerebral edema after TBI and only in mild/moderate HI cases. All the nine patients noticed clinical improvement and none suffered any complications related to steroid usage. The timing of steroid usage and dose of steroids are important key aspects that might determine its efficacy in TBI. With these factors taken into consideration, future prospective trials with strict inclusion/exclusion criteria may confirm/refute the findings of this study and the possible role of steroids in delayed cerebral edema.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, *et al.* Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the third national acute spinal cord injury randomized controlled trial. National acute spinal cord injury study. JAMA 1997;277:1597-604.
2. Chen G, Shi JX, Hang CH, Xie W, Liu J, Liu X. Inhibitory effect on cerebral inflammatory agents that accompany traumatic brain injury in a rat model: A potential neuroprotective mechanism of recombinant human erythropoietin (rhEPO). Neurosci Lett 2007;425:177-82.
3. Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 2011;335:2-13.
4. Dearden NM, Gibson JS, Gibson RM, Cameron MM. Effect of high-dose dexamethasone on outcome from severe head injury. J Neurosurg 1986;64:81-8.
5. Donkin JJ, Vink R. Mechanisms of cerebral edema in traumatic brain injury: Therapeutic developments. Curr Opin Neurol 2010;23:293-9.
6. Gabrielian L, Helps SC, Thornton E, Turner RJ, Leonard AV, Vink R. Substance P antagonists as a novel intervention for brain edema and raised intracranial pressure. Acta Neurochir

Suppl 2013;118:201-4.
7. Hellal F, Bonnefont-Rousselot D, Croci N, Palmier B, Plotkine M, Marchand-Verrecchia C. Pattern of cerebral edema and hemorrhage in a mice model of diffuse brain injury. Neurosci Lett 2004;357:21-4.
8. Hue CD, Cho FS, Cao S, Bass CR, Meaney DF, Morrision B 3rd. Dexamethasone potentiates *in vitro* blood-brain barrier recovery after primary blast injury by glucocorticoid receptor-mediated upregulation of ZO-1 tight junction protein. J Cereb Blood Flow Metab 2015;35:1191-8.
9. Klatzo I. Presidental address. Neuropathological aspects of brain edema. J Neuropathol Exp Neurol 1967;26:1-14.
10. Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. Neurosurg Focus 2007;22:E1.
11. Nag S, Manias JL, Stewart DJ. Pathology and new players in the pathogenesis of brain edema. Acta Neuropathol 2009; 118:197-217.
12. Nimmo AJ, Cernak I, Heath DL, Hu X, Bennett CJ, Vink R. Neurogenic inflammation is associated with development of edema and functional deficits following traumatic brain injury in rats. Neuropeptides 2004;38:40-7.
13. Prasad GL, Anmol N, Menon GR. Outcome of traumatic brain injury in the elderly population: A tertiary center experience in a developing country. World Neurosurg 2018;111:e228-34.
14. Prasad GL, Gupta DK, Mahapatra AK, Sharma BS. Surgical results of decompressive craniectomy in very young children: A level one trauma centre experience from India. Brain Inj 2015;29:1717-24.
15. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, *et al*. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): Randomised placebo-controlled trial. Lancet 2004;364:1321-8.
16. Shigemori Y, Katayama Y, Mori T, Maeda T, Kawamata T. Matrix metalloproteinase-9 is associated with blood-brain barrier opening and brain edema formation after cortical contusion in rats. Acta Neurochir Suppl 2006;96:130-3.
17. Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. Neuroscience 2004;129:1021-9.

How to cite this article: Prasad GL. Steroids for delayed cerebral edema after traumatic brain injury. Surg Neurol Int 2021;12:46.