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Original Article

Short course of low-dose steroids for management of delayed pericontusional edema after mild traumatic brain injury – A retrospective study

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ABSTRACT

Background: Secondary insults such as brain edema is commonly observed after traumatic brain injury (TBI) and remains an important cause of neurological deterioration. Based on the corticosteroid randomisation after significant head injury (CRASH) trial findings, Brain Trauma Foundation guidelines recommend against giving steroids in TBI. However, the findings of two recent clinical studies suggest that there may be a subset of patients who may benefit from steroids.

Methods: This study was a retrospective, single-center, 4-year study. The study analyzed patients who had received systemic corticosteroids for pericontusional delayed edema after TBI. The time interval to steroid prescription, drug dosage, time to symptomatic improvement, and complications were analyzed.

Results: There were 19 males and eight females. Mean age was 42.1 years (range, 21–91 years). Except for one, all were mild TBI categories. All patients had brain contusions on computed tomography. Dexamethasone was used in tapering doses over 5–10 days, starting with 12 mg/day. The mean interval to steroid prescription after the trauma was 5.9 days, and the mean and median duration was 7 days. All, except one, had symptomatic improvement. The mean time to complete improvement in symptoms was 2.8 days. There were no complications pertinent to steroid usage in any of our cases.

Conclusion: This is the third clinical study to document the efficacy of systemic corticosteroids for delayed cerebral edema after TBI. As steroids are excellent drugs for vasogenic edema, the timing and dosage of steroids are two important factors that will determine their efficacy in TBI. We strongly feel that there needs to be more robust clinical trials with good patient numbers to confirm these findings.

Keywords: Cerebral edema, Corticosteroids, Dexamethasone, Steroids, Traumatic brain injury

INTRODUCTION

Secondary insult such as brain edema is commonly observed after traumatic brain injury (TBI) and remains an important cause of neurological deterioration.[13,19] Multiple inflammatory mediators are known to be released after TBI, which may alter blood-brain barrier (BBB) permeability. Steroids are potent anti-inflammatory drugs, stabilize cell membranes, and reduce cellular permeability, thus leading to a reduction in edema.[3,21,23] Multiple studies before 2000 could not provide definite conclusions either for/against the use of steroids in TBI.[1,2,4,6,8] However, based on the CRASH trial findings, Brain Trauma Foundation guidelines recommend

against giving steroids routinely in TBI.[18-20] However, findings of recent two clinical studies suggest that there may be a subset of patients who may benefit from steroids.[14,18] This present study aims to analyze the outcomes of patients with TBI (predominantly mild category) who received systemic steroids for delayed cerebral edema.

MATERIALS AND METHODS

This was a retrospective study over 4 years and was a single-center study. Patients in whom there was worsening/non-improvement of symptoms and radiological evidence of persisting/worsening edema despite administration of standard cerebral decongestants such as mannitol/hypertonic saline were prescribed steroids. As a protocol, no patients received steroids before a trial of decongestants. All patients received dexamethasone as the systemic steroid. It was administered parenterally for 24–48 h and was later converted to oral formulation, in tapering doses, for a total duration of 5–10 days.

Patient data were retrieved from hospital records. The following variables were analyzed: age, gender, mechanism of injury, Glasgow coma scale (GCS) score on admission, pupillary reactivity, radiological findings (contusion, subdural hematoma, basal cisterns, midline shift [MLS], etc.), time interval from initial trauma to deterioration (drop in GCS score or new/worsening of symptoms), symptoms (headache, giddiness, focal neurological deficits, and neurological deterioration), steroid dose prescribed, duration of steroids, time interval to clinical improvement, Glasgow outcome scale score at discharge and follow-up, and duration of follow-up.

RESULTS

We analyzed 27 cases in this study period. There were 19 males and eight females. The mean age of our study cohort was 42.1 years (range 21–91 years), and the median age was 41 years. Except for three, the mode of TBI was road traffic accidents (RTA) in all the other patients. There were 26 mild and one moderate head injury, and the latter was predominantly due to low verbal output due to left temporal contusion. The mean and median admission GCS scores were 13.9 and 15, respectively. There were no pupillary abnormalities or focal neurological deficits in any of the patients on admission. Two patients had hypertension.

Except for the patient with a moderate head injury, who had a drop in GCS score by 2 points, all others developed new-onset disabling headache or worsening of headache. Four patients had disabling vertigo as an additional new symptom. As noted earlier, steroids were prescribed only after a trial of cerebral decongestants (mannitol/hypertonic saline) and normalization of hyponatremia, if present.

On admission computed tomography (CT) scan, all patients were noted to have brain parenchymal contusions (14 unifrontal, seven bifrontal, and six temporal). Three patients had additional thin acute subdural hematoma (SDH), two patients had temporoparietal extradural hematoma (EDH) (operated), and one patient each had additional posterior fossa EDH, frontal EDH and cerebellar contusion. There was partial effacement of basal cisterns in five cases. Five patients had MLS, and the mean MLS was 1 mm (range, 0-6mm). In all cases, there was worsening of brain edema on CT imaging performed at the time of clinical worsening, with blooming of contusion noted in seven cases.

The mean time to steroid administration after the trauma was 5.9 days (range, 4–10 days), and the median time interval was 5 days. The mean duration of steroid prescription was 7 days (range, 5–10 days), and the median duration was 7 days. Symptomatic improvement was noted in all patients except one. The mean and median time to symptom resolution was 2.8 days and 3 days, respectively. In 14 cases, we performed a repeat CT after steroids. On follow-up scans, we noted that the cerebral edema persisted as earlier in five cases, while there was a reduction noted in nine cases. The mean and median GCS score at discharge was 15. There were no complications attributable to the steroids in any of our patients. The mean follow-up duration was 5.1 months (range, 2–10 months).

Since there was only one case that failed treatment with steroids, we did not perform statistical analysis as there won't be any meaningful results from the analysis.

Representative case description

A 49-year-old male presented to our emergency services after an alleged RTA on the day of admission. He had occasional dull, aching, non-disabling headaches. On examination, he was conscious and alert with bilaterally reactive pupils. CT brain showed bilateral basifrontal contusions with focal mass effect [Figure 1a]. He had mild hyponatremia, which was corrected. Three days later, he developed a moderate-to-severe disabling headache. His GCS score was 15/15, with no pupillary abnormalities or focal deficits. A repeat CT brain showed an increase in the pericontusional edema [Figure 1b]. Serum sodium was within normal limits. Serum creatinine was near high normal values. He was started on hypertonic saline but had no improvement in his symptoms in the next 2 days. Later, he 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. He noted significant improvement in his headache within 36 h, and the headache was completely resolved in 5 days. He did not develop any adverse effects attributable to steroids. Follow-up CT done after 1 month showed resolution of edema and contusions [Figure 1c].

Table 1 summarizes the clinicoradiological parameters of the study cohort.

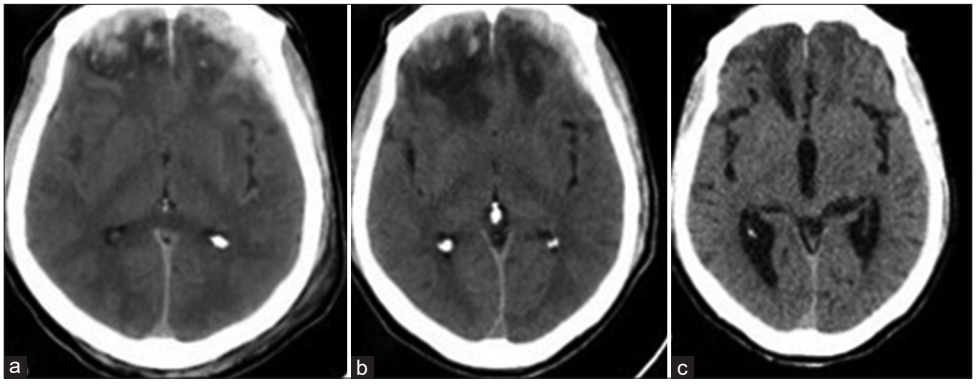

Figure 1: (a) Plain computed tomography (CT) brain showing small bifrontal contusions with mild focal edema. (b) CT scan performed after the onset of the headache showed an increase in perilesional edema. (c) CT scan was done 3 weeks later, showing resolution of cerebral edema.

Table 1: Summarizing the clinico-radiological details of the cohort.

Case no	Age/ sex	GCS score	MOI	Initial CT findings	Steroids administration-day of injury	Steroid duration (d)	Time to complete symptom improvement (d)	FU duration (m)
1	53/M	13	RTA	L frontal contusion, thin SDH	10	7	4	7
2	42/M	15	Fall	PF EDH, bifrontal contusions	8	6	3	5.5
3	40/M	13	Fall	Bifrontal contusions	7	7	4	6.5
4	35/F	15	RTA	Bifrontal contusions	5	6	3	6
5	47/F	11	RTA	L temporal contusion, thin SDH	7	7	5	5
6	45/M	15	RTA	R frontal contusion	7	5	4	6.5
7	32/M	15	RTA	R Frontal contusion	8	5	3	4
8	35/M	15	RTA	L frontal contusion	6	7	5	5
9	41/F	15	RTA	L frontal contusion	5	7	4	5.5
10	35/M	15	Fall	L frontal contusion, thin SDH	7	7	2	3
11	21M	15	RTA	Bifrontal contusion	5	7	3	4
12	43/M	15	RTA	R frontal contusion	4	10	3	6
13	41/M	14	RTA	R temporal contusion	5	7	3	7
14	46/F	14	RTA	R frontal contusion	5	7	2	5.5
15	49/M	15	RTA	L frontal contusion	6	10	3	6.5
16	91/M	15	RTA	R temporal contusion	4	7	2	4
17	35/F	15	RTA	Bifrontal contusion	4	7	2	3
18	37/M	15	RTA	Operated R TP EDH, R temporal contusion	5	7	2	8
19	49/M	15	RTA	Bifrontal contusion	5	10	2	10
20	58/M	14	RTA	R frontal, L cerebellar contusions	5	7	2	4
21	45/F	15	RTA	Bifrontal contusion	5	7	2	6
22	36/M	15	RTA	R frontal contusion	5	2	No improvement	3
23	38/F	15	RTA	L temporal contusion	6	7	3	2
24	41/M	15	RTA	L frontal contusion	5	7	3	6
25	42/F	15	RTA	R frontal contusion	5	7	2	4
26	25/M	15	RTA	Frontal EDH, R temporal contusion	8	7	2	2
27	32/M	15	RTA	Operated R TP EDH, R frontal contusion	7	5	2	2

All patients had worsening of pericontusional edema. All patients had worsening/persistent headache as their symptom, except case 1, who had a drop in GCS score by 2 points. No patient had pupillary abnormalities or focal deficits on admission. No patient had 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, SDH: Subdural hematoma, MLS: Midline shift, PF EDH: Posterior fossa extradural hematoma, NP: Not performed, F: Female, R: Right, L: Left, TP: Temporo-parietal, EDH: Extradural hematoma

DISCUSSION

The initial primary injury after trauma is followed by a secondary phase, which includes neuroinflammation, oxidative stress, and excitotoxicity.[22] Brain edema has been shown in experimental studies to be biphasic, an initial cytotoxic type followed by a vasogenic type.[7,10,12,25] Studies have shown that there is the release of various inflammatory mediators after TBI, which contribute to the development of accentuation of brain edema. They include arachidonic acid and its metabolites, glutamate, nitric oxide, histamine, kinins (bradykinins, substance P), free oxygen radicals, and matrix metalloproteinase (MMP)-9.[13,15,21,23] Multiple animal studies have also observed increased levels of pro-inflammatory cytokines, nuclear factor-kappa B, and intercellular adhesion molecule-1.[3,7,18] The Majority of the above-mentioned inflammatory mediators contribute to edema by modulating the BBB permeability, and many authors have concluded that attenuating BBB permeability and neurogenic inflammatory responses with substance P antagonists, recombinant human erythropoietin could potentially serve as a promising approach for managing brain edema and possibly improving functional outcomes.[3,9,16]

Glucocorticoids are among the most potent anti-inflammatory agents known to date. Inhibition of gene expression of pro-inflammatory molecules appears to be the primary mechanism of action of steroids.[5] Multiple animal studies have elucidated the effects of steroids after TBI. Steroids stabilize the cell membranes and reduce cellular permeability, reduce neuroinflammation, suppress microglia activation, reduce apoptosis, improve neuronal survival, and reduce interleukin-1 expression.[22,24] Since multiple inflammatory mediators are released after trauma that interferes with BBB permeability, theoretically, steroids should be able to treat the inflammatory edema leading to a reduction in ICP. One recent animal study also showed BBB recovery potentiated by dexamethasone after primary blast injury.[11]

Before 2000, a number of randomized trials (with fewer participants) were published with regard to steroids and head injury. The majority of them were conducted in severe head injuries, and patients received high-dose steroids in the acute period.[2,4,6,8] In 2000, Alderson and Roberts published the results of their Cochrane review wherein they included and analyzed 19 randomized trials with 2295 participants. They concluded that neither moderate benefits nor moderate harmful effects of steroids could be excluded in patients with TBI and called for a larger randomized trial[1] and then came the landmark multicentric double-blinded randomized trial (CRASH-corticosteroid usage in severe head injury). This study included 10008 adult TBI patients with an initial GCS ≤14 and was randomized to either a 48-h methylprednisolone infusion or placebo treatment, started within 8 h of the injury, similar to the national acute spinal cord injury study (NASCIS)-2 trial. The results showed that there was no reduction in mortality with corticosteroids, but on the contrary, there was a small increase in deaths in the steroid group. The authors concluded that steroids should not be used routinely in TBI.[20] Based on this level 1 evidence, the Brain Trauma Foundation guidelines recommended against using steroids in TBI, and subsequently, no clinical studies were conducted on steroids in TBI.[18]

Recently, two clinical studies (one retrospective and one prospective) were published regarding the efficacy of dexamethasone in TBI-related contusions with surrounding edema. In the first study, steroids were prescribed to patients (the majority were mild TBI, severe TBI excluded) with contusions and pericontusional edema after a few days of the initial trauma, which was termed delayed cerebral edema. Steroids were given for a mean duration of 6.3 days, and the mean time interval from trauma to prescription was 7 days. It was concluded that low-dose steroids might benefit a subset of patients with pericontusional edema and persisting symptoms.[18] This present study is an extension of that pilot study, conducted at the same center with similar doses of steroids and inclusion criteria. During the same period, a similar study involving dexamethasone in TBI was published by a group of Western investigators. It was a prospective-observational diffusion tensor imaging (DTI)-magnetic resonance imaging-based study where they included only brain contusions with vasogenic pericontusional edema and divided into two groups (of 15 patients each) based on whether they received steroids or not. By observing the apparent diffusion coefficient (ADC) and diffusion-weighted imaging values of the cerebral edema, it was demonstrated that pericontusional edema is actually more of a vasogenic type. Dexamethasone was given in tapering doses for 10 days, starting from the day of trauma. After treatment with dexamethasone, they found a reduction in edema volume, a decrease in the ADC value, and an increase in the fractional anisotropy values. They, however, did not consider the impact on the functional outcomes of steroid treatment.[14] The same group of researchers is presently recruiting patients for their multicentric randomized triple-blind, placebo-controlled trial and the DEXCON TBI trial. They intend to initially recruit 60 patients (total recruitment would be 600 patients) with brain contusions and pericontusional edema, and outcomes will include both radiological improvements in edema and functional outcomes.[17]

With the results of these two clinical studies, one may take note of the fact that the CRASH trial results may not be uniformly applicable to all TBI patients. A subset of patients with contusions and vasogenic edema may benefit from corticosteroids. The following may be the reasons for contradictory observations between the medical research council (MRC)-CRASH trial and the recent two clinical studies: (a) First, the timing of administration of steroids. In the CRASH trial, steroids were given within 8 h of trauma, during which the edema is actually cytotoxic, and steroids

have practically no benefit in such cytotoxic edema. (b) Second, the dosage of steroids used. In the CRASH trial, the steroid dose (high-dose methylprednisolone) was similar to the NASCIS trial. We feel that the spinal cord and TBI are different entities, and hence, similar dose steroids may not be beneficial or rather harmful in TBI. On the contrary, in the recent two studies, both the steroid formulation and doses were different to that in the CRASH trial (but similar between those two studies), wherein low-dose dexamethasone was prescribed in tapering doses for around 7–10 days. (c) Third, TBI is a very heterogeneous group and comprises diffuse axonal injury, contusions, subarachnoid hemorrhage, SDH, etc. The MRC-CRASH trial included all categories of TBI (GCS ≤ 14) and all radiological lesions such as acute SDH, diffuse edema, and contusions, while only mild TBI cases with contusions with pericontusional edema were included in the recent two studies.

In the present study, low-dose dexamethasone was prescribed in cases with contusions and pericontusional edema, and we did not include severe head injury cases. As noted in our previous pilot study, there may be a lag period between radiological improvement and clinical improvement.[18] Given the potent anti-inflammatory effects of steroids and an array of inflammatory mediators released after TBI, the beneficial role of steroids in TBI cannot be completely overlooked. We feel that the dose and timing are very important and should be given only in contusions with edema. Given the incidence of TBI, it looks surprising that we had only 27 cases over 4 years. This small sample size in our study was primarily due to the fact that we chose to prescribe steroids in a delayed phase, in only mild TBI patients and after a trial of decongestants in those with new/worsening/persisting symptoms (mainly headache). Second, some attendings were hesitant to give steroids to their patients, given the absence of robust data regarding the efficacy of steroids. We noticed that all, except one, had symptomatic improvement as early as 24–48 h of steroid administration. In the patient who failed steroid treatment, an additional decongestant in high dose was given with an increase in analgesic dose along with aggressive correction of serum sodium. We felt that it was unwise to give steroids for pericontusional edema as an initial drug. Hence, steroids were given only after a trial of decongestants. However, if the results of the DEXCON TBI trial are promising, then upfront low-dose steroids can be prescribed for patients with brain contusions and pericontusional vasogenic edema. This will help clinicians to have a clear understanding of the beneficial effects of dexamethasone in that subset of TBI patients.

CONCLUSION

This is only the third clinical study to document the efficacy of systemic corticosteroids for delayed cerebral edema after TBI. As steroids are excellent drugs for vasogenic edema, the timing and dosage of steroids are two important factors that will determine their efficacy in TBI. Steroids may be of significant benefit to a subset of patients in whom the conventional decongestants have not benefited. We strongly feel that there needs to be more robust clinical trials with good patient numbers to confirm these findings.

Merits of the study

Only the third clinical study to document the efficacy of steroids in cases of TBI for delayed cerebral edema, post-CRASH trial results.

Drawbacks

The retrospective nature of the study, single-center study, and the smaller sample size were the main drawbacks of the study. The reasons for the small sample size have been mentioned earlier. Further, there was only one patient who failed steroid treatment, and hence, statistical analysis would not yield meaningful conclusions.

Ethical approval

The Institutional Review Board approval is not required as it is a retrospective study.

Declaration of patient consent

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

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Nil.

Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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