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Effects of dexamethasone in traumatic brain injury patients with pericontusional vasogenic edema

A prospective-observational DTI-MRI study

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Abstract

Cerebral edema is a frequent and serious complication in traumatic brain injury (TBI) patients. The objective is to study the effect of dexamethasone in patients with brain contusions, and to assess its effect on the vasogenic component of the pericontusional edema.

Prospective-observational study to quantify, using magnetic resonance imaging, the volume of the edema before and after 10 days of dexamethasone in patients with brain contusions. Using diffusion tensor imaging, we have examined the effect of dexamethasone on fractional anisotropy (FA) and apparent diffusion coefficient (ADC). To assess changes, the pre- and post-treatment values for each patient were compared using a paired-samples Student *t* test.

We included 30 TBI patients, 15 in each group. The volume of the vasogenic edema in the group of patients treated with dexamethasone decreased from 22 to 19 mL and this decrease was statistically significant ($P < .05$). Nevertheless, in the non-steroids group the volume of the vasogenic edema increased from 11 to 15 mL. There was a significant decrease in the ADC value (from 1.78–1.59; $P < .05$); and a significant increase in the FA value (0.09–0.11; $P < .05$) in the patients treated with dexamethasone.

Using diffusion tensor imaging we have shown in a selected group of TBI patients with vasogenic pericontusional edema, a reduction of edema volume, a decrease in the ADC and an increase in the FA after treatment with dexamethasone. However, we have no data if such results are beneficial in terms of improving functional outcome.

Abbreviations: ADC = apparent diffusion coefficient, BBB = blood-brain barrier, CT = computed tomography, DTI-MRI = diffusion tensor imaging, DWI = diffusion-weighted imaging, FA = fractional anisotropy, FLAIR = fluid-attenuated inversion recovery, FOV = field of view, MRI = magnetic resonance imaging, ROI = regions of interest, TBI = traumatic brain injury.

Keywords: brain contusions, dexamethasone, diffusion tensor imaging, pericontusional edema, traumatic brain injury

1. Introduction

Cerebral edema is a frequent and serious complication in traumatic brain injury (TBI) patients.[1] Cerebral edema is usually classified as cytotoxic (due to energy failure, loss of ion gradients and shift of water from the extracellular to intracellular space) or vasogenic (due to leaking capillaries and increased water in interstitial spaces).[2] Published clinical studies, some of them using diffusion-weighted imaging (DWI) magnetic resonance imaging (MRI), have described the presence of a mixed picture of vasogenic and cytotoxic edema changes around traumatic brain contusions.[3–5]

Based on the results of the MRC CRASH trial,[6] current guidelines[7] do not recommend the use of high dose methylprednisolone to improve the outcome in the general population of TBI patients. Nevertheless based on the experience with patients with brain tumors, dexamethasone is commonly administered to patients undergoing a variety of neurosurgical procedures,[8] and is currently under investigation in specific subgroups of TBI patients like patients with chronic subdural hematomas.[9,10] Among the groups of patients that occasionally receive dexamethasone are patients with brain contusions and pericontusional edema where steroids are believed to improve the vasogenic component.

The objective of this prospective and observational project is to study the effect of dexamethasone in a very specific group of TBI

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patients: patients with brain contusions, and to assess its effect on the vasogenic component of the pericontusional edema. Using MRI we have quantified the volume of the edema before and after the treatment with dexamethasone. Also, using diffusion tensor imaging (DTI-MRI), we have examined the effect of this glucocorticoid on the diffusion parameters: fractional anisotropy (FA) and apparent diffusion coefficient (ADC). The use of edema type to guide the patient's treatment could be useful in TBI patients with contusions, because it has been demonstrated that steroids are indicated for vasogenic edema (like in brain tumors) but not for cytotoxic edema.[8,11]

2. Material and methods

Ethical approval was obtained from the Comité de Ética de la Investigación de las Islas Baleares (reference number CEIC-IB 3189/16), and written informed consents from the patient or from the next of kin where appropriate, were obtained in all cases to perform this prospective-observational study.

2.1. Subjects

Thirty TBI patients (25 males and 5 females), median (range) age 60 (32–75) years were recruited from the neurosurgical ward and the neurosurgical intensive care unit of the Son Espases Hospital (Palma de Mallorca, Spain) between February 2016 and February 2019. Patients with brain contusions and pericontusional edema visualized in conventional computed tomography (CT) were selected for the study. Patients were excluded if they had suffered a previous TBI, other neurological disease, or had any contraindication to MRI imaging.

Seventeen patients were admitted to the neurosurgical intensive care unit and 13 were in the neurosurgical ward. Two patients required surgery on admission to drain a subdural and an epidural hematoma respectively, but none of the patients required craniotomy for the brain contusions. All brain contusions were managed medically. All patients were managed by current Brain Trauma Foundation Guidelines.

Currently, the Brain Trauma Foundation Guidelines recommend against the use of high dose methylprednisolone to improve outcome in TBI patients.[7] Nevertheless based on the experience with patients with brain tumors, dexamethasone is administered to patients undergoing different neurosurgical procedures. In this study dexamethasone was administered to TBI patients that presented a brain contusion and pericontusional edema on the CT, in an effort to treat the vasogenic component of the edema. The administration of dexamethasone was decided by the attending neurosurgeon based on each case symptoms and CT findings. The dexamethasone dose in this specific group of TBI patients was as follows: 4 mgr q 6 hours for 2 days; 4 mgr q 8 hours for 2 days; 2 mgr q 6 hours for 2 days; 2 mgr q 8 hours for 2 days and 1 mgr q 8 hours for 2 days. This dosing, with gradual weaning, is commonly used in neuro-oncology and is considered to provide the best balance in terms of clinical efficacy and risks.[12] This dose and duration are similar to other studies currently ongoing in TBI patients.[9,10]

2.2. Imaging

All subjects were scanned using a 3Teslas, Sigma HDxt; software version HD23 (General Electric Medical System, Chicago, IL) within the Son Espases University Hospital (Palma de Mallorca, Spain).

To ensure that the slice locations used correspond as closely as possible in all the patients, the subject's head position and tilt was recorded. At least one of the slices was taken through a prominent anatomical landmark, mainly the anterior-posterior comisure line.

During the study period there were no major changes or upgrades to the scanner or software. The sequences obtained were structural sequences including:

1) 1 to 3 planes localizer;
2) Sagital CUBE fluid-attenuated inversion recovery (FLAIR): a 3D isotropic GE sequence of the whole brain with a field of view (FOV) 25'6 mm, a slice thickness 1.3 mm and matrix of 320x192. Total time sequence 4:51 minutes;
3) Axial diffusion: 2D sequence of pure axial slices from skull to foramen magnum with a FOV of 24 mm, a slice thickness 5 mm, b-value 1000 and matrix of 164x164. Total time sequence 2:10 minutes;
4) Axial T2 FLAIR: 2D sequence of pure axial slices from skull to foramen magnum with a FOV 24 mm, a slice thickness 4 mm, TR8300ms, TE120ms, TI2200ms and matrix of 352x256. Total time sequence 2:46 minutes;
5) Axial T2 FRFSE: 2D fast spin echo sequence of pure axial slices from skull to foramen magnum with a FOV 24 mm, TR3500ms, TE100ms, a slice thickness 4 mm and matrix of 512x512. Total time sequence 2:20 minutes;
6) Axial T2* MERGE: a 2D GE gradient echo sequence of pure axial slices from skull to foramen magnum with a FOV 24 mm, TR670ms, TE6ms, a slice thickness 4 mm and matrix of 352x256. Total time sequence 2:25 minutes;
7) Axial T1 SE: 2D spin echo sequence of pure axial slices from skull to foramen magnum with a FOV 24 mm, TR580ms, TE minimum full, slice thickness 4 mm and matrix of 320x224. Total time sequence 3:30 minutes;
8) Axial DTI: a 2D diffusion tensor imaging of 25 diffusion directions based on an echo planar imaging sequence of pure axial slices from skull to foramen magnum with a FOV 24 mm, 1 b-values ranging of 1000 sec mm-2, TR8000ms, TE minimum, a slice thickness 5 mm and matrix of 128x128. Total time sequence 3:40 minutes.

2.3. Lesion based analysis

Lesions were defined in axial FLAIR by a single neurorradiologist (AM) (Fig. 1A and Fig. 1B). Then, the lesions were divided into core contusion and pericontusional edema using FLAIR and gradient echo. Because most of the patients presented more than one contusion, only the biggest one was analyzed. The size of the contusion was measured of the CT by the ABC/2 method.

Because FLAIR imaging does not distinguish between cytotoxic and vasogenic edema, DWI and ADC maps were used. Hyper-intense areas in DWI with decrease ADC represent cytotoxic edema, and isointense areas in DWI with increased ADC represent vasogenic edema (Fig. 1C and Fig. 1D).[5,11]

2.4. Imaging processing

ADC and FA maps were created using the following post-processing software (Fig. 1): Advantage Window VolumeShare of General Electric Medical System, Software version 4; Functool 9.4 (General Electric Medical System, Chicago, IL).

The ADC provides a measure of the rate of diffusion of water molecules, which is usually averaged over all directions.[13,14]

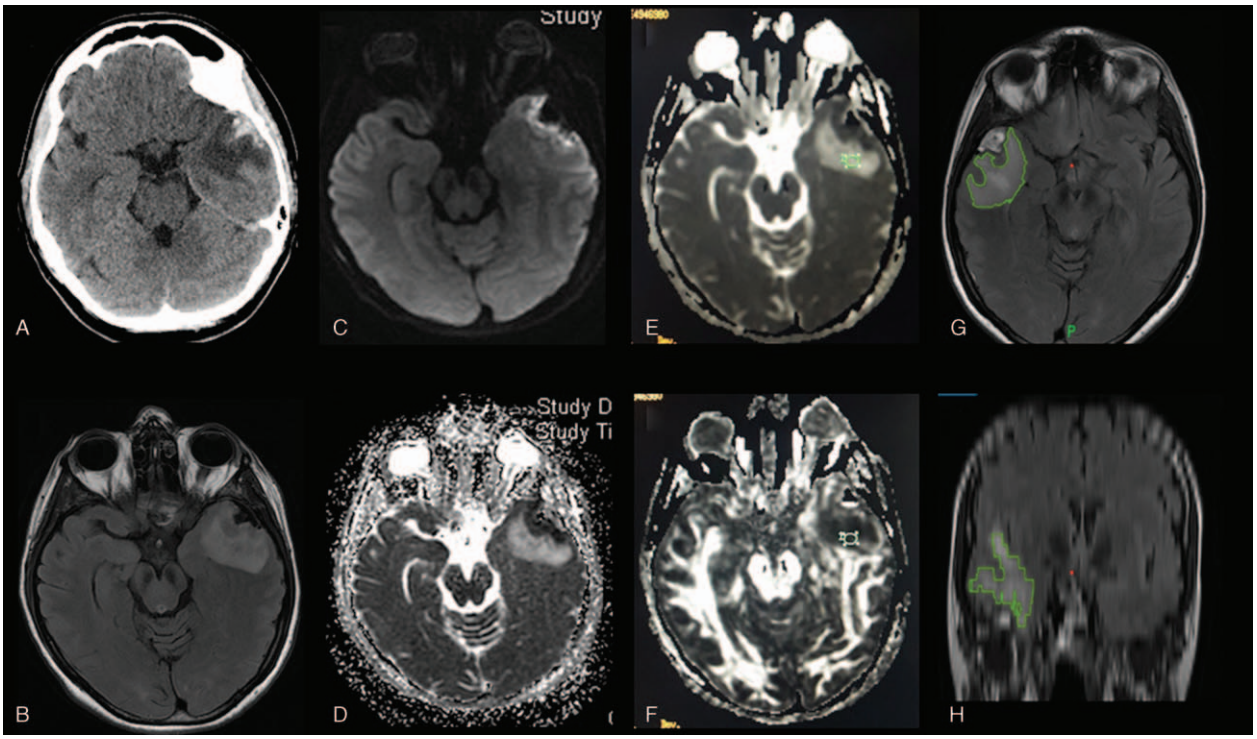

Figure 1. Example of a traumatic brain injury patient with a brain contusion and pericontusional edema. A. Computed tomography showing a left temporal contusion with pericontusional edema. B. Fluid-attenuated inversion recovery sequence showing the pericontusional edema. C. Axial diffusion map that shows a reduction in signal in the left temporal pericontusional area. D. Apparent diffusion coefficient map that shows an increased signal in the left temporal pericontusional area. E. Apparent diffusion coefficient map obtained with the Advantage Window VolumeShare of General Electric Medical System, Software version 4; Functool 9.4 program (General Electric Medical Systems, Chicago, IL). The regions of interest can be visualized and it is placed in the left temporal pericontusional vasogenic edema. F. Fractional anisotropy map obtained with the Functool 9.4 program. The regions of interest can be visualized and is placed in the left temporal pericontusional vasogenic edema. G. Example of volume measurement using the Medtronic Navigation (StealthViz 1.3.0.34). Volume measured in the left temporal contusion seen in the axial cube- fluid-attenuated inversion recovery sequence and coronal cube-flair sequence (Fig. 1H).

Fractional anisotropy is a normalized measurement that can describe the degree of directionality of diffusion.[13] A FA value of zero represents that the diffusion is uniform in all directions, whereas values approaching to one indicate that the diffusion is exclusively along a single axis.[13,14] FA is 1 in normal white matter. On the other hand, FA is close to zero in the cerebrospinal fluid.[13,14]

Gradient echo maps were used to assess whether areas of apparently low ADC were secondary to true restricted diffusion, or because of signal drop out from blood products.

2.5. Region of interest analysis

To quantify the ADC and the FA, regions of interest (ROI) were manually drawn in the areas of the vasogenic edema of the traumatic pericontusional tissue. Because these patients usually present with large brain lesions with great anatomic distortion in conventional imaging techniques, a standard ROI of 40 mm^2 was used in all cases to determine the parameters of water diffusion. For each patient, the ROI was placed in all the slices were edema was visualized.

Mean ADC and mean FA was calculated for each ROI using the General Electric post-processing software described previously (Fig. 1E and Fig. 1F).

2.6. Volume analysis

The 3 dimensional volume was calculated using a proprietary formula provided by Medtronic Navigation (StealthViz 1.3.0.34). This program uses the images from the sagital cube-FLAIR sequence. The formula calculates the 3 dimensional volume by evaluating dimension and number of voxels in the volume and then using a scalating factor in each dimension to then determine the 3 dimensional volume. (Fig. 1G and Fig. 1H)

2.7. Statistical analysis

Demographic, clinical, and radiological characteristics of the patients were described using median and range.

Individual ROIs were treated independently, as they represent a clinically relevant method of segmenting the brain. To obtain the ADC and FA values in each patient, we calculated the mean of the values of all the slices where edema was visualized.

To assess whether changes in MRI parameters were significant, the pre- and post-treatment values for each patient were compared using a paired-samples Student t test. P-value$\leq$.05 was accepted as significant. Statistical analyses were conducted using SPSS (SPSS 18.0, Chicago, IL).

3. Results

The patient demographic details are summarized in Table 1. A total of 60 MRIs were performed. In 2 patients the ADC and FA parameters could not be measured correctly because of artifact movements. The measurement of the edema volume was done in all the 30 patients. Patients treated with dexamethasone were

Table 1

Patients demographic characteristics.

Characteristics	TBI with steroids	TBI without steroids
n	15	15
Age, yr (median, range)	62 (32–75)	58 (36–74)
Gender		
Male (n,%)	12 (80%)	13 (87%)
Female (n,%)	3 (20%)	2 (13%)
Mechanism of injury		
RTC (n,%)	2 (13%)	3 (20%)
Fall (n,%)	11 (74%)	11 (74%)
Assault (n,%)	2 (13%)	1 (6%)
ISS (median, range)	16 (16–29)	22 (9–29)
GCS (median, range)	14 (9–15)	14 (6–15)
Motor score (n;%)		
M6 (obeys commands)	13 (86%)	11 (73%)
M5 (localizes pain)	1 (7%)	3 (20%)
M4 (withdrawals pain)	1 (7%)	1 (7%)
Volume of the contusion (mL) (median,range)	9 (3–25)	7 (3–30)
ICP monitoring (n,%)	5 (33%)	5 (33%)
Craniotomy (n,%)	0	2 (13%)
Time from injury to first scan, d (median, range)	4.4 (2–8)	4.9 (1–15)
Time from injury to second scan, d (median, range)	14.4 (11–17)	13.1 (10–16)
D in ICU (median, range)	8 (0–18)	3 (0–46)
D in hospital (median, range)	16 (6–31)	11 (4–67)
GOSe (6 mo) (median, range)	7 (1–8)	7 (1–8)

slightly older. The median Glasgow Coma Scale was the same in both groups, but 2 patients in the group without steroids presented a Glasgow Coma Scale below 8 and a lower percentage of patients followed commands on the neuro exam. The first MRI exam was done on the fourth day after the TBI in both groups, and the second exam was done slightly later in the dexamethasone group compared to the control group.

3.1. Effect of the dexamethasone on the volume of the vasogenic edema

The size of the contusion was bigger in the treatment group (Table 1). The volume of the vasogenic edema in both groups, before and after the treatment, is presented in Table 2 and Figure 2. The volume of the vasogenic edema in the group of patients treated with dexamethasone decreased from 22 to 19 mL and this decrease was statistically significant ($P < .05$). Nevertheless, in the non-steroids group the volume of the vasogenic edema not only decreased, but increased from 11 to 15 mL.

3.2. Effect of the dexamethasone on DTI-MRI parameters

The values of FA and ADC in both groups, before and after treatment, are presented in Table 2 and Figure 3. There was a significant decrease in the ADC value and a significant increase in the FA value after steroid treatment ($P < .05$).

4. Discussion

In this study we used DTI-MRI to examine whether dexamethasone had any beneficial effects within the pericontusional vasogenic edema. The results of the current study show that the volume of the edema is significantly reduced after 10 days of treatment with dexamethasone. Not only the volume of the edema was reduced with the treatment, but also the DTI-MRI parameters (ADC and FA) were statistically significant improved. Since DTI-MRI predominantly measures the mobility of water molecules in the extracellular space, these data suggest that dexamethasone acts by reducing the extracellular water fraction.

To our knowledge, this is the first study reporting the beneficial effect of dexamethasone in TBI patients with brain contusions using DTI-MRI. Other authors have also characterized using DTI-MRI, the water diffusion properties of peritumoral vasogenic edema.[15,16] These studies have shown that the treatment with dexamethasone reduced the ADC values (like in our study) but did not improve the FA values. This difference with our results could be because in the studies with brain tumor patients, the second MRI was performed only 48 to 72 hours of treatment with dexamethasone while in our study we completed a 10 day treatment course.

DTI-MRI has been an important imaging tool to study mild TBI. Several review articles have described the utility of DTI-MRI in examining the microstructural abnormalities in patients with TBI. These studies have shown significant abnormalities in white matter integrity post-TBI and correlation with functional outcome at chronic time points.[17,18] ADC provides a measure of the rate of diffusion of water molecules, which is usually averaged over all directions.[13,14] Fractional anisotropy, on the other hand, provides a measure of the degree of uniformity in the direction of the diffusion, with values ranging from 0 to 1.[13,14] An FA of 0 indicates that there is a complete lack of uniformity in the direction of the movement of water molecules in fibers, and 1 indicates that diffusion occurs in only 1 direction (parallel to the axon) and is completely restricted in all other directions.[14] Whereas low FA and high ADC values indicate that a nerve fiber is injured or poorly developed, high FA and low ADC values are believed to indicate white matter integrity.[13,14] In our study both DTI-MRI parameters improved with dexamethasone in the treatment group but not in the control group. Interestingly the dexamethasone administration also affected the FA, which value increased, and can represent an improvement of the axonal organization.

Published clinical studies described changes around traumatic contusions, with some of them reporting the presence of a mixed picture of vasogenic and cytotoxic edema.[3,5] The rim of vasogenic edema that surrounds brain contusions is thought to be because of either a transient breakdown in the blood-brain barrier (BBB) and/or the presence of hydrostatic and oncotic pressure gradients between the hematoma and surrounding tissue.[19] BBB breakdown after experimental brain injury is typically biphasic in nature.[20] Onset of the early phase is rapid: the permeability of the BBB typically reaches a maximum within a few hours and subsequently declines.[20] The onset of the second phase is delayed, starting from 3 to 7 days following injury, and probably constitutes part of the brain's response to the injury.[21] For most patients, clinical data indicate that BBB permeability returns to normal within days to weeks following BBB.[22] For this reason, it is possible that a therapeutic window of opportunity for treatment with steroids in this type of patients could exist. The type of edema to guide treatment protocol could be useful to initiate corticosteroids in some TBI patients because it is well known that steroids are indicated for vasogenic edema (like brain tumors) but not for cytotoxic edema.[11] This line of approach certainly could have potential in the future treatment of patients with brain contusions with a predominance of pericontusional vasogenic edema.

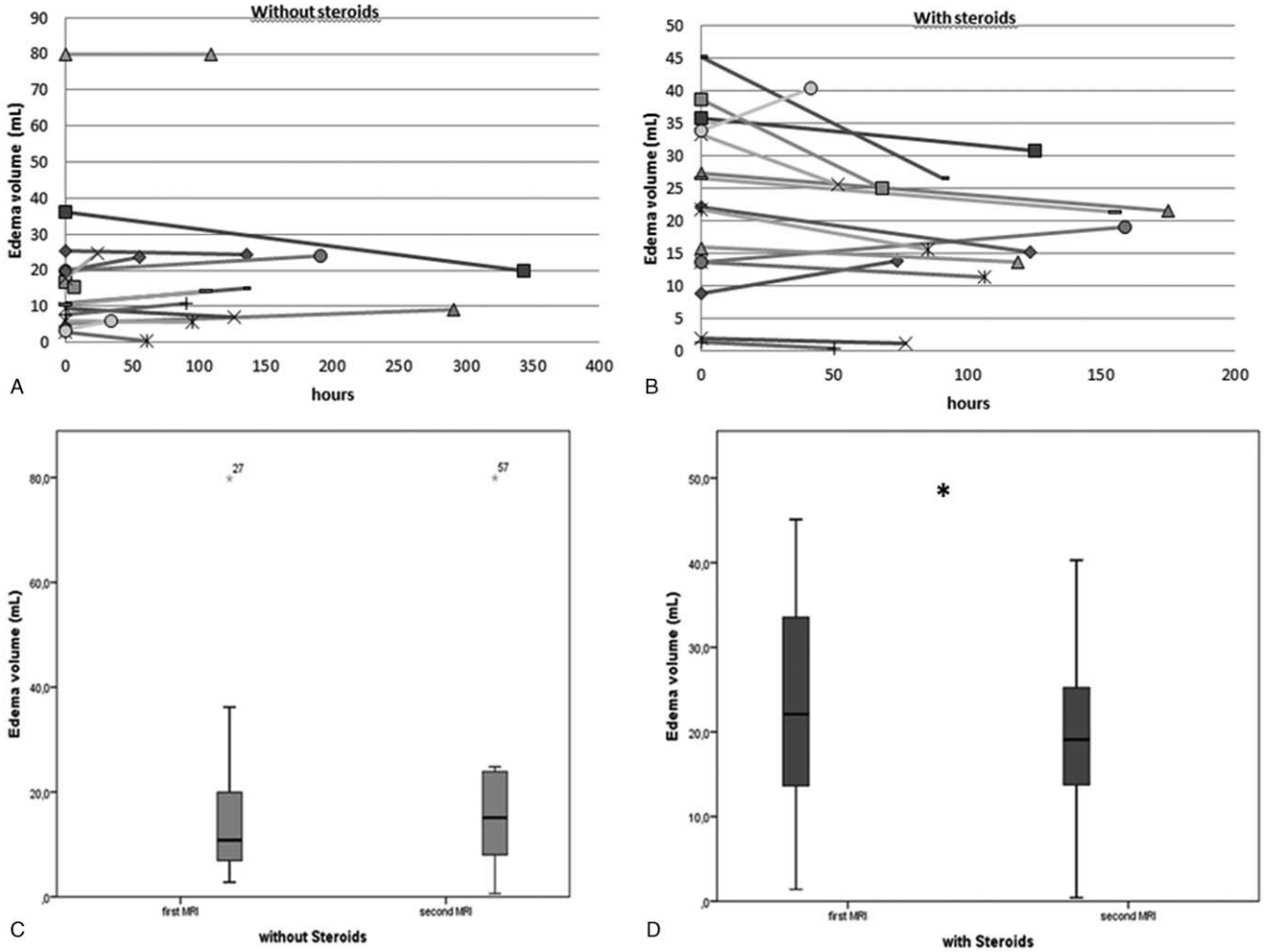

Figure 2. Figures 2A and 2B illustrates the volume change in pericontusional vasogenic edema over time for all 15 patients who did not receive dexamethasone (Fig. 3A) and 15 patients who received dexamethasone (Fig. 3B). Time 0 is the first magnetic resonance imaging. C and D. summarize the change in volume edema in both groups: without steroids (Fig. 3C) and with (Fig. 3D). The central lines in the boxes denote the median values, the upper and lower edges the 75th and 25th percentiles, and the error bars the 90th and 10th percentiles. The decrease of the volume of the vasogenic edema in the group of patients treated with dexamethasone was statistically significant ($^{*}P < .05$) (paired samples Student t test).

4.1. Limitations of the study

There are several important limitations to this study. First, the study was not randomized and the treatment was given based on the clinical judgement of the attending physician. Steroids are not routinely given to TBI patients, but in this study a short course of dexamethasone was administered to those TBI patients who presented a brain contusion and edema on the CT, in an effort to treat the vasogenic component of the pericontusional edema. There is a wide experience in clinical practice with the dosing of dexamethasone used in this study and no severe adverse events related to the treatment were described. In second place, this group of patients represents a convenience sample of participants

Table 2

Volume of the pericontusional vasogenic edema and DTI values in the 2 groups.

	TBI with steroids n = 15 First MRI second MRI	TBI without steroids n = 15 First MRI second MRI
Volume of the pericontusional edema (mL)	22* 19	11 15
Median (range)	(2–45) (1–40)	(3–79) (1–80)
ADC (10^{-9} m^2 /sec)	1.78* 1.59	1.67 1.7
Median (range)	(1.2–2.2) (1.2–2)	(0.08–1.9) (1.27–1.84)
FA	0.09* 0.11	0,14 0.12
Median (range)	(0.07–0.14) (0.08–0.16)	(0.08–0.28) (0.07–0.14)

* $P < .05$. Paired samples Student t test comparing the values from the first and second magnetic resonance imaging in both groups: patients with and without dexamethasone.

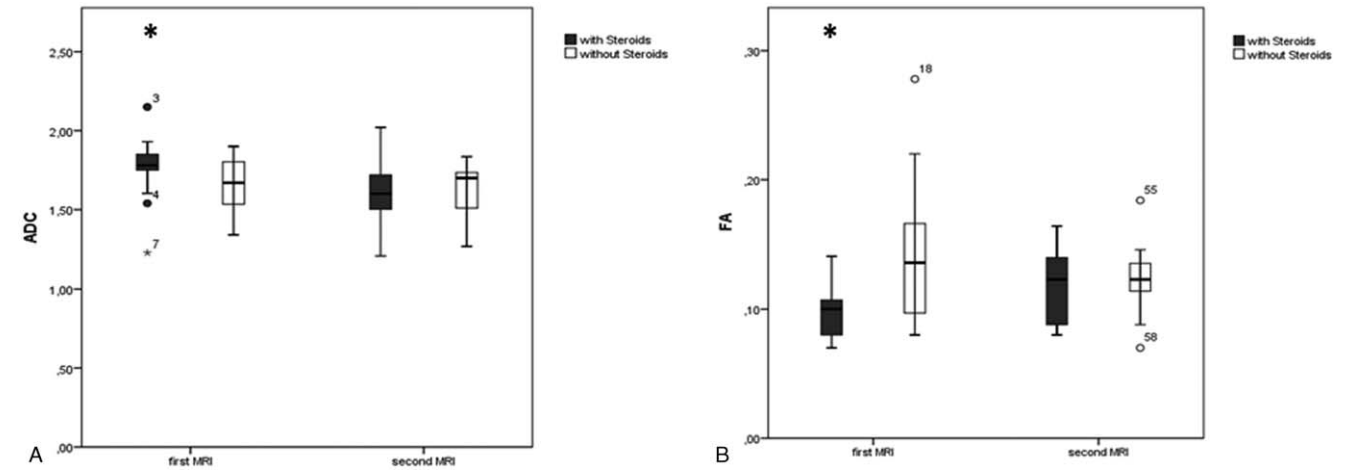

Figure 3. Apparent diffusion coefficient (Fig. 3A) and fractional anisotropy (Fig. 3B) in patients who received dexamethasone (black bars) and patients who did not received steroids (white bars) comparing the results from the first and second magnetic resonance imaging. The central lines in the boxes denote the median values, the upper and lower edges the 75th and 25th percentiles, and the error bars the 90th and 10th percentiles. The changes in apparent diffusion coefficient and fractional anisotropy in the group of patients treated with dexamethasone were statistically significant (*$P < .05$) (paired samples Student t test).

in which an MRI could be obtained. The MRIs in both groups were not done at the exact time point, although they were similar. Also, both groups are not equal although from a radiological point of view, the patients in the dexamethasone group had bigger size contusions and more pericontusional edema. All these limitations can alter the results described in this study. Finally, the number of patients imaged is small. However, even with this number of subjects the effect of dexamethasone on the edema volume and on the water diffusion parameters of pericontusional edema is clear.

Another limitation is due to the image analysis. The most commonly used form of DTI-MRI analysis is the ROI analysis that has the advantage of being relatively easy to implement and does not require spatial normalization, especially in patients with focal lesions in conventional imaging techniques, as the ones included in our study.[13,14] In our study this variability was tried to be reduced with a proper region selection by a trained neuroradiologist. In the moment of image analysis, the neuroradiologist did not know if the patient was treated or not with dexamethasone. Finally, some authors using diffusion kurtosis[23] have described the presence of increased mean kurtosis values in TBI patients at the subacute stage that could reflect gliosis rather than edema. Gadolinium studies to interrogate the BBB function might have helped with this issue which was not done in our study.

In summary, in this prospective observational study using DTI-MRI we have shown in a selected group of TBI patients with vasogenic pericontusional edema, a reduction of edema volume, a decrease in the ADC value and an increase in the FA value after treatment with dexamethasone. However, we have no data on whether such results are beneficial in terms of improving functional outcome. For this reason a firm recommendation for clinical use of this treatment requires a clinical trial. However, we can use the data from this study to refine the design of a future therapeutic trial of dexamethasone in a selected group of patients with brain contusions and pericontusional vasogenic edema, as to guide the treatment in these patients based on the type of edema can be useful approach.

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