https://doi.org/10.31925/farmacia.2019.1.19 **ORIGINAL ARTICLE**

THE USEFULNESS OF DEXAMETHASONE IN THE TREATMENT OF CHRONIC SUBDURAL HEMATOMAS

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Abstract

The purpose of this study was to assess whether the use of dexamethasone in patients with chronic subdural hematomas (CSDH) could lead to avoidance of surgical treatment. Data in the literature showed benefits of dexamethasone in selected patients, sometimes grouped in large cohorts, but studies comparing groups of patients who received or not this medication, from the point of view of surgical therapy prevention, are missing. We analysed 38 patients with the diagnostic of chronic subdural hematoma, separated in 2 groups on the basis of presence or absence of dexamethasone therapy. We found that 59.1% of patients who received dexamethasone didn't need surgical intervention, while only 18.7% of patients who were not treated with dexamethasone escaped surgery. In conclusion, the conservative treatment with dexamethasone can be a safe and efficient therapeutic option for CSDH, which can be used with few risks even in elderly patients with important co-morbidities, when the surgical option would be hazardous. With few exceptions, CSDH should not be considered a neurosurgical emergency, treatment with dexamethasone being usually attempted without significant risk for 48 - 72 hours. Conservative therapy eliminates the complications related to surgery, some of which are severe. Essentially, dexamethasone therapy involves shorter hospitalization, lower costs, rare severe complications and the possibility for outpatient treatment and follow up. Dexamethasone medication should not be considered a substitute for surgery but an alternative in the majority of cases.

Rezumat

Scopul acestui studiu a fost de a evalua dacă utilizarea dexametazonei la pacienții cu hematoame subdurale cronice (HSDC) ar putea duce la evitarea tratamentului chirurgical. Datele din literatura de specialitate au arătat beneficii ale dexametazonei la pacienți selectați, uneori grupați în cohorte mari, dar nu au fost realizate studii care să compare grupuri de pacienți care au primit și, respectiv, nu au primit acest medicament din punctul de vedere al posibilității evitării terapiei chirurgicale. Au fost analizați 38 de pacienți cu diagnosticul de hematom subdural cronic în decursul a doi ani, separați în 2 grupe pe baza prezenței sau absenței terapiei cu dexametazonă . Am descoperit că 59,1% dintre pacienții cărora li s-a administrat dexametazonă nu au avut nevoie de intervenție chirurgicală, în timp ce doar 18,7% dintre pacienții care nu au fost tratați cu dexametazonă au scăpat de operație. În concluzie, tratamentul conservator cu dexametazonă poate fi o opțiune terapeutică sigură și eficientă pentru HSDC, care poate fi utilizată cu un risc redus chiar și la pacienții foarte vârstnici cu co-morbidități importante, la care opțiunea chirurgicală ar fi periculoasă. Cu mici excepții, HSDC nu ar trebui să fie considerat o urgență neurochirurgicală, tratamentul cu dexametazonă putând fi, de obicei, încercat fără riscuri semnificative timp de 48 - 72 ore. Terapia conservatoare elimină complicațiile, unele dintre ele severe, legate de intervențiile chirurgicale. În esență, terapia cu dexametazonă implică spitalizare mai scurtă, costuri mai mici, complicații grave rare și posibilitatea tratamentului și monitorizării pacientului în ambulatoriu. Tratamentul cu dexametazonă nu ar trebui să fie considerat un înlocuitor al intervenției chirurgicale, ci o alternativă, în majoritatea cazurilor.

Keywords: chronic subdural hematomas, dexamethasone

Introduction

Dexamethasone is a glucocorticoid with a good oral absorption which can also be administered intra-muscularly and intravenously. It has a plasma half-life of approximately 3 hours, but the duration of action is much longer. Dexamethasone is about 70% protein bound and undergoes hepatic glucuronidation and sulfation to inactive by-products that are excreted by kidney [1]. Dexamethasone is used in neurosurgery since 1961, when it has been introduced for the treatment of neoplastic cerebral oedema. In that year Galicich and French published a paper based on previous research studies concerning the effect of

dexamethasone in patients with brain oedema [6]. Nowadays, dexamethasone is the standard drug for the treatment of tumour-related vasogenic cerebral oedema [16, 18]. The vasogenic oedema is typically encountered in patients with intracranial tumours and is produced by the increased permeability of the blood-brain-barrier (BBB), while in the other type of cerebral oedema, the cytotoxic oedema, the BBB remains intact but an intracellular retention of sodium and water occurs due to a severe disruption of cellular metabolism [19]. The effect of dexamethasone seems to be the decrease of the abnormal vascular permeability [2, 9] this explaining its effect only in vasogenic oedema. In brain trauma there is a mixed cerebral oedema, both vasogenic and cytotoxic, but with the large predominance of the latter. For this reason, dexamethasone is not useful in traumatic brain injuries and it is even banned in acute situations because some studies have proven an associated increased mortality [3]. Nevertheless, there is a post-traumatic situation when, as shown by recent studies, dexamethasone may be useful: chronic subdural hematomas.

A subdural hematoma is a blood clot located in the subdural space and has mainly a traumatic origin. It is called acute in the first 72 hours after onset, sub-acute between days 3 and 21 and chronic after three weeks. Chronic subdural hematoma (CSDH) consists of liquefied blood frequently surrounded by membranes developed apparently as an inflammatory response triggered by the presence of blood-lysis products in the subdural space. This membranes can, sometimes, have a considerable thickness, impeding the spontaneous resorption of CSDH, causing recurrences in operated CSDH and being an important factor that promotes the enlargement of the subdural fluid collection through a cycle of re-bleeding - fibrinolysis [4, 10].

The incidence of CSDH is about 2 persons/100000 inhabitants/year in the general population but it is much higher in people older than 70 (58/100000/year) [4, 7, 22]. Risk factors for developing a CSDH beside age are alcoholism and coagulation disturbances (coagulopathies and anticoagulant treatment). Such patients can present blood accumulation in the subdural space even after minor head trauma followed by slow venous bleeding. Symptoms can appear several weeks after the traumatic event, frequently the patient being unable to recall it.

Symptomatic large (more than 1cm thickness) CSDH are usually operated. Although the surgical interventions are, in most cases, minimally invasive and the post-operative neurological outcome is, generally, very good, complications are not infrequent. Patients can present infections of the wound or even subdural empyema, *ex-vacuo* intracerebral haemorrhage or tension pneumocephalus [4, 21, 22]. Death can sometimes occur postoperatively, especially in elderly patients. Additionally, the recurrence rate for operated CSDH is between 16 and 25 % [4, 17, 22, 24]. All this facts have determined physicians to try to find alternative conservative ways of treatment to surgery. One of this non-operative measures attempted in the management of CSDH is the use of systemic glucocorticoids [4, 22, 23, 25, 26].

Materials and Methods

We performed a retrospective analysis using data collected from medical records of all patients admitted in the Neurosurgical Department of "Sf. Pantelimon" Emergency Hospital, Bucharest, Romania with the diagnostic of chronic subdural hematoma during two years, between 01.01.2016 and 31.12.2017.

The inclusion criteria were: patients of both genders, age > 18 years old; hypodense or isodense subdural collection on CT-scan; patients with grade 1 - 3 on modified Rankin Scale (mRS) (Table I) at admission. Type I collagen of bovine origin was extracted by the currently.

Table I

Modified Rankin Scale (mRS)

Score	Functional status
0	No symptoms
1	No significant disability, able to carry out all usual activities despite some symptoms
2	Slight disability. Able to look after personal affairs without assistance but unable to carry out all previous activities
3	Moderate disability. Requires some help, but able to walk unassisted
4	Moderate severe disability. Unable to attend to own body needs without assistance and unable to walk unassisted
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent
6	Dead

The exclusion criteria were: age < 18 years; remnants of fresh blood images on CT scan (subacute hematomas or rebleeding in chronic hematomas); other brain lesions (stroke, aneurysms, brain tumours); patients with grade ≥ 4 on modified Rankin Scale (mRS) at admission; patients operated in the first 24 hours after admission on emergency basis due to poor neurological condition; patients with midline shift on CT- scan more than 5 mm.

We found 38 eligible patients who were divided into two groups: group A, comprising the patients who received dexamethasone, and which included 22 subjects of both gender (15 female and 7 male), aged between 48 and 86 years old, (71.18 ± 8.11) and group B, comprising the patients who didn't receive dexamethasone which included 16 patients of both gender (11 female and 5 male), aged between 48 and 89 years old, (72.12 ± 9.38). There were no significant differences between groups ($p > 0.05$) regarding gender distribution, mean age and proportion of patients who

were on anticoagulant treatment prior to admission (Table II).

Table II

The demographic characteristics of the group who received dexamethasone (Group A) and the group who did not received (Group B)

Parameters	Group A (n = 22)	Group B (n = 16)	p
Age (years), Mean ± SD	71.18 ± 8.11	72.12 ± 9.38	0.74
Gender (f/m) n (%)	 15/7 68.18/31.81	 11/5 68.75/31.25	 0.98
Anticoagulant therapy n (%)	 7/22 32%	 5/16 31%	 0.94

The study was performed according to ethical regulations derived from the Declaration of Helsinki. For each case, a written informed consent was signed by the patient or a relative regarding the acceptance of the treatment either conservative or surgical.

Treatment protocol

Dexamethasone in group A was administered following the same protocol in all patients: 8 mg *per* day, every day during the first week, then 4 mg daily in the second week, and, finally, 4 mg once every 2 days in the third week (Table III).

Table III

Dexamethasone treatment protocol

Dose	Day
4 mg at 12 hours	1 - 7
4 mg once a day	8 - 14
4 mg once every two days	15 - 21

The drug was administered intravenously or intra-muscularly. In 9 patients (40.9 %) the protocol had to be interrupted because their condition was not improving or was even getting worse and they underwent a surgical procedure. Surgery was performed between the third and the twelfth day of surveillance.

The patients of group B were closely monitored and treated with bed rest and fluid restoration if needed. In 13 patients (81.3 %) a surgical intervention had to be eventually performed between the third and the eighth day of surveillance.

Patients with midline shift on CT- scan between 1 and 5 mm, both in group A and B, received mannitol 20% 125 mL/day. Those with midline shift more than 5 mm were operated. All patients were monitored with CT-scans every 7 days or whenever their condition was deteriorating.

The primary outcome measure was to assess the rate of need for surgical intervention in the first 3 weeks after admission for patients with CSHD treated/non treated with dexamethasone. The success rate of the conservative treatment is defined as the number of patient who did not required surgical interventions in each group.

Statistical analysis

The statistical analysis was performed using the SPSS statistical software version 20.0. The Student test was used to check for differences between quantitative data and the Chi-square test was used for qualitative variables; differences were considered statistical significant for $p < 0.05$.

Results and Discussion

We have compared the two groups regarding the possibility to avoid surgical intervention in non-emergent cases with CSDH.

Table IV

The comparison between the groups regarding the need of surgical intervention

Parameters	Group A Dexamethasone treatment (n = 22)	Group B No dexamethasone treatment (n = 16)	p
OPERATED n (%)	 9 40.9%	 13 81.3%	0.0128
NONOPERATED n (%)	 13 59.1%	 3 18.7%	

Table V

The clinical outcome at 3 weeks using the modiefied Rankin Scale

GROUP A					GROUP B				
	Admission		3 weeks			Admission		3 weeks	
mRS Grade	n = 22	%	n = 22	%	mRS Grade	n = 16	%	n = 16	%
0	0	0	10	45.45	**0**	0	0	6	37.50
1	4	18.18	11	50.00	**1**	3	18.75	5	31.25
2	11	50.00	1	4.54	**2**	7	43.75	2	12.50
3	7	31.82	0	0	**3**	6	37.50	2	12.50
4	0	0	0	0	**4**	0	0	0	0
5	0	0	0	0	**5**	0	0	0	0
6	0	0	0	0	**6**	0	0	1	6.25

In group A (patients treated with dexamethasone) in 13 patients (59.1%) surgery was avoided, while in group B only 3 patients (18.7%) were successfully treated conservatively. There is a significant difference between the results in the two groups, showing a clear benefit of the dexamethasone treatment over observation alone in preventing the need of a surgical decompression ($p < 0.05$) (Table IV).

We have analysed the clinical outcome at 3 weeks using the modified Rankin Scale (mRS); the results are summarized in Table V.

Regarding the complications related to the treatment, we had mortality 0 in group A. Among all patients enrolled in this study, there was only one death, in an 89-years old male patient from group B who suffered a massive postoperative *ex-vacuo* intracerebral hematoma.

In group A, adverse events occurred in 5 patients (22.7%) represented by hyperglycaemias in 3 cases (13.6%) among which 2 were mild, requiring only diet measures and slight adjustment of oral antidiabetic drugs doses and one severe, in an insulin- dependent patient, situation that imposed suppression of the dexamethasone treatment and surgical intervention. There were also, 2 urinary infections (9.1%) that occurred postoperatively in patients who needed Foley bladder catheter for more than 48 hours.

In group B, 5 morbidities were present in 4 cases (25%), all in operated patients: 1 urinary infection, 1 *Clostridium difficile* infection, 1 bronchopneumonia and 2 increased postoperative motor deficits.

If we analyse the 22 operated cases, in both groups, we find a postoperative mortality of 4.5% (1 case) and 31.81% (7 cases) morbidity, compared with 0 mortality and 18.75% morbidity in non-operated patients.

In Table VI there are summarize the treatment complications in operated *versus* non-operated patients.

Table VI

The treatment complications in operated *versus* non-operated patients

Complications	Operated patients (n = 22)		Non-operated patients (n = 16)	
	N	%	N	%
Death	1	4.50	0	0
Urinary infection	3	13.63	0	0
Hyperglycemia	0	0	3	18.75
Worsening of motor deficit	2	12,50	0	0
Infection with *Clostridium difficile*	1	4.50	0	0
Bronchopneumonia	1	4.50	0	0
Total complications	8	36.36	3	18.75

Even though dexamethasone had a long history in CSHD treatment, its role is still controversial and is a very actual subject of debate, reason for which larger studies are initiated worldwide [11, 15].

The reason for using glucocorticoids in CSDH is based on their capacity to block the inflammatory changes that occur when the hematoma develops. Their effect is more obvious in the blockage of neo-membranes formation by inhibiting inflammatory mediators like lymphokins and prostaglandins in parallel with the stimulation of lipocortin, which is a powerful inhibitor of inflammation and oxidative stress [5, 8, 12, 22]. Glucocorticoids are also stimulating the secretion of the inhibitor of plasminogen which reduces the lysis-rebleeding cycle of the clot [4, 13]. Another effect is the inhibition of angiogenesis [22].

Experimental studies using murine models showed neo-membrane inhibition after dexamethasone administration [12].

Several studies in the last twenty years have observed the effects of dexamethasone on CSDH. Most of them enlisted small numbers of patients and the results were promising regarding the recurrence rate, morbidity and mortality of this patients. A large study accomplished in 2009 in Spain [4] showed that only 22% of the patients with CSDH treated with dexamethasone needed eventually a surgical intervention. The morbidity rate among these patients was quite high (27.8%), the more frequent complications encountered being hyperglycaemia, infections and gastrointestinal bleeding. The protocol of dexamethasone administration consisted of a daily oral or intravenous dose of 12 mg, fractionated in 3 portions, in the first three days, followed by slow-tapering of the daily dose (reducing 1 mg every three days) until the complete withdrawal [4].

More recently, in 2017, a study performed in China [26] included 24 patients with recurrent CSDH who underwent dexamethasone treatment. Among them, 17 (70.8%) were treated successfully conservatively and only 7 required reoperation. Complications appeared in 3 (12.5%) patients (hyperglycaemia, urinary tract infection, and pneumonia). There was one death registered (4.2%) because of massive brain infarction.

A double-blind, randomized, clinical study, called: "*Role of dexamethasone in the conservative treatment of chronic subdural hematoma"*, conducted in Quebec [19], started in 2007 but was terminated earlier than estimated, in 2016, because of numerous severe adverse events. Participants allocated to the treatment group received a daily dosage of 12 mg (4 mg three times *per* day) of dexamethasone for three weeks. Corticosteroid treatment was then tapered off over the next week

(8 mg for 48 hrs, 4 mg for 48 hrs, 2 mg for 48 hrs and 1 mg for 24 hrs).

In our study, in order to prevent a high rate of complications due to dexamethasone administration, we have chosen a lower daily dose, of 8 mg in the first week, followed by 4 mg in the second week and 4 mg once every two days in the third week. Furthermore, we treated our patients with omeprazole 20 mg/day to protect them from gastrointestinal bleedings.

In comparison with other similar studies, the prevention of surgery for patients with CSDH who were subjected to dexamethasone treatment had a lower rate (59.1%), possibly due to smaller doses used in our study. Another factor involved in that difference could be a more strict surgical indication. On the other hand, adverse events related to dexamethasone administration were less frequent and less severe in our study.

Conclusions

Conservative treatment with dexamethasone can be a safe and efficient therapeutic option for CSDH as has been shown in literature. This assertion is also supported by our experience, materialized in this study. Dexamethasone can be used with fewer risks even in elderly patients with important co-morbidities, when the surgical option would be hazardous. Good results have been obtained even in cases of hematomas with important midline shift or neurological deficits.

With few exceptions, CSDH should not be considered a neurosurgical emergency and conservative treatment with dexamethasone and other measures can be usually attempted without significant risk for 48 - 72 hours. From our experience, in at least 60% of cases, operation can be avoided by treating the patients with CSDH with dexamethasone.

The conservative therapy eliminates the complications related to surgery, some of which are severe. On the other hand, complications related to dexamethasone administration are, basically, hyperglycaemia and propensity to infections, which, except a few severe cases, can be easily dealt using common therapeutic measures. Essentially, dexamethasone therapy involved shorter hospitalization, lower costs, rare severe complications and the possibility for outpatient treatment and follow up.

This relatively new trend in the treatment of CSDH contradicts the traditional view of neurosurgeons who have the tendency to indicate early surgery in most of the patients. Dexamethasone medication should not be considered a substitute for surgery but an alternative in the majority of cases.

Our study is a retrospective one and it included only a limited number of subjects. Another limitation of our study was the inability to evaluate patients for a longer interval, due to lack of compliance and absence for control visits. This is why conclusions cannot be generalized and further studies are necessary.

Conflicts of interest

The authors declare no conflicts of interests.

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