ORIGINAL ARTICLE

A Pilot Placebo Controlled Randomized Trial of Dexamethasone for Chronic Subdural Hematoma

Michel Prud'homme, François Mathieu, Nicolas Marcotte, Sylvine Cottin

ABSTRACT: ***Background:*** Current opinions regarding the use of dexamethasone in the treatment of chronic subdural hematomas (CSDH) are only based on observational studies. Moreover, the use of corticosteroids in asymptomatic or minimally symptomatic patient with this condition remains controversial. Here, we present data from a prospective randomized pilot study of CSDH patients treated with dexamethasone or placebo. ***Methods:*** Twenty patients with imaging-confirmed CSDH were recruited from a single center and randomized to receive dexamethasone (12 mg/day for 3 weeks followed by tapering) or placebo as a conservative treatment. Patients were followed for 6 months and the rate of success of conservative treatment with dexamethasone versus placebo was measured. Parameters such as hematoma thickness and clinical changes were also compared before and after treatment with chi-square tests. Adverse events and complications were documented. ***Results:*** During the 6-month follow-up, one of ten patients treated with corticosteroids had to undergo surgical drainage and three of ten patients were treated surgically after placebo treatment. At the end of the study, all remaining patients had complete radiological resolution. No significant differences were observed in terms of hematoma thickness profile and impression of change; however, patients experienced more severe side effects when treated with steroids as compared with placebo. Dexamethasone contributed to many serious adverse events. ***Conclusions:*** Given the small sample size, these preliminary results have not shown a clear beneficial effect of dexamethasone against placebo in our patients. However, the number of secondary effects reported was much greater for corticosteroids, and dexamethasone treatment was responsible for significant complications.

RÉSUMÉ: Étude pilote randomisée, contrôlée par placebo, de la dexaméthasone dans l'hématome sous-dural chronique. ***Contexte:*** L'opinion qui prévaut actuellement concernant l'utilisation de la dexaméthasone pour traiter l'hématome sous-dural chronique (HSDC) n'est fondée que sur des études observationnelles. De plus, l'utilisation de corticostéroïdes chez des patients asymptomatiques ou peu symptomatiques présentant un HSDC demeure controversée. Nous présentons les données d'une étude pilote prospective randomisée chez des patients ayant reçu de la dexaméthasone ou un placebo. ***Méthode:*** Vingt patients dont l'HSDC avait été confirmé par imagerie ont été recrutés dans un seul centre et randomisés à la dexaméthasone (12 mg/jour pour 3 semaines, puis à dose décroissante) ou à un placebo comme traitement conservateur. Les patients ont été suivis pendant 6 mois et le taux de succès du traitement conservateur à la dexaméthasone versus placebo a été évalué. Nous avons utilisé le test du $\sum$-carré pour comparer les paramètres tels l'épaisseur de l'hématome et les changements cliniques avant et après traitement. Nous avons également noté les événements indésirables. ***Résultats:*** Au cours des 6 mois du suivi, 1 des 10 patients traités par des corticostéroïdes a dû subir un drainage chirurgical et 3 patients sur 10 sous placebo ont été traités par chirurgie. À la fin de l'étude, la résolution radiologique était complète chez tous les autres patients. Aucune différence significative n'a été observée quant à l'épaisseur de l'hématome et à l'impression de changement. Cependant, les patients ont présenté des effets secondaires plus importants sous stéroïdes que sous placebo. La dexaméthasone a contribué à plusieurs événements indésirables. ***Conclusions:*** Étant donné que la taille de l'échantillon est petite, ces résultats préliminaires n'ont pas montré que la dexaméthasone ait un effet bénéfique clair par rapport au placebo chez nos patients. Cependant, le nombre d'effets secondaires rapportés était beaucoup plus grand chez les patients traités par des corticostéroïdes et le traitement par la dexaméthasone a donné lieu à des complications importantes.

Keywords: Asymptomatic or mildly symptomatic, corticosteroids, chronic subdural hematoma, randomized controlled pilot study

doi:10.1017/cjn.2015.393 Can J Neurol Sci. 2016; 43: 284-290

Chronic subdural hematoma (CSDH) is a common neurosurgical condition which predominantly affects the elderly.[1] Other predisposing factors include antithrombotic or anticoagulant therapy, long-term alcohol abuse, or recurrent falls.[2,3] Incidence of CSDH in Western countries has been estimated at 8 to 13/100,000 in the general population,[4] but increases for those aged 70 years and older (58 per 100,000 per year).[5] However, these numbers will most likely continue to rise as the proportion of people aged 65 years and older is expected to double worldwide between 2000 and 2030[6] and because the use of anticoagulants for management of cardiovascular disease is also increasing.[7]

Given the heterogeneity of symptoms and severity in CSDH, a wide range of treatment options has been used. Asymptomatic or minimally symptomatic patients can be managed with rest and observation or are occasionally prescribed drugs such as steroids,

From the Centre de recherche du CHU de Québec, Axe neurosciences, Université Laval, Quebec City, Canada.

Received December 4, 2014. Final Revisions Submitted April 15, 2015.

Correspondence to: Sylvine Cottin, Hôpital de l'Enfant-Jésus, Department of Neurological Sciences, 1401, 18e rue, Quebec City, QC, Canada G1J1Z4.
Email: sylvine.cottin.cha@ssss.gouv.qc.ca

mannitol, or angiotensin-converting enzyme inhibitors.[1,8-10] In contrast, for more severe cases, surgical intervention is the treatment of choice with burr-hole craniostomy, twist-drill craniostomy, or craniotomy, with or without insertion of a subdural drain.[11,12] There is, however, a growing interest for conservative approaches given the increasing number of older patients who often suffer from multiple comorbidities, have higher prediction for recurrence, and carry a high risk of surgery-related complications.[4]

Based on a recent meta-analysis reviewing the safety and effectiveness of various treatment strategies used for chronic subdural hematoma including corticosteroids,[11] the authors concluded that there is a lack of evidence to support or refute the use of corticosteroids in CSDH and suggested additional randomized clinical trials to better define their role in this clinical setting. Given this lack of quality evidence, several national surveys have shown that the use of corticosteroids, their dosage, and the length of therapy varies widely between individual neurosurgeons and neurosurgical centers. Approximately one-half of the neurosurgeons in the United Kingdom and Ireland prescribe steroids in CSDH patients managed conservatively,[1] whereas only 13% of Canadian neurosurgeons consider corticosteroids in the treatment of CSDH.[13] The use of corticosteroids as adjuvant therapy after surgery is recommended by 38% of French neurosurgeons,[14] and 28% of Dutch neurosurgeons would administer corticosteroids in case of mild symptoms.[15] Furthermore, there are important concerns associated with immunosuppressive and metabolic effects of these drugs, especially when used in elderly populations.[16]

In this context, we proposed to investigate the safety of dexamethasone as a conservative treatment for CSDH in a preliminary prospective study of a small sample of patients. As a primary research outcome, we looked at the rates of success of conservative management in a group of patients randomly assigned to dexamethasone treatment versus placebo. As a secondary research goal, we compared both groups in terms of size of the hematoma over time, clinical changes, treatment-associated secondary effects, and complications. To our knowledge, this study represents the first double-blind randomized controlled trial addressing these questions.

Methods

Patients

Recruitment for this single-center double-blind randomized placebo-controlled study was performed between January 2007 and May 2009. Patients were enrolled based on the following inclusion criteria: age 18 years and older with evidence of subacute or chronic supratentorial subdural hematoma on computed tomography scan or magnetic resonance imaging and classified between 0 and 2 using the Markwalder grading scale.[17] Exclusion criteria included contraindications or intolerance to corticosteroid therapy or patients already undergoing steroid treatment for any other indication, previous neurological surgery up to 1 year before being considered for the study, concomitant cerebral pathology of neoplastic or presumed infectious origin, anticoagulant therapy that could not be stopped for 6 months, and refusal to participate in the study. If at any time patients developed a sudden increase in hematoma volume, a midline displacement of greater than 1 cm, or a deterioration of their level of consciousness, they were removed from the conservative study protocol to undergo surgery.

This study was approved by the research ethics board at CHU de Québec (project identification PEJ-378) and registered at clinicaltrials.org (project identification NCT02362321). Written and fully informed consent was obtained from each participant. Unblinded data were monitored by the ethics committee when severe adverse events were reported and an intermediate report was produced.

Randomization

Allocation to each group was done in a 1:1 ratio, with block sizes ranging from 4 to 6, to one of the two arms; a treatment arm in which participants received dexamethasone according to the protocol; and a control group in which they received placebo. Randomization was performed via a web-based service by a pharmacist, who was not involved in any other part of the study. Both investigators and participants were blinded to treatment allocation.

Treatment

Participants allocated to the treatment group received a daily dosage of 12 mg (4 mg three times a day) of dexamethasone for three weeks. Corticosteroid treatment was then tapered off over the next week (8 mg for 48 hours, 4 mg for 48 hours, 2 mg for 48 hours, and 1 mg for 24 hours). Identical oral capsules filled with lactose were administered to the control (placebo) group for 28 days. Participants were returned home with blister packs containing their medication for each day of the trial and were asked to return empty packs to ensure compliance with the assigned treatment. The treatment (placebo or dexamethasone) was discontinued if a patient required surgical drainage of the hematoma or suffered from significant side effects. All blister packs were returned and 100% compliance was observed.

Evaluation and Follow-up

The primary outcome of this pilot study the rate of success of conservative management with dexamethasone as compared with placebo for CSDH graded 0 to 2 on the Markwalder grading scale. The rate of success was defined as the percentage of patients not requiring surgery or not presenting a serious adverse event resulting from the treatment in each treatment group during the 6 months following enrollment.

Eligible patients who consented to the study underwent the routine standard of care. This included (1) a complete medical history review and neurological physical examination, (2) head computed tomography or magnetic resonance imaging with measurement of maximal hematoma thickness (in mm), midline shift , and (3) and measurement of blood and vital parameters. In addition, patients were asked to complete detailed questionnaires evaluating symptoms typically associated with subdural hematomas.

Follow-up appointments were scheduled 2 weeks and 1, 2, and 6 months after initiation of treatment. At each visit, the three components of the clinical evaluation described previously were repeated. Moreover, a seven-point categorical scale was used to evaluate patient's global impression of change relative to the initial state (unchanged, very much improved, much improved, minimally improved, minimally worse, much worse, very much worse). Treatment-related side effects were also inquired about and collected using an 11-point Likert scale at each follow-up visit.

https://doi.org/10.1017/cjn.2015.393 Published online by Cambridge University Press

The rate of success of conservative management was defined as the percentage of patients not requiring surgery or not presenting a serious adverse event because of the treatment in each treatment group during the 6 months following enrollment. Radiological progression of the hematoma in terms of thickness and magnitude of midline shift was recorded throughout the study. Hematoma-related symptoms were graded by the patients using an 11-point Likert scale, and medication-related side effects were self-reported by the patients and carefully collected during the treatment period.

Statistical Analyses

Sample Size

We hypothesized that dexamethasone would need to reduce the operation rate by 50% or more to give a reasonable effect size. There is no clearly defined rate for the surgical management of asymptomatic or mildly symptomatic patients in the literature. Sun et al published a rate of 0.5 in a relatively small study,[18] but we set a rate of 0.3 in keeping previous experience managing this patient population at our center. Using the exact Fisher test and, to detect an odd ratio between the operation rate with placebo and the operation rate with dexamethasone of two or more with a power of 80% and a type I error of 5%, the sample size was 84 in each arm. To prevent potential dropout of patients, we included 10% more patients in each group increasing the sample size to 93 in each group.

Demographical characteristics, baseline neurological status, and hematoma size and location were compared for both groups using a Mann-Whitney test for continuous variables and a chi-square test for categorical variables.

To compare the rate of success, a categorical frequency comparison with the Fisher's exact test was used. For the other outcome measures, we used Mann-Whitney U test and Student's *t* test for normally distributed variables and chi-square or Fisher's exact test for categorical frequencies. All statistical tests were done with the SPSS software, version 16.0, and the significance threshold was set at $p < 0.05$.

Results

Patient Characteristics

Twenty patients were enrolled in this study (10 placebo, 10 dexamethasone group). Table 1 shows baseline characteristics of our patient population. The mean age was 69.4 years (55-82 years) for the placebo group and 72.3 years (64-82 years) for the treatment group. The male:female ratio was 9:1 (18 males and 2 females). Both groups were relatively well-matched in terms of comorbidities and antiplatelet or anticoagulant medication use. CSDHs were located in the frontal (65%), parietal (30%), or frontoparietal (5%) lobe. The mean hematoma thickness was 15.1 mm (16.8 mm placebo group, 13.4 mm dexamethasone) and the midline shift was higher in the control group with a mean of 8 mm. Most patients had a Markwalder score of 0 at presentation (6/10 in placebo and 7/10 in dexamethasone group), showing a normal neurological status, all the remaining participants had Markwalder score of 1 with no neurological deficits but mild symptoms.

Headache, mental deterioration, and gait disturbance were the most common presenting symptoms. Three patients reported low muscle strength (one placebo, two dexamethasone) and two patients had transitory language impairment (both in placebo group). Sixteen patients (80%) had an established history of head trauma (8/10 in each group).

Table 1: Patients' demographic and clinical characteristics at baseline

	Treatment group	
	Placebo	**Dexamethasone**
Number of patients	10	10
Mean age (years ± SD)	69.4 ± 8.8	72.3 ± 6.3
Men (N)	10	8
Concomitant disease (N)		
Hypertension	7	7
Ischemic heart disease	4	3
Diabetes	4	2
COPD	2	1
Dementia	1	0
Arrhythmia	0	1
CVA/TIA	0	1
Pharmacotherapy at admission (N)		
Antiplatelet	6	7
Anticoagulant	1	1
Hematoma location (N)		
Frontal	7	6
Parietal	1	0
Frontoparietal	2	4
Mean thickness (mm ± SD)	20.4 ± 6.1	19.5 ± 7.9
Mean midline shift (mm ± SD)	8.0 ± 3.4	3.7 ± 3.3

COPD: chronic obstructive pulmonary disease; CVA/TIA: cerebrovascular accident/transient ischemic attack; SD: standard deviation.

Clinical and Radiological Outcomes of Conservative Management

Among the 20 patients, four underwent surgical drainage between 3 and 18 days after entering the study; a larger portion of these patients were receiving placebo (3/4). Additionally, three patients in

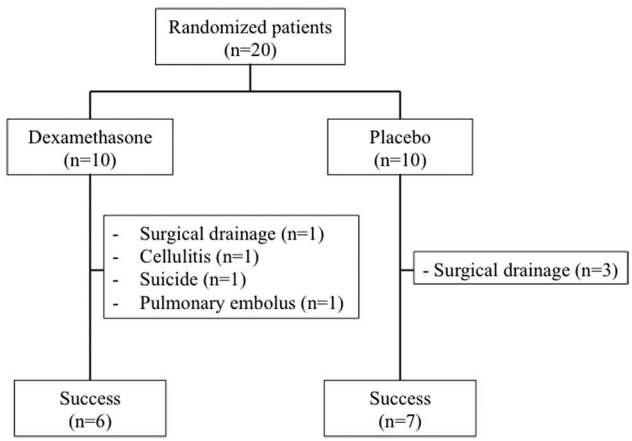

Figure 1: *Flow chart of the study with the primary outcome.*

https://doi.org/10.1017/cjn.2015.393 Published online by Cambridge University Press

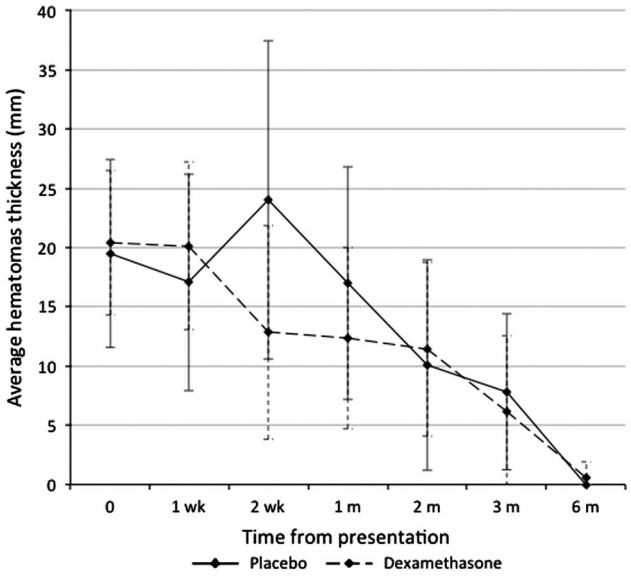

Figure 2: *Average hematoma thickness over time. The thickness is expressed as a percentage of the thickness measured at presentation.*

the dexamethasone group failed the conservative treatment because of a serious adverse event (Figure 1). Although, the rate of success of conservative management in corticoid-treated patients was 60% (95% confidence interval [CI], 0.48-0.72) against 70% (95% CI, 0.59-0.81) in the placebo group, and did not differ significantly between both groups (p = 0.2910).

Despite a trend toward lower hematoma thickness at 2 weeks and 1 month in patients receiving steroids, both groups showed a similar radiological progression overall with a complete regression at 6-month follow-up (Figure 2).

A majority of patients reported a positive impression of change over the course of the study (Figure 3). More patients in the treatment group reported feeling worse than at the previous visit after 2 weeks (30%) and 1 month (45%) of treatment compared with those assigned to placebo, but this was not statistically significant. Overall, both groups showed a similar impression of change over time.

We did not observe any significant between-group differences in terms of hematoma-related symptoms progression (data not shown).

Side Effects and Adverse Events

During the course of treatment, there were no significant changes in blood cell counts or hematological and liver functions (data not shown). Mortality was not statistically different in both groups, although there were two deaths at 6 months in the dexamethasone group and none in the placebo group.

Side effects associated with corticosteroid use were more frequently observed in the dexamethasone group (Table 2). The most common were fatigue (10/10), increased appetite and weight gain (9/10), shortness of breath, muscle weakness (8/10), and depressive symptoms (7/10). A week after the beginning of the conservative treatment, muscle pain appeared to be more severe in placebo-treated patients (p = 0.0344). However, after 2 weeks, the dexamethasone patients were complaining of more dyspepsia and increases in appetite than their counterparts (p = 0.035 and 0.049, respectively). At the end of the treatment period (30 days), shortness of breath, muscle weakness, fatigue, and depressive symptoms were significantly more severe in patients treated with dexamethasone (p = 0.0021-0.024).

In addition, some patients in the treatment group suffered serious adverse events (Table 3).Three of the four patients identified with hyperglycemia were in the dexamethasone group, and this was severe enough to require antihyperglycemic agents. For two patients, hyperglycemia was transitory (a few hours), but the third patient still required endocrinology follow-up at the end of the study. One subject in the control group also had one episode of hyperglycemia (blood glucose, 10.5 mmol/L), although this patient had preexisting uncontrolled diabetes (blood glucose, 20.5 mmol/L) at initial screen. One patient was admitted to the intensive care unit for cellulitis of the left arm roughly 1 month after starting dexamethasone therapy, which resolved after appropriate antibiotic therapy. Another patient committed suicide 2 weeks after steroids were discontinued. Although many factors likely contributed to this event, the temporal relationship between dexamethasone withdrawal and the event suggests that steroids might have played a role. One participant also died of a pulmonary embolus 22 days after the end of the treatment period, but it remains unclear whether this event was related to steroid therapy. Last, one subject in the dexamethasone group was readmitted to the hospital for acute pulmonary edema 17 days after starting treatment. No patient in the placebo group suffered a serious adverse event during the 6-month study period.

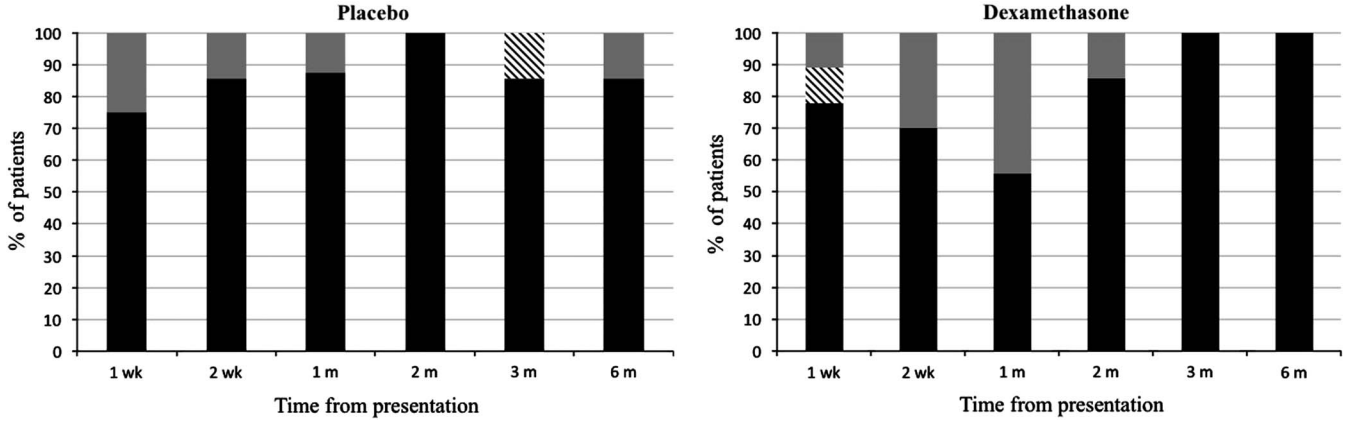

Figure 3: *Patient global impression of change. Black bar, condition improved (scoring 1, 2, or 3); gray bar, condition worsened (scoring −1, −2, or −3); hatched bar, condition unchanged (scoring 0).*

https://doi.org/10.1017/cjn.2015.393 Published online by Cambridge University Press

Table 2: Side effects reported by patients during treatment

		Day 7		Day 14		Day 30		
Self-reported side effects		**Severity**	**p value**	**Severity**	**p value**	**Severity**	**p value**	**Frequency (/10)**
Headache	Placebo	4 (1.37-6.63)	0.13	2.86 (0.64-5.08)	0.078	1.43 (0-2.86)	0.28	7
	Dex.	1.6 (0.05-3.15)		1.4 (-0.45 to 3.25)		3.13 (0.66-5.6)		5
Insomnia	Placebo	3.13 (0.29-5.97)	0.25	1.86 (0.37-3.35)	0.5	1.43 (-0.08 to 2.94)	0.19	4
	Dex.	4 (1.11-6.89)		2.5 (-0.03 to 5.03)		3.88 (0.87-6.89)		6
Increased hunger	Placebo	1.5 (-0.06 to 3.06)	0.45	0.71 (-0.46 to 1.88)	**0.035**	1.57 (-0.1 to 3.24)	0.21	3
	Dex.	0.9 (0.05-1.75)		3.3 (1.34-5.26)		0		9
Weight gain	Placebo	0.5 (-0.37 to 1.37)	0.41	0.71 (-0.06 to 1.48)	0.10	0.67 (-0.34 to 1.68)	0.34	5
	Dex.	0.8 (-0.4 to 2)		2.4 (0.39-4.41)		0		9
Dyspepsia	Placebo	0	0.25	0	**0.049**	1.0 (-0.18 to 2.18)	0.40	2
	Dex.	1.2 (-0.37 to 2.77)		1.6 (0.08-3.12)		1.0 (-0.64 to 2.64)		5
Shortness of breath	Placebo	1.75 (0.52-2.98)	0.484	0.43 (-0.05 to 0.91)	0.33	0.86 (-0.11 to 1.83)	**0.0021**	5
	Dex.	1.8 (0.5-3.1)		0.8 (0.04-1.56)		5.29 (4.24-6.34)		8
Muscle pain	Placebo	1.88 (0.67-3.09)	**0.0344**	1.0 (-0.18 to 2.18)	0.4052	0.71 (0.12-1.30)	0.305	6
	Dex.	0.3 (-0.29 to 0.89)		1.0 (0.18-1.82)		3.43 (0.78-6.08)		6
Muscle weakness	Placebo	2.13 (0.18-4.08)	0.4483	1.86 (0.52-3.20)	0.2946	0.86 (-0.11 to 1.83)	**0.015**	6
	Dex.	2.3 (0.67-3.93)		2.6 (1.16-4.04)		4.86 (2.92-6.8)		8
Diarrhea	Placebo	1.25 (-0.18 to 2.68)	0.281	0	0.2643	0.14 (-0.1 to 0.38)	0.4761	3
	Dex.	0.2 (-0.19 to 0.59)		0.9 (-0.28 to 2.08)		0.14 (-0.1 to 0.38)		4
Constipation	Placebo	1.38 (-0.27 to 3.03)	0.4129	0.57 (-0.37 to 1.51)	0.4052	1.29 (-0.17 to 2.75)	0.4761	3
	Dex.	1.8 (-0.07 to 3.67)		1.0 (-0.31 to 2.31)		2.0 (-0.24 to 4.24)		6
Rectal bleeding	Placebo	0	0.484	0	0.4801	0	0.352	0
	Dex.	0		0		1.29 (-0.82 to 3.4)		1
Fever or chills	Placebo	0	0.484	0	0.4801	0	0.352	1
	Dex.	0		0		0.57 (-0.37 to 1.51)		1
Hallucinations	Placebo	0	0.484	0	0.3859	0	0.3594	0
	Dex.	0		0.5 (-0.48 to 1.58)		0.43 (-0.27 to 1.13)		1
Fatigue	Placebo	3.38 (1.83-4.93)	0.5	3.14 (1.85-4.83)	0.2946	1.43 (-0.13 to 2.99)	**0.0091**	7
	Dex.	3.7 (1.67-5.73)		2.5 (0.74-4.26)		5.57 (4.45-6.69)		10
Depressive symptoms	Placebo	1.88 (0.58-3.18)	0.3936	1.86 (0.65-3.07)	0.4404	1.43 (1.19-1.67)	**0.0239**	5
	Dex.	1.8 (0.21-3.39)		2.1 (0.72-3.48)		3.0 (1.21-4.79)		7

Data are presented as mean severity with 95% confidence interval, p values, and frequency. Dex: dexamethasone; **bold** type: statistically significant difference.

Discussion

There is a long history of exploring mechanisms underlying the formation of CSDH. Several lines of experimental data support the theory of dysfunctional angiogenesis and inflammation as the cause of CSDH.[19]

Since the first paper describing patients treated with a conservative multimodal therapy in combination with corticosteroids in 1962,[20] the role of glucocorticoids in CSDH is still discussed controversially because of a lack of evident data. The prevailing rationale for using corticosteroids in CSDH is based on their inhibitory effects against the cycle of inflammation, neovascularization, and fibrinolysis presumed to underlie hematoma pathogenesis.[21,22] This view is supported by basic science research shown in animal models that dexamethasone blocks the formation of neocapillaries in the hematoma membrane and interferes with fibrinolytic activity within the accumulated blood.[22-24] Regardless of the true nature accounting for their effects, there still lacks persuasive clinical evidence to support an indication or contraindication for corticosteroids in the conservative treatment of CSDH. Moreover, conservative drugs are associated with severe side effects such as gastric mucosal hemorrhage, edema, and increased risk of infection, which are associated with steroids.[25]

Our study aimed to compare the safety of dexamethasone treatment for asymptomatic or mildly symptomatic patients with chronic subdural hematomas versus an observation-only (placebo) approach. To our knowledge, this represents the first randomized controlled trial addressing this question. Because of the low number of patients enrolled in each arm, our design did

https://doi.org/10.1017/cjn.2015.393 Published online by Cambridge University Press

Table 3: Serious adverse events occurred during the study

	Placebo-treated group		Dexamethasone-treated group	
Serious adverse event	**N events**	**N of subjects with event (%)**	**N events**	**N of subjects with event (%)**
Hyperglycemia	1	1 (10)	4	4 (40)
Hypertension	0		1	1 (10)
Pulmonary embolus	0		1	1 (10)
Cellulitis	0		1	1 (10)
Pulmonary edema	0		1	1 (10)
Suicide	0		1	1 (10)

not allow us to draw clear conclusions with regard to the rate of success of dexamethasone compared to placebo in the conservative management of CSDH. Few previous retrospective studies have explored the role of steroid monotherapy in CSDH. Delgado-Lopez et al reported a secondary intervention rate of 21.8% (22/101) in patients treated with 4 mg dexamethasone every 8 hours for 2 to 3 weeks.[10] Similarly, in a study published by Sun et al, 15.4% of patients (4/26) treated with steroids failed conservative treatment compared with 50% of patients in the observation group (2/4) .[18] However, we must keep in mind that the absence of randomization, use of different outcome measures, and lack of standardized follow-up in these observational studies preclude a clear statement on the efficacy of this approach.

In our study, corticosteroid treatment did not result in significant improvements in terms of patients' impression of change, severity of hematoma-related symptoms, or radiological progression than placebo. In fact, there was a trend for steroid patients to report feeling worse during the course of steroid administration. Moreover, corticosteroid therapy was associated with important side effects and severe adverse events, possibly leading to patient death in two cases.

In terms of radiological features, most studies have suggested a modest benefit from corticosteroid therapy, with a reduced time to complete radiological resolution in subjects treated with dexamethasone.[9,24,26] In contrast, we did not observe any overall differences in radiological progression between both groups, despite a transient trend toward a reduction in hematoma thickness at 2 and 4 weeks in dexamethasone-treated subjects. More importantly, this trend was not accompanied with greater subjective improvement or reduced symptomatology in the treatment group. Our findings thus stand in contrast with those of a few retrospective studies suggesting a favorable clinical response to corticosteroids.[10,25,27,28] Bender et al reported accelerated neurological improvement in patients prescribed 60 mg of prednisone by mouth once daily compared with observation.[26] However, these findings are biased by the fact that treatment allocation was dictated by initial symptoms severity and other clinical features at presentation.

Furthermore, in the present study, corticosteroid treatment was associated with considerable side effects and a few severe adverse events. Delgado-Lopez and colleagues reported hyperglycemia in 14.8% of patients treated with dexamethasone for CSDH.[10] Steroid-induced hyperglycemia was much more commonly observed in our study, with rates approaching 40.0%. In three of four cases, the hyperglycemia was severe enough to require administration of insulin or other antihyperglycemic agents.

We observed a similar infection risk to what has been reported in the literature for elderly populations receiving oral glucocorticoid therapy.[16,24,29,30] In a pooled analysis of 71 controlled clinical trials, Stuck et al calculated an overall risk of serious infection of 13% in patients taking more than 10 mg of glucocorticoids daily versus 7% in those receiving placebo.[16] Interestingly, the risk of lethal and nonlethal infection was the highest in patients with neurological diseases (relative risk of 2.8 compared with placebo ; 95% CI, 1.9-4.3), raising concerns for the use of steroids in CSDH and other intracranial pathologies. In our study, one patient in the dexamethasone group had to be admitted to the intensive care unit for left arm cellulitis toward the end of the treatment period. Dexamethasone was immediately withdrawn and the patient fully recovered from his hematoma a few weeks after enrolling in our trial. Another patient in this group succumbed to a pulmonary embolism 22 days after the end of the treatment period, but it remains unclear whether steroid use played any part in this event.

In one case, tapering and ultimate withdrawal of dexamethasone after the 30-day treatment period could have been related to a participant committing suicide. Although other factors likely contributed to this patient's psychological distress, we can afford that steroid treatment might have played a role given the temporal and dose-response relationships that we observed. The adverse mental effects associated with corticosteroid use have been extensively described and previous reports of steroid-related suicides have been published.[31-35] Although this may be a rare event, the seriousness of the outcome warrants caution in individuals showing psychiatric symptoms after initiation of therapy, or those from which it is not possible to obtain a thorough psychiatric history.

The optimal dexamethasone dosage and duration of treatment in CSDH remains controversial, and regimens vary widely across neurosurgical centers.[25] In the current study, the treatment schedule was based on previously published reports and the experience of neurosurgeons at our institution. It is possible that lower doses and/or shorter duration of treatment would favor clinical recovery while minimizing steroid-related adverse effects. Additional studies exploring dose-response relationships are needed to better establish the risk-benefit profile of corticosteroid treatment in CSDH.

In short, despite its limitations, our study suggests that neurosurgeons should not underestimate the risks associated with the use of glucocorticoids in the conservative management of subdural hemorrhages. Although this treatment approach might slightly lower the need for a surgical intervention, it carries considerable risks for the patient. In selected cases, close observation might be superior to steroid therapy.

Acknowledgments and Funding

We thank Danielle Fortin and Danielle Petit, research nurses in the Department of Neurological Sciences at Hôpital de l'Enfant-Jésus for their help with clinical assessments and questionnaire administration. We also want to acknowledge the contribution of several neurosurgeon colleagues, residents, and students in the Department of Neurosurgery who helped with recruitment and/or with compilation and analysis of data.

The study was funded by the Fondation du CHU de Québec.

Disclosures

MP has applied for and received a grant from the Fondation du CHU de Quebec. FM, NM, and SC have nothing to disclose.

References

1. Santarius T, Lawton R, Kirkpatrick PJ, Hutchinson PJ. The management of primary chronic subdural haematoma: a questionnaire survey of practice in the United Kingdom and the Republic of Ireland. Br J Neurosurg. 2008;22:529-34.
2. Aspegren OP, Astrand R, Lundgren MI, Romner B. Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. Clin Neurol Neurosurg. 2013;115:981-4.
3. Baechli H, Nordmann A, Bucher HC, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. Neurosurg Rev. 2004;27:263-6.
4. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly—a North Wales experience. J Royal Soc Med. 2002;95:290-2.
5. Kudo H, Kuwamura K, Izawa I, Sawa H, Tamaki N. Chronic subdural hematoma in elderly people: present status on Awaji Island and epidemiological prospect. Neurol Med Chir. 1992;32:207-9.
6. Kinsella KG, Velkoff VA, United States. Bureau of the Census. An aging world: 2001. Washington, D.C.: U.S. Department of Commerce, Economics and Statistics Administration; 2001.
7. Kirley K, Qato DM, Kornfield R, Stafford RS, Alexander GC. National trends in oral anticoagulant use in the United States, 2007 to 2011. Circ Cardiovasc Qual Outcomes. 2012;5:615-21.
8. Parlato C, Guarracino A, Moraci A. Spontaneous resolution of chronic subdural hematoma. Surg Neurol. 2000;53:312-5.
9. Weigel R, Schilling L, Schmiedek P. Specific pattern of growth factor distribution in chronic subdural hematoma (CSH): evidence for an angiogenic disease. Acta Neurochir. 2001;143:811-8.
10. Delgado-Lopez PD, Martin-Velasco V, Castilla-Diez JM, Rodriguez-Salazar A, Galacho-Harriero AM, Fernandez-Arconada O. Dexamethasone treatment in chronic subdural haematoma. Neurocirugia. 2009;20:346-59.
11. Almenawer SA, Farrokhyar F, Hong C, et al. Chronic subdural hematoma management: a systematic review and meta-analysis of 34829 patients. Ann Surg. 2013;259:449-57.
12. Gelabert-Gonzalez M, Iglesias-Pais M, Garcia-Allut A, Martinez-Rumbo R. Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin Neurol Neurosurg. 2005;107:223-9.
13. Cenic A, Bhandari M, Reddy K. Management of chronic subdural hematoma: a national survey and literature review. Can J Neurol Sci. 2005;32:501-6.
14. Dran G, Berthier F, Fontaine D, Rasenrarijao D, Paquis P. Effectiveness of adjuvant corticosteroid therapy for chronic subdural hematoma: a retrospective study of 198 cases. Neurochirurgie. 2007;53:477-82.
15. Berghauser Pont LM, Dippel DW, Verweij BH, Dirven CM, Dammers R. Ambivalence among neurologists and neurosurgeons on the treatment of chronic subdural hematoma: a national survey. Acta Neurol Belg. 2013;113:55-9.
16. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. Rev Infect Dis. 1989;11:954-63.
17. Markwalder TM, Steinsiepe KF, Rohner M, Reichenbach W, Markwalder H. The course of chronic subdural hematomas after burr-hole craniostomy and closed-system drainage. J Neurosurg. 1981;55:390-6.
18. Sun TF, Boet R, Poon WS. Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. Br J Neurosurg. 2005;19:327-33.
19. Stanisic M, Lyngstadaas SP, Pripp AH, et al. Chemokines as markers of local inflammation and angiogenesis in patients with chronic subdural hematoma: a prospective study. Acta Neurochir. 2012;154:113-20.
20. Ambrosetto C. Post-traumatic subdural hematoma. Further observations on nonsurgical treatment. Arch Neurol. 1962;6:287-92.
21. Frati A, Salvati M, Mainiero F, et al. Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study. J Neurosurg. 2004;100:24-32.
22. Labadie EL, Glover D. Physiopathogenesis of subdural hematomas. Part 1: histological and biochemical comparisons of subcutaneous hematoma in rats with subdural hematoma in man. J Neurosurg. 1976;45:382-92.
23. Glover D, Labadie EL. Physiopathogenesis of subdural hematomas. Part 2: inhibition of growth of experimental hematomas with dexamethasone. J Neurosurg. 1976;45:393-7.
24. Tang J, Ai J, Macdonald RL. Developing a model of chronic subdural hematoma. Acta Neurochir Suppl. 2011;111:25-9.
25. Berghauser Pont LM, Dirven CM, Dippel DW, Verweij BH, Dammers R. The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. Eur J Neurol. 2012;19(11):1397-403.
26. Bender MB, Christoff N. Nonsurgical treatment of subdural hematomas. Arch Neurol. 1974;31:73-9.
27. Jones S, Kafetz K. A prospective study of chronic subdural haematomas in elderly patients. Age Ageing. 1999;28:519-21.
28. Decaux O, Cador B, Dufour T, et al. Nonsurgical treatment of chronic subdural hematoma with steroids: two case reports. Revue Med Interne. 2002;23:788-91.
29. Dixon WG, Kezouh A, Bernatsky S, Suissa S. The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study. Ann Rheum Dis. 2011;70:956-60.
30. Dixon WG, Abrahamowicz M, Beauchamp ME, et al. Immediate and delayed impact of oral glucocorticoid therapy on risk of serious infection in older patients with rheumatoid arthritis: a nested case-control analysis. Ann Rheum Dis. 2012;71:1128-33.
31. Naber D, Sand P, Heigl B. Psychopathological and neuropsychological effects of 8-days' corticosteroid treatment. A prospective study. Psychoneuroendocrinology. 1996;21:25-31.
32. Brown ES, Khan DA, Nejtek VA. The psychiatric side effects of corticosteroids. Ann Allergy Asthma Immunol. 1999;83:495-503.
33. Patten SB, Neutel CI. Corticosteroid-induced adverse psychiatric effects: incidence, diagnosis and management. Drug Safety. 2000;22:111-22.
34. Warrington TP, Bostwick JM. Psychiatric adverse effects of corticosteroids. Mayo Clin Proc. 2006;81:1361-7.
35. Matsumoto Y, Shimizu K, Kinoshita H, Shimizu C, Uchitomi Y. Suicide associated with corticosteroid use during chemotherapy: case report. Jap J Clin Oncol. 2010;40:174-6.

https://doi.org/10.1017/cjn.2015.393 Published online by Cambridge University Press