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Corticosteroids as an Adjuvant Treatment to Surgery in Chronic Subdural Hematomas: A Multi-Center Double-Blind Randomized Placebo-Controlled Trial

Sam Ng,^{1,*} Julien Boetto,^{1,†} H el ena Huguet,^{2,3} Pierre-Hugues Roche,⁴ St ephane Fuentes,⁵ Michel Lonjon,⁶ St ephane Litrico,⁶ Anne-Marie Barbanel,⁷ Pascal Sabatier,⁸ Luc Bauchet,⁹ Hugues Chevassus,^{2,9} and Nicolas Lonjon^{1,10}; on behalf of the HEMACORT Study Group^{**}

Abstract

Chronic subdural hematoma (CSDH) is a common condition necessitating surgery; however, recurrence occurs in 15–25% of cases despite surgical management. The HEMACORT trial was a prospective randomized, double-blind, placebo-controlled, multi-centric study (NCT01380028). The aim of this trial was to determine the effect of corticosteroids as an adjuvant treatment to surgery on CSDH recurrence at 6 months. After surgery, participants were assigned by block-randomization to receive either placebo or oral prednisone at a dose of 1 mg/kg/day followed by weekly stepwise tapering in steps of 10 mg/day. The primary outcome was CSDH recurrence, defined by the need for reoperation and/or radiological progression of CSDH. Secondary outcomes were one-year death, radiological changes, safety, neurological status, and quality of life. The trial was discontinued at midpoint of expected inclusions: 78 participants received prednisone and 77 received placebo controls. In an intention-to-treat analysis, CSDH clinico-radiological recurrence was not different between prednisone and placebo groups (21.8% vs. 35.1%, respectively; hazard ratio 0.56; 95% confidence interval 0.30–1.02; $p = 0.06$), although *post hoc* analyses concluded to statistical significance ($p = 0.02$). Earlier radiological resolution was observed after prednisone administration, but reoperation rates (reaching 5.8% overall) and functional outcomes were not different at 6 months. Among adverse events, sleep disorders occurred more often in the prednisone group (26.1% vs. 9.1%, $p = 0.02$). The HEMACORT trial data suggest that prednisone, as an adjuvant treatment to surgery, may reduce early radiological recurrence of CSDH, although clinical benefits are unclear. In view of these findings, the authors suggest that shorter treatment duration should be assessed for safety and efficacy in future trials.

Keywords: chronic subdural hematoma; corticosteroid; surgery

Introduction

Chronic subdural hematoma (CSDH) is one of the most frequent entities necessitating neurosurgery. The incidence is 15 per 100,000 person-years in the general population, increasing to 127.1 per 100,000 person-years in patients aged over 80 years.^{1,2} Because the elderly population is growing, CSDH prevalence is constantly increasing, becoming a significant public health problem.³⁻⁵ In addition, results of conventional treatments including surgical evacuation are heterogeneous with 15% recurrence after one year increasing to 25% in high-risk patients.⁶⁻⁸ Beyond its classic traumatic etiology, the development of CSDH involves complex mechanisms of inflammation leading to a self-sustaining process of neoangiogenesis and fibrinolysis that is mediated by proinflammatory cytokines.⁹⁻¹¹

Surgical removal of the hematoma is effective in reducing the mass effect induced by the hematoma,^{7,12,13} but does not treat the underlying pathophysiological mechanisms. Consequently, adjuvant therapies to surgery are under evaluation, including atorvastatin,¹⁴ angiotensin converting enzyme inhibitors,^{15,16} middle meningeal artery embolization^{17,18} and corticosteroids.¹⁹ Among these, corticosteroids are widely used as an adjuvant treatment or as an alternative to surgery in patients with mild neurological impairment,²⁰ but there is no clear demonstration of their efficacy in CSDH, with only retrospective studies or preliminary studies supporting its efficacy.²¹⁻²³ Recently, a randomized trial even suggested that patients under corticosteroids may have fewer favorable outcomes and more adverse events, although patients experienced fewer reoperations.²⁴

This study presents the results from HEMACORT, a trial assessing the efficacy of corticosteroids as an adjuvant treatment to surgery in CSDH.

Methods

Study design

HEMACORT was a multi-center, double-blind, placebo-controlled, randomized 1:1, parallel group trial. This study was conducted in five hospitals in France (Marseille Nord University Hospital, Marseille La Timone University Hospital, Perpignan Hospital, Nice Pasteur University Hospital, and Montpellier University Hospital). This trial was sponsored by Montpellier University Hospital (France, UF8545). The study was approved by the French institutional ethics committee "Comité de Protection des Personnes Sud Méditerranée IV Montpellier Saint-Eloi" and conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation guidelines for Good Clinical Practice and French regulatory requirements. All patients gave written informed consent. The study was registered on the United States clinical trial database before the first patient inclusion.²⁵

Participants

Eligible patients were men and women over age 18, weighing less than 104 kg, who underwent surgery for a one-sided or bilateral CSDH in the previous 72 h. Pre-operative radiological eligibility criteria included hypodense or isodense collection (in case of multiple component hematomas, the thickness of the low-density component [<50 Hounsfield units] had to represent $>50\%$ of the maximal thickness of the hematoma), and CSDH size measured greater than 3 mm (documented on pre-operative axial computed tomography [CT]). All radiological evaluations were performed by an independent radiologist.

Exclusion criteria were: a past history of CSDH, a past history of cranial surgery, Glasgow Coma Scale score under 9 at admission, ongoing infection, diabetes mellitus necessitating medical treatment, uncontrolled arterial hypertension, uncontrolled psychotic state, gastric ulcer, osteoporosis, organ failure, pregnancy, and breastfeeding.

Sample size and randomization

Using estimated recurrence rates of CSDH after surgical treatment of 10% in the corticosteroid group and 20% in the placebo group²¹ for $\alpha = 5\%$, $\beta = 20\%$ and using a two-sided log-rank test, 148 participants were required in each group. Taking into account a probable dropout rate of 15%, a total of 340 participants were randomized. Sample size was determined for the primary outcome using nQuery Advisor, version 4.0 (Statistical Solutions, Boston, MA).

We stratified the randomization by center with a 1:1 allocation using block sizes of four patients. Eligible patients were randomized by the pharmacy department of their center in the first 72 h after surgery. Each pharmacy department had an independent randomization list produced with SAS software, version 9 (SAS Institute, Cary, NC).

Interventions

Subjects randomized into the corticosteroid group received oral prednisone at an initial dose of 1 mg/kg (rounded to the nearest 10 mg) once daily for seven days. The treatment was started the day after randomization. Of note, 5 mg of prednisone is an equivalent dose to 0.75 mg of dexamethasone and to 4 mg of methylprednisolone. Patients then underwent a decrease in the dose of 10 mg/day every seven days. After completing seven days at the dose of 10 mg/day, patients received 5 mg/day for seven days before treatment was stopped.

The treatment duration thus varied from one participant to another depending on participant weight. For instance, a patient weighting 80 kg was administered one week of treatment at the dose of 80 mg/day followed by a weekly taper (70 mg/day for one week, then 60 mg/day

for one week, etc.) and finally 5 mg on its ninth and last week of treatment. The same treatment procedure was applied in the placebo group using nonpharmacologically active agents. Prednisone tablets were masked by administration in the same capsules used to prepare the placebo, all capsules being indistinguishable.

Study drug adherence was checked by the pharmacy centers at two end-points: (1) after 28 days of treatment (first outpatient period) and (2) at the end of the treatment (second outpatient period, depending on the treatment duration). Adherence was expressed as the ratio (%) between consumed and prescribed treatment units. Participants, investigators, and caregivers remained blinded throughout the study. Additional cholecalciferol (vitamin D3; 800 UI/day) and calcium (1 g/day) was given to all patients during the treatment.

Outcomes

The primary outcome was the clinicoradiological recurrence rate of CSDH within six months after surgery. The CSDH clinicoradiological recurrence was a composite criterion defined by the onset of one or more of the following clinical and/or radiological issues: recurrence of clinical symptoms of CSDH necessitating a second cranial surgery; any radiological bleeding (defined as an increase in Hounsfield densities) and/or any enlargement of the subdural space (defined as an increase of the maximum thickness compared with the immediate post-operative CT scan). The primary outcome was evaluated blindly by an independent team (one neurologist and one radiologist).

Secondary outcomes were: mortality rate one year after surgery; neurological status (assessed by the Markwalder Grading Scale [MGS]),²⁶ quality of life (assessed by the Nottingham Health Profile [NHP] questionnaire),²⁷ autonomy (assessed by the Karnofsky scale), safety, and the percentage of decrease in hematoma size (based on maximal thickness) at one month and six months after the immediate post-operative assessment.

Study procedures

Briefly, after giving informed consent, subjects were assessed for eligibility before surgery by a full physical examination and a CT scan. Although the surgical technique was left to the discretion of each participating center, data for the use of subdural drain, duration of the drainage, and the use of a percutaneous/nonpercutaneous technique were collected.

Randomly assigned treatment was initiated in hospital within 72 h after the surgery, immediately after a baseline CT scan was performed. Three evaluation visits were planned at one month, three months, and six months (at least 150 days after randomization) after discharge. A blood sample was obtained at the one-month visit for investigation of electrolyte and glycemic impairments. Death at one year was assessed by telephone interview of relatives. The Time and Events schedule and safety checkpoints are detailed in Table 1.

Early discontinuation of the trial

Premature discontinuation of the trial was decided by the sponsor because of funding not matching costs incurred, mainly because of placebo supply problems. It was therefore decided to perform a final analysis at the midpoint of the patient inclusion.

Statistical methods

All analyses were conducted on data from the intention to-treat population. The study population is described using mean and standard deviation (SD) for quantitative variables and frequencies for qualitative variables. Continuous variable distributions were tested with the Shapiro-Wilk statistic. Quantitative variables were compared using the parametric Student *t* test, when the distribution was Gaussian or otherwise with the Mann-Whitney test. For qualitative variables, groups were compared using the chi-square test or Fisher test. The clinicoradiological recurrence analysis was pre-specified as a recurrence-free

Table 1. Time and Events Schedule

	Admission and surgery		Hospital stay	First visit (1 month)		Second visit (3 months)	Third visit (6 months)		12 months
Clinical examination	x	x		x		x		x	
Informed consent	x			x		x		x	
Inclusion/exclusion criteria	x								
Randomization			x ^a						
Treatment			x ^a	x	x				
CT scan	x		x ^a	x				x	
Blood sample	x		x	x					
Adverse event			x	x		x		x	
MGS				x				x	
NHP				x				x	
Karnofsky scale				x				x	
Telephone interview									x

CT, computed tomography; MGS, Markwalder Grading Scale; NHP, Nottingham Health Profile.

^aIn the first 72 h after surgery.

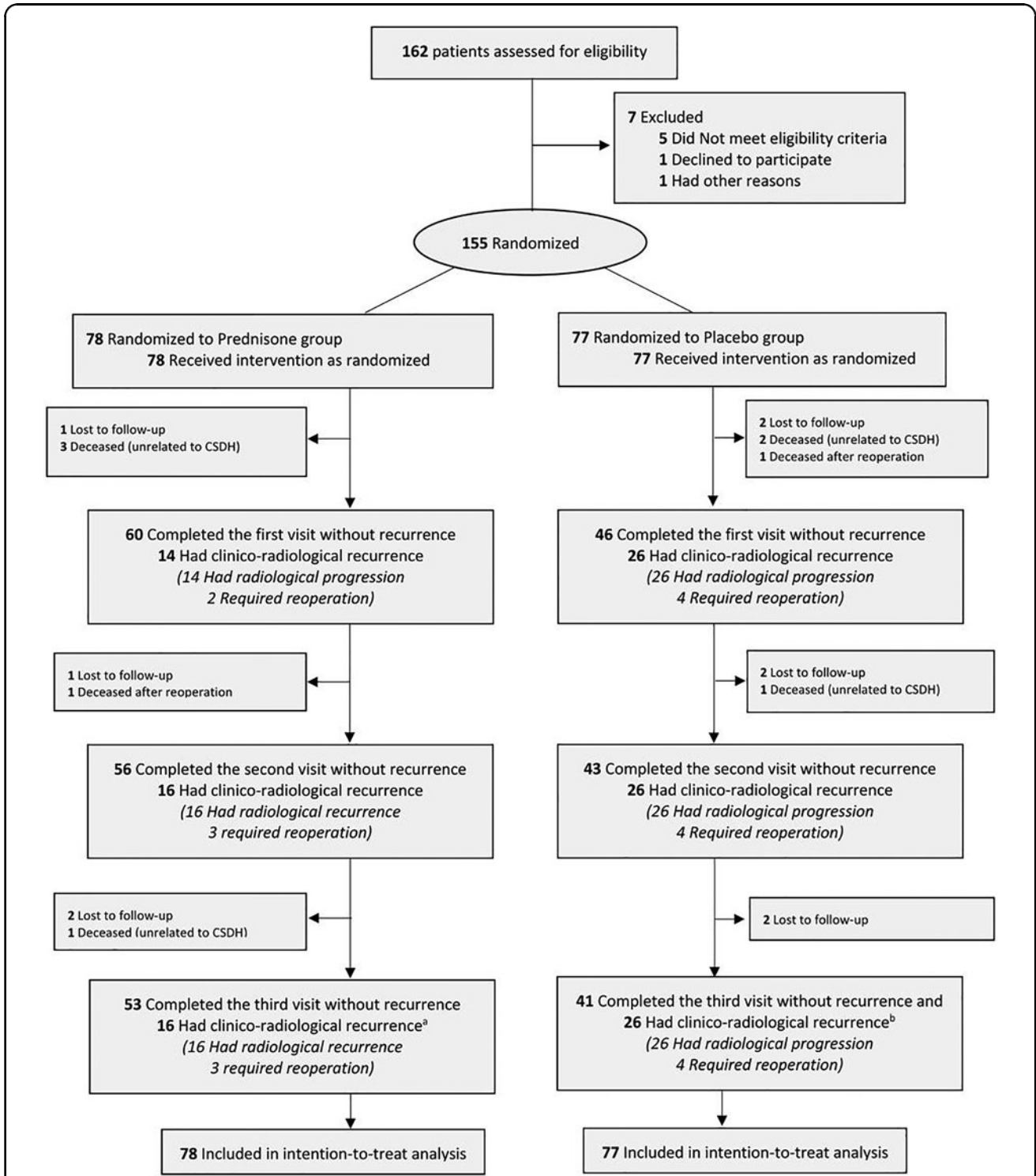


FIG. 1. Flowchart. CSDH, chronic subdural hematoma. ^aOverall, 17 patients had clinico-radiological recurrence, including patients with deaths related to CSDH recurrence. ^bOverall, 27 patients had clinico-radiological recurrence, including patients with deaths related to CSDH recurrence.

Table 2. Demographics and Main Characteristics at Baseline

Characteristic	Corticosteroid group N = 78	Placebo group N = 77	p
Demographics			
Age (year), mean - SD	75.6 - 10.6	72.7 - 15.0	0.47
Sex, No. (%) Males	56 (71.8)	58 (75.3)	0.62
Females	22 (28.2)	19 (24.7)	
Medical history			
Trauma history, No. (%)	50 (64.9)	52 (67.5)	0.73
Chronic alcoholism, No. (%)	10 (12.8)	13 (16.9)	0.48
Smoking, No. (%)	9 (11.5)	10 (13.0)	0.78
Hypertension, No. (%)	40 (51.3)	33 (42.9)	0.29
Use of antiplatelet or anticoagulants drugs, No. (%)	41 (52.6)	31 (40.3)	0.12
Brain atrophy, No. (%)	27 (34.6)	24 (31.2)	0.65
Symptoms at admission			
Cephalalgia, No. (%)	49 (62.8)	42 (54.6)	0.30
Motor deficit, No. (%)	60 (76.9)	65 (84.4)	0.24
Ataxia, No. (%)	3 (3.9)	4 (5.2)	0.72
Seizure, No. (%)	2 (2.6)	2 (2.6)	0.99
Consciousness disorders, No. (%)	31 (39.7)	28 (36.4)	0.66
Vomiting, No. (%)	3 (3.9)	4 (5.2)	0.72
Cognitive impairment, No. (%)	44 (56.4)	46 (59.7)	0.68
CSDH radiological characteristics			
Side, No. (%) Left	30 (38.5)	28 (36.4)	0.92
Right	28 (35.9)	30 (39.0)	
Bilateral	20 (25.6)	19 (24.7)	
Evolution of thickness after surgery (72 hours) from preoperative CT, mean - SD	-9.4 - 7.0	-9.0 - 6.0	0.68
Pre-surgical maximum thickness, mean - SD	22.3 - 7.5	23.8 - 6.6	0.09
Post-surgical maximum thickness, mean - SD	12.8 - 5.1	14.9 - 5.2	0.02
Surgical technique			
Percutaneous	20 (26.0)	13 (16.9)	0.24
Nonpercutaneous	57 (74.0)	64 (83.1)	
Subdural drainage			
No drain	1 (1.3)	1 (1.3)	0.11
1 drain	60 (76.9)	63 (81.8)	
2 drains	17 (21.8)	13 (16.9)	
Duration of subdural drainage			
1 day or less	26 (33.3)	31 (40.3)	0.65
2 days	38 (48.7)	36 (46.7)	
3 days	9 (11.6)	8 (10.4)	
4 days or more	5 (6.4)	2 (2.6)	
Duration (days), mean - SD	1.92 - 0.95	1.74 - 0.77	0.28

SD, standard deviation; CSDH, chronic subdural hematoma; CT, computed tomography.

Reported percentages may not add up to 100% because of rounding.

survival analysis. Patients lost to follow-up or deceased from causes other than CSDH were considered as censored.

The recurrence-free survival rate was described by the Kaplan-Meier method and compared with a log-rank test. A *post hoc* multi-variate analysis was performed with the

Cox proportional-hazard regression model to calculate adjusted hazard ratios and 95% confidence intervals by adjusting on relevant factors showing baseline group difference at a *p*-value <0.20. Statistical significance was set at 0.05, and analyses were performed using SAS version 9 software (SAS Institute, Cary, NC).

Results

Participants

Of the 162 participants screened, 155 patients were randomized, and 78 participants received oral corticosteroids and 77 participants received a placebo. Figure 1 shows the participant flow. Baseline characteristics for the prednisone and placebo groups, including surgical technique features, are provided in Table 2.

Patients randomized to the corticosteroid group were more likely to be receiving antiplatelet or anticoagulant therapy (52.6% vs. 40.3%). The post-surgical maximum thickness of the hematomas was lower in the prednisone group than in the placebo group (12.8 - 5.1 mm vs. 14.9 - 5.2 mm, *p* = 0.02, respectively) although the comparative evolution of thickness of the hematomas immediately after surgery from pre-operative CT was not significantly different. The total treatment duration never exceeded 10 weeks because no patients weighing more than 90 kg were included.

Adherence in the first outpatient treatment period was 80.5 - 30.2% in the prednisone group and 79.8.5 - 31.0%

in the placebo group (*p* = 0.93). Adherence for the second outpatient treatment period (i.e., at the end of the treatment) was 77.9 - 33.3% in the prednisone group and 80.0 - 32.8% in the placebo group (*p* = 0.67).

Primary outcome results

Primary outcome results are detailed in Table 3. Overall, 44 (28.4%) patients experienced a clinicoradiological recurrence within the first six months after surgery, including 17 participants (21.8%) in the prednisone group, and 27 (35.1%) participants in the placebo group (*p* = 0.06). The Kaplan Meier method estimate of the probability of recurrence-free survival at six months was 77% (95% confidence interval [CI]: 66% to 85%) in the prednisone group and 63% (95% CI: 51% to 73%) in the placebo group (*p* = 0.054). Kaplan-Meier plots describing radiological progression and reoperation over time are displayed in Figure 2A, 2B, respectively.

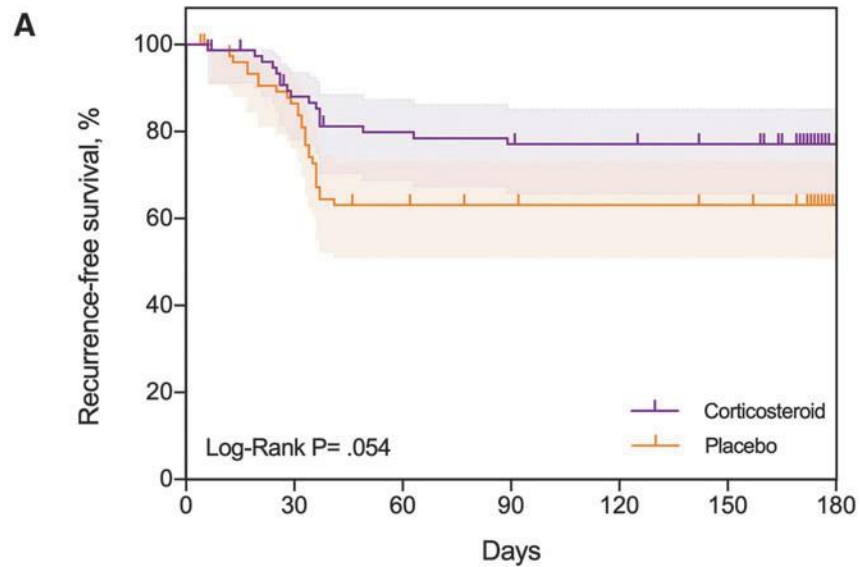
Table 3. Primary Outcome Results

	Corticosteroid group N = 78	Placebo group N = 77	HR (95% CI)	p	HR _{adjusted} ^a	p ^a
Primary outcome ^b	17 (21.8)	27 (35.1)	0.56 [0.30 ; 1.02]	0.06	0.48 [0.26 ; 0.89]	0.02
Reoperation	4 (5.1)	5 (6.5)	0.75 [0.20 ; 2.77]	0.66	0.59 [0.16 ; 2.27]	0.45
Radiological recurrence ^b	17 (21.8)	27 (35.1)	0.56 [0.30 ; 1.02]	0.06	0.48 [0.26 ; 0.89]	0.02

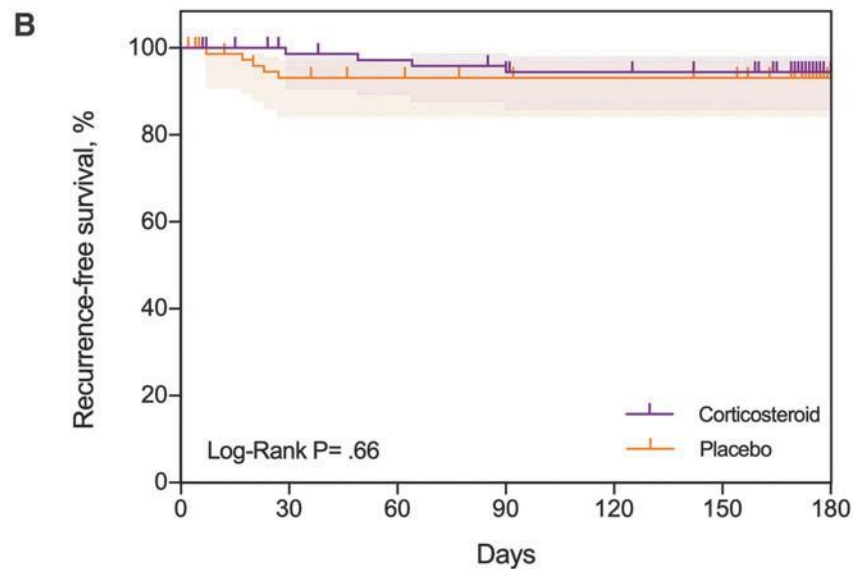
HR, hazard ratio; CI, confidence interval.

^aComparisons were adjusted for histories of antiplatelet and anticoagulant drugs and for post-surgical hematoma thickness.

^bNote that all participants with reoperation firstly experienced a radiological recurrence.



No. at risk							
Corticosteroid	78	66	58	56	55	53	28
Placebo	77	64	45	43	42	41	21



No. at risk							
Corticosteroid	78	67	65	63	62	61	33
Placebo	77	72	70	68	65	63	33

FIG. 2. Time to chronic subdural hematoma recurrence from randomization. The shaded areas indicate 95% confidence interval. (A) Kaplan-Meier plot describing the time to radiological progression; (B) Kaplan-Meier plot describing the time to reoperation. Color image is available online.

Post hoc analyses adjusting the recurrence-free survival at six months to antiplatelet and anticoagulant drug use and to post-surgical hematoma thickness concluded to a significantly higher recurrence-free survival in the prednisone group than in the placebo group ($p=0.02$).

Reoperation, a subcomponent of the primary outcome, occurred in four (5.1%) participants in the prednisone group and five (6.5%) participants in the placebo group ($p = 0.66$). Note that all patients requiring a reoperation presented a concomitant radiological progression.

Radiological progression, the second subcomponent of the primary outcome, occurred in the same proportions as clinicoradiological recurrence.

Secondary outcome results

Results for death, hematoma size, and Karnofsky index are provided in Table 4.

Nine deaths occurred during the trial—five in the corticosteroid group and four in the placebo group. Among these, the monitoring board estimated that 1 one in each group was related to CSDH recurrence. In the placebo group, the other causes of death were pneumonia (two participants), ischemic stroke, and gastrointestinal bleeding. In the corticosteroid group, the other causes of death were pneumonia (two participants), digestive cancer progression, and ischemic stroke.

Details regarding percentage of decrease in hematoma size are provided in Figure 3. The percentage decrease in hematoma size at one month after the immediate post-operative assessment was significantly higher in the corticosteroid group than in the placebo group (-35.5 - 48.1% vs. -11.9 - 49.0%; $p=0.001$), although no significant difference was observed at six months. Complete data for NHP and MGS score are detailed in Table 5. The Sleep score from the NHP was significantly higher in the corticosteroid group at one month ($p=0.01$), although again no differences between groups were found at six months.

Safety

Table 6 summarizes adverse events recorded at the time of data lock. Thirty-one (20.0%) participants experienced infections, 11 (7.1%) participants experienced gastrointestinal disorders, and 13 (8.4%) participants experienced

Table 4. Mortality, Hematoma Size and Karnofsky Index Results

Outcomes	Prednisone group	Placebo group	p
Mortality			
No. of death at 12 months, No. (%)	5/71 (7.0)	4/69 (5.8)	> 0.99
Hematoma size			
Size at 1 month (mm), mean - SD ^a	8.7 - 6.4	12.7 - 6.3	< 0.001
Size at 6 months(mm), mean - SD ^b	2.8 - 5.1	3.7 - 4.6	0.10
Relative evolution at 1 month from immediate post-operative CT, mean percentage - SD ^c	-35.5 - 48.1	-11.9 - 49.0	< 0.001
Relative evolution at 6 months from immediate post-operative CT, mean percentage - SD ^d	-81.0 - 35.8	-76.9 - 30.2	0.17
Karnofsky index			
KI at 1 month, mean - SD ^e	90.7 - 15.4	86.7 - 16.2	0.11
KI at 3 months, mean - SD ^f	92.0 - 15.3	93.6 - 11.8	0.71
KI at 6 months, mean - SD ^g	95.5 - 11.4	95.6 - 11.2	0.74

SD, standard deviation; CT, computed tomography; KI, Karnofsky Index.

Patients with data available for analyses were (a) 73 vs. 71, (b) 64 vs. 61, (c) 72 vs. 70, (d) 63 vs. 60, (e) 73 vs. 67, (f) 66 vs. 62, (g) 65 vs. 60 in the prednisone group and placebo group, respectively.

metabolic and general disorders during the trial, without any difference found between groups. Insomnia occurred more frequently in the prednisone group than in the placebo group (26.1% vs. 9.1%, $p=0.02$).

Discussion

The results of this double-blind, randomized, placebo-controlled study suggest that prednisone as an adjuvant treatment to surgery may reduce early radiological progression of CSDH, although clinical outcomes (including reoperation rate, death, neurological and functional outcomes) did not seem to be modified by prednisone administration.

In contrast to the findings of Hutchinson and associates,²⁴ we report no significant difference in functional outcomes and reoperation rates between patients who received corticosteroids and placebo at six months, although we observed quite close rates of reoperation in the whole population (5.8% vs. 1.7-7.1% in the study by Hutchinson and associates²⁴). Despite the fact that we used a significantly longer period of corticosteroid treatment, we observed no effect of corticosteroids on the occurrence of metabolic diseases and infections. The therapeutic protocol used in our study was not harmless, however, with significant psychiatric comorbidities.

Surgery remains the treatment of choice for symptomatic CSDH, because it is effective in reducing intracranial hypertension.^{28,29} Nevertheless, the risk of clinicoradiological recurrence after surgery is high and leads to high rates of post-surgical morbidity. Corticosteroids have been introduced in CSDH management because of the potential local inflammatory reactions leading to a self-sustaining process of neoangiogenesis and fibrinolysis. In practice, despite the lack of high-quality studies providing evidence of corticosteroids effectiveness, the use of corticosteroids currently ranges 13-55%, depending on the institution,^{30,31} with the aim of either avoiding surgical management or reducing CSDH recurrence after surgery.

Our results are more nuanced than previous non-randomized studies that have suggested favorable results with corticosteroids in reducing CSDH recurrence rate as an adjunctive treatment to surgery^{22,32} or as a peri-operative treatment.³³ We were not able to confirm the findings of Dran and coworkers,²¹ a retrospective study in which patients who received corticosteroids as an adjuvant to surgery had a significantly higher rate of survival than patients without corticosteroid treatment, although the treatment protocol was not strictly comparable (prednisone was initiated at a dose of 0.5 mg/kg/day for one month followed by tapering).

The definition of CSDH recurrence is a key point for better estimation of success and failure rates in the management of CSDH.³⁴ To better illustrate the resolution of the disease, we decided to use a composite criterion

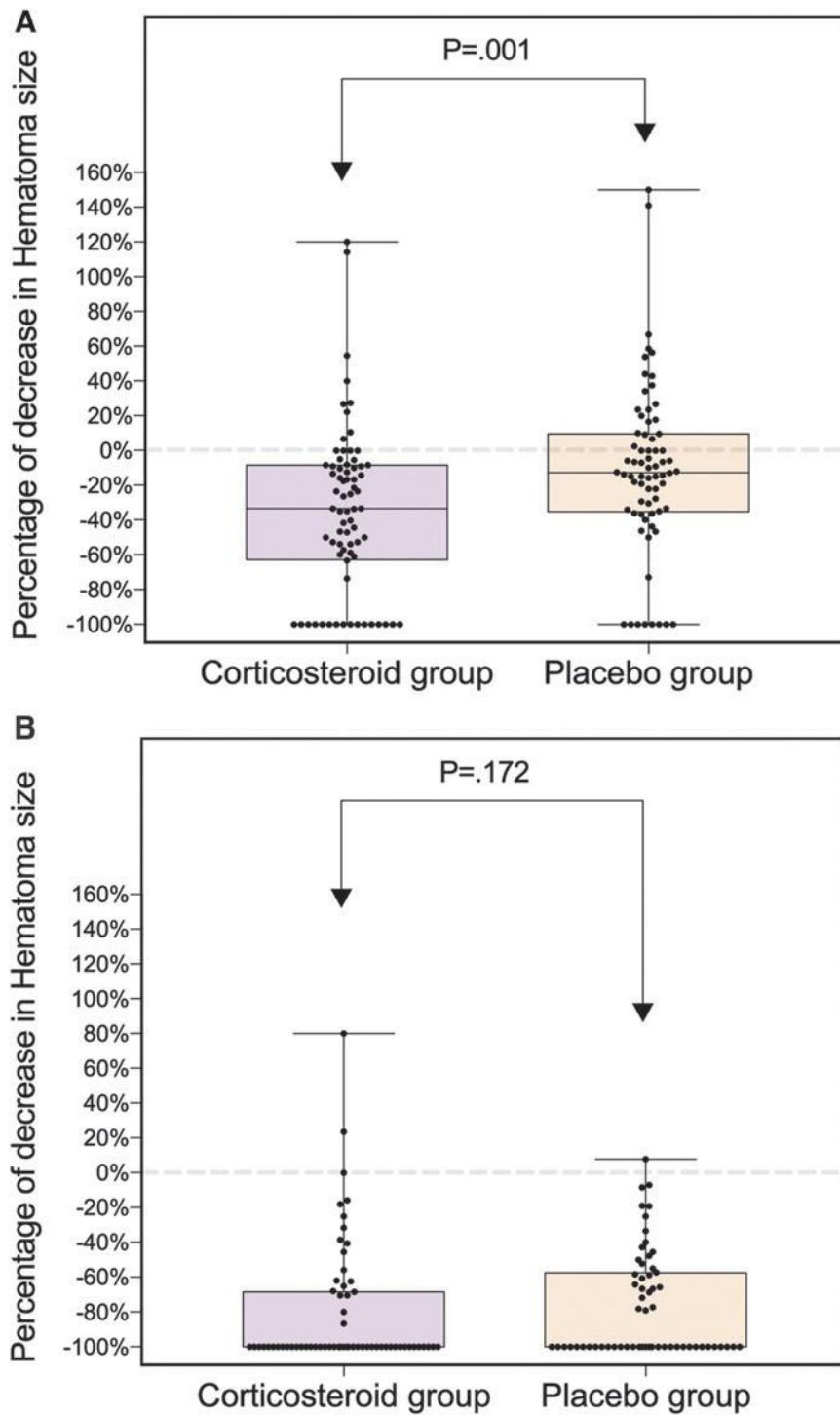


FIG. 3. Percentage of evolution in hematoma size from post-operative assessment to 1 month (A) and 6 months (B) post-surgery. The horizontal line in the boxes indicates the median, the top and bottom of the box indicates the 25th and 75th percentiles, and I bars indicate the extreme upper and lower values. Color image is available online.

Table 5. Markwalder Grading Scale and Nottingham Health Profile Scores at 1 and 6 Months

Outcome	Prednisone group	Placebo group	p
MGS, No. (%)			
1 month ^a			0.77
Grade 0	52 (72.2)	45 (68.2)	
Grade 1	15 (20.8)	17 (25.8)	
Grade 2	5 (7.0)	4 (6.1)	
6 months ^b			0.45
Grade 0	58 (92.1)	52 (86.7)	
Grade 1	5 (7.9)	7 (11.7)	
Grade 2	0 (0.0)	1 (1.6)	
NHP, mean - SD			
1 month ^c			
Energy	39.9 - 37.0	41.3 - 38.7	0.87
Isolation	6.8 - 16.1	7.4 - 16.5	0.70
Pain	9.0 - 18.1	13.2 - 17.5	0.02
Mobility	16.0 - 25.0	21.4 - 23.6	0.09
Emotion	11.3 - 16.2	6.8 - 10.7	0.13
Sleep	28.4 - 32.9	15.7 - 24.6	0.01
6 months ^d			
Energy	25.0 - 32.9	23.8 - 35.1	0.67
Isolation	4.8 - 13.4	6.6 - 18.6	0.78
Pain	8.2 - 16.5	6.6 - 11.0	0.94
Mobility	11.2 - 18.7	12.3 - 19.0	0.87
Emotion	7.3 - 17.3	5.8 - 13.0	0.60
Sleep	13.1 - 22.7	13.9 - 24.8	0.86

MGS, Markwalder Grading Scale; NHP, Nottingham Health Profile; SD, standard deviation.

Each subcategory from Nottingham Health Profile is rated on a total of 100 points. A greater score indicates a lower quality of life.

Patients with data available for analyses were (a) 72 vs. 66, (b) 63 vs. 60, (c) 69 vs. 63, (d) 60 vs. 69 in the prednisone group and placebo group, respectively.

including surgical reoperation and any reaccumulation of CSDH on the basis of immediate post-operative imaging. We considered that the occurrence of a second surgery was insufficient as a single indicator of treatment failure.

In routine clinical practice, a conservative attitude is frequently observed in elderly patients presenting progressive regrowth of CSDH without symptoms or with mild neurological impairment,⁷ with an unknown impact on the clinical management. At this stage, steroid therapy may be used to postpone a potential reoperation,^{22,35} and it can be assumed that clinicians usually delay the resumption of concurrent anticoagulant therapy, leading to additional medical appointments, neuroimaging modalities, and health-related costs. Because there are no guidelines providing decision support in this situation, the therapeutic choice is based mainly on the surgeon's experience, institutional practices, patient age, and comorbidities, and CSDH radiological features.^{31,36}

Finally, the reduction in clinicoradiological recurrence observed during prednisone administration was related mainly to a lower rate of radiological regrowth of residual CSDH during the early post-surgical period. These findings must be tempered, because no long-term clinical benefits were observed and there was a notable level of side effects, an observation already highlighted by the recent findings of Hutchinson and colleagues.²⁴ Therefore, the authors suggest that a shorter treatment duration should be assessed for safety and efficacy in future trials.

Hypertension at 1 month	3 (4.4)	5 (7.6)	0.49
Glycemic disorders at 1 month	0 (0.0)	0 (0.0)	> 0.99
Hypertriglyceridemia	0 (0.0)	1 (1.5)	0.49

Table 6. Main Complications Reported as Possible Adverse Events by Treatment

Complications	Prednisone group N=69 No. (%)	Placebo group N=66 No. (%)	p
Patients with infection ^a	14 (20.3)	17 (25.8)	0.45
Superficial wound infection	1 (1.5)	0 (0)	> 0.99
Subdural empyema	7 (10.1)	5 (7.6)	0.60
Pneumopathy	3 (4.4)	3 (4.6)	0.24
Bronchitis	0 (0.0)	3 (4.6)	0.11
Urinary tract infection	4 (5.8)	4 (6.1)	> 0.99
Tooth infection	0 (0.0)	2 (3.0)	0.49
Vaginal mycosis	1 (1.5)	0 (0.0)	> 0.99
Oral candidiasis	1 (1.5)	0 (0.0)	> 0.99
Herpes simplex	0 (0.0)	1 (1.5)	0.49
Eye infection	1 (1.5)	0 (0.0)	> 0.99
Patients with psychiatric symptoms ^a	26 (37.7)	8 (12.1)	< 0.001
Insomnia	17 (24.6)	6 (9.1)	0.02
Agitation	8 (11.6)	2 (3.0)	0.06
Euphoric mood	0 (0)	1 (1.5)	0.49
Aggression	3 (4.4)	2 (3.0)	> 0.99
Patients with gastrointestinal disorders ^a	7 (10.1)	4 (6.1)	0.39
Gastritis	1 (1.5)	0 (0)	> 0.99
Gastric ulcer	1 (1.5)	0 (0)	> 0.99
Abdominal pain	3 (4.4)	1 (1.5)	0.62
Abdominal pain upper	2 (2.9)	2 (3.0)	> 0.99
Esophageal hemorrhage	0 (0)	1 (1.5)	0.49
Patients with metabolic and general disorders ^a	6 (8.7)	7 (10.6)	0.71
Weight increase	2 (2.9)	0 (0.0)	0.50
Glaucoma	0 (0.0)	1 (1.5)	0.49
Cutaneous rash	3 (4.4)	0 (0.0)	0.24
Patients with ischemic stroke	1 (1.5)	1 (1.5)	> 0.99

*Multiple events may have been reported for a single participant, including multiple events in the same subcategory.

Limitations

The main limitation of these results is that final data analysis was performed at the midpoint of patient inclusions because of early discontinuation of the trial. In addition, the surgical technique was left to the discretion of each participating center and was not stratified. Further, the choice of the perioperative management of antiplatelet and anticoagulant drugs was also left to each recruiting center, although this factor was considered in *post hoc* adjusted analyses. The ideal management of these medications and their impact on CSDH recurrence would certainly require a specific additional study.³⁷

The authors also acknowledge that the safety of the therapeutic protocol used in this study was not formally demonstrated. Psychiatric disorders were more frequent after corticosteroid administration ($n = 26$, 37.7%), which is not insignificant in an elderly population. Among these patients, most reported insomnia ($n = 18$), and some patients had agitation ($n = 11$), although only insomnia occurred significantly more frequently in the corticosteroid treatment group. Nevertheless, these adverse events

appeared reversible, as suggested by the comparable results for the NHP (sleep score) at six months between both groups.

No case of corticosteroid-induced diabetes mellitus was reported during the trial. Although patients had a weekly taper of their prednisone dose, however, glycemic disorders and adrenal insufficiency may have been underdiagnosed because biochemical assessment took place only during the initial hospital stay and at one month post-operatively.

Conclusion

The results of the HEMACORT trial suggest that prednisone as an adjuvant treatment to surgery may reduce early CSDH radiological recurrence, although clinical benefits remain unclear with similar reoperation rates, and similar neurological, functional, and survival outcomes. Additional data are also required to support the safety of this treatment, because a high rate of sleep disorders was transiently observed. In view of these findings, the authors suggest that a shorter treatment duration should be assessed for safety and efficacy in future trials.

Authors' Contributions

NL, HC, and LB designed the study protocol. The HEMACORT Study Group contributed to data collection. SN, HC, JB, HB and NL contributed to data analysis. HB and HC conducted statistical analysis. SN wrote the first draft of the article. All authors helped in interpreting the findings, contributed toward subsequent revisions and approved the submitted article.

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