Are Steroids Useful to Treat Cerebral Venous Thrombosis?

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Background and Purpose—No randomized controlled trial has evaluated the efficacy of steroids in acute cerebral venous thrombosis (CVT). We aimed to analyze the effect of steroids on the outcome of patients in the International Study on Cerebral Veins and Dural Sinus Thrombosis (ISCVT).

Methods—ISCVT is a prospective observational study that included 624 CVT patients. Death or dependence at 6 months was compared between cases (patients treated with steroids) and controls (patients not treated with steroids), using 3 designs: (1) Matched case–control study (each case matched with a control for prognostic factors); (2) Nonmatched case–control study of the ISCVT cohort; (3) Case–control study in different strata according to the number of poor prognostic variables in each patient.

Results—One hundred and fifty (24%) patients were treated with steroids. (1) In the matched case–control study, poor outcome was similar in the two groups of patients (26/146 versus 17/149, OR = 1.7; 95% CI 0.9 to 3.3, \( P = 0.119 \)). (2) In the ISCVT cohort, no significant difference in poor outcomes was found whether patients were treated with steroids or not (26/146 versus 60/469, OR = 1.5; 95% CI 0.9 to 2.4). Patients without parenchymal lesions treated with steroids had worse prognosis than those treated without steroids (8/45 versus 9/184, OR = 4.2, 95% CI 1.6 to 11.6, \( P = 0.008 \)). (3) Treatment with steroids was not associated with a better outcome in any strata of patients according to the number of poor prognostic factors.

Conclusions—Steroids in the acute phase of CVT were not useful and were detrimental in patients without parenchymal cerebral lesions. These results do not support the use of steroids in CVT (evidence level III). (Stroke. 2008;39:105-110.)

Key Words: cerebral venous thrombosis ■ dural sinus ■ steroids ■ treatment

Cerebral venous and dural sinus thrombosis (CVT) is an infrequent disease occurring mostly in young and middle age patients, for which there is poor evidence concerning the best medical management. Anticoagulation is considered the standard treatment in the acute phase of decreasing the risk of poor outcome. Treatment with corticosteroids is an area of uncertainty in CVT management, as shown by the high variation (from 3.3% to 72%) of its use across participating centers in the International Study on Cerebral Veins and Dural Sinus Thrombosis (ISCVT). Although some consider that steroids could decrease vasogenic edema that develops with CVT and reduce intracranial hypertension, others argue that steroids could be harmful because of their potential prothrombotic properties. No randomized controlled trial or case–control study has so far analyzed the efficacy of steroids in this setting.

The aim of our study was to assess the efficacy of steroids in the ISCVT cohort.

Methods

Study Population

This study comprised patients with proven CVT who were included in the ISCVT. The ISCVT study is described in detail elsewhere. Briefly, ISCVT is a prospective multinational observational study that included 624 consecutive adult patients with symptomatic CVT, from 89 centers in 21 countries. The diagnosis of CVT was confirmed by conventional angiography, CT venography, MRI combined with MR venography, or at surgery or autopsy, following established diagnostic criteria.

The choice of the treatment for individual patient was left to the treating physician, but all treatments were listed and systematically recorded.

Data Collection

The following data were obtained in the ISCVT study: demographics; dates of onset of symptoms, hospital admission and confirmation of the diagnosis by imaging; symptoms and signs from onset to diagnosis; Glasgow Coma Scale (GCS) score on admission; location of the thrombus; number, type (edema, infarct or hemorrhage), size, and location of parenchymal lesions; risk factors for CVT; treatment; and outcome. Presenting syndromes were dichotomised as isolated

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intracranial hypertension (any combination of headache, vomiting, and papilloedema with or without visual loss or VI nerve paresis, without other neurological symptoms or signs) and other presenting syndromes. Outcome was classified according to the modified Rankin Scale at discharge at 6 months of follow-up, 1 year, and yearly thereafter. Outcome was classified as independent recovery (complete [mRankin 0 or 1]), incomplete [mRankin 2], and dependence or death [mRankin 3 to 6].

Prognostic Factors of CVT
The following variables were previously reported by us to be predictors of poor prognosis of CVT in a logistic regression model of the ISCVT cohort: age (>37 years), male gender, hemorrhagic lesion at admission CT scan or MRI, deep cerebral venous thrombosis, mental status disturbances, coma (GCS <9), central nervous system infection, and malignancy.

Therapeutical Intervention
Therapeutical intervention was treatment with steroids (any type, dosage, or duration) after the diagnosis of CVT. This information was based in the question “steroid use? Yes or No” and dates of “start/stop” of steroids in the inclusion form.

Outcome
Primary outcome was dependence or death (mRankin 3 to 6) at 6 months of follow-up.

Statistical Analysis
To investigate the effect of steroids in the outcome we performed the following analysis:

Primary Statistical Analysis: Matched Case–Control Study
For each patient treated with steroids a control was retrieved from the ISCVT cohort with the same prognostic variables: age (37 years, male gender, hemorrhagic lesion at admission CT scan or MRI, deep cerebral venous thrombosis, mental status disturbances, coma (GCS <9), central nervous system infection, and malignancy.

We compared the outcome of cases treated with steroids with controls with the χ² test (with Yates correction when necessary). A difference between the groups was considered significant if P<0.05. We calculated the odds ratio (OR) and 95% CI, as estimates of the relative risk between the 2 groups. Anticoagulant therapy was compared between the 2 groups.

An additional sensitivity analysis compared the outcome measure in the 2 groups after excluding patients when the decision to treat with steroids could have been influenced by the underlying disease (vasculitis, inflammatory disease, malignancy, and infection).

Secondary Statistical Analysis: Nonmatched Case–Control Study of the ISCVT Cohort
We compared the outcome of patients treated or not treated with steroids using the χ² test (with Yates correction when necessary). A difference between the 2 groups was considered significant if P<0.05. We calculated the OR and 95% CI. Distribution of poor prognostic variables, risk factors for CVT, parenchymal lesions on admission CT scan or MRI, and anticoagulant therapy in therapeutic dosage was compared between treatment groups.

A logistic regression analysis (backwards method) was repeated to identify the independent predictors of death or dependence at 6 months and the variable “steroid treatment” was forced in the list of covariates. Variables previously known as prognostic factors were selected to the logistic regression.

Case–Control Study in Different Strata According to the Number of Poor Prognostic Variables
The probability of having a poor outcome at 6 months increases with the number of variables of poor prognosis in each patient, mainly the 3 outcome predictor variables with an OR higher than 2 in the multiple regression analysis: mental status disorder, GCS <9, and deep CVT. Malignancy was not included because it could be the direct cause of death or dependence. We stratified patients into 3 strata, according to the number of poor prognostic factors (0, 1, >1). For each stratum we compared the outcome of patients treated or not treated with steroids, using the χ² test (with Yates correction when necessary). A difference between groups was considered significant if P<0.05. We calculated the OR and 95% CI.

Sensitivity Analysis
Because the effect of steroids in decreasing vasogenic edema could be different in the presence of blood-barrier breakdown, we performed sensitivity analysis to compare the outcomes in patients: (1) with and without parenchymal lesions on CT scan or MRI at admission; and (2) with the clinical presentation of isolated intracranial hypertension.

Results
Six hundred twenty-four adult patients were included in the ISCVT. Patients were more often female (74.5%), with a median age of 37 years; 22% had mental status disturbance, 10.9% deep CVT, and 5.2% were in coma (GCS <9) at admission. 22.9% of patients presented with isolated intracranial hypertension, 62.9% of patients had parenchymal lesion, and 39% of patients had hemorrhagic lesion on admission CT or MRI. Acute case fatality was 4.3%. At 6 months of follow-up 14% of patients were dead or dependent.

One hundred fifty (24%) patients were treated with steroids. Median duration of steroids treatment was 11 days (mean 16 days, SD 17 days). 25% of patients treated with steroids had isolated intracranial hypertension, 69.3% had parenchymal lesion on CT scan or MRI at admission, 6% died in the acute phase of CVT, and 17.8% were dead or dependent 6 months after CVT.

Primary Statistical Analysis: Matched Case–Control Study
For this analysis we compared the outcome between 150 cases and 150 matched controls.

The outcome was similar between cases and controls (Table 1). There was no significant difference in the proportion of anticoagulated patients in both groups (P=0.071). A
trend toward poorer prognosis was found in the subgroup of patients treated with steroids without lesion on the CT or MRI (Table 1).

No significant difference was found in the poor outcome of patients treated with steroids with (5/33 [15%] versus 2/31 [6.5%], OR = 2.6, 95% CI 0.5 to 14.5, P = 0.4) or without isolated intracranial hypertension (21/113 [18.6%] versus 15/118 [13%), OR = 1.6, 95% CI 0.8 to 3.2, P = 0.2).

Because decision to use steroids could have been influenced by the underlying pathology, we repeated the analysis excluding all patients with vasculitis, malignancy, inflammatory disease, and infection. This left 102 cases and 102 controls. Again, no difference in the 6th month outcome was found between patients who did or did not use steroids (P = 0.774).

Secondary Statistical Analysis

Nonmatched Case–Control Study of the ISCVT Cohort

For this analysis we compared the outcome of 150 cases with that of 474 controls. Patients with “vasculitis” and “inflammatory disease” were more often treated with steroids. No other differences were found between patients treated or not treated with steroids (Table 2). No difference in the number of dead or dependent patients was found at 6-month follow-up between those treated or not treated with steroids (26/146 [17.8%] versus 60/469 [12.8%], OR = 1.5, 95% CI 0.9 to 2.4, P = 0.127). The variable “steroids treatment” was not retained in the logistic regression analysis model as an independent predictor of outcome at 6 months of follow-up.

No benefit was found for the subgroup of patients with parenchymal lesions on CT or MRI treated with steroids compared with patients with parenchymal lesions not treated with steroids (18/101 [17.8%] versus 51/284 [18%], OR = 0.9, 95% CI 0.6 to 1.8, P = 0.98). The subgroup of patients without parenchymal lesions treated with steroids had a poorer outcome at 6 months (8/45 [17.8%] versus 9/184 [4.9%], OR = 4.2, 95% CI, 1.6 to 11.6, P = 0.008).

Patients with the clinical presentation of isolated intracranial hypertension treated with steroids had a trend toward a poorer outcome (5/33 [15.2%] versus 5/110 [4.5%], OR = 3.8, 95% CI 1.0 to 13.9, P = 0.088).

Because of the small number obtained in the 2 last strata we merged 2 and 3 PPF in the same group. For each stratum, death or dependence at 6 months was similar whether patients were treated or not treated with steroids (Table 3). No difference in the use of anticoagulation was found for each stratum between patients treated or not with steroids.

In the subgroup of patients without lesions on the CT or MRI, treatment with steroids was associated with a worse prognosis in the stratum of patients without any poor prognostic factor (7/39 [17.9%] versus 6/163 [3.7%], OR = 5.7, 95% CI 1.8 to 18.2, P = 0.004). For the other strata, no significant differences were found according to the presence of lesion on the CT or MRI.
Discussion

Cerebral venous thrombosis is an infrequent disease. This explains to a large extent the paucity of randomized controlled trials evaluating the efficacy and safety of treatments in the acute phase. CVT treatment focuses on 2 types of interventions: (1) dissolution of the thrombus, and (2) decreasing intracranial hypertension. Only 2 randomized controlled trials (RCT) have examined the efficacy of anticoagulant therapy. The meta-analysis of the 2 trials shows a 6% relative risk reduction of death or dependency on anticoagulants compared with placebo. Two other trials including 57 and 40 patients performed in India were not included in the meta-analysis, because the diagnosis of CVT was confirmed by CT and only abstract information was available. Both favored heparin: 15% versus 40% mortality in the Maiti trial and recovery in all heparin-treated patients contrasting with 2 deaths and 1 patient with a residual hemiparesis in the control group in the Nagajara trial.

No randomized controlled trial was performed concerning treatment for intracranial hypertension. In particular, the efficacy of steroids in the acute phase of CVT has not been studied previously in a RCT. Neither have we found case–control studies analyzing the effect of steroid treatment on the outcome of CVT. Therefore, this remains an area of treatment uncertainty, as was shown by the wide variation in steroid prescription among participants in the ISCVT.

Although cytotoxic edema may contribute to cerebral edema in CVT, as recently shown by MRI studies and in experimental animal models, venous thrombosis is associated mainly with a combination of vasogenic and cytotoxic edema. Therefore corticosteroids may theoretically have a beneficial effect in patients with CVT. On the other hand they may be harmful, by not only promoting thrombosis or inhibiting thrombolysis, but also by producing severe complications, including gastrointestinal bleeding, infection, avascular osteonecrosis, or exacerbation of, or de novo induction, hyperglycemia. Indeed, several cases of CVT occurring after corticosteroid treatment have been reported, again suggesting that they can be potentially harmful.

Because of this controversy we decided to analyze the data available in the ISCVT cohort and to study the effect of steroids on outcome. ISCVT was an observational study and was not designed to study the effect of treatments, which were prescribed according to the decision of the investigators. One problem that can arise from a nonrandomized study is that allocation of treatment could be influenced by noncontrolled factors that are themselves associated with the prognosis. In the ISCVT we found that there was wide variation in steroids use. The main variables influencing steroids allocation were country/center and not the characteristics of the patients (except for etiology), as illustrated by the balance we found in the distribution of patient characteristics including baseline severity and frequency of poor prognostic factors, lesions on CT, and anticoagulation between treatment groups.

We used 3 different and complementary methodological statistical designs to increase the strength of the results: a matched case–control study, adjustment for the variables associated with poor outcome in the cohort, and stratification according to the number of variables of poor outcome. With these methods we intended to have patients with similar characteristics in both treatment arms. We added the third design to overcome possible “overmatching”, which could result from case–control allocation. With these complementary analyses we have shown that steroids in the acute phase of CVT were not associated with improvement in outcome.

Because a steroid effect on decreasing vasogenic edema could be present, we looked at subgroups of patients with hemorrhagic infarcts or parenchymal edema. Even in patients with lesions in CT or MRI, who theoretically could have had greater benefit from steroids, we did not find any added benefit for steroids. On the other hand, steroid treatment was associated with a trend toward a worse prognosis in cases without lesions on CT or MRI.

In addition to its nonrandomized and nonblinded design, this study has other limitations. We did not register systematically the type, route of administration, and dosage of steroid therapy. We do not have information about safety and complications associated with treatment with steroids. Furthermore, we cannot exclude that we were not able to reveal a significant difference between cases and controls in the analyses performed because of the sample size. To demonstrate a significant difference in outcome between the 2 treatments, having a power of 80%, and a probability of α error type of 5%, we would need at least 312 cases in the matched case–control study and 532 cases in the first nonmatched analysis. In both analyses, however, the benefit would be for patients not treated with steroids. On the other hand, we cannot also exclude that the results suggesting that steroids might be deleterious to patients without cerebral lesions on CT may be related with a false-positive result because of small numbers, as reflected in the large 95% confidence interval.

Despite these methodological limitations, this study is the first to report information about the effect of steroids in the treatment of CVT. Its results may have clear implications for clinical practice:

1. The study provides no evidence to support the routine use of steroids in the acute phase of CVT (evidence level III), except if indicated for the treatment of the underlying disease.
2. Steroids can be harmful and should be avoided in CVT patients without CT or MRI parenchymal lesions (evidence level III).

The benefit of corticosteroids has not been proven in the medical treatment of ischemic or hemorrhagic cerebrovascular diseases, although large RCTs are lacking. Further animal studies and use of cerebral imaging techniques are required to fully understand the pathophysiology of parenchymal injury in cerebral venous thrombosis, and eventually to test the effect of steroids in animal models of CVT.

Appendix

List of Participants

The following centers and investigators participated in the ISCVT (International Study on Cerebral Vein and Dural Sinus Thrombosis). The number of patients included at each center is given in parentheses.
Hôpital Lariiboisiére Paris, France (49, M.G. Bousser and I. Crassard); Instituto Nacional de Neurología y Neurocirugía, México City (42, F. Barrinagarrementeria and C. Cantú); Hospital das Clínicas da Universidade de São Paulo, Brazil (30, A. Massaro and E. Camargo); Hospital de Santa Maria Lisbon, Portugal (28, J.M. Ferro, P. Canhão, T.F. Melo); Centre Hospitalier Régional et Universitaire de Lille, France (27, D. Levy, M.A. Mackowick-Cordoliani, and O. Godefroy); Centre Hospitalier Universitaire- Hôpital Central Nancy, France (22, X. Ducrocq and J.-C. Lacour); Hospital São Marcos Braga, Portugal (17, J. Fontes, J. Figueiredo, E. Lourenço, and R. Maré); Hospital Egas Moniz Lisbon, Portugal (16, M.V. Baptista and I. Palma); Hospitais da Universidade de Coimbra, Portugal (15, M.A. Ferro, M.C. Macário and B. Rodrigues); Universidade Heidelberg, Germany (15, W. Hacke and C. Berger); University of Giessen, Germany (14, E. Stolz and T. Gerriets); Academic Medical Centre Amsterdam, The Netherlands (13, J. Stam); CHU-Dijon, France (11, M. Giroid and S.-E. Meherbi); Parma University, Italy (12, U. Scoditti and G. Buccino); University Hospital of Lund, Sweden (11, A. Lindgren); Escola Paulista de Medicina de São Paulo, Brazil (10, M.M. Fukushima); Hospital Geral de Santo António Porto, Portugal (10, G. Lopes, M. Correia, A.M. Silva and C. Correia); Neurologische Klinik Charité Berlin, Germany (10, K. Einhäupl, J.M. Valdueza and M. Weihe); Institut Català de la Salut - Ciutat Sanitària i Universitària de Bellvitge Barcelona, Spain (10, F. Rubio and M. Jato); Hospital Civil de Guadalajara, Mexico (10, J.L. Ruiz Sandoval); Hospital Garcia de la Horta, Almada, Portugal (9, F. Pita); Hôpital D’Adultes de la Timone Marseille, France (9, L. Manuel); IRCSS Policlinico San Matteo Pavia, Italy (9, M. Martinelli); and F. Lussana); University Hospital Gasthuisberg Leuven, Belgium (8, R. Vandenberghe); Ospedale Niguarda Ca’Granda Milano, Italy (8, R. Sterzi and A. Ciccone); Instituto de Neurocircugia Santiago, Chile (8, P. Lavados); University of Pennsylvania Medical Center, USA (8, S.E. Kasner, B. Cucchiara and D.S. Liebeskind); University of California at Los Angeles, USA (2, S. Sen); University of Texas Southwestern Medical Center, USA (2, S. Lavados); University of Pennsylvania, USA (8, R. Vandenberghe); University of Oxford, UK (8, R. Sterzi and A. Ciccone); Hospital de Clínicas-Universidad de Montevideo, Uruguay (1, J. Altamirano and F. Solis).

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**Disclosures**

None.

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