FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Ana Luisa Carvalho Rocha

Avaliação do prognóstico das Tromboses Venosas Cerebrais

março, 2014

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

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Avaliação do prognóstico das Tromboses Venosas Cerebrais

Mestrado Integrado em Medicina

Área: Neurologia

Trabalho efetuado sob a Orientação de:
Doutora Marta Maria de Pinho Dias Oliveira Carvalho Monteiro

Trabalho organizado de acordo com as normas da revista:
International Journal of Stroke

março, 2014

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UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

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Ana Luísa Carvalho Rocha

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13746523	ana_rocha99@hotmail.com	913773325

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
080801020	16/03/2014

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Dedico este trabalho aos meus pais, ao meu irmão e aos meus avós.

Title: Prognostic evaluation of cerebral vein and dural sinus thrombosis

Authors: Ana Rocha[1], Helena Rocha[1,2], Marta Carvalho[1,2]

Affiliations:

1 –Faculty of Medicine, University of Porto, Porto, Portugal;

2 - Department of Neurology, Centro Hospitalar de São João, Porto, Portugal

Address of all authors:

Ana Rocha (corresponding author)

Serviço de Neurologia

Faculdade de Medicina do Porto

Alameda Prof. Hernâni Monteiro

4200-319 Porto

Portugal

ana_rocha99@hotmail.com

Helena Rocha

Serviço de Neurologia

Hospital São João

Alameda Prof. Hernâni Monteiro

4200-319 Porto

Portugal

helen.roch@gmail.com

Marta Carvalho

Serviço de Neurologia

Hospital São João

Alameda Prof. Hernâni Monteiro

4200-319 Porto

Portugal

martacv@med.up.pt

Key Words: cerebral venous thrombosis, prognosis, risk factors

Word Count: 2 642

No conflicts of interest declared.

Abstract

Background: Although the overall outcome of cerebral vein and dural sinus thrombosis (CVT) is good, about 25% of patients develop complications, and mortality rate is 3-15%. Identification of prognostic factors is crucial for selecting the proper treatment for each case (aggressive versus conservative). A risk score comprising six clinical variables with different hazard ratios was proposed by Ferro *et al*, 2009, to predict CVT outcome. Aims: to evaluate the ability of this score in predicting the prognosis of our CVT patients. Methods: retrospective analysis of consecutive adult patients admitted with CVT from 2006 to 2012 in our tertiary hospital, with at least 6 months of follow up. The prognostic variables and score were analysed and compared with outcome at six months, using a simplified regression model (R>0.5 suggesting a strong relationship). Results: 59 patients; 83.1% females; mean age: 40.1 years-old. The value of R between the result of the weighted risk scale and outcome was 0.344. When the 6 variables were combined but not weighted, and compared with outcome, R value was 0.548. For the combination of “malignancy”, “intracranial haemorrhage on admission” and “thrombosis of deep venous system” the R value was 0.523. There was no significant correlation between other variables independently or combined. Conclusions: In our population, the proposed risk score did not show a strong correlation with prognosis. However the combination of intracranial haemorrhage, malignancy and thrombosis of deep venous system had a stronger correlation with outcome, being probably the most important predictive factors in clinical practice.

Introduction

Cerebral venous and sinus thrombosis (CVT) is an uncommon form of cerebrovascular disease, representing only 0.5 to 1% of all strokes[1], with an incidence estimated at 2 to 5 per 1 million[2]. It affects mostly young people, although it can happen at any age[3-5], and women are more likely to suffer from CVT, with a female/male ratio of 3 to 1[4].

CVT diagnosis can be difficult, not only because of the low incidence, but also because it may present with a wide variety of symptoms, which may be categorized in two main syndromes: signs of acute focal brain injury due to venous infarct, edema or hemorrhage; or more insidious symptoms of increased intracranial pressure. The diagnosis is usually based on magnetic resonance imaging with magnetic resonance venography, although contrast-enhanced computed tomography or CT venography may also help in the diagnostic process[6].

The basis of the treatment of an acute CVT is anticoagulation, with unfractionated heparin or low molecular weight heparin[7]. Some complications demand specific treatment. In case of seizures, antiepileptic drugs are effective[8]. Intracranial hypertension may be treated with acetazolamide[9], mannitol along with hyperventilation[10, 11], serial lumbar punctures or lumboperitoneal shunt[12]

In more serious cases of CVT, more aggressive measures may be necessary. In the presence of clinical deterioration or elevated intracranial pressure, local thrombolytic therapy may improve recanalization [13]. Descompressive craniectomy is sometimes used in cases of lesions producing mass-effect and clinical deterioration, with good rates of clinical recovery[14].

In order to prevent CVT recurrence, some patients may have indication for long term anticoagulation, depending on the risk factors, namely the presence of inherited or acquired thrombophilia.

Although most patients have a good prognosis, 5% die in the acute phase [15, 16]. In long term follow up, mortality and morbidity rates are about 15%[4, 17]. In the acute phase, the main complications are hydrocephalus, intracranial hypertension and seizures including status epilepticus[6], and patients die primarily due to neurological complications, being the main cause of early mortality transtentorial herniation[15]. Late possible complications are recurrent CVT, chronic headaches, epilepsy, visual loss and the development of dural arteriovenous fistula[6]. Late deaths are mainly due to underlying conditions, like malignancy[6]. Early diagnosis and treatment are essential to decrease the risk of permanent neurological impairment and death. Therefore it is very important to identify patients with worse prognosis, so that they can be provided with close vigilance and more aggressive treatment. On the other side, identification of patients with a better prognosis is relevant so that more aggressive diagnostic and therapeutic procedures are avoided.

Some poor prognostic factors have been consistently appointed: depressed consciousness or coma, mental status disturbance, thrombosis of the deep venous system, right hemisphere hemorrhage, posterior fossa lesion [15], involvement of the straight sinus [18], neurological deficit and severity, encephalopathy [19], venous infarction, the existence of an underlying coagulopathy or hereditary thrombophilia [20], hemiparesis, intracranial hemorrhage, seizures, central nervous system infection, any malignancy, age >37 years and male gender[4].

Recently, six prognostic factors related to worse outcome at six months were described in a sample of CVT patients. These factors are: underlying malignancy, presentation as coma, thrombosis of the deep venous system, presentation as mental status disturbance, male gender and intracranial hemorrhage[17]. These prognostic factors where combined in a weighted risk score, in which each variable was punctuated as 1 or 2 depending on the hazard ratios. Malignancy, coma and thrombosis of the deep venous system had a punctuation of 2 and the others punctuated 1. According to this risk score, if the total punctuation is greater than 2 then the patient is considered to have a poor outcome prognosis.

It is of a great importance to validate this score in daily practice so that it can become a routine tool in the evaluation of CVT patients.

Aim

The objective of this study was to test the scale in a Portuguese population of CVT patients, and evaluate the impact of the scale and the prognostic factors individually in the prediction of the outcome of our patients.

Methods

We conducted a retrospective study of adult patients with a final diagnosis of CVT admitted to the Neurology Department of Hospital de São João, Porto, Portugal, between the years of 2006 and 2012. Those without follow up at 6 months were excluded. Demographic, clinical, radiological, etiological and prognostic data were collected. Outcome was evaluated at 6 months, and classified as good when modified Rankin Scale (mRS) was between 0 and 2, and as bad when mRS was greater than 2.

The presence of each one of the six risks factors previously mentioned[17] was evaluated and the proposed risk score was applied. The correlation of the outcome with the weighted risk score, as well as with each variable independently or simply combined was measured. The data were analyzed by using Statistical Package for the Social Sciences version 21 (SPSS 11.5 for Windows, Chicago, IL, USA). For continuous variables, means and standard deviations were calculated. For categorical variables, numbers and percentages for each category were tabulated. In order to assess the relationship of the mentioned risk factors for bad outcome with the prognosis, simple linear correlation was calculated between the outcome of the patients and the proposed variables individually or combined in the score. Statistical significance level was accepted as $p < 0.05$, and the R value was considered relevant when greater than 0.5.

This study was approved by the Hospital's Ethics Committee.

Results

A total of 59 patients were included. The median age at presentation was 40.1 years (19-73), and 83.1% were female.

The most common symptom at presentation was headache (table 1)(78% of patients). Time from symptoms' onset to diagnosis is shown in table 2, but only 33.9% of the patients had symptoms for more than one week. Most of the patients (69.5%) had affection of multiple sinuses (table 3). The most common risk factors (table 4) were estrogen-containing drugs (44.1%), genetic prothrombotic conditions (42.4%) and acquired prothrombotic conditions (33.9%). The treatment received is described in

table 5. Most of the patients were treated with low molecular weight heparin (49.2%) in the acute phase.

Analyzing the outcome at 6 months, 8.5% of our patients had a bad outcome (mRS greater than 2).

Concerning prognostic factors included in the score, 27.1% of the patients presented with mental status disturbance, 16.9% were male, 8.5% had intracranial hemorrhage, 8.5% had an underlying malignancy and 5.1% had thrombosis of the deep venous system (table 6). None of our patients presented with coma. When we applied the weighted score, 8.5% of the patients had a score greater than 2, predicting a bad prognosis.

In the simple linear regression between the weighted risk score and the actual outcome, the R value was 0.344. On the other side, analyzing all the prognostic variables simply combined (not weighted as in the risk score) compared with the outcome, the R value was 0.548.

When the individual variables were compared with the score, only three of them were significantly related to the prognosis. The presence of hemorrhage at presentation, compared with the outcome, had an R value of 0.344, as well as the presence of a underlying malignancy. When both are taken in account, the R value was 0.459. The combined presence of hemorrhage, malignancy and thrombosis of the deep venous system showed an R value of 0.523 and the other variables showed no significance (table 7).

Discussion

The identification of CVT patients with a worse prognosis is very important in clinical practice, having in mind the existence of more aggressive treatments, from which most patients would not obtain any additional benefit, but that can be useful in those patients whose clinical status is more likely to deteriorate. Many studies tried to identify the factors of bad prognosis, and the more consensual factors were combined in the score above mentioned [17], which we applied retrospectively to our population. According to our data, the correlation between the weighted prognostic risk score and the outcome was weak. On the other hand, taking in account all the prognostic variables proposed but not combined in the weighted score, a stronger correlation was found. When the variables where compared individually with the outcome, only three of them were significant: the presence of hemorrhage at presentation was the one that had a better correlation with the outcome of our patients, with the same R value as the whole risk score. When there was an underlying malignancy and the thrombosis of the deep venous system was summed to the presentation with hemorrhage, a higher correlation was found, although it was still not very strong. One of the main problems about CVT studies is the fact that its very low incidence makes it difficult to have big samples. Besides that, most of the patients have good prognosis, and the risk factors proposed in the score are not common. All these factors may have contributed to the weak correlation found in our study between the score and the prognosis. It is also possible that our population had different characteristics when compared to the populations used to validate the original score, and the relative importance of risk factors may be different, being the presentation with hemorrhage, thrombosis of deep venous system and the existence of an underlying malignancy more important than the other variables. It is also

possible that other risk factors not included in the primary study may be more relevant. The fact that this was a retrospective study may also have influenced the results we obtained.

Taking into account our results, we suggest that more aggressive management decisions should probably be taken in CVT patients with intracranial hemorrhage, particularly when an underlying malignancy is present and the thrombosis occurs in the deep venous system.

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Table 1: Symptoms at presentation

Symptoms at presentation	Prevalence (%/n)
Headache	78% (46)
Papilledema	30.5% (18)
Motor deficit	23.7% (14)
Sensitive deficit	23.7% (14)
Acute symptomatic seizures	22% (13)
Visual disturbance	20.3% (12)
Aphasia	16.9% (10)

Table 2: Time from symptoms' onset to diagnosis

Time from symptoms' onset to diagnosis	Prevalence (%/n)
< 24 hours	20.3% (12)
2 to 4 days	23.7% (14)
5 to 7 days	15.3% (9)
> 7 days	33.9% (20)
Unknown	6.8% (4)

Table 3: Affected sinuses

Affected sinuses	Prevalence (%/n)
Superior sagittal	8.5%(5)
Sigmoid	8.3%(5)
Transverse	6.8%(4)
Cortical Veins	5.1%(3)
Straight	1.7%(1)
Combined	69.5%(41)

Table 4: Risk factors

Risk factors	Prevalence (%/n)
Estrogen-containing drugs	44.1%(26)
Genetic prothrombotic factor	42.4%(25)
Acquired prothrombotic factor	33.9%(20)
Cephalic infection (otitis, mastoiditis, sinusitis)	22%(12)
Thyroid pathology	8.5%(5)
Previous CVT	5.1%(3)
Family history of venous thrombosis or thrombophilia	5.1%(3)
Pregnancy/puerperium	3.4%(2)
Systemic infection	3.4%(2)

Table 5: Treatment

Treatment	Prevalence (%)
Low molecular weight heparin	49.2%(29)
Non-fractionated heparin	39%(23)
Vitamin K antagonists	6.8%(4)
No treatment	5.1%(3)

Table 6: Prognostic factors at admission

Prognostic factors at admission	Prevalence (%/n)
Mental status disturbance	27.1%(16)
Male sex	16.9%(10)
Intracranial hemorrhage	8.5%(5)
Malignancy	8.5%(5)
Thrombosis of deep venous system	5.1%(3)
Coma	0%(0)

Table 7: Correlation between risk score prognostic variables and poor outcome

	R Value
Weighted risk score	0.344
Score variables simply combined (not weighted)	0.548
Malignancy	0.344
Intracranial hemorrhage	0.344
Thrombosis of deep venous system	0.207
Male sex	0.025
Mental status disturbance	-0.049
Malignancy + intracranial hemorrhage	0.459
Malignancy + mental status disturbance + thrombosis of deep venous system	0.523

Agradecimentos

Agradeço aos meus pais por sempre me apoiarem e me darem força nos momentos mais difíceis.

Agradeço ao meu irmão por, apesar de todas as zangas, ser a pessoa mais importante da minha vida, e estar sempre pronto para aquele abraço quando preciso dele.

Agradeço aos meus avós paternos, por me criarem, e por serem eles que sempre me incentivaram a ser médica, e me ensinaram que esta é a profissão mais bonita do mundo.

Agradeço aos meus avós maternos por sempre me acarinharem e serem pessoas tão especiais.

Agradeço a todo o resto da minha família, porque mesmo que os veja poucas vezes, quando estamos juntos é sempre uma festa.

Agradeço a todos os meus amigos, por existirem, por serem parte da minha vida, e me terem proporcionado momentos que vão ficar para sempre na memória.

Agradeço à Dra. Helena, por me ter fornecido os dados e por ter estado sempre disponível quando eu precisei de ajuda.

E por último mas não menos importante, agradeço à minha orientadora. Obrigada por toda a disponibilidade, pelos e-mails respondidos na hora, por atender sempre às minhas dúvidas por mais ilógicas que fossem, pelas oportunidades que me proporcionou e pelos conselhos que me deu, relacionados com este trabalho e muito para além disso. Obrigada Dra. Marta.

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Text
Typically this type of piece will have headings; however, the authors are encouraged to adopt their own style, please refer to previous editions of the International Journal of Stroke.

References Please refer to references section.

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No more that 250 words
• Rationale
• Aims and/or hypothesis
• Design
• Study outcome(s)
• Discussion

Introduction and rationale

Methods
• Design
• Patient population - inclusion and exclusion criteria
• Randomization
• Treatment or intervention
• Primary outcomes
• Secondary outcomes
• Data Monitoring Body
• Sample size
• Statistical analyses
• Study organization and funding Discussion This section is to contain the thoughts and rationale behind important points of study set-up.

Summary and conclusions

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Abstract
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• Background
• Aims and/or hypothesis
• Methods
• Results
• Conclusions

Text
Introduction
Aims and/or hypothesis
Methods
Results
Discussion
References

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Standard journal
Siebke H, Breivik H, et al. Survival after 40 minutes submersion without cerebral sequel. Lancet 1995;1:1275-7.

Section of a book
Talley NJ, O'Connor S. Clinical Examination. 5th ed. Minnesota: Churchill Livingstone, 2005;114-17.

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Buckley WE, Nunn T. A rational response to the threat of bioterrorism. In: Plant GW, Blair A, Winston JH Jnr, editors. Primary care in the third millennium. Washington: R McGeddon Inc., 2006;457-72.

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Drug-interactions.com [homepage on the Internet]. Indianapolis: Indiana University Department of Medicine; 2003 [updated 17 May 2006; cited 30 May 2006]. Available from: http://medicine.iupui.edu/flockhart/

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Contact us

Editor-in-Chief – Geoffrey Donnan - gdonnan@unimelb.edu.au
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Associate Editor – Professor Peter Rothwell - peter.rothwell@clinical-neurology.oxford.ac.uk

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3. Always write and edit your work so that nothing can be misunderstood.
4. Say what you mean to say, clearly and simply.
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6. Use short paragraphs.
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10. Use verbs for action.
11. Avoid clichés and jargon.
12. If in doubt, leave it out.