Interim result analysis of the ongoing registry on Decompressive Surgery in Cerebrovenous Thrombosis – Part 2 (DECOMPRESS – 2)

Multicentric International Prospective Cohort Study

Análise intercalar dos resultados do registo sobre Cirurgia Descompressiva na Trombose Venosa Cerebral – Parte 2 (DECOMPRESS – 2)

Estudo de Coorte Prospectivo de base Multicêntrica Internacional

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Abstract

Background and purpose: Previous retrospective studies seem to indicate that decompressive surgery in context of cerebral venous and dural sinus thrombosis is a life-saving procedure in patients at high risk for transtentorial herniation. An interim analysis of the ongoing prospective registry for Decompressive Surgery in Cerebrovenous Thrombosis was performed in order to identify potential outcome predictors and assess for the feasibility of a larger registry.

Methods: Patients were included in a multicentric prospective cohort with pre-specified eligibility criteria. Primary endpoint was defined as death or dependency at 6 months follow-up, and two other secondary endpoints were chosen to differentiate effects on short and long-term outcomes: deaths within 30 days after symptom onset; and late deaths or dependencies at 6 months follow-up.

Results: Twenty-two participants were enrolled from 8 different countries. Mortality at 6 months was of 23.8%, whereas death or dependency rate for the same period reached 57.1%. A primary endpoint predictor with significant effect in the short-term outcome was new haemorrhagic transformation before first neurosurgical intervention (*P*=0.029), while overall outcome predictors with significant influence on the long-term were: post-operative complication with an extracranial infection (*P*=0.016); and smaller bone flap sizes during craniectomy (*P*=0.044).

Conclusions: The low mortality rates with decompressive surgery continue to support the indications for this procedure. Defining an appropriate size for decompressive craniectomy, as well as strategies to minimize haemorrhagic transformation events could further improve patients' outcome.

Resumo

Enquadramento teórico e objectivos: A cirurgia descompressiva na trombose venosa cerebral tem-se afirmado cada vez mais como um procedimento *life-saving* em doentes com risco de desenvolver herniação transtentorial. Neste sentido fez-se uma análise intercalar do registo sobre Cirurgia Descompressiva no contexto desta entidade clínica, com o objectivo de identificar potenciais variáveis preditoras do prognóstico, bem como aferir sobre a viabilidade de se proceder a um registo de grande escala.

Métodos: Procedeu-se a uma coorte prospectiva de base multicêntrica internacional com critérios de selecção previamente definidos. O indicador principal do prognóstico foi definido como a ocorrência de morte ou dependência aos 6 meses de seguimento, enquanto dois indicadores secundários foram escolhidos para distinguir se o poder preditor das variáveis se verificava essencialmente para o curto ou longo prazo. Esses indicadores foram: morte dentro do período de 30 dias após o início dos sintomas; e morte tardia ou dependência aos 6 meses.

Resultados: Vinte e dois doentes de 8 países foram incluídos. A mortalidade aos 6 meses foi de 23.8%, enquanto a proporção de mortes ou dependência foi de 57.1%. Dos preditores gerais do prognóstico que foram também significativos para o curto termo, destaca-se a ocorrência de transformação hemorrágica antes da primeira intervenção neurocirúrgica (P=0.029), enquanto para os que tiveram efeito concomitante no longo termo se salienta: complicação pós-operatória com infecção extracraniana (P=0.016) e retalho ósseo de menor dimensão produzido aquando da craniectomia (P=0.044).

Conclusões: A taxa de mortalidade associada à cirurgia descompressiva continua a suportar a indicação para execução deste procedimento. Consideramos que a melhoria prognóstica destes doentes passa por definir um limite mínimo para a extensão da craniectomia descompressiva, bem como desenvolver estratégias para minimizar a ocorrência de transformação hemorrágica.

Introduction

Cerebral venous and dural sinus thrombosis (CVST) are rare forms of stroke, that usually appear to affect more frequently young adults and children [1]–[3]. Although most patients with CVST have favourable clinical outcomes, a proportion of these (13-25%) are at high risk for early death or dependency in the long-term [1], [4]. Acute deaths are mainly attributed to transtentorial herniation, as a consequence of large venous infarction and intraparenchymatous haemorrhage [5], [6]. Recent evidence has been published about the benefits of decompressive surgery in the outcome of these patients and, presently, it is considered a life-saving procedure associated with good functional outcome [7]. Nevertheless, scarce information has been published in the matter of outcome assessment of this group of patients, and most of it comes from uncontrolled retrospective studies. Our aim with this investigation is to produce an interim analysis of the ongoing registry for *Decompressive Surgery in Cerebrovenous Thrombosis*, in order to identify potential outcome predictors and verify if post-operative decompressive surgery outcomes justify the investment in proceeding with a large case series registry.

Patients and Methods

Study design

This study is a multicentric international prospective cohort which includes patients from different medical centres around the world. In order to do this, a formal invitation was made to previous active investigators on the area of cerebral venous and sinus thrombosis and to any other medical doctor that may have been considered or manifested interest in CVST and neurointensivism. Patient inclusion in the study assumes an accomplishment of the eligibility criteria, which are subsequently described. The maximum follow-up period was 12 months, with periodic clinical assessments occurring preferably by direct interview in an outpatient clinic visit, at 6 and 12 months.

Eligibility Criteria

The investigators were asked to report all the cases of CVST who: were diagnosed by an imaging method such as Magnetic Resonance, Magnetic Resonance Venography, Computerized Tomography Venography or Intra-arterial Venography; who had a documented parenchymal lesion (ischaemic or haemorrhagic) or diffuse brain oedema by CT or MR; and who were treated by decompressive craniectomy or haematoma evacuation. They were excluded all the cases of CVST which diagnosis was only supported by angiography (or by any other means than the ones defined) and also the situations when there was an association with head trauma or other intracranial disease with a potential indication for decompressive surgery. The study was approved by local ethics committees and patients or relatives gave informed consent.

Variables

We provide a brief description of the baseline characteristics of the selected sample, with regard to demographics, clinical manifestations, neuroimaging results, risk factors, clinical course, treatments and complications. Our results were measured according to a primary endpoint of the outcome, which was defined as death or dependency at 6 months (modified Ranking Scale score, mRS, equal or greater than 3). We chose the outcome assessment from 6^{th} month follow-up as primary endpoint because, as our investigation is still ongoing, this was the parameter were we had information from the largest number of patients, factor that in our perspective was critical to confer some reliability to the produced statistical inferences. Two other secondary endpoints were defined: early deaths (deaths within 30 days after symptom onset) and late deaths or dependencies at 6 months follow-up. The main objective of our analysis was to examine significant statistical relationships between relevant characteristics of our sample and our primary endpoint, in order to identify potential predictors for unfavourable outcome in CVST patients submitted to decompressive surgery. Bivariate cross-match with secondary endpoints was performed with the purpose of distinguishing short-term from long-term unfavourable outcome predictors. We believe that doing this split we yield a better assessment of the clinical deterioration impact that each predictor variable produces on the outcome.

Data measurement

The timing, type and technical details of the neurosurgical intervention were left to the initiative and option of the local investigator and neurosurgeons. Outcome was measured at the day of hospital discharge, 6^{th} month and 12^{th} month follow-up assessments. It was used the modified Rankin Scale [8], which score was evaluated by an investigator not directly involved in the surgical intervention.

Bias

This study was conceived with the objective of validating previous conclusions about the impact of decompressive surgery on the outcome of complicated CVST. To date, most of the scientific evidence on the topic comes from retrospective and case-report studies. In order to control potential sources of bias, we designed a prospective registry so that every patient who accomplished eligibility criteria had the opportunity to be incorporated in the investigation, thereby minimizing the risk for selection bias. We also defined a form and a protocol for registering and communicating data to the coordinating centre. We believe to be reducing any sources of information bias with this procedure.

Statistical analysis

Descriptive statistics for baseline variables were calculated, using frequencies for categorical variables and means and standard deviation for continuous variables. Bivariate analysis of the outcome with predictor variables was performed for categorical data with Fisher exact test and Mann-Whitney U test for continuous variables. Every variable with a p-value <0.05 was considered statistically significant. Phi coefficient was used as a measure of the degree of association between categorical predictors and the outcome. Predictor variables with Phi coefficients between 0.3 and 0.7 (or -0.3 and -0.7) were considered to have a positive (or negative) moderate association with the outcome. Values above 0.7 (or below-0.7) were considered to show a strong positive (or negative) association. An absent or negligible association was attributed to variables with Phi coefficients between -0.3 and 0.3. All the cases with missing observations on the tested variables were excluded from that analysis. Data were analysed with SPSS 21.0 for Windows.

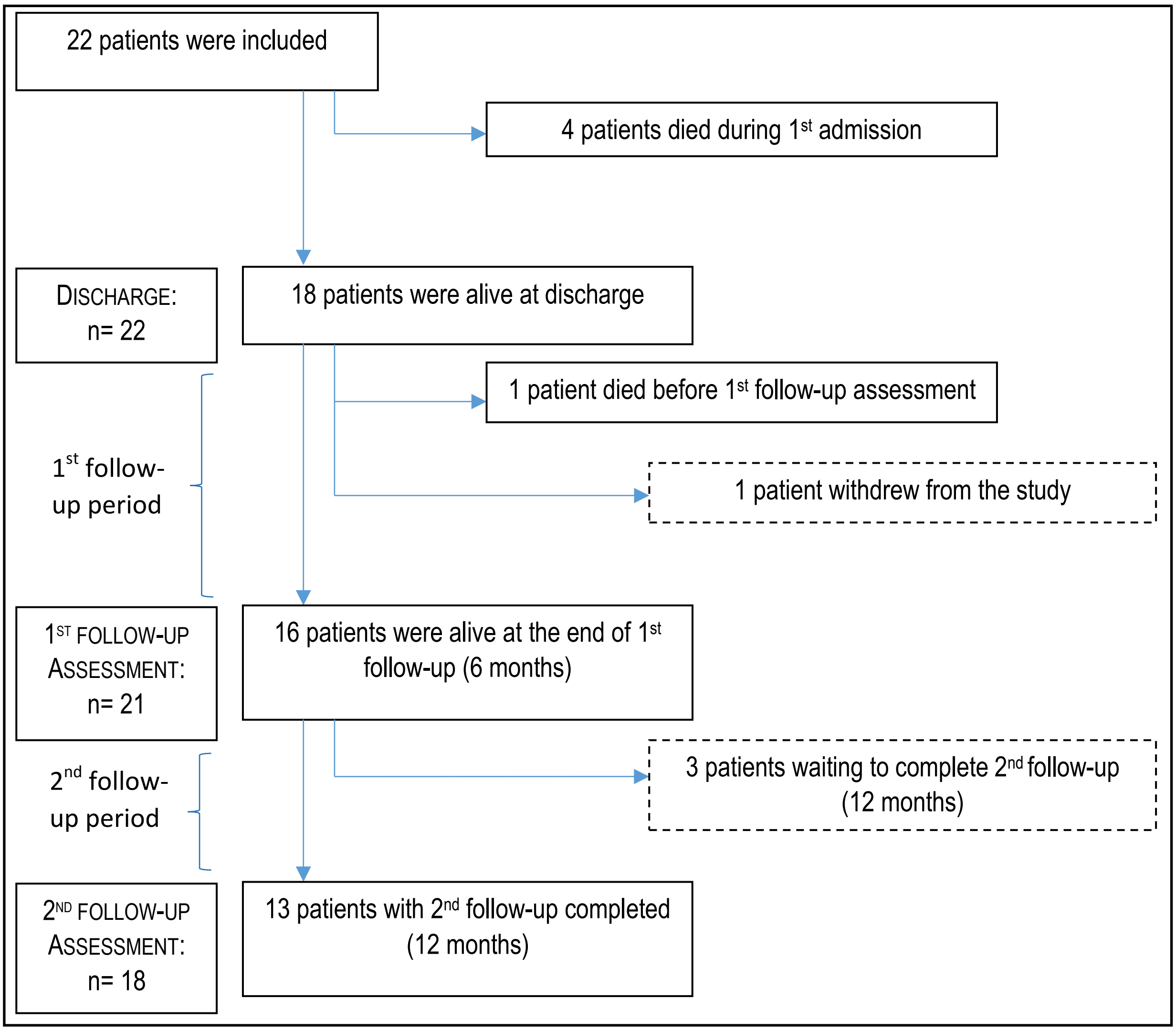

Figure 1. Flow chart from patient enclosure in each stage of the investigation

Results

Table I. Demographics, occluded sinuses/veins and mode of symptoms onset

N=22	No. of Cases	Missing Data	%
Demographics			
Mean age (y) = 37,6 (range 22-51), std. deviation 9,53			
Median age (y) = 38			
Female	19		86.4
Male	3		13.6
Occluded sinus/vein			
Superior sagittal sinus	12		54.5
Left lateral sinus	11		50
Right lateral sinus	5		22.7
Straight sinus	2		9.1
Deep venous system	1		4.5
Cortical veins	9	1	42.9
Left jugular vein	7		31.8
Right jugular vein	2		9.1
Mean sinus score = 2,1 (range 1-6), std. deviation 1,13			
Mode of onset			
Acute (<48h)	10		45.5
Subacute (48 to 30 days)	11		50
Chronic (>30 days)	1		4.5

Participants in the study came from 11 different medical centres situated in 8 different countries. Presently, we count with a total of 22 patients already included. Patient inclusion in each stage of the investigation and mortality data are displayed in Figure 1.

With regard to baseline characteristics, mean patient's age was of 37.6 years and 19 from 22 patients were female (86.4%) (see Table I). The diagnosis of CVST was established by CT venography in 15 patients (68.1%) and by MRI/MR venography in 6 (27.2%) and DWI/PWI in 1 (4.5%). Most frequent occluded sinuses/cerebral veins (Table I) were superior sagittal sinus (12 patients, 54.5%), left lateral sinus (11 patients, 50%) and cortical veins (9 patients, 42.9%). We calculated a mean sinus score of 2.1 (SD 1.13). Mode of symptoms onset (Table I) was predominantly acute (10 cases, 45.5%) and subacute (11 cases, 50%) rather than chronic (1 case, 4.5%).

Table II. Clinical features and GCS on admission

N=22	No. of Cases	Missing Data	%
Symptoms and signs			
Headache	21	1	100
Decreased visual acuity	5	1	23.8
Papilledema	3	4	16.7
Neck stiffness	2	1	9.5
Diplopia	2	1	9.5
Aphasia	14		63.6
Ataxia	1	1	4.8
Visual field defect	6	2	30
Nausea	11	1	52.4
Left paresis	7	1	33.3
Right paresis	9	1	42.9
Any paresis	14	1	66.7
Focal seizure	8		36.4
Generalized seizure	8		36.4
Any seizure	10		45.5
Mental status disturbance	15		68.2
Decreased alertness	18		81.8
Glasgow coma score on admission			
15	5		22.7
9 to 14	8		36.4
<9	9		40.9

Median delay from onset of symptoms to diagnosis was of 2 days (mean=4.41; SD 5.32 days) where most prominent symptoms (Table II) were headache (22 cases, 100%), decreased alertness (18, 81.8%), mental status disturbance (15, 68.2%), any paresis (14, 66%) aphasia (14 patients, 63.6%) and nausea (11 patients, 52.4%). Nine patients (40.9%) were comatose (GCS<9) at admission (Table II).

Eighteen patients (81.6%) were identified with cerebral oedema and 21 patients (95.5%) had a documented parenchymal lesion (Table III).

Table III. Imaging features

N=22	No. of Cases	Missing Data	%
Summary of imaging results			
Cerebral oedema	18		81.6
Parenchymal lesion	21		95.5
Non-haemorrhagic lesion	6		27.3
Haemorrhagic infarction	17		77.3
Intracerebral hematoma	11		50
Subdural hematoma	2		9.1
Subarachnoid haemorrhage	5		22.7
Bilateral lesion	4	1	19
Multiple lesion[1]	10	1	47.6
Left hemisphere	16		72.7
Right hemisphere	9		40.9
Posterior fossa	2		9.1
Midline shift	16		72.7
Transtentorial herniation	7		31.8
Compression of brainstem/IV ventricle	7		31.8
Mean lesion size (cm) = 6.25, std. deviation 2.18			

[1] Only a maximum of 2.

Table IV. Risk factors

N=22	No. of Cases	Missing Data	%
Risk factors	21		95.5
Transient	20		90.9
Pregnancy	2		9.1
Puerperium	5		22.7
Any infection	4		18.2
Systemic infection	1		4.5
SNC infection	2		9.1
ENT infection	4		18.2
Severe dehydration	2		9.1
Oral contraceptives	8		36.4
Other prothrombotic drugs	2		9.1
Permanent	10		45.5
Genetic thrombophilia	3		13.6
Malignancy	1		4.5
Severe anaemia	3	1	14.3
Inflammatory bowel disease	2		9.1

Table V. Pre-operative clinical course

N=22	No. of Cases	Missing Data	%
Type of worsening			
Decreased alertness	16	3	84.2
Mental state disturbance	9	3	47.4
Worsening of previous motor/focal defect	9	3	47.4
New motor/focal defect	2	3	10.5
New seizure	1	3	5.3
Decreased visual acuity	1	3	5.3
Neuroimaging			
New non-haemorrhagic lesion	3	3	15.8
Haemorrhagic transformation	5	3	26.3
New intracerebral haemorrhage	5	3	26.3
Enlargement of previous haemorrhage	6	3	31.6
Increasing in brain oedema	16	3	84.2
Midline shift	21	1	100
Transtentorial herniation	15	1	71.4
Compression of brainstem/IV ventricle	15	1	71.4
Mean diameter of largest lesion (cm) = 8.37 (range 6-13), std. deviation 2.11			

This lesion was associated with haemorrhagic infarction in 17 cases (77.3%) and intracerebral hematoma in 11 (50%). It was preferably located in left hemisphere in 16 (72.7%), [versus 9 patients (40.9%) in right hemisphere], and it was bilateral in 4 (19%). In 16 patients (72.7%), the lesion produced a significant mass effect leading to an identifiable midline shift of cerebral structures and also, simultaneously, in 7 cases (31.8%) to transtentorial herniation. See Table VI for further details on midline shift degree. The maximal diameter of largest lesion at admission had a mean of 6.25 cm with a standard deviation (SD)=2.18 cm.

Considering risk factors (Table IV), 21 patients (95.5%) had at least one risk factor for CVST. We recognised transient risk factors in 20 patients (90.9%) and permanent ones in 10 patients (45.5%). The most common transient risk factors identified were oral contraceptives, puerperium and ear, nose or throat infection. Most common permanent risk factor was genetic thrombophilia. There was a median of 2 risk factors per patient (mean=2,05; SD=1,13).

Changes to clinical course (Table V) were predominantly marked by decreased alertness (16 cases, 84.2%), mental state disturbance (9 cases, 47.4%) and worsening of previous motor/focal defect (9, 47.4%). Five additional patients became comatose before surgery (GCS<9) reaching a total of 16 (76.2%).

Table VI. Comparison between midline shift degree on admission and before surgery

Midline shift degree	At admission (n=22)		Pre-surgery (n=21)	
	No. of cases	%	No. of cases	%
< 5 mm	11	50	2	9.5
5 to 10 mm	6	27.3	7	33.3
> 10 mm	5	22.7	12	57.1

Table VII. Neurosurgery

N=22	No. of Cases	Missing Data	%
Decompressive craniectomy	15		68.2
Hematoma/brain tissue evacuation	1		4.5
Both procedures	6		27.3

Before surgery, every patient had a recognisable midline shift (see Table VI for comparison with midline shift degree on admission), 16 patients (84.2%) increased in brain oedema and 15 (71.4%) suffered transtentorial herniation and compression of brainstem or fourth ventricle. With respect to clinical deterioration pathogenesis, there was an enlargement of previous haemorrhage in 6 cases (31.6%), new intracerebral haemorrhage in 5 (26.3%), haemorrhagic transformation (5, 26.3%) and new non-haemorrhagic lesion (3, 15.8%). The mean diameter of the largest lesion shifted to a mean of 8.37 cm, SD=2.11cm before surgery (Table V).

Table VIII. Post-operative complications, new neurosurgery requirement, medical treatments

N=22	No. of Cases	Missing Data	%
Complications after surgery			
Seizure	3	1	14.3
Sinking flap	1		4.5
Paradoxical herniation	1		4.5
External brain tamponade	1		4.5
Intracranial bleeding			
Intracerebral	2		9.1
Epidural	1		4.5
Infection			
Meningitis	1		4.5
Operative wound	1		4.5
Extracranial infection	9		40.9
Sepsis	3		13.6
Pulmonary	3		13.6
Other	5		22.7
Pulmonary embolism	1		4.5
Cardiac	2		9.1
Other (pericarditis and sinus tachycardia)	4		18.2
New neurosurgery	3		13.6
Hematoma/brain tissue evacuation	2		9.1
External ventricular drainage	2		9.1
Cranioplasty	2		9.1
Medical treatments			
IV heparin	11		50
SC heparin/LMWH, prophylactic dosages	14		63.6
SC heparin/LMWH, therapeutic dosages	17		77.3
Any heparin	19		86.4
Oral anticoagulants	7		33.3
Antiplatelet drugs	1		4.5
Mechanical thrombolysis	1		4.5
Anti-epileptic drugs	11		50
Diuretics	5		22.7
Anti-osmotics	9		40.9
Sedation and mechanical ventilation	19		86.4
ICU	17		77.3

The neurosurgery intervention (Table VII), at admission, was essentially marked by two different procedures: decompressive craniectomy (DC) and brain tissue/haematoma evacuation (BTHE). Fifteen patients (68.2%) did DC alone, and one (4.5%) did BTHE. Six patients (27.3%) were submitted to both.

Most common complications after surgery (Table VIII) were the occurrence of an extracranial infection (9 patients, 40.9%) and seizures (3 patients, 14.3%). Three patients (13.6%) had to be submitted to a second neurosurgery (Table VIII) before discharge, mainly for external ventricular drainage and new BTHE. Medical treatments (Table VIII) were, essentially, use of sedation and mechanical ventilation (19 patients, 86.4%), anticoagulation with any form of heparin (19 patients, 86.4%), hospitalisation in an intensive care unit (17 patients, 77.3%) and use of anti-epileptic drugs (11 patients, 50%). Mean hospital stay at discharge was of 34.9 days (median 22.5) with an SD=32.5 days.

As far as follow-up period is concerned, after patient discharge and before 6th month clinical assessment, the most frequent events (Table IX) were seizures (3 patients, 20%), venous thrombotic events in another territory (2, 12.5%) and the occurrence of sinking skin flap (2, 13.3%).

Table IX. First follow-up assessment (6 months)

n=18	No. of Cases	Missing Data	%
Events since last observation			
Death	1	2	6.3
Other venous thrombotic event	2	2	12.5
Visual loss	1	2	6.3
Seizure	3	3	20.0
Sinking skin flap	2	3	13.3
Infection			
Intracerebral	1	2	6.3
Pulmonary	1	2	6.3
Other events	1	2	6.3
Hospital admission	11	2	68.8
New neurosurgery	8	2	50
External ventricular drainage	2	2	12.5
Ventriculo-peritoneal/atrial shunt	1	2	6.3
Lumbar-peritoneal shunt	1	2	6.3
Cranioplasty	7	2	43.8

Table X. Second follow-up assessment (12 months)

n=16	No. of Cases	Missing Data	%
Events since last observation			
Seizure	6	3	46.2
Intracranial bleeding			
Intracerebral	1	3	7.7
Infection			
Other (non-CNS, pulmonary or sepsis)	1	3	7.7
Hospital admission	5	4	41.7
New neurosurgery	4	3	30.8
Cranioplasty	4	3	30.8

Eight patients (50%) required a new neurosurgical intervention, from 11 (68.8%) which had been admitted to the hospital. After 6th month follow-up and before last clinical assessment (which occurred at 12th month) (please see Table X), seizures continued to be the most frequent complication (6 patients, 46.2%). Four patients (30.8%) required a neurosurgical intervention during this period from 5 (41.7%) who had new hospital admissions. New surgical interventions during follow-up periods happened fundamentally to perform cranioplasty.

Table XI. Outcome at discharge, first and second follow-ups

mRS[1]	Outcome at Discharge (n=22) No. of Cases	%	Outcome at 6 months (n=21) No. of Cases	%	Outcome at 12 months (n=18) No. of Cases	%
0	0	0	2	9.5	1	6.3
2	2	9.1	7	33.3	7	43.8
3	3	13.6	4	19	5	27.8
4	7	31.8	3	14.3	0	0
5	6	27.3	0	0	0	0
Death	4	18.2	5	23.8	5	27.8
CR[2]	0	0	2	9.5	1	6.3
DD[3]	20	90.9	12	57.1	10	55.6

[1]Modified Rankin Scale; [2]Complete Recovery; [3]Death or dependency

Outcome data

Most of deaths were verified during admission (4 patients, 18.2%). Additionally, death or dependency was also the highest on discharge, counting with 20 patients (90.9%). On the other hand, no complete recoveries were achieved on this stage. At first follow-up period (before 6 months assessment), one new death was recorded, increasing total mortality rate up to 23.8%. Conversely on first follow-up assessment (6 months), death or dependency was reduced to 57.1% and two complete recovery cases were identified (9.5%). At last follow-up period (before 12 months assessment), despite 3 patients are still completing this stage, no new deaths have been registered. On second follow-up assessment (12 months), death or dependency proportion continued to diminish within our sample (55.6%). For further details please see Table XI.

Bivariate analysis

Death or dependency at 6 months (our primary endpoint to assess unfavourable outcome) showed significant statistical association with the following categorical variables: new haemorrhagic transformation before first neurosurgical intervention (p value= 0.029, Phi coefficient= 0.555) and complication of the post-operative period with an extracranial infection (p value= 0.016, Phi coefficient= 0.556). In relation to the produced bone flap size during craniectomy, we found that smaller bone grafts were more frequently associated with unfavourable outcome patients' subgroup. Mann-Whitney U test was used and it was achieved a level of significance of 0.044. Descriptive data from bone flap size for "death or dependency at 6 months" subgroup was the following: mean= 11.0 cm, SD= 3.30 cm (versus a mean=13.0 cm, SD= 2.06 cm for the distribution of the patients with better outcome).

In the matter of predictors of death within 30 days after symptoms onset (early deaths), a significant statistical relationship was displayed for new haemorrhagic transformation before first neurosurgical intervention (p value= 0.010, Phi coefficient=0.725), localization of the lesion in the posterior fossa (p value= 0.026, Phi coefficient= 0.671), and use of intravenous heparin as therapeutic approach (p value= 0.045, Phi coefficient= -0.471). In relation to the extent of the parenchymatous lesions assessed before surgery, it was also noted that early deaths' subgroup tend to have larger lesion diameters than the rest of the sample. Mann-Whitney U test showed a level of significance of 0.040. Descriptive data on pre-surgery largest lesion size for the early deaths' subgroup showed a mean of 10.7 cm with a SD= 1.16 cm (versus a mean of 8.0 cm with a SD=2.00 cm for the other patients).

Concerning late deaths or dependencies at 6 months (long-term unfavourable outcome), significant association was achieved with the manifestation in the post-operative period of an extracranial infection (p value= 0.003, Phi coefficient= 0.764). Smaller bone flap sizes (p value= 0.038) were also more frequent among this subgroup of patients, where bone grafts had a mean of 10.7 cm with a SD= 1.70 cm (versus a mean of 13.0 cm with a SD=2.06 cm for independent patients).

Discussion

Primary outcome, which was death or dependency at 6 months, reached a frequency of 57.1% what is considerably above death or dependency frequencies previously reported at last follow-up assessments in previous studies (see Table XII). Mortality at 6 months was, however, within described percentages interval (Table XII). It attained a proportion of 23.8% of patients.

Primary endpoint predictors for unfavourable outcome were new haemorrhagic transformation before first neurosurgical intervention, smaller bone flap sizes produced during craniectomy, and complication of the post-operative period with an extracranial infection. With regard to specific early death predictors, they were identified positive associations with localisation of parenchymatous lesions in the posterior cranial fossa, larger lesions assessed immediately before surgery and new haemorrhagic transformation before first neurosurgical procedure. A negative association was found with the use of intravenous heparin as medical treatment. Specific late death and dependency predictors at 6 months were smaller bone flap sizes produced during craniectomy and extracranial infection as a complication of the post-operative period.

Strengths of the study are the clear definition of inclusion and exclusion criteria and the prospective registry of data, which eliminates the risk for selection and recall bias. Furthermore, as we are investigating a group of patients with very rare characteristics, the inclusion of individuals from diverse countries in the world increases the external validity of conclusions verified in the study by reducing the importance of local environmental confounding factors. It is also the first prospective registry with multicentric investigational contribution that has been done on the topic. Limitations of the study were the short number of patients that was achieved for this interim analysis, which restricts the power of statistical analysis of predictors' relationship with the outcome. The observational character of the study may also be a limitation when considering the elimination of any sources of bias, by opposition to randomized controlled trials. However, control with placebo is unsuitable for this type of life-saving intervention as it may be considered unethical.

Twelve previous case series of patients with CVST submitted to decompressive surgery have been published (see Table XII). It is reported only one small prospective study, with patients from one single centre [9], while the other investigations are mainly retrospective in nature, or correspond to multiple case-reports. Considering series with a minimum of 5 patients submitted to surgery (which have happened since 2010), we observe that mortality in this group of patients ranges from 12.5-29%. Favourable outcome (with mean/median last follow-up assessments taking place between 7 and 35 months) was achieved in a proportion of 56.5-76% patients.

Table XII. Previous case-series publications on CVST patients submitted to Decompressive Surgery

Investigator	Year of publication	Duration	Type	Patients provenience	No. of patients undergoing surgery	Time of outcome assessment	Mortality	Death or dependence/ unfavourable outcome	Independence/ favourable outcome	Complete recovery
Raza E[1]	2014	12 years	Retrospective	Pakistan	7	18 months (median)	29%	43%	57%	?
Aaron S[2]	2013	10 years	Retrospective	India	44	1 year /6 months	20%/20%	39%/44%	61%/56%	48%/38%
Vivakaran T[3]	2012	2 years	Retrospective	India	34	12 months (mean)	17.7%	24%	76%	?
Zuurbier S[9]	2012	4 years	Prospective	Netherlands	10	12 months	20%	30%	70%	50%
Ferro J[6]	2011	NA	Retrospective + Systematic Review	Multicentric	69	12 months (median)	15.9%	43.5%	56.5%	37.7%
Mohindra S[10]	2011	6 years	Retrospective	India	13	35 months (median)	15%	31%	69%	?
Théaudin M[11]	2010	7 years	Retrospective	France	8	23 months (median)	12.5%	25%	75%	75%
Lath R[12]	2010	6 years	Retrospective	India	11	7 months (mean)	27%	27%	73%	?
Lanterna L[13]	2009	3 years	Retrospective	Italy	3	1-6 months	0%	33%	67%	?
Coutinho J[14]	2009	2 years	Case-report series	Netherlands	3	NA	33%	33%	67%	?
Keller E[15]	2005	4 years	Case-report series	Switzerland	4	NA	0%	0%	100%	?
Stefini R[16]	1999	?	Case-report series	Italy	3	NA	0%	33%	67%	67%

CVST – cerebral and venous sinus thrombosis; NA – non applicable; ? – unknown;

This classification was mainly attributed to patients having a maximum score of 2 in mRS scale or a minimum score of 4 in Glasgow outcome scale. Many studies do not report complete recovery rates, nevertheless, an interval between 37.7% and 75% is described. In our series, as previously mentioned, mortality is in accordance to the percentages defined in the literature, although we verified higher dependency rates and less complete recoveries. There are some reasons that can be pointed out to explain this discrepancy of data: First of all, our outcome reference comes from a follow-up which happened 6 months after discharge, while published references had mostly a minimum of 12 months follow-up. Aaron *et al.* mentions that mRS scale continues to improve even after 6 months [2]. Secondly, we are conducting a multicentric prospective cohort which may eliminate some potential sources of bias. We can observe that discrepancies were predominantly noted in dependencies classification, (which result from the subjective assessment of the investigator), rather than mortality that is a quite objective criterion. In this regard, we understand that morbidity in this high risk group of patients may be higher than what was previously considered. These results continue to support the execution of decompressive surgery in this high risk group of patients, as mortality without this procedure would be close to 100% [11], though we recognise the limitations of our statistical inference, particularly because of a small patient sample. We expect to answer more clearly to this question when our study is complete with a sample close to 100 patients.

According to what is said in the literature about the outcome predictors in cerebral venous thrombosis patients, haemorrhagic infarction, transformation of previous ischemic lesions and expanding haemorrhagic infarcts are considered a major risk factor for poor outcome [1], [4], [9], [17], [18]. In our study, the haemorrhagic transformation (HT) of a previous ischemic infarct lesion, before first neurosurgical intervention, was one of the most important predictors identified for unfavourable outcome. It demonstrated a moderate positive association with death or dependency at 6 months and a strong positive association with death within first 30 days after clinical onset. In this way, we interpret HT as an early mortality predictor, which aetiology requires clarification. To date, the only published scientific evidence we have on this process comes from major clinical trials of acute ischemic stroke interventions, which demonstrated increasing haemorrhagic rates with endovascular interventions, as well as with increased time lapses between stroke onset and vessel recanalization [19]–[21]. Despite the need for new efforts on clarifying HT causes and precipitants in the context of cerebral venous thrombosis, we perspective, as it was earlier recognised by Mohindra *et al.*, that there may be a role in defining an optimal time for surgical intervention [10], in order to minimize this type of event. Further investigation on endovascular treatment approaches as a substitute or complementary method is also required. Nevertheless, Lath *et al.* suggests that "decompressive craniectomy may be beneficial in patients who develop haematoma following thrombolysis therapy" [12].

With regard to bone flap size produced at decompressive craniectomy, it is already reported a concern, in previous investigations of CVST patients, about producing wide and extensive craniectomies with the objective of preventing damage to the swollen brain by the edges of the bony opening [10] and to avoid or reverse transtentorial herniation [9]. In our series, smaller bone flap sizes were associated with poorer outcome rankings at six months, either in the view of general outcome predictors as well as long-term outcome predictors. Patients with unfavorable outcome had a mean of 11 centimeters bone flap sizes, while favorable outcome group achieved a mean of 13 centimeters. There is recent evidence in the matter of decompressive hemicraniectomies (DHC) that if a minimum threshold of 12 centimeters for DHC size and decompression to the temporal base are observed, a smaller craniectomy is equally effective in relieving intracranial hypertension and does not increase the risk for early secondary complications such as parenchymal shear stress, hemorrhage and swelling [22]. It still needs to be studied if this reported lower threshold size for DHC assures the same favourable outcome in long-term and if it is applicable to other craniectomy types (other than DHC). No surgical risk and complications data have yet been clearly defined for very extensive craniectomies, although some authors suggest it may predispose to the occurrence of sinking skin flap syndrome [23]. Considering the exposed evidence, we are in favour of the execution of larger craniectomy bone flaps with a minimum of 13 cm, as it corresponds to the average bone flap size of favourable prognosis patient group.

Extracranial infection during first hospitalisation appears to be a frequent post-operative complication. Raza *et al.* reports that in their patient series investigation, "every hospital stay was complicated with a hospital acquired non-central nervous system infection" [1]. Most frequent types of infection reported within this category are urinary, pulmonary tract infections and sepsis [1]–[3]. Within our patients, 41% had an extracranial infection, which was correlated with an unfavourable outcome at 6 months, especially through the expression of an increased rate of dependencies at 6th month follow-up. In this fashion it is suggested that extracranial infection may be a long-term predictor of unfavourable outcome. Nevertheless, we believe that this variable may result from an important neurologic deficit that impairs mobility, as well as other important physiologic functions, predisposing in this matter to infection. Considering this true, this variable would not actually be an independent predictor of the outcome but instead a result variable of a severe dependence already present on admission. We therefore recognise extracranial infection as a possible marker for unfavourable outcome, although we do not believe that any prophylactic attempt of preventing this type of infection with antibiotics would be beneficial for overall patient outcome. Same observations have been made in analogous studies for acute stroke [24], [25].

Posterior cranial fossa lesions and larger lesions assessed immediately before surgery were apparently associated with the occurrence of deaths during first admission. Treatment with intravenous heparin suggests reducing the frequency of these early deaths. In this regard, Canhão *et al.* already described posterior cranial fossa lesions as an independent predictor of death in CVST patients [26]. Many authors have considered the occurrence of large venous infarcts as high mortality risk factor, and which constitutes one of the prime indications for decompressive surgery [2], [6], [12], [27]. No considerations have conversely been made about parenchymal lesion size within this high group of patients. With regard to heparin use in CVST, its indication as primary therapy has long been considered although such recommendations are based on limited evidence from clinical trials [7], [28], [29]. A beneficial effect in early deaths is here suggested with the use of intravenous heparin. We should, however, take into account that the former three variables did not show a significant correlation with primary endpoint, which was death or dependency at 6 months. We therefore consider that, despite an identifiable correlation with secondary endpoints from the study, association with primary endpoint needs to be retested in a larger case series, in order to accurately define the real contribution, (and consequently the clinical relevance) of these predictor variables on patients outcome.

In conclusion, previous mortality rates in the order of 20-30% were confirmed in our investigation for CVST patients submitted to decompressive surgery. This supports the execution of decompressive surgery in this high risk group of patients, as mortality without this procedure would be almost certain. Our results, however, suggest a higher dependencies proportion and smaller complete recovery frequencies, which require confirmation through large scale prospective case studies. Haemorrhagic transformation before neurosurgery intervention was found to be an important marker of unfavourable outcome and early mortality. Strategies to minimize this type of event require further investigation. Defining an optimal time for surgical intervention and the assessment of endovascular treatment use may have a role in this process. Smaller bone flap sizes at craniectomy procedure appear to predict for poor outcome and lower recovery rates in the long-term. A mean of 13 cm of bone flap size was found in favourable outcome patients' subgroup. Long-term beneficial effects of larger craniectomies need to be tested in further studies. Extracranial infection was associated with overall and long-term unfavourable outcomes, although its contribution as an independent risk factor is unlikely. Any attempt of its prophylactic prevention with antibiotics is therefore not recommended at this stage. Other predictors have been signalized as potential markers and contributors of the outcome, matter that we expect to clarify when our study is complete, with a sufficiently large patient sample.

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