Neurosurgical Clipping versus Endovascular Coiling for treating Ruptured Intracranial Aneurysm
– A study of 98 patients from Western Sweden

Master thesis in Medicine

Hugo Jakobsson

Supervisor: Daniel Nilsson M.D., Ph.D.

Department of Neurosurgery

Sahlgrenska University Hospital

UNIVERSITY OF GOTHENBURG

Programme in Medicine

Gothenburg, Sweden 2015

Table of contents

Abstract

Neurosurgical Clipping versus Endovascular Coiling for treating Ruptured Intracranial Aneurysm – A study of 98 patients from Western Sweden,

Master thesis - Programme in Medicine, Hugo Jakobsson 2015, Department of Neurosurgery, Sahlgrenska University Hospital, Gothenburg, Sweden

Background and purpose

A ruptured intracranial aneurysm can be treated either by endovascular coiling (EVT) or neurosurgical clipping (NST). International Subarachnoid Aneurysm Trial (ISAT), a multicenter prospective randomized study, was conducted to compare the two treatment alternatives. Criticism has been raised against the low external validity of the study. The purpose of this study was to analyze the ISAT material collected at Sahlgrenska university hospital (SU) to compare the treatment modalities in the patient population of a single center.

Method

The protocols from ISAT were reviewed and a database was created. The primary end-points were neurological outcome, assessed with modified Rankin scale (mRS), at two months, one year and five years. Length of stay in intensive care unit (ICU), neurosurgical ward, total period under care, rate of shunt dependent hydrocephalus (SDHC), occurrence of epileptic seizures, rebleeding and need for retreatment were also studied.

Results

This study found a good neurological outcome (mRS 0-2) in 76.9%, 84.4% and 76.9% of the EVT-patients at two months, one year and five years respectively. The corresponding figures for the NST-group were 69.6%, 78.3% and 78.3%. Six (11.5%) EVT-patients developed SDHC, 5 (9.6%) EVT-patients had at least one epileptic seizure. Seven (15.2%) EVT-patients developed SDHC and 7 (15.2%) had at least one epileptic seizure. EVT-patients spent on average 8.8 (SD 7.6) days in ICU, 16.8 (SD 8.8) days in neurosurgical ward and 44.3 (SD 85.4) days total under care. The NST-patients spent on average 10.6 (SD 7.9) days in ICU, 18.7 (SD 7.8) days in neurosurgical ward and 62.0 (SD 77.4) days total under care.

Conclusions

EVT entails a better neurological outcome than NST at two months and one year, but the difference diminishes over time. EVT is followed by shorter periods in ICU, neurosurgical ward and total period under care. The risk of SDHC is equal for the methods, although patients with a high Fisher grade and high age treated with NST are at lower risk than those treated with EVT and vice versa for patients with low Fisher grade and low age.

Background

An aneurysmal subarachnoid hemorrhage (aSAH) is a serious condition with a mortality rate up to 40 % at one month [1]. The incidence of aSAH varies greatly; from 2.0/100 000 population in Beijing, China, to 22.5/100 000 population in Finland [2]. If untreated, the surviving patients are at high risk for rebleeding from the aneurysm. A mortality rate of 22% in occurrence of rebleeding has been observed [3].

Cerebral aneurysms have traditionally been treated by applying a metal clip to the aneurysm neck, preventing further bleeding. This procedure involves craniotomy and dissection of cerebral blood vessels [4]. Possible complications after the neurosurgical treatment (NST) are cerebral infarction, postoperative hematoma, wound infection, meningitis and cranial nerve palsy [5]. Advantages include definitive diagnosis of aneurysm rupture in case of multiple aneurysms and definitive treatment with a low risk for incomplete aneurysm occlusion and regrowth [5-7]. Theoretically the opening of the subarachnoid spaces and irrigation of blood can decrease the risk of vasospasm and hydrocephalus after aSAH.

Endovascular embolization became an alternative treatment method of cerebral aneurysms when Guido Guglielmi introduced the detachable coil [8]. The endovascular treatment (EVT) uses a micro catheter guided from a. femoralis, via the arterial system, into the lumen of the aneurysm where platinum coils are deployed. The platinum coils are detached from the guide wire by applying a low positive direct current to the delivery wire. The positive electric current attracts negatively charged particles in the blood and causes thrombosis of the aneurysm. Possible complications after EVT are periprocedural aneurysm rupture, distal thromboembolism, mechanical vasospasm, coil migration and groin complication [5, 6]. Incomplete treatment with residual aneurysm have been seen in 22-42 % of cases and retreatment after EVT is more often needed than after NST [5-7].

Koivisto et al. published the first randomized trial comparing the two methods. Their study included 109 patients, 57 patients were assigned to NST and 52 to EVT. The outcome was measured at 3 and 12 months. Similar results in neurological- and neuropsychological outcome were obtained with the two methods [9].

Two major studies comparing results between EVT and NST after the study of Koivisto are the International Subarachnoid Aneurysm Trial (ISAT) and Barrow Ruptured Aneurysm Trial (BRAT) [10, 11].

ISAT was a prospective randomized study conducted by Molyneux et al. It included 2143 patients from forty-two centers in North America, Australia and Europe. Patients who were equally suited for NST and EVT were eligible for the study. For detailed inclusion and exclusion criteria see Molyneux et al., 2002 [11]. The study showed a significant higher proportion with good neurological outcome at two months and one year in patients treated endovascularly compared to those treated neurosurgically [12]. In the long-term follow up, published in 2009, this difference in the surviving patients was no longer significant. Further it showed a higher risk for rebleeding and retreatment after EVT than NST [13].

The ISAT has been criticized for bias in patient selection. The results are not generalizable to the whole population since a significant part of the eligible patients were excluded. A total of 9559 patients were treated for aSAH in the participating centers. Of these 2143 patients (22.4%) fulfilled the criteria for inclusion in ISAT, and consented. One thousand seventy three were randomized to EVT and 1070 to NST. At one year 2110 patients were eligible for assessment of the neurological outcome, 22.1% of the total cases of ruptured intracranial aneurysms. Further, the inclusion rate ranged between the participating centers from 1% to 44%. This characterizes the heterogeneity of the patient assessment [11, 12].

Spetzler et al. published in July 2013 the three years result of BRAT. In this study all patients admitted with a ruptured intracranial aneurysm that consented were randomized. Two hundred thirty three were assigned to EVT, of these 38% crossed over to NST. Two hundred thirty eight were assigned NST, of these 2% crossed over to EVT. At one year there was a significant higher risk for bad neurological outcome in patients treated neurosurgically. The result at three years showed, in contrast to the one-year result, no significant difference regarding bad neurological outcome [10]. The great number of crossovers from EVT to NST makes the results less reliable.

This study, which is based on the data collected for ISAT at the Department of Neurosurgery, Sahlgrenska University hospital (SU), lacks some of these weaknesses. The patient inclusion rate was slightly higher than ISAT, 27.4%. Of these, a greater part of the patients were followed up. At five years, mRS was missing from 3 (3.1%) patients compared to 202 (9.4%) patients in ISAT long-term follow up [13]. The patients were treated in a neurovascular center serving a large population, with well-developed routines for aSAH patients. This allowed for the patient to be treated without delays and by physicians who perform the procedures on a regular basis. This provides safety regarding the uniformity of the procedures and treatment protocols and the assessment of the endpoints. Further, 87 % of the patients had an aneurysm in the anterior circulation compared to 97% in ISAT [11]. This reflects the proportion of the whole aSAH population better [14].

Shunt dependent hydrocephalus

Some studies suggest that the risk of shunt dependent hydrocephalus (SDHC) is higher in patients treated endovascularly compared to those treated neurosurgically. Nam et al. studied the risk for SDHC in a retrospective study of 839 patients. They showed that the risk for SDHC in patients with Fisher grade 4 was significantly lower if they were treated neurosurgically. Also that in patients with Fisher grade 2 treated endovascularly the risk for SDHC was significantly lower [15].

Retreatment

Studies have indicated that EVT is associated with a better short-term neurological outcome, but that the differences diminish over time. However, it has been shown that EVT is associated with a higher rate of retreatment. In ISAT it was concluded that the patients treated endovascularly were 6.9 times more likely to undergo a late retreatment (at least 1 month after the first NST or 3 months after the first EVT) [7].

Aim

The aim of this study was to determine possible differences between endovascular coiling and neurosurgical clipping, primarily in neurological outcome, in the cohort treated at SU from ISAT. Further endpoints were rate of SDHC, rebleeding, need for retreatment, occurrence of epileptic seizures, and length of stay in ICU, neurosurgical ward and total period under care. Possible factors in the baseline data correlating with neurological outcome or SDHC was to be identified.

Methods

Population and data collecting

This study is based on the patients included in ISAT at the Department of Neurosurgery, SU, between March 1997 and April 2002. The patient data were collected at SU according to the ISAT-protocol [11]. For the present study the data was collected from the 100 ISAT charts, each patient chart was reviewed. The protocol over the excluded patients was reviewed and the reason for exclusion and treatment method were noted. Crossovers were considered to the randomized group.

Variables

The baseline data and endpoints were collected from the patient material of the ISAT. The baseline data was age at aneurysmal subarachnoid hemorrhage, sex, Fisher grade, localization of aneurysm (anterior/posterior circulation), aneurysm size, aneurysm neck size (>/≤4mm), vasospasm (angiographic) and treatment method. Neurological outcome at two months, one year and five years were the primary endpoints.

Neurological outcome was assessed at two months, one year and five years after aSAH. It was assessed according to the modified Rankin scale (mRS, defined in table 1) [16]. Good neurological outcome was defined as mRS 0-2, and bad neurological outcome mRS 3-6.

Time in intensive care unit (ICU), time in neurosurgical ward. In cases where death occurred before discharge, the number of days elapsed until death was recorded.

Total length of care was defined as days from hospital admission to the return to home.

Epileptic seizure. Patients that suffered at least one epileptic seizure during the follow up time of 5 years were recorded.

Shunt dependent hydrocephalus. Patients that had a shunt inserted during the follow up period were recorded. Several patients may have temporarily had ventricular drainage during the acute stage, but these were not recorded in this study.

Retreatment. The patients that underwent at least one retreatment during five years after aSAH were recorded.

Rebleeding events were recorded during the follow up time of five years.

Table 1. modified Rankin scale (mRS)

mRS	Symptoms
0	No symptoms
1	No significant disability. Able to carry out all usual activities, despite some symptoms.
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability. Requires some help, but able to walk unassisted.
4	Moderately severe disability. Unable to attend to own bodily needs without assistance or unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden.
6	Dead.

Statistical analysis

The baseline data were analyzed with Mann-Whitney U-test (age), Mantel Haenszel Chi-square test (Fisher grade, aneurysm size and WFNS grade), Fisher's exact test (aneurysm neck size, location of the aneurysm, vasospasm and gender). End point analysis included; for comparison between groups Fisher's exact test was used for dichotomous variables (retreatment, SDHC, vasospasm and epileptic seizures), Mantel-Haenzel Chi-square exact test was used for ordered categorical variables (neurological outcome) and the Mann-Whitney U-test was used for continuous variables (days in ICU, neurosurgical ward, total period under care). To investigate factors that could predict a bad neurological outcome and SDHC, bivariate prediction was used. Spearman correlation analysis was performed to investigate the correlation between neurological outcome and baseline variables. The level of significance was set to $p<0.05$.

Ethics

ISAT was approved by the local ethical board. No separate ethical approval was considered necessary for this study as only previously collected, coded data, was used and reanalyzed.

Results

Figure 1 represents a flow chart where treatment method and reason for exclusion for the patients excluded in the SU cohort of ISAT are shown. Of the 100 patients included in ISAT 2 withdrew and 2 crossed over (1 EVT-NST and 1 NST-EVT).

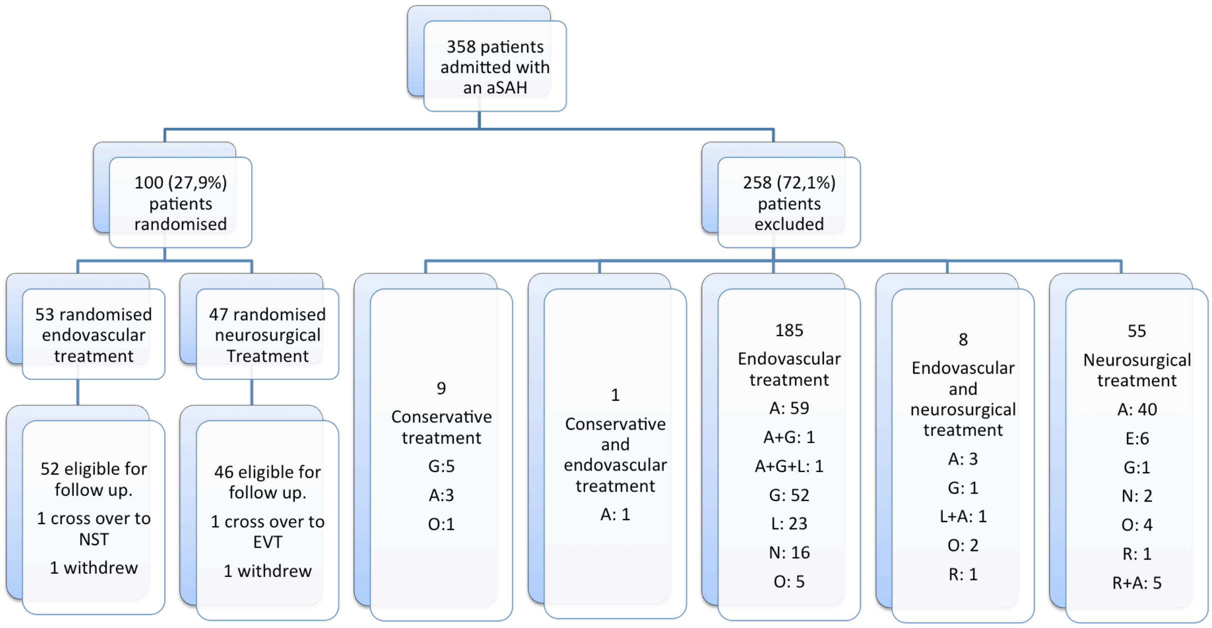

Figure 1- G=WFNS grade or age, A= unsuitable anatomy, O= other, L= aneurysm localization, N=non availability of radiologist or surgeon, R=refused consent, E= hematoma that needed evacuation

The baseline characteristics of the two groups were similar, except vasospasm at inclusion where 0 EVT-patients and 8 NST-patients were observed, p=0.002. The data are presented in table 2.

Table 2- Baseline characteristics				
	EVT	NST	Total	P-value
Age				
Mean (SD)	52.8 (10.7)	53.4 (9.7)	53.1 (10.2)	0.827
Median (min, max)	54.0 (20, 72)	54.5 (29, 71)		
Sex				
Male	17 (32.7%)	20 (43.5%)	37 (37.8%)	0.302
Female	35 (67.3%)	26 (56.5%)	61 (62.2%)	
Fisher grade				
0	0 (0.0%)	1 (2.2%)	1 (1.0%)	0.615
1	2 (3.8%)	5 (10.9)	7 (7.1%)	
2	14 (26.9%)	10 (21.7%)	24 (24.5%)	
3	18 (34.6%)	12 (26.1%)	30 (30.6%)	
4	18 (34.6%)	18 (39.1%)	36 (36.7%)	
WFNS grade pre procedure				
1	30 (57.7%)	28 (60.9%)	58 (59.2%)	0.544
2	14 (26.9%)	13 (28.3%)	27 (27.6%)	
3	2 (3.8%)	1 (2.2%)	3 (3.1%)	
4	5 (9.6%)	4 (8.7%)	9 (9.2%)	
5	1 (1.9%)	0 (0.0%)	1 (1.0%)	
Aneurysm lumen size				
≤5 mm	26 (50.0%)	23 (50.0%)	49 (50.0%)	1.000
6-10 mm	20 (38.5%)	18 (39.1%)	38 (38.8%)	
≥11 mm	5 (9.6%)	5 (10.9%)	10 (10.2%)	
Data missing	1 (1.9%)	0 (0.0%)	1 (1.0%)	
Aneurysm neck size				
>4 mm	22 (42.3%)	20 (43.5%)	42 (42.9%)	1.000
≤4 mm	30 (57.7%)	26 (56.5%)	56 (57.1%)	
Aneurysm localization (circulation)				
Anterior	45 (86.5%)	40 (87.0%)	85 (86.7%)	1.000
Posterior	7 (13.5%)	6 (13.0%)	13 (13.3%)	
Aneurysm localization (main artery)				
a. Carotis int.	13 (25.0%)	5 (10.9%)	18 (18.4%)	
a. Cerebri ant.	4 (7.7%)	2 (4.3%)	6 (6.1%)	
a. Cerebri med.	9 (17.3%)	9 (19.6%)	18 (18.4%)	
a. Cerebri post. inf.	0 (0.0%)	1 (2.2%)	1 (1.0%)	
a. Comm. ant.	19 (36.5%)	24 (52.2%)	43 (43.9%)	
a. Comm. post.	7 (13.5%)	5 (10.9%)	12 (12.2%)	
Vasospasm at inclusion				
No	52 (100%)	38 (82.6%)	90 (91.8%)	0.002
Yes	0 (0%)	8 (17.4%)	8 (8.2%)	

An overview of the neurological outcome is shown in tables 3-5. Of the patients randomized to EVT, 40 (76.9%) had a good neurological outcome (mRS 0-2) at two months and 32 (69.6%) of the NST-patients. The absolute difference was 7.3%, p=0.554. At one year 44 (84.6%) EVT-patients had a good neurological outcome, and 36 (78.3%) of the NST-patients, p=0.585. At five years, data was missing from three patients, 40 (78.4%) of the EVT-patients had a good neurological outcome and 36 (81.8%) of the NST-patients, p=0.878.

Table 3. Neurological outcome at 2 months			
	Randomized treatment		
mRS score	EVT	NST	Total
0	16 (30.8%)	8 (17.4%)	24 (24.5%)
1	15 (28.8%)	9 (19.6%)	24 (24.5%)
2	9 (17.3%)	15 (32.6%)	24 (24.5%)
3	2 (3.8%)	5 (10.9%)	7 (7.1%)
4	1 (1.9)	0	1 (1.0%)
5	4 (7.7%)	6 (13.0%)	10 (10.2%)
6	5 (9.6%)	3 (6.5%)	8 (8.2%)
0-2	40 (76.9%)	32 (69.6%)	72 (73.5%)
3-6	12 (23.1%)	17 (30.4%)	18 (18.4%)
P=0.554			

Table 4. Neurological outcome at 1 year			
	Randomized treatment		
mRS score	EVT	NST	Total
0	19 (36.5%)	8 (17.4%)	27 (27.6%)
1	13 (25.0%)	12 (26.1%)	25 (25.5%)
2	12 (23.1%)	16 (34.8%)	28 (28.6%)
3	1 (1.9%)	2 (4.3%)	3 (3.1%)
4	0	1 (2.2%)	1 (1.0%)
5	2 (3.8%)	3 (6.5%)	5 (5.1%)
6	5 (9.6%)	4 (8.7%)	9 (9.2%)
0-2	44 (84.6%)	36 (78.3%)	80 (81.6%)
3-6	8 (15.4%)	10 (21.7%)	18 (18.4%)
P=0.585			

The patients in the EVT-group spent on average 8.75 days (SD 7.56) in ICU, 16.8 (SD 8.8) in neurosurgical ward and the total length of care was 44.3 days (SD 85.4). The corresponding figures for the NST-group were 10.6 days (SD 7.9) in ICU, 18.7 days (SD 7.8) in neurosurgical ward and 62.0 days (SD 77.4) of total length of care. The difference of time in ICU and neurosurgical ward was not significant, p=0.0937 respectively p= 0.1534, but significant in total length of care, p=0.0130. Figures 2-4 shows how the time spent in ICU, neurosurgical ward and total length of care was distributed.

Table 5. Neurological outcome at 5 years			
	Randomized treatment		
mRS score	EVT	NST	Total
0	19 (37.3%)	12 (27.3%)	31 (32.6%)
1	14 (27.5%)	9 (20.5%)	23 (24.2%)
2	7 (13.7%)	15 (34.1%)	22 (23.2%)
3	2 (3.9%)	1 (2.3%)	3 (3.2%)
4	0	0	0
5	3 (5.9%)	3 (6.8%)	6 (6.3%)
6	6 (11.8%)	4 (9.1%)	10 (10.5%)
0-2	40 (78.4%)	36 (81.8%)	76 (80.0%)
3-6	11 (21.6%)	8 (18.2%)	19 (20.0%)
P=0.878			

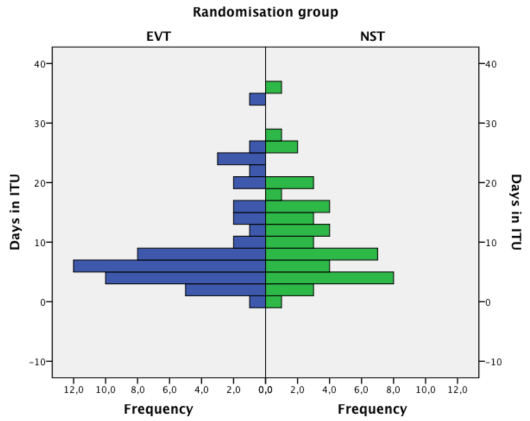

Figure 2. Days spent in neurosurgical ward

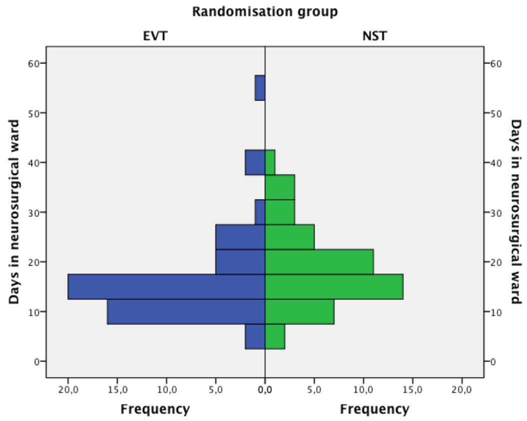

Figure 3. Days spent in ICU

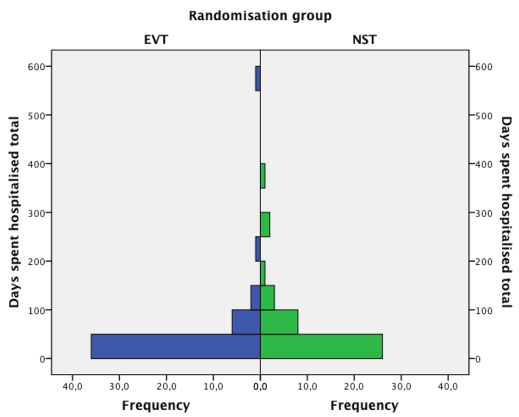

Figure 4. Total length of care

Six (11.5%) EVT-patients and 7 (15.2%) NST-patients developed SDHC, p=0.8098. Five (9.6%) EVT- and 7 (15.2%) NST-patients had at least one epileptic seizure during the follow up period, p=0.5915. In the EVT-group, 6 (11.5%) patients were retreated, 4 neurosurgically, one endovascularly and one with EVT two times and one time NST. Of those randomized to neurosurgical clipping, 2 (4.3%) patients were retreated with EVT. The difference was not significant, p=0.276.

The result from the Spearman correlation analysis (to investigate factors in the baseline data that could influence the neurological outcome) is shown in table 6-8. For the total population, the correlation was significant for Fisher grade and neurological outcome at two months, one year and five years with p-values of <0.0001, 0.0015 and 0.0065 respectively. Age and neurological outcome had a Spearman correlation coefficient of 0.19716 (p=0.0517). The Spearman correlation coefficient for neurological outcome and randomization group was 0.17426 (p=0.0861), 0.19699 (p=0.0519) and 0.10893 (p=0.2933) at two months, one year and five years respectively.

Table 7 shows the result of Spearman correlation analysis of the EVT population. Significance was achieved in Fisher grade and neurological outcome at two months, one year and five years, p=0.0044, p=0.0448 respectively p=0.0157. As well as aneurysm size and neurological outcome at five years, p=0.0424. The Spearman correlation analysis of the NST-group showed significance for age and neurological outcome at two months, p=0.0159, Fisher grade and neurological outcome at two months and one year, p=0.0004 and 0.0074, and sex and neurological outcome at five years, p=0.0205. Table 8 shows the result of the Spearman correlation test for the NST patients.

Table 6. Spearman correlation – whole study population				
	mRS at:	2 months	1 year	5 years
Age	Rho:	0.20	0.08	0.09
	P:	0.052	0.45	0.37
Localization	Rho:	-0.12	-0.10	-0.03
(ant./post.)	P:	0.22	0.31	0.78
Fisher grade	Rho:	0.43	0.32	0.28
	P:	<0.0001	0.0015	0.0065
Aneurysm size	Rho:	0.02	0.09	0.12
	P:	0.84	0.38	0.25
Neck size	Rho:	0.10	0.12	0.12
(>/≤4mm)	P:	0.32	0.25	0.25
EVT/NST	Rho	0.17	0.20	0.11
	p:	0.09	0.05	0.29
Rho=spearman correlation coefficient, p=p-value				

Table 7. Spearman correlation – EVT patients				
	mRS at:	2 months	1 year	5 years
Age	Rho:	0.10	-0.09	0.02
	P:	0.50	0.55	0.88
Localization	Rho:	-0.01	-0.04	0.03
(ant./post.)	P:	0.92	0.77	0.82
Fisher grade	Rho:	0.39	0.28	0.34
	P:	0.004	0.04	0.02
Aneurysm size	Rho:	0.15	0.27	0.29
	P:	0.30	0.05	0.04
Neck size	Rho:	0.14	0.13	0.15
(>/≤4mm)	P:	0.33	0.36	0.31
Rho=spearman correlation coefficient, p=p-value				

Table 8. Spearman correlation – NST patients				
	mRS at:	2 months	1 year	5 years
Age	Rho:	0.35	0.28	0.17
	P:	0.02	0.6	0.27
Localization	Rho:	-0.21	-0.16	-0.07
(ant./post.)	P:	0.16	0.29	0.64
Fisher grade	Rho:	0.50	0.39	0.24
	P:	0.0004	0.008	0.12
Aneurysm size	Rho:	0.-0.19	-0.16	-0.11
	P:	0.20	0.28	0.48
Neck size	Rho:	0..1	0.08	0.07
(>/≤4mm)	P:	0.93	0.60	0.67
Rho=spearman correlation coefficient, p=p-value				

Table 9 shows the result obtained from the bivariate prediction of SDHC analysis. Odds ratio (OR) is the ratio for the odds for an increase of the predictor of one unit. In the total population an OR of 1.09 (CI=1.01-1.16, p=0.0227) was found for age and SDHC. The prediction of SDHC for Fisher grade gave the OR 2.11 (CI=0.98-4.53, p=0.0548). In the EVT population prediction of SDHC for Fisher grade showed an OR=8.14 (CI=1.07-62.16, p=0.0432) and for age OR=1.15 (CI=1.02-1.30, p=0.0222). The NST population showed no significant factors for development of SDHC.

Table 9. Bivariate prediction of SDHC										
		Tot.			EVT			NST		
		No.	OR (95% CI)	p-value	No.	OR (95% CI)	p-value	No.	OR (95% CI)	p-value
Age	20-49	1			0			1		
	50-57	5			2			3		
	58-72	7	1.09 (1.01-1.16)	0.23	4	1.15 (1.02-1.30)	0.02	3	1.04 (0.95-1.14)	0.39
Circulation	Ant.	11			5			6		
	Post.	2	1.22 (0.24-6.27)	0.81	1	1.33 (0.13-13.5)	0.81	1	1.13 (0.11-11.5)	0.92
Fisher grade	0	0			0			0		
	1	0			0			0		
	2	1			0			1		
	3	5			1			4		
	4	7	2.11 (0.98-4.53)	0.55	5	8.14 (1.07-62.2)	0.04	2	1.30 (0.59-2.87)	0.52
Size (mm)	2-4	6			3			3		
	5-6	5			3			2		
	7-15	2	0.80 (0.61-1.05)	0.11	0	0.66 (0.39-1.13)	0.13	2	0.88 (0.64-1.21)	0.43
Aneurysm neck size	≤4 mm	8			4			4		
	>4 mm	5	0.81 (0.24-2.68)	0.73	2	0.65 (0.11-3.91)	0.64	3	0.97 (0.19-4.93)	0.97
Randomization group	EVT	6								
	NST	7	1.38 (0.43-4.44)	0.59						

The complete result of the bivariate analysis for prediction of bad neurological outcome (mRS 3-6) is shown in table 10. At two months, one year and five years, age and Fisher grade was significantly associated with bad neurological outcome.

Table 10. Bivariate prediction of bad neurological outcome (mRS 3-6)										
		2 months			1 year			5 years		
		No.	OR (95% CI)	p-value	No.	OR (95% CI)	p-value	No.	OR (95% CI)	p-value
Age	20-49	5	1.07 (1.02-1.13)	0.008	3	1.07 (1.01-1.13)	0.028	3	1.07 (1.01-1.14)	0.02
	50-57	7			7			7		
	58-72	14			8			9		
Sex	Male	11			9			8		
	Female	15	0.77 (0.31-1.92)	0.58	9	0.54 (0.19-1.51)	0.24	11	0.85 (0.31-2.36)	0.75
circulation	Ant.	24			18			19		
	Post.	2	0.46 (0.10-2.24)	0.34	0	N/A	0.12	0	N/A	0.15
Fisher grade	0	0			0			0		
	1	0			0			0		
	2	2			1			1		
	3	7			6			6		
	4	17	3.27 (1.68-6.38)	0.0005	11	2.74 (1.31-5.71)	0.007	12	3.08 (1.46-6.49)	0.003
Size (mm)	2-4	9			7			6		
	5-6	7			3			5		
	7-15	10	1.00 (0.87-1.16)	0.95	8	1.05 (0.89-1.23)	0.55	8	1.07 (0.91-1.25)	0.42
Aneurysm neck size	≤4 mm	14			10			11		
	<4 mm	12	1.20 (0.49-2.96)	0.69	8	1.08 (0.39-3.03)	0.88	8	1.00 (0.36-2.77)	1.00
Randomization group	EVT	12			8			11		
	NST	14	1.46 (0.59-3.59)	0.41	10	1.53 (0.55-4.27)	0.42	8	0.81 (0.29-2.23)	0.68

Discussion

This study found that a larger proportion of the patients treated endovascularly had a good neurological outcome (mRS 0-2) at two months. The difference was not significant and diminished over time. At five years the proportion of NST-patients with a good neurological outcome was slightly higher than for the EVT-patients. Similar pattern was found in ISAT and BRAT, where they found a significantly better neurological outcome for EVT at the short term follow up, but at the long term follow up in ISAT and at the 3 years follow up in BRAT the difference was no longer significant [10, 13]. In this study mRS was missing from 2 patients in the NST-group and 1 patient in the EVT-group, which could have influenced the result.

Another finding worth noticing was that the neurological outcomes recorded in this study were better than those of ISAT. In ISAT 73.9% of the EVT-patients and 63.1% of the NST patients had a good neurological outcome at two months [12]. Reasons for this may be a well developed pre- and in-hospital treatment algorithm for aSAH patients, where all patients are referred without delay to a specialized neurosurgical center (SU) after diagnosis of aSAH. The hospital also serves a large population, which gives the operators experience in the procedures. This is supported by a meta-analysis by Boogaarts et al. They found that neurovascular centers with a high number of treated patients achieved better outcomes [17]. Inconsequent assessment of mRS-score and inappropriate patient exclusion in the participating centers should also be considered as reasons.

The absolute difference in proportion of patients suffering at least one epileptic seizure during the follow up time was 5.6% favoring EVT, p=0.5915, and in line with the result of ISAT. The authors of ISAT concluded that a significant larger proportion of the aSAH-patients treated with NST had epileptic seizures than those treated with EVT [18]. NST involves brain retraction and it is possible that the higher rate of epileptic seizures depends on this.

In this study 6 (11.5%) of the EVT patients and 2 (4.3%) of the NST patients had to undergo at least one extra procedure, p=0.276. Similar results were found in ISAT when comparing the rate of retreatment between the two methods. In the EVT group, retreatment was performed in 191 (17.4%) of 1096 cases compared to 39 (3.8%) 1012 cases in the NST group. The authors concluded that the patients were 6.9 times more likely to need a late retreatment (at least 1 month after NST or 3 months after EVT) after endovascular coiling [7].

The purpose of treating a ruptured intracranial aneurysm is to prevent rebleeding. In previous studies the neurosurgical method has proven to provide sufficient protection to rebleeding. In this study two of the EVT patients and none of the NST patients rebled. The difference was not significant but in ISAT, the endovascular method had a higher risk of rebleeding. The UK-cohort of ISAT was analyzed with a follow up time of 10-18.5 years and over three times as many EVT-patients as NST-patients rebled [19]. Despite the difference in rebleeding, no difference was found in neurological outcome. The average age of the patients in this study was 53.1 years (SD 10.2). Taking into consideration that many patients have an expected remaining lifetime of almost 30 years, it must be ascertained that EVT provides a secure protection for that period of time. Further analyzes with longer follow up time of the ISAT material would be useful to conduct, in order to assess the endurance of the endovascular treatment.

Craniotomy and subsequent rinsing of the subarachnoid spaces may decrease the risk of developing hydrocephalus after aSAH. Nam et al. concluded, in a retrospective study of 839 patients with aSAH, that patients with Fisher grade 4 treated neurosurgically have a lower risk of developing SDHC compared to those treated endovascularly, and patients with Fisher grade 2 treated endovascularly have a lower risk of developing SDHC than those treated neurosurgically. This study found no difference in rate of SDHC between the treatment modalities during the follow up time of 5 years. However, the bivariate prediction analysis showed that Fisher grade significantly predicts SDHC rate in the EVT group, p=0.0432, but not in the NST group, p=0.5174. Similar results were obtained between age and SDHC. High age was correlated to a smaller increase of risk of developing SDHC than high Fisher grade. Hence high age and, especially high Fisher grade might be associated with an increased risk of developing SDHC in patients treated endovascularly but not in patients treated neurosurgically. Thus, patients with Fisher grade 4 could be treated with NST to minimize the risk of SDHC. These conclusions also implicate a reversed relationship for patients with low Fisher grade. The risk of SDHC development is higher in younger NST-patients with low Fisher grade than the EVT-patients with the same age and Fisher grade.

Concerning the total period under care, a significant difference was found in favor for EVT. EVT patients spent shorter periods in ICU and neurosurgical ward as well, but the differences were not significant, p=0.1534 respectively 0.0937. These findings reflect the results of neurological outcome, where NST patients had higher mRS scores at two months, indicating they needed longer time to recover. In addition to patients suffering, this is interesting in a health economic perspective where a prolonged stay in ICU, neurosurgical ward and total length of care increases the costs. An analysis comparing the overall costs for EVT and NST, from randomization to 24 months after treatment, was made in a subgroup of ISAT. The authors did not find a significant difference despite the higher cost of the endovascular procedure per se [20].

The analysis for identifying predictors for bad neurological outcome showed that a high Fisher grade was the most prominent factor; age had a significant influence as well. The factors investigated were age, aneurysm localization, Fisher grade, aneurysm size, aneurysm neck size and randomization group. The bivariate prediction of mRS 3-6 showed that a high Fisher grade entailed a significantly greater risk of death or dependency at two months. Age could predict the risk of bad neurological outcome as well, though the odds ratio was not as high as for Fisher grade. A study by Orbo et al. based on 44 aSAH-patients treated neurosurgically support the finding that Fisher grade is an important predictor of neurological impairment [21].

EVT or NST

The endovascular method has an initially better neurological outcome in this study as well as in ISAT and in BRAT. There are still concerns about which method is to be preferred. One of the difficulties has been the design of the trials. ISAT included only patients, which were judge to benefit equally from EVT and NST. In consequence a large part of the patients were excluded, 72.6% in this study and 76.6% in ISAT. This limits the possible conclusions, and they are not applicable to the excluded patients. BRAT on the other hand included all patients. Patients admitted one day was treated with EVT, and the patients admitted the following day was treated with NST. The last 100 patients had the procedure selected by randomization. After the patients were allocated to a procedure, the responsible physicians could change procedure if in their opinion the patient was better suited for the other procedure. This resulted in a large group of crossovers from coiling to clipping. Thus no study can show that the results obtained in ISAT and BRAT can be applicable to all aSAH patients.

Although many studies show that EVT is followed by a shorter time of recovery as well as a better initially neurological outcome in the studied population, the neurological outcome tells just how well the patient endures the procedure and recovers from the aSAH. It does not measure the explicit effect of the treatment and durability. A suitable endpoint to survey the efficacy of the treatment is the rate of retreatment or rebleeding. If the trend to treat aSAH with EVT continues there must be more safety data regarding the durability of the coil treatment. Molyneaux et al. have investigated the rate of rebleeding in the UK cohort of ISAT. The follow up time was 10-18.5 years and the rate of rebleeding was higher in the EVT group. Thirteen (1.6%) of the 809 EVT patients and 4 (0.5%) of the 835 NST patients rebled from the target aneurysm in the study [19]. It would be useful to know how this develops over an even longer time. Since the mean age for aSAH was 53.1 in this study, the patients have a mean remaining lifetime of almost 30 years. Therefore the coils must be able to provide protection from rebleeding and regrowth for a longer time than what has been investigated.

ISAT Part II is a trial that is currently in the data-collecting phase. It is planned to enroll at least 1896 patients to achieve adequate power to show significance and it is estimated to take 12 years to complete the trial. It addresses the insecurities after the original ISAT. The study will investigate neurological outcome for patients that would have been excluded in the original ISAT, the patients with aneurysms that were unsuitable for EVT because of technical limitations at the time and now can be treated endovascularly, and factors that could indicate a difference in neurological outcome with one of the procedures [22]. To optimize aneurysm treatment of aSAH patients both modalities need to be available as the best treatment may differ between aneurysm types. For optimal outcome, excellent aneurysm treatment and ICU treatment is paramount, preferably in a high volume center.

Methodological considerations

The material of this study was collected between 1997 and 2003. Since then technical advances have been made, especially in the endovascular intervention field, which have made it possible to treat patients who previously were unsuitable for EVT.

The inclusion rate of this study was 27.4%. Although higher than overall ISAT, a significant part of the aSAH-patients was excluded. This limits the generalizability of the conclusions.

Many statistical analyses were performed, which obviously increases the risk of type I errors.

Conclusions and implications

EVT entails an initially better neurological outcome in the studied populations, the difference diminishes over time. EVT patients spend shorter time in hospital. The rates of rebleeding and retreatment are higher for EVT. The risk of SDHC in patients with a high Fisher grade is lower when treated with NST than with EVT. Further studies must be conducted to assess aneurysm regrowth and rebleeding in the long term for EVT.

Populärvetenskaplig sammanfattning

Ett aneurysm är en säckformig utbuktning på en artär som löper en stor risk att brista. I så fall sker en subarachnoidalblödning. Detta är ett allvarligt tillstånd med en dödlighet på upp till 40 % [1]. Behandlingens syfte är att förhindra att ytterligare blödningar från aneurysmet inträffar. Det finns två behandlingsalternativ. Endovaskulär embolisering som går ut på att man för en kateter från en artär i ljumsken till aneurysmet som man sedan fyller med platinaspiral, på så vis kan man få blodet i aneurysmet att koagulera och minska risken för ytterligare blödning. Det kirurgiska behandlingsalternativet innebär att skallen öppnas och en metallklämma appliceras på aneurysmhalsen. På så vis tätas aneurysmhalsen och blod förhindras från att fylla aneurysmet.

Denna studie syftade till att undersöka skillnader i behandlingsresultat mellan metoderna. Det primära utfallsmåttet var neurologiskt tillstånd som mättes med modified Rankin Scale (mRS).

Resultatet visade fördel för den endovaskulära metoden i neurologiska tillstånd vid två månader och ett år, men vid fem år hade skillnaden krympt. Andel patienter som behandlats endovaskulärt med bra neurologiskt tillstånd (mRS 0-2) var 76.9% vid 2 månader, 84.6% vid 1 år och 76.9% vid 5 år. Motsvarande siffror för patienter behandlade kirurgiskt var 69.6%, 78.3 % och 78.3%. Dock pekade denna studie på en högre risk för att nya blödningar från aneurysmet inträffar och behov av ytterligare behandling vid endovaskulär behandling.

Att utreda vilken behandling som ger bäst resultat för en viss patientgrupp kan ge många patienter bättre förutsättningar att få en behandling som ger störst möjlighet att återgå till ett normalt liv efter blödning från ett intrakraniellt aneurysm. Denna studie kommer vara till gagn för patienter som drabbats av aneurysmala subarchnoidalblödningar, då resultatet kan användas som beslutsunderlag vid behandlingen av patienter med subarachnoidalblödning.

.

Acknowledgments

Contributions from others were essential in the creation of this thesis and I owe my deepest gratitude to the people involved.

To my supervisor Daniel Nilsson, for excellent guidance and support with great patience throughout the process.

To Gudrun Barrows, for providing the material used in this study.

To the people who collected the original data for ISAT at Sahlgrenska University hospital.

To the statisticians Nils-Gunnar Pehrsson and Anders Pehrsson for the contribution to the statistical analysis.

References

1. van Asch, C.J.J., et al., *Incidence, case fatality, and functional outcome of intracerebral haemorrhage overtime, according to age, sex, and ethnic origin: a systematic review and meta-analysis.* Lancet Neurology, 2010. **9**(2): p. 167-176.
2. Ingall, T., et al., *A multinational comparison of subarachnoid hemorrhage epidemiology in the WHO MONICA stroke study.* Stroke, 2000. **31**(5): p. 1054-61.
3. Solenski, N.J., et al., *Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study.* Crit Care Med, 1995. **23**(6): p. 1007-17.
4. Dandy, W.E., *Intracranial Aneurysm of the Internal Carotid Artery: Cured by Operation.* Ann Surg, 1938. **107**(5): p. 654-9.
5. Taha, M.M., et al., *Endovascular embolization vs surgical clipping in treatment of cerebral aneurysms: morbidity and mortality with short-term outcome.* Surg Neurol, 2006. **66**(3): p. 277-84; discussion 284.

6. Natarajan, S.K., et al., *Outcomes of ruptured intracranial aneurysms treated by microsurgical clipping and endovascular coiling in a high-volume center.* AJNR Am J Neuroradiol, 2008. **29**(4): p. 753-9.
7. Campi, A., et al., *Retreatment of ruptured cerebral aneurysms in patients randomized by coiling or clipping in the International Subarachnoid Aneurysm Trial (ISAT).* Stroke, 2007. **38**(5): p. 1538-44.
8. Guglielmi, G., et al., *Electrothrombosis of saccular aneurysms via endovascular approach. Part 1: Electrochemical basis, technique, and experimental results.* J Neurosurg, 1991. **75**(1): p. 1-7.
9. Koivisto, T., et al., *Outcomes of early endovascular versus surgical treatment of ruptured cerebral aneurysms - A prospective randomized study.* Stroke, 2000. **31**(10): p. 2369-2377.
10. Spetzler, R.F., et al., *The Barrow Ruptured Aneurysm Trial: 3-year results.* J Neurosurg, 2013. **119**(1): p. 146-57.
11. Molyneux, A., et al., *International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial.* Lancet, 2002. **360**(9342): p. 1267-1274.
12. Molyneux, A.J., et al., *International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion.* The Lancet, 2005. **366**(9488): p. 809-817.
13. Molyneux, A.J., et al., *Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up.* Lancet Neurol, 2009. **8**(5): p. 427-33.
14. Saveland, H., et al., *Overall outcome in aneurysmal subarachnoid hemorrhage. A prospective study from neurosurgical units in Sweden during a 1-year period.* J Neurosurg, 1992. **76**(5): p. 729-34.
15. Nam, K.H., et al., *Risk of Shunt Dependent Hydrocephalus after Treatment of Ruptured Intracranial Aneurysms : Surgical Clipping versus Endovascular Coiling According to Fisher Grading System.* J Korean Neurosurg Soc, 2010. **48**(4): p. 313-8.
16. Rankin, J., *Cerebral vascular accidents in patients over the age of 60. II. Prognosis.* Scott Med J, 1957. **2**(5): p. 200-15.
17. Boogaarts, H.D., et al., *Caseload as a factor for outcome in aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis.* Journal of Neurosurgery, 2014. **120**(3): p. 605-611.
18. Hart, Y., et al., *Epilepsy after subarachnoid hemorrhage: the frequency of seizures after clip occlusion or coil embolization of a ruptured cerebral aneurysm: results from the International Subarachnoid Aneurysm Trial.* J Neurosurg, 2011. **115**(6): p. 1159-68.
19. Molyneux, A.J., et al., *The durability of endovascular coiling versus neurosurgical clipping of ruptured cerebral aneurysms: 18 year follow-up of the UK cohort of the International Subarachnoid Aneurysm Trial (ISAT).* Lancet, 2015. **385**(9969): p. 691-7.

20. Wolstenholme, J., et al., *Treatment pathways, resource use, and costs of endovascular coiling versus surgical clipping after aSAH.* Stroke, 2008. **39**(1): p. 111-119.
21. Orbo, M., et al., *Predictors for cognitive impairment one year after surgery for aneurysmal subarachnoid hemorrhage.* J Neurol, 2008. **255**(11): p. 1770-6.
22. Darsaut, T.E., et al., *International Subarachnoid Aneurysm Trial - ISAT part II: study protocol for a randomized controlled trial.* Trials, 2013. **14**: p. 156.