

Research Article

Intra Hospital Delay Increases Mortality and Poor Outcome in Endovascular Coiling of Ruptured Intracranial Aneurysms

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- Sub arachnoid hemorrhage
- Timing

Abstract

Background: The purpose of the study was to investigate the effects of intra hospital delay and time of admission on mortality and neurological outcome in endovascular coiling of ruptured intracranial aneurysms.

Methods: A retrospective analysis of a database comprising all consecutive cases of proven ruptured intracranial aneurysms admitted to the Neurocenter at Odense University Hospital was performed. All aneurysms admitted in a period of 5 years and 3 months were investigated for inclusion in. Mortality was measured as death at 180 days.

Results: 237 patients were included in the study. In 82,7% of patients, the procedure of endovascular coiling was started before 24 hours, in 17,3% beyond 24 hours. Mortality at six months was 15.3% in the <24H group vs. 39.0% in the ≥ 24H group, $p < 0, 0001$. Increasing age was a significant predictor of delayed coiling (OR=1.046, $p = 0.002$).

Patients admitted during non-office time had 180 days mortality of 14.3% compared to 30.3 % in patients admitted during office hours, $p = 0.004$.

Conclusions: The presence of intra hospital delay was confirmed. Delayed endovascular coiling of ruptured intracranial aneurysms increased mortality and poor neurological outcome significantly. High age was a predictor of delayed treatment. The survival and outcome was improved when the patients arrived during non-office time.

INTRODUCTION

The purpose of the study was to investigate the effects of intra hospital delay and time of admission on mortality and neurological outcome in endovascular coiling of ruptured intracranial aneurysms. Because of short distances and substantial Emergency Medical Service resources [1,2], Subarachnoid haemorrhage (SAH) patients are admitted very early to the Neurocenter after ictus for confirmation of subarachnoid hemorrhage by head CT. If SAH is confirmed, the patient is assessed by a team of

neurosurgeons and neuroanesthesiologists and prepared for final treatment of a ruptured aneurysm by either neuroradiological intervention by digital or craniotomy with clipping for aneurysm repair.

In general, acute SAH patients are highly prioritized for early intervention, in the case of endovascular coiling within a minimum of 24 hours [3,4]. Intrahospital delay due to lack of capacity and untoward logistics seems to compromise timely intervention.

Our hypothesis was that the chain of survival is compromised after admission to the Neurocenter, due to intrahospital delay and that intrahospital delay would be associated with increased mortality and poor neurological outcome. Furthermore, we hypothesized that time of admission was a factor in delaying optimum treatment of a life threatening condition for the same reasons. Thus, death from any cause at six months was primary outcome and neurological outcome, time from admission to a Neurocenter to initiation of the procedure of endovascular coiling and time of admission were secondary outcomes in the Door-To-Cath Study.

MATERIALS AND METHODS

A retrospective analysis of a database comprising all consecutive cases of proven ruptured intracranial aneurysms admitted to the Neurocenter at Odense University Hospital, Denmark, was performed. Permission from the Danish Data Protection Agency was issued on August 26th 2011 (# 2012-41-0824). The regional Ethics Committee was consulted and did not require a permission to perform the study.

Inclusion

The database was prospectively updated and contained all consecutive patients with ICD codes comprising diagnoses of SAH admitted to the Neurocenter at Odense University Hospital. All aneurysms admitted from January 1st 2007 to March 31st 2012 were investigated for inclusion in the Door-To-Cath Study. 237 patients were included in the study.

Exclusion

Cases of SAH due to other reasons than aneurysm, i.e. trauma, dissection, arteriovenous malformation, benign perimesencephal venous bleeding or from unknown causes were excluded. Furthermore, patients with a wrongful diagnosis were excluded from the study. Patients who underwent open surgery for aneurysm clipping were excluded as well as the cases with insufficient or missing valid data. 302 patients with proven ruptured aneurysm were assessed for inclusion. 34 patients had craniotomy and clipping for aneurysm repair and were excluded from the study. The data of 31 patients were insufficient and subsequently, these patients were excluded as well (Figure 1).

Data collection

Patient demographics were recorded. The first recorded Glasgow Coma Scale (GCS), Hunt & Hess (H&H) Scale Score and Extended Glasgow Outcome Scale (GOS-E) were obtained for all patients. The exact time of admission to the Neurocenter and the time from admission to initiation of the coiling procedure were recorded using Odense University Hospital patient and procedure registration systems Cambio COSMIC® (Cambio Healthcare Systems, Aarhus, Denmark), General Electric Web PACS® and Sectra PACS Gateway® (GE healthcare, Barrington, IL, USA). Mortality at 30 and 180 days was recorded using the Danish National Personal Registry System [5].

Aneurysm anatomic location was recorded for all cases from neurointerventional files.

The term "Poor Grade SAH" used in other articles on aneurysm

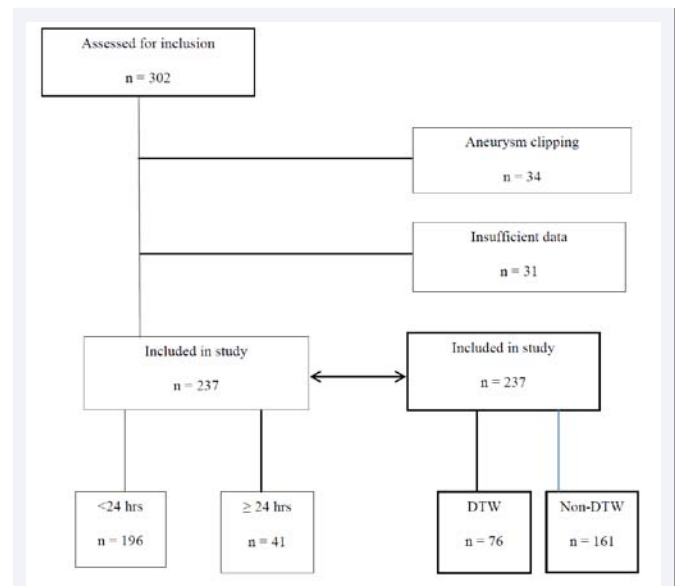


Figure 1 Door to Cath study Flow Chart.

depicting H&H Scale Scores ≥ 4 was implemented and used on the included patients.

Guidelines were implemented to ensure data collection consistency.

Despite electronic databases and state of the art registration systems, data are occasionally incoherent or wrongfully recorded.

Patient following

SAH was diagnosed by head CT in all cases. Intracranial aneurysm was diagnosed by digital subtraction angiography (DSA) or Computerized Tomographic Angiography (CTA). In all cases, a DSA was performed prior to and in conjunction with aneurysm coil embolization. There was a policy within the Neurocenter that all ruptured aneurysms should be treated within 24 hours from ictus.

In the study of time of admission to the Neurocenter, we defined day-time weekdays (DTW) or office time as Monday thru Friday from 08.00 – 16.00.

Non day-time weekdays (non-DTW) or non-office time were defined as Monday thru Friday 16.00 – 08.00 and all weekends and holidays.

When a ruptured aneurysm was detected, a joint decision between the on-call neurosurgeon and neurointerventional radiologist on the optimum treatment was made, based on patient history, actual clinical status and radiological findings.

The coiling procedure was performed by consultant neurointerventional radiologist. Patients were in general anesthesia, performed by specialist neuroanesthesiologists. Systemic heparinization in concordance with national and local guidelines was standard procedure.

During the study period, all patients received Tranexamic Acid as per protocol before transfer or on admission to the Neurocenter and up until eight hours before the procedure was

initiated. Patients that were treated very early after admission did not receive Tranexamic Acid.

After the procedure, all patients were admitted to the neuro intensive care unit for post procedure treatment, receiving routine Nimodipine and adjunct treatment according to local guidelines to prevent vasospasm. All patients had routine Trans Cranial Doppler for vasospasm detection within 24 hours from coil embolization. Adverse events and complications were treated according to local, national and international guidelines. Emergency procedures, i.e. reintubation, insertion of external drainage, intraarterial Nimodipine treatment during DSA for vasospasm etc. were performed according to national and local guidelines.

Power calculation

A difference of 10% in mortality between the two groups was considered to be clinically relevant. Using a standard comparison of two independent proportions, it was found that a sample of n=36 in each of the groups was required to render this difference significant at the 5% level. This was fulfilled for the < 24H group (n=196) as well as for the ≥ 24H group (n=41). Likewise, for the DTW group (n=76) and non-DTW group. (n=161)

Statistical analysis

Non-normally distributed continuous data were given as the median (interquartile range) range and tested with the Wilcoxon rank sum test. Normally distributed continuous variables were reported as the means ± standard deviations and tested with Students t-test. Categorical variables were given as numbers with percentages and tested with the χ^2 -test. Multivariate Logit regression analysis was used, and simple Odds Ratio (OR) for <24h on outcome measures were compared to partial ORs (controlled for confounding with other variables). Relative risk, Efficacy and Numbers Needed to Treat (NNT) were calculated with treatment >24 h as the reference treatment. The level of statistical significance was set at p = 0.05. Data were analyzed

with the Stata/IC 12.1 software package (Stata Corp, College Station, TX).

RESULTS

Time Door-To-Cath

- In 196 (82.7%) patients, the procedure of endovascular coiling was started within 24 hours. In 41 (17.3%) patients, the procedure was initiated beyond 24 hours (Table 1).
- The differences in initial GCS Score and H&H Score between groups were non-significant. However, the average age was significantly lower in the <24H group (53.7 ± 12.8 years vs. 60.9 ± 12.2 years, (p=0.001)).
- The difference in gender distribution was non-significant, (p=0.33).
- The proportion of poor grade SAH (H&H Scores ≥ 4) was higher in the ≥ 24H group, (p=0.045).
- Differences in localisation of aneurysm in the two groups were non-significant. (p=0.058).
- Mortality at six months was 15.3% in the <24H group vs. 39.0% in the ≥ 24H group, (p<0.0001). In multiple regression analysis increasing age was a significant predictor of coiling beyond 24 hours OR=1.046, p=0.002). When adjusting for age, poor grade SAH was not a significant predictor of delayed intervention (OR=1.919, p=0.098). Extended Glasgow Outcome Scale (GOS-E) Score had a median of 2 (interquartile rank 1 – 5) in the < 24H group while only 1 (interquartile rank 1 - 2) in the ≥ 24H group. A chi-square test for equal distribution showed that the distribution across GOS-E differed significantly across the two groups (p=0.048).
- Simple and partial ORs from Logit regressions for effect of <24H on the outcomes mortality within 30 days,

Table 1: Patient demographics, patients characteristics, 30- and 180-day mortality: Comparison of <24h and ≥ 24h treatment (Within 24 hours and beyond 24 hours from admission to neuro center), Time Door-To-Cath.

	< 24 hours	≥ 24 hours	p	test	comment
Number	196 (82.7)	41 (17.3)			number, percentage of total
Male	68 (34.7)	11 (26.8)	0.33	chi ²	number, percentage
Age	53.7 ± 12.8	60.9 ± 12.2	0.001	t-test	normal distributed, mean and sd
Initial GCS	14 (12-15)	14 (5.5-15)	0.34	wilcoxon (Mann-Whitney)	not normal distributed, median and interquartile range
Hunt and Hess	2 (1-3)	2 (1.5-4)	0.10	wilcoxon (Mann-Whitney)	not normal distributed, median and interquartile range
Poor grade, HH ≥ 4	35 (17.9)	13 (31.7)	0.045	chi ²	number, percentage
Anterior circulation	145 (74.0)	36 (87.8)	0.058	chi ²	number, percentage
Mortality					
30 days	27 (13.8)	12 (29.3)	0.015	chi ²	number, percentage
180 days	30 (15.3)	16 (39.0)	<0.0001	chi ²	number, percentage
Time Door-To-Cath	12 (4.25-16)	41 (28.5-58)	<0.0001	wilcoxon	median and interquartile range

Abbreviations: SAH: Subarachnoid Hemorrhage; GCS: Glasgow Coma Scale; Anterior Circulation: ICA, ACA, AComA, MCA; Time Door-To-Cath: Time from Admission to Neurocenter to Initiation of the Endovascular Procedure of Aneurysm Coil Embolization

mortality within 180 days and GOS-E scores are reported in Table (2). The simple effect of <24H was significant for all three outcome measures, while the partial effect was insignificant for 30 days mortality, slightly significant for 180 days mortality (p=0.07, i.e. one-sided p =0.035), and significant for GOS-E score (p=0.03).

- NNT were calculated to be 6.45, assuming that coiling <24 hours is the new treatment and coiling >24 hours is the current treatment (Table 3).

Time of admission

- 76 (32.07%) patients were admitted during DTW and 161 (67.93%) were admitted during non-DTW.
- The proportion of coiling >24 hrs was significantly higher in the DTW group (26.31% vs. 11, 80%, (p=0.012)) (Table 4).
- Overall mortality at six months was significantly higher in the DTW group (30.3% vs. 14.3%, (p=0.004%)).
- Time from admission to coiling was longer in the group admitted in DTW (median 18.5 hrs (3-24) vs. 13 (8-18),

(p=0.62), NS).

- Average ages, GCS Scores and H&H Scores were comparable.
- In multiple regression analyses, time of admission was non-significant in delaying coiling (OR=5.98, 95% CI=7.20-8.36, (p=0.884)).
- NNT were calculated to be 9.35, assuming that coiling in DTW is the new treatment and coiling in non-DTW is the current treatment (Table 5).

DISCUSSION

In this study, we have demonstrated that endovascular coiling of ruptured intracranial aneurysm beyond 24 hours significantly increased mortality and poor outcome in SAH. This is in accordance with other studies where the time from onset of symptoms to intracranial aneurysm repair had been investigated. In these studies early intervention within 24 hours also improved survival and outcome after aneurysmal SAH [3-5]. In these studies, the patient phase and prehospital phase were accountable for at least some of the delay. In our study, attention

Table 2: Simple and partial Odds Ratios for <24H on outcome measures.

Outcome measure	Simple OR	Partial OR
30 days mortality	0.39 (p=0.01)	0.55 (p=0.30)
180 days mortality	0.28 (p=0.0008)	0.37 (p=0.07)
Glasgow GOS-E	2.78 (p=0.004)	2.79 (p=0.03)

Note. Partial ORs were controlled for age, gender, GCS, H-H, Anterior and Time Door-to-Cath.

Table 3: Numbers needed to treat.

Calculation of NNT in the present population of patients if coiling > 24 hours is the current treatment and coiling < 24 h is the new treatment reducing the risk of death

Risk of death		Risk difference	Number of deaths per 1000 patients		Reduction in number of deaths	NNT
>24 h	<24 h		>24 h	<24 h		
12/41	27/196					1000/155
0.293	0.138	-0.155	293	138	155	6.45

Table 4: Patient demographics, patients characteristics, 30- and 180-day mortality: Comparison of treatment in Day Time Weekdays (DTW) vs. Non-Day Time Weekdays (Non-DTW): Admission to neurocenter Monday thru Friday 08.00 – 16.00 vs. Monday thru Friday 16.00 - 08.00 and Weekends/holidays), Time Door-To-Cath

	DTW	Non-DTW	p	test	comment
Male Number	30.3% 76 (32,1)	34.9% 161 (67,9)	0.49	chi ²	Percentage number, percentage of total
Age	57.6 ± 12.8	53.7 ± 12.8	0.029	t-test	normal distributed, mean and sd
Initial GCS	14 (7-15)	14 (13-15)	0.034	wilcoxon (Mann-Whitney)	not normal distributed, median and interquartile range
Hunt &Hess	2 (1-3.8)	2 (1-3)	0.14	wilcoxon (Mann-Whitney)	not normal distributed, median and interquartile range
Mortality 30 days	23.7%	13.0%	0.039	chi ²	percentage
180 days	30.3%	14.3%	0.004	chi ²	percentage
Time Door-To-Cath	18.5 (3-24)	13 (8-18)	0.62	wilcoxon (Mann-Whitney)	median and interquartile range

Abbreviations: SAH: Subarachnoid Hemorrhage; GCS: Glasgow Coma Scale; Anterior Circulation: ICA, ACA, A Com A, MCA; Time Door-To-Cath: Time from admission to Neurocenter to Initiation of the Endovascular Procedure of Aneurysm Coil Embolization. P-values refer to the results of statistical test applied to describe the differences between the < 24 hours group and the ≥ 24 hours group.

Table 5: Numbers needed to treat. Calculation of NNT in the present population of patients if coiling during non-office hours is the current treatment and coiling during office hours is the new treatment reducing the risk of death.

Risk of death		Risk difference	Number of deaths per 1000 patients		Reduction in number of deaths	NNT
DTW	Non DTW		DTW	non-DTW		
18/76	21/161					1000/107
0.237	0.130	-0.107	23	130	107	9.35

was directed at the intra hospital delay alone, i.e. the time from admission to the Neurocenter to initiation of the endovascular procedure, since the time from ictus to final intervention has been addressed in other studies.

The importance of reducing the time from symptoms to treatment has also been observed in acute myocardial infarction [7,8] and acute ischaemic stroke [9,10]. The proportion of patients treated >24 hours was relatively small, indicating that the medical ambition of coiling within 24 hours was fulfilled in the majority of cases, but still, a proportion of the patients were not treated timely. Thus our hypothesis that treatment was compromised due to intra hospital delay was confirmed.

Furthermore, the present study also showed that time of admission had an important influence on treatment and mortality, addressing the subsequent intra hospital delay that inadvertently occurs in complex hospital structures with uncontrollable influx of emergency patients in competition with scheduled elective patients. Thus, our second hypothesis that the time of admission was important was also confirmed. Surprisingly, patients admitted on non-office time had a better survival, suggesting that the readiness during day time should be enhanced in our Neurocenter. The treatment delay is probably due to reluctance to cancel scheduled elective surgery to create space for acute operations. This reluctance may be associated with hospital administrators' fear of complaints from cancelled patients and pressure from patient organizations, suggesting that cancellation of scheduled procedures in favour of emergency patients remains a controversial option.

The improved outcome of patients admitted in non-office time as compared to patients admitted in office time has to our knowledge not been described before. This is a single center study but identical problems might be found in other hospitals. We suggest that other Neurocenters investigate any treatment delay in relation to time of admission.

Several phases of subarachnoid haemorrhage have been described.

Patient phase is the time from ictus with onset of severe headache with or without neurological deficits to call for help, i.e. dialling 911 or calling the family doctor. In the Western hemisphere and especially Scandinavia, attention to symptoms of stroke is at forefront in the mindset of the population due to community outreach information on prevention and symptoms of stroke. In our opinion, the flow of patients is optimized in our country.

Prehospital phase is the time from the dispatch of a prehospital resource to arrival at a Neurocenter. In Denmark in general and in the Region investigated, prehospital resources are substantial. Ambulances, mobile emergency care units and

physician-manned helicopters are all available within minutes. The patient may be taken to a local hospital without neuro facilities for head CT, but in the event of findings suggesting SAH, transfer to a Neurocenter is rapid and highly prioritized. In an increasing number of cases, patients with symptoms of severe stroke are taken directly to the Neurocenter by helicopter or ambulance. It will be difficult in many Western countries to further optimize the prehospital phase.

In hospital phase is the time from arrival at the hospital to final treatment of ruptured intracranial aneurysm. Upon arrival at the Neurocenter, patients with CT proven SAH are admitted to the Neurocenter for treatment. In the cases without any contact with prehospital units, the patient is admitted to the Emergency Room and head CT is performed rapidly if symptoms are consistent with SAH. If CT confirms SAH, the patient is referred to the Neurocenter for further treatment. In this study, we have demonstrated a treatment delay dependent on the time of admission and on patient age but not on gender.

Rebleeding is the major cause of mortality and poor outcome and the primary concern until the aneurysm has been secured. In this study, we did not record rebleeding, since it was not necessarily confirmed by head CT in all cases and represented a clinical diagnosis. Likewise, the discussion among the treating clinicians to withhold therapy due to dismal clinical condition was not possible to document from patient files, since it may have been informal discussions that were not necessarily documented. In future prospective studies, we suggest that these considerations should be included in the analysis.

In our study, increasing age was associated with delayed endovascular coiling of ruptured intracranial aneurysms. High age alone should not be a limiting factor for intensive treatment but in the case of high age and multiple comorbidities withholding therapy might be an option [11]. In the present study, the delay in treatment of the older patients was however not a deliberate action but a reluctance in clinicians' decisions regarding advanced intervention in the aging population. This is in accordance with other studies showing an irrational reluctance in offering intensive care to the older population [12].

The gender distribution in this study was in concordance with what is expected in SAH in general, reflecting that female patients are predominant in numbers. However, female patients were not overrepresented in relative risk of death in multiple regression analysis. This is accordance with the findings of Hamdan et al. [13].

Given that the study was based on retrospective data, there may be a risk of selection bias affecting the measured outcome in terms of mortality and GOS-E. Although it is not possible to fully control for such a bias, we expect that it is reduced by involving

the available potential confounders when estimating effects on outcome.

CONCLUSION

This study demonstrates that delayed endovascular coiling of ruptured intracranial aneurysms increased mortality and poor neurological outcome significantly, compared with treatment within 24 hours. We also observed an intrahospital delay in the treatment of several patients with SAH. Furthermore, we have demonstrated that time of admission influenced mortality and poor outcome strongly. Surprisingly, we found that admission in non-office time was more favourable in terms of mortality. This should be investigated in other Neurocenters.

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